Objective Diagnosis of Circadian Rhythm Disorders

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Summary: Circadian sleep–wake disorders are common. Because they represent conflict between the timing of the patient's endogenous rhythms and desired timing of sleep, the presenting complaints may include both difficulty of sleep initiation or maintenance and undesired or unplanned daytime or early evening sleepiness. Therefore, circadian disorders may be misdiagnosed as either a primary insomnia or a hypersomnia disorder, depending on which complaint is more troublesome for the patient. Objective information about sleep and wake patterns over long periods is crucial for accurate diagnosis. Actigraphy provides long-term information about the rest/activity pattern about an individual. However, caution should be applied in interpretation of the results because the information provided only includes information of movements, and activity is only an indirect circadian phase marker. Timing of light and melatonin therapy is critical for successful treatment of circadian rhythm disorders. Therefore, results of actigraphy are useful and should be used in conjunction with additional measurements, including 24 hours sleep–wake history, sleep log, and melatonin measurements.

Key Words: Circadian rhythm disorders, Actigraphy.

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Circadian rhythms are among the two key processes that regulate the timing and continuity of sleep and wakefulness. Directed by the suprachiasmatic nucleus, the circadian system influences a wide variety of functions, including metabolism, hormone release, sleep–wake propensity, and activity.

CIRCADIAN RHYTHM DISORDERS

Circadian rhythm sleep–wake disorders (CRSWDs) are characterized by a misalignment between the desired timingof sleep and the ability to fall asleep and remain asleep. Although circadian rhythm disorders usually manifest asextremely early or late sleep times, they may also frequently present as insomnia and/or excessive daytime sleepiness. When a patient is attempting to sleep at a conventional clock time instead of aligning sleep according to his or her underlyingcircadian rhythm of sleep–wake propensity, they would expe- rience difficulty initiating or maintaining sleep. Conversely, when that patient tries to stay awake and remain alert during theendogenous sleep phase of their circadian cycle, he or she will experience excessive daytime sleepiness, as commonly seen with night-shift workers or patients with delayed sleep–wake phase disorder. Regardless of type, circadian rhythm sleep disorders can cause a major impairment of work, school, and social activities, lead to disruptions of social and family life, and increase the risk of developing many other medical com- plaints and disorders.

Although prevalence in the population remains unknown,[1] some estimates hold that up to 3% of the adult population suffers from a CRSWD,[2] with a higher prevalence (7%–16%) in adolescents and young adults.[1]

Despite their high prevalence, CRSWDs are commonly misdiagnosed as a primary insomnia disorder or, in some situations, a hypersomnia disorder because of insufficient history taking. In these cases, hypnotic treatments for insomnia or wake promoting treatments for hypersomnia symptoms are often unsuccessful and expensive and sometimes harmful or lead to delay in accurate diagnosis and effective treatment when there is an underlying CRSWDed. The diagnosis of CRSWD is based on a careful sleep history. Although these disorders are presumed to their name implies that they result from an abnormality of the circadian timing system, current diagnostic criteria do not require assessment of circadian rhythms in the diagnosis of a CRSWD. However, measurable and/or objective evidence is needed to better assess the sleep–wake pattern to support an accurate diagnosis and tailoring of the timing of administration of appropriate light therapy and melatonin or other medication or behavioral treatment options.

Currently, multiple instruments including sleep logs and sleep diaries are used in the diagnostic process and standardized questionnaires about chronotype (Morningness-Eveningness Questionnaires, Munich Chronotype Questionnaire).[3,4] Plasma melatonin and salivary dim light melatonin onset (DLMO) measurements and core body temperature are used in research applications and aid diagnostic precision of CRSWDs[5,6] but have remained of limited utility in usual clinical practice settings because of their labor intensiveness, expense, and special resources and settings that are required for accurate measurement, so these are typically not used for routine clinic use, although home sampling of DLMO may be considered (see further discussion in the Circadian Rhythm Disorder Assessment DLMO section). Urinary 6-sulfatoxymelatonin may be useful in very specific clinical situations such as non_24-hour sleep_wake disorder.[7] Polysomnography, although a gold standard for assessment of sleep duration and quality, does not provide information about circadian phase and is not routinely used with CRSWD patients unless a comorbid sleep disorder is suspected. Actigraphy is an objective measure that is useful in clinical practice for assessment of multiday sleep–wake patterns to aid diagnosis of CRSWDs.

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ACTIGRAPHY

Actigraphy is helpful for the diagnosis and management of insomnia, circadian rhythm disorders, and excessive daytime sleepiness because it provides objective data regarding longitudinal sleep–wake patterns in the patient's usual home and work environment. Actigraphy, in addition to a sleep log, is particularly helpful for the evaluation and treatment of CRSWDs.[1,8] An actigraph is a small, lightweight wrist (or ankle)-worn computerized accelerometer with the ability to measure rest–activity patterns continuously over long periods (several days or as long as weeks to months).[10,11] After at least7 days of data collection (to include both weekdays and a weekend), data are downloaded to a computer where off-line analysis is performed.

Minimal actigraph technical requirements include: a triaxial accelerometer, the ability to record data in 30 seconds or 1-minute epochs, battery power to record data, the ability to store at least 7 days of data, and support for both device and software. Additional recommended features include a waterproof case, an ambient light sensor, an event marker, a nonvolatile memory, a battery that can store data for a minimum of 2 weeks, and a small, comfortable profile.[9] Although actigraphs provide objective data about rest–activity patterns, supplemental information from a sleep log or diary recording the patient's habitual, bed and wake times and any awakenings and their durations, a light sensor, as well as a sensor to light spectrum, and an event marker can improve the usefulness and accuracy of the activity data. Data collected over longer periods can be useful in the diagnosis of non–24-hour or irregular sleep–wake rhythm disorder.[11] Most activity monitors come with automated software packages that score the data as sleep or wake, and the estimates of sleep and wake are typically improved by manual overscoring, referencing the additional data provided by sleep logs and light detection patterns to correctly interpret the actigraphy data. Scoring algorithms differ between manufacturers and can produce different sleep–wake scoring on the same data file. Some are optimized for specific patient populations (adult vs. pediatric).

The evaluation of the sensitivity, specificity, and agreement of actigraphy compared with polysomnography is related to the device itself, the software (algorithm) used to analyze the data, and often settings within the software that can be adjusted by the user. Actigraphy tends to overestimate sleep and underestimate wake time and the accuracy declines as sleep quality declines.[11–14]

Various actigraphy devices and software algorithms have been compared in validation studies to polysomnography with high levels of sensitivity and specificity for rest/activity patterns reported in various patient populations, in terms of rest/activity patterns.[11,15–17] However, it is important to remember that the diagnosis of CRSWDs circadian rhythm disorders does not routinely include polysomnography, which classically in the United States captures a single night of sleep, and thus does not provide information about long-term sleep–wake patterns that are necessary to observe for accurate diagnosis of CRSWDs.[28]

CIRCADIAN RHYTHM DISORDER ASSESSMENT—DLMO

To accurately determine the timing of the circadian system in a patient with a suspected CRSWD, an at-home or clinic assessment of their dim light salivary melatonin onset may be useful.[19–21] Melatonin is a hormone produced by the pineal gland, and production of melatonin is suppressed by light. Melatonin levels are typically undetectable during the daytime hours and begin to rise in the evening, 1 to 2 hours before the individual's usual bedtime. The levels reach a peak in the middle of the usual sleep episode and then decline throughout the latter part of the night, reaching undetectable levels again the next day. Because of suppression by light, melatonin levels must be measured in dim light conditions (ideally less than 20 lux). DMLO measurements are traditionally performed in a laboratory over several days but can also be performed by the patient in their home.[21] For CRSWD patients, a sleep log should be used to determine usual bedtime. The DLMO assessment process should begin 5 to 7 hours before usual bedtime (average time from the past week), with the patient maintained in a dim light environment throughout the study, including for 1 h before the first sample is taken and ensuing hourly saliva samples that are collected every hour from the start until at least 1 hour after usual bedtime. Each sample is frozen after collection, and the next day, the samples are transferred to an assay facility where a commercial ELISA or RIA kit is used to determine the melatonin level in each sample. Linear interpolation between the resulting assay values is used to determine the time at which melatonin values rise above a set threshold (typically 3 pg/mL; 22), the dim light salivary melatonin onset. The timing of the dim light salivary melatonin onset in the patient can then be compared with their usual sleep onset time, and with normative data, to guide diagnosis and treatment.

TIMING AND EFFECT OF LIGHT

The period (cycle length) of the circadian system is close to (although not exactly) 24 hours. In healthy sighted humans, the endogenous period/cycle length averages 24.2 hours, ranging from about 23.5 to 24.5 hours.[23,24] The endogenous circadian clock must be regularly reset to remain synchronized to the 24-hour clock time in the environment, a process called entrainment. Light is the most powerful environmental influence on the human circadian timing system, and it is through regular light–dark exposure that the circadian timing system of humans is synchronized on a daily basis and is reset when traveling across time zones. Many features of the light to which we are exposed determine the entrainment or resetting process, including the spectral composition, intensity, duration, timing, and overall pattern (including timing and duration of darkness).[25] One feature of the circadian response to light is that it is phase dependent. It means that the same light stimulus when applied at different phases (times of day) can produce different responses. Light in the late afternoon or early evening (i.e., 4–7 PM) produces phase delay shifts (shifts to a later hour), whereas light exposure in the late biologic night or early morning biologic day produces phase advance shifts (shifts earlier), as determined by relationship of light exposure to the body core temperature nadir point in the early morning hours. Light exposure in the middle of the biologic day typically produces only minimal changes in phase. These responses can be summarized in a phase response

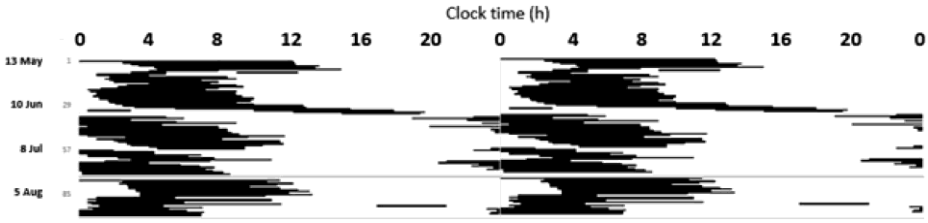

FIG. 1. Actigraphy data of case 1.

curve.[26,27] From our understanding that most humans have a circadian period longer than 24 hours, most people need their overall daily light exposure to produce a slight phase advance (on average 0.2 hours, or 12 minutes) to remain entrained. To achieve entrainment, most people need to get more morning light exposure than evening light exposure. Being able to correctly identify the timing of the circadian phase is critical for effective light therapy for CRSWDs. Mistiming the light by even a few hours can result in either no effect on phase or a phase shift in the wrong direction, which can exacerbate misentrainment and resultant symptoms of insomnia or hypersomnia.

CASES

Case 1

A 27-year-old nonsighted man presented to clinic with a complaint of inability to control a shifting sleep schedule. The patient lost his sight 7 years earlier because of retinitis pigmentosa but was otherwise in good health. After vision loss, his bedtime continually shifted 15 to 30 minutes later each night with a corresponding drift in his awakening time. After 3 to 4 weeks, he would reset to an earlier bedtime and the shifting would begin again. Four months of actigraphy data are shown below in the form of a double raster plot, which compresses the activity data over long periods. Activity, shown by the dark bars, and sleep time, shown by the white space, shift gradually later until they reset after approximately 2 weeks (Fig. 1). This pattern is consistent with non–24-hour sleep–wake phase disorder.

Actigraphy is more accurate than sleep logs, particularly for long periods. Although melatonin is more sensitive than actigraphy, in this case, multiple samples would be required because of the shifting circadian phase. History and actig- raphy confirmed diagnosis of non–24-hour sleep–wake disorder.

Case 2

A 44-year-old woman reported lifelong difficulty awakening and performing any cognitive tasks in the morning and preferred performing work-related tasks at night, and it was most common for her to go to her office late in the evening and work overnight until 5 to 6 am.

The top graph shows the daily activity pattern over 7 days (Fig. 2). A cumulative graph of the activity pattern for this patient is shown below (Fig. 3). As this patient's activity pattern was fairly consistent over the course of the recording, this combined graph allows easier visualization of the activity pattern, with minimal activity between 7 AM and 2:30 PM Because DLMO usually precedes typical bedtime by 1 to 2 hours, based on this activity pattern, one might expect that the patient's DLMO is close to 4 to 5 AM. However, the following melatonin profile was obtained:

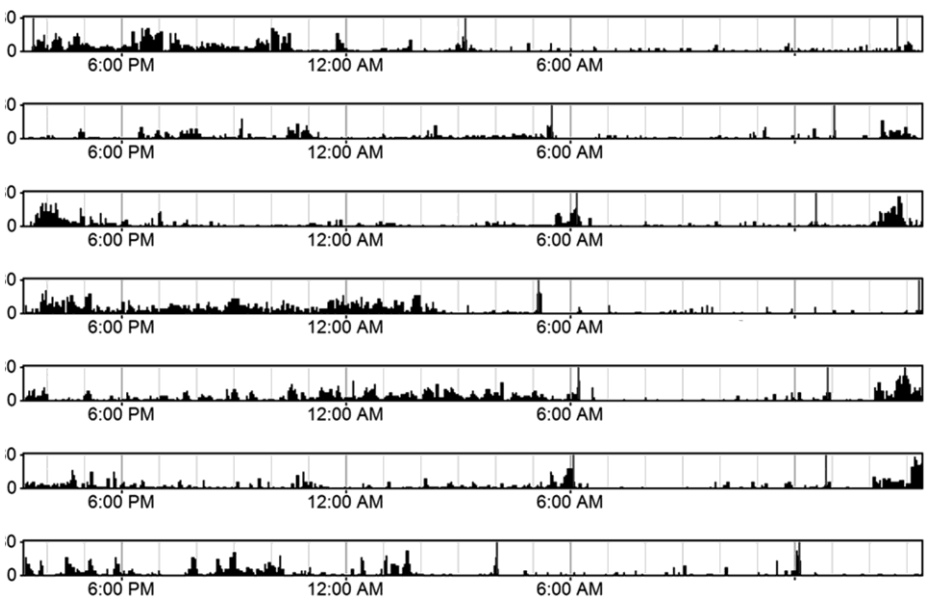

FIG. 2. Melatonin levels (pg\mL) of case 2 by time.

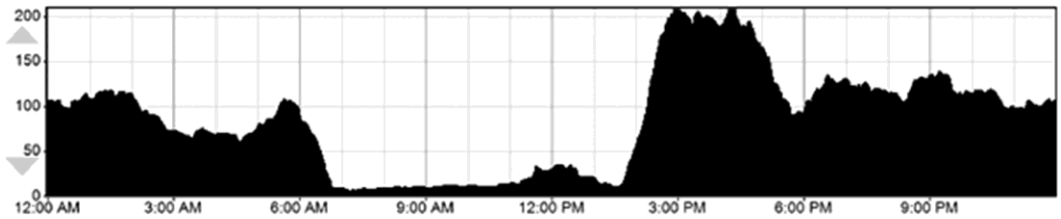

FIG. 3. Daily activity patterns of case 2 (cumulative graph).

As seen, dim light salivary melatonin onset was earlier at 12:30 AM (Fig. 4). For treatment, melatonin 0.5 mg was used to advance this patient's sleep phase, taken at 11:30 PM, and maintaining light levels low after that. Based on the patient's sleep log and actigraphy data, light therapy given at 8 AM, the patient's desired rise time might fall on the part of the phase response curve that would produce phase delay. However, the melatonin measurements provide more precise information, and thus, light therapy at rise time may be beneficial to help advance this patient's sleep phase.

Case 3

An 82-year-old man was reported by his family to have a 5-year history of short-term memory loss, paralleled by erratic sleep habits. Before his memory loss began, he had a regular sleep schedule with a usual 10 PM bedtime and 6 AM awakening time. However, for the last 2 to 3 years, he would become agitated in the evenings, and he would often be unable to initiate sleep until 1 AM and would awaken by 4 or 5 AM, frequently noted to doze off and on through the daytime hours, and he would also take two or three naps, each lasting 1 to 2 hours in duration throughout the afternoon and early evening. His actigraphy is shown below.

Actigraphy shows a highly chaotic sleep–wake schedule, without an average consistent bed or rise time, several short bouts of inactivity and probable sleep, with intervening brief periods of movement and wakefulness (Fig. 5).

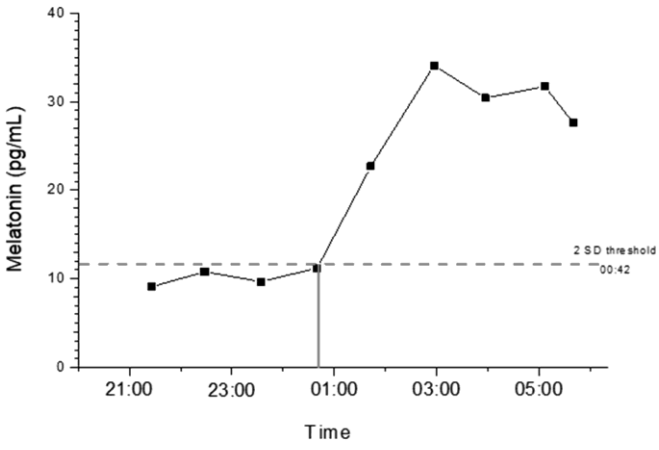

FIG. 4. DLSMO of case 2. DLSMO, dim light salivary melatonin onset.

These actigraphy findings support the clinical history and diagnosis of an irregular sleep–wake rhythm disorder. This disorder is most common in elderly individuals with a neurodegenerative disorder and likely arise from degeneration of the suprachiasmatic nucleus, the brain's master clock that coordinates circadian rhythmicity and a consolidated sleep–wake schedule. Less frequently, this disorder may also be seen in children or adolescents with an underlying neurodevelopmental disorder.

SUMMARY AND CONCLUSIONS

Actigraphy provides an objective, relatively inexpensive, and helpful information about long-term patterns of activity and rest, which can be helpful in evaluating patients with circadian rhythm sleep–wake disorders. Actigraphy provides data on sleep–wake patterns and is not a specific circadian phase marker, so any information provided by actigraphy should be reviewed in the context of each individual patient's clinical scenario, sleep log, and if possible, results of DLMO profile for optimal guidance of therapy.

Appendix

Section 1: Diagnostic Criteria for Delayed Sleep–Wake Phase Disorder

A. There is a significant delay in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint by the patient or a caregiver of the inability to fall asleep and difficulty awakening at a desired or required clock time.
B. The symptoms are present for at least 3 months.
C. When patients are allowed to choose their ad libitum schedule, they will exhibit improved sleep quality and duration for age and maintain a delayed phase of the 24- hour sleep–wake pattern.
D. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate a delay in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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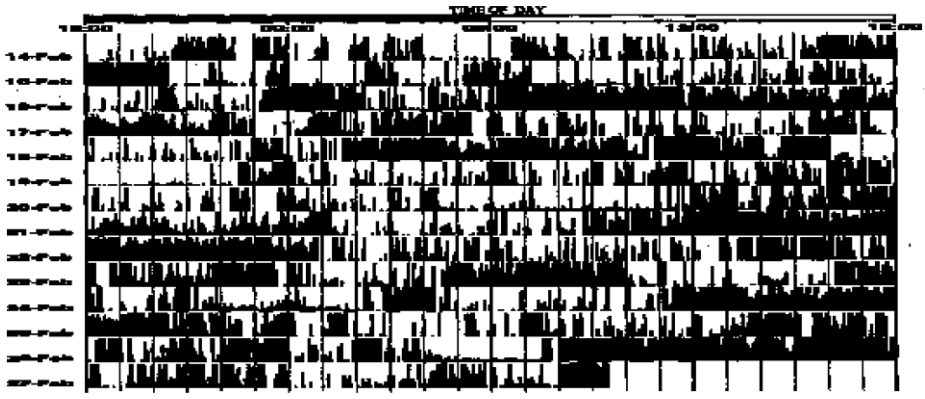

FIG. 5. Actigraphy of case 3.

Section 2: Diagnostic Criteria for Advanced Sleep–Wake Phase Disorder

A. There is an advance (early timing) in the phase of the major sleep episode in relation to the desired or required sleep time and wake-up time, as evidenced by a chronic or recurrent complaint of difficulty staying awake until the required or desired conventional bedtime, together with an inability to remain asleep until the required or desired time for awakening.
B. Symptoms are present for at least 3 months.
C. When patients are allowed to sleep in accordance with their internal biologic clock, sleep quality and duration are improved with a consistent but advanced timing of the major sleep episode.
D. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate a stable advance in the timing of the habitual sleep period. Both work/school days and free days must be included within this monitoring.
E. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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Section 3: Diagnostic Criteria for Irregular Sleep–Wake Rhythm Disorder

A. The patient or caregiver reports a chronic or recurrent pattern of irregular sleep and wake episodes throughout the 24-hour period, characterized by symptoms of insomnia during the scheduled sleep period (usually at night), excessive sleepiness (napping) during the day, orboth.
B. Symptoms are present for at least 3 months.
C. Sleep log and, whenever possible, actigraphy monitoring for at least 7 days (preferably 14 days) demonstrate no major sleep period and multiple irregular sleep bouts with at least three brief sleep periods during a 24-hour period.
D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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Section 4: Diagnostic Criteria for Non–24-Hour Sleep–Wake Rhythm Disorder

A. There is a history of insomnia, excessive daytime sleepiness, or both, which alternate with asymptomatic episodes, because of misalignment between the 24-hour light–dark cycle and the nonentrained endogenous circadian rhythm of sleep–wake propensity.
B. Symptoms persist over the course of at least three months.
C. Daily sleep logs and actigraphy for at least 14 days, preferably longer for blind persons, demonstrate a pattern of sleep and wake times that typically delay each day, with a circadian period that is usually longer than 24 hours.
D. The sleep disturbance is not better explained by another current sleep disorder, medical or neurologic disorder, mental disorder, medication use, or substance use disorder.

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The Clinical Process in Psychiatry: A Clinimetric Approach

Giovanni A. Fava, MD; Chiara Rafanelli, MD, PhD; and Elena Tomba, PhD

Objective: The aim of this review was to examine the clinical process in psychiatry, with special reference to clinimetrics, a domain concerned with the measurement of clinical phenomena that do not find room in customary taxonomy.

Data Sources: A MEDLINE search from inception to August 2010 was performed for English-language articles using the keywords *clinical judgment*, *clinimetric*, *staging*, *comorbidity*, *sequential treatment*, and *subclinical symptoms* in relation to psychiatric illness. It was supplemented by a manual search of the literature.

Study Selection: Choice of assessment strategies was based on their established or potential incremental increase in clinical information compared to use of diagnostic criteria.

Data Extraction: Contributions were evaluated according to the principles of clinimetrics.

Results: Several innovative assessment strategies were identified: the use of diagnostic transfer stations with repeated assessments instead of diagnostic endpoints, subtyping versus integration of different diagnostic categories, staging methods, and broadening of clinical information through macroanalysis and microanalysis. The most representative examples were selected.

Conclusions: Current assessment strategies in psychiatric research do not reflect the sophisticated thinking that underlies clinical decisions in practice. The clinimetric perspective provides an intellectual home for the reproduction and standardization of these clinical intuitions.

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Psychiatric diagnosis and classification have attracted considerable attention in the past decades.[1] The introduction of diagnostic criteria for the identification of psychiatric syndromes, such as the *DSM*,[2] has considerably decreased the variance of diagnoses due to different assessors and the use of inferential criteria rather than direct observation.

However, clinicians have become increasingly aware of the limitations of the current diagnostic systems[3] and concerned about future *DSM* or *ICD* developments.[4] The customary clinical taxonomy in psychiatry does not include patterns of symptoms, severity of illness, effects of comorbid conditions, timing of phenomena, rate of progression of illness, responses to previous treatments, and other clinical distinctions that demarcate major prognostic and therapeutic differences among patients who otherwise seem to be deceptively similar since they share the same psychiatric diagnosis.

Little consideration has been given to the clinical process in psychiatry, that is, how clinical judgment leading to medical decisions is formulated. The main emphasis has been given to the standardization of the assessment process by use of rating scales leading to diagnostic configuration.[5]

In 1967, Alvan Feinstein dedicated a monograph to an analysis of clinical reasoning that underlies medical evaluations, such as the appraisal of symptoms, signs, and the timing of individual manifestations.[6] In 1982, he introduced the term *clinimetrics*[7] to indicate a domain concerned with the measurement of clinical issues that do not find room in customary clinical taxonomy. Such issues include the types, severity, and sequence of symptoms; rate of progression in illness (staging); severity of comorbidity; problems of functional capacity; reasons for medical decisions (eg, treatment choices); and many other aspects of daily life, such as well-being and distress.[8] Feinstein, in his book on clinimetrics,[8] quotes Molière's bourgeois gentleman who was astonished to discover that he spoke in prose as an example of clinicians who may discover that they constantly communicate with clinimetric indices. Indeed, in clinical practice, psychiatrists weigh factors such as the progression of disease, the overall severity of the disorder, the patient's social support and adaptation, resilience and reaction to stressful life circumstances, and response to previous treatment.[9] However, current formal strategies of assessment fail to capture most of this information.

We will examine some emerging trends and perspectives in the clinical process in psychiatry, with special reference to the diagnostic process, the staging method, and the organization of information.

DATA SOURCES AND STUDY SELECTION

A review of the literature, based on a MEDLINE search from inception to August 2010 using the keywords *clinical judgment*, *clinimetric*, *staging*, *comorbidity*, *sequential treatment*, and *subclinical symptoms* in relation to psychiatric illness was performed. It was supplemented by a manual search of the literature. Choice of assessment strategies was based on clinimetric principles[8] and on the concept of incremental validity,[10] which refers to the unique contribution or incremental increase in predictive power associated with the inclusion of a particular assessment procedure in the

Clinical Points

- Exclusive reliance on diagnostic criteria has impoverished the clinical process and does not reflect the complex thinking that underlies decisions in psychiatric practice.
- The accuracy of clinical judgment can be greatly increased with specific strategies: global formulations, staging methods, and a better organization of clinical information (encompassing macroanalysis and microanalysis).
- The concept of disease is no longer adequate to guide psychiatric care; therefore, clinical decision making should be addressed to attainment of individual goals.

clinical decision process.[11,12] We will then discuss the implications that a renewed interest in these assessment strategies may entail.

DIAGNOSTIC ENDPOINTS VERSUS TRANSFER STATIONS

In most instances of diagnostic reasoning in psychiatry, the process ends with the identification of a disorder,[13] often subsumed under a rubric of the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*). A single assessment generates the prognostic and therapeutic judgments of the clinician. A *DSM* diagnosis (eg, major depressive disorder), however, encompasses a wide range of manifestations, comorbidity, seriousness, prognosis, and responses to treatment.

The majority of patients with mood and anxiety disorders do not qualify for 1, but for several Axis I and Axis II disorders.[14] As Cloninger[15] remarks, mental disorders can be characterized as manifestations of complex adaptive systems that are multidimensional in their description and multifactorial in their origins, and they involve nonlinear interactions in their development. As a result, efforts to describe psychopathology in terms of discrete categorical diagnoses result in extensive comorbidity and do not lend themselves to adequate treatment strategies.[15]

Very seldom do comorbid diagnoses undergo hierarchical organization (eg, generalized anxiety disorder and major depression) or is attention paid to the longitudinal development of mental illnesses. There is comorbidity that wanes upon successful treatment of 1 mental disease, eg, recovery from panic disorder with agoraphobia may result in remission from co-occurring hypochondriasis, without any specific treatment for the latter.[10] Other times, treatment of 1 disorder does not result in the disappearance of comorbidity. For instance, successful treatment of depression may not affect preexisting anxiety disturbances.[16]

The diagnostic criteria are particularly helpful in setting a threshold for conditions worthy of clinical attention. Accordingly, the diagnostic criteria for a major depressive disorder identify a syndrome that may be responsive to antidepressant drugs. At least 5 of a set of 9 symptoms should be present (and 1 should be either depressed mood or loss of interest). However, according to the psychometric model, all items are weighed the same, unlike in clinical medicine, where major and minor symptoms are often differentiated (eg, Jones criteria for rheumatic fever).[7] As a result, a patient with severe and pervasive anhedonia, incapacitating fatigue, and difficulties concentrating, which make him unable to work, would not be diagnosed with a major depressive disorder, despite the clinical intuition of potential benefit from pharmacotherapy. This diagnosis could be performed in a patient who barely meets the criteria for 5 symptoms. The hidden conceptual model is psychometric: severity is determined by the number of symptoms, not by their intensity or quality, to the same extent that a score in a depression self-rating scale depends on the number of symptoms that are scored as positive.[10] This is not surprising in view of the fact that the development of psychometrics took place outside of the clinical field, mainly in educational and social areas.[17] Since the phenomena under observation in the development of psychometric principles were not clinical, they could not be automatically adapted to clinical psychology and psychiatry.

Similar considerations apply to the longitudinal development of the disorder (prodromal phase, the fully developed disorder, and residual states).[9] Detre and Jarecki[18] provided a model for relating prodromal and residual symptomatology in psychiatric illness, defined as the rollback phenomenon, ie, as the illness remits, it progressively recapitulates, even though in a reverse order, many of the stages and symptoms that were seen during the time it developed. The rollback phenomenon has been substantiated in mood and anxiety disorders.[19,20] There is limited awareness of the fact that the current patient's symptomatology may have developed over the years and have reflected previous treatments.

Feinstein[13] remarks that, when making a diagnosis, thoughtful clinicians seldom leap from a clinical manifestation to a diagnostic endpoint. The clinical reasoning goes through a series of "transfer stations," where potential connections between presenting symptoms and pathophysiological process are drawn. These stations are a pause for verification or change to another direction.[13] This strategy particularly applies to psychiatric disorders. An initial state of generalized anxiety may assume phobic connotations at some later point in time. If major depression then ensues, mood symptomatology may overshadow the previous anxiety disturbances, but the diagnosis of depression is only a transfer from prodromal to residual anxiety.

Some assessment strategies have been developed to overcome the flat, cross-sectional view of *DSM*.

Repeated Assessments

The use of diagnostic transfer stations has been suggested by the sequential treatment model,[21] an intensive, 2-stage approach, that includes the use of 1 treatment (eg, pharmacotherapy) after remission has been achieved. One type of treatment is thus employed to address the residual

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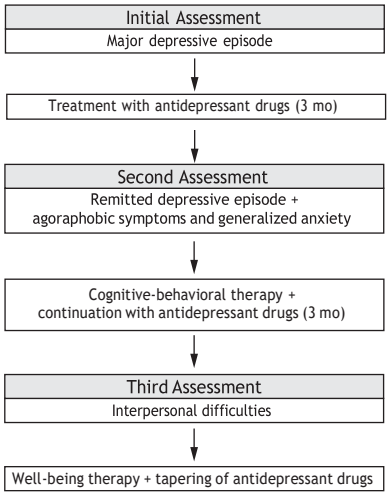
Figure 1. Effects of Repeated Assessments on the Development of a Diagnostic Work



symptomatology that the other treatment was unable to affect. The sequential model relies on repeated assessments (after each line of treatment has been completed) that may modify an initial diagnosis (eg, preexisting anxi- ety disturbances may emerge after pharmacotherapy of a major depressive episode). Robins and Guze[22] developed the primary/secondary dichotomy in depression, which was based on chronology and course of follow-up. An episode of depression was defined as secondary when it was superimposed on a preexisting psychiatric or medical disease. The *DSM-IV*,[2] however, does not differentiate primary and secondary manifestations of depressive illness, as is performed in general medicine (eg, hypertension). As outlined in Figure 1, in view of the rollback phenomenon, Robins and Guze's primary/secondary distinction[22] becomes feasible: the major depressive episode appears to be superimposed on long-standing agoraphobic fears and avoidance and generalized anxiety. Symptoms are qualitatively differentiated (eg, the fact they persisted upon treatment against a background of improved symptomatology). They may be elicited by a diary or daily rating scales, which yield information that is not readily apparent in interview.

Subtyping

The need for subtyping major depressive disorder, since this category is too broad to yield meaningful treatment implications, has been recently underscored.[23,24] Lichtenberg and Belmaker,[23] for instance, differentiate between depression with anxiety (maintains functioning, positive response to favorable news or pleasurable activities) and late-life depression (no prior depressive history, reduced energy and interest, impaired cognitive function). Bech[24] has re- vived Robins and Guze's hierarchical primary/secondary distinction (eg, postnatal depression, poststroke late-life depression).[22] The basic assumption is that clinical manifestations that share the diagnosis of major depressive disorder may display substantial differences in prognostic and therapeutic terms.[23,24]

The underlying assumption is to increase the amount of clinical information that is conveyed by diagnosis. This requires use of instruments that yield a broad spectrum of information, such as hostility, irritable mood, and phobic avoidance, and are not ordinarily available.[24]

Building Unitary Concepts

Tyrer and associates[25] remarked that what is shared by syndromes such as anxiety, panic, phobic disturbances, and irritability may be as important as the differences between them, and conditions that are apparently comorbid could be part of the same clinical syndrome. They argued that the combination of mixed anxiety and depressive disorders together with a certain type of abnormal personality (excessive timidity, poor-self-esteem, avoidance of anxiety-provoking situations, and dependence on others) constitutes a single syndrome, the general neurotic syndrome.[25] The syndrome was shown to be associated with a poor response to treatment, frequent symptoms throughout the neurotic diagnostic spectrum, and tendency to relapse. The concept of neurosis, in its phenomenological[26] and psychodynamic[27] traditions, still has a lot to teach in terms of clinical thinking.[28]

Another example of search for unitary mechanisms of symptom formation is van Praag's Scale for Personality Disturbances.[29] On the basis of a structured interview, the rater is asked to score the following experiential qualities: (1) basic feelings of discontent with one's life situation and psychological make up, (2) unhappiness with one's personal relationships, and (3) emotional instability. The scale aims to overcome the difficulties in incorporating the I and II Axes of *DSM* and was found to allow important differentiations from residual symptomatology.[30]

The concept of allostatic load (the cumulative effects of stressful experiences in daily life) originated from basic science.[31] However, it offers another clinical opportunity of assessing the presence of a source of distress in the form of recent life events and/or chronic stress that exceed the individual's coping skills together with symptomatic manifestations encompassing psychological symptoms.[32] These approaches may be subsumed under the clinimetric rubric of global assessment indices. While the sensitivity of these methods is acknowledged in drug trials, where they often yield the most sensitive discrimination between drug and placebo effects,[33] the clinical value of these global evaluations in assessment and treatment planning is currently underestimated.

STAGING

In 1993, Fava and Kellner[9] introduced the clinimetric concept of staging in psychiatric classification. Unlike in clinical medicine, where this method had achieved wide currency (eg, the New York Heart Association Functional Classification, the Ann Arbor staging classification of Hodgkin's disease), staging was largely neglected in psychiatry. Staging

Table 1. Stages of a Psychiatric Disorder

Stage 1: Prodromal phase
Stage 2: Acute manifestations
Stage 3: Residual phase
Stage 4: Chronic (in attenuated or persistent form)

Table 2. Staging of Levels of Treatment Resistance

Stage 0: No history of failure to respond to therapeutic trial
Stage 1: Failure of at least 1 adequate therapeutic trial
Stage 2: Failure of at least 2 adequate therapeutic trials
Stage 3: Failure of 3 or more adequate therapeutic trials
Stage 4: Failure of 3 or more adequate trials including at least 1 concerned with augmentation/combination

Table 3. Staging of Loss of Therapeutic Effects During Continuation or Maintenance Treatment

Stage 0: No loss of therapeutic effect
Stage 1: Loss of therapeutic effects after adequate response in a therapeutic trial
Stage 2: Loss of therapeutic effects after adequate response in 2 therapeutic trials
Stage 3: Loss of therapeutic effects after adequate responses in 3 or more therapeutic trials

differs from the conventional diagnostic practice in that it not only defines the extent of progression of a disorder at a particular point in time but also reveals a person's current location on the continuum of the course of illness. Thus, once an index defines the existence of a particular disease state, its seriousness, extent, and longitudinal characteristics need to be evaluated.[8]

Fava and Kellner[9] developed staging methods for unipolar depression, bipolar disorder, panic disorder, and schizophrenia. Table 1 outlines the basic steps of development of a psychiatric disorder, ranging from the prodromal to the residual and chronic forms, in a longitudinal view of development of disturbances. Staging models have subsequently been refined in schizophrenia,[34] mood disorders,[35–38] and agoraphobia,[28] and they have been introduced in anorexia.[39] Staging instruments have also been developed.[40,41] In 2 randomized controlled trials,[42,43] psychotherapeutic intervention was applied according to a staging method and was found to yield long-term benefits.[44,45]

Further, the staging method has been applied to treatment response in depression.[46–48] It appears that the more information included in the method, the stronger its predictive value.[49] This information may encompass the number of trials completed,[49] the intensity/optimization of each trial,[49] issues of pseudoresistance (nonresponse to inadequate treatment in terms of duration, doses, or indications),[50] or occurrence of loss of therapeutic effects after clinical response.[51] Table 2 provides an illustration of the various levels of treatment resistance. By a clinical viewpoint, it is quite different to treat a patient with a major depressive episode who displayed positive responses to previous therapeutic trials (stage 0) and a patient who failed to respond to various adequate trials, including one concerned with augmentation/combination (stage 4). Similarly, if we encounter a depressed patient who repeatedly displayed loss of therapeutic response using various antidepressant drugs (Table 3), we should be aware that use of a new antidepressant is likely to yield the same phenomenon, probably because of a mechanism of oppositional tolerance.[51] For instance, many patients who did not respond to initial treatment in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial and went through various types of treatments, including augmentation/combination, were characterized by a refractory state with low remission, high relapse, and high intolerance rates.[35] Accordingly, their likelihood of lasting remission would be very low, as indicated by the staging methods of Tables 2 and 3.

Motivation to treatment and changing behavior has also been submitted to a staging system and may yield valu- able insights into psychological resistances of the patient.[52]Di Clemente and Prochaska[52] developed a helpful staging method: "precontemplation" (people do not recognize that a problem exists and have no intention to change), "contemplation" (individuals accept that a problem exists but are ambivalent about it), "preparation/determination" (a perceived discrepancy between current and desired study), "action," and "maintenance" of the new patterns. It is difficult to suggest a psychotherapeutic treatment, despite pertinent indications, to a patient who is in the "precontemplation" stage. However, this is seldom considered, particularly in randomized controlled trials of psychotherapy.

ORGANIZATION OF CLINICAL INFORMATION

The information we previously mentioned adds to other customary domains of the clinical evaluation, such as psychiatric history, background of alcohol and other substance abuse, general medical history, physical examination, laboratory tests, and diagnostic interviews, whether they follow specific instruments or a more personal format.[5] There are other areas, however, that need to be addressed and are currently neglected.

Subclinical Distress and Illness Behavior

A diagnostic interview and a set of criteria have been used extensively in psychosomatic research.[53–55] The Diagnostic Criteria for Psychosomatic Research allow one to translate in clinical terms the spectrum of manifestations of illness behavior, ie, the ways in which individuals experience, perceive, evaluate, and respond to their health status.[53–55] The 2 main forms of abnormal illness behavior (illness affirming and illness denying) have several common expressions in psychiatric practice. However, the psychopathology of insight—as defined by Lewis[56]—is seldom examined. When this happens, the results can be quite interesting. For instance, in a recent investigation on the spectrum of anxiety disorders in the medically ill, agoraphobia without history of panic attacks was found to be closely related to the Diagnostic Criteria for Psychosomatic Research illness denial.[57] Persistent denial of having a medical disorder and

needing treatment frequently occurs in the medical setting.[53] If panic attacks have not taken place (illness denial was not associated with panic disorder and agoraphobia), agoraphobic fears tend to be highly rationalized and do not lead individuals to seek medical attention.[57] The identification of these fears requires careful expert interviewing, well beyond the checklist use of diagnostic instruments, to overcome the denial that underlies agoraphobia and other distress manifestations. The linking between agoraphobia without history of panic attacks and Diagnostic Criteria for Psychosomatic Research illness denial provides an explanation for some discrepancies that have occurred in the literature as to the prevalence of agoraphobia in clinical samples compared to epidemiologic studies.[28] Other important constructs covered by the Diagnostic Criteria for Psychosomatic Research are demoralization,[58] irritable mood,[53] and alexithymia.[27,59]

Psychological Well-Being

An area that is currently neglected in assessment is psychological well-being, despite the availability of validated instruments and its growing importance in establishing resilience.[3,60] Dimensions such as environmental mastery, personal growth, purpose in life, autonomy, self-acceptance, and positive relations with others were found to affect vulnerability to life adversities and complex balance between positive and negative affects in mood and anxiety disorders.[60]

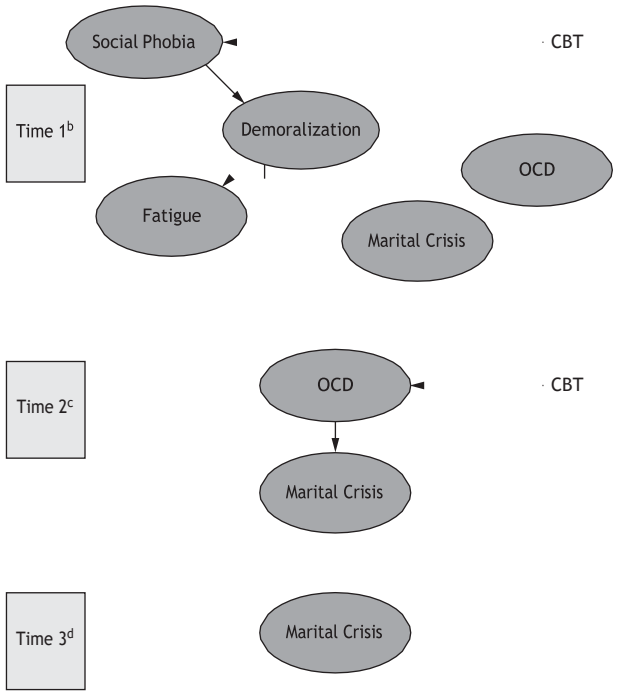
Mezzich and Salloum[3] developed the Person-centered Integrative Diagnosis, which encompasses both the positive and negative aspects of health, in an interactive way, within the person's life context. The Person-centered Integrative Diagnosis includes both the symptomatology of mental disorders and the positive aspects of health (adaptive functioning, protective factors, quality of life, etc) according to a holistic view of the person (including his/her dignity, values, and aspirations).[3] Rehabilitation of mental disorders is targeted as much on the patient's strengths and wishes as it is on alleviating symptoms and psychopathology.[61]

Macroanalysis and Microanalysis

Feinstein, when he introduced the concept of comorbidity, referred to any "additional coexisting ailment" separate from the primary disease, even if this secondary phenomenon does not qualify as a disease per se.[62] Indeed, in clinical medicine, the many methods that are available for measuring comorbidity are not limited to disease entities.[63]

A method has been developed in psychiatry for organizing clinical data as variables in clinical reasoning. Emmelkamp et al[64,65] have introduced the concept of macroanalysis (a relationship between co-occurring syndromes and problems is established on the basis of when treatment should commence). Fava and Sonino[54] have applied macroanalysis to assessing the relationship between medical and psychological variables. Macroanalysis starts from the assumption that, in most cases, there are functional relationships with other more or less clearly defined problem areas[64] and that the targets of treatment may vary during the course of disturbances.[54]

Figure 2. Example of Macroanalysis[a]



[a]A patient presents with work situational social phobia, demoralization, fatigue, obsessive-compulsive disorder (OCD) symptoms, and marital crisis.
[b]At time 1, the therapist could give priority to cognitive-behavioral therapy (CBT) of social phobia, expecting a consequent improvement in demoralization and sense of fatigue.
[c]At time 2, the therapist could decide to intervene on OCD symptoms by using CBT techniques to emphasize the negative effects of the patient's excessive preoccupation for order and precision, leading to a chronic malaise and communicative difficulties with the partner.
[d]At posttherapy assessment (time 3), the therapist could determine the relationship of OCD symptoms to marital crisis.

For instance, a patient may present with work situational social phobia (which leads him or her to avoid important opportunities for improving his or her job), demoralization (which increases his or her sense of fatigue), marital crisis (as a result of obsessional traits of mental order incompatible with that of his or her spouse), and obsessive ruminations (which lead to a chronic state of indecision). In terms of macroanalysis, the clinician, after a thorough interview with the patient, could place into a hierarchy the syndromes and symptoms of comorbidity by considering also the patient's needs. The clinician could thus give priority to the cognitive-behavioral treatment of social phobia, leaving to posttherapy assessment the determination of the relationship of social phobia to demoralization, marital crisis, and obsessional ruminations. Will they wane as anxious epiphenomena or will they persist, despite some degree of improvement? Should, in this latter case, further treatment be necessary? What type of relationship do demoralization and obsessive-compulsive symptoms entertain? If the clinical decision of tackling one syndrome may be taken during the initial assessment, the subsequent steps of macroanalysis require a reassessment after the first line of treatment has terminated (Figure 2).

The hierarchical organization that is chosen may depend on a variety of factors (urgency, availability of treatment tools, etc) that include also the patient's preferences and priorities. Macroanalysis is a tool that allows the therapist to not only increase accuracy in clinical decision making but also inform the patient about the relationship between different problem areas and motivate the patient for changing.[64,65] The concept of shared decision making is getting increasing attention in clinical medicine,[66] but it is still seldom practiced in psychiatry.[67] Macroanalysis also requires reference to the staging method, whereby a disorder is character- ized according to seriousness, extension, and longitudinal development.[9] For instance, certain psychotherapeutic strategies can be deferred to a residual stage of depression when state-dependent learning has been improved by use of antidepressant drugs.[68] The planning of treatment thus requires determination of the symptomatic target of the first-line approach (eg, pharmacotherapy) and tentative identification of other areas of concern to be addressed by subsequent treatment (eg, psychotherapy).

Macroanalysis should be supplemented by microanalysis, a detailed analysis of specific symptoms (onset and course of the complaints, circumstances that worsen symptoms and consequences).[64,65] For instance, when anxiety characterizes the clinical picture, it is necessary to know under which circumstances the anxiety become manifest and how the patient responds when he/she becomes anxious, and also to know whether an avoidant behavior occurs and, if so, what are the long-term consequences of the avoidant behavior.

Targum and associates[69] have developed specific criteria (SAFER) to be used in drug trials for improving the assessment accuracy of symptoms: State versus trait (the identified symptoms must reflect the current state of illness and not long-standing traits), Accessibility, Face validity, Ecological validity, and Rule of the 3 *p*'s (symptoms must be present, persistent, and pathological). The SAFER criteria inventory constitutes a valid method of microanalysis. Microanalysis also consists of dimensional measurements, such as observer or self-rating scales for assessing anxiety and fears. Choice of these instruments is dictated by the clinimetric concept of incremental validity.[10–12] Each distinct aspect of psychological measurement should deliver a unique increase in information in order to qualify for inclusion. The concept can also be applied to the selection of instruments in a psychometric battery. In clinical research, several highly redundant scales are often used under the misguided assumption that nothing will be missed. On the contrary, violation of the concept of incremental validity leads to only conflicting results. Microanalysis is consequential and secondary to macroanalysis and leads to overcoming the assumption that there is a common assessment strategy for all clinical encounters.

CONCLUSION

Part of the challenge and, at the same time, fascination of being a clinician lies in applying scientific methods in the care of patients and in understanding disease.[70] Greater knowledge should result in significant benefits for the patients, and, in a sense, continued development on the part of the physician.[71] We are witnessing, however, a progressive detachment of clinicians from research, which is often accompanied by a sense of personal stagnation and tiredness.[71] This detachment is mainly the reflection of an intellectual crisis that has become more and more manifest in recent years.[71–73]

In 1967, Feinstein[6] urged clinicians to develop a "basic science" of their own—to study the clinical phenomena directly, to specify the importance of different types of clinical data, to create appropriate systems of taxonomy for classifying the information, and to develop intellectual models and pragmatic methods that would articulate the clinical process and use the results for quantified analyses.

More recently, Tinetti and Fried[74] have argued that time has come to abandon disease as the focus of medical care. Clinical decision making for all patients should be addressed to attainment of individual goals and identification and treatment of all modifiable and nonbiological factors, rather than solely to the diagnosis and treatment of individual diseases.[74]

Often, in their clinical practice, psychiatrists use sophisticated forms of clinical judgment that are suitable for clinical challenges but are not addressed by current research strategies. Exclusive reliance on diagnostic criteria has impoverished the clinical process and does not reflect the complex thinking that underlies decisions in psychiatric practice. The use of transfer stations with repeated assessments instead of diagnostic endpoints, the building of global formulations of clinical integration, staging methods, and a better organization of clinical information (encompassing subclinical distress, illness behavior, psychological well-being, macroanalysis, and microanalysis) may be an antidote to oversimplified models that derive from biological reductionism, neglect individual responses to treatment, and clash with clinical reality.[71,75]

The clinimetric perspective provides an intellectual home for the reproduction and standardization of the clinical intuitions. It allows the clinician to make full use of the clinical information that is available. It opens a new exciting area of research that is likely to yield improved targets for neurobiological studies and treatment trials.

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Sequential Combination of Cognitive-Behavioral Treatment and Well-Being Therapy in Depressed Patients with Acute Coronary Syndromes: A Randomized Controlled Trial (TREATED-ACS Study)

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Keywords

Acute coronary syndrome · Cognitive-behavioral therapy · Depression · Sequential treatment · Well-being therapy

Abstract

Introduction: Randomized controlled trials (RCT) of psychotherapeutic interventions have addressed depression and demoralization associated with acute coronary syndromes (ACS). The present trial introduces psychological well-being, an increasingly recognized factor in cardiovascular health, as a therapeutic target. ***Objective:*** This study was designed to determine whether the sequential combination of cognitive-behavioral therapy (CBT) and well-being therapy (WBT) may yield more favorable outcomes than an active control group (clinical management; CM) and to identify subgroups of patients at greater risk for cardiac negative outcomes. ***Methods:*** This multicenter RCT compared CBT/WBT sequential combination versus CM, with up to 30 months of follow-up. One hundred consecutive depressed and/or demoralized patients (out of 740 initially screened by cardiologists after a first episode of ACS) were randomized to CBT/WBT associated with lifestyle suggestions (n = 50) and CM (n = 50). The main outcome measures included: severity of depressive symptoms according to the Clinical Interview for Depression, changes in subclinical psychological distress, well-being, and biomarkers, and medical complications and events. ***Results:*** CBT/WBT sequential combination was associated with a significant improvement in depressive symptoms compared to CM. In both groups, the benefits persisted at follow-up, even though the differences faded. Treatment was also related to a significant amelioration of biomarkers (platelet count, HDL, and D-dimer), whereas the 2 groups showed similar frequencies of adverse cardiac events. ***Con-***

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clusions: Addressing psychological well-being in the psychotherapeutic approach to ACS patients with depressive symptoms was found to entail important clinical benefits. It is argued that lifestyle changes geared toward cardiovascular health may be facilitated by a personalized approach that targets well-being.

Introduction

There is extensive evidence that the presence of depressive symptoms in acute coronary syndromes (ACS) is associated with poor therapeutic adherence, a higher frequency of relapses, and increased mortality [1]. Mood disturbances may consist of major or minor depressive episodes, chronic depression, and demoralization [1–3], which is characterized by a sense of subjective incompetence [4].

The relationship of depression to ACS has generated the hypothesis that treatment of mood disturbances may yield improved medical and psychological outcomes. A number of randomized controlled trials (RCT) have indicated the effectiveness of antidepressant drugs compared to placebo in relieving depression, yet a favorable effect on cardiovascular events was not detected [1] or could not be generalized [5]. Similar findings have been reported for the application of cognitive-behavioral therapy (CBT) to ACS [6], pioneered by the ENRICHD trial [7].

Psychotherapeutic approaches, however, have been mainly shifted to the side of psychological dysfunction and have neglected psychological well-being. There is increasing evidence of the role of positive psychological assets on lifestyle and cardiovascular health [8].

In this trial, the sequential use of distress and well-being psychotherapeutic strategies was selected. The first phase of treatment (CBT) was concerned with distress associated with hospitalization and medical events. In the second phase, well-being therapy (WBT), a specific psychotherapeutic approach for modulating psychological well-being [9], was introduced and suggestions for lifestyle modifications geared to cardiovascular health were provided [10]. The sequential combination of CBT and WBT has been found to yield enduring clinical benefits in the setting of psychiatric disorders [9, 10], with particular reference to recurrent depression [11].

The aim of the trial was to evaluate the efficacy of the sequential combination of CBT and WBT, compared to clinical management (CM), in terms of depressive symptoms (primary outcome), psychological distress, and well-being, as well as cardiovascular events, biomarkers, and mortality (secondary outcomes), both after treatment and up to a 30-month follow-up. The identification of subgroups of patients at greater risk for cardiac negative outcomes was included.

Materials and Methods

Sample

Participants were patients hospitalized for a first episode of acute myocardial infarction or unstable angina at the Cardiology Divisions of Maggiore Hospital (Bologna, Italy) and Molinette Hospital (Torino, Italy). Myocardial infarction was documented based on cardiac symptoms (presence of acute chest, epigastric, neck, jaw, or arm pain or discomfort or pressure without an apparent noncardiac source) and signs (acute congestive heart failure or cardiogenic shock in the absence of non-CHD causes) associated with ECG findings (characteristic evolutionary ST-T changes or new Q waves) and/or cardiac biomarkers (blood measures of myocardial necrosis, specifically CK, CK-MB, CK-MBm, or troponin, and cTn). Instable angina was documented based on cardiac symptoms (chest pain lasting less than 20 min) with likely ECG findings (ST-segment depression and an abnormal T-wave) in absence of myocardial necrosis biomarkers.

Medically eligible patients underwent a psychological evaluation by 2 clinical psychologists with expertise in the field of psychosomatic aspects of cardiovascular diseases about 30 days after ACS. The inclusion criteria were: a current diagnosis of major/minor depression or dysthymia according to DSM-IV-TR [12] and/or demoralization according to Diagnostic Criteria for Psychosomatic Research (DCPR) criteria [13]. The exclusion criteria included a positive history of bipolar disorder (DSM-IV-TR), major depression with psychotic features, a positive history of substance abuse/dependence during the previous 12 months, suicide risk, and current use of antidepressants and/or psychotherapy.

A psychological evaluation was performed in 288 patients with a first episode of ACS, and the first 100 depressed and/or demoralized consecutive patients were enrolled (Fig. 1).

Assessment

Medical Variables

Data on ACS, traditional cardiac risk factors (smoking habit, hypertension, dyslipidemia, a family history of cardiovascular disease, diabetes mellitus, and left ventricular ejection fraction <40), medications, and comorbidities were collected from medical records. The cardiologists involved in this study evaluated the patients at intake and once every 6 months to monitor changes in the clinical course of cardiac disease. Data from electrocardiograms, echocardiograms, X-rays, blood pressure and blood samples (cholesterol levels, creatinine, glycosylated hemoglobin, C-reactive protein, and coagulation/fibrinolysis biomarkers) were provided at intake. The Global Registry of Acute Coronary Events (GRACE) risk index [14] was calculated during hospital admission for ACS to determine the risk of morbidity and mortality both in hospital and 6 months after discharge. From the beginning of the psychological treatment and up to a 30-month follow-up after the end of the intervention, information about cardiac negative outcomes,

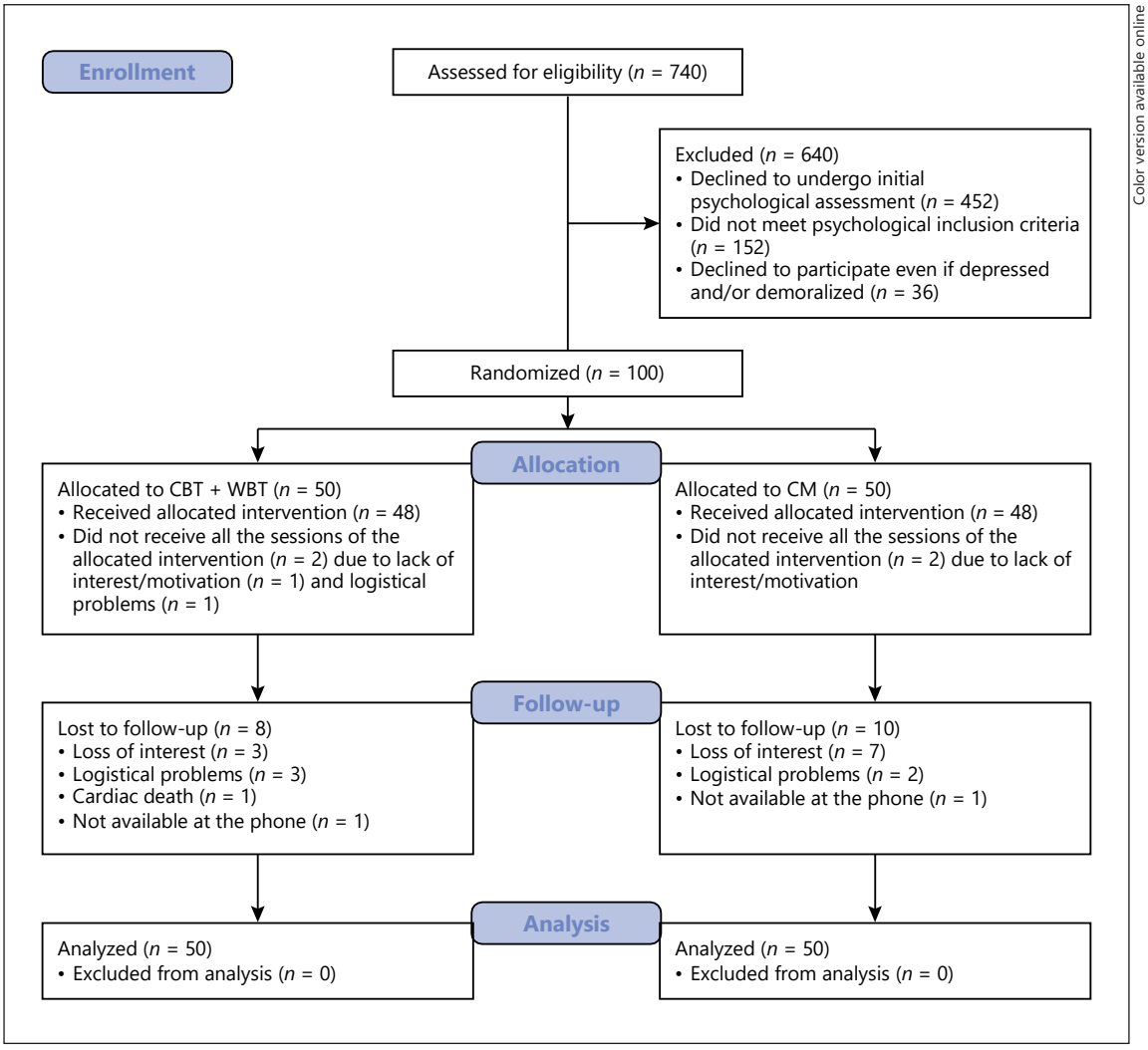

Fig. 1. CONSORT flow diagram of this study.

such as rehospitalizations due to cardiac complications, acute myocardial infarction, unstable angina, angioplasty, cardiac surgery, and cardiac mortality after the first ACS, was collected.

Psychological Variables

Psychological assessment included both observer-rated and self-reported measures before the beginning of the interventions (baseline, pretreatment), at the end (posttreatment), and 3, 6, 12, and 30 months after the end of treatment. The Structured Clinical Interview for DSM-IV-TR, Axis I Disorders [15], was used to investigate the presence of major/minor depression and dysthymia. The Semi-Structured Interview based on the DCPR (SSI-DCPR) [16] was administered to assess the presence of demoralization [17]. This interview has shown excellent interrater reliability, with κ values ranging from 0.69 to 0.97 [18]. The 20-item change version of the Clinical Interview for Depression (CID) [19, 20], a modified version of the Hamilton Rating Scale for Depression [21, 22], was used to perform a comprehensive assessment of affective symptoms. It contains 20 items rated on a 7-point Likert scale, with specification of each anchor point based on the severity, frequency, and/or quality of the symptoms. The higher the score, the worse the psychological condition. The CID has been shown to be a sensitive assessment tool in clinical trials [20]. The Symptom Questionnaire (SQ) [23, 24] is a 92-item self-report questionnaire that yields 4 main scales, i.e., depression, anxiety, hostility-irritability, and somatization. The higher the score, the higher the psychological distress. The Psychological Well-Being scales (PWB) [25–26], an 84-item questionnaire, was used to evaluate 6 psychological well-being dimensions (autonomy, environmental mastery, personal growth, positive relations, purpose in life, and self-acceptance). Higher scores correspond to greater psychological well-being.

Study Design

This study is a 2-center RCT with a longitudinal and prospective design. The enrolled patients were randomly assigned to either CBT/WBT or CM and assessed at the beginning and the end of the CBT/WBT or CM sessions, and at subsequent follow-ups up to 30 months after the conclusion of the interventions. Treatment allo-

cation was accomplished through random computerized assignment that allocated 50% of the patients to each treatment group, with assignments concealed until the time of group assignment. Patients were assessed by 2 clinical psychologists, who were blind to treatment assignment, at pretreatment and posttreatment, and 3, 6, 12, and 30 months after the end of treatment. Both the sequential combination of CBT/WBT and the CM were performed by psychotherapists who had received specific training. Both interventions consisted of 12 weekly, 45-min sessions. The sequential administration of CBT (8 sessions) and WBT (4 sessions) was based on a written protocol [9–10]. The WBT techniques were used to improve or balance one or more of the 6 dimensions of psychological well-being (environmental mastery, purpose in life, personal growth, autonomy, self-acceptance, and positive relations with others), and they were supplemented with suggestions for lifestyle modifications geared toward cardiovascular health, including treatment adherence.

CM entails the same amount of time and attention from a professional figure than the experimental group, but specific interventions (such as exposure strategies, diary work, and cognitive restructuring) were proscribed [27]. Such a form of active control – unlike in previous trials that have used treatment as usual [6] – allows discrimination of specific and nonspecific ingredients of the psychotherapeutic approach. It consists of empathic listening, review of the patient's clinical status and providing opportunities for disclosure of distress and worries, and encouragement of treatment adherence.

Statistical Analyses

Data were analyzed using SPSS 20.0 (SPSS Inc., Chicago, IL, USA). The quality of data collection was monitored regularly to assure accuracy and completeness. For all tests performed, significance level was set at 0.05 (two-tailed). The sample size was estimated using Piface software, which identified a minimum of 16 participants per arm to detect the expected superiority of CBT/WBT on CM [11], with a power of 80% and a significance level of 5%. Thus, with 50 patients per group we expected a "large" effect size (Cohen's $d = 0.8$) [28].

A multivariate ANOVA was used to examine differences in dimensional psychological variables (i.e., CID-20 total score and PWB and SQ scale scores) between patients assigned to CBT/WBT and CM at preintervention.

A mixed-model ANOVA (repeated measures) was performed to test differences between groups (CBT/WBT or CM) on the CID-20 total score, PWB scales, and SQ scales scores at different follow-up evaluations. All analyses were performed by using intention-to-treat analysis, where missing values were managed by means of a multiple-imputations procedure. Greenhouse-Geisser correction was applied when appropriate. All analyses were adjusted for cardiac illness severity (i.e., GRACE index for the 6-month probability of cardiac mortality) [14].

Each biomarker was dichotomized around the baseline median of the sample in order to identify subgroups of patients at a higher cardiovascular risk. The McNemar test (applied to contingency tables) was used to identify significant changes over time in the frequencies of DSM, DCPR diagnoses, and subgroups of patients at a higher cardiovascular risk.

Survival analyses (Cox Regression and Kaplan-Meier) to identify cardiac events and mortality that occurred between pretreatment and the 30-month follow-up were performed.

Results

Baseline Profile of the Sample

The first 100 consecutive depressed and/or demoralized patients 1 month after ACS were enrolled, yielding 50 patients in each treatment group. The mean age of the sample was 58.8 years (SD = 10.5, range 40–84). The participants were mainly men (69%), married (69%), employed (58%), and graduated from high school (44%). No significant differences based on group allocation were found (Table 1).

As for the cardiac profile of the sample, ST-elevation myocardial infarction (STEMI) was the most frequent form of ACS (66%) and almost all of the patients (94%) underwent percutaneous transluminal coronary angioplasty – 77% with the application of a single stent and 17% with 2 or more stents. The most frequent cardiovascular risk factors registered at hospital admission were dyslipidemia (58%) and hypertension (52%). No differences concerning ACS-related aspects or GRACE risk scores were found when comparing CBT/WBT versus CM (Table 1).

Among the medications prescribed at discharge, the most frequent were statins (96%), β-blockers (96%), and platelet aggregation inhibitors (96%). Patients allocated to CM were prescribed significantly more frequentlyβ-blockers, calcium antagonists, and α-adrenergic re-ceptor inhibitors compared to the CBT/WBT group (Table 1). The sample presented with a number of med- ical comorbidities; the most frequent were gastrointes- tinal (43%) and endocrine diseases (14%). As for comor-bid medical diagnoses and levels of biomarkers assessedat baseline, the 2 groups did not show any significant difference (Table 1). From the psychological point of view, the most frequent diagnosis was demoralization (91%), followed by minor depression (56%). The 2 groups did not show any statistical difference, except for PWB "personal growth" scores ($F = 4.45$; df = 1, 98; $p = 0.038$) and frequency of depression/demoralization comorbidity ($\chi^2 = 4.86$; df = 1; $p = 0.028$), which were significantly higher among the CBT/WBT patients (Table 1).

Pre-/Postintervention Modifications

Psychological Variables

Forty-eight patients completed the CBT/WBT treatment, and 48 patients attended CM sessions. Two patients in each group dropped out early, mainly due to a lack of interest or motivation. Forty and 38 patients, respectively, completed follow-up evaluations (Fig. 1).

Table 1. Baseline sociodemographic, medical, and psychological profile of the sample

Variable	CBT/WBT group (n = 50)	CM group (n = 50)
Mean age (SD), years	57.64 (9.99)	60.02 (10.94)
Sex, *n* (%)		
Males	31 (62)	38 (76)
Females	19 (38)	12 (24)
Marital status, *n* (%)		
Single	4 (8)	7 (14)
Married	33 (66)	36 (72)
Separated	5 (10)	4 (8)
Divorced	2 (4)	1 (2)
Widow/widower	6 (12)	2 (4)
Occupation, *n* (%)		
Employed	34 (68)	24 (48)
Unemployed	1 (2)	4 (8)
Retired	13 (26)	19 (38)
Homemaker	2 (4)	3 (6)
Education, *n* (%)		
Primary school	5 (10)	5 (10)
Middle school	16 (32)	18 (36)
High school	19 (38)	25 (50)
University	8 (16)	1 (2)
Postgraduate education	2 (4)	1 (2)
Type of ACS, *n* (%)		
STEMI acute myocardial infarction	33 (66)	33 (66)
NSTEMI acute myocardial infarction	14 (28)	13 (26)
Unstable angina	3 (6)	4 (8)
Medical procedure for ACS, *n* (%)		
Single PTCA	38 (76)	39 (78)
PTCA with 2 or more stents	9 (18)	8 (16)
None	3 (6)	3 (6)
Drug-eluting stent	24 (51.1)	18 (38.3)
Cardiovascular risk factors, *n* (%)		
Dyslipidemia	31 (62)	27 (54)
Hypertension	27 (54)	25 (50)
Smoker (current)	22 (44)	20 (40)
Familiarity	17 (34)	11 (22)
Diabetes	10 (20)	9 (18)
LVEF <40	4 (8)	3 (6)
Mean GRACE risk index at admission (mortality) (SD)		
In-hospital risk, %	3.51 (8.58)	4.56 (7.90)
6-month risk, %	6.60 (11.60)	8.69 (10.57)
Mean GRACE risk index at admission (mortality + AMI) (SD)		
In-hospital risk, %	15.50 (9.85)	16.56 (10.49)
6-month risk, %	25.30 (12.73)	27.50 (15.00)
Medications, *n* (%)		
Cholesterol reducers	49 (98)	47 (94)
β-blockers*	46 (92)	50 (100)
Platelet aggregation inhibitors	48 (96)	48 (96)
Cardioaspirin	47 (94)	48 (96)
Vasodilators	36 (72)	35 (70)
Angiotensin-converting enzyme inhibitors	31 (62)	35 (70)
Polyunsaturated fatty acids – omega-3	11 (22)	10 (20)
Antihyperglycemics	6 (12)	8 (16)
Diuretics	6 (12)	5 (10)
Angiotensin receptor blockers	5 (10)	4 (8)
Calcium antagonists*	1 (2)	6 (12)

Table 1 (continued)

Variable	CBT/WBT group (n = 50)	CM group (n = 50)
α-adrenergic receptor inhibitors*	0 (0)	4 (8)
Antihyperuricemics	0 (0)	2 (4)
Antiarrhythmic	1 (2)	0 (0)
Heart rate reducers	0 (0)	1 (2)
7 or more medications*	11 (22)	23 (46)
Medical comorbidities, *n* (%)		
Digestive system diseases	18 (36)	25 (50)
Endocrine diseases	9 (18)	5 (10)
Circulatory/cardiac comorbidities	2 (4)	4 (8)
Prostatic and male reproductive system diseases	3 (6)	2 (4)
Urinary system diseases	2 (4)	2 (4)
Orthopedic diseases	1 (2)	3 (6)
Asthma	3 (6)	1 (2)
Chronic obstructive pulmonary disease	2 (4)	1 (2)
Stroke/aneurysm	2 (4)	1 (2)
Heteroplasia/neoplasia	2 (4)	1 (2)
Hyperuricemia	0 (0)	3 (6)
Glaucoma	1 (2)	0 (0)
Multiple sclerosis	1 (2)	0 (0)
Cluster headache	1 (2)	0 (0)
Cushing disease	1 (2)	0 (0)
Sarcoidosis	1 (2)	0 (0)
Thalassemia	0 (0)	1 (2)
Rheumatoid arthritis	0 (0)	1 (2)
2 or more medical comorbidities	12 (24)	13 (26)
Mean biomarkers (SD)		
Hemoglobin, g/dL	13.91 (1.21)	13.93 (1.33)
Platelets, $n \times 10^3/mm^3$	235.42 (57.64)	232.96 (50.20)
Creatinine, mg/dL	0.94 (1.78)	0.95 (0.20)
Triglycerides, mg/dL	115.96 (52.91)	121.69 (58.68)
HDL cholesterol, mg/dL	51.98 (16.59)	46.51 (12.01)
LDL cholesterol, mg/dL	87.40 (25.48)	93.96 (29.25)
Total cholesterol, mg/dL	156.44 (31.07)	160.90 (37.45)
Glycated hemoglobin, mmol/mol	41.20 (8.36)	42.97 (10.21)
Fibrinogen, mg/dL	347.84 (66.04)	356.49 (68.28)
D-dimer, mg/L FEU	0.68 (1.39)	0.45 (0.39)
HRV[a], ms	51.10 (27.66)	41.50 (12.29)
C-reactive protein		
BO, mg/dL	0.19 (0.21)	0.39 (0.69)
TO, mg/L	0.28 (0.39)	0.64 (1.16)
Mean SQ (SD)		
Anxiety	8.60 (4.73)	7.24 (4.67)
Depression	7.92 (4.77)	6.90 (4.87)
Somatization	9.82 (5.65)	7.82 (5.12)
Hostility	4.70 (4.00)	5.34 (4.36)
Mean PWB (SD)		
Autonomy	62.20 (9.18)	61.80 (9.25)
Environmental mastery	55.28 (11.52)	55.32 (10.65)
Personal growth*	60.48 (9.88)	56.18 (10.50)
Positive relations with others	61.26 (13.26)	60.20 (10.68)
Purpose in life	56.80 (11.51)	56.22 (11.59)
Self-acceptance	54.48 (11.63)	55.80 (13.68)
Mean CID-20 (SD)		
CID-20 total score	38.18 (8.48)	36.20 (8.57)
Depression (DSM), *n* (%)	35 (70)	27 (54)

Table 1 (continued)

Variable	CBT/WBT group (n = 50)	CM group (n = 50)
Major depression	2 (4)	3 (6)
Minor depression	32 (64)	24 (48)
Dysthymia	1 (2)	0 (0)
History of depression (DSM), *n* (%)	34 (68)	26 (52)
Demoralization (DCPR), *n* (%)	47 (94)	44 (88)
History of demoralization (DCPR), *n* (%)	36 (72)	32 (64)
Comorbidities, *n* (%)		
Depression + demoralization*	32 (64)	21 (42)
Chronicity of depression/demoralization, *n* (%)		
Current + previous episode of depression	26 (52)	19 (38)
Current + previous episode of demoralization	35 (70)	31 (62)

ACS, acute coronary syndrome; AMI, acute myocardial infarction; CBT, Cognitive-Behavioral Therapy; CID- 20, 20-item Clinical Interview for Depression; CM, clinical management; DCPR, diagnostic criteria for psychosomatic research; GRACE, Global Registry of Acute Coronary Events; HRV, heart rate variability; LVEF, left ventricular ejection fraction; NSTEMI, non-ST-segment elevation myocardial infarction; PTCA, percutaneous transluminal coronary angioplasty; PWB, Psychological Well-Being scales; SQ, Symptom Questionnaire; STEMI, ST-segment elevation myocardial infarction; WBT, Well-Being Therapy; BO, Bologna; TO, Torino. * $p \leq 0.05$. [a] Assessed only in Torino.

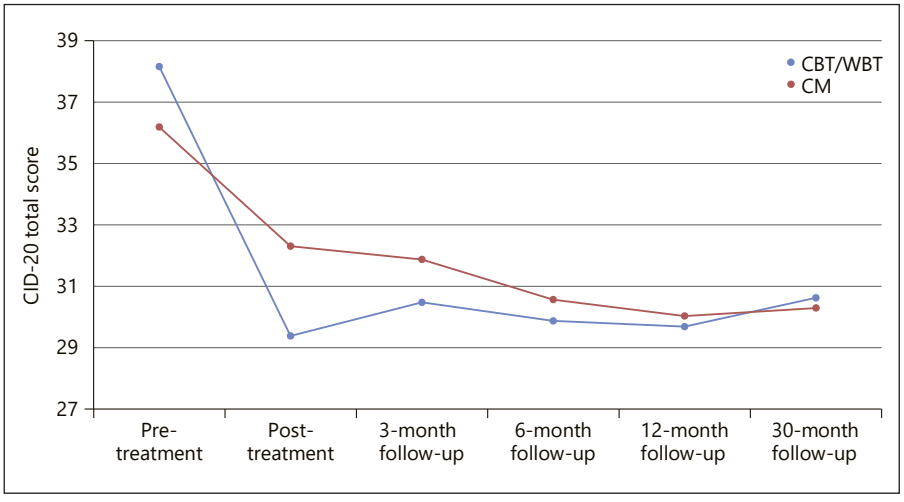

Fig. 2. CID-20 total scores at different time points (intention-to-treat analysis).

As for the CID-20 total score, a significant interaction between group allocation and time was found (F = 2.75; df = 3.85; $p < 0.05$; Fig. 2). Significant decreases in symptom scores from pre- to posttreatment were found in both the CBT/WBT ($p < 0.001$) and CM ($p < 0.01$) groups. However, the effect sizes for score modifications were strong in the CBT/WBT treatment group (Cohen's d = 1.161 and 1.393, respectively) and weak/medium among CM patients (Cohen's d = 0.492 and 0.589, respectively) (Table 2). Patients allocated to CBT/WBT reported significant lower scores posttreatment (p = 0.040) compared to those assigned to CM. Starting from the 3-month follow-up, the CID-20 score differences between the 2 groups were no longer significant. The benefits, however, tended to persist in both groups.

No significant interactions were found between time and group allocation in relation to SQ and PWB mean scores, except for hostility as assessed by the SQ (F = 3.12;

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Table 2. Effects of treatment groups on psychological characteristics

Variable	Pretreatment	Posttreatment	3-month follow-up	6-month follow-up	12-month follow-up	30-month follow-up	Time × group			Cohen's *d**	Within-group score change*, [a]
							F	df	*p* value		
Intention-to-treat analysis											
CBT/WBT group (*n* = 50), mean (SD)											
PWB autonomy	62.20 (9.18)	64.58 (9.42)	64.54 (9.24)	64.40 (9.12)	65.50 (8.53)	64.93 (9.67)	0.173	3.846	0.948	–0.26	–2.38 (–5.51 to 0.76)
PWB environmental mastery	55.28 (11.52)	57.33 (12.93)	59.48 (11.32)	58.02 (11.83)	58.36 (12.15)	58.69 (10.97)	0.309	4.353	0.886	–0.17	–2.09 (–5.61 to 1.43)
PWB personal growth	60.48 (9.88)	61.46 (9.92)	61.95 (9.91)	60.79 (9.58)	60.55 (9.54)	59.94 (9.34)	0.982	4.253	0.420	–0.10	–0.93 (–3.91 to 2.06)
PWB positive relations	61.26 (13.26)	61.82 (13.50)	61.88 (12.86)	60.60 (13.08)	61.27 (12.08)	60.48 (11.60)	0.709	4.183	0.592	–0.04	–0.57 (–3.33 to 2.19)
PWB purpose in life	56.80 (11.51)	57.31 (11.21)	58.35 (10.09)	57.88 (10.85)	57.42 (9.81)	57.63 (9.70)	1.104	3.803	0.353	–0.04	–0.49 (–4.14 to 3.17)
PWB self-acceptance	54.48 (11.63)	55.70 (14.36)	57.59 (13.51)	55.83 (14.19)	56.66 (11.92)	56.15 (13.90)	1.593	4.325	0.170	–0.09	1.30 (–4.48 to 1.89)
SQ anxiety	8.60 (4.73)	7.04 (5.23)	6.60 (4.87)	6.67 (4.19)	6.62 (4.51)	6.00 (4.35)	1.008	4.180	0.405	0.31	1.54 (–0.10 to 3.19)
SQ depression	7.92 (4.77)	7.21 (5.42)	6.38 (5.03)	7.06 (5.22)	6.91 (5.08)	5.99 (4.64)	0.605	4.180	0.667	0.14	0.70 (–0.98 to 2.37)
SQ somatization	9.82 (5.65)	8.80 (5.73)	8.67 (5.42)	8.96 (5.02)	9.49 (5.19)	8.17 (5.00)	0.787	3.981	0.534	0.18	1.04 (–0.75 to 2.84)
SQ hostility	4.70 (4.00)	5.19 (4.96)	5.18 (4.46)	4.41 (3.71)	5.32 (4.71)	3.81 (3.37)	3.121	4.288	0.013	–0.11	–0.51 (–1.91 to 0.89)
CID-20 total score	38.18 (8.48)	29.39 (6.55)	30.48 (5.81)	29.89 (5.88)	29.70 (6.51)	30.64 (7.02)	2.748	3.853	0.030	1.16	8.73 (5.39 to 12.07)
CM group (*n* = 50), mean (SD)											
PWB autonomy	61.80 (9.25)	62.82 (8.77)	63.20 (8.51)	63.21 (9.00)	64.57 (9.34)	63.71 (9.26)				–0.11	–1.02 (–4.16 to 2.11)
PWB environmental mastery	55.32 (10.65)	56.69 (8.81)	57.81 (10.15)	57.51 (8.78)	58.03 (11.19)	58.81 (8.10)				–0.14	–1.33 (–4.85 to 2.19)
PWB personal growth	56.18 (10.50)	56.54 (8.70)	56.67 (9.65)	57.10 (8.90)	57.64 (10.24)	57.00 (8.85)				–0.04	–0.41 (–3.40 to 2.57)
PWB positive relations	60.20 (10.68)	59.90 (10.93)	59.93 (12.13)	58.78 (10.82)	58.95 (11.54)	60.56 (10.78)				0.03	0.31 (–2.45 to 3.07)
PWB purpose in life	56.22 (11.59)	54.97 (9.41)	55.47 (10.32)	55.96 (10.12)	55.63 (10.82)	57.76 (8.16)				0.12	1.23 (–2.42 to 4.89)
PWB self-acceptance	55.80 (13.68)	56.03 (11.52)	57.86 (12.84)	58.32 (12.39)	59.69 (13.38)	59.94 (10.52)				–0.02	–0.15 (–3.34 to 3.04)
SQ anxiety	7.24 (4.67)	6.39 (4.41)	6.13 (4.21)	7.10 (5.14)	6.33 (5.09)	5.69 (4.07)				0.19	0.87 (–0.78 to 2.51)
SQ depression	6.90 (4.87)	5.94 (4.22)	5.83 (4.75)	6.80 (5.45)	6.22 (5.09)	5.83 (4.18)				0.21	0.98 (–0.69 to 2.66)
SQ somatization	7.82 (5.12)	8.24 (4.90)	7.87 (4.58)	8.15 (5.64)	7.90 (5.38)	7.61 (4.72)				–0.08	–0.44 (–2.23 to 1.36)
SQ hostility	5.34 (4.36)	4.12 (3.78)	4.71 (3.92)	6.01 (4.73)	5.17 (4.14)	4.56 (4.11)				0.30	1.24 (–0.16 to 2.64)
CID-20 total score	36.20 (8.57)	32.30 (7.26)	31.89 (7.11)	30.59 (7.28)	30.03 (7.05)	30.30 (6.82)				0.49	3.97 (0.63 to 7.31)

All analyses were adjusted for the GRACE index (6-month probability of cardiac mortality). CID-20, 20-item Clinical Interview for Depression; CBT, Cognitive-Behavioral Therapy; CM, clinical management; PWB, Psychological Well-Being scales; SQ, Symptom Questionnaire; WBT, Well-Being Therapy. * Pre-/posttreatment scores change. [a] Values are expressed as mean dif- ferences (95% CI).

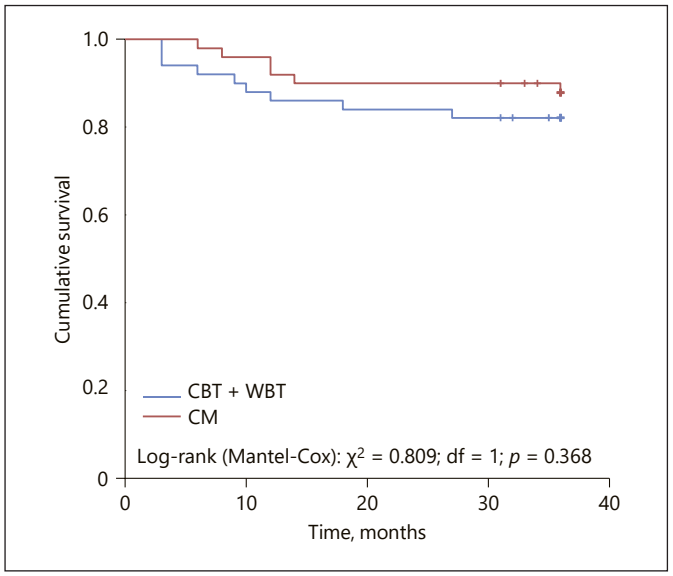

Fig. 3. Survival curves of the CBT/WBT and CM groups.

Color version available online

df = 4.29; $p < 0.05$), with CM group showing significantly higher scores at the 6-month follow-up than CBT/WBT ($p = 0.039$; Table 2).

Biomarkers

At the 3-month post-intervention follow-up, we observed a significant reduction of the frequencies of patients with biomarker levels considered to be at risk (below or above the median) only among patients allocated to the CBT/WBT group. In particular, we found a significant decrease in cases with a high platelet count (from 52 to 36%; $p < 0.05$; median = 226 × 10^3/mm^3), lower HDL cholesterol (from 52 to 34%; $p < 0.05$; median = 47 mg/dL), and a higher D-dimer level (from 56 to 40%; $p < 0.05$; median = 0.31 mg/L FEU) in patients assigned to CBT/WBT compared to those receiving CM. No significant decrease in patients with risky levels of biomarkers was observed in the CM group.

Survival Analyses

Within 36 months from baseline, 15% of the total sample had an adverse cardiac outcome. As for cardiac morbidity and mortality, we did not find any significant difference between the CBT/WBT and CM groups in terms of survival. Indeed, among the patients allocated to CBT/WBT 16% ($n = 8$) had nonfatal cardiac events and 1 patient (2%) had a cardiac death (occurring after 18 months from baseline), whereas among the CM patients 10% ($n = 5$) had nonfatal events and 1 patient (2%) had a cardiac death (after 36 months from baseline). Nonetheless, the CBT/WBT patients displayed most of the negative cardiac outcomes within the first 9 months, with almost half of them (4 out of 9) relapsing during treatment sessions. On the contrary, CM participants were more likely to relapse after a longer period (starting after 8 months from baseline) (Fig. 3).

Stratifying the sample by group allocation, among CBT/WBT patients the probabilities of cardiac death, both in hospital (Wald = 4.235; df = 1; HR = 1.040; 95% CI 1.002–1.079; $p = 0.040$) and at 6 months postdischarge (Wald = 4.594; df = 1; HR = 1.031; 95% CI 1.003–1.060; $p = 0.032$) as calculated with GRACE indices, were found to predict a worse cardiac prognosis. On the contrary, in the CM group adverse cardiac outcomes were predicted by baseline scores of depression, as assessed by CID (Wald = 5.540; df = 1; HR = 1.204; 95% CI 1.031–1.404; $p = 0.019$).

Discussion

To our knowledge, this is the first RCT demonstrating a significant improvement in depressive symptoms and biomarkers in patients with ACS following sequential CBT/WBT when compared with CM. This study provides new important clinical insights regarding the treatment of depression in the setting of ACS. The sequential combination of CBT/WBT was effective in significantly decreasing depressive symptoms compared to CM. In both groups the benefits persisted at follow-up, even though the differences between them faded (Fig. 2). It is noteworthy the different trend observed in the 2 groups concerning hostility, since it represents a key variable in the literature on the psychological issues embedded in depressive states [29] and it has been found to have a negative effect on the cardiac prognosis [30].

Medical outcomes did not differ between the 2 groups, yet among the CBT/WBT patients a negative cardiac prognosis was associated with a greater severity of the cardiac illness (as indicated by the GRACE indexes and the timing of relapses), whereas in the CM group it was associated with the severity of baseline depressive symptomatology. Moreover, patients who were assigned to the treatment group displayed significant decreases in placement according to normative values of platelet counts, HDL cholesterol, and D-dimer. There is evidence that these biomarkers may indicate a prognostic significance of the occurrence of cardiovascular events [31–33].

The findings are important in view of the methodology that was used. The patients were not assessed during hospitalization but rather after 1 month, when stress linked to hospitalization and the impact of acute illness are likely to subside and the evaluation of depressive symptoms is likely to be more reliable [34]. The impact of the CBT/WBT sequential combination was not compared to treatment as usual, as occurred in other studies [6], but rather to CM, where patients received the nonspecific elements of psychotherapy [27, 35]. Indeed, also CM yielded significant improvement in affective symptoms. This indicates that nonspecific support after ACS may be important, but specific psychotherapeutic strategies are associated with greater benefits and it underlines the need to schedule booster sessions (i.e., WBT or brief CBT) in order to reinforce progress or address potential obstacles to the continuance of the positive changes made during the therapy.

WBT is a short-term psychotherapeutic strategy that emphasizes self-observation of psychological well-being via the use of a structured diary, cognitive restructuring of interfering thoughts and/or behaviors, and homework assignments [9, 10]. The working hypothesis was that lifestyle changes could only be achieved with a personalized approach that targets psychological well-being [9]. Based on examples taken from post-ACS everyday life, the patients allocated to CBT/WBT were instructed on how to overcome specific obstacles concerning lifestyle (i.e., specific strategies for medication adherence, scheduling of gradual physical exercises, and dietary modification according to specific prescriptions following hospital guidelines). In the phase that immediately follows ACS, interventions that bring the person out of negative functioning and distress may be important, and this was the target of the first phase of psychotherapy (CBT). However, facilitating progression toward restoration of the positive ("there is life after ACS") and appreciation of healthy lifestyle is another target that requires specific interventions (WBT). The results of this investigation confirm previous studies on the role of psychotherapeutic strategies in the setting of ACS [6] and provide a valid alternative/integration to pharmacological strategies, which carry the disadvantages of side effects of antidepressant drugs [36–37], with particular reference to cardiovascular safety [38]. The sequential psychotherapeutic strategy that was used may also be applied after pharmacological treatment of depression, if appropriate, and may have potential in extending therapeutic benefits beyond the time of medication administration, as it has been found to be the case in psychiatric settings [39].

This therapeutic approach may be potentially extended to cardiovascular rehabilitation in view of the suitability of WBT for the rehabilitation process [40] and the adverse prognostic role of an unhealthy lifestyle and depressive symptoms in these settings [41–43]. A number of clinical situations (delayed recovery after treatment, discrepancy between cardiovascular status/functioning, presence of a psychological comorbidity, problems with lifestyle and risky behavior, and presence of stressful circumstances) may be addressed by the sequential strategy we have outlined.

The findings of this investigation targeting psychological well-being in ACS should be seen as preliminary and await proper replication studies. It should also be noted that more than a quarter of the ACS patients diagnosed with depression and/or demoralization (36 out of 136; 26.5%) refused to join the RCT. This percentage, however, is lower than the refusal rates found in the literature on secondary prevention programs, which range from 31.4 [44] to 72.2% [45] among depressed patients. Moreover, about half of the 740 patients initially screened by the cardiologists refused to undergo psychological assessment and almost half of those who agreed refused to join the trial or revoked the initial consent. The results are thus likely to reflect a self-selected population. Nonetheless, they indicate a road to the practice of lifestyle medicine [46] that is worth perusing.

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Statement of Ethics

This study was approved by the institutional review board of the ethics committees of both centers (identifier: Studio CE 09058). Written informed consent was secured from all of the patients for both the initial psychological evaluation and trial participation, after the procedures had been fully explained to them. The participants did not receive any compensation. The authors assert that all of the procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Conflict of Interest Statement

The authors have no conflict of interests to declare.

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Author Contributions

C.R., G.A.-D., and G.A.F. conceptualized and designed this study. C.R., S.G., G.A.-D., and G.A.F. collected, analyzed, and interpreted the data. C.R., S.G., and G.A.F. wrote the first draft of this paper. S.G. performed the statistical analyses. All of the authors critically revised this work for important intellectual content and provided administrative, technical, or material support. C.R., G.A.-D. and G.A.F. supervised the whole process.

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REVIEW ARTICLE

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Insomnia disorder: State of the science and challenges for the future

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Summary

Insomnia disorder comprises symptoms during night and day that strongly affect quality of life and wellbeing. Prolonged sleep latency, difficulties to maintain sleep and early morning wakening characterize sleep complaints, whereas fatigue, reduced attention, impaired cognitive functioning, irritability, anxiety and low mood are key daytime impairments. Insomnia disorder is well acknowledged in all relevant diagnostic systems: Diagnostic and Statistical Manual of the American Psychiatric Association, 5th revision, International Classification of Sleep Disorders, 3rd version, and International Classification of Diseases, 11th revision. Insomnia disorder as a chronic condition is frequent (up to 10% of the adult population, with a preponderance of females), and signifies an important and independent risk factor for physical and, especially, mental health. Insomnia disorder diagnosis primarily rests on self-report. Objective measures like actigraphy or polysomnography are not (yet) part of the routine diagnostic canon, but play an important role in research. Disease concepts of insomnia range from cognitive-behavioural models to (epi-) genetics and psychoneurobiological approaches. The latter is derived from knowledge about basic sleep-wake regulation and encompass theories like rapid eye movement sleep instability/restless rapid eye movement sleep. Cognitive-behavioural models of insomnia led to the conceptualization of cognitive-behavioural therapy for insomnia, which is now considered as first-line treatment for insomnia worldwide. Future research strategies will include the combination of experimental paradigms with neuroimaging and may benefit from more attention to dysfunctional overnight alleviation of distress in insomnia. With respect to therapy, cognitive-behavioural therapy for insomnia merits widespread implementation, and digital cognitive-behavioural therapy may assist delivery along treatment guidelines. However, given the still considerable proportion of patients responding insufficiently to cognitive-behavioural therapy for insomnia, fundamental studies are highly necessary to better understand the brain and behavioural mechanisms underlying insomnia. Mediators and moderators of treatment

response/non-response and the associated development of tailored and novel interventions also require investigation. Recent studies suggest that treatment of insom- nia may prove to add significantly as a preventive strategy to combat the global burden of mental disorders.

KEYWORDS
anxiety, CBT-I, depression, insomnia, insomnia models, prevention, treatment guidelines

1 | DEFINITION AND DIAGNOSIS OF INSOMNIA DISORDER (ID)—DSM-5, ICSD-3, ICD-11

In the last 50 years all medical diagnostic classification systems have included ID. DSM (Diagnostic and Statistical Manual of the American Psychiatric Association) in its previous versions DSM-III-R/DSM-IV (American Psychiatric Association, 1987, 1998) suggested a distinction between primary and secondary insomnias, whereas DSM-5 (American Psychiatric Association, 2013) heralded a paradigmatic change by establishing ID as an overarching diagnostic category, eliminating artificial distinctions. The ICSD (International Classification of Sleep Disorders) in its third version (American Academy of Sleep Medicine, 2014) confirmed this new nosology (see Table 1; diagnostic criteria for chronic ID according to ICSD-3).

The ICD-10 (International Classification of Diseases, 10th edition; World Health Organization, 1993) distinguished between organic and non-organic sleep disorders; however, ICD-11 will follow the avenue paved by DSM-5 and ICSD-3 (World Health Organization, 2019). When analysing the "new" criteria for ID all systems list both night-time and daytime symptoms and, notably, the symptom of non-restorative sleep was dropped from the criteria due to lack of specificity.

Abandoning the distinction between primary/secondary insomnia constituted a major advance in acknowledging that insomnia frequently is not just a symptom of any other somatic or mental disorder, but constitutes an independent disorder, deserving specific consideration in clinical practice. It is important to note that insomnia probably more frequently occurs as a co-morbid condition together with somatic and mental disorders, than it does occur in its isolated form. DSM-5, ICSD-3 and ICD-11 pay respect to this by explicitly allowing co-morbidity. Furthermore, it turned out that cognitive-behavioural treatment for insomnia (CBT-I) not only has decisive effects on sleep/insomnia complaints, but also positively influences somatic/mental co-morbidities and quality of life. At present, evidence is accumulating that insomnia treatment with CBT-I may even have surplus benefits with respect to general treatment and prevention especially of mental disorders (Benz et al., 2020; Cheng et al., 2019; Hertenstein et al., 2022; Irwin et al., 2022; Leerssen et al., 2021).

Nevertheless, ID as a "one size fits all" category is seen critical by many working in the field. There is still a lively and ongoing discussion about different insomnia phenotypes, for example focussing on the main nocturnal complaint, that is, insomnia with or without "objective" short sleep (Vgontzas et al., 2013), or sleep-onset insomnia versus sleep-maintenance insomnia (Pillai et al., 2015). Indeed, the profile of dominant sleep complaints matters for the risk of developing first-onset major depressive disorder (Blanken et al., 2020). However, subtyping based on sleep characteristics may not be that robust, even across 2 nights (Johann et al., 2017), let alone across months or years (Edinger et al., 2011). Apparently, insomnia complaints change over time. More robust insomnia subtypes surfaced by multivariate profiling of personality features rather than sleep features (Blanken, Benjamins et al., 2019).

As it would be beyond the scope of this article to comprehensively describe the diagnostic and differential diagnostic procedure for insomnia, the interested reader is referred to Riemann et al. (2022) and other textbooks (Sateia & Buysse, 2010). Some important issues

TABLE 1 Diagnostic criteria for chronic ID according to ICSD-3 (AASM, 2014)

A. The patient reports, or the patient's parent or caregiver observes, one or more of the following:
   1. Difficulty initiating sleep.
   2. Difficulty maintaining sleep.
   3. Waking up earlier than desired.
   4. Resistance to going to bed on appropriate schedule.
   5. Difficulty sleeping without parent or caregiver intervention.
B. The patient reports, or the patient's parent or caregiver observes, one or more of the following related to the night-time sleep difficulty:
   1. Fatigue/malaise.
   2. Attention, concentration or memory impairment.
   3. Impaired social, family, occupational or academic performance.
   4. Mood disturbance/irritability.
   5. Daytime sleepiness.
   6. Behavioural problems (e.g. hyperactivity, impulsivity, aggression).
   7. Reduced motivation/energy/initiative.
   8. Proneness for errors/accidents.
   9. Concerns about or dissatisfaction with sleep.
C. The reported sleep/wake complaints cannot be explained purely by inadequate opportunity (i.e. enough time is allotted for sleep) or inadequate circumstances (i.e. the environment is safe, dark, quiet and comfortable) for sleep.
D. The sleep disturbance and associated daytime symptoms occur at least three times per week.
E. The sleep disturbance and associated daytime symptoms have been present for at least 3 months.
F. The sleep/wake difficulty is not better explained by another sleep disorder.

Abbreviation: ICSD-3, International Classification of Sleep Disorders, 3rd version.

concerning diagnostic procedures, however, should be highlighted here. The use of sleep diaries constitutes an integral part of insomnia assessment for both research and/or clinical purposes (e.g. consensus sleep diary by Carney et al., 2012). Sleep diaries are easy to apply and to evaluate. Sleep diaries focus on the experience of sleep and can be reviewed by the clinician as they are presented, but the inherent information can also be used to create highly informative graphical displays of sleep and bedtimes (Figure 1).

Beyond sleep diaries, other insomnia-specific questionnaires like the Insomnia Severity Index (Bastien et al., 2001) or the Sleep Condition Indicator (Espie et al., 2014) should be used.

For both clinical and fundamental research, it is favourable to take note of the recommendations for a standard research assessment of insomnia (Buysse et al., 2006). Several paradigms were developed to elucidate specific aspects of insomnia, for example, the attentional bias paradigm (Espie et al., 2006; Harris et al., 2015). This paradigm suggests that patients with chronic insomnia have developed a bias in their perception and processing of stimuli related to insomnia. Other highly promising paradigms investigate failing overnight amelioration of distress, which seems key to persistence of hyperarousal (Wassinget al., 2016; Wassing, Benjamins et al., 2019; Wassing, Lakbila-Kamal,et al., 2019; Wassing, Schalkwijk, et al., 2019). At present, not yet being ready for standard clinical practice, it is conceivable that these paradigms might be used in the future to measure responsiveness to CBT-I, also in combination with neuroimaging methods.

As the diagnosis of insomnia is solely based on subjective complaints and their measurement, it remains a matter of long-standing debate what the role of technical methods like actigraphy or polysomnography (PSG) might be. It is a highly controversial issue as to whether PSG should be part of the diagnostic process. Doubtlessly PSG helps to unravel suspected occult pathology of sleep, that is, periodic limb movements during sleep (periodic limb movement disorder) or sleep apnea (obstructive sleep apnea syndrome). US guidelines clearly deny the usefulness of PSG to diagnose insomnia (Kushida et al., 2005), whereas guidelines of the German and the European Sleep Research Society (Riemann, Baum, et al., 2017; Riemann, Baglioni, et al., 2017) suggest that PSG be used for patients with therapy-refractory insomnia who have not responded to a previous adequate "dose" of pharmaco- or psychotherapy.

The frequently described discrepancy between subjective (i.e. data from sleep diaries) and objective data (PSG) called paradoxical insomnia or sleep state misperception is seen as a major clinical and scientific challenge. PSG contrasted with subjective data does not reveal as pronounced disturbances of sleep as indicated by subjective data (Feige et al., 2008). A PSG meta-analysis revealed mean total sleep time differences between insomnia and good sleepers of about 25 min, whereas subjective estimates demonstrated an almost 2-hr difference (Baglioni, Regen, et al., 2014; Baglioni, Spiegelhalder, et al., 2014). Traditional PSG reveals only a glimpse of the brain activity during sleep. Advanced analyses have commenced to reveal electroencephalogram (EEG) correlates of subjective wakefulness during sleep, like simultaneous wake-like and sleep-like brain activity in people with insomnia (Christensen et al., 2019; Stephan et al., 2021). Furthermore, classification of individual insomnia patients based on their PSG and EEG power-spectral variables can distinguish between those with objective short sleep and those with sleep state misperception (Kao et al., 2021). Accordingly, the "misperception" may in fact be "mismeasurement": an inappropriate use or interpretation of traditional PSG features by clinicians, rather than inappropriate interpretation of subjective experiences by people with insomnia. It is important to bear in mind that these same challenges apply to mental disorders in general. There is no objective "test" for depression, anxiety or psychosis. The validation of any such tests needs to apply self-report coupled with clinical judgement as the "gold-standard."

Vgontzas and colleagues have postulated that the long-term health consequences of insomnia may be related specifically to objective short sleep duration of less than 6 hr (Vgontzas et al., 2013). However, patients with short sleep insomnia during one night do not fulfil that criteria on another night, and an increased risk of hypertension in short sleeping insomnia could not be replicated (Johann et al., 2017). Also, the hypothesis that the presence of objectively documented short sleep may be of relevance for the choice of therapy (Riemann et al., 2011), that is, pharmacotherapy for insomnia patients with objective short sleep duration versus psychotherapy for insomnia patients with objective normal sleep duration, has yet to be resolved and deserves further consideration (Vgontzas et al., 2013). More details will be provided in the aetiology/pathophysiology section. Figure 2 gives some examples of PSG determined sleep profiles of a good sleeper and two patients with ID.

2 | EPIDEMIOLOGY OF INSOMNIA AND INSOMNIA AS A RISK FACTOR FOR OTHER DISORDERS

Insomnia more frequently afflicts females than males (60% versus 40%), and its prevalence increases with age (for an overview, see Ohayon, 2002). The European Academy for CBT-I has summarized prevalence data for ID across some European countries (Baglioni et al., 2020), varying strongly from country to country. Data for Germany indicate a prevalence of 5.7%, whereas French surveys indicate figures up to 20%. On average, approximately 10% of the adult European population suffer from chronic insomnia. The heterogenous data clearly stress the need for the prospective collection of pan-European samples with state-of-the-art methods to obtain the full picture for planning of insomnia healthcare services.

The costs of insomnia for the individual and society are staggering: it was demonstrated that insomnia conveys increased risks for cardiovascular diseases (Li et al., 2014), obesity and diabetes (Anothaisintawee et al., 2016; Chan et al., 2018), depression (Baglioni et al., 2011; Hertenstein et al., 2019), anxiety (Hertensteinet al., 2019) and suicide (Pigeon et al., 2012). Wickwire (2019) reported that untreated insomnia leads to increased all-cause healthcare utilization based on a randomly selected and nationally representative sample from the USA. Data from Norway indicate that insomnia strongly predicts sick leave and disability pension (Overland

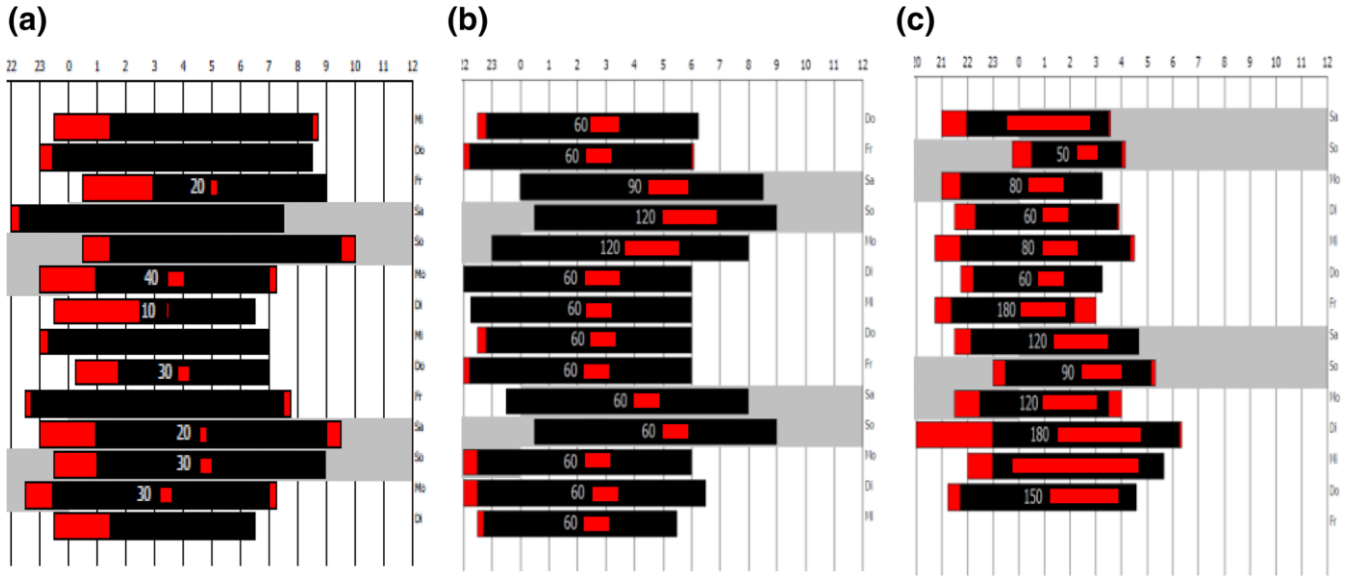

FIGURE 1 Sleep diary data from different patients with insomnia. (a) An insomnia patient who shows an increased sleep-onset latency. (b) A patient with insomnia experiencing difficulty in maintaining sleep. (c) A patient with mixed insomnia showing difficulty in both sleep onset and sleep maintenance

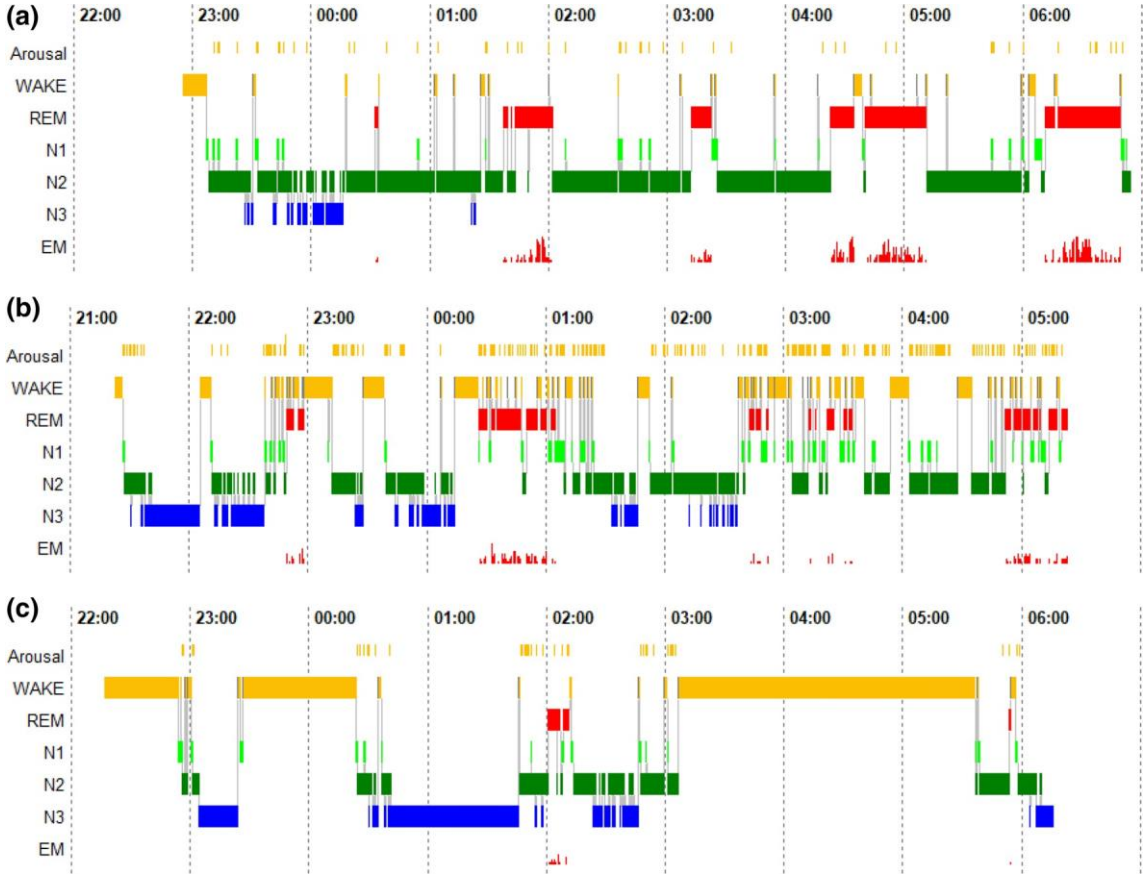

FIGURE 2 Polysomnographic (PSG) profiles of a good sleeper (upper panel; a) and patients with insomnia (lower panels; b,c). The *y*-axis displays arousal (micro-arousals), wake and sleep stages (rapid eye movement [REM], stage N1, N2 and N3) as well as eye movements. The *x*-axis is the time axis. (b) A patient with insomnia who has only a slightly reduced total sleep time, but a high number of arousals during sleep and a fragmented REM sleep. (c) A patient with insomnia who has an objectively shortened sleep duration

et al., 2008; Sivertsen et al., 2009). Data from France indicated a sum of 2 billion USD in 1995 (Leger et al., 1999). Data from the USA resulted in a sum of 150 billion US dollars for direct and indirect costs of insomnia (Reynolds & Ebben, 2017). A Canadian study (Daleyet al., 2009) reported total annual costs for ID alone to be about 6.5 billion Canadian dollars. Recent data indicate that treatment using digital CBT-I reduces healthcare expenditure, and Markov health economic modelling indicates that digital CBT-I may be highly cost-effective when offered at scale (Darden et al., 2021). Further details of the costs and risks of insomnia are given in the European Academyfor Cognitive Behavioural Therapy for Insomnia Report (Baglioniet al., 2020). An important clinical and research question relates to the hypothesis that adequate insomnia treatment might not only effectively target insomnia symptoms but might reduce subclinical and clinical psychopathology, and also be of general preventive value for mental disorders and physical diseases.

3 | AETIOLOGICAL AND PATHOPHYSIOLOGICAL CONSIDERATIONS

Recent reviews synthesized current neurobiological, cognitive, behavioural and emotional models for insomnia and its relationship to psychopathology (Figure 3; Espie, 2022; Riemann et al., 2020; Van Someren, 2021).

Current theoretical approaches span from cognitive-behavioural to neurobiological models, and models taking into account both levels simultaneously.

The basic structure of the model depicted in Figure 3 is taken from the so-called 3P model of insomnia (Spielman et al., 1987). The 3Ps signify: predisposing, precipitating and perpetuating factors.

"Predisposing" factors come from the areas of (epi-)genetics and early life stress that contribute to individual differences at the level of brain function and personality. Genetic and epigenetic factors have been shown to be involved in the aetiology of insomnia by family and twin studies (for an overview, see Palagini et al., 2014). Genome-wide association studies point to an involvement of a very large number of genes, each with a very small contribution, and shared genetic factors for insomnia and restless legs, cardiometabolic, and especially psychiatric traits (Jansen et al., 2019; Lane et al., 2019). Interestingly, the brain tissues and cell types expressing sets of insomnia risk genes are not primarily part of the known circuitry regulating sleep but are rather part of circuitries involved in emotion regulation (Van Someren, 2021).

Still, for completeness, a discussion on the development and maintenance of insomnia should include the neurobiological mechanisms of sleep, notably homeostatic and biological time-keeping mechanisms (Borbély, 1982). The flip-flop switch model of sleep regulation (Saper et al., 2005) suggests a bistable switch mechanism between sleep and wake promoting centres of neuronal cell groups. Wakefulness is governed by a network of cell populations in the hypothalamus (including orexinergic neurons), basal forebrain and brain stem, activating thalamus and cortical structures. These structures include and extend beyond the cell groups in the reticular formation of the brainstem (originally described as ascending reticular activating system). The main sleep-inducing centres are located in the ventrolateral-preoptic nucleus (VLPO), which becomes active during sleep and inhibits all major wake-promoting centres in the hypothalamus and brain stem, with the neurotransmitters galanin and gamma-aminobutyric acid. The VLPO receives afferent input from each of the major monoaminergic systems, and is inhibited by noradrenaline and serotonin. A mutual inhibitory circuit between both systems, the wake and the sleep system, leads to a flip-flop switch with "sharp" transitions between sleeping and waking. Thus, insomnia on this level can be conceptualized as imbalance between sleep-inducing and wake (i.e. arousal)-inducing mechanisms. A hyperactivity of the arousal system or a hypoactivity of the sleep system or both simultaneously could thus "drive" the insomnia. Circadian and homeostatic mechanisms are also involved in this switch process, and it has been speculated that a dysfunctional "key switch" (see above) could play a role in the pathogenesis of insomnia. According to the two-process model of sleep regulation (Borbély, 1982), sleep–wake behaviour is governed by circadian time-keeping mechanisms and a homeostatically controlled process S, representing the sleep drive. Being out of synchrony with the internal body clock (e.g. due to shift work) or having a decreased sleep drive would logically result in sleep complaints. Indeed, the main effective component of CBT-I, sleep restriction, is hypothesized to act on the sleep drive (Maurer et al., 2018), and long-term effectiveness of CBT-I improves with the addition of circadian interventions (Dekker et al., 2020; Leerssen et al., 2021). Notwithstanding these effects, decades of research in insomnia have failed to reveal circadian and homeostatic mechanisms as primary factors involved the origin and pathophysiology of the majority of people suffering from ID (Van Someren, 2021). One might conclude that enhancement of homeostatic sleep pressure and support of circadian rhythm amplitude alleviates insomnia, but that we may have to look beyond hourglass and clock to find underlying causes predisposing to insomnia.

A third factor involved in sleep and predisposing to insomnia is emotion (Saper et al., 2005). This factor is frequently overlooked, in spite of the ubiquitous experience that sleep initiation is difficult under threatening conditions—no matter what our hourglass and clock suggest. Indeed, from an evolutionary perspective this would be extremely disadvantageous. An increasing number of observations suggests a key role of this third factor in the origin and pathophysiology of the predisposition to insomnia (for review, see Van Someren, 2021). For example, the trait to exhibit a pronounced dis-turbed sleep response to stressful events has been shown to be a major risk factor for insomnia (Drake et al., 2014). Also other personal-ity traits related to emotion regulation have been linked to insomnia, including neuroticism, perfectionism, sensitivity to anxiety symptoms, and the tendency to internalize problems (Dekker et al., 2017; van de Laar et al., 2010). The major early developmental factors predisposing to insomnia involve emotion as well: risk genes seem to have a prefer-ence for brain circuitries involved in emotion regulation, and early childhood adversity likewise affects these circuitries (Van Someren, 2021).

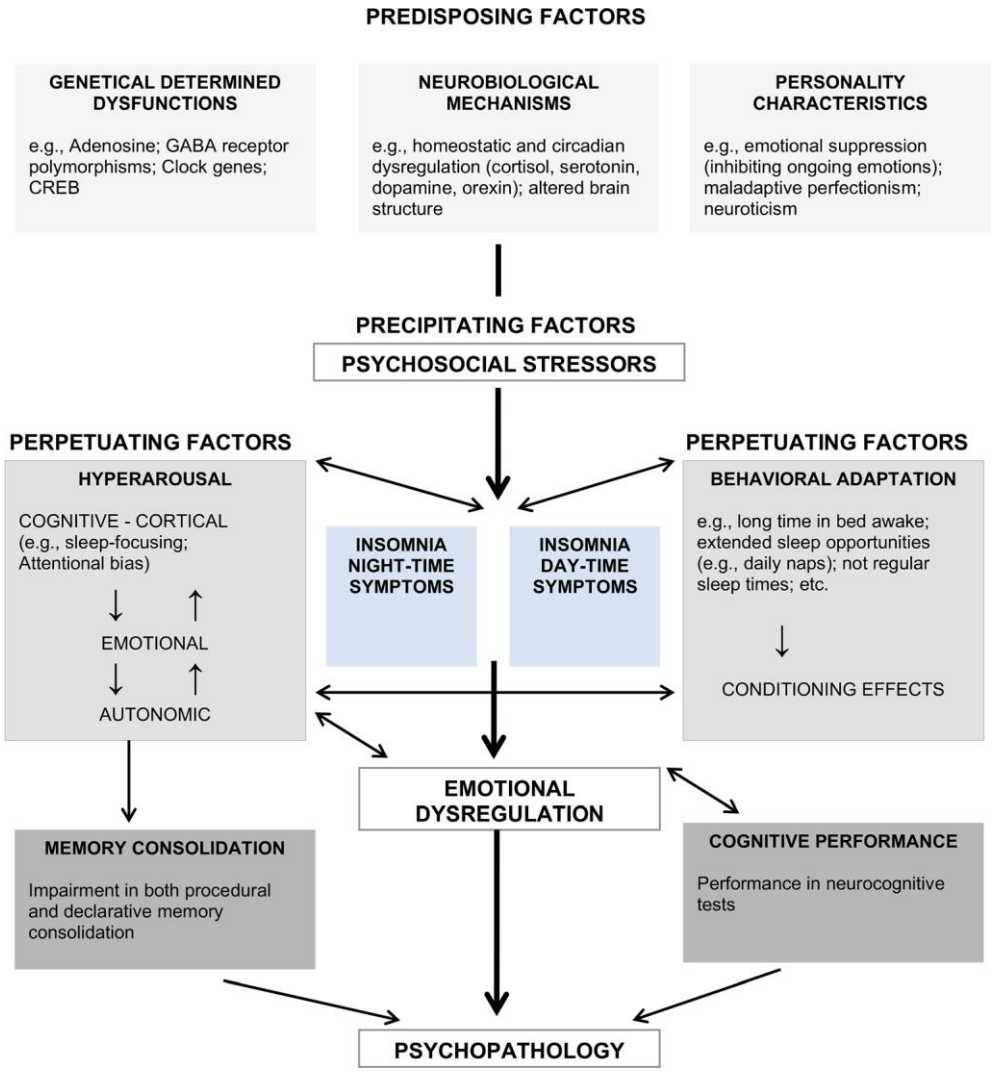

FIGURE 3 Comprehensive insomnia model (see text)

"Precipitating" factors can be readily identified in many cases. These are usually significant life events that facilitate the onset of acute episodes of insomnia. Most frequently, reported triggers of acute episodes of insomnia are stressful life events related to a threat of security to family, health and work-school living that are coupled with negative emotional valence. Fortunately, not everyone exposed to stress in adulthood develops insomnia, most likely only those that have a predisposing profile.

"Perpetuating" factors can be discussed with respect to hyperarousal, which can be conceptualized as overactivity of the arousal-promoting systems, out of balance with the activity in sleep-inducing systems. Hyperarousal includes physiological, cognitive and emotional components, and has been considered a stable characteristic of people with insomnia both during the night and during the day (Morin et al., 2015; Riemann et al., 2010, 2015). It has been demonstrated that patients with insomnia show increased levels of autonomic activity (though the issue is discussed critically with respect to heart rate variability; Dodds et al., 2017) and an overactivity of the HPA-axis, as documented by increased levels of cortisol output during day- and night-time (see meta-analysis by Dressle et al., 2022). Central nervous system (CNS) indicators of hyperarousal in people with insomnia are increased amounts of micro-arousals and increases in fast EEG frequencies (in the sigma and beta bands) during sleep (Christensen et al., 2019; Feige et al., 2013; Perlis et al., 1997, 2001; Spiegelhalder et al., 2012), and also wake EEG shows signatures of increased excitation (Colombo, Ramautar, et al., 2016; Colombo, Wei, et al., 2016) and somatic awareness and responsivity (Wei et al., 2016; Wei, Blanken, & Van Someren, 2018; Wei, Ramautar, et al., 2018). Although still too small for voxel-wise consistent findings (Tahmasian et al. 2018), the rapidly increasing number of neuroimaging studies on insomnia (Riemann et al., 2015) suggests an overactivity of cortico-limbic networks relative to sleep-promoting neuronal networks. Most interestingly, in recent years a special role of rapid eye movement (REM) sleep disturbance (REM sleep instability/restless REM sleep) has been postulated to be of utmost relevance for the experience of insomnia, and specifically their altered perception of sleep and inability to discard hyperarousal (Riemann et al., 2012; Van Someren, 2021). This lead was primarily based on the finding of increased micro-arousals during REM sleep in insomnia (Feige et al., 2008)—further studies revealed that upon awakening out of REM sleep, patients with insomnia

more frequently stated having been awake compared with non-REM (NREM) sleep and good sleepers (Feige et al., 2018). Following up on these findings, Feige et al. (2021) used an event-related potentials paradigm to demonstrate that ID patients differed from good sleepers by showing reduced P2 amplitudes only in phasic REM sleep. These studies highlight a special role of REM sleep for insomnia.

The mechanisms underlying this special role of REM sleep in the predisposition, perpetuation and psychiatric consequences were addressed in a series of seminal studies (Wassing et al., 2016; Wassing, Benjamins, et al., 2019; Wassing, Lakbila-Kamal, et al., 2019; Wassing, Schalkwijk, et al., 2019). In brief, Wassing et al. showed that the restless REM sleep that is characteristic of people with insomnia interferes with overnight adaptation in limbic circuits of the brain. The consequential difficulties with dissolving of distress could be key to the development and perpetuation of hyperarousal as well to the risk of developing psychiatric disorders, as supported by other studies (Halonen et al., 2021; Pesonen et al., 2019). Restless sleep lacks the prolonged silencing of the locus coeruleus and consequential drop in cerebral noradrenaline that characterizes normal restful REM sleep (Kjearby et al., 2020). Because REM sleep is a period of pronounced limbic reactivation of emotional memory traces, it has been hypothesized that the increased level of noradrenaline during restless REM sleep interferes with the synaptic plasticity processes underlying adaptation of the neuronal engrams that represent distress, and could even result in sensitization, indicating maladaptive sleep (Van Someren, 2021). Others have proposed that the low level of noradrenaline during REM sleep is key to restore the noradrenergic tone, to enable a low tonic and high phasic locus coeruleus activity during wakefulness (Goldstein & Walker, 2014).

Restless REM sleep thus has a specific contribution to "emotional" perpetuating factors, and may explain why patients with insomnia are so prone to develop anxiety and depressive disorders in the long run. Indeed, sleep has been conceptualized as a basic psychophysiological process that is fundamental for stress, behaviour and emotion regulation (Hagger, 2010; Palmer & Alfano, 2017). Consistently, most mental disorders are associated with sleep impairment (Baglioni et al., 2016), and insomnia-related problems in children have been linked with difficulties in socio-emotional development (Sadeh et al., 2014; Vermeulen et al., 2021). In adults, insomnia has been found to be a predictor of years-long lingering of emotional distress (Wassing et al., 2016; Wassing, Lakbila-Kamal, et al., 2019), of depression, and of anxiety disorders (Baglioni et al., 2011; Hertensteinet al., 2019; Leerssen et al., 2021). Experimental studies have shown that patients with insomnia report more negative emotions than good sleepers (McCrae et al., 2008; Scott & Judge, 2006). Psychophysiological studies have also evidenced an emotional bias in people with insomnia to sleep-related stimuli with negative valence compared with good sleepers (Baglioni et al., 2010; Baglioni, Spiegelhalder,et al., 2014).

Perpetuating factors also include inadequate "behaviours", like prolonged bedtimes, irregular sleep–wake schedules, napping during the day and other maladaptive behaviours, such as using alcohol to combat insomnia. Usually, these strategies are attempted to compensate for lost sleep; however, in the end insomnia is maintained and exacerbated by decreasing sleep drive.

In addition, "cognitive perpetuating factors" have been identified, such as beliefs, worry and attentional bias (Espie, 2002; Harvey, 2002; Morin et al., 2007). These cognitions include unrealistic beliefs about sleep requirements and excessive worry for not meeting these standards. In recent years, the literature has emphasized the role of selective attention processes in people with insomnia. Specifically, it has been argued that the attentional system of patients with insomnia may be abnormally sensitive to sleep-related information (Harris et al., 2015). It has been hypothesized that such attention bias may exacerbate sleep-related rumination and lead to sleep effort (Espie et al., 2006; Harvey, 2002).

Summarizing, acute precipitating life events can "set the wheels in motion"—acute insomnia is triggered. The question of why most individuals who develop acute insomnia do not go on to develop the chronic condition has not yet been clarified (Ellis et al., 2012)—but likely involves genetic and early life stress-induced neurobiological vulnerability to keep "the train rolling." A complex network of associated symptoms including cognitive-, emotional- and cerebral hyperarousal, unstable REM sleep and maladaptive behaviours will keep the furnace burning. Sleep-preventing learned associations (conditioning effects) are strongly involved in this process as well, giving credit to Bootzin's assumption that in insomnia the original connection between the bed (stimulus) and the behaviour of sleep (response) has been lost or "unlearned" (Bootzin et al., 1991).

The CBT-I (see below) mainly targets the perpetuating factors, for example, relaxation techniques and mindfulness aim to address psychophysiological hyperarousal; sleep hygiene, stimulus control and sleep restriction try to correct maladaptive behaviours and enhance sleep drive; whereas cognitive strategies aim to alter "racing thoughts", dysfunctional beliefs and attitudes, and to reduce nocturnal worrying and ruminations.

4 | TREATMENT (S)—FOCUS ON PSYCHOLOGICAL APPROACHES: PRESENT GUIDELINES, WHAT IS CBT-I, STEPPED CARE AND DIGITAL CBT-I?

All insomnia-related guidelines published in the last 5 years agree that CBT-I should be the first-line treatment for insomnia, based on the accumulated scientific evidence from the literature. These guidelines include the American College of Physicians (Brasure et al., 2016; Kathol & Arnedt, 2016; Qaseem et al., 2016; Wilt et al., 2016), the American Academy of Sleep Medicine (AASM; Edinger et al., 2021a, b), the German and the European Sleep Society (Riemann, Baum, et al., 2017; Riemann, Baglioni, et al., 2017), and the British Association for Psychopharmacology consensus statement (Wilsonet al., 2019). Overall, these guidelines make a strong case for CBT-I asfirst-line treatment for insomnia, and hypnotics are recommended for short-term use and only if CBT-I is either not available or ineffective. As hypnotics in this context, melatonin agonists, benzodiazepines,

benzodiazepine receptor antagonists, some sedating antidepressants and orexin receptor antagonists are recommended mainly for short-term use (less than 4 weeks) only. An overview of the present state of hypnotic treatment can be found in reviews (Herring et al., 2019; Riemann & Nissen, 2012; Roehrs & Roth, 2012).

The CBT-I comprises a family of interventions and is not "one" homogenous therapeutic strategy *per se* (Table 2).

The CBT-I is in essence a multicomponent approach, comprising cognitive and behavioural parts, within each of which domain there is a wide range of treatment options. The principal behavioural therapies are sleep restriction and stimulus control. Cognitive techniques include reappraisal, cognitive control and paradoxical intention. There is also a range of relaxation therapies, and sleep hygiene education, although not effective as a standalone treatment, is commonly part of the CBT-I toolkit. A brief description of these techniques is given in the table. For further details, the interested reader is referred to a new CBT-I textbook that will be published in 2022 (Baglioniet al., 2022). A new clinician handbook on insomnia will also be avail- able shortly (Espie, 2022).

Logically therefore CBT-I is not "a treatment" but is "a system of cognitive and behavioural therapeutics", akin to pharmacotherapy (which is not a drug treatment but a "pharmaceutical approach" to clinical care; Espie, 2022). The history of evidence-based psychotherapy (in most disorders) reveals a period of time during which there was a tendency towards "lumping" of therapeutic elements, rather than the creation of precision techniques that "may" be used in combination. This is certainly true of the non-pharmacological management of insomnia, and the term CBT-I has for the past 20 years or more been used rather generically in the literature because the majority of studies have deployed a CBT-I package.

In earlier times there was a focus upon more specific interventions. For example, comparing the effectiveness of abbreviated progressive relaxation, stimulus control therapy and paradoxical intention (Espie et al., 1989), or even investigating components of a single therapy (Woolfolk & McNulty, 1983: compared progressive relaxation, progressive relaxation without tension release, imagery with tension release, and imagery without tension release). Interestingly, of late, there has been renewed interest in single-component therapies. We now find ourselves unpicking or deconstructing CBT to evaluate its active component treatments, and even its active treatment ingredients. The best example is sleep restriction therapy (SRT), widely regarded to be the most effective element of CBT (Edinger et al., 2021a; Maurer, Schneider et al., 2021). A series of laboratory-based experiments has recently explored the homeostatic, arousal and circadian mechanisms of sleep restriction (Maurer et al., 2020, 2022; Maurer, Ftouni et al., 2021).

In support of this is the fact that CBT protocols are effective even when they vary. The AASM practice parameters task force recently grappled with the question, what are the "minimal characteristics" of effective CBT (Edinger et al., 2021a). They concluded that "all studies included SRT, stimulus control and some form of cognitive therapy"; however, the cognitive component varied widely. Whether or not relaxation strategies or sleep hygiene were included in the CBT-I regimen varied across studies as well. It was beyond the scope of this (group) to recommend a specific CBT protocol, and "these variations did not appear to systematically impact the effectiveness of the treatment" (p. 261). This evidences the versatility and robustness of what is sometimes now referred to as CBTx (cognitive and behavioural therapeutics), that is, a "therapeutic formulary", where not everyone needs the same content, or the same order of content (Espie, 2022). Analysis of how SRT is configured suggests there is gross variability between studies and protocols (Kyle et al., 2015); it would be prudent to establish what is the most effective combination of SRT parameters, including tailoring to presenting insomnia phenotype. Indeed, the widespread development of "precision medicine" (Ginsburg & Willard, 2009; Jain, 2002) has spawned interest in how "personalized behavioural sleep medicine" for insomnia may evolve in the future (Kyle et al., 2014).

Despite the impressive evidence base for CBT-I, its recognition internationally as the treatment of first choice for the management of insomnia and the fact that the CBTx formulary of treatments is quite wide ranging, in practice the majority of insomnia patients seeking medical help continue to receive medication. The issue here is not so much overprescribing of drugs as it is under-provision of CBT-I. Two innovations have been developed to address this problem. The first, at the level of the treatment itself there has been growing interest in, and a rapidly accelerating evidence base for digital CBT-I, that is CBT-I delivered by fully automated web and mobile means. The second, at the level of the service, has been the development of the "stepped care" model of insomnia service delivery.

The effectiveness of digital CBT-I has been robustly and rigorously demonstrated against psychological placebo (Espie et al., 2012), attention control (Christensen et al., 2016; Kaldo et al., 2015), sleep hygiene (Espie et al., 2019; Ritterband et al., 2017; Vedaa et al., 2020), waitlist (Zachariae et al., 2018) and usual care (Freeman et al., 2017) in a range of clinical and co-morbid populations. Several meta-analyses report large between-group effects on insomnia severity, and medium effects on sleep diary outcomes (Seyffert et al., 2016; Sohet al., 2020; Zachariae et al., 2016), and benefits to sleep are durable, being maintained up to a year and beyond (Blom et al., 2017; Luik et al., 2020; Vedaa et al., 2019). Whereas meta-analyses report effect sizes in the range of face-to-face CBT-I thereby suggesting non-inferiority, head-to-head comparisons have shown mixed findings (Blom et al., 2015; De Bruin et al., 2016; Kallestad et al., 2021; Lancee et al., 2016). It seems likely, however, that the evolution of highly engaging clinically evidenced software will address engagement and treatment implementation challenges that are apparent for all forms of CBT-I delivery. It may also be the case that differences exist between different digital CBT-I formats (Hasan et al., 2022). These outstanding questions warrant further investigation.

Beyond improved sleep, digital CBT-I, like "traditional" CBT-I, yields benefits to additional clinical and functional outcomes of relevance to insomnia. Several studies have documented reductions in symptoms of anxiety and depression, including in individuals with clinically significant depressive symptoms (Blom et al., 2015, 2017; Cheng et al., 2019; Henry et al., 2021; Pillai et al., 2015; van der Zweerde

TABLE 2 CBT-I ingredients (from Baglioni et al., 2020)

CBT-I strategy	Description
Sleep restriction	*Behavioural strategy*: A method that aims at strengthening homeostatic sleep pressure and stabilizing circadian control of sleep and wakefulness, by decreasing the opportunity to sleep over successive nights. Patients are instructed to restrict their time in bed to match their average (self-report in sleep diaries) total sleep duration. The time in bed is then gradually increased until reaching patients' optimal sleep need. An alternative method, called *sleep compression*, consists in gradual constriction of time in bed until reaching the optimal sleep need.
Stimulus control	*Behavioural strategy*: Several instructions aiming at strengthening the bed as a cue for sleep, weakening it as a cue for activities that might interfere with sleep, and helping the insomniac acquire a consistent sleep rhythm, based on operant conditioning model: (1) lie down to go to sleep only when you are sleepy; (2) do not use your bed for anything except your sleep and sexual activity; (3) if you find yourself unable to fall asleep, get up and go to another room. Stay up as long as you wish, and come back to bed when you feel sleepy; (4) If you still cannot fall asleep, repeat step (3). Do this as often as is necessary throughout the night; (5) Set your alarm and get up at the same time every morning irrespective of how much sleep you got during the night; (6) no napping during daytime.
Sleep hygiene education	Behavioural and educational strategy: General health instructions about internal and external factors that might influence sleep (e.g. sport, light, temperature, etc.).
Relaxation	Behavioural and cognitive strategy: A set of methods aiming at reducing somatic or cognitive hyperarousal (e.g. progressive muscle relaxation, autogenic training, imagery training, meditation).
Cognitive reappraisal	Cognitive strategy: Strategies directed to reduce dysfunctional beliefs, attitudes, concerns and false beliefs about the cause of insomnia and about the inability to sleep.
Cognitive control/ Worry time	Cognitive strategy: The patient is instructed to sit comfortably in an armchair, and write down a list of worries and list of what to do the next day. The rationale of this strategy is to prevent emotionally loaded intrusive thoughts during the sleep-onset period, as all worries have been "already" processed before going to bed.
Paradoxical intention	Cognitive strategy: Strategy aimed at reducing the anticipatory anxiety at the time of falling asleep. Patients are instructed to remain still in bed with the eyes closed and to try to keep awake as long as they can. This takes away the responsibility to try to fall asleep, which in turn often leads to falling asleep quicker.

Abbreviation: CBT-I, cognitive-behavioural treatment for insomnia.

et al., 2019). From a scientific perspective, digital CBT-I confers advantages such that it permits examination of potential mediators of treatment effects using a standardized therapeutic approach. Large randomized-controlled trials and secondary analyses show that insomnia symptom reduction mediates improvements in mental health symptoms (Freeman et al., 2017; Henry et al., 2021), and improvements in quality of life, health and wellbeing, and cognitive function (Espie et al., 2019; Kyle, Hurry, et al., 2020). This evidence therefore supports treating insomnia complaints whenever it presents. Emerging data also suggest that demographic variables including age, race, gender or socio-economic status do not moderate the effectiveness of digital CBT-I (Cheng et al., 2019).

Real-world evidence further underscores the value of digital CBT-I. Recent uncontrolled data evaluating digital CBT-I in existing healthcare settings in the UK show reductions in insomnia and augmentation of the effects of in-person therapy for anxiety and depression (Cliffe et al., 2020; Luik et al., 2017; Stott et al., 2021). Importantly, from a health economic perspective, analyses suggest that digital CBT-I is cost-effective, and may lead to cost savings if made available at scale (Darden et al., 2021; Sampson et al., 2021). This growing body of evidence behind digital CBT-I has led to increased recognition of it as a viable and effective treatment option. Indeed, in the USA, Somryst has been cleared by the FDA as a prescription digital therapeutic (Morin, 2020). Likewise, Sleepio (www.sleepio.com) is widely available in the USA, integrated into healthcare pathways and on the digital formulary, and is available in major parts of the UK National Health Service.

By overcoming the barriers preventing access to therapist-delivered CBT-I, digital CBT-I has the potential to provide access to clinically effective, evidenced-based and guideline-recommended insomnia treatment. These fundamental properties of effectiveness and scalability make digital CBT-I attractive as a first-line insomnia intervention, providing an accessible alternative to pharmacotherapy (Figure 4).

The stepped-care model is a population health service approach to providing people with insomnia with access to evidence-based care (Espie, 2009; Espie et al., 2013). Stepped care is often conceptualized as a pyramid consisting of different levels, with at the bottom the least specialized help applicable for those with less severe and more generic complaints and highly specialized help for those with more severe, complex and rare problems as the top. The level of intervention is naturally not arbitrary; treatment is tailored to and based on the needs of the patient and the nature of their complaints. The number of steps in any stepped care model would be determined by the levels of intervention that are proven and available, and by what within the healthcare system would be affordable. Stepped care models have been recommended for use in insomnia (Baglioni et al., 2020, 2022), and are sometimes adopted in healthcare systems (Vincent & Walsh, 2013).

With regard to insomnia, therefore, digital CBT might be particularly suitable to be one of the entry-level methods for the treatment

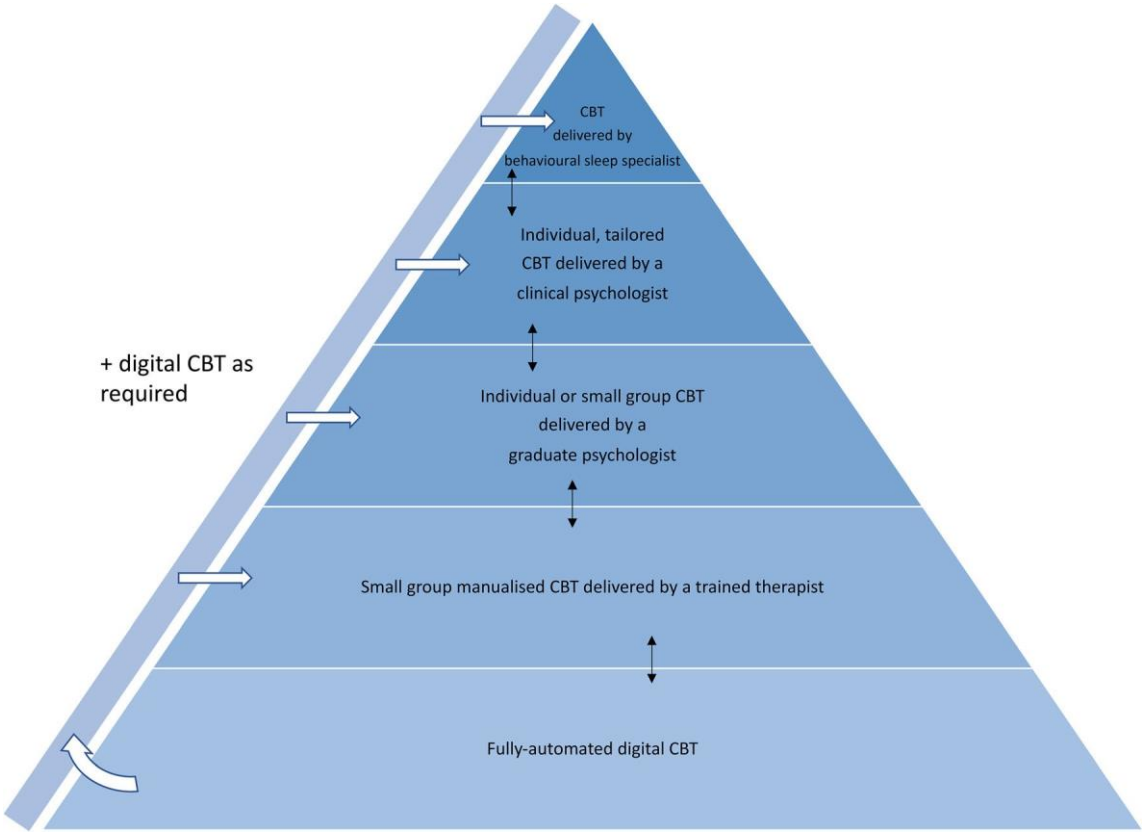

FIGURE 4 A proposed stepped care model for delivery of cognitive-behavioural therapy (CBT) as clinical guideline care. Digital CBT offers accessible treatment for all, but also may be integrated into the care pyramid supporting in-person therapy. The stepped care model conserves expert resources for more complex and treatment-resistant cases

of insomnia, as it has considerable "scalability", particularly when fully automated. Another approach at this level might be using self-help books of good standing, perhaps as part of a "books on prescription" scheme. Next in the hierarchy might be insomnia services that require some in-person support, but thought would be given to how such care could be provided with efficiency. Examples here might include telehealth rather than in a clinic, and the use of small group therapy rather than individual treatment. Other factors to be considered would be the nature of the treatment itself and the expertise of the therapist. For example, it could be possible to train healthcare workers in the provision of manualized CBT-I without them having to have a deep understanding of sleep medicine or mental health (training primary care nurses, for example). This approach is very protocol-driven and can be readily standardized (Kyle, Madigan, et al., 2020). As you then continue up the hierarchy there is greater need for insomnia-specific expertise and for the use of tailored therapy. At the peak of the pyramid the likelihood is that not only specialist expertise but also specialized facilities such as those available at a sleep centre may be required to address the needs of the most complex patients.

Stepped care systems require decision algorithms for two processes. First, to ensure that people are correctly allocated to the appropriate level of care in the first instance; and secondly, to ensure that people are able to step up to more advanced care depending on their treatment response.

5 | FUTURE PERSPECTIVES WITH RESPECT TO DIAGNOSIS, MEASUREMENT, AETIOLOGY AND PATHOPHYSIOLOGY; NEW TREATMENTS

Given the drastic changes we have been witnessing concerning insomnia and its diagnosis, pathophysiology/aetiology and treatment in the last 30 years, one might be tempted to answer the question "Can we rest yet?" (Harvey & Tang, 2003) with "Yes!." However, this would be premature and inadequate with respect to the many open questions still facing us in the insomnia field. Therefore, at this point, we would like to highlight some issues/avenues for future research and clinical practice we consider of utmost importance.

Given the fact that at present we have reached the unique situation that all major diagnostic systems (DSM-5, ICSD-3, ICD-11) have agreed upon ID (American Academy of Sleep Medicine, 2014; American Psychiatric Association, 2013; World Health Organization, 2019), the situation seems ideal that all types of studies into ID use more or less the same diagnostic criteria, which would be ideal to make data coming from all over the world easily comparable. This would also entail homogenization of our diagnostic and research instruments (questionnaires, PSG, etc.). However, as mentioned before, there definitely are different insomnia phenotypes that should not be neglected. A data-driven approach to delineate and characterize these

phenotypes seems warranted (Blanken, Benjamins, et al., 2019; Kao et al., 2021), possibly further refined by adding physiological data by means of PSG to questionnaire datasets.

In this regard, pooling data from different sleep labs could be beneficial in order to address the issues of small sample sizes and poor replicability in the insomnia field. This would require the use of standard methodology and paradigms across different labs. The UK Biobank (www.ukbiobank.ac.uk; see Allen et al., 2014 for a detailed description), a large biomedical database including a sample of about 500,000 adults, has already proven to be useful for insomnia research (Jansen et al., 2019; Kyle et al., 2017; Lane et al., 2019). Although the UK Biobank is not specifically optimized for insomnia research, cross-validation showed the available phenotype to very accurately match diagnosed insomnia patients (Hammerschlag et al., 2017).

Given the costs and artificiality of the traditional sleep laboratory, home-based easy to apply measures need to be developed, allowing repetitive CNS-based measurements in the natural environments of our patients, reaching beyond actigraphy (Debener et al., 2015; Mikkelsen et al., 2019). This would allow to study the dynamics of features reflecting the sleep drive and REM sleep characteristics longitudinally and in relation to different treatments and their outcomes in much more detail.

Given the prominence of the hyperarousal concept in almost all insomnia models, one should also start to think about developing a hyperarousal test, which at best could be applied during daytime or routine office/hospital hours. One could think about a stress/challenge paradigm, measuring autonomous nervous system activity (e.g. heart rate, galvanic skin response, etc.), cortisol as main marker of the stress response and EEG during baseline, rest and different stress conditions. One of the best accepted stress paradigms now is the Trier social stress test—its usefulness has already been tested (Chen et al., 2017). Alternatively, probably just the instruction "please try to sleep now" probably might offset a marked stress response in insomniacs. Such a psychophysiological paradigm administered during the day can also easily be coupled with neuroimaging methods, that is, functional magnetic resonance imaging. Needless to say, these data should be coupled with descriptive questionnaire data. Assuming that it will be possible to develop an easy to apply and valid hyperarousal test, this instrument could be used for phenotyping, relating the data to (epi-)genetic data, general diagnostics, differential-therapeutics and therapy outcomes. Given the emerging evidence of maladaptive sleep (Van Someren, 2021), essential insights could require repeated assessment of hyperarousal from evening to morning across recorded nights. Analyses can then address which sleep features determine the overnight fate of distress—which could range from full adaptation even to maladaptive sensitization (Wassing, Benjamins, et al., 2019; Wassing, Lakbila-Kamal, et al., 2019). Nevertheless, deeper insights into the mechanisms of hyperarousal in insomnia, its causes and consequences for cognitive processes and brain health in general are needed. This will help to further increase the value of the hyperarousal concept for insomnia research and could also help to identify a valid hyperarousal test.

Interestingly, also with therapeutics at present we have reached a unique situation concerning treatment—all presently published relevant guidelines agree that CBT-I should be the first-line treatment for insomnia. A statement like this would have caused a lot of many raised eyebrows even just 10 years ago! This development is probably because on one hand, the CBT-I literature is blooming and has generated a solid and ever-increasing evidence base, but on the other hand maybe also due to a stagnation in the sector of hypnotic development and the withdrawal of many major players in psychopharmacology from CNS-oriented Research & Development. It has to be judged in the next few years whether the worldwide introduction of orexin receptor antagonists will markedly alter the hypnotic market. From a future perspective, we would like to suggest that research into the roles of histamine and noradrenaline and sleep regulation could lead to new discoveries (Thakkar, 2011; Van Someren, 2021). Maybe also approaches encompassing non-invasive brain stimulation might complement insomnia treatment strategies (Herrero Babiloni et al., 2021).

A better understanding of the psychoneurobiological mechanisms of insomnia is urgently needed to monitor and evaluate treatment effects of CBT-I beyond subjective measures, and further develop complementary treatment strategies. First, preliminary findings suggest that 1 night of experimental sleep restriction (delaying bedtime by 2 hr) may help to stabilize restless REM sleep (Kao et al., 2021). However, it remains to be seen whether this stabilization is observed in therapeutic SRT, and whether it translates into improvements in regulation of emotional distress, hyperarousal and the risk of developing mental disorders. Second, notwithstanding the established efficacy of CBT-I, it is important to acknowledge that two out of five patients do not show full remission, even after boosting CBT-I effects with subsequent pharmacological treatment (Morin et al., 2020). We still have very limited insight into who will respond and who will not. Novel graph theory-based analyses like network outcome analysis and network intervention analysis may reveal how non-responders differ in their initial symptom profiles and trajectories of change of symptoms during the intervention (Blanken, Benjamins, et al., 2019; Blanken et al., 2020; Blanken, van der Zweerde, et al., 2019). Pinpointing such differences could provide leads to novel strategies.

Also the gradual wearing off of initial benefits of CBT-I deserves attention (van der Zweerde et al., 2019). Two recent studies indicate that beneficial effects of CBT-I may be preserved longer if CBT-I is combined with interventions aimed at supporting circadian rhythms (Dekker et al., 2020; Leerssen et al., 2021).

What we consider probably the most important challenge for the future is the integration of CBT-I into the standard treatment of patients with mental disorders, especially anxiety and depression. It is known that almost all mental disorders are afflicted with disturbances of sleep continuity (Baglioni et al., 2016), and we also know that paying proper therapeutic respect to including insomnia-related components into the overall therapeutic concept will improve outcomes in general and speed up the therapeutic process (Gee et al., 2019; Hertenstein et al., 2022; Manber et al., 2008). Models how to do this have been suggested by several authors (Kraepelien et al., 2022; Schneider et al., 2020)—thus, the times seem right to postulate insomnia as a transdiagnostic mechanism for mental disorders (Harvey et al., 2011, 2021; Van Someren, 2021) and also insomnia treatment

based on CBT-I as a basic mode in psychiatric/psychotherapeutic treatment.

One step further will address the primary prevention of mental disorders. There is a strong probability that adequate insomnia treatment will reduce the incidence and recurrence of depressive episodes and anxiety disorders (Benz et al., 2020; Cheng et al., 2019; Irwin et al., 2022; Leerssen et al., 2021). In a first step, one might address risk groups especially prone to mental illness and offer sleep treatment versus a control condition and compare longitudinal outcomes, as recently demonstrated by Leerssen et al. (2021). In a next step it might be tested whether educating and training of the general population to utilize the principles that underlie CBT-I could prevent insomnia. Such efforts may be especially relevant to prevent mental disorders that tend to surface during important transition periods, like in students moving from high school to university.

CONFLICT OF INTEREST

Dieter Riemann is a member of the Executive Board of FAVT (Freiburg Institute for Behavioural Therapy/non for profit), a salaried activity. He is Editor-in-Chief of the *Journal of Sleep Research*, which is owned by the European Sleep Research Society (non-profit body) and receives payments for this task. Dieter Riemann receives royalties from publishing and honoraria for lecturing (no pharmaceutical industry), and is funded by several grants from the German Federal state. Colin A. Espie reports research support from NIHR-HTA (UK), receiving payments from book publishing and lecture fees. He also reports being a cofounder and Chief Scientist of Big Health Ltd (the developer of Sleepio). He is a shareholder of and receiving salary from Big Health. Alasdair L. Henry is employed by, receives a salary from and is a shareholder of Big Health. All other authors report no conflicts of interest.

AUTHOR CONTRIBUTIONS

Dieter Riemann provided an outline of the article and did the final editing. All the other authors contributed equally.

DATA AVAILABILITY STATEMENT

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Review

A systematic review of socio-ecological factors contributing to risk and protection of the mental health of refugee children and adolescents

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ABSTRACT

In the past decade, millions of children and adolescents have been forced to flee from protracted or newly erupted violent conflicts. Forcibly displaced children are particularly vulnerable for developing mental health problems. However, a timely and systematic review of the current evidence is lacking. We conducted a sys- tematic review of factors contributing to the mental health of refugee children across different socio-ecological levels (individual, family, community, sociocultural). We systematically searched the databases Medline, Psy- cINFO, Web of Science, and Cochrane for English studies published in peer-reviewed journals between August 2010 and May 2020. Of the 2413 identified studies, 63 were included in the analyses. Only 24 studies were considered to be of high quality. Pre-migration individual (risk: exposure to war-related trauma, female gender) and post-migration family factors (risk: parental mental health problems and impaired parenting, protective: family cohesion) currently have the best evidence base. Post-migration community (protective: schoolconnectedness, support by peers) and sociocultural factors (risk: discrimination and acculturative stress, pro- tective: integrative acculturation) have gained some support in high-income settings. Prevention and interven- tion approaches should integrate factors across different socio-ecological levels. More longitudinal studies and research in low- and middle-income countries are needed to advance our knowledge on causal mechanisms behind factors contributing to refugee youth's mental health.

1. Introduction

According to the latest report of the United Nation High Commis-sioner for Refugees (UNHCR), the global number of people forcibly displaced by persecution, conflict and organized violence has increased from 43.3 million in 2009 up to 70.8 million in 2018 (UNHCR, 2019).This population consists of 25.9 million refugees, who fled across na- tional borders, 41.3 million internally displaced people (IDP) and 3.5 million asylum seekers (UNHCR, 2019). Within the past decade, a number of new conflicts have erupted, e.g. civil wars in Syria and South Sudan as well as the Rohingya crisis, while protracted crises such as in Afghanistan, Somalia, and the Democratic Republic of Congo continue to displace millions of people. About 85% of all refugees flee to neigh- boring countries, which are often low- and middle-income countries (LMIC) (UNHCR, 2019). In fact, the four countries hosting the largestnumbers of refugees in 2018 were Turkey, Pakistan, Uganda and Sudan (UNHCR, 2019). This means that only a small number of refugees embark on the often long journey to high-income countries (HIC), e.g. Europe, North America, and Australia. In the European Union, the highest numbers of refugees, mostly from Syria, Afghanistan and Iraq, arrived in 2015 and 2016 with about 1.3 million asylum applications in each year (Eurostat, 2020).

Children and adolescents below 18 years of age make up about half of the worldwide refugee population (UNHCR, 2019). They have to face the atrocities of conflict-related violence and the numerous hardships of flight and resettlements during crucial phases of their physical, emotional, social and cognitive development. This makes youth partic- ularly vulnerable to mental health problems following war, uprootingand flight (Reed, Fazel, Jones, Panter-Brick, & Stein, 2012). Accord- ingly, prevalence rates of up to 53% for posttraumatic stress disorder (PTSD), up to 33% for depression and up to 32% for anxiety disorders have been reported for young refugees resettled in European countries

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(Kien et al., 2019). A systematic review focusing on refugee youth living in refugee camps reports similar peak rates for depression and anxiety, and rates for PTSD of up to 87%, yet there was large variation in prevalence rates of mental health problems across studies (Vossoughi, Jackson, Gusler, & Stone, 2018). Although the prevalence of mental health problems is high in refugee children and adolescents, it is important to note that a substantial number of refugee children does not develop mental health problems and is able to adjust to the new living situation. This finding has stimulated research on the notion of resilience in war-affected children, which refers to good developmental outcomes despite exposure to significant adversity (Luthar, Cicchetti, & Becker, 2001). The identification of factors that contribute to risk and resiliencein displaced children provides the foundation for any effort to support these children's healthy development (Fazel, Reed, Panter-Brick, & Stein, 2012).

From a socio-ecological perspective (Bronfenbrenner, 1979), child development is viewed as a dynamic process arising from complex interactions between different levels of the social ecology (e. g. indi- vidual, family, school, community, society). Such a framework has been applied to conceptualize not only the stressful experiences that refugee children face, but also the protective resources they may draw on (Betancourt & Khan, 2008; Elbedour, ten Bensel, & Bastien, 1993; Reed et al., 2012).Factors contributing to risk and protection can further be classified according to their temporal occurrence within the refugee experience, i.e. pre-, peri-, and post-migration (Lustig et al., 2004). In their home countries, youth are often exposed to severe interpersonal violence. During their flight, they may experience detention, deprivation of food or separation from their guardians. In the host country, refugee children continue to face many challenges, in part depending on where they resettle. While the conditions in HIC may ensure safety from external harm and provide basic necessities, youth may struggle to cope in an often completely different society and culture. They have to learn a new language, may face discrimination by peers or encounter bureaucratic obstacles related to school and their asylum process. In LMIC, refugee children often resettle in large refugee camps with high levels of violence, bad sanitary conditions, lack of food and material resources and overcrowded housing. Inde- pendent of the specific setting, all these daily post-migration stressors
represent a significant risk for refugees` mental health and wellbeing over and above pre-migration traumatic experiences (Li, Liddell, & Nickerson, 2016; Miller & Rasmussen, 2010).

The most comprehensive systematic reviews of factors contributing to refugee children's mental health to date have been conducted by Fazel et al. (2012) for children in HIC and by Reed et al. (2012) forchildren in LMIC. Both reviews included studies that had been published before July 2010. Since then research has advanced and various studies focusing on refugee children's mental health and factors that influence psychological outcomes have been published. However, a comprehen-sive systematic review that synthesizes and evaluates the essential re- sults and implications of these studies is lacking. Several systematic and narrative reviews have been recently published, but these mostly focused on specific subpopulations, e.g. Syrian or unaccompanied refugee children (Mitra & Hodes, 2019; Mohwinkel, Nowak, Kasper, & Razum, 2018; Yaylaci, 2018), particular mental health outcomes, e.g. PTSD and depression (El Baba & Colucci, 2018; Reavell & Fazil, 2017; Tam, Houlihan, & Melendez-Torres, 2017), or specific factors, e.g. placement type (O'Higgins, Ott, & Shea, 2018) or acculturative stressors (d'Abreu, Castro-Olivo, & Ura, 2019). Other reviews adopted a broader focus (Eruyar, Huemer, & Vostanis, 2018; Hodes & Vostanis, 2018), yet did not apply systematic methods including rigorous selection criteria or evaluate the quality of included studies. In this systematic review, we systematically investigate the factors contributing to risk and protection of the mental health of refugee children and adolescents from a socio- ecological perspective.

2. Methods

2.1. Study selection

The electronic databases Medline, PsycINFO, Web of Science, and Cochrane were systematically searched for studies in English that were published in peer-reviewed journals between August 2010 and May 2020. The following search terms were used: ("asylum seeker" or "refugee" or "displaced person" or "migrant") and ("child" or "adolescent" or "young" or "minor" or "teenage" or "youth") and ("psychiatr*" or "psycholog*" or "psychosocial" or "mental" or "wellbeing" or "adaptation" or "adjustment" or "emotion" or "behaviour" or "behavior" or "trauma" or "traumatic" or "PTSD" or "posttraumatic stress" or "internalizing" or "externalizing" or "anxiety" or "depression") and ("resilience" or "protective factor" or "modifying factor" or "recovery" or "outcome" or "risk factor" or "vulnerability factor"). Moreover, reference lists of previous related reviews and key studies were manually reviewed to identify additional studies. Studies were selected based on the following inclusion and exclusion criteria, all of which had to be fulfilled:

Criterion A: The study investigated the mental health of refugee or internally displaced children in HIC or LMIC. Studies about other topics than refugee mental health, e.g. politics, general health care, physical health, or child maltreatment, were excluded.

Criterion B: The mean age of study participants was 18 years or younger. Studies with older refugees were excluded.

Criterion C: The study had a cross-sectional or longitudinal design and presented quantitative data with a minimum sample size of 50 participants. Qualitative studies were not eligible for inclusion. Simi- larly, other kinds of empirical studies, e.g. intervention or validation studies, and scientific works, e.g. reviews or commentaries, were excluded.

Criterion D: The study assessed factors contributing to refugee children's mental health. Studies reporting only prevalence rates of mental health problems without investigating potential factors of influence were excluded.

Criterion E: The majority of participants were directly exposed towar and flight. Studies with children whose parents were refugees and who were born in the host country, and studies with non-refugee sam- ples such as immigrants or non-displaced children in conflict zones were excluded.

Criterion F: The study applied a statistical analysis that theoretically allowed for the control of potentially confounding factors, e.g. age, gender and time since displacement, on refugee children's mental health, e. g. (M)ANCOVA, regression analysis or structural equation modeling. However, studies were not required to actually control for potentially confounding variables. Studies using only bivariate correlational analyses or simple group comparisons to draw inferences about contributing factors were excluded.

After the removal of duplicates, the titles and abstracts of the remaining articles were screened for eligibility according to these criteria in a hierarchical manner from criteria A to E. Most studies were excluded for several reasons, but were attributed to the category of the highest unmet criterion. Fig. 1 graphically displays the study selection process.

The large variability and lack of consistency across studies in terms of research designs, study samples, relationships and outcomes assessed, all of which have been shown to be influential confounds in research on refugee children's mental health (Fazel et al., 2012; Kien et al., 2019; Vossoughi et al., 2018), precluded a meta-analysis of the data. However, as we aimed to provide a comprehensive overview of the recent developments in research on refugee children's mental health, we adopted a broad focus and did not pose limits on certain factors, samples or outcomes. Therefore, we opted for a detailed narrative synthesis of the included studies.

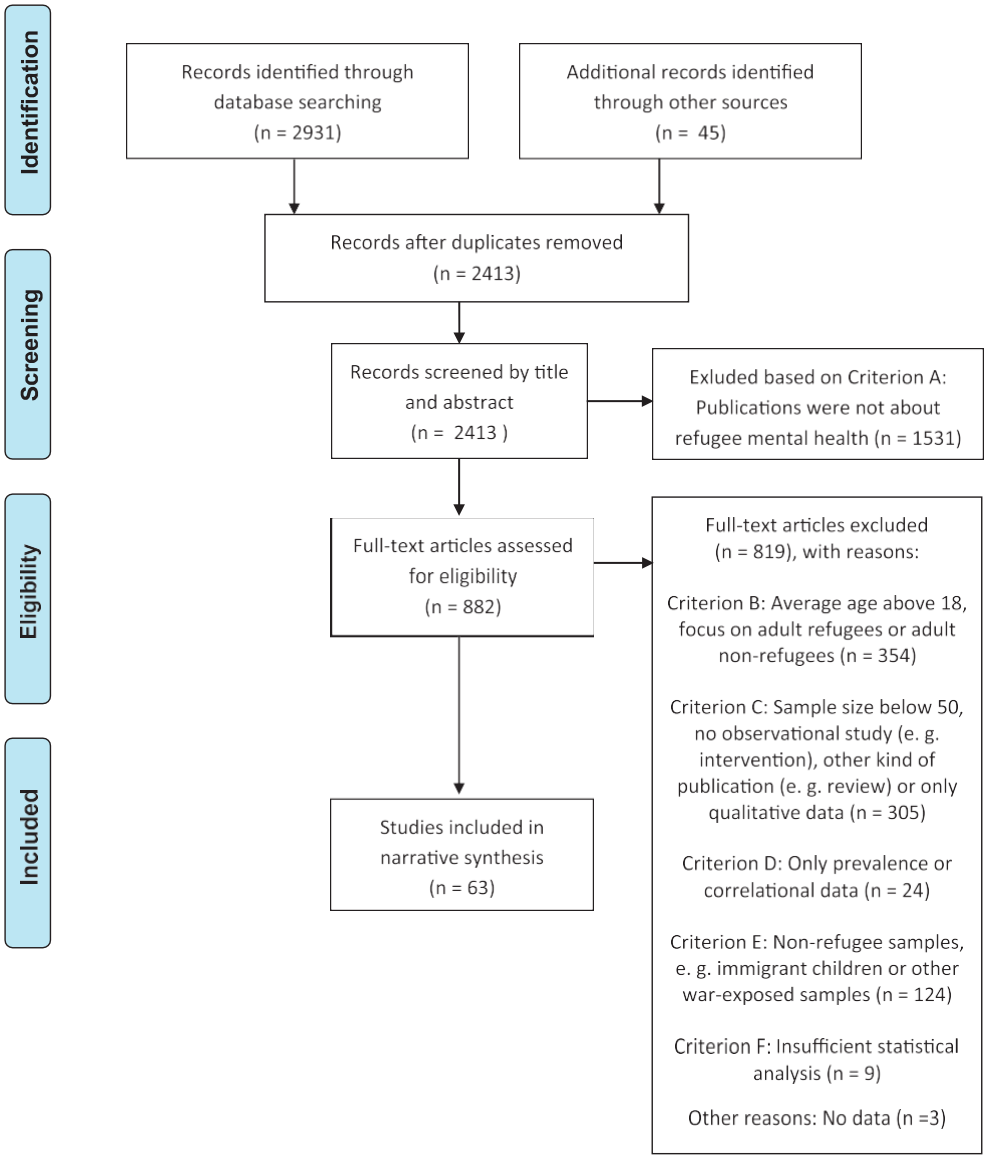

Fig. 1. Flow diagram of the study selection process. Template from Moher, Liberati, Tetzlaff, and Altman (2009).

2.2. Quality appraisal

We used the Systematic Assessment of Quality in Observational Research (SAQOR) system to evaluate the quality of the studies to be included in the systematic review. SAQOR was developed to assess the quality of observational studies in the field of psychiatry within six domains: sample, control/comparison group, quality of exposure/outcome measures, follow-up, distorting influences and reporting domains (Ross et al., 2011). Each domain is further broken down into sub-criteria, for instance the 'sample' domain includes the criteria representativeness of the population, clearly stated source of sample, explicitly stated sampling method, sample size/power calculation and inclusion/exclusion criteria. The presence of each criterion is rated as 'yes' (satisfied), 'no' (not satisfied), 'unclear' or 'not applicable'. The entire domain is evaluated as 'adequate` if a minimum of 3 out of 5 criteria are fulfilled or otherwise as 'inadequate'. A final quality level (high, moderate, low) is determined based on the assessments of the six domains.

To increase the flexibility and sensitivity of the rating system with regard to the specific type of study, we adapted SAQOR according to its use by Betancourt et al. (2013) in their systematic review on the psychosocial adjustment and mental health in former child soldiers: the 'control/comparison group' domain was only considered for those studies that actually included such a group and the 'follow-up' domain was only required for longitudinal studies. Given certain methodological and practical challenges inherent to research with conflict-affected populations in often unstable settings we considered the criterion 'representativeness' within the sample domain met if a randomized sample was chosen from a base population across multiple sources (i.e. refugee camps, schools). Following Betancourt et al. (2013), the qualityof longitudinal studies was rated 'high' if at least four out of five (without comparison group) or five out of six domains (with comparison group) were rated as adequate; for observational studies, at least three out of four (without comparison group) and four out of five (with comparison group) adequate domains were required for a rating of 'high' quality. 'Moderate' quality was assigned to longitudinal and observational studies with two (without comparison group) or three adequate domains (with comparisnon group). Longitudinal studies rated inadequate in four or more domains and observational studies rated inadequate in three or more domains were considered 'low' quality. Two of the authors independently conducted the quality ratings.

3. Results

3.1. Characteristics of the included studies

Out of the 63 selected studies, 41 were conducted in HIC and 22 were conducted in LMIC according to the World Bank classification (World Bank, 2019). The refugee children came from 53 different countries: Africa (21 countries), Asia (17), Middle and South America (10) and Eastern Europe (5). The most frequent countries of origin were Syria, Iraq, Afghanistan, Iran, Burma, Somalia, South Sudan, and Eritrea. In total, 15 studies included unaccompanied refugee minors (URM). Themajority of studies had a cross-sectional one-group design, 7 cross- sectional studies included a comparison group and 12 studies had a longitudinal one-group design. Table 1 shows a detailed description ofthe included studies.

3.2. Results of quality appraisal

Of the 63 studies, 13 were rated as 'low' quality, 26 as 'moderate' quality, and 24 as 'high' quality. The two independent raters agreed in the overall rating of 42 studies and resolved disagreements in the other 21 studies through discussions. Studies deemed 'low' quality were retained in the systematic review in order to provide a comprehensive and unbiased view of the evidence base. The results of the quality appraisal are displayed in detail in Supplementary Tables A1-A3.

3.3. Study findings

The findings are structured according to the different levels of the socio-ecological framework (individual, family, community, society and culture), similar to previous systematic reviews (Fazel et al., 2012; Reed et al., 2012) The findings of the individual studies are displayed in SupplementaryTable B.

3.4. Individual level

3.4.1. Exposure to trauma

About half of the studies (n 31) investigated the association be- tween pre-migration exposure to war-related traumatic events and children's mental health. Cumulative exposure to traumatic events was related to higher levels of mental health problems, including PTSD, depression, anxiety, and externalizing problems in most studies (e. g. Bronstein, Montgomery, & Dobrowolski, 2012; Jensen, Skar, Andersson,& Birkeland, 2019; Lincoln, Lazarevic, White, & Ellis, 2016; Müller, Büter, Rosner, & Unterhitzenberger, 2019; Vervliet et al., 2014). A few studies looked at singular traumatic events and found that particularly those involving severe interpersonal violence (Nasıroğlu, Çeri, Erkork- maz, & Semerci, 2018; Sapmaz et al., 2017) and family members as victims (Çeri & Nasıroğlu, 2018; Gormez et al., 2018) were associated with worse mental health outcomes. Studies that did not report a consistent association between traumatic exposure and psychopathol- ogy often indexed trauma exposure by single items or trauma types (Beiser & Hou, 2016; Flink et al., 2013; Nasıroğlu & Çeri, 2016; Oppedal & Idsoe, 2012). Longitudinal studies with URM indicated that pre- migration trauma continued to impact their mental health years after arrival in the host country (Jensen et al., 2019; Keles, Friborg, Idsøe,Sirin, & Oppedal, 2016b; Vervliet, Lammertyn, Broekaert, & Derluyn, 2014). The role of post-migration trauma has only been assessed in two studies: Trauma exposure after arrival was not associated with mental health problems in one study (Jensen et al., 2019), whereas an increasein stressful life events after arrival predicted an increase in PTSD symptoms in another study (Jensen, Skårdalsmo, & Fjermestad, 2014). However, as the authors of the latter study note, events classified asoccurring after arrival may have included pre-migration events that were not recalled or reported before.

3.4.2. Physical, psychological or developmental disorders

There has been scant investigation of the impact of pre-existing health and developmental conditions on refugee children's mentalhealth. In a study with Syrian refugee children, the effect of war expo- sure on PTSD was strongest for highly sensitive children with low levels of childhood adversities, whereas sensitivity did not moderate the effect of war on PTSD for children with high childhood adversities (Karam et al., 2019). Variants of the monoamine oxidase A (MAOA) gene in Syrian boys were associated with decreases in psychosocial distress over time (Clukay et al., 2019). This link was most pronounced in childrenwith either low trauma exposure or high resilience. Children's poorer physical health as rated by parents was related to more emotional and behavioral problems (Lau et al., 2018), while children with a positive history of a psychiatric disorder were more likely to receive a psychiatric diagnosis than children with a negative history (Sapmaz et al., 2017). Longitudinal studies suggest that refugee minors' depressive symptoms represent a risk factor for the development of later PTSD symptoms (Müller et al., 2019; Smid, Lensvelt-Mulders, Knipscheer, Gersons, & Kleber, 2011).

3.4.3. Time since displacement

Evidence on the association between length of stay in the host country and mental health is inconsistent. Seven studies, six of which were conducted in HIC, found that longer duration of time spent in the host country was related to lower levels of mental health problems and higher well-being (Correa-Velez, Gifford, & Barnett, 2010; Goosen, Stronks, & Kunst, 2014; Khamis, 2019; Lincoln et al., 2016; Müller, Gossmann, et al., 2019; Oppedal & Idsoe, 2012, 2015). A recent longi- tudinal study reported an amelioration of PTSD, depression and anxiety symptoms from baseline to follow-up assessment 1 year later (Müller, Gossmann, et al., 2019). Other longitudinal studies with URM provide evidence for a chronic trajectory of mental health problems (Jakobsen, DeMott, Wentzel-Larsen, & Heir, 2017; Jensen et al., 2019, 2014; Keleset al., 2016b; Vervliet, Lammertyn, et al., 2014). Two studies conductedin refugee camps suggest that an increased length of stay in camp set- tings was associated with exacerbated mental health problems (Braun- Lewensohn & Al-Sayed, 2018; Nasıroğlu et al., 2018).

3.4.4. Age and gender

The findings regarding age are inconsistent. The evidence is largely based on studies with older children and adolescents above 11 years of age and there is very limited information on young and middle childhood. In studies including adolescents until the age of 18, youth aged 16 and older had higher levels of internalizing problems (Braun-Lewensohn & Al-Sayed, 2018; Meyer, Yu, et al., 2017; Smid et al., 2011). Older URM were also more likely to develop late-onset PTSD (Smid et al., 2011), probably due to their higher exposure to traumatic experiences, an association also found in a number of other studies (Eruyar, Maltby, & Vostanis, 2018; Müller, Büter, et al., 2019; Oppedal & Idsoe, 2015). In a sample of refugee youth ranging from 13 to 27 years of age (mean 18.9), older age was related directly to fewer conduct problems, but indirectly to more depressive symptoms through less host culture competence and more outgroup hassles (Oppedal & Idsoe, 2012). Children who arrived in the Netherlands at an older age, i.e., between 4 and 11 or between 12 and 17 rather than in the first three years of life, had an increased risk of mental distress as recorded by asylum health services (Goosen et al., 2014). A study with repatriated adolescents between 11 and 18 years found that, for children who had a residence permit in the host country, peer problems decreased with age, whereas the opposite was true for children without a residence permit in the host country (Zevulun, Post, Zijlstra, Kalverboer, & Knorth, 2018). Notwithstanding, other studies with predominantly adolescent samples found that older age was a protective factor for internalizing problems (Ahmad, Smetana, & Klimstra, 2015; Lau et al., 2018; Park, Lee, & Jeon, 2017) and a substantial number of studies did not find associations between youth's age and mental health outcomes (Betancourt et al., 2012; Buchanan, Abu-Rayya,

Table 1
Description of included studies.

Authors (year)	Study site	Study population	Age in years (mean)	Domain assessed Socio-ecological/Temporal	Measurements
Ahmad et al. (2015)	Jordan	491 Palestinian refugee youth in a refugee camp	14–17 (15)	Individual, family/pre- and peri-migration	Adapted measures of maternal control, knowledge, solicitation, parent-child relationship and norm-breaking, family climate and secretiveness with mothers, SCARED
Beiser and Hou (2016)	Canada	152 refugee and 326 immigrant mother-child-dyads	11–13	Individual, family, community, society/ pre-, peri- and post-migration	Self-developed and adapted scales for emotional problems, aggressive behavior and other study variables
Beni Yonis et al. (2019)	Jordan	1773 Syrian refugee adolescents	12–18 (14.5)	Individual, family, society/pre- and peri-migration	Culturally adapted version of CPSS
Betancourt, Salhi, et al. (2012)	Ethiopia	Caregiver-child dyads in a refugee camp (T1: 168 adolescents, 162 caregivers T2: 153 adolescents, 152 caregivers)	11–18	Family, community/ peri-migration	Adapted version of YSR and CBCL, HSCL-25, multidimensional scale of perceived social support, self-developed items
Betancourt, Yudron, et al. (2012)	Russia	183 internally displaced Chechen youth	10–17 (13.6)	Individual, family, community, society/ pre- and peri-migration	YSR, adapted school connectedness scale, self-devised questions
Braun-Lewensohn and Al-Sayed (2018)	Unspecified refugee camp in Europe	110 Syrian refugee adolescents	12–18 (15.5)	Individual, family, community, society/ pre- and peri-migration	YSR, SOC, self-developed scales for other study variables
Bronstein et al. (2012) Bronstein et al. (2013)	UK	222 male Afghan URM	13–18 (16.3)	Individual, society/ pre- and post-migration	SLE, RATS, categorial indicators for asylum and care status SLE, HSCL-37A
Bryant et al. (2018)	Australia	394 refugee caregivers of 639 children	5–18 (12)	Family, society/pre- and post-migration	HTQ, PTSD-8, SDQ parent report, Postmigration Stressor Index (self-developed), warmth scale of Child Rearing Questionnaire, hostility scale of Early Chilhood Longitudinal Study of Children
Buchanan et al. (2018)	Australia	106 refugee youth and 223 non-refugee immigrant youth	Refugees: 13–21 (16.8) Immigrants: 13–18 (15.4)	Indidvidual, society/ pre- and post-migration	RSES, adapted scales for school adjustment, perceived discrimination and language proficiency
Çeri & Nasıroğlu (2018)	Turkey	77 Syrian refugee minors	7–17 (12.1)	Individual, family/pre- and post-migration	SDQ parent-report, self-devised questions for other study variables
Clukay et al. (2019)	Jordan	Syrian refugee youth in urban centers (T1: 399. T2: 263, T3: 157)	12–18 (14.3)	Individual/pre-migration	TEC, PSS, Human Distress and Human Insecurity, AYMH, SDQ, CRIES-8, CYRM, genetic analysis
Correa-Velez et al. (2010) Correa-Velez et al. (2015)	Australia	97 Refugee youth from 11 different countries (Wave 1) Wave 1: 120 Wave 5: 51	11–19 (15.1) Wave 5: 18–27 (22.8)	Individual, family, community, society/ pre- and post-migration	Subjective well-being measure (WHOQOL-BREF), adapted scales for other study measures, purposive-built items for subjective health and happiness, RSES
Elklit et al. (2012)	Denmark	119 Bosnian refugee youth	15–27 (18.5)	Individual, community/pre-, peri- and post-migration	HTQ, CSQ, CSS
Eruyar et al. (2018) Eruyar et al. (2020)	Turkey	263 Syrian child-parent dyads 322 Syrian refugee children	8–18 (11.6)	Individual, family/pre- and post-migration	SDQ parent- and self-report, GHQ-12, PSI, SLE, CRIES-8 CRIES-8, SDQ, Security Scale, Egna Minnen Betraffande Uppfostran for Children
Flink et al. (2013)	Colombia	Primary caretakers of 279 internally displaced and non-displaced children	2–6 (4.2)	Individual, family, community/pre- and post-migration	CBCL, GHQ-12, K-SADS-PL PTSD traumatic event checklist, general functioning scale of family assessment device (FAD), categorical indicator of social support
Giordano et al. (2019)	Italy	271 Syrian and Palestinian children in transit to Northern Europe	6–14 (10)	Individual (trauma exposure)/pre-migration	CWTQ, PTSRC, SDQ parent report, CYRM-28
Goosen et al. (2014)	Nether-lands	8047 accompanied asylum-seeking children	4–17	Individual, family, society/pre-, peri- and post-migration	Electronic database indicators, International Classification of Primary Care codes

Gormez et al. (2018)	Turkey	218 Syrian refugee children	9–15 (12)	Individual, society/ pre- and post-migration	Self-developed tool for traumatic events, UCLA-PTSD-RI, SCAS, SDQ
Jakobsen et al. (2017)	Norway	Male URM from Afghanistan, Somalia, Algeria and Iran (T1: 138, T2: 101, T3: 84, T4: 69)	14–20 (15.22)	Individual, family, society/pre- and post-migration	HSCL-25, SLE, HTQ
Javanbakht et al. (2018)	USA	53 Syrian refugee families (mostly with 2 parents) with 131 children	6–17 (11)	Family/post-migration	UCLA-PTSD-RI, SCARED, PCL-C, HSCL-25
Jensen et al. (2014)	Norway	URM (T1: 93, T2: 75)	T1: 13.8	Individual, family,	HSCL-37A, CPSS, SLE, Self-developed check
Jensen et al. (2019)		(T1: 95, T2: 78, T3: 47)	T2: 16.5 T3: 20.0	community, society/ pre- and post-migration	list for postmigration trauma, DSSYR, FSSQ
Karam et al. (2019)	Lebanon	549 Syrian refugee children and adolescents	7–17 (11.9)	Individual/pre-migration	UCLA-PTSD-RI, self-developed war exposure checklist, ISPCAN Child Abuse Screening Tool,

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Table 1 (*continued*)

Authors (year)	Study site	Study population	Age in years (mean)	Domain assessed Socio-ecological/Temporal	Measurements
					self-developed list of childhood adversities, Highly Sensitive Child Questionnaire
Keles, Friborg, Idsøe,	Norway	895 URM with a permanent	18.6	Individual,	CES-D, YCC Hassles Battery, self-developed
Sirin, and Oppedal (2016a, 2016b)		residence permit (T1: 918, T2: 580, T3: 229)	18.8–19.17	community, society/ pre- and post-migration	scales for host and heritage culture competence, self-developed pre-migration trauma checklist
Khamis (2019)	Lebanon, Jordan	1000 Syrian refugee children	7–18 (11.30)	Individual, family, community, society/ pre- and post-migration	Trauma Exposure Scale, structured clinical interview for PTSD DSM-IV Criteria, DERS-SF, KidCope, Family Environment Scale, School Environment Scale
Khawaja et al. (2017)	Australia	221 refugee and immigrant youth (55.8% refugees)	11–18 (14.9)	Individual, community, society/ post-migration	SCWBS, Acculturation and Resilience Scale, Psychological Sense of School Membership, Support Functions Scale
Kim et al. (2015)	South Korea	144 North Korean refugee youth	13–21 (18.2)	Individual, society/ pre- and post-migration	HSCL-25, UCLA PTSD-RI DSM-IV, ASC, self-developed Ego Resiliency Scale
Lau et al. (2018)	Australia	426 caregivers of 694 refugee children and adolescents	5–17	Individual, family, community/pre-, peri- and post-migration	SDQ-parent and child versions, self-developed items for study variables in individual, family, school and community domains
Lee et al. (2020)	South Korea	157 North Korean refugee youth	13–26 (18.7)	Individual, family/pre- and post-migration	ACE questionnaire, ERQ, CES-D, Conners-Wells Adolescent Self-Report Scale-Short Form
Lincoln et al. (2016)	USA	135 Somali adolescent refugees	11–20 (15.4)	Individual, society/ pre- and post-migration	Behavioral Acculturation Scale from LIB, Family Hassles Subscale of Acculturative Hassles Inventory, WTSS, UCLA-PTSD-RI, DSRS
Mace, Mulheron, Jones, and Cherian (2014)	Australia	332 refugee children reviewed by a health service	4–17 (9.58)	Family, society/pre- and peri-migration	Revised health-screening questionnaire for new patients at the Refugee Health Service
MacLean et al. (2019)	USA	425 immigrant children held at US detention centers and their mothers (UCLA self-report data for 150 children)	4–17 UCLA data: 13.4	Family/peri-migration	SDQ parent report, UCLA-PTSD-RI
McGregor et al. (2015)	Australia	50 resettled refugee youth from 16 different countries	12–21 (16.6)	Individual, family/pre- and peri-migration	CPSS, CCSC, YES-R
Meyer, Steinhaus, Bangirana, Onyango-Mangen, and Stark (2017) Meyer, Yu, Rieders, and Stark (2020)	Uganda	463/470 South Sudanese caregiver-adolescent dyads in two camps	13–17 (14.6)	Individual, family, society/pre- and peri-migration	IPSCAN Child Abuse Screening, SCARED, MFQ-C, HSCL-25, purposive-built questions for socioeconomic status and child labour
Meyer, Yu, Hermosilla, and Stark (2017)	Rwanda, Uganda	129 Congolese and 471 South Sudanese refugee adolescents in three camps	13–17	Individual, family/pre- and peri-migration	SCARED, MFQ-C, SDQ
Müller, Büter, et al.	Germany	30 Accompanied and 68	16.3	Individual, family,	CATS, HSCL-37A, ERSS
(2019) Müller, Gossmann, et al. (2019)		unaccompanied refugee minors 1-year-follow-up (T2: 72)	17.3	society/pre-. peri- and postmigration	
Nasıroğlu & Çeri (2016) Nasıroğlu et al. (2018)	Turkey	55 Yazidi refugee children and their parents (46 families) 136 Yazidi refugee children	6–17 (11)	Individual, family/pre- and peri-migration	K-SADSPL-T
Oppedal and Idsoe	Norway	566 URM	13–27 (18.9)	Individual, family,	Adapted scales for conduct problems, CES-D,
(2012) Oppedal and Idsoe (2015)		895 URM	18.6	community, society/ pre- and post-migration	purposive-built items for impact of war-related trauma, acculturation hassles, perceived discrimination and social support, Host and Heritage Culture Competence Scale for Adolescents

Oppedal et al. (2018)	Turkey	285 Syrian children in a refugee camp	12.5	Individual, family, community/pre- and post-migration	CDI, SLE, Social Provisions Scale
Park et al. (2017)	South Korea	136 North Korean adolescent refugees	12–24 (18.5)	Individual, family, community/pre- and postmigration	CDI, AUDIT, CRIES, Aggression Questionnaire, BRS, purposive-built questions for social support
Park et al. (2019)	South Korea	North Korean adolescent refugees (T1: 174, T2 (1-year-follow-up): 108	13–26 (17.8)	Individual, family, community/pre- and post-migration	CES-D, ERQ, RSES, BRS, purposive-built questions for social support
Samara et al. (2019)	UK	149 refugee children and 120 non-refugee British-born children	6–16	Family, community/ post-migration	Satisfaction with Life Scale, CPSS, Coopersmith Self-Esteem Inventory, Cambridge Hormones and Moods Friendship Questionnaire, Popularity Questionnaire, self-developed scale for bullying and victimization, SDQ parent (below 11) and child versions, Psychosomatic and Health Questionnaire
Sapmaz et al. (2017)	Turkey	89 refugee children	5–18 (10)	Individual, family/pre- and post-migration	K-SADSPL-T, SDQ parent (over 11) and child versions
Sierau et al. (2018)	Germany		14–19 (17.3)		MSSI, PCL-5, PHQ-9, GAD-7, SSS-8, SDQ

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Table 1 (*continued*)

Authors (year)	Study site	Study population	Age in years (mean)	Domain assessed Socio-ecological/Temporal	Measurements
		105 male URM living in group homes		Individual, family, community/pre- and post-migration	
Sim et al. (2018)	Lebanon	291 Syrian refugee children's mothers	2–12 (7.4)	Family/post-migration	TEC, HESPER, PCL–C, DASS, PARQ, Discipline Module of UNICEF's Multiple Indicator Cluster Survey, SDQ
Sleijpen, van der Aa, Mooren, Laban, and Kleber (2019)	Nether-lands	117 refugee adolescents and 138 Dutch peers	12–17 (14.3)	Individual/pre- and postmigration	CRIES, SDQ, Satisfaction with Life, Resilience Scale
Smetana and Ahmad (2018)	Jordan	277 Iraqi, 275 Syrian and 331 Palestinian refugee youth	15.01	Individual, Family/pre- and post-migration	Adapted measures of adolescents` war exposure and norm-breaking, mothers` and fathers` support, knowledge, behavioral and psychological control, harsh punishment, BSI-18
Smid et al. (2011)	Nether-lands	URM (T1: 920, T2: 582)	11–17.5	Individual, society/ pre- and post-migration	HSCL-25, SLE, RATS
Tozer et al., 2018)	Australia	93 refugee students at a special English language school	12–18 (15.5)	Individual, community, society/ pre- and post-migration	HSCL-25, SCWBS, PSSM, AARS, R-MATS
Vervliet, Lammertyn, et al. (2014)	Norway, Belgium	307 URM (risk factor analysis only for the 291 males)	14–18 (16.1)	Individual, family/pre-migration	HSCL-37A, SLE; RATS, HTQ
Vervliet, Meyer Demott, et al. (2014)	Belgium	URM (T1: 103, T2: 79, T3: 77)	16.0 at T3	Individual, family, community, society/ pre- and post-migration	HSCL-37A, SLE, RATS, DSSYR
Wiegersma et al. (2011)	Nether-lands	297 asylum-seeking children in reception centers	4–16 (9.9)	Individual, family, society/pre-. peri- and post-migration	SDQ parent, child and teacher versions, medical files
Zevulun et al. (2018)	Kosovo, Albania	106 repatriated asylum-seeking children	11–18 (14.4)	Individual, family, community, society/ post-migration	BIC-Q, SDQ child report
Zwi et al. (2018)	Australia	Asylum-seeking children in detention (48) and in community (38)	4–15 (8.4)	Society /peri-migration	SDQ parent-version

Note: Studies that are based on largely the same sample are listed in one row, URM, unaccompanied refugee minors. Instruments: AARS, Adult Acculturation and Resiliency Scale; ACE, Adverse Childhood Experiences; ASC, Acculturation Stress Scale; AUDIT, Alcohol Use Disorders Identification Test; AYMH, Arab Youth Mental Health Scale; BIC-Q, Best Interests of the Child-Questionnaire; BSI-18, Brief Symptom Inventory; CATS, Child and Adolescent Trauma Screen; CBCL, Child Behavior Checklist; CCSC, Children's Coping Strategies Checklist–Revision 1; CRIES, Children's Revised Impact of Events Scale; CPSS, Child Posttraumatic Stress Disorder Symptom Scale; CYRM, Child and Youth Resilience Measure; CDI, Children's Depression Inventory; CES-D, Center for Epidemiologic Studies Depression Scale for adolescents; CSQ, Coping Style Questionnaire; CSS, Crisis Support Scale; CSSI-8, Children's Somatization Inventory Short form; CWTQ, Childhood War Trauma Questionnaire; DASS, Depression Anxiety and Stress Scale; DSRS, Depression Self-Rating Scale; DSSYR, Daily Stressors Scale for Young Refugees; DERS-SF, Emotion Regulation Scale Short Form; ERSS, Everyday Resources and Stressors Scale; FSSQ, Duke-UNC Functional Social Support Questionnaire; GAD-7, Generalized Anxiety Disorder Scale; GHQ-12, General Health Questionnaire 12-item; HESPER, Humanitarian Emergency Settings Perceived Needs Scale; HSCL-25/37A, Hopkins Symptom Checklist; HTQ, Harvard Trauma Questionnaire; K-SADS-PL(—T), Kiddie Schedule for Affective Disorders and Schizophrenia - Present and Lifetime Version (—Turkish); LIB, Language, Identity and Behavioral Acculturation Scale; MFQ-C, Mood and Feelings Questionnaire Child Self Report; MSSI, Multi- Sector Social Support Inventory; PARQ, Parental Acceptance Rejection Questionnaire; PCL-5/C, PTSD Checklist (Civilian); PHQ-9, Patient Health Questionnaire; PSI, Parenting Stress Index; PSS, Perceived Stress Scale; PSSM, Psychological Sense of School Membership; PTSD-8, Post-Traumatic Stress Disorder–8 items; PTSRC, Post-Traumatic Stress Reaction Checklist – Child Version; RATS, Reactions of Adolescents to Traumatic Stress; R-MATS, Resilience Questionnaire for Middle-Adolescents in Township Schools; RSES, Rosenberg Self-Esteem Scale; SCARED, Screen for Child Anxiety Related Emotional Disorders; SCAS, Spence Children's Anxiety Scale; SCWBS, Stirling Children's Well-being Scale; SDQ, Strength and Difficulties Questionnaire; SLE, Stressful Life Events Questionnaire; SOC, Sense of Coherence Scale; SSS-8, Somatic Symptoms Scale; TEC, Traumatic Events Checklist of HTQ; UCLA-PTSD-RI, University of California at Los Angeles Posttraumatic Stress Disorder Reaction Index; WTSS, War Trauma Screening Scale; WHOQOL-BREF, World Health Organization Quality of Life-Bref, YCC, Youth, Culture and Competence Study Hassles Battery; YES-R, Youth Expe- rience Scale for Refugees; YSR, Youth Self-Report.

Kashima, Paxton, & Sam, 2018; Giordano, Cipolla, Ragnoli, & Bruno, 2019; Jensen et al., 2019; Tozer, Khawaja, & Schweitzer, 2018; Vervliet, Meyer Demott, et al., 2014).

The evidence for gender differences yields a more consistent picture. Eleven studies found that girls were at a higher risk of internalizing problems than boys (e. g. Ahmad et al., 2015; Betancourt, Salhi, et al., 2012; Çeri & Nasıroğlu, 2018; Keles et al., 2016b; Meyer, Steinhaus, Bangirana, Onyango-Mangen, & Stark, 2017; Oppedal & Idsoe, 2015). Girls were also more likely to have higher levels of PTSD symptoms in a number of studies (Beni Yonis et al., 2019; Braun-Lewensohn & Al-Sayed, 2018; Elklit, Ostergard Kjaer, Lasgaard, & Palic, 2012; Jensen et

al., 2019). Six studies found no differences between girls and boys regarding PTSD (Giordano et al., 2019; Karam et al., 2019; Khamis, 2019) and other mental health problems (Lau et al., 2018; Samara, El Asam, Khadaroo, & Hammuda, 2019; Tozer et al., 2018). One study found male gender to be associated with a higher PTSD risk (Gormez et al., 2018). Three studies corroborate evidence that boys are at an increased risk for externalizing problems (Çeri & Nasıroğlu, 2018; Eruyar, Maltby, & Vostanis, 2020; Oppedal & Idsoe, 2012). There is also some evidence for an interaction of age and gender. In pre-pubertal children, boys had a higher risk for mental health problems than girls, whereas in adolescents, girls were at a higher risk (Goosen et al., 2014; Wiegersma, Stellinga-Boelen, & Reijneveld, 2011). In a study with Syrian children in a Turkish camp, gender differences in depression were observed only in children 13 or older, which was attributable to significantly lower levels of depression in older compared to younger

boys (Oppedal, Özer, & Şirin, 2018).

3.4.5. Education and academic performance

A longer period of schooling was associated with fewer PTSD symptoms (Müller, Büter, et al., 2019) and fewer self- and parent-rated emotional and behavioral problems (Wiegersma et al., 2011). A higher educational level of South Sudanese adolescents in a Ugandan camp was associated with fewer anxiety symptoms (Meyer, Yu, et al., 2017). Mi- nors reporting 3 or fewer years of education were significantly morelikely to develop late-onset PTSD in a longitudinal study (Smid et al.,2011). Two Australian studies found that better self-perceived (Correa- Velez et al., 2010) and parent-reported school performance (Lau et al., 2018) were linked to higher psychological wellbeing and fewer emotional and behavioral problems respectively. In an Australian study (Tozer et al., 2018), fewer years of schooling prior to arrival was asso- ciated with higher levels of depression in bivariate, but not multivariate, analysis and in a longitudinal study education level did not predict PTSD symptoms and other mental health problems (Jensen et al., 2014).

3.4.6. Personal resources

Mental health and well-being are likely to be influenced by the way refugee children cope in the aftermath of war and flight. A study with Syrian children who resettled in Jordan and Lebanon found that coping through acquiring social support and trying to think differently about events was associated with fewer PTSD symptoms (Khamis, 2019), while a higher use of the emotion regulation strategy of cognitive reappraisal differentiated North Korean youth with consistently low levels of depressive symptom from those whose depressive symptoms deterio- rated over a one year period (Park, Kim, Lee, & Jun, 2019). However, greater use of problem-focused coping strategies was related to PTSD in Bosnian adolescents who were waiting for their asylum decisions (Elklit et al., 2012), which suggests that engaging too much with problems and circumstances that cannot be actively changed may increase youth's psychological symptoms. On the other hand, avoiding the engagement with problems and distressing emotions through behavioral and cogni- tive efforts has also been found to be associated with the presence of PTSD (Elklit et al., 2012; Khamis, 2019) and higher levels of depressive symptoms (Lee, Lee, Jun, & Park, 2020; Park et al., 2019). However, the association between avoidant coping and PTSD disappeared when controlling for the avoidance symptoms related to PTSD in one study (McGregor, Melvin, & Newman, 2015). Children's appraisals of their life circumstances and their future appear to be important as well. A higher sense of coherence, a personal resource reflecting individuals` ability to cope with and make meaning of adverse events, was associated withlower levels of PTSD symptoms, internalizing and externalizing prob- lems (Braun-Lewensohn & Al-Sayed, 2018). In the same study, higher hopeful expectations for the future were related to children's fewer externalizing problems, whereas future-oriented wishes were not linked to mental health outcomes. Youth experiencing more control over their life also reported higher levels of psychological and physical well-being (Correa-Velez et al., 2010). Other more practical personal resources, such as physical activity (Lau et al., 2018) as well as instrumental and social competence (Beiser & Hou, 2016) were not associated with ado- lescents` emotional and behavioral problems.

A number of studies investigated the role of protective personal re- sources using different conceptualizations of resilience. Lower resilience conceptualized as an individual's perceived ability to bounce back from stress was related to higher levels of depression in North-Korean youth in two cross-sectional (Kim, Cho, & Kim, 2015; Park et al., 2017) and one longitudinal study (Park et al., 2019) and influenced whether a longer stay as an asylum seeker was associated with more or fewer emotional problems (Sleijpen, van der Aa, Mooren, Laban, & Kleber, 2019). Higher levels of resilience viewed as a set of interpersonal and intrapersonal strengths were related to higher levels of well-being (Khawaja, Ibrahim, & Schweitzer, 2017; Tozer et al., 2018), while resilience assessed as protective factors on different socio-ecological levels predicted reductions in Syrian children's psychosocial stress over time (Clukay et al., 2019).

3.5. Family level

3.5.1. Family composition

Youth who were separated from immediate family members had higher levels of PTSD symptoms than youth who stayed in Australia with all their immediate family members (McGregor et al., 2015). Both pre- vious and current separation from the nuclear family was associated with a diagnosis of PTSD (Mace, Mulheron, Jones, & Cherian, 2014). Children in an US detention center who had been separated from their mothers had higher levels of mother-rated emotional and behavioral problems compared to children who had not been separated from their mothers (MacLean et al., 2019). Having left one parent behind in the country of origin was associated with more self- and teacher-reported emotional and behavioral problems in a Dutch study (Wiegersmaet al., 2011). The only study comparing unaccompanied and accompa- nied youth found that being unaccompanied was associated with a higher exposure to traumatic events and with more externalizingproblems (Müller, Büter, et al., 2019). Although the integrity of the whole family unit appears to be crucial, other findings indicate that the presence of at least one biological parent is already protective (Correa- Velez et al., 2010; Lau et al., 2018; Meyer, Steinhaus, et al., 2017).

Evidence regarding the role of parental loss is inconsistent. In two studies in LMIC, adolescents who had lost one or both parents were more likely to have PTSD (Beni Yonis et al., 2019) and higher levels of internalizing problems (Meyer, Yu, et al., 2017). In a study with URM shortly after their arrival in Belgium and Norway, the death of one or both parents was not associated with mental health outcomes (Vervliet, Meyer Demott, et al., 2014). Household size did not seem to be associ- ated with mental health problems in two studies (Beni Yonis et al., 2019; Meyer, Yu, et al., 2017), but a smaller family size was associated with more parent- and teacher-rated emotional and behavioral problems of adolescents resettled in the Netherlands (Wiegersma et al., 2011).

3.5.2. Family functioning and parental mental health

A more positive, i.e. warm and stable, family climate was associated with lower levels of anxiety for Palestinian adolescents living in refugee camps in Jordan (Ahmad et al., 2015). Higher connectedness, i.e. perceived understanding, care and respect, by the family predicted lower levels of internalizing problems in displaced Chechen youth, particularly in boys (Betancourt, Salhi, et al., 2012). A family environ- ment that encouraged the direct expression of emotions was related to a decreased risk for PTSD in Syrian children (Khamis, 2019).

Supporting evidence for the role of refugee parents` wellbeing for their children's mental health has been found by 10 studies in both HIC and LMIC (e. g. Beiser & Hou, 2016; Bryant et al., 2018; Meyer, Stein- haus, et al., 2017; Sim, Bowes, & Gardner, 2018). For instance, higher caregiver distress was prospectively associated with higher levels of internalizing and externalizing problems in Eritrean adolescents livingin a camp in Ethiopia (Betancourt, Yudron, Wheaton, & Smith-Fawzi, 2012). In a study with Syrian parent-child dyads living in Turkey, parental psychopathology was not related to children's PTSD symptoms, but to higher levels of parent- and child-reported emotional and parent- reported behavioral problems (Eruyar, Maltby, & Vostanis, 2018). Poorer caregiver mental health and lower family functioning were associated with more internalizing and externalizing problems in young displaced Colombian children, but not in non-displaced children (Flink et al., 2013). While these studies focused on parent-child dyads and mostly mothers, a study with Syrian families who resettled in the USA found only mothers`, but not fathers` psychopathology to be associated with children's anxiety symptoms (Javanbakht, Rosenberg, Haddad, & Arfken, 2018).

Two studies investigating a potential mechanism underlying these associations suggested that parents` own exposure to war trauma and

post-migration stressors were associated with higher levels of parental mental health problems, which in turn were related to more negative parenting behaviors (e. g. harsh parenting), which in turn negatively impacted their children's mental health (Bryant et al., 2018; Sim et al., 2018). In further support of this, children and adolescents` self-reported experiences of maltreatment by parents were associated with higher levels of mental health problems including PTSD (Karam et al., 2019), depression (Lee et al., 2020; Meyer, Steinhaus, et al., 2017; Meyer, Yu, et al., 2017), anxiety (Meyer, Steinhaus, et al., 2017; Meyer, Yu, et al., 2017) and attention deficit hyperactivity disorders symptoms (Lee et al., 2020). An insecure attachment to mothers and fathers as perceived by Syrian children was related to higher levels of PTSD symptoms, general mental health and conduct problems (Eruyar et al., 2020), whereas a positive mother-child relationship was related to lower levels of anxiety for Palestinian adolescents living in camps (Ahmad et al., 2015). Parenting styles perceived as negative, i.e. low in emotional warmth and support, harsh, rejecting and controlling, were associated with higher levels of internalizing and externalizing problems (Eruyar et al., 2020; Lau et al., 2018; Smetana & Ahmad, 2018). In contrast, positive, i.e. supportive and emotionally warm parenting was linked to lower levelsof emotional and behavioral problems (Lau et al., 2018; Smetana & Ahmad, 2018; Zevulun et al., 2018).

3.5.3. Household assets and parental education

While no study has systematically assessed preflight socioeconomic status (SES), findings suggested that post-migration SES could be particularly relevant in very poor settings: in an Ethiopian camp, the possession of valuable household assets, i.e. a radio and cattle, was associated with lower levels of adolescents` internalizing problems (Betancourt, Yudron, et al., 2012). In a study in a Ugandan camp, higher SES conceptualized as lower household hunger, caregiver employment status and number of valuable household assets was related to lower levels of adolescents` depression (Meyer, Steinhaus, et al., 2017). In resource-poor settings, such as refugee camps, low SES may also be an indirect risk factor for children's wellbeing as it increases their risk to be engaged in child labor, which was associated with higher levels of depression (Meyer, Yu, Rieders, & Stark, 2020). Fathers` current unemployment was associated with an increased risk of a psychiatric disorder in refugee children living in a Turkish city (Sapmaz et al., 2017). Having a less educated father was linked to higher levels of children's emotional problems in one study (Çeri & Nasıroğlu, 2018), whereas no independent association between parents' level of education and child mental health outcomes was found in other studies (Beiser & Hou, 2016; Beni Yonis et al., 2019; Sapmaz et al., 2017).

3.6. Community level

3.6.1. Social support

Social support can be provided by various persons within children's social ecology, e.g. by family members, friends, teachers or other adults within the community, and thus operates both on the micro- and exosystem. Although a number of studies investigated associations between social support and refugee children's adjustment, they varied considerably in their conceptualization and assessment of social support. Studies that assessed social support in general and did not differentiate between sources of support produced mixed findings, with some studies reporting no independent associations with mental health problems (Elklit et al., 2012; Flink et al., 2013; Jensen et al., 2019) and others presenting links between general social support and higher wellbeing (Correa-Velez, Gifford, & McMichael, 2015; Khawaja et al., 2017) as well as lower levels of depression (Oppedal et al., 2018). One study differentiated between the type of support and found that lower psychological, but not practical support by family, friends and other people predicted North Korean youth's depression (Park et al., 2017). Some studies separately investigated the role of social support provided by family members, peers and community members. Lower support by mentors and peers, but not by the family, increased the risk of PTSD and depression (mentors) as well as anxiety (mentors and peers) after stressful life events (Sierau, Schneider, Nesterko, & Glaesmer, 2018). In another study, social support within the family was not significantly associated with unaccompanied and accompanied minors' mental health, whereas social support in the host country was related to lower levels of anxiety symptoms (Müller, Büter, et al., 2019). In a study with URM in Norway (Oppedal & Idsoe, 2015), both support from family and friends were associated with lower depression levels directly (family)and indirectly through promoted acculturation (family and friends). Connectedness with the family appeared to be more important in protecting displaced Chechen adolescents from internalizing problems than connectedness with peers and adult community members (Betancourt, Salhi, et al., 2012). Caregiver-rated ethnic and religious community support was not associated with children's emotional and behavioral problems in an Australian study (Lau et al., 2018).

3.6.2. Neighborhood quality

Caregiver-perceived neighborhood friendliness and safety were not associated with children's emotional and behavioral problems in an Australian study (Lau et al., 2018). Similarly, poor neighborhood quality as perceived by refugee youth in Canada was not related to their internalizing and externalizing problems (Beiser & Hou, 2016). In refugee camps, the existence of and access to NGO's services may benefit the livelihoods of communities and families and thus children's adjustment. Caregiver-perceived access to health services was associated with lower levels of youth's internalizing and externalizing program in an Ethiopian camp and for youth who were satisfied with an education program offered by an NGO, the association between caregiver distress and ad- olescents' mental health problems was weaker compared to those who were not satisfied (Betancourt, Yudron, et al., 2012). However, receiving aid from organizations was not associated with mental health problems in Syrian adolescents living in a European refugee camp (Braun-Lew- ensohn & Al-Sayed, 2018). Housing quality was not associated with children's psychopathology in two studies (Beni Yonis et al., 2019; Betancourt, Salhi, et al., 2012).

3.6.3. School and peer relationships

Schools can play a vital role for the adjustment and wellbeing of resettled refugee children and youth, as they not only provide opportunities of learning and academic progress, but also constitute the context in which a major part of socialization and acculturation pro- cesses take place. Feeling accepted and supported by teachers and fellow students at school was associated with lower levels of aggressive behavior (Beiser & Hou, 2016), emotional dysregulation (Khamis, 2019) and psychological distress (Tozer et al., 2018) and with higher levels of wellbeing (Khawaja et al., 2017; Tozer et al., 2018). On the other hand, perceived discrimination by teachers and peers was related to more emotional and behavioral problems in one study (Beiser & Hou, 2016) and being bullied by peers at school was associated with lower levels of self-esteem (Samara et al., 2019) and happiness (Correa-Velez et al., 2010). The importance of having supportive and understanding friends for children's mental health was underlined by findings from two studies (Correa-Velez et al., 2010; Samara et al., 2019).

3.7. Society and culture

3.7.1. Post-migration difficulties

Higher cumulative exposure to daily hassles was associated with URMs' higher levels of PTSD symptoms, internalizing and externalizing problems as well as somatization 5 years after their arrival in Norway (Jensen et al., 2019). In a longitudinal follow-up of URM in Belgium, the number of daily stressors, particularly experiences of discrimination, increased over time and predicted PTSD symptoms, depression and anxiety 18 months after arrival, over and above the effects of pre-migration war exposure (Vervliet, Lammertyn, et al., 2014). Apart

from these direct effects, two studies found cross-sectional evidence for an indirect effect of post-migration difficulties on refugee children's mental health by increasing parental psychopathology and subsequently negative parenting behaviors (Bryant et al., 2018; Sim et al., 2018). With the exception of one study (Sim et al., 2018), accumulated daily hardships and their relations to youth's mental health have not been investigated in LMIC where refugees often live in camp settings with precarious living conditions such as widespread violence, poverty and bad sanitary conditions (Reed et al., 2012).

3.7.2. Acculturation

A number of studies from HIC investigated the role of sociocultural adaptation and its relation to refugee children's mental health using the concept of acculturation. While its definition and assessment have stir- red controversy (Oppedal & Idsoe, 2012), the studies generally sup- ported the idea that acculturation refers to the dynamic process of psychological and behavioral change that arises from a prolonged confrontation with a new culture's norms, customs and values (Berry, 2005). Higher levels of integration into the host society, i.e. adoptingaspects of the new culture while maintaining values and practices of the original culture, were associated with lower levels of depression andanxiety (Tozer et al., 2018) as well as with higher levels of well-being (Khawaja et al., 2017; Tozer et al., 2018) in refugee youth resettled in Australia. Increased competence, i.e. knowledge and skills about inter- personal behaviors and underlying values, regarding both host and heritage culture, was related to lower levels of depression in URM in Norway (Oppedal & Idsoe, 2012, 2015). Support from family and co- ethnic friends was associated with ethnic competence, while support from Norwegian friends was related to host culture competence (Oppedal & Idsoe, 2015). A higher social status of the family within the broader Australian community (Correa-Velez et al., 2010), but also a stronger ethnic identity (Correa-Velez et al., 2015), were linked to
refugee youth's well-being and happiness respectively. While a balance between adaptation to the host and heritage culture appears to be associated with better mental health, marginalized (disengaging both from host and heritage culture) and separated (maintaining high levelsof heritage culture/identity while avoiding contact with the host culture/society) acculturation styles were associated with higher levels of depression in Somali adolescents resettled in the USA (Lincoln et al.,2016).

Learning the host country's dominant language is a crucial part of sociocultural adaptation. Poorer German language proficiency was related to higher levels of PTSD and depression symptoms (Müller, Büter, et al., 2019) and better perceived English skills were associated with higher self-esteem and school adjustment (Buchanan et al., 2018). However, two studies did not find an association between children's proficiency in the host language and their adjustment (Correa-Velez et al., 2015; Gormez et al., 2018).

Part of the acculturation process may be exposure to a number of stressful experiences for refugee children and youth, such as conflicts with family and in-group members, discrimination and ethnic identity crisis (Keles, Friborg, Idsøe, Sirin, & Oppedal, 2016a). More severe family-related acculturative hassles, such as being criticized for codes (e.
g. clothes, behaviors) adopted from the host culture and having to translate for parents were associated with higher levels of PTSD symptoms and depression, particularly in youth with a marginalized acculturation style (Lincoln et al., 2016). Higher perceived discrimination was related to higher levels of depression (Oppedal & Idsoe, 2015) and lower levels of self-esteem and school adjustment (Buchanan et al., 2018) as well as lower happiness (Correa-Velez et al., 2015). Higher cumulative acculturation stress was associated with higher levels of depression in cross-sectional studies (Keles et al., 2016a; Kim et al., 2015) and with an increase in depression symptoms over time in a longitudinal study with unaccompanied minors in Norway (Keles et al., 2016b). A decrease in acculturative stressors was related to a decrease indepressive symptoms over time in the latter study. No study has investigated acculturation-related factors in LMIC.

3.7.3. Resettlement location

Refugee camps are one of the most common displacement settings for refugees worldwide, particularly in LMIC. However, only 9 studies were actually conducted in camp contexts and no study assessed whether children currently residing in a camp were at greater risk for mental health problems than children living in other forms of accommodation. Living in a camp (Beiser & Hou, 2016; Lau et al., 2018) and duration of stay in a camp (Elklit et al., 2012) before coming to a HIC were not related to youth's emotional and behavioral problems and PTSD. Living in proximity to ongoing war and/or in poorly developed regions may perpetuate children's feelings of insecurity and helplessness. The prevalence of PTSD was higher among Syrian adolescents living in a Jordanian city close to the Syrian border with limited access to jobs, health and education compared to those living in a more distant and industrialized city (Beni Yonis et al., 2019). In a similar vein, rates of PTSD were higher among Syrian youth living in Lebanon compared to Jordan, which is probably attributable to relatively higher levels of post-migration stressors (e.g. discrimination, bad sanitary conditions, and restrictive living arrangements) in Lebanon (Khamis, 2019). However, in a study with internally displaced Chechen youth perceived insecurity in the region of resettlement was not related to internalizing problems (Betancourt, Salhi, et al., 2012). Not being satisfied with life in Turkey was associated with more conduct problems in one study with Syrian children (Çeri & Nasıroğlu, 2018), but no independent association with children's mental health was found in another study (Gormez et al., 2018). For asylum-seeking children who had returned to Kosovo and Albania, living in a rural or urban area was not related to emotional and peer problems (Zevulun et al., 2018).

3.7.4. Ethnic origin

African-born youth reported higher levels of well-being than youth from other regions in a Australian study (Correa-Velez et al., 2010). In another study, parents of children with African origin reported more emotional and behavioral problems for their children than children from the Middle East and Eastern Europe in a Dutch study (Wiegersma et al., 2011). In a database study of accompanied asylum seeking children in the Netherlands (Goosen et al., 2014), children from Iran had the highest and children from Iraq the lowest risk of mental distress recorded by medical services. Belonging to a visible minority (e.g. Afghan, Sri Lan- kan) was associated with more emotional problems reported by refugee youth resettled in Canada (Beiser & Hou, 2016). Repatriated children who belonged to the Ethnic Roma minority faced a lower quality of child-rearing environment, which was linked to more internalizing problems (Zevulun et al., 2018).

3.7.5. Placement type and immigration process

The comparability of findings regarding the asylum process is limited due to country-specific regulations. However, the type and quality of living arrangements as well as the outcome of the asylum decision appear to be particularly important with regard to refugee youth's mental health and wellbeing. Studies with URM suggest that staying in settings characterized by lower supervision and support, e.g. living independently or in large-scale reception centers, is associated with higher levels of PTSD, depression and anxiety when compared to settings with more support and supervision, e.g. foster care or living groups (Bronstein et al., 2012; Jakobsen et al., 2017; Smid et al., 2011). A Norwegian longitudinal study found that URM who were assessed as 18 years or older and were subsequently placed in low-support adult reception centers had higher levels of psychological distress at follow- up assessments compared to youth who remained in high-support reception centers for youth (Jakobsen et al., 2017). However, thetype of living arrangements was not associated with Afghan URMs' emotional and behavioral problems when controlling for age, pre- migration trauma and length of stay in the UK (Bronstein,

Montgomery, & Ott, 2013). Post-migration detention is a form of placement that seems to be especially harmful to children's wellbeing. Both past and current mandatory detention was associated with an increased likelihood of PTSD, depression and anxiety (Mace et al., 2014) and children who were detained on a small island on their way to Australia had significantly higher levels of parent-rated emotional and behavioral problems than children living in a community setting in Australia (Zwi, Mares, Nathanson, Tay, & Silove, 2018). Evidence about the influence of changes in the living situation within the host country is inconsistent. A high annual relocation rate was associated with an increased risk for mental distress particularly in children who had experienced violence and whose mother had PTSD or depression (Goosen et al., 2014). However, the number of relocations was not related to emotional and behavioral problems as reported by children themselves, parents, and teachers in another study (Wiegersma et al., 2011).

The time spent waiting for the asylum decision is marked by great uncertainty about the future and constant fear of deportation. Increased length of stay as an asylum seeker in the Netherlands was associated with adolescents` lower levels of life satisfaction and individual resil- ience (Sleijpen et al., 2019). In another study, time until determination of asylum status was not related to URMs` externalizing problems (Bronstein et al., 2013). Two longitudinal studies found that minors whose asylum applications had been rejected between assessments (compared to those who were granted asylum) had significantly higher levels of PTSD symptoms and externalizing problems (Müller, Goss- mann, et al., 2019) as well as depression and anxiety symptoms(Jakobsen et al., 2017; Müller, Gossmann, et al., 2019). Asylum status was not associated with children and adolescents` mental health prob- lems in two cross-sectional studies, which was explained by the unequal distribution by the respective variable (Bronstein et al., 2012) and the potentially higher relevance of other context variables such as maternal mental health and family size (Wiegersma et al., 2011). Having a per- manent visa was related to higher levels of wellbeing in a Australian study (Tozer et al., 2018), while a stable residence permit in the host country was related to a higher-quality child rearing environment and in turn lower levels of internalizing problems in repatriated children (Zevulun et al., 2018).

4. Discussion

Within the past decade, an unprecedented number of people, of which many are minors, have been forced to flee their homes due to ongoing and emerging violent conflicts and wars in the world. Re- searchers have responded to the need to better understand which factorscontribute to the mental health and well-being of vulnerable refugee youth by conducting various new studies. Table 2 summarizes the contributing factors identified by this systematic review across different socio-ecological levels (individual, family, community, society/culture)and stages of the refugee experience (pre-. peri- and post-migration).

Several limitations of the recent research studies have to be taken into account when interpreting the findings: first, there is a lack of evidence on pre- and peri-migration factors, particularly on the family, community and societal level, as well as the role of experiences during flight and migration. Second, there are few studies from LMIC and particularly refugee camps. While this may be due to the ethical and practical challenges related to conducting research in these settings (Reed et al., 2012), it means that findings do not encompass the lived realities of most refugees worldwide. Third, the current evidence is largely based on cross-sectional studies without comparison groups, which preclude firm conclusions on the direction of associations be- tween presumed factors of influence and outcomes. Fourth, the studies are very heterogeneous in the applied research designs, measures and target refugee populations, thereby making it difficult to draw unifying conclusions. For instance, some studies used instruments that were specifically created or adapted for the study context, whereas others applied established measures that were not validated for the samples` cultural background.

Notwithstanding these limitations, our synthesis of the individual findings provides useful information by strengthening the evidence base for some established factors and shedding light on hitherto underexplored factors. Our findings corroborate previous evidence establishing children's exposure to pre-migration trauma as significant individual-level factor contributing to the risk of developing mental health prob- lems (Fazel et al., 2012; Reed et al., 2012). This is in line with the building block effect of trauma (Neuner et al., 2004), which specifies a dose-response relation between the number of traumatic event types and

Table 2
Factors contributing to risk and protection of refugee children's mental health according to socio-ecological context and stage in the refugee phase.

	Individual	Family	Community	Society/culture
Pre-migration	EXposure to war-related traumatic events (risk)[22] (25) Being female (risk for internalizing symptoms and PTSD)[14] (21) Being male (risk for externalizing symptoms)[3] (3) **Longer period of schooling (protective)[6]**	**Loss of a parent (risk)[2]**		
Peri-migration	**Length of current stay in a refugee camp (risk)[2]**	Separation from immediate family members (risk)[4] (3) **Socioeconomic status in a refugee camp (protective)[2]**		**Detention (risk)[2]**
Post-migration	**Depression and anxiety symptoms (risk)[2]** **Better perceived school performance (protective)[2]** **Avoidant coping strategies (risk)[4]** **Individual resilience (protective)[6]**	**Living with at least one biological parent (protective)[2]** Parental mental health problems (risk)[10] (2) **Negative parenting behaviors (risk)[5]** **Parental abuse (risk)[4]** Family cohesion (protective)[4] (3) **Warm parent-child relationship (protective)[3]**	Support by peers (protective)[2] (4) **Close relationships with friends (protective)[2]** School connectedness (protective)[4] (3) **Cumulative exposure to daily stressors (risk)[5]**	Perceived discrimination (risk)[4] (3) **Integrative acculturation style (protective)[6]** **Exposure to acculturation stressors (risk)[4]** **Resettlement in a poor region (risk)[2]** **Low-support living arrangements (risk for unaccompanied minors)[3]** **Asylum granted in host country (protective)[4]**

Note: Only factors that were found in at least two studies are shown. Factors not included in the previous reviews by Fazel et al. (2012) and Reed et al. (2012) are highlighted in bold. The numbers indicate the number of studies that found the respective factor in the current review (witho ut brackets) and in the reviews by Fazel et al. (2012) and Reed et al. (2012) (with brackets).

the severity of PTSD and other trauma-related psychopathology. While girls have been identified at heightened risk for internalizing symptoms before (Fazel et al., 2012; Reed et al., 2012), the more recent studies also provide evidence for female gender as contributing to the risk for PTSD. A newly found factor contributing to resilience is a longer period of pre-migration schooling, underscoring the pivotal role of education for the well-being and development of conflict-affected children (Nicolai & Triplehorn, 2003). Our review suggests several individual-level factors contributing to risk (internalizing symptoms, avoidant coping) and protection (better perceived school performance, individual resilience) in the post-migration phase. However, these are based on a small number of studies solely from HIC.

The new evidence on family-level factors strengthens the view that the family constitutes a powerful source of both risk and resilience to the mental health and wellbeing of conflict-affected children (Betancourt & Khan, 2008). In particular, a link between parents` own mental health problems and refugee children's mental health has been found across a variety of cultural and socioeconomic settings. The mechanisms underlying this intergenerational transmission of psychopathology remain to be elucidated in refugee families. This review provides preliminary evidence for the mediating role of maladaptive parenting behaviors, which goes along with research on other conflict-affected populations documenting the complex interplay between war trauma, family violence and children's mental health problems (Catani, 2018). How- ever, some studies show the protective nature of a cohesive and sup- portive family environment for refugee youth's mental health after resettlement in the host country, which has also been found in previous reviews (Fazel et al., 2012). In line with previous reviews (El Baba & Colucci, 2018; Fazel et al., 2012), being separated from family members before and during flight constitutes a factor contributing torefugee youth's risk. However, there is a lack of studies comparing accompanied and unaccompanied youth and investigating the role of family separa- tions in LMIC.

Evidence on post-migration community-level and on sociocultural factors comes almost exclusively from HIC, precluding the generalizability of these findings beyond these settings. In line with previous reviews (d'Abreu et al., 2019; Fazel et al., 2012), higher exposure to acculturative stressors in the host country, in particular perceived discrimination, was associated with worse mental health outcomes for refugee youth. In keeping with research with non-refugee immigrant youth (Abu-Rayya & Sam, 2017), an integrative acculturation style, i.e. being engaged both in the host and heritage culture, appears to be associated with refugee youth's higher wellbeing. Even though discrimination and other acculturation stressors may be particularly salient in HIC whose culture is often quite different from the home countries of most refugees, studies from LMIC with seemingly similar cultures of refugees and host societies would be valuable. Discrimination may be also prevalent in contexts where refugee and host communities compete for scarce resources. Relatedly, the nature of daily stressors differs for refugee youth in these contexts and consist rather in a severe lack of material resources and ongoing threats to safety (Reed et al., 2012). In terms of factors contributing to protection, the review expands the evidence base for an important role of school connectedness and self-reported support by peers for refugee youth (Fazel et al., 2012). In line with specialized systematic reviews (Mitra & Hodes, 2019; O'Higgins et al., 2018), being placed in living arrangements characterized by lower support, e.g. semi-independent care or reception centers, puts URM at an increased risk for mental health problems compared to more supportive arrangements, e.g. foster care. Unsurprisingly, acceptance of asylum claims in the host country appears to be protective, marking the end of a period of uncertainty and offering a long-term perspective.

Placing the current evidence in the wider context of clinical psychological research with children and adolescents, it can be noted that the contributing factors on the family and community level such as parental mental health problems, maladaptive parenting and peer support are for the most part well in line with established evidence from non-refugee populations (Lambert, Holzer, & Hasbun, 2014; McLeod, Weisz, & Wood, 2007). On the one hand, this supports a universal perspective on refugee children's development and well-being and emphasizes the importance of proximal socio-ecological contexts, particularly the family. On the other hand, our systematic review is the first to establish the importance of these factors for the mental health of refugee children. In fact, they may be particularly salient in this population given the consistently higher prevalence rates of mental health problems found in adult refugees compared to the general population (Silove, Ventevogel, & Rees, 2017). Besides more or less universal factors, our review also identified a number of factors that can be considered unique for the context of refugee children and adolescents, at least those resettling in HIC, such as acculturation, discrimination, placement type (for URM) and the asylum decision. Overall, our systematic overview emphasizes the joint consideration of a range of universal and specific contributing factors across the pre-, peri- and post-migration phases and different ecological contexts in order to understand mental health risk and resilience of refugee youth.

4.1. Recommendations for future research

Future studies should aim to expand the evidence base for the factors identified by this and previous systematic reviews. This way the status of factors with inconsistent evidence should be clarified (e.g. age, time since displacement) and potentially relevant factors that have been understudied so far should be examined (e.g. refugee youth's attribution of events, intra-familial communication, genetic and biological factors, neighborhood characteristics, ideological and religious beliefs). Most importantly, studies should strive to use longitudinal designs to eluci- date causal pathways between socio-ecological factors and refugee youth's mental health and adjustment at different stages of their expe- rience and development. While it may be extremely difficult to track children across their flight journey, studies could include children shortly after their arrival at a camp or reception center and prospectively assess post-migration factors and mental health at multiple regular follow-ups. In doing so, it will be important to record the relevant pre- dictor and outcome variables at each time point and model complex research designs such as cross-lagged panel and latent growth models to examine causal mechanisms of change. Among the reviewed studies, positive examples for longitudinal and rather complex designs are the high-quality study by Smid et al. (2011), which combined multinomial
regression and path analysis to examine the interplay of individual-level (trauma exposure, age, and internalizing symptoms) and socio-cultural (supervision) variables in shaping PTSD symptomatology over time, as well as the study by Keles et al. (2016b), which used a person-based approach to identify pre-migration (trauma exposure and gender) and post-migration (acculturative stressors) risk factors for long-term trajectories of depression symptoms among URM. The inclusion of comparison groups, for example accompanied and unaccompanied minors, repatriated and non-repatriated youth, children in refugee camps and in community settings, is also important. Ultimately, the validity and generalizability of research findings depend both on the psychometric quality and the cultural applicability of the used assessment in- struments. Researchers should aim to strike a balance between using established measures that enhance comparability between studies and taking into account culture-bound mental health concepts to improvethe cultural applicability of measures. Finally, more research in LMICand particularly in refugee camps is needed to adequately represent the experience realm of the vast majority of refugee youth worldwide.

4.2. Practical implications

Factors on multiple socio-ecological levels contribute to risk and resilience among refugee youth. Consequently, practical efforts aiming to support this vulnerable group's mental health should be integrated across these levels and target several factors. Existing interventions and

challenges related to the delivery and implementation of mental health services for refugee youth in HIC and LMIC have been reviewed and discussed recently (Eruyar et al., 2018; Fazel & Betancourt, 2018; Hodes & Vostanis, 2018). At this point we briefly present what we consider direct practical implications of the contributing factors with the best current evidence base.

The pervasive impact of pre-migration war trauma calls for trauma-focused treatments such as narrative exposure therapy for children (Ruf et al., 2010) and trauma-focused cognitive behavioral therapy (Unterhitzenberger, Wintersohl, Lang, König, & Rosner, 2019). Early screening for mental health problems and established factors contributing to mental health risk shortly after resettlement and regular follow-ups for vulnerable children could help to quickly introduce children to existing service programs and prevent the development of late-onset disorders. On a policy level, governments and international organizations should make any effort to protect children from exposure to violent conflicts and wars in the countries of origin if international agreements such asthe United Nation's Convention on the Rights of the Child shall have any meaning. On a family level, the findings further suggest parents` mental health and parenting as key targets for interventions, which need to be tailored both to the cultural background of families and to the demandsof the specific setting. Moreover, fast reunification of youth with their parents and other family members needs to be prioritized by authorities and organizations. Within children's exosystem, schools are not only important in terms of formal learning, but they are also hubs for social relationships with peers and friends. Educational authorities should consider activities and programs in the school setting that encouragesocial support and cohesion among peers. The post-migration challenges refugee youth and their families face in HIC may often be directly modifiable by policy makers. This includes, for example, the provision of high-support living arrangements for unaccompanied youth as well as the swift, yet careful and transparent, resolution of asylum claims. The potentially beneficial impact of an integrative acculturation style may be promoted through targeted activities on a family, school and community level, which aid refugee youth to adopt elements of the host culture andat the same time maintain bonds to their heritage culture's traditionsand values.

4.3. Limitations of review

First, owing to the marked heterogeneity of included studies in terms of the study designs, populations and measures used, we were not able to conduct a meta-analysis of the evidence. Second, we only included quantitative studies in our review. However, we emphasize that qualitative research is important to gain further insights into refugee youth's perspectives and to capture aspects that may be missed by quantitative approaches. Third, although our strict application of inclusion and exclusion criteria probably increased the validity of the findings, we also had to exclude studies with interesting findings.

5. Conclusions

Exposure to violent conflict, flight and the challenges of resettlement can adversely affect refugee youth's mental health and well-being. However, risk and resilience is determined by a complex interplay of various factors in youth's socio-ecological environment at different stages of their life experience. Although research has provided valuable insights, there is still much to learn about the conditions that shape refugee children's adjustment. More longitudinal studies that take into account moderating and mediating factors on different contextual levels are needed. In the meantime, evidence on established factors contrib- uting to risk (exposure to war-related violence, female gender, care- givers` mental health problems and parenting, acculturative stress and discrimination) and protection (family cohesion, school connectedness, peer support, integrative acculturation style) has to be transferred to practice by developing and evaluating interventions and by informing policy. This serves both to prevent detrimental long-term consequences to the well-being of refugee youth and to contribute to peaceful and prosperous societies characterized by diversity, solidarity and mutual respect.

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Contributors

FS and TH designed the study. FS and TH conducted the literature search and study selection. FS and EK rated study quality. FS wrote the first draft of the manuscript and all authors contributed to and haveapproved the final manuscript.

Declaration of Competing Interest

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Targeting the Proximal Mechanisms of Stress Adaptation in Early Adolescence to Prevent Mental Health Problems in Youth in Poverty

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ABSTRACT

Objective: This study used a randomized clinical trial design to evaluate the success with which The Building a Strong Identity and Coping Skills intervention (BaSICS) engaged the proximal mechanisms of poverty-related stress's impact on the psychosocial functioning and mental health of young adolescents living in high poverty contexts.

Method: 129 youth from very low-income families were randomized to receive the 32-hour group-based intervention or no-treatment control – 16 of these families withdrew before the intervention groups began. The remaining 113 youth aged 11–12 (53% assigned to intervention; 54% female; 40% Hispanic, 63% Black, 20% White) participated in the study, which included four assessment waves: pretest, posttest, 6-month follow-up and 12-month follow-up assessments. Primary control, secondary control, and disengagement coping were assessed via a combination of parent and youth reports as well as via interviews and questionnaires. Hypothalamic-pituitary-adrenal axis (HPA) reactivity was assessed via salivary cortisol responses occurring during a lab-based stress induction (Trier Social Stress Test).

Results: Multilevel regression models with repeated measures nested within subjects revealed that in comparison to controls, intervention youth had sustained significant increases in their knowledge about primary control coping (e.g., problem solving, emotion modulation), knowledge and utilization of secondary control (e.g., cognitive restructuring) coping, as well as decreased reliance on disengagement coping. These were accompanied by decreased cortisol reactivity in intervention versus control youth.

Conclusions: These findings support that BaSICS engages several proximal mechanisms of poverty-related stress' impact on early adolescent mental health – coping skills and HPA reactivity – during the neurodevelopmentally plastic pubertal period.

Abundant longitudinal research has shown that exposure to chronic adversity such as poverty and its accompanying stressful events (poverty-related stress; PRS; Wadsworth & Berger, 2006) is robustly associated with both internalizing and externalizing problems and disorders in children and adolescents (Grant et al., 2004; Wadsworth et al., 2016). As noted by Compas et al. (2017), stress exposure isa distal risk factor for the development of mental health problems, which operates through more prox-imal processes such as coping, self-regulation, and supportive social resources. Disengagement coping such as avoidance, for example, is generally asso- ciated with poorer mental health outcomes in the face of stressful conditions than is active, engagement coping such as problem solving. Importantly, eco- nomic hardship and poverty-related stress are, on average, positively associated with utilization of *typically maladaptive* disengagement coping and negatively associated with use of *typically adaptive* engagement coping (Cory et al., 2020; Santiago et al., 2012). In addition, the physiologic systems that support regulation during stress, such as the hypothalamic-pituitary-adrenal axis (HPA), also show atypical activation patterns in the face of pov- erty-related stress, which are associated with mental health problems (Duprey et al., 2021). Hence, "mala- daptive" or what Wadsworth (2015) referred to as "stress-adapted" coping repertoires (reduced engage- ment and enhanced disengagement) and physiologic "dysregulations" (e.g., HPA) appear to constitute proximal mechanisms linking poverty and poverty-related stress to child and adolescent mental health problems over time. Despite the important role

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played by poverty and chronic stress in mental health, stress and its regulatory adaptations have received little attention in interventions for youth living with PRS (for an exception see, Grant et al.,2014). This is unfortunate because targeting mechan- isms common to multiple health problems has the potential to prevent numerous health problemssimultaneously (e.g., Raghavan et al., 2019).

Building on the Research Domain Criteria approach to understanding psychopathology (e.g., Cuthbert, 2015), the National Institute of Mental Health (NIMH) has articulated an experimental therapeutics approach to early-phase clinical trial research. This approach is characterized by identification and engage- ment of empirically and theoretically derived mechan- istic intervention targets in the service of treating and/or preventing mental disorders (National Institute ofMental Health, 2015). The Building a Strong Identity and Coping Skills (BaSICS; Wadsworth et al., 2020) program uses the experimental therapeutics approachby targeting important mechanisms of poverty-related risk – stress, stress-adapted coping, diminished coping resources, and stress adapted HPA responsivity – inorder to prevent the development of psychopathology in young adolescents living in high poverty contexts. This study reports results of tests of first the phase of experimental therapeutics – mechanism engagement –in a randomized control trial (RCT) of BaSICS ina sample of young adolescents living in poverty. Engagement of target mechanisms across multiple systems (biological, cognitive, and behavioral) is examined.

Adaptation to Poverty-Related Stress

Chronicity and uncontrollability, which characterize PRS for many children and youth, are the two dimensions of stress most robustly linked with negative outcomes such as depression and self-regulation problems (e.g., Landis et al., 2007), as well as damage to and dysregulation of the physiologic stress response (e.g., HPA; Koss & Gunnar, 2018). Chronic and uncontrollable stressors are also particularly challenging for children because these stressors simultaneously demand ongoing coping behaviors while also reducing adult support and coping assistance (e.g., Reife et al., 2020). Studies have consistently found higher levels of cognitive and behavioral avoidance in samples of low-income children (e.g., Kim et al., 2016). Importantly, a number of studies have found that avoidant coping in absence of adult support (Reife et al., 2020) or in the context of highly uncontrollable stressors such as community violence exposure, is not associated with mental health problems, at least in the short-term (Cory et al., 2020; Santiago & Wadsworth, 2009).

Children facing PRS also report using less primary control coping (active attempts to problem solve and manage emotions), a type of coping typically associated with better functioning. Research has suggested that the chronic and uncontrollable nature of PRS makes it difficult for children to identify active coping solutions – a phenomenon common to uncontrollable stress (e.g., Newman et al., 2011). Secondary control coping (efforts to accommodate oneself to stress via acceptance, cognitive reframing, and distraction) tends to be more helpful in coping with uncontrollable stress, but children facing PRS report using less of this type of coping as well (Wadsworth & Berger, 2006).

Primary reliance on disengagement coping, while potentially and at least temporarily helpful in the face of PRS (e.g., Cory et al., 2020), will not necessarily equip children to cope with stressors across multiple domains such as school and peers and can instead leave them vulnerable to the development of mental health problems (Kim et al., 2016). Hence findings suggest that living with chronic stress can constrain the development of and/or ability to use typically efficacious coping (Santiago et al., 2012) and instead promote disengagement coping. Therefore, the coping and self-regulation differences evident in poor youth do not necessarily reflect skill deficits, but rather adaptations that currently have (or once had) utility in coping with the volume, intensity, and uncontrollability of stressors that characterize life in poverty (e.g., Reife et al., 2020). Stress-adapted skills and reactivity nevertheless often have negative tradeoffs in other domains such as mental health (Ellis & Del Giudice, 2019; Wadsworth, 2015).

Paralleling the development of stress-adapted coping, the physiologic stress response system also adapts to chronic uncontrollable stress such as poverty. In its efforts to maintain homeostasis in the face of ongoing uncontrollable stress, the HPA adjusts its setpoints (e.g., Ellis & Del Giudice, 2019). The HPA's feedback mechanisms become sensitized over time, leading to an exaggerated response or what has been termed hyperactivation (increasingly easy to activate and increasingly difficult to down-regulate) and over time, theoretically eventuates in a hypo-active response (inability to mount a stress response; Booij et al., 2013). Stress-adapted HPA patterns are associated with psychopathology, especially internalizing problems (Ellis & Del Giudice, 2019)

As noted by Wadsworth (2015), stress-adapted coping is valuable and comes at a cost. The tradeoffs that come with stress adapted coping and regulation are not optimal and hence attention to how to lessen tradeoffs is

warranted. Given the variety and volume of conditions and events that comprise PRS, coping with poverty requires many different types of strategies; including those typically considered beneficial such as emotion regulation and problem solving as well as strategies typically considered detrimental such as avoidance and wishful thinking. In PRS affected youth, pervasive, repeated, and primary use of avoidance over time, for example, portends mental health problems, whereas strategic, periodic use of avoidance along with active coping strategies does not (Edlynn et al., 2008; Santiago & Wadsworth, 2009). This suggests that stress-adapted coping repertoires do not need to be replaced, but rather expanded and honed to meet the heightened demands of PRS.

Why Early Adolescence?

Appropriately timed interventions occurring during periods of enhanced neuroplasticity represent opportunities for making meaningful, qualitative shifts in development that can change a child's life trajectory. Puberty represents one such period, marked by neural plasticity, substantial maturation and reorganization of physiologic stress response systems, and rapid growth of cognitive, emotional, and behavioral abilities, includingcoping (Skinner & Zimmer-Gembeck, 2007). The early adolescent period is also when youth begin spending substantially more time out of the home without parents and are likely to encounter a wider variety of stressful exposures in multiple settings that they must increasingly navigate independently (Farahmand et al., 2011). The middle school years therefore represent a particularly important developmental period for intervention with stress-exposed youth in which stressful exposures are increasing, coping abilities are expanding, and the brain has enhanced plasticity (e.g., Gunnar et al., 2019).

Building a Strong Identity and Coping Skills

Guided by the Adaptation to Poverty Related Stress model (Wadsworth et al., 2018), the Building a Strong Identity and Coping Skills intervention (BaSICS) is a developmentally timed coping and empowerment program for middle schoolers that aims to foster growth in youth's individual and collaborative coping repertoires and improve youth's ability to regulate emotions and physiologic stress responses. The APRS model acknowledges that there are not universally beneficial or maladaptive coping strategies – coping strategies that are effective in resource-rich contextsmay be less effective in resource-deprived contexts. A such, context-specific coping repertoires can confer protection in the face of poverty-related stress (PRS)and mitigate its effects on stress physiology and mental health problems. Hence the first module of BaSICS entails teaching about emotions, stress, and diverse coping strategies – building a strong core of funda- mental knowledge and regulation abilities (Wadsworth & Berger, 2006; Wadsworth & Santiago, 2008). The second module of BaSICS targets cultural identity development as a coping resource, connecting youth with their supportive communities, fostering identification of one's own values and sense of self, and developing appreciation for their cultural roots (e.g., Spencer et al., 2003) – all in the service of pre- paring youth for collaborative coping (e.g., community social action). The final module of BaSICS targets col- laborative problem-solving *vis á vis* collective socialaction to give youth tools for agentic and empowering ways to cope with PRS alongside others (Zimmermanet al., 2011). More details about the 32-hour curricu- lum can be found in Wadsworth et al. (2018).

Core Mechanisms of Action – Targets to Be Engaged

According to the APRS model, the BaSICS intervention will lead to improvements on a variety of coping skills, both increasing use of engagement coping such as cognitive reframing and emotion regulation and reducing primary reliance on avoidance and denial, for example. Other program elements such as cultural identity development are viewed as important resources to support the difficult work of coping with PRS but are not in themselves considered mechanisms of action. These are therefore not tested in this exam- ination of core mechanisms. As children acquire a broader repertoire of coping and self-regulation skills, their ability to down-regulate their physiologic reac-tions in the face of stress should also improve. Hence, HPA axis hyper-responsivity should be reduced over time. Then, according to the APRS model, enhanced coping repertoires and better regulated stress reactivity will prevent the emergence of depression, anxiety, and post-traumatic stress symptoms – testing of this second experimental therapeutic goal will be addressed elsewhere.

After enrolling the first five cohorts of youth (N = 84), a proof-of-concept study was conducted to ensure that initial results suggested positive, non-iatrogenic effects on core mechanisms and psychological outcomes in

these highly vulnerable youth. Findings of that study's pretest-posttest analyses confirmed differential acquisition of engagement coping skill knowledge (e.g., problem solving steps and cognitive reframing), reductions in cortisol reactivity for intervention but not control youth, and reductions in parent and youth reported internalizing symptoms. Hence, these early findings suggested that BaSICS was safe and potentially efficacious (Wadsworth et al., 2020), but did not constitute a strong test of mechanism engagement, which the current study is designed to address.

The Current Study

The refinement and evaluation of the BaSICS intervention was supported by the NIMH (R21/61 mechanism) experimental therapeutics program. The current study builds on the promising proof-of-concept findings and was designed to evaluate the intervention's longer-term success in engaging the multiple mechanisms in the intended population of young adolescents living in chronically stressful high poverty contexts. The current study consists of a rigorous evaluation of engagement of target mechanisms across multiple systems over four timepoints, out to 12 month follow-up for the full sample of 129 intervention versus control youth. [Note that the COVID-19 pandemic precluded enrolling the final two cohorts of youth that would have resulted in a total N = 150.] Specifically, we hypothesized that across the 12 months of the study, (1) youth assigned to intervention would show increased knowledge about and use of active, engagement coping as compared to control youth, (2) intervention youth would show less reliance on disengagement coping after intervention, and (3) HPA reactivity would be reduced in intervention youth as compared to control youth. Prevention programs are generally expected to show differential change in *symptoms* over time wherein, for example, the control group's mental health worsens over time in comparison to the treatment group. Skill acquisition resulting froma prevention program, on the other hand, may not follow this type of linear change pattern. Continuedgrowth of acquisition of skills after an intervention ends is not expected. Rather, acquisition of skills appear- ing at posttest or later and then being retained over time would be the logical predicted pattern of mechanism engagement. Hence, in this study, a differential linear change model is tested for thoroughness, but it was anticipated that a model of post-intervention change maintained over time would better represent the acquisition of skills and abilities targeted in BaSICS.

Methods

Study Procedures

All study components were approved by The Pennsylvania State University's institutional review board. Parents and guardians completed informed consent procedures, and youth completed assent to participate. Parent-child dyads were recruited from two adjacent low-income communities located in highly disadvantaged urban neighborhoods in a medium-sized city in Pennsylvania (Kind & Buckingham, 2018). The median household income (~$35,000), poverty level (~29%), and unemployment (~27%) rates are notably worse than the county aver- age ($58.900, 12.7%, and 18.0%, respectively) in these "distressed" majority African American (~ 45%) and Latinx (~19%) communities (Distressed Communities Index, 2020). This city has very high homicide andviolent crime rates (FBI Uniform Crime Report, 2020), its public schools are all designated Title I, and 87% of the students in the school district are classified as "economically disadvantaged" by the commonwealth (Pennsylvania Department of Education).

Dyads were recruited using flyers placed at community agencies and local schools, and in person at events through informational brochure and goody bag distribution at community and school events by staff who lived locally. Program events included parent-teacher events, religious and church-affiliated events, community festivals, block parties, recreational youth programs, and back to school programming, with a focus on events with high likelihood of parent attendance. The breadth of recruitment efforts used was employed to increase the generalizability of study findings. 65% of participating youth were recruited from the community and 35% of youth were recruited from middle schools.

Recruitment materials detailed the purpose of the study of investigating how BaSICS can improve a child's skillset in managing stress, which can, in turn, support greater physical and mental health. Families were apprised that participation in the study was voluntary and confidential, and that no information would be given to the child's school. Recruiters underwent training and demonstrated the ability to explain research protocol including monetary incentives, time commitments, and answer questions regarding the BaSICS intervention, randomization, and the evaluation components. Families who expressed interest were then contacted by program staff to begin checking for eligibility.

Youth aged 11 and 12 years were eligible if they did not demonstrate clinically significant levels of anxiety or depression that would require more intensive

intervention (i.e., treatment) or evidence of an autism spectrum disorder or intellectual disability, had families with an income of ≤ 200% FPL, and had at least one parent or guardian who was willing to complete the study. Figure 1 provides information about enrollment, randomization, and follow-up of participants. Of the 369 youths assessed for eligibility, 240 were excluded from the study. Of the 240 excluded youth, 81 were ineligible because they did not meet the full eligibility criteria as previously described and 159 youth declined to participate. Many families declined to participate dueto time commitment issues or lack of interest in participation by the time they were contacted to schedule their pretest assessment. Of the 159 youth who declinedto participate, 62% were recruited from the community and 38% from schools.

Eligible parent-youth dyads attended a three-hour pretest assessment appointment in which they consented for the study and to randomization. In-person pretest appointments occurred in either the youth's school or the project offices located in one of the communities between 4:00 pm and 7:00 pm. During these visits, participants were assessed using interviews, questionnaires, and the modified Trier Social Stress Task (TSST-M; Yim et al., 2010). Parent-youth dyads were assessed simultaneously, with parents independently completing measures on tablets while youth completed measures on tablets with the assistance of an examiner. Youth were then randomly assigned to either an intervention or control condition. Twenty-four sets of either 0 or 1 were printed out, placed in sealed envelopes, and given to children as generated by Research Randomizer (randomizer.org). The randomization ratio was 50:50 (I:C) for

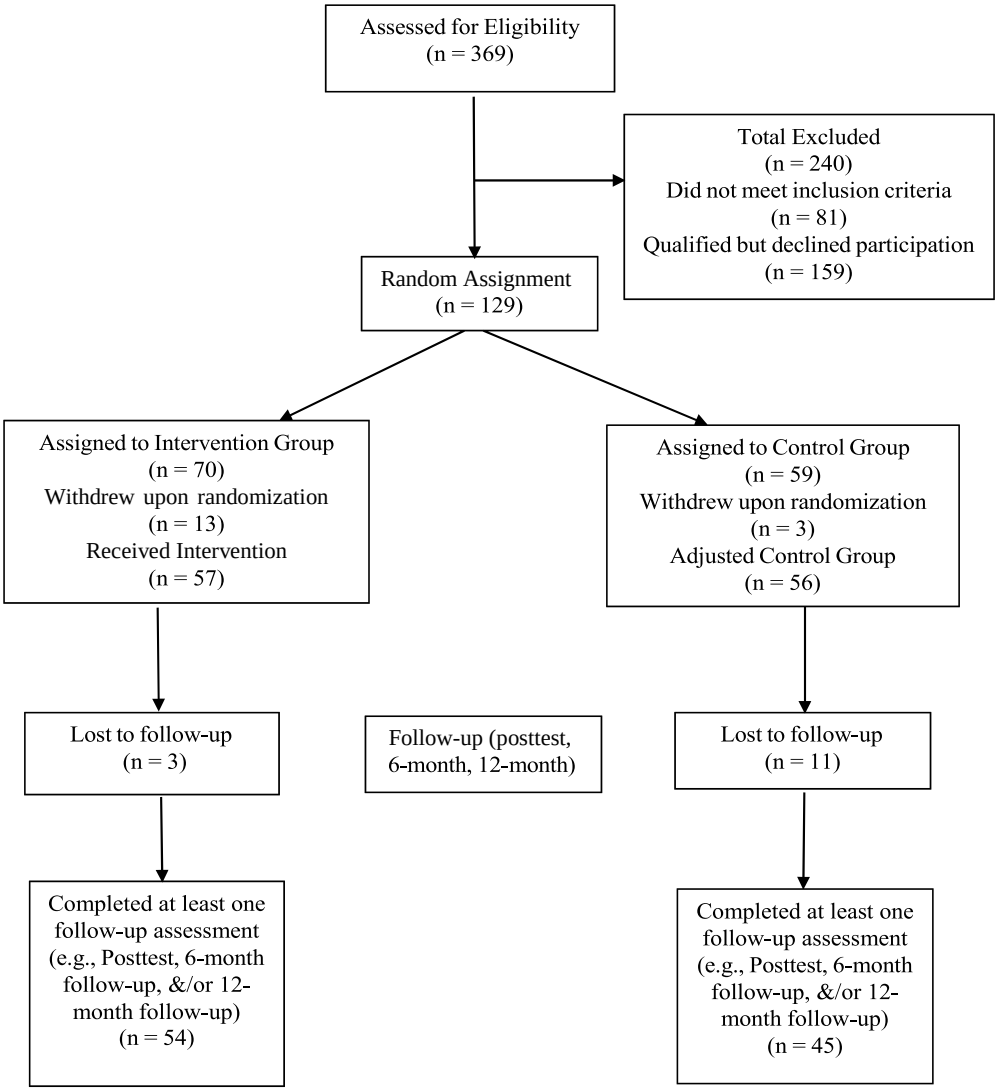

Figure 1. Consort table.

most cohorts but was adjusted to 60:40 (I:C) for cohorts 5 and 6 to adjust for differential withdrawal from the study by intervention recruits. Youth in the intervention participated in 16 sessions over the course of 8 weeks. Parents themselves did not participate in the intervention.

Participants and parents completed a posttest assessment two weeks after the final intervention session, ensuring 10–12 weeks between pre- and posttest assessment to minimize the practice effects of the TSST (Petrowski et al., 2012). Participants and parents then completed two additional follow-up assessments six and twelve months, respectively, after their posttest assessment. All post-intervention assessments were identical to pretest assessment. Families were compensated for completing assessments as follows: $40 pretest, $60 posttest, $80 six-month follow-up, and $100 twelve-month follow-up.

Participants

One hundred twenty-nine parent-child dyads (58% of children and 94% of caregivers were female) were recruited into the study, consented to the study, and completed pretest measures (Figure 1). Seventy youth were assigned to the intervention and 59 youth were assigned to the control group. Sixteen dyads withdrew from the study upon randomization but prior to the start of the intervention (13 had been randomized to the intervention group and 3 to the control group). Most parents of the 16 youth who withdrew from the study upon receiving their randomization assignmentindicated that their or their child's schedules no longer permitted participation in biweekly intervention groups or were disappointed in their assignment. There were no significant differences between the with- drawn participants and those remaining in the study on demographic measures or variables of interest assessed at pretest except for parent report of child primary control (Supplementary Table 1). There were no sig- nificant differences between the intervention and con- trol groups on the demographic or pretest variables of interest (Supplementary Table 2). All data reported in tables and text were restricted to the analysis sample.

On average, children were 11.82 years old (*SD* = 0.57) and were 43% Hispanic/Latino. Over half of the children identified as Non-Hispanic Black (59%), 15% identified as Non-Hispanic White, and 26% identified as Other/Multiracial. Parent age ranged from 26–63 years of age (*M* = 39.31, *SD* = 8.01), and parents were 34% Hispanic/Latino. About half of parents identified as Non-Hispanic Black (53%), 20% identified as Non-Hispanic White, and 27% identified as Other/Multiracial. Average household income was $23,102 (*SD* = $31,608) with an average household size of 5.06 (*SD* = 1.97), which was below the 2017 federal poverty threshold for a family of five set at $28,780 (Fontenot et al., 2018). Most caregivers were employed (54%), 21% were unemployed, 15% received disability, and 10% were homemakers, full-time students, or retired. Thirty percent of parents did not complete high school, 27% had a high school diploma or GED, and 43% had schooling beyond high school. Many participating families received public assistance (41%) and reported food insecurity (70%). Lastly, 41% of parents were single, 15% were cohabitating, 22% were married, and 22% were widowed, separated, or divorced.

Sixteen dyads officially *withdrew* from the study upon receiving their assignment (prior to the commencement of any intervention sessions), stating they could no longer meet the requirements of the study due to various household and scheduling changes and were hence no longer eligible to be in the study. Fourteen additional dyads did not withdraw officially but did not return for any assessments following the pretest – these dyads are classified as *attrition*. Both withdrawn and attritted dyads are included in the analyses in order to adhereto strict Intent-to-Treat guidelines. Out of the 57 non- withdrawn participants who received the intervention assignment, 54 participants completed at least one fol- low-up assessment (retention rate of 95%), whereas 45 of the 56 non-withdrawn participants assigned to the control group completed at least one follow-up assess- ment (retention rate of 80%). The only significant differ-ences between participants who completed at least one follow-up assessment and those who did not were child race, youth report of externalizing problems, and pub- ertal staging (Supplementary Table 3). As can be seen in Supplementary Table 3, participants who did not return for any follow-up sessions, were less likely to identify as Black, have lower level of externalizing problems, and more likely to have more advanced pubertal development.

Intervention

Eight cohorts with a mean of 7.3 children attended an average of 12.6 (mode = 16 sessions) sessions taught by two lead facilitators and one assistant facil- itator. Groups met for two hours twice a week for8 weeks. Sessions took place in the community health center and two middle schools within the targeted neighborhoods.

In the BaSICS curriculum, the first unit of content focuses on coping training over the course of 5 weeks. During this unit, youth are taught primary control coping skills (e.g., problem-solving), secondary control coping skills (e.g., distraction), and relaxation techniques

(e.g., progressive muscle relaxation). Throughout this unit and in subsequent units, strategies to help children learn to engage in primary and secondary control coping are implemented. The STEPS (Say the problem, Think of solutions, Examine each solution, Pick one and try it out, See if it worked) acronym is used to teach problem-solving action steps. The THINK (Think positively, Help from a friend, Identify the good things, Name a fun activity, Keep trying-don't give up) acronym is used to teach problem-solving, distraction, and positive thinking. The second unit of content focuses on positive identity development over the course of 6 weeks. During this unit, youth focus increasingly on social stressors – putting their personal experiences at home, school, and in their neighborhoods into a broader con- text. They learn about social justice, intersectionality, and community engagement and have opportunities to practice coping skills learned in unit 1 in an expanded range of situations. The third unit of the program entails working collaboratively with each other and with adults in the community to identify revitalization "opportunity zones" in their neighborhoods and to develop and implement a revitalization project in their neighborhood. Each week, parents are phoned by their child's group leader who gives them feedback about their child's participation in the intervention and share an overview of the content covered in the week's lessons.

Participant Satisfaction

At the end of each unit, participants completed surveys about their satisfaction with the sessions and the group facilitators. Participants were asked to rate BaSICS on several variables on a scale from (0 = not at all, 1 = a little bit, and 2 = very much). Participants were asked questions related to the content of each session, such as "*How much did you like the overall session?"* and *"How much did you like progressive muscle relaxation?"*

Measures

Demographics

Youth age, sex, race, and ethnicity were reported by parents. Parents also reported their own sex, race, ethnicity, immigrant status, marital status, annual household income, education level, and receipt of public assistance.

Coping Skills Knowledge Acquisition

Acquisition of knowledge about primary control (problem solving) and secondary control (distraction and positive thinking) coping was assessed using the Coping Skills Scale (CSS; Raviv & Wadsworth, 2010). The CSS assesses participants' ability to describe problem solving steps taught during the BaSICS intervention as well as steps necessary to engage in positive thinking and distraction. The CSS was administered orally, and responses were recorded on paper by research assistants. First, participants were asked to imagine stressful situations and identify potential solutions (e.g., "Imagine that your best friend is feeling very disappointed because her family cannot afford to go to the movies. What can your friend do to solve this problem? Think of as many solutions as you can."). Second, they were asked to list out the components of the STEPS acronym. Third, they were asked to identify ways in which cognitive restructuring could be used in these stressful situations. Fourth, they were asked to think of other coping strategies that could be used in these stressful situations. Fifth, they were asked to describe what the THINK acronym stands for.

Trained coders who were blind to participants' experimental conditions coded the recorded participant responses. Responses to the first item were coded based on whether a solution was proposed and the quality of solution (if it was logical, feasible, or realistic) on a scale from 1 (the solution proposed is no logical, feasible, or realistic) to 4 (the solution is highly developed, realistic, possible, and beneficial). Responses regarding the STEPS and THINK acronyms were coded based on youth's ability to accurately name each problem-solving step or way to think positively, respectively (0 = No, 1 = Yes). Questions targeting cognitive restructuring and other coping strategies were coded for each replacement thought the child provided and for each replacement activity that the child identified (0 = No, 1 = Yes). Coding was then checked for reliability (at least 80%) and two master coders coded 30% of responses to establish adequate inter-rater reliabilities for the primary control (κ = .70 – .90) and secondary control (κ = .86 – .94) sum scores. Primary control and secondary control sum scores were calculated.

Responses to Stress Questionnaire

Youth's use of primary control (e.g., problem solving, emotion regulation), secondary control (e.g., acceptance, distraction), disengagement coping (e.g., avoidance, wishful thinking), and involuntary responses to stress were assessed with parent- and self-report using the Family Stress version of the Responses to Stress Questionnaire (RSQ; Connor- Smith et al., 2000). In the RSQ, participants were first asked to report whether they had experienced any of 12 presented family stressors (e.g., "your par- ents arguing with each other," "your sibling(s) mes-sing up, breaking, or taking your belongings") in their lifetime. Then, participants were asked to keep these selected family stressors in mind when

responding to 57 stress response items that each assessed the frequency with which participants used different coping strategies or endorsed different typesof stress responses when they experienced family stress. Participants rated each of these 57 items ona Likert scale from 1 "*not at all*" to 4 "*a lot*."

The current study used primary control, second- ary control, and disengagement coping factors. As recommended by Connor-Smith et al. (2000), pro- portion scores were calculated to control for response bias and individual differences in base rates of item endorsement, by dividing the totalscore for each factor by the total score for the entire Responses to Stress Questionnaire. For example, primary control coping is the ratio of one'sendorsed primary control coping responses to total responses to stress. Primary control (α = .74;α = .84), secondary control (α = .76; α = .83), anddisengagement coping (α = .76; α = .83) had ade- quate internal consistency at pre and post time- points, respectively.

Puberty

Pubertal status was assessed using the Pubertal Development Scale (PDS; Petersen et al., 1988). Parents reported on youths' height, skin changes, and body hair growth. Girls' menarche and breast growth were also assessed; girls' average pretest PDS score was 2.42 (SD = 0.57; range 1.0–3.6). Boys' facial hair growth was assessed in addition to height, skin changes, and body hair; boys' average pretest PDS score was 1.76 (SD = 0.44; range 1.0–2.6).

Salivary Cortisol

Six saliva samples were taken via passive drool(Davis et al., 2002); immediately preceding the Trier Social Stress Test (TSST-M) (T1; 40 minutes post arrival at lab), immediately following TSST-M (T2; 15 minutes after T1), and at four 10-minute intervals thereafter (T3-T6). Given the 10- to 30- minute delay in cortisol's appearance in saliva, and as predicted, T3 represented the average peak corti- sol level in the sample (Kirschbaum et al., 1993). To control for external factors that influence cortisol, participants were directed not eat a large meal, eat dairy products, brush their teeth, or drink sugary beverages an hour before their appointment. Saliva samples were stored in a biomedical grade freezer prior to the analysis at the CORE Biomarker Lab at Penn State University. Cortisol levels were deter- mined using duplicates, with detection levels in the range of 0.003 to 3.0 Kg/dL (range, 0.08Y82.77 nmol/L) using a commercial expanded-range high-sensitivity enzyme immunosorbent assay kit (Lot #'s 1,410,510 and 1,502,503; Salimetrics, LLC, State College, PA). As per current best prac- tices (e.g., Miller et al., 2018) T3 peak controlling for T1 baseline level was used to index reactivity.

Data Reduction and Preprocessing

Outliers more than 3 SD from the mean were win-sorized to 3 SD (Smyth et al., 2013). In 6 saliva samples, insufficient saliva was collected for analysis (occurring randomly across participants). These 6 values were replaced with the mean cortisol value for the corresponding time point. Natural log (*ln*) transformation was used to normalize all salivary cortisol data (Smyth et al.).

Covariates

Because cortisol levels fluctuate with age, pubertal devel- opment, and by sex, it is recommended that these vari- ables be accounted for in analyses capturing variability in cortisol levels (e.g., Shirtcliff et al., 2012). In addition, rates of internalizing and externalizing symptoms and disorders are known to vary according to race, ethnicity, and family structure in addition to age, sex, and pubertal maturation (e.g.,Natsuaki et al., 2009; Pomerantz et al., 2017; Shirtcliff et al., 2012). Hence, age in months, sex (0 = male, 1 = female), pubertal maturation, parental marital status (0 = not married, 1 = married), cohort (0 = cohorts 1–5, 1 = cohorts 6–8), Black race (0 = no, 1 = yes), White race (0 = no, 1 = yes), and Hispanic ethnicity (0 = no, 1 = yes) were therefore included in all statistical models.

Analytic Models

Study outcomes were analyzed with multilevel regres- sion models to accommodate repeated measures nested within subjects, using SAS PROC MIXED. These models are well suited for this study as they allow for inclusion of incomplete data from respondents who did not pro- vide measures in all waves or dropped out of the study. All 129 participants are included in the analytic models to meet criteria for Intent to Treat design. Random intercepts were specified to account for clustering due to repeated measures. Separate models were used for each outcome with the above covariates included. Child's age at time of assessment was also included asa predictor, centered at the last follow-up measurement period. We tested for inclusion of a random slope to represent variation in change over time across subjects. In all models, however, there was insufficient variance within subjects for both random intercepts and random slopes so the latter term was excluded in final models. Finally, we tested for but did not find evidence of quad-ratic effects in any of the models – hence these terms

were also excluded from the final models. We first implemented models that assessed overall group differences from posttest through both follow-up periods, controlling for the corresponding pretest score for the outcome. This model provides a statistical test of overall effects for group differences on average post-intervention across waves 2 through 4, regardless of change over time. Second, we implemented models examining differential change between groups from pretest through the 12-month follow-up assessment. In this second model a test of the interaction between time and intervention condition served as a test of whether differential change was occurring.

Results

Pretest, posttest, 6-month follow-up, and 12-month follow-up means and standard deviations by intervention group are presented in Table 1; correlations between study outcomes at pretest are presented in Table 2. Results from multilevel regression analyses are provided in Table 3. Results of the differential change models are presented in Supplemental Table 4. In general, the means reflect the modeling results. As indicated by the large effect sizes, scores on the CSS primary and secondary control skills increased dramatically for intervention youth from baseline to posttest and remained elevated in comparison to control youth out to the 12-month follow- up. Similar patterns but with a moderate effect sizewere found for parent report RSQ for secondary control coping, reflecting sustained increases in sec- ondary control coping for intervention youth as com- pared to controls. Finally, disengagement coping responses and cortisol reactivity both showed declines over time for intervention youth but not controls, with small-to-moderate effect sizes. Sex was correlated with several coping variables as wellas pubertal maturation.

Statistical differences between intervention and control groups were found for the overall effect models, controlling for the covariates listed above. For the observed CSS scores, the intervention participants demonstrated significantly higher coping skills than the control group for both primary and secondary control coping. No significant differences were found on parent or child report RSQ for primary control coping. However, statistical models indicated significant intervention effects for parent-reported coping for secondary

Table 1. Means and standard deviations of parent and adolescent reported coping and peak cortisol levels.

	Baseline		Posttest (3 Months)		6 Months		12 Months	
	Control	BaSICS	Control	BaSICS	Control	BaSICS	Control	BaSICS
Measure	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*	*M (SD)*
CSS-PCC	0.040 (0.19)	0.089 (0.28)	0.085 (0.37)	1.720 (1.88)	0.069 (0.37)	1.229 (1.66)	0.040 (0.20)	0.800 (1.11)
CSS-SCC	0.180 (0.43)	0.143 (0.35)	0.171 (0.45)	1.219 (1.26)	0.103 (0.30)	0.686 (0.99)	0.040 (0.20)	0.432 (0.85)
PRSQ-PCC	.188 (.044)	.190 (.045)	.185 (.032)	.200 (.038)	.191 (.039)	.194 (.047)	.183 (.037)	.207 (.044)
PRSQ-SCC	.252 (.045)	.246 (.041)	.237 (.039)	.242 (.034)	.225 (.036)	.250 (.047)	.227 (.049)	.254 (.039)
PRSQ-DC	.149 (.029)	.149 (.026)	.154 (.027)	.146 (.023)	.157 (.023)	.144 (.022)	.146 (.019)	.131 (.017)
CRSQ-PCC	.179 (.039)	.182 (.042)	.190 (.032)	.188 (.043)	.180 (.041)	.191 (.039)	.169 (.036)	.189 (.051)
CRSQ-SCC	.249 (.052)	.240 (.045)	.244 (.047)	.253 (.039)	.243 (.046)	.258 (.048)	.261 (.040)	.258 (.039)
CRSQ-DC	.152 (.030)	.151 (.028)	.158 (.024)	.147 (.026)	.161 (.030)	.147 (.029)	.143 (.028)	.141 (.025)
Peak Cortisol	.084 (.08)	.088 (.09)	.092(.09)	.067 (.05)	.078 (.07)	.062 (.04)	.080 (.06)	.065 (.04)

Note: CSS-PCC = Coping skills scale, primary control coping, CSS-SCC = Coping skills scale, secondary control coping. PRSQ = parent report RSQ, CRSQ = child report RSQ. RSQ scores are computed as proportion scores (i.e., PCC/Total RSQ score). Cortisol levels are µg/dL.

Table 2. Correlations among baseline parent and adolescent reported coping and peak cortisol levels.

	Sex	Age	Puberty	CSS-PCC	CSS-SCC	PRSQ-PCC	PRSQ-SCC	PRSQ-DC	CRSQ-PCC	CRSQ-SCC	CRSQ-DC	Peak Cortisol
Sex	–											
Age (months)	.089	–										
Puberty	.546***	.392***	–									
CSS-PCC	−.083	−.046	−.090	–								
CSS-SCC	.067	−.125	−.082	.196†	–							
PRSQ-PCC	.268**	.087	.123	−.087	−.137	–						
PRSQ-SCC	.057	.165	.001	.057	−.037	.400***	–					
PRSQ-DC	−.265**	−.009	−.086	−.078	.130	−.510***	−.249*	–				
CRSQ-PCC	.255**	−.013	−.012	.052	.012	.140	.006	−.088	–			
CRSQ-SCC	.048	.140	.062	−.045	.078	.113	.120	−.132	.285**	–		
CRSQ-DC	−.166	.067	.001	.051	−.156	−.256*	−.003	.187†	−.473***	−.324***	–	
Peak Cortisol (*ln*)	.068	−.122	.136	.056	−.104	−.021	.006	.032	.052	.095	−.040	–

† = p > .10, * = p < .05, ** = p < .01, *** = p < .001

Table 3. Multilevel regression models. Analytic results for study outcomes intervention effects (regression coefficients, standard errors, p-values, and effect sizes).

	Coping Skills Scale (observed)						Responses to Stress Questionnaire (parent report)								
	Primary control (STEPS)			Secondary control (THINK)			Primary control			Secondary control			Disengagement coping		
	b	Std.err	p-value	b	Std.err	p-value	b	Std.err	p-value	b	Std. err	p-value	b	Std. err	p-value
Intercept	0.002	0.472	.996	0.360	0.479	.455	0.633	0.407	.123	0.348	0.368	.348	−0.571	0.407	.165
Gender (female = 1)	0.443	0.237	.065	0.298	0.230	.200	−0.074	0.200	.712	−0.088	0.175	.618	0.113	0.189	.551
Race (black = 1)	−0.008	0.236	.973	0.058	0.225	.798	−0.178	0.189	.352	−0.072	0.167	.669	0.237	0.181	.196
Whether married	0.492	0.211	.021	0.290	0.213	.176	0.251	0.185	.177	−0.071	0.169	.675	−0.089	0.180	.622
Whether hispanic	−0.007	0.223	.976	−0.063	0.212	.769	−0.138	0.181	.450	−0.159	0.159	.323	−0.104	0.172	.549
Puberty status	−0.383	0.147	.010	−0.428	0.159	.008	−0.205	0.139	.144	−0.095	0.132	.473	0.172	0.141	.227
Cohort (later = 1)	−0.210	0.252	.407	−0.360	0.245	.146	−0.083	0.214	.701	−0.069	0.190	.716	0.044	0.203	.828
Outcome pretest score	0.268	0.091	.004	−0.023	0.098	.817	0.452	0.085	<.0001	0.536	0.076	<.0001	0.301	0.083	.001
Age	−0.371	0.114	.001	−0.292	0.126	.022	0.015	0.114	.896	0.208	0.107	.055	−0.302	0.115	.010
Condition	0.941	0.206	<.0001	0.935	0.194	<.0001	0.244	0.173	.163	0.350	0.147	.021	−0.408	0.162	.015
Condition Effect size:	0.90			0.84			–			0.41			0.45		

	Responses to Stress Questionnaire (child report)									Salivary cortisol		
	Primary control			Secondary control			Disengagement coping			Reactivity (logged)		
	b	Std.err.	p-value	b	Std.err.	p-value	b	Std.err.	p-value	b	Std. err.	p-value
Intercept	0.002	0.406	.996	0.215	0.386	.579	0.401	0.408	.328	0.557	0.469	.239
Gender (female = 1)	0.217	0.204	.290	−0.052	0.190	.784	−0.207	0.197	.297	−0.106	0.220	.631
Race (black = 1)	0.004	0.195	.984	−0.037	0.192	.846	−0.180	0.191	.348	0.177	0.216	.416
Whether married	−0.097	0.181	.594	−0.086	0.170	.613	0.084	0.179	.639	0.134	0.207	.519
Whether Hispanic	−0.466	0.186	.015	−0.186	0.180	.303	0.309	0.183	.096	−0.172	0.201	.395
Puberty status	−0.012	0.133	.926	0.011	0.122	.930	−0.062	0.133	.640	−0.127	0.152	.405
Cohort (later = 1)	−0.085	0.208	.686	0.006	0.200	.977	−0.043	0.205	.833	0.134	0.412	.746
Outcome pretest score	0.415	0.089	<.0001	0.550	0.081	<.0001	0.258	0.084	.003	0.417	0.090	<.0001
Age	−0.165	0.104	.116	0.055	0.095	.563	0.002	0.105	.982	0.097	0.134	.470
Condition	0.218	0.169	.200	0.020	0.165	.906	−0.308	0.165	.067	−0.378	0.186	.047
Condition Effect size:	–			–			0.34			0.41		

All models control for the pretest score for the outcome, gender, race (whether black), marital status (whether married), cohort (whether later cohort), whether Hispanic, and puberty status. Multilevel regressions include specified random intercept to accommodate repeated measures nested within subjects. Regression coefficients are standardized with respect to model outcomes (mean = 0, standard deviation = 1). Effect sizes represent standardized meandifferences between Conditions (Cohen's D), calculated from model-adjusted means relative to model variance combined across levels.

control and disengagement coping. There was no significant difference on child-reported coping for secondary control, and a marginally non-significant result for child-reported disengagement coping. Finally, the analytic model examining group differences in measured salivary cortisol (log-transformed) showed that intervention children were significantly lower than the control group. Not shown in Table 3, the random intercept terms representing variation in the average outcome over time across respondents was found to have statis- tically significant variance in all models except for par- ent-reported secondary and disengagement coping. The pretest score significantly predicted the outcome in all models except for CSS-STEPS and CSS-THINK. Consistent with predictions, intervention group assignment was significant in many models, but differential change over time (time X group) was not significant for any of the models.

78% of participating youth reported liking the BaSICS program very much and none reported disliking it; 89% noticed positive changes in their own behavior; 95% reported that they had been better able to control their feelings since being in the program, and 92% stated that they would tell their friends they should participate in the program.

Discussion

This study tested the success of the BaSICS intervention in engaging its putative mechanisms of action, including acquisition of knowledge about how to apply primary and secondary control coping skills and demonstrated usage of these skills. Further, we examined the extent to which utilization of these active coping responses was accompanied by lessened reliance on disengagement coping responses such as avoidance and reduced HPA reactivity to the TSST-M. The findings suggest that

BaSICS was successful in engaging some, but not all of the proximal mechanisms of poverty-related stress' effects on young adolescent mental health set forth in the APRS theoretical model. Namely, medium and large (e.g., Cohen's d) treatment effects were found in salivary cortisol peaks, child-reported coping knowledge, and parent-reported child coping usage, showing hypothesized improvements for youth assigned to intervention versus control. The findings herein replicate the findings of the proof-of-concept study wherein the safety of the intervention was established and posttest improvements in STEPS, THINK, and cortisol reactivity were found. The current study also extended these initial findings in important ways, including establishing that the initial effects were sustained out to a year, revealing the emergence of several positive effects on the parent-report RSQ over time, and showing intervention-related changes across reporters and in stress biology.

As noted previously, skills and knowledge acquired in an intervention would be expected to be evident shortly after program completion and maintained over time. Additional acquisition of skills after an intervention ends would not be expected – for mental health problems, differential change is expected wherein control youth's mental health problems continue to worsen overtime but intervention youth's mental health does not. The pattern of effects found in this study is therefore consistent with the expected model of skill acquisition change – post-intervention change maintained over time. A differential linear change model was tested for thoroughness (see Supplemental Table 4), but was not expected to adequately capture the acquisition and maintenance of skills and abilities targeted by BaSICS. The differential change models were also likely underpowered to detect small or medium interaction effects.

Coping Skill Knowledge Acquisition

Intervention youth were taught acronyms to helpthem learn and remember the steps involved in problem solving and in reframing one's cognitions. Borrowed with permission from the Families Coping with Economic Strain project (FaCES, Raviv & Wadsworth, 2010), the STEPS and THINK procedures were taught early in the intervention and used repeatedly throughout the 16 BaSICS sessions. Group facilitators were instructed to capitalize on interpersonal disputes and other difficulties that arose in the group setting as opportunities to practice using STEPS or THINK. Thus, early adolescents learned and practiced flexibly implementing problem solving and positive thinking on a regular basis using their own real-world problems. This developmentally appropriate "saturation" model of learning the planning, execution, and feedback procedures empirically linked to psychological adjustment (Cheng, Lau & Chan, 2014), appears to have been effective in teaching STEPS and THINK, as indicated by large effects. Problem solving and flexible thinking are fundamental skills needed for successfully engaging with the world, which make it possible for an individual to navigatean increasingly complex social world as they grow and develop. That the youth in the intervention were able to free recall both STEPS and THINK is indicativethat they both learned how to use primary (STEPS)and secondary control (THINK) coping, and to distinguish between them.

Coping Skill Utilization

Both parents and youth completed the Responses to Stress Questionnaire (RSQ) to assess the relative use of primary control, secondary control, and disengagement coping in everyday life by youth participants across the four timepoints. Utilization of proportionally more secondary control coping skills and less disengagement coping was evident in parent reports of their child's coping. Children's reports on the RSQ did not show the increased utilization of secondary control copingthat their parents' reports did. Parent-child cross-informant agreement on psychological constructs such as emotional and behavioral problems is generally low and is understood to reflect the unique perspectives of raters in context (De Los Reyes, 2011). Hence parents may have reported on improved coping that they observed in the home environment, whereas children's reports reflected their perceived coping across multiple domains. Both parents and youth reported reductions in disengagement coping following BaSICS, and while the youth reports failed to achieve statistical significance, the small-medium effect size (D = .34) of the youth-report effect suggests meaningful cross-informant convergence. Disengagement coping is likely more observable than the types of coping captured by secondary control such as acceptance and cognitive restructuring.

The pattern of findings across these measures and reporters suggests that intervention youth acquired knowledge about and increased their utilization of several cognitive, behavioral, and emotional coping skills, which were sustained across the 12 months of the study and were not evident in control youth. Avoidance, the defining feature of disengagement coping is, of course, a critical component of anxiety disorders and post-traumatic stress problems, and decreasing avoidance is a common goal of treatment. Coping is also prevalent in cognitive and behavioral models of depression, for

example, and acquisition of active coping skills and knowledge may be particularly critical to preventing the onset of depressive problems (Compas et al., 2010). Therefore, the concurrent reduction in disengagement coping and increases in active engagement coping knowledge and behavior show promise for preventing both anxiety and depressive problems (Compas et al., 2017).

Positive effects for usage of primary control strategies did not emerge in either child or parent RSQ reports. This may stem from the fact that the family stress domain includes many stressors over which a youth themself may have little control, such as arguments between parents and siblings taking or breaking one's belongings. The chronic and uncontrollable nature of PRS often makes it difficult for children to identify active coping solutions – a phenomenon common to uncontrollable stress (e.g., Cory et al., 2020). While primary control coping may be effective when youth face controllable stressors, it is not necessarily a good fit in cases where stressors are uncontrollable (Clarke, 2006; Jaser et al., 2005). Secondary control coping (efforts to accommodate oneself to stress through acceptance, cognitive reframing, distraction) tends to be more effective in coping with uncontrollable stress, but children facing toxic stressors like PRS often report using less of this type of coping as well (e.g., Wadsworth & Compas, 2002). The significant small-to-medium-sized effects for parent-reported secondary control coping and large effects of child-reported CSS-THINK also represent cross-informant evidence that low-income youth can learn to use these skills – which have enhanced utility for difficult-to-control stressors like PRS – in a culturally appropriate, developmentally timed intervention like BaSICS.

Still, it is important for youth to have ways to take action to respond to PRS and other large stressful burdens, which is why BaSICS strives to build up children's support networks and internal resources so that they can engage in collective actions with others. The family stress RSQ may not have picked up on youth's ability to engage in this active collaborative coping, which will be an important direction for future research. It is possible that, as with the secondary control and disengagement RSQ coping findings which were not evident at post but emerged after that, primary control effects could emerge over time when and if youth find more instances where problems can be solved collaboratively.

Cortisol Reactivity

It is encouraging that cortisol reactivity decreased significantly for intervention youth at the same time asand following the same pattern as improvements in several types of coping addressed in the intervention. A single small-to-medium finding of attenuated corti- sol reactivity in intervention versus control youth does not in itself constitute evidence that the HPA has been changed or recalibrated. It is however promising, and certainly warrants additional attention as a possible outcome of psychosocial stress-focused prevention programs. As noted earlier, the pubertal period appears to be a neuroplastic window in which to intervene, especially on stress and stress responses. Across pub- erty, the HPA axis undergoes significant reorganization and change, and has been shown to be capable of what has been termed "pubertal recalibration," which is a normalizing of a "dysregulated" HPA response following an intervention or significant change in environmental context (DePasquale et al., 2019). The promise of interventions targeting stress and stress responses during puberty is therefore substantial.

Conclusions

The patterns of findings reported in this study provide continued evidence of successful engagement of some of our theoretically and empirically derived target mechanisms, but not all of them – primary control coping did not emerge as an effect on either the child or parent RSQ. Primary control coping, as assessed by the CSS-STEPS measure did, however, show a large intervention effect, indicating that intervention youth do retain knowledge about primary control coping, even if it is not immediately evident in their behavior. It is certainly possible that the RSQ was not sensitive to changes in youth primary control coping – several coping focused interventions using the RSQ as a skill acquisition measure have consistently found smaller or nil effects for primary control coping in comparison to secondary control coping (e.g., Watson et al., 2014). It is also possible that transfer of knowledge (STEPS) to action (RSQ primary control coping) did not occur for the youth in this trial. It has already been noted that the context of poverty often limits opportunities for problem solving, which is why BaSICS includes action-oriented collaborative coping (social action) to equip youth with agentic ways to address PRS, which the family RSQ is not designed to measure. Further, parent and youth reports on relatively covert psychological constructs such as coping rarely show high convergence and this phenomenon is understood to arise from the fact that different informants have different vantage points from which they view a child's behavior (De Los Reyes, 2011). It is therefore promising that there was some concordance across reporters and in no case did parent and child reports show divergent effects.

Finally, the study findings are notable in several respects. Most of the enrolled youth were living in families with household incomes well below the federal poverty threshold in a community marked by concentrated economic disadvantage, high levels of crime and community violence, and failing schools. Yet, families signed on to participate in the complex, time consuming research. The youth assigned to the intervention came to 80% of the afterschool sessions on average (12.6 out of 16), participated in the activities, and learned many skills. Parents transported their children to assessments and intervention sessions, participated in assessments themselves, and noticed positive changes occurring in their children. Satisfaction ratings by the youth were uniformly high, but the burden of participating in an RCT was also high for families. Many parent-youthdyads who dropped out of the study after receiving the intervention condition indicated that the twice weekly after-school timing of the program conflicted with after school activities such as sports or with changing parental availability due to inconsistent work schedules. All of this suggests that BaSICS is an appealing intervention that families and youth are likely to want to participate in, especially once the intense constraints of a clinical trial are no longer required. In addition, alternative delivery modes should be considered to reduce parental burden and increase accessibility.

Limitations

The study is limited by the design and implementa-tion of the RCT. First, the BaSICS RCT was unfortu- nately upended by the COVID-19 pandemic, limiting our final enrollment numbers and complicating fol- low-up assessments. This of course reduced our power to detect small effects, and precluded examin- ing effects by race or sex, or testing various potential moderators of effects such as facilitator, dosage, and/ or intervention location. That said, we includeda wide variety of covariates known to be associatedwith effects of poverty on psychological adjustment,including race, ethnicity, sex, age, pubertal status, parental marital status.

Further, upon receiving their randomization assignment, 16 families decided that they were unable to make the time commitment of completing the study and withdrew. Recruitment staff on the project were trained to thoroughly explain the substantial time commitment involved in participating in the study and to obtain parent and child agreement to participate regardless of the eventual group assignment. Still, in a population where changes in employment, child-care, child extracurriculars, and residence can disrupt schedules, it was not surprising that 12% of families were unable to fulfill their com- mitment when the time came.

Third, the scope and sustainability of intervention youth's collaboration on a community action projectwas somewhat constrained by the relatively short time frame allotted for the after-school BaSICS groups to complete projects and plan for sustaining them. Asa result, community projects were modest in scope and difficult to sustain over time. Future applications ofBaSICS will likely benefit from integration into theongoing work of community groups and organizations. In this way opportunities for youth to apply primary control coping skills to a collaborative action project andto see their positive contributions to community pro- blem-solving can continue beyond the 8 weeks of the intervention.

Implications for Research, Policy and Practice

The next step in evaluating BaSICS using the experimental therapeutics approach will be to assess the extent to which engaging these mechanisms translates into lasting effects on psychological outcomes. As indicated in Wadsworth et al. (2020), initial treatment effects were evident at posttest for the first five RCT cohorts on internalizing and PTSD symptoms. Future studies will examine treatment effects over the course of a year and the mechanistic role of the skills, capacities, and stress responses evaluated in this study in transmitting positive mental health outcomes. It is certainly plausible to expect success in this regard, given the success of other interventions for youth facing chronic stress, wherein intervention-related increases in secondary control coping skills, for example, substantially mediated the association between the intervention and mental health benefits (e.g., Compas et al., 2010).

Finally, this BaSICS evaluation was an efficacy-effectiveness hybrid design by necessity. Practicaland psychological barriers precluded conductingthis RCT in a university lab. Hence, the research and intervention were all conducted in community settings, including schools, a community health cen-ter, and a research office rented in one of the pri- mary recruitment neighborhoods. Therefore, the results of this study are particularly promising aswe have already demonstrated that BaSICS can be successfully implemented and rigorously evaluatedeven in very disadvantaged community settings.

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Does psychological well-being change following treatment? An exploratory study on outpatients with eating disorders

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Abstract

Psychological well-being changes following cognitive-behavioral therapy-based treatment were investigated in outpatients with eating disorders (ED). While it is known that CBT reduces symptomatology in EDs, less is known about how changes in positive functioning may ensue. One-hundred and eighty five ED outpatients were analyzed for pre-treatment and post-treatment changes in psychological well-being (PWB) by last observation carried forward – Wilcoxon signed rank tests. Significant gains in all PWB dimensions were found, with moderate effect size correlations in environmental mastery ($r = -.418$), personal growth ($r = -.351$) and self-acceptance ($r = -.341$). A subsample of patients in remission ($n = 51$) was selected and compared to healthy controls in PWB post-treatment scores through Mann–Whitney U tests. Remitted patients showed significantly lower psychological well-being in two dimensions compared to controls: PWB-positive relations ($r = -.360$) and PWB-self-acceptance ($r = -.288$). However, more than 50% of ED outpatients in remission had PWB scores that fell below the 50th percentile of healthy controls in all psychological well-being dimensions, despite significant treatment response. Several mechanisms of psychological well-being change following CBT-based treatment are discussed. The assessment of treatment outcome in EDs may benefit from considering changes in positive functioning such as psychological well-being, in addition to the standard measurement of BMI, symptomatology and behavioral parameters. CBT-based treatment outcomes may be strengthened by promoting the development of optimal domains particularly in the interpersonal realm, such as building of quality and warm relationships and focusing on enhancing self-acceptance.

1. Introduction

Widely used criteria for treatment response in eating disorders are typically focused on the reduction of psychopathological symptomatology as well as modifications of physical and behavioral aspects [1,2]. Recently, the concept of euthymia, a term used in psychiatry to define when patients no longer meet criteria of a disorder, has been revisited by authors who recommend the inclusion of positive gains as criteria for mental health outcomes [3]. Indeed, gains in positive functioning are frequently not considered, despite findings indicating the persistence of impairment in positive qualities such as psychological well-being in various psychiatric illnesses including eating disorders (EDs) [4]. Such impairments may be associated with increased vulnerability to future adversity [5,6].

The focus on the improvement of positive characteristics falls within the realm of positive psychology, whose purpose is to broaden definitions of mental health towards the inclusion of optimal functioning and a focus on building the best qualities. Positive psychology represents a clear paradigm shift from the historical negativity bias of the fields of psychiatry and psychology originally based on the disease model [7] and from a preoccupation only with repairing the worst aspects of life [8]. Such a shift has profound clinical implications. Bringing an individual out of negative functioning is one form of success, while facilitating progression towards the restoration of positive functioning is quite another [8,9]. Indeed, the World Happiness Report 2016 Update [10] found that autonomy, positive affect, generosity and social support were highly associated with quality of life and overall well-being, a correlation which was non-existent with negative affect, commonly the sole target for psychiatric disorder treatment.

Several definitions of well-being in psychology have been attempted, the most widespread being various conceptualizations

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of *subjective well-being*, that is an individuals' perceptions and evaluations of their own lives in terms of their psychological and social functioning and affective states. Subjective well-being is frequently limited to and operationalized as the presence of positive emotions and satisfaction [8]. Alternatively, one of the most rigorously tested models of *psychological well-being*, introduced by Ryff [11], synthesizes clinical and personality theorists' conceptions of positive functioning, constituting a more comprehensive model of well-being. Ryff's model expands subjective well-being definitions towards a broader conceptualization of positive functioning. The author's eudaimonic model [11] derived from Jahoda's mental health criteria [12] considers specific domains that contribute to the development of optimal functioning and the fulfillment of one's potential including six interrelated psychological dimensions: autonomy, self-acceptance, a sense of continued growth and development, the belief that life is purposeful and meaningful, quality relationships with others, and the capacity to master effectively one's environment. A number of clinical studies on psychiatric populations have yielded substantial support to this model, finding that psychological well-being was frequently impaired [9,13,14]. Unlike other well-being definitions, this model of psychological well-being has not only been operationalized into an empirically validated instrument, Ryff's Psychological Well-Being Scales [11] but is also the theoretical basis for a specific psychotherapeutic intervention, well-being therapy [5], recently tested in EDs [15].

However, to date when positive mental health has been considered in eating disorders, there has been an exclusive focus on well-being in terms of subjective well-being and quality of life [16–19]. In our previous controlled study, a paucity of optimal positive functioning, in terms of psychological well-being, correlated with eating disorder symptomatology in ED out-patients. The lack of psychological well-being was independent of the presence of psychological distress and the severity of the disorder [4]. Furthermore, very few studies on EDs have focused on gains in positive functioning following treatment. Recently, a study investigated how a specific cognitive-behavioral intervention (Identity Intervention Program) increased positive self-schemas and psychological well-being in a sample of ED patients [20]. No studies have instead explored if such changes in psychological well-being are observable following first-line standard CBT-based and nutritional rehabilitation treatment for EDs [21], and whether such changes reach healthy levels. Therefore, the aim of this study is to examine whether dimensions of psychological well-being in ED out-patients change after CBT-based and nutritional rehabilitation treatment and whether any observed gains in remitted patients reach optimal levels found in matched healthy controls.

2. Materials and methods

2.1. Sample

A convenience sample of consecutively screened female out-patients (n = 195) who met DSM IV-TR diagnostic criteria for EDs [22], began an integrated treatment in an ED specialized out-patient clinic (Bologna, Italy). ED diagnoses were established at intake by the consensus of a psychiatrist and a clinical psychologist independently using the Structured Clinical Interview for DSM-IV (SCID) [23]. Patients who completed treatment were evaluated for remission from EDs status through face-to-face interviews by the consensus of a psychiatrist and the treating psychotherapist independently. Remission was defined as diagnostic, behavioral, BMI and psychological criteria, following Ackard et al.'s [24] suggestions, specifically in our study as: no current eating disorder according to DSM-IV-TR criteria using the SCID; body mass index (BMI) (kg/m^2) improvement; full absence of binge-eating, purging or fasting (in the past three months); a total score below the cut-off of 30 by the end of treatment in the Eating Attitudes Test [25].

Fifty-five controls matched for socio-demographic characteristics (sex and age) were recruited by advertisements from the general population and included in the study after excluding the presence of current psychiatric disorders with SCID face-to-face interviews.

2.2. Treatment

Treatment consisted in cognitive-behavioral therapy for EDs [26] and a nutritional rehabilitation program, as recommended by the practice guidelines for the treatment of ED patients [21]. Treatment was provided in a multidisciplinary clinical outpatient setting and consisted in individual weekly sessions composed of one hour psychotherapy sessions, provided by PsyD-level psychotherapists trained in CBT, either preceded or followed by one-hour sessions with a nutritional physician specialized in EDs. Average duration of treatment is one year, roughly 48 sessions. Main elements of the treatment include cognitive-behavioral techniques such as cognitive restructuring, assertiveness training, self-monitoring through the use of the diary, behavioral homework, exposure to avoided foods, and nutritional rehabilitation elements, such as psychoeducation on nutrition, on weight restoration, on health consequences of the illness. Integration is facilitated by daily case discussions between psychotherapists and nutritional physicians of clinically useful information in order to tailor sessions to emerging themes and needs.

Treatment integrity was checked by submitting eight randomly selected recorded sessions to two independent assessors, who correctly identified presence of treatment elements (see above) in the course of the provided sessions, by using a checklist created ad-hoc by the multidisciplinary équipe.

The study, conducted between January 2012 and December 2014, was approved by an institutional review board and informed consent was obtained from all participants.

2.3. Assessment

All ED patients were evaluated using the following self-report instruments at intake, at session number 16, 32,

and finally at session 48, considered the post-treatment assessment session:

The Eating Attitude Test (EAT-40) is a 40-item screening measure designed to identify behaviors and cognitive patterns of EDs. Items are constructed on a 0–3 four-point Likert scale, yielding three subscale scores for dimensions of dieting, body, and food preoccupation, oral control, and a total score ranging from 0 to 120. Higher scores indicate higher eating-related pathology and greater risk of developing an ED in the general population. Cronbach's alpha coefficient ranged from .79 in female patients with AN to .94. Test–retest reliability was .84, and the validity coefficient was .87 (25). In this study, the Italian validation of the EAT-40 was applied, which reports subscale Cronbach alphas of .80 for dieting, .70 for bulimic preoccupations, and .83 for oral control [27].

The General Health Questionnaire (GHQ-30) [28] is a 30-item instrument with a four-point Likert scale with item scores ranging from 0 to 3, aimed at assessing depressive and anxiety symptoms, sleeping problems, social functioning, well-being, and coping abilities. A total score is used ranging from 0 to 90, with higher scores indicating greater mental distress. Cronbach's alpha coefficients tested in various empirical studies in community samples ranged from approximately .82–.93. Test–retest reliability coefficients varied from .50 to .90. In this study, the Italian version, with Cronbach alpha of .81, was applied [29].

The Psychological Well-being Scales (PWB) 84 items version [30] measures the six dimensions of PWB according to Ryff's model: autonomy, environmental mastery, personal growth, positive relationships with others, purpose in life, and self-acceptance. Items are constructed on a six-point 1–6 Likert scale, yielding six subscale scores ranging from 14 to 84. Cronbach's alpha coefficients in a sample of 321 individuals from the general population for the six scales ranged from .85 to .91. Test–retest reliability varied between .81 and .88, whereas validity correlations extended between .25 and.73 (30). PWB scales were also administered to controls matched for socio-demographic characteristics. The Italian version was used [31] with the following Cronbach alphas reported by Gremigni and Stuart-Brown [32]: autonomy – .86, environmental mastery – .78, personal growth – .75, positive relations – .84, purpose in life – .73, and self-acceptance – .71.

Socio-demographic characteristics (age, marital status, and education level) were also collected for all participants while clinical variables (BMI, illness duration) were also collected for patients. BMI was calculated at the intake visit by the nutritional physician and monthly during treatment.

2.4. Analyses

Descriptive analyses of the whole sample were run. The Kolmogorov–Smirnov normality test was performed and determined that the samples' scores in psychometric measures did not conform to a normal distribution. Therefore, changes between pre-treatment and post-treatment in PWB scales and eating disorder-related and general psychopathology in terms of EAT and GHQ scores were analyzed by Wilcoxon signed rank tests with last-observation carried forward (LOCF) for missing data. In order to address any baseline differences that may constitute sampling biases, χ^2 test and the independent t test were used to compare any treatment completers and drop-outs, test completers and non-completers.

Descriptive analyses were run to verify the clinical characteristics of remitted patients according to the applied remission criteria. Independent t test were run to compare remitted patients and controls in socio-demographic characteristics (age, education levels, and married status). To evaluate whether psychological well-being reached normative levels in remitted patients, Mann–Whitney U tests were conducted to compare their post-treatment PWB scale scores to those of healthy controls.

In order to better understand in clinical terms the resulting PWB scores after treatment in remitted patients, we first computed the quartiles of the scores for each of the six PWB dimensions of healthy controls to utilize as reference for optimal functioning. Secondly, we calculated how many remitted patients (reported in percentages) scored below and above the median score of the control group, corresponding to the 50th percentile.

All analyses were performed using SPSS version 20.0 with statistical significance set at a p level of .05. Effect sizes were calculated using Rosenthal's [33] formula for effect size correlations: $r = Z/\sqrt{N}$. Multiple testing was corrected statistically by adjusting for the number of hypothesis tests performed using Bonferroni single-step adjusted p values.

3. Results

Out of the 195 consecutively screened patients entering treatment, 76.9% completed treatment ($N = 150$) while 23.1% ($N = 45$) dropped out. Ten drop-out patients did not have any baseline data and were excluded from the analyses.

No statistically significant differences emerged in age, illness duration, BMI, and psychometric measures (PWB scale scores, GHQ and EAT total scores) between treatment completers and drop-outs and between the subsample that completed all assessment measures at post-treatment with those who did not. For descriptive data on controls, ED patients and, χ^2 and t test results see Table 1.

The patient sample entered in LOCF analyses ($n = 185$) was composed of 150 treatment completers and 35 drop-outs. In terms of ED diagnoses, 57 patients had AN, 32 BN, 62 BED and 34 had EDNOS with mean duration of

Table 1
Descriptive data of whole sample, treatment completers and drop-outs, test completers and non-completers.

Variables	Total control sample (N = 55)	Total ED sample M ± SD (N = 185)	Treatment completers M ± SD (n = 150)	Drop outs M ± SD (n = 35)	p[a]	Test completers M ± SD (n = 75)	Test non-completers M ± SD (n = 75)	p[b]
Age (y)	29.27 ± 10.42	28.89 ± 10.25	28.95 ± 10.30	27.09 ± 7.86	.979	27.97 ± 9.38	29.85 ± 11.09	.277
Educational level	5.4%middle school 53.6% high school 39.3% college	18.9% middle school 41.1% high school 34.1% college	17.9% middle school 46.4% high school 35.7% college	26.2% middle school 35.7% high school 38.1% college	.363	18.6% middle school 48.6% high school 32.9% college	17.7% middle school 43.5% high school 38.7% college	.776
ED diagnosis	–	AN: 17.3% BN: 30.8% BED:33.5% EDNOS:18.4%	AN:16.7% BN: 32.7% BED: 31.3% EDNOS:19.3%	AN:17.7% BN: 22.2% BED:40.0% EDNOS 13.3%	.523	AN: 17.3% BN: 34.7% BED: 32.0% EDNOS:16.0%	AN: 17.3% AN BN: 29.3% BED: 34.6% EDNOS: 18.6%	.697
Illness duration (y)	–	9.03 ± 8.24	9.12 ± 8.37	8.65 ± 7.13	.583	7.97 ± 7.38	10.75 ± 9.38	.060
BMI (kg/m^2)	21.24 ± 3.21	AN: 17.62 ± 4.74 BN: 22.11 ± 4.95 BED:33.42 ± 6.24 EDNOS: 22.28 ± 5.46	AN: 16.23 ± 1.76 BN: 22.47 ± 5.44 BED:33.20 ± 6.11 EDNOS: 22.89 ± 5.67	AN: 21.76 ± 7.95 BN: 20.66 ± 1.38 BED:33.97 ± 6.91 EDNOS: 19.41 ± 3.37	.291	AN:15.82 ± 1.72 BN:23.11 ± 6.21 BED: 33.95 ± 5.75 EDNOS: 22.850 ± 6.04	AN: 16.72 ± 1.77 BN: 21.67 ± 4.29 BED:32.30 ± 6.54 EDNOS: 22.95 ± 5.58	.738
EAT total score	7.46 ± 3.92	32.19 ± 20.61	32.41 ± 20.74	29.17 ± 19.67	.374	34.53 ± 21.54	31.48 ± 20.14	.398
GHQ total score	4.29 ± 5.49	12.98 ± 9.04	12.73 ± 9.39	12.81 ± 7.71	.960	13.15 ± 9.51	12.91 ± 9.40	.881
PWB autonomy	61.58 ± 12.10	51.89 ± 14.16	52.41 ± 14.02	50.49 ± 14.69	.686	52.41 ± 14.49	51.61 ± 13.88	.738
PWB environmental mastery	59.76 ± 10.25	47.32 ± 13.54	47.33 ± 13.76	44.09 ± 12.31	.657	45.48 ± 14.44	48.70 ± 12.77	.163
PWB personal growth	66.11 ± 8.92	60.72 ± 11.49	60.17 ± 11.67	62.20 ± 9.97	.142	59.61 ± 12.12	60.45 ± 11.52	.676
PWB positive relations	67.80 ± 11.62	59.34 ± 14.58	58.58 ± 13.34	61.56 ± 18.71	.060	57.12 ± 13.37	59.27 ± 13.30	.340
PWB life purpose	63.82 ± 11.30	55.36 ± 13.63	54.87 ± 13.45	54.69 ± 14.71	.181	53.75 ± 14.55	55.46 ± 12.39	.453
PWB self-acceptance	62.38 ± 12.60	46.88 ± 16.01	47.59 ± 16.41	40.73 ± 14.27	.614	44.79 ± 17.00	49.66 ± 15.54	.078

Abbreviations – AN, anorexia nervosa; BED, binge-eating disorder; BN, bulimia nervosa; BMI, body mass index; EAT, Eating Attitudes Test; ED, eating disorder; EDNOS, eating disorder not otherwise specified; GHQ, General Health Questionnaire; M, mean; PWB, Psychological Well-being Scales; SD, standard deviation; p, 2-tailed significance p value.

[a] Comparison between treatment completers and drop-outs.

[b] Comparison between test completers and non-completers.

Table 2
EAT, GHQ, and PWB scales changes between pre-treatment and post-treatment in ED outpatients (N = 185).

Outcome variable	Before treatment M ± SD	After treatment M ± SD	Before treatment median	After treatment median	Standardized test statistic (Z)	p	Effect size (r)
EAT total score	32.19 ± 20.61	25.28 ± 19.41	27.00	20.00	−5.835	<.0001*	−.429
GHQ total score	12.98 ± 9.04	9.80 ± 8.57	13.00	8.00	−5.779	<.0001*	−.425
PWB autonomy	51.89 ± 14.16	53.94 ± 14.40	53.00	55.00	−3.654	.0002*	−.269
PWB environmental mastery	47.32 ± 13.54	51.42 ± 13.70	46.00	51.00	−5.691	<.0001*	−.418
PWB personal growth	60.72 ± 11.49	63.62 ± 10.92	63.00	65.00	−4.769	<.0001*	−.351
PWB positive relations	59.34 ± 14.58	60.70 ± 12.71	59.00	63.00	−3.063	.002*	−.225
PWB life purpose	55.36 ± 13.63	57.85 ± 12.97	55.00	60.00	−3.893	<.0001*	−.286
PWB self-acceptance	46.88 ± 16.01	50.69 ± 14.98	47.00	51.00	−4.632	<.0001*	−.341

Abbreviations: EAT, Eating Attitudes Test; GHQ, General Health Questionnaire; M, mean; PWB, Psychological Well-being Scales; r, Pearson's r; SD, standard deviation; p, 2-tailed significance p value; Z, standardized Wilcoxon signed rank value.
* Statistical significance reached and maintained after alpha adjustments for multiple testing.

illness 9.03 ± 8.241 years. The mean age of the patient group was 28.89 ± 10.25 (age range 13–59 years). Mean body mass index (BMI) by diagnostic subgroup was 17.62 ± 4.74 kg/m^2 for AN, 22.10 ± 4.95 kg/m^2 for BN, 33.42 ± 6.24 kg/m^2 for BED, and 22.28 ± 8.19 kg/m^2 for EDNOS. About a fifth of patients were married (20.5%) and two-thirds (73%) were single. A third had a college degree (34.1%), 41.1% had a high school diploma, while 18.9% had completed middle school. Mean treatment length measured in number of sessions was 52.09 ± 24.69, while the median number of sessions was 46.

With regards to changes in psychological well-being over time (see Table 2), LOCF Wilcoxon signed rank tests showed significant improvements in ED outpatients in all psychological well-being scales with moderate effect sizes for environmental mastery (Z = −5.691; p < .0001; r = −.418), personal growth (Z = −4.769; p < .0001; r = −.351), and self-acceptance (Z = −4.632; p < .0001; r = −.341). Psychopathology in terms of EAT total score (Z = −5.835; p < .0001; r = −.429) and GHQ total score (Z = −5.779; p < .0001; r = −.425) significantly decreased with moderate effect sizes between pre- and post-treatment. All changes remained statistically significant when compared to the α critical level adjusted for multiple testing (p = .00625).

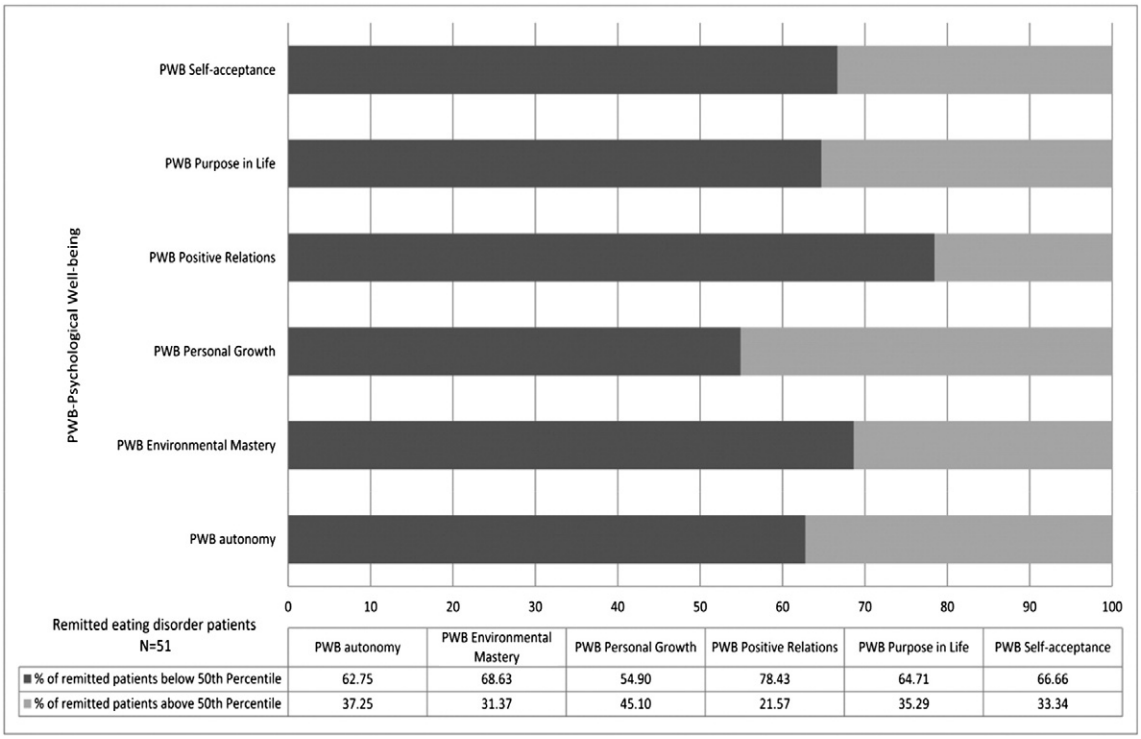
Fifty-one ED patients (34% of treatment completers) were defined as remitted following strict remission criteria [24]: 8 with AN, 20 with BN, 8 with BED, and 15 with EDNOS. Mean BMI at end of treatment was 21.49 ± 2.23 kg/m^2 for BN, 19.86 ± 1.31 kg/m^2 for AN, 23.37 ± 1.06 kg/m^2 for BED, and 21.76 ± 2.36 kg/m^2 for EDNOS. Remitted patients had a mean EAT total score of 14.13 ± 8.12 at post-treatment. Mean age was 27.71 ± 8.56 years with mean illness duration of 8.16 ± 6.97 years.

Remitted completers of treatment and healthy controls did not differ significantly in socio-demographic characteristics such as age, education levels, and married status. Mann–Whitney U tests between remitted completers of treatment (N = 51) and healthy controls (N = 55) (see Table 3) showed that post-treatment PWB median scores of patients in remission reached those of healthy controls with the exception of three scales that remain impaired and significantly lower with moderate and small effect sizes: PWB-autonomy (Z = −2.064, p = .039, r = −.200), PWB-positive relations (Z = −3.710, p = .002, r = −.360)

Table 3
Comparison between ED patients in remission (N = 51) and healthy controls (N = 55).

Outcome variable	Groups	n	Median	IR	Minimum	Maximum	Standardized test statistic (Z)	p	Effect size (r)
PWB autonomy	ED remitted patients	51	55.50	24	26	81	−2.064	.039	−.200
	Controls	55	62.00	16	23	81			
PWB environmental mastery	ED remitted patients	51	54.00	25	22	80	−1.863	.062	−.181
	Controls	55	61.00	16	28	77			
PWB personal growth	ED remitted patients	51	67.50	13	38	83	−.378	.706	−.037
	Controls	55	69.00	14	46	80			
PWB positive relations	ED remitted patients	51	62.00	20	35	83	−3.710	.002*	−.360
	Controls	55	71.00	13	25	84			
PWB purpose in life	ED remitted patients	51	61.00	22	25	77	−1.766	.077	−.172
	Controls	55	67.00	17	32	81			
PWB self-acceptance	ED remitted patients	51	55.00	24	22	79	−2.970	.003*	−.288
	Controls	55	62.00	17	35	102			

Abbreviations: ED, eating disorder; IR, interquartile range; M, mean; PWB, Psychological Well-being Scales; r, Pearson's r; SD, standard deviation; p, 2-tailed significance p value; Z, standardized Mann–Whitney U value.
* Statistical significance reached and maintained after alpha adjustments for multiple testing.



Remitted eating disorder patients N=51	PWB autonomy	PWB Environmental Mastery	PWB Personal Growth	PWB Positive Relations	PWB Purpose in Life	PWB Self-acceptance
% of remitted patients below 50th Percentile	62.75	68.63	54.90	78.43	64.71	66.66
% of remitted patients above 50th Percentile	37.25	31.37	45.10	21.57	35.29	33.34

Fig. 1. Percentages of remitted eating disorder patients below and above 50th percentile of Psychological Well-Being (PWB) control group scores.

and PWB-self-acceptance ($Z = -2.970$, $p = .003$, $r = -.288$). Applying adjustments to α levels for multiple testing (lowered critical $p = .008$), differences remain statistically significant ($p < .008$) in PWB-positive relations and PWB-self-acceptance.

While statistical analyses show that only two PWB scales remained impaired in remitted patients compared to controls, Fig. 1 illustrates that more than 50% of ED outpatients in remission have PWB scores that fall below the 50th percentile of healthy controls in all psychological well-being dimensions, despite significant treatment response.

4. Discussion

While it is known that CBT reduces symptomatology in EDs [1], less is known about how changes in positive functioning may ensue. Previous studies have investigated well-being impairment among ED patients and compared such scores to general population controls [4], as well as investigated psychological well-being after a psychotherapeutic intervention [20]. However, no studies had yet evaluated psychological well-being changes in ED patients following standard CBT-based treatment.

The current exploratory study, documenting remission rates similar to those reported by Ackard et al. [24], provides evidence of an improvement in psychological well-being in domains concerning autonomy, mastery over one's environment, positive evaluation of one's self, a sense of continued growth and development, the belief that life is purposeful and meaningful, and the possession of quality relationships with others following first-line ED treatment. Remitted ED patients, however, still exhibit impaired positive relations with others and self-acceptance after treatment compared to controls. Remitted patients did not greatly differ from controls in psychological well-being after treatment, but remained below healthy optimal levels. Such results are in line with previous studies exploring other positive gains in EDs, such as quality of life and social functioning, which improve with treatment but do not reach general population levels [2,34].

Several mechanisms of change following treatment in psychological well-being domains observed in the current study may be hypothesized based on the available literature on EDs. The increase in a sense of personal growth may be a consequence of CBT's efficacy in the reduction of symptoms [1] (such as food and body preoccupations, calorie counting, binging episodes, and obsessive thinking about food), giving patients a chance to invest their time and energy in themselves and their continued self-realization rather than in their disorder. Indeed, in AN patients, eating disorder symptoms were found to correlate significantly with a lack of existential well-being, encompassing also a lack of satisfaction in life progress [35].

The observed significant gains in environmental mastery in the current sample are in line with previous results in the literature in which a similar construct of self-efficacy improves in ED patients following cognitive behavioral-based treatment [36]. CBT may enhance environmental mastery by reducing

negative attributional styles and cognitions frequently concentrated in eating disorder patients on thoughts of self-blame and feelings of inadequacy and subjective incompetence. AN patients have been found to focus their ability to control and master their environment on their bodies and weight [38,39] which may be related to their perceived feelings of inadequacy and low ability to master their external lives and environment [4,37-39].

Autonomy was also found to significantly improve. In the individual suffering from an eating disorder, both psychodynamic and cognitive models underline the etiological role of the struggle for independence and autonomy, in the onset and maintenance of the disorder, respectively in terms of family enmeshment and problematic beliefs about the self and lack of control [22,40]. CBT through behavioral techniques such as self-monitoring, weekly weighing and regular eating may enhance autonomous behaviors and personal responsibility in the recovery process. Additionally, CBT may promote a sense of autonomy through cognitive strategies which reduce negative self-talk. However, the improvements in both environmental mastery and autonomy compared to controls were marginal. Such dimensions may require more specific and targeted intervention strategies than those offered in standard treatment in EDs for ratings to consistently reach and maintain healthy levels.

Purpose in life was found to improve in our sample. Women with AN symptoms commonly report low existential meaning in their lives compared to their unaffected peers [35] and may attribute purpose in life to their oral control [41]. Moreover, former ED patients identify reaching a healthy sense of purpose unrelated to eating behaviors and body issues as an important aspect in their quality of life post-treatment [42]. The ability to excessively self-regulate in terms of oral control and dietary restraints, is responsible for weight loss and may be linked with the patients' sense of accomplishment and self-worth, contributing to a greater distorted sense of purpose in life [38,41,43]. Through behavioral exercises aimed at exploring other qualities and abilities in life, cognitive restructuring, and nutritional rehabilitation, CBT integrated treatment may be able to break the dysfunctional association between meaning and purpose and dietary behaviors.

Wilson [44] had argued that self-acceptance, defined as holding a positive regard towards oneself, constitutes a pivotal aspect in EDs and should be considered a critical target for effective interventions. Self-acceptance improved in the current study but did not reach healthy levels in our remitted sample. CBT in general, in addition to primarily focusing on changing maladaptive behavior, includes several strategies which may promote acceptance of unchangeable aspects, such as body shape, in a healthy way. In our treatment, such strategies included education about body weight and eating and cognitive restructuring which modifies the patient's tendency of defining their self-worth in terms of body shape and weight [45], a hallmark feature of AN and BN [46].

Interpersonal maintenance models of eating disorders have recently been proposed according to which deficits in social skills, social anxiety, low assertiveness, and high aggressiveness play a role in the maintenance of EDs [47]. In our remitted patients, scores in positive quality relationships did not reach those of controls. This is consistent with previous findings according to which social functioning has been found to improve with treatment, but remain significantly below levels of the general population in spite of improvements in depressive and eating disorder symptomatology [48]. The observed improvements may be attributable to behavioral exposure to social situations and cognitive restructuring concerning dysfunctional thoughts regarding others.

From a clinical standpoint, the current exploratory study underscores an important finding, that is, the majority of patients considered remitted by strict criteria still exhibit impaired positive functioning. When psychological well-being remains compromised after standard pharmacological or psychotherapeutic treatment, much like the persistence of psychological symptoms [6,49] patients may be at higher risk of relapse [6,48-50] as reported in other remitted psychiatric populations [51–53]. Such considerations are important in EDs that are particularly hard to treat and in which drop-out and relapse are common phenomena [54,55]. More specifically, a higher dropout risk has been found to be associated with a lack of positive psychological characteristics, such as a low ability to pursue life goals [55].

The study has several limitations such as the lack of a control group to test whether gains in PWB may spontaneously happen in patients awaiting treatment. However, Ryff's theorized dimensions do not necessarily present fluctuations in the short-term, representing both state and trait elements [6]. Other limits include applying LOFC analyses for missing post-treatment data in psychometric measures in a large subset of treatment completers, and not controlling for psychopathology. While the small sample size and subsequent lack of adequate statistical power may be a limit, this lowers the risk for type I error possibly indicating replicable findings.

5. Conclusions

The assessment of treatment outcome in EDs may benefit from considering changes in positive functioning [2,34,40] such as psychological well-being, in addition to the standard measurement of BMI, symptomatology and behavioral parameters. CBT-based treatments for EDs may be strengthened by promoting the development of optimal domains particularly in the interpersonal realm, such as building of quality and warm relationships and focusing on enhancing self-acceptance.

As the development of novel approaches to improve recovery rates is needed in eating disorders [1], the integration of new psychotherapeutic strategies in standard treatment aimed at the promotion of balanced levels of psychological well-being may aid ED patients in their

recovery process. Future studies are warranted to investigate whether optimal functioning gains are maintained in the long-term. Moreover, future studies may explore the possible predictive role of psychological well-being in treatment outcomes in eating disorders.

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Annual Review of Clinical Psychology

Measurement-Based and Data-Informed Psychological Therapy

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Abstract

Outcome measurement in the field of psychotherapy has developed considerably in the last decade. This review discusses key issues related to outcome measurement, modeling, and implementation of data-informed and measurement-based psychological therapy. First, an overview is provided, covering the rationale of outcome measurement by acknowledging some of the limitations of clinical judgment. Second, different models of outcome measurement are discussed, including pre–post, session-by-session, and higher-resolution intensive outcome assessments. Third, important concepts related to modeling patterns of change are addressed, including early response, dose–response, and nonlinear change. Furthermore, rational and empirical decision tools are discussed as the foundation for measurement-based therapy. Fourth, examples of clinical applications are presented, which show great promise to support the personalization of therapy and to prevent treatment failure. Finally, we build on continuous outcome measurement as the basis for a broader understanding of clinical concepts and data-driven clinical practice in the future.

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INTRODUCTION

> A whole class of loosely related errors made in the clinical case conference arises from forgetting (on the part of the psychologist) or never having learned (in the case of the psychiatrist and social worker) certain elementary statistical or psychometric principles.
>
> Meehl 1973, p. 232

The above quote from Paul Meehl's essay "Why I Do Not Attend Case Conferences" is more than 40 years old; however, the topic of measurement in clinical practice is more current than ever. In recent decades, numerous randomized clinical trials (RCTs) have helped to establish psychological therapies as effective interventions to treat a broad range of psychological disorders (Barkham & Lambert 2021, Cuijpers et al. 2019). As a consequence, the implementation of psychological

treatments has become an important asset in most health care systems around the world. However, research demonstrating their average effectiveness does not mean that psychological treatments work for all patients under all circumstances. Furthermore, negative treatment response is rarely identified or reported in clinical trials and meta-analytic reviews that focus on average effects. As a consequence, monitoring actual clinical progress in routine care and using such data to improve treatment is a necessary supplement to psychological therapy implementation and has the potential to substantially change the way we think about psychotherapy as a science.

Outcome measurement has developed impressively over the past decade. New technological developments such as the Internet and computerized data assessment and feedback tools have made outcome measurement easier to implement than in the past. Recent developments in outcome measurement make use of the information to improve the clinical decision-making process by grounding clinical practice in empirical data. For example, psychometric and demographic data can be used by clinicians to personalize the selection of therapeutic techniques and to monitor a patient's response to therapy in real time (Lutz et al. 2021). Therefore, outcome measurement can be seen as an important and integral part of clinical competence, practice, and training. This is comparable to many other areas in the health care system, where continuous monitoring of health indicators is common in day-to-day clinical practice (e.g., temperature, blood pressure). In this sense, continuous outcome measurement forms the basis of modern measurement-based and data-informed psychological therapy (Delgadillo & Lutz 2020, Lutz et al. 2022). This move toward the adoption of data-informed psychological treatment is strongly justified in view of the limitations of clinical judgment, which have become better understood in recent decades.

Approaches that Guide Decision Making in Psychological Therapy

The assessment of treatment response is an issue that therapists have been grappling with since the early history of psychotherapy. Despite their theoretical differences, influential theorists like Sigmund Freud, B.F. Skinner, Aaron Beck, Carl Rogers, John Bowlby, and others recognized that psychological disturbances cannot be observed directly; rather, they are latent (i.e., hidden) phenomena that can be inferred from behavior, introspection, and self-report. In many traditions of psychological treatment, latent change is assumed to operate at two levels: the process level (i.e., maintaining factors or conflicts) and the consequence level (i.e., symptoms, interpersonal and behavioral problems). As such, the practice of psychotherapy implicitly or explicitly involves the monitoring of these changes to determine whether treatment is working as expected and whether it will ultimately benefit the patient. The central theme of this review concerns the continuous monitoring of change, which is referred to as routine outcome monitoring in contemporary literature, and the monitoring of related processes of change.

Broadly speaking, therapists can monitor treatment response via qualitative (i.e., as part of the therapy dialogue) and quantitative methods (i.e., using validated questionnaires or idiographic measures). Such information must somehow be processed and interpreted to inform treatment decisions. Clinical decision making is based on one of two general approaches: clinical judgment or actuarial methods. The first approach relies on intuition, which is a function of the therapist's way of processing (qualitative/quantitative) data, their clinical experience, theoretical orientation, and consultation with others. This method has been referred to as informal (Grove & Meehl 1996) since it is not usually based on a structured set of decision rules or equations, and it is highly variable within (i.e., changes over time) and between therapists. The second approach, referred to as formal or algorithmic, involves using structured decision rules or equations to combine and interpret data to reach a clinical decision.

The Limitations of Clinical Intuition

In a review of decision making in the field of clinical psychology, Garb (2005) argued that psychologists' judgments are error-prone because of the influence of heuristics and biases, as defined in Tversky & Kahneman's (1974) seminal work. For example, the representativeness heuristic may partly explain the modest interrater reliability of therapists' diagnostic assessments, as these judgments are influenced by how closely a patient resembles the diagnostic prototype that each assessor uses to make a diagnosis (Evans et al. 2002). The influence of selection and confirmation biases in therapists' clinical interviews and interactions is a related issue, as therapists vary widely in the extent to which they gather key information (e.g., symptoms) to determine a diagnosis (Miller et al. 2001). Another bias that has received attention in the field of psychotherapy is clinical overoptimism, as exemplified in the classic study by Hannan et al. (2005) in which therapists' prognostic assessments of their patients significantly underestimated the number of patients who eventually made little improvement and the number of those who deteriorated after therapy (as determined using psychometric patient-reported data). In another example, Walfish et al. (2012) showed that therapists estimate that about 85% of their patients have improved or recovered, a success rate far higher than those found based on measured outcomes in clinical trials and routine care. Furthermore, 90% of clinicians rate themselves in the upper quartile of successful therapists, and none consider themselves below average. This overly positive self-assessment is known as the better-than-average effect and can also be found in other areas and professions (e.g., Zell et al. 2020). In part, these biases of clinical intuition are a result of therapists having to rely on indirect (i.e., proxy indicators of latent factors) and often subjective information (i.e., the patient's experiences narrated verbally) to make judgments. Experts in the field of decision making agree that accurate intuition can be developed in situations that provide regular and highly objective feedback, enabling judges to refine their pattern-recognition abilities (Kahneman & Klein 2009). Hence, it is not surprising that clinical intuition is not highly reliable in psychotherapy in the absence of systematic routine outcome monitoring and empirically derived decision-support tools.

Therefore, there is a strong case for the additional use of formal and empirical methods. Of course, formal methods of routine outcome monitoring are also imperfect, but they offer additional empirical data to support clinical decision making. The aim of this article is to review the history of formal routine outcome monitoring methods, their strengths and limitations, their implementation, and their future development. Over the years, several terms have been used to describe this line of research, including practice-oriented research, patient-focused research, practice-based evidence, and routine outcome monitoring (Barkham & Lambert 2021; Castonguay et al. 2013, 2021; Lutz et al. 2021). In this review, we use the terms patient-focused feedback research and measurement-based as well as data-informed psychological therapy. These terms highlight the clinical decision-support function of such endeavors and the new trend to use such data to personalize treatment (Delgadillo & Lutz 2020).

MEASURING OUTCOMES

Supporting clinical decision making with empirical data can be seen as a major advance in the field of psychotherapy. This process can rely on sparse data (i.e., collected pre- and posttherapy) or continuous and intensive data collection (i.e., collected during therapy). In this section we first present a theoretical framework for data-informed psychological therapy. Then we describe the classical pre–post treatment method before moving on to multiple assessments, session-by-session assessments, and intensive longitudinal assessments.

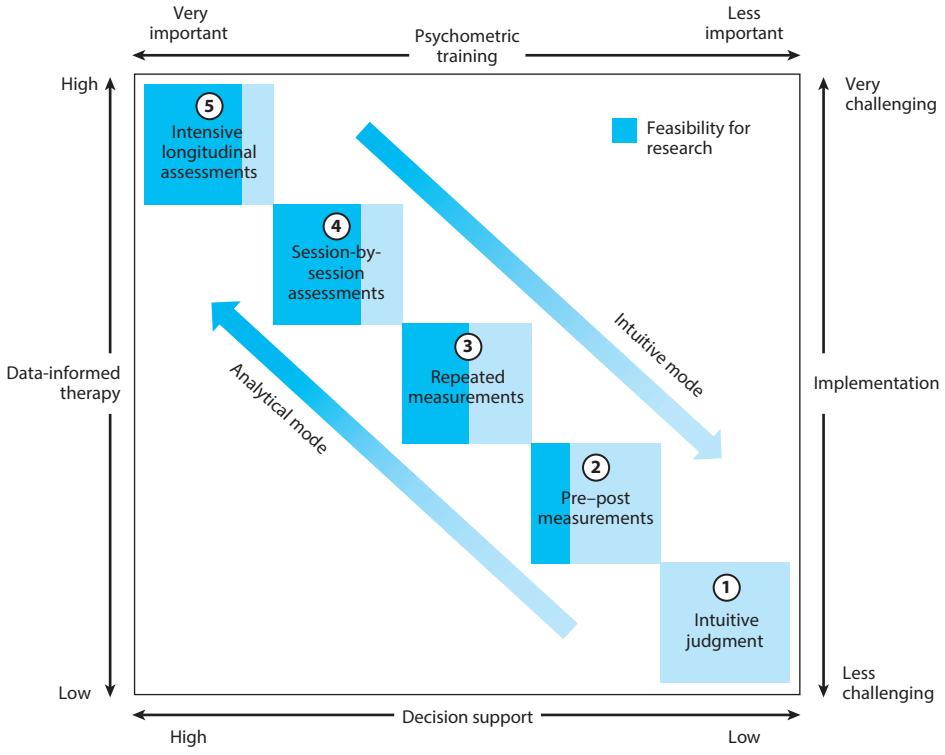

Figure 1

Matrix of assessment modes in measurement-based and data-informed psychological therapy. Darker shades of blue indicate greater feasibility for research.

Practice-Based Evidence and Clinical Decision Making

Figure 1 displays a matrix of assessment modes in clinical practice and their relation to empirically supported clinical decision making. The matrix is based on Hammond's (1978) modes of inquiry in evaluation research and includes five modes and six dimensions. It has been adapted to describe modes and dimensions of measurement-based and data-informed psychological therapy. The six dimensions include (*a*) the potential for data-informed psychological therapy based on the information provided by the assessment structure, ranging from very low to very high (left vertical axis in **Figure 1**), (*b*) the extent of empirically based support to generate practice-based evidence for clinical decision making (lower horizontal axis in **Figure 1**), (*c*) the challenge of implementing specific data collection modes into a clinical routine, ranging from less challenging to very challenging (right vertical axis in **Figure 1**), (*d*) the intensity of psychometric training, which is necessary to make use of the collected information (upper horizontal axis in **Figure 1**), (*e*) the usefulness of the data collection strategy for practice-oriented research (darker shades of blue in **Figure 1** indicate greater usefulness), and (*f*) the mode of cognition, ranging from analytical to intuitive thought (blue arrows in **Figure 1**).

Mode 1 represents the predominant use of intuitive clinical decision making, not influenced by outcome measures. This is the traditional psychotherapy mode and likely represents the most common mode to date. Therapists working in this mode adapt their clinical approach based on experience with similar patients while often simultaneously following guidelines set out by

professional organizations, employers, or policy makers. This may be a conscious choice (i.e., a preference for intuitive decision making) or may be due to lack of training, resources, or time to implement routine outcome monitoring. Nevertheless, this means that clinical decision making is mainly conducted without routine outcome assessments. Furthermore, in mode 1, empirically based decision support is nonexistent, and practice-based evidence is not systematically generated.

Pre–Post and Repeated Assessments

Mode 2 represents the first step of implementing data into clinical practice. Data collection and clinical decision making are based on a pre–post treatment data collection design (or direct collection of posttreatment information only). This mode allows conclusions to be drawn about the effectiveness of treatments under routine conditions and is relatively easy to implement in clinical practice. However, this form of assessment is often limited by substantial missing data, as patients often drop out, leave treatment early, or do not fill out the final questionnaire for other reasons. This becomes an even larger issue when longer-term follow-up assessments are added. Mode 3 includes repeated measurements over the course of treatment—for example, every four or five sessions or weeks. Such a repeated-measurement setup has greater potential to support clinical decision making and research. For example, expected treatment response (ETR) models (covered later on) can be developed and used to monitor and adjust therapy in real time. These modes require basic training and knowledge of psychometrics to make use of the data for clinical decisions regarding individual patients, groups, and services.

Session-by-Session Assessments

Most studies on routine outcome monitoring and the effectiveness of psychometric feedback in clinical practice focus on assessments on a weekly or session-by-session basis (see mode 4 in **Figure 1**). Such an assessment structure provides the context for the effective use of measurement-based treatments, especially in combination with clinical support tools (CSTs) for patients at high risk of treatment failure (e.g., Lutz et al. 2022). As indicated in **Figure 1**, here the potential for data-informed psychological treatment is high. However, more psychometric knowledge and therapist training are needed to make use of the information and integrate it into clinical practice. Of course, the implementation of a session-by-session outcome assessment structure is more challenging; however, the potential value of the generated information for further research is also high.

Furthermore, this mode includes a data-generation strategy, which has laid the foundation for several new developments in clinical research over the last decade. Usually, clinical concepts are developed based on theory, or intuitively based on expert clinical experience, and then tested in RCTs (or meta-analyses) applied to evaluate the effectiveness of treatment orientations or packages (Cristea et al. 2021). However, there are limitations to thinking about clinical concepts of psychological therapies exclusively based on RCTs and meta-analyses, as was recently pointed out by Baldwin & Imel (2020). The categorization of different variants or orientations of psychological therapy can be difficult (in comparison, for example, to most somatic treatments) and is usually based on arbitrary boundaries and theoretical arguments about the predominance of certain change processes being more or less relevant in specific forms of treatment. Therefore, this line of research requires a complementary approach that can be routinely implemented in clinical practice and that continuously uses research results to improve treatment outcomes in routine clinical practice (e.g., Howard et al. 1996, Lambert et al. 2001). Therapists not only deliver treatment but simultaneously collect data by assessing patients' progress session by session over the course of treatment (Lutz et al. 2019). Large databases generated in this way can then be analyzed

using advanced statistical analyses (e.g., growth curve modeling, multilevel modeling, machine learning algorithms) to develop clinical decision-support tools. This allows therapists not only to track progress (and potential side effects) on an individual level but also to measure the variability of change as a function of patient characteristics, treatment interventions, therapists, and clinics/services (Barkham & Lambert 2021). For example, on an aggregated level, the data can serve to investigate side effects, treatment dosage, therapist effects, and clinic effects (e.g., McKay & Jensen-Doss 2021). The session-by-session assessment structure is accompanied by statistical and methodological developments to analyze the nested structure of longitudinal data (e.g., Raudenbush & Bryk 2002). Such multilevel models allow a better disentanglement of variance components at the session, patient, therapist, and service levels. They also allow the disentanglement of between-patient and within-patient variance components to study mechanisms of change (e.g., Hamaker & Wichers 2017).

On a larger scale, such session-by-session information holds the potential to establish a community or national data collection system to which independent research groups can be granted access. Such endeavors have just begun to emerge in the field, as exemplified by the Improving Access to Psychological Therapies (IAPT) initiative in England (see Clark 2018). In combination with technological innovations, session-by-session assessments and clinically informative data-driven decision-support tools can facilitate the development of large scientist-practitioner infrastructures.

Intensive Longitudinal Assessments

Despite the advances that session-by-session assessments have made possible for data-informed therapy, in recent years, even more fine-grained measurements have been applied in psychotherapy research. Proponents of these intensive longitudinal assessments have argued that higher resolution is necessary to obtain useful information about dynamic changes in patients' everyday experiences.

Data from such high-frequency measurements can be obtained via ecological momentary assessment (EMA), a real-time, within-subject assessment allowing measurements several times a day (mode 5 in **Figure 1**). EMA has also been referred to as ambulatory assessment or experience sampling (Ebner-Priemer & Trull 2009). During the last two decades, technological innovations have drastically facilitated these measurements, allowing laborious paper-and-pencil diaries to be replaced by technological devices such as smartphones, smartwatches, and other mobile high-tech devices (Miller 2012). EMA circumvents the problem of retrospective bias, is more ecologically valid as it can be conducted within patients' daily lives, and has higher resolution and can thus better represent intrapersonal processes (Ebner-Priemer & Trull 2009). It can simultaneously collect psychological, physiological, and behavioral variables, allowing the examination of situation-specific relationships and feedback to the patient in real time. Furthermore, EMA is face-valid, convenient, and unobtrusive for patients (Miller 2012).

EMA is most often used to collect self-report questionnaires, which patients complete on their own or with the help of a smartphone. The ability to collect psychometric measures multiple times a day supports data-informed therapy and—in principle—allows for a high level of decision support (**Figure 1**). In psychotherapy research, intensive longitudinal assessments have been used to improve the prediction of early change (Husen et al. 2016), treatment response (Fisher et al. 2019, Wichers et al. 2012), and treatment dropout (Lutz et al. 2018). At the same time, more therapist training in psychometrics is necessary compared to lower-frequency assessment methods, and implementation of the assessments is more challenging, often leading to higher dropout rates during assessments. Furthermore, when implementing EMA, decisions must be made about the duration,

frequency, scope (number of items), and timing of assessments. To date, intensive longitudinal assessments have been implemented very heterogeneously, and a consensus on EMA survey design standards is lacking. However, some authors have already offered suggestions to improve transparency and user acceptability (e.g., Fisher et al. 2021). An important limitation of intensive longitudinal assessments concerns patient burden (completion of questionnaires): Longer questionnaires, rather than higher assessment frequency, increase the burden and affect data quantity and quality (Eisele et al. 2022).

In addition to the high-frequency collection of psychometric measures, EMA can be used to collect biological and physiological measures (e.g., heart rate, electrodermal activity, motor activity, sleep). For example, wristbands that collect physiological parameters are already better than chance at predicting epileptic seizures (Meisel et al. 2020). Smartwatches and associated mobile sensors enable the passive and continuous collection of huge amounts of data within patients' daily lives with minimal patient burden (e.g., Jacobson et al. 2019, Wright & Woods 2020). This type of data collection has been referred to as digital phenotyping and has recently been applied in psychotherapy research to identify diagnostic groups, symptom severity, and patterns of change as well as to inform treatment selection (e.g., Hehlmann et al. 2021, Jacobson et al. 2019, Webb et al. 2022).

Intensive longitudinal data can also help to optimize the assessment of therapy processes during treatment. This allows intraindividual changes to be assessed with a higher resolution and standardized change measurements to be supplemented by idiographic approaches. Intensive longitudinal assessments are also necessary for the continuous evaluation of video and audio recordings of a therapy session. For example, physical movements of the patient and therapist (Ramseyer & Tschacher 2011), speech content and prosodic features (Imel et al. 2014, Paz et al. 2021), and emotions based on gestures and facial expressions (Baur et al. 2020) can be recorded automatically. This allows a patient, a patient–therapist dyad, and the entire therapeutic process to be captured not only unidimensionally based on known pretherapy self-report items but also multidimensionally based on high-frequency data from different modalities (e.g., audio, video, self-report, physiology).

Recently, data-driven tools have been developed to provide therapists with personalized feedback by dynamic visualizations of intensive longitudinal data (e.g., Bringmann et al. 2021, Hehlmann et al. 2021). However, these approaches still have to contend with a number of problems in addition to the challenging implementation and large training effort. These data require the use of sophisticated statistical analysis methods, which are currently still being developed and refined (Bringmann 2021). In addition, many analytical options and decisions need to be made during data preparation and evaluation, whereby small changes can lead to significant differences in the results. Therefore, these approaches are currently more likely to be found in the context of pilot and proof-of-concept studies.

Summary

Practice-based evidence and clinical decision making are based on data assessed before, during, and after treatment. In measurement-based and data-informed psychological therapy, outcomes are measured and observed at varying frequencies: (*a*) Pre–post assessments are easy to implement but are limited by missing data and can represent only simple changes, (*b*) repeated measures throughout treatment can help to model patterns of change, to inform treatment decisions, and to enable psychometric feedback, (*c*) session-by-session assessments allow progress to be tracked on an individual level to develop CSTs and examine variability in change as a function of patient, therapist, and/or treatment characteristics, and (*d*) intensive longitudinal assessments can improve the representation of high-frequency intrapersonal processes in patients' daily lives. Currently,

however, these high-frequency measurements still face several problems, and therefore session-by-session assessment remains the best-suited method to assess treatment progress and to inform decisions in routine care.

MODELING PATTERNS OF CHANGE

Interest in how patients change over time has been documented for several decades in the field of psychotherapy, although earlier investigations were hampered by unreliable methods of assessing longitudinal patterns of change. In the last 35 years, however, a large body of empirical research on this topic has accumulated. To a great extent, the development of brief psychometric measures that could be regularly collected during psychotherapy led to important methodological and conceptual advances. Patients are not sufficiently described by their diagnoses because they are quite different from each other across several other demographic, clinical, and interpersonal characteristics that are related to treatment response (e.g., Lutz et al. 2021). These individual differences influence the longitudinal trends that characterize symptomatic change over time as well as symptom fluctuations that can be used to develop empirically supported clinical decision rules. These concepts and related findings are discussed below.

Dose–Response

Research on trajectories of change can be traced back to Kenneth Howard and colleagues' seminal examination of the dose–response effect (Howard et al. 1986). Alluding to the pharmacological notion of a relationship between the dose of medication and its expected effects, Howard et al. (1986) aggregated routine outcomes data from 2,431 psychotherapy patients across 15 studies and modeled the statistical relationship between the number of treatment sessions (dose) and symptomatic improvements. This relationship was nonlinear and characterized by a negatively accelerating (log-linear) trend, where most of the improvements were observed in the earlier sessions, showing diminishing improvements thereafter. They proposed that an optimal dose of therapy could be defined as an interval between the point at which at least 50% of cases respond to treatment and the point after which response rates plateau, which in their study was around 8–26 sessions. Conceptually, the dose–response notion is based on the assumption that therapy sessions cause change and have a cumulative effect (more sessions are better), but the potency of this effect diminishes over time. This study motivated a surge of investigations over the following decades in clinical samples with various diagnoses and treatment modalities (e.g., Baldwin et al. 2009, Barkham et al. 1996). Despite the diversity of statistical methods applied in these studies, a systematic review of over 20 dose–response studies (Robinson et al. 2020a) concluded that a curvilinear relationship between treatment duration and outcomes has been extensively replicated, although the "optimal dose" apparently varies according to clinical heterogeneity (e.g., impairment level), treatment intensities (e.g., guided self-help versus psychotherapy), and treatment settings (e.g., student counseling, outpatient care, inpatient care). Consistent with these assumptions, more recent investigations (Robinson et al. 2020b) of highly standardized treatments and more diagnostically homogeneous samples report differential dose–response patterns according to diagnosis [e.g., posttraumatic stress disorder (PTSD) requires lengthier treatment than generalized anxiety disorder] and treatment intensity [e.g., the dose effect of guided self-help plateaus sooner than that of cognitive behavioral therapy (CBT)].

Additional research has revealed that not all patients follow a uniform dose–response relation and that subgroups of patients follow different latent trends of change (e.g., Lutz et al. 2014, Owen et al. 2015). Such findings motivated the proposal of an alternative perspective, the "good-enough level" (GEL) model. Barkham et al. (1996) argued that the classic log-linear model could be a

statistical artifact that results from the aggregation of data from cases that in fact have heterogeneous treatment response patterns (i.e., early responders, gradual responders, nonresponders with lengthy treatments, and those that drop out). Rather than assuming uniformity across all patients, the GEL model assumes that the number of sessions needed to attain improvement varies from case to case, resulting in a process of "responsive regulation" of treatment duration (Barkham et al. 2006, Stiles et al. 1998). Several studies have provided support for this model, although studies comparing the goodness of fit between the dose–response and GEL models have tended to yield mixed findings (e.g., Stulz et al. 2013). A systematic review of 15 studies in this area found empirical support for some of the assumptions of the GEL model, such as the observations that higher intake severity tends to require lengthier treatments and that some subgroups of cases show curvilinear change while others show linear change (Bone et al. 2021a).

Overall, the dose–response and GEL models have empirical support and together indicate that (*a*) subgroups of patients change in similar ways, (*b*) change is most often nonlinear, (*c*) intake severity influences the linearity and duration of treatment, (*d*) although some patients respond early and others more gradually, the net benefit of therapy tends to occur within a predictable window of time, and (*e*) patients who remain in treatment beyond a typical optimal dose without showing reliable change are more likely to be nonresponders. The precise operationalization of the latter two points, however, remains a matter of controversy and debate in the field (e.g., Nordmo et al. 2020, Robinson et al. 2020a). Consequently, predicting and monitoring which patients are likely to require shorter or lengthier interventions is a goal that is empirically justified and clinically important.

Early Response

Early response refers to symptomatic improvement during the initial phase of treatment (usually the first month[1]). Over the last three decades, numerous studies have investigated early response and its prognostic value in different conditions, such as major depressive disorder, panic disorder, generalized anxiety disorder, and eating disorders, and in samples of patients with heterogeneous presenting problems (e.g., Chang et al. 2021, Delgadillo et al. 2014, Lutz et al. 2014, Moggia et al. 2020). A systematic review aggregated available data from 15 studies in a random-effects meta-analysis and reported a large pooled effect size ($g = 0.87$; Beard & Delgadillo 2019). Early responders had significantly better posttreatment outcomes compared to patients without early response. The detected effect seems to be larger in anxiety measures ($g = 1.37$) compared to depression measures ($g = 0.76$). Furthermore, early response seems to be a phenomenon that occurs in a variety of treatment models, such as CBT, the cognitive behavioral analysis system of psychotherapy (CBASP), behavioral activation, interpersonal psychotherapy (IPT), psychodynamic therapy, guided self-help, Internet-based CBT, and group therapy (Beard & Delgadillo 2019, Moggia et al. 2020).

Expected Treatment Response

The development of ETR models was key to the rise of measurement-based care. The ETR concept was first proposed by Lutz et al. (1999), who used archival data from a large routine outcome monitoring database and generated an expected recovery curve for individual patients based on

[1]Early response is often conceptualized by reliable and/or clinically significant change (Jacobson & Truax 1991). However, several studies have also used growth mixture models to identify patients' early change patterns (e.g., Lutz et al. 2014, Moggia et al. 2020).

growth curve modeling and seven predictors (well-being, symptoms, life functioning, past use of therapy, problem duration, treatment expectations, global assessment of functioning). Finch et al. (2001) applied a similar ETR model including 80% tolerance intervals around the predicted ETR curve to identify the 10% of cases that were at risk of deteriorating (outside the upper tolerance interval, also referred to as a failure boundary). This model was applied as an empirical decision rule in several progress feedback studies to identify patients who are on track (meaning their symptom change is within the expected course of treatment) or not on track (meaning their symptom trajectory is worse than expected and crosses the upper failure boundary) (e.g., Lambert 2017).

After these early applications, further ETR approaches were developed to model change and support clinical decision making. For example, Lutz et al. (2005) modeled ETR for patients using the machine learning algorithm called nearest neighbors (NN). The NN approach allows the generation of an ETR model for each patient based on a similar reference group (their nearest neighbors) with similar intake characteristics. The predictive accuracy of this advanced ETR model increased further when information on early response was included and ETR curves were dynamically adapted over the course of treatment (Bone et al. 2021b, Lutz et al. 2019). Furthermore, methods modeling latent growth trajectories for outcome and suicidal ideation (e.g., growth mixture models) have also been developed to generate ETRs based on change patterns of similar subgroups (e.g., Kyron et al. 2019, Lutz et al. 2014, Saunders et al. 2016, Stulz et al. 2013). Other variations on the ETR concept include systems that model expected change patterns for type of treatment. For example, Lutz et al. (2006) generated individual NN ETR models for patients receiving CBT and patients receiving an integrative CBT and IPT treatment to predict the optimal modality before patients begin treatment. Further ETR models have been developed to monitor and provide feedback on treatment dropout, common factors and therapeutic processes such as the patient–therapist alliance, outcome expectations, empathy, and substance use (e.g., Crits-Christoph et al. 2012, McClintock et al. 2017, Miller et al. 2005).

Nonlinear Change: Sudden Gains and Losses

As described above, an individual patient's treatment response can substantially deviate from aggregated or predicted group trends, and dismissing this phenomenon as error variance leads to a loss of information (e.g., Krause 2018). The investigation of sudden gains and losses is an area of research dealing with nonlinear change patterns (e.g., Tang & DeRubeis 1999). A sudden gain or loss is defined as a significant symptomatic positive (gain) or negative (loss) change between two consecutive sessions during the course of treatment. In their seminal work on the topic, Tang & DeRubeis (1999) identified 79% of patients with (at least one) sudden gain in a group of patients with a positive outcome in CBT for depression. In most cases, these gains occur early in treatment; this finding suggests that the phenomenon is related to the early response concept described above. However, gains also occur between later sessions, and some therapists seem to be better than others at facilitating and initiating such gains (Deisenhofer et al. 2021). Aderka et al. (2012) conducted a meta-analysis including 16 studies that identified sudden gains not only in major depressive disorder but also in social anxiety disorder, PTSD, and other anxiety problems as well as different treatment approaches (e.g., CBT, IPT, supportive expressive therapy). Overall, the analysis showed that sudden gains had an effect on primary outcome measures at posttreatment ($g = 0.62$) as well as at follow-up ($g = 0.56$). Although only a few studies have been conducted on sudden losses, their findings are still useful for the development of clinical decision rules (e.g., Krüger et al. 2014, Lutz et al. 2013). Patients with sudden losses seem to benefit less from treatment than patients with sudden gains or patients with no significant shifts. Furthermore, sudden losses are less frequent and more equally distributed over the course of treatment than sudden gains.

Monitoring Clinical Processes and Mechanisms

In most applications of measurement-based care, outcome measures are tracked and feedback is provided to therapists. Therefore, mainly treatment outcome predictors and moderators are relevant, and they are applied in the development of decision rules. While predictors and moderators provide information about for whom treatment works, mediators inform us about how treatment works (e.g., Kraemer et al. 2001). However, in recent years, several investigations using repeated assessments of process and outcome variables over the course of therapy (e.g., session by session) and multilevel modeling have allowed advancements in the establishment of mechanisms and outcome relations by separating within- and between-patient variance components of the process–outcome relation (e.g., Falkenström et al. 2016). Therefore, several within- and between-patient associations among processes (e.g., coping skills, therapeutic alliances/ruptures, emotional involvement, competence and skills) and symptom change in psychological therapy have been successfully investigated (e.g., Crits-Christoph & Connolly Gibbons 2021; Gómez Penedo et al. 2022; Lorenzo-Luaces & DeRubeis 2018; Rubel et al. 2017, 2020; Strunk et al. 2012; Zilcha-Mano 2017).

Furthermore, measures on change mechanisms have been added to applications of measurement-based care to enrich the clinical usefulness of such systems (e.g., McAleavey et al. 2021, Miller et al. 2005, Lutz et al. 2019). Several authors have recently argued that psychotherapy practice and research should focus on therapy processes instead of treatment schools or the classical illness model of psychopathology and should move toward a process-based and transdiagnostic approach with a focus on monitoring and targeting central evidence-based therapeutic procedures and processes (e.g., Goldfried 2019, Hofmann & Hayes 2019, Lutz & Schwartz 2021).

Complex Models and Critical Instability

Critical transitions represent another line of research on nonlinear patterns of change (Scheffer et al. 2009). These transitions refer to sudden changes in the state of a complex system, which thereby tips from one state (e.g., symptoms meeting diagnostic criteria for a mental disorder) to another distinct state (e.g., full remission of symptoms). This phenomenon has already been observed in ecosystems, the climate, the financial market, and neurological disorders (e.g., Lenton et al. 2008, May et al. 2008).

Conceptually comparable, critical instability can be seen as a universal early warning signal (EWS) that indicates the system's increasing instability and thus the increasing probability of a change of state (Scheffer et al. 2009). These warning signals show the critical slowing down of a system (i.e., decelerated recovery from small perturbations) that occurs when a system is approaching a transition. For example, a flurry of obsessional thoughts and related emotions may increase temporarily, immediately preceding the transition toward a state of remission of symptoms of obsessive–compulsive disorder (Heinzel et al. 2014). This can be measured in time-series data by, for example, detecting increasing autocorrelation and regression at low lags, increasing variance, changing spectral properties, and increasing skewness and kurtosis (Dakos et al. 2012). However, few studies have investigated intraindividual change in EWS (Wichers et al. 2016). For example, Olthof et al. (2020) found EWSs in a large sample to be associated with sudden gains and losses. In a feasibility study on seven cases, time-varying change point autoregressive models detected gradual and abrupt changes in continuously measured physiological stress levels that might improve outcome prediction (Hehlmann et al. 2021). However, actual intraindividual changes of EWS and their predictive power need to be investigated in future studies (Bringmann 2021).

Network models of psychopathology are also examples of complex models. The network approach assumes that symptoms (e.g., affect, thoughts, behavior) influence each other rather than

being triggered by an underlying latent disease factor (e.g., Borsboom 2017, Hofmann & Hayes 2019, Wright & Woods 2020). Network analysis models the connections (edges) between the symptoms (nodes) and allows the calculation of so-called centrality measures, which indicate the centrality of a variable within the network and thus its potential influence on other nodes. This approach was applied to identify relevant psychopathological variables via their centrality in a network and the dynamics among symptoms (Contreras et al. 2019). Beyond psychopathology, it was used in process research to identify bridges between intersession processes and symptom stress (Kaiser & Laireiter 2018) as well as in outcome research to predict treatment dropout (Lutz et al. 2018) and recovery from major depressive disorder (van Borkulo et al. 2015).

Recently, however, the fit of network models and centrality measures to psychological data has been questioned. Especially the idea of betweenness of a node, but also the assumption of symptoms as distinct nodes, has been discussed (Bringmann 2021). Furthermore, networks of symptoms have been found to be unstable—a finding that calls into question their reliability and validity—and this methodological heterogeneity challenges the comparability and interpretability of the results (Bringmann 2021). Therefore, more sophisticated models need to be developed, and the acceptability of new applications needs to be evaluated under real-world clinical conditions (Epskamp 2020). For example, in a pilot study on 12 patient–therapist dyads, Frumkin et al. (2021) found that patients were willing to participate in these assessments, were interested in the results, and tended to evaluate the data and models as useful, while therapists were less open to this method and were not yet convinced of the added value of the results.

Summary

Four findings on patterns of change are especially important for outcome monitoring in clinical practice: (*a*) Change, outcome, and dropout are influenced by patients' intake characteristics, (*b*) change is influenced by patients' early response to treatment, (*c*) change is influenced by nonlinear phenomena such as sudden gains and sudden losses, and (*d*) probably most importantly, individual patient change can vary widely, deviating from general trends or symptom trajectories derived from clinical samples. This information can be used to identify patients at risk for treatment failure.

CLINICAL DECISION TOOLS

Identifying empirically derived decision rules to support clinical decision making is one of the central goals of clinical research (e.g., Meehl 1973). In this section, we provide examples of some of the key developments arising from routinely collected data, which enable data-informed psychological therapy and decision making.

Rational Versus Empirical Decision Rules

Two distinct approaches to develop decision rules using empirical data have been applied in studies that monitor progress and tailor treatments to patients' needs (cf. Lambert et al. 2002). Rationally derived models are based on clinical assessments and the predefined classification of patients. A widely used model is based on the concepts of reliable change and clinically significant improvement (Jacobson & Truax 1991). Typically, routine outcome monitoring is applied to enable a prognostic assessment (e.g., likelihood of response to treatment) based on symptomatic change since the initial intake assessment. Thereby, reliable change criteria are used as a classification rule. Studies applying these methods show that these classification rules reliably predict treatment response in diverse treatment settings and clinical populations (e.g., Delgadillo

et al. 2014, Flood et al. 2019, Lutz et al. 2006). Another example of a rationally derived model is the routine outcome monitoring method applied in IAPT services in England. In these services, all patients complete depression and anxiety questionnaires on a session-to-session basis, and therapists apply conventional cutoff scores to assess treatment progress. Symptom reductions below the cutoff on at least one of the two measures indicate a favorable response, while a reduction below both measures' cutoffs is considered a full recovery (Clark 2018).

In contrast, empirically derived methods are based on prediction models and the above-described ETR concept and associated developments. Some newer applications also include prediction models and critical failure boundaries (beyond which the probability of negative treatment outcome is greater than positive outcome) for individual patients by dynamically recalculating failure boundaries based on current progress data—that is, assessments from previous treatment sessions (e.g., Bone et al. 2021b, Lutz et al. 2019). For example, Bone et al. (2021b) used session-by-session self-report depression and anxiety measures from 42,992 patients in IAPT services to train a dynamic prediction model (adapting failure boundaries over the course of treatment) using iterative logistic regression analysis. Subsequently, the model was evaluated on an external test sample of 30,026 patients. This dynamic prediction model improved the accuracy of empirically derived decision rules to identify patients at risk for treatment failure.

Prognostic Indices and Treatment Selection Models

Prognostic models can complement the therapist's clinical impression and thus support decision making. Data-informed prognostic indices (PIs) and prediction models based on patient information have recently been developed using machine learning approaches (see review by Chekroud et al. 2021). These PIs and prediction algorithms can be used as criteria for treatment selection to identify the optimal treatment package or treatment strategy that suits the individual best. For example, Lorenzo-Luaces et al. (2017) found that patients with a worse prognosis (i.e., an unfavorable PI) benefited more from CBT than from treatment as usual or brief therapy, while the treatment alternative made no difference if the overall prognosis was good.

Another option for treatment selection is to estimate the therapy outcome for each treatment alternative, and to recommend the treatment with the most favorable prognosis, that is, with the best outcome prediction. For this purpose, Lutz et al. (2005) used an NN model to predict patient-specific differential response to treatments. Another concept, the Personalized Advantage Index (PAI), was introduced by DeRubeis et al. (2014); it represents the difference of two predictions and quantifies the estimated superiority of one treatment model over another one (a PAI of zero means that both treatments should be equally effective for a given patient). Patients who received their recommended treatment have been shown to have better outcomes in studies evaluating a wide range of treatment packages, such as cognitive, interpersonal, person-centered, and psychodynamic therapy as well as antidepressant medication and eye movement desensitization and reprocessing (Cohen et al. 2021, Delgadillo et al. 2020, Deisenhofer et al. 2018, Huibers et al. 2015, Webb et al. 2019). Another line of research focuses not on predictions of different treatment packages but rather on expected change in clinical modules, strategies, and mechanisms (e.g., such as problem-solving and motivation-oriented interventions) to tailor clinical interventions within a treatment package (e.g., Gómez Penedo et al. 2022; Lutz et al. 2019; Ng et al. 2021; Rubel et al. 2018, 2020).

In addition, recent studies have begun to cross-validate treatment selection models using independent holdout data (e.g., Delgadillo & Gonzalez Salas Duhne 2020, Schwartz et al. 2021) and data from another study (cross-trial validation; van Bronswijk et al. 2021), or to apply these models prospectively in clinical trials (Delgadillo et al. 2021, Lutz et al. 2022).

In the future, predictions and recommendations based on pretherapy assessments collected at one point in time could be complemented by EMA data (Fisher et al. 2019, Webb et al. 2022; see mode 5 on intensive longitudinal assessments above). Furthermore, variables from different data sources can be integrated multimodally to improve predictions and recommendations (e.g., clinical and video data; Atzil-Slonim et al. 2021).

Therapist–Patient Matching

Variability in treatment outcomes between therapists (also known as therapist effects) has been extensively documented in the psychotherapy literature (Baldwin & Imel 2013). Even if they apply the same treatment protocol (e.g., CBT) for the same target problem (e.g., depression), some therapists attain impressive clinical outcomes compared to their peers, while others are less effective than average. Studies indicate that therapist effects may be partly related to patients' features, such that highly effective therapists are especially helpful for patients with severe levels of distress and risk of self-harm (Saxon & Barkham 2012). Furthermore, therapist effects also appear to be related to therapists' interpersonal skills (Heinonen & Nissen-Lie 2020) and particularly their ability to work effectively in highly challenging cases (Anderson et al. 2016). It logically follows that matching some patients to specific therapists could be a potentially effective method of treatment allocation. Recent research shows that, in fact, patients with certain combinations of demographic (e.g., employment status) and clinical features (e.g., comorbidity of depression and anxiety, symptom severity) respond better to therapy with some therapists rather than other therapists (Delgadillo et al. 2020). On this basis, using archival clinical data, it is possible to predict the likely outcome for new patients assigned to specific therapists (i.e., percent probability of recovery), potentially enabling an evidence-based approach to patient–therapist matching (Constantino et al. 2021).

Clinical Support Tools

In the context of routine outcome monitoring, CSTs have been developed. They implement several findings from psychotherapy process research to support clinical decision making. As monitoring symptom change alone does not provide any information on how to adjust the treatment strategy, the goal of such clinical problem-solving tools is to alert therapists to potential obstacles to treatment progress and to provide suggestions for interventions to improve treatment for patients at risk of treatment failure (Boswell et al. 2015). Numerous CST models have been developed and applied in the field of psychotherapy.

One such model is Lambert's assessment of signal cases (e.g., Lambert 2017), which guides therapists to routinely monitor four domains using a validated patient-reported questionnaire that covers therapeutic alliance, social support, motivation, and negative life events. If a patient is not on track according to feedback from routine outcome measures, the therapist is prompted to assess problems across one or more of these domains and to apply clinical skills that target the perspective problem (e.g., rupture repair for alliance deficits, a decisional balance exercise for motivational deficits). A meta-analysis of controlled trials that supplemented progress feedback with this clinical problem-solving approach concluded that the addition of CSTs significantly improves clinical outcomes (Shimokawa et al. 2010). Subsequent secondary analyses of data from these trials indicated that not-on-track signals were significantly associated with elevated scores on the domains of social support and adverse life events (Probst et al. 2020, White et al. 2015).

A unidimensional approach to CSTs is featured in the Partners for Change Outcome Management System (PCOMS; e.g., Miller et al. 2005), in which clinicians routinely monitor a measure of the therapeutic alliance (Session Rating Scale) in addition to treatment outcomes (Outcome

Rating Scale). This is based on the well-known association between alliance and treatment outcomes (e.g., see Flückiger et al. 2020) and follows the hypothesis that poor progress is likely to be related to alliance problems and potentially rectified by close attention to the alliance. However, a meta-analysis of clinical trials applying the PCOMS system found that subgroup analyses excluding studies that did not use the Session Rating Scale (i.e., did not systematically monitor the alliance) did not influence the overall meta-analytic finding that simple outcome monitoring (using the Outcome Rating Scale) improves treatment outcomes (Østergård et al. 2020).

Another multidomain model (Lutz et al. 2019) involves the routine monitoring of five domains: (*a*) risk/suicidality, (*b*) motivation/therapy goals, (*c*) therapeutic alliance, (*d*) social support and critical life events, and (*e*) emotion regulation/self-regulation. Each domain is assessed at every fifth session using a battery of validated patient-reported questionnaires. Like previous CST systems, this model primes the therapist to assess potential problems across these domains in cases where clinical outcomes are classed as not on track using computerized feedback. In an analysis of archival data from over 400 patients who were monitored using this battery of measures, Schilling et al. (2021) found that patients classed as not on track had significantly elevated scores on the domains of risk/suicidality and social support and critical life events.

Summary

The collection and systematic investigation of outcome measures in routine care have generated several new options to make use of continuous data assessments in clinical practice. Research findings allow the generation of clinically meaningful decision rules for the selection of treatment options as well as the monitoring of treatment and the early detection of negative developments. In particular, the development of CSTs to supplement outcome monitoring seems to constitute a step forward to improve psychological therapy for those patients who are at greatest risk of poor treatment response.

IMPLEMENTING MEASUREMENT-BASED AND DATA-INFORMED PSYCHOLOGICAL THERAPY

Continuous assessment of change during treatment enables clinicians to adapt their decisions about the best available treatment option, and it also allows the immediate application of research findings into clinical practice. A particular strength of data-rich health research and medicine is the ability to develop individualized diagnosis and treatment options. This has also been demonstrated in other public health areas; examples include the development of tailor-made immune cells and tumor therapies, the search for genes that can influence the risk of heart disease and life-threatening pulmonary hypertension, and therapy options for Parkinson's disease (e.g., Han et al. 2020, Stoker & Barker 2020).

Feedback-Informed Treatment

Important developments, such as brief psychometrically validated self-report measures, their repeated administration in routine care, and the advancement of methods such as the ETR models discussed above, have enabled the development of a new paradigm of measurement-based care. This approach uses psychometric and statistical methods to support the delivery of effective care in a way that enables therapists to make timely decisions that are supported by evidence rather than by clinical judgment alone. Furthermore, since most commonly used measurement-based care approaches use patient-reported measures (of symptoms, alliance, processes, goals, etc.), this approach places the patient's perspective at the center of the therapeutic process.

Feedback-informed treatment (FIT) is one of the most well-established examples of measurement-based care (FIT is also known as outcome feedback or patient-focused feedback research) (Howard et al. 1996, Lambert et al. 2001). FIT involves regularly monitoring a patient's response to treatment by comparing their response to predicted trajectories of improvement (clinical norms). These clinical norms are derived from ETR models (e.g., Finch et al. 2001) or other advanced statistical approaches, such as NN analysis (Lutz et al. 2006) or dynamic prediction models that are recalibrated from session to session (Bone et al. 2021b). Typically, patients are asked to complete questionnaires about their symptoms before every therapy session, and the results are entered into a computerized FIT system. The system compares each patient's symptoms to those observed in hundreds of similar patients and then provides a prognosis: Either the patient is on track (likely to recover) or not on track (unlikely to recover). This feedback is provided to therapists every week, which prompts them to quickly identify and resolve obstacles to improvement in cases classified as not on track.

There are now over 50 clinical trials and several meta-analyses indicating that FIT systems can help improve treatment outcomes, prevent dropout, and improve the efficiency of psychological treatment (for comprehensive narrative and meta-analytic reviews, see de Jong et al. 2021, Lambert et al. 2018). In particular, the evidence is stronger for studies that offered evidence-based psychological treatments for depression and/or anxiety problems, supplemented by a FIT system, and it appears to generalize to different countries and health care systems. Furthermore, supplementing FIT technology with CSTs has been shown to enhance the effects of FIT (Lambert et al. 2018).

Moderator analyses of FIT trials reveal that the effects of feedback are enhanced by using ETR-based models to track treatment response and supplementing these systems with training for therapists and with CSTs (de Jong et al. 2021). Providing feedback to therapists and patients, rather than only to therapists, also seems to enhance its effectiveness (de Jong et al. 2014). Importantly, the extent to which individual clinicians adhere to the use of feedback systems determines the extent to which measurement-based therapy will be effective (see Lutz et al. 2021). As such, there is already compelling evidence demonstrating that FIT is more effective than usual psychological care (purely guided by clinical judgment) in terms of symptomatic improvement and dropout prevention (de Jong et al. 2021), but adequate adherence by therapists varies considerably even in clinical trials. Thus, the current challenges and research questions in this field concern how to optimize the implementation of feedback systems in routine practice. Numerous obstacles to implementation have been identified in prior studies, such as organizational, technological, practical, and attitudinal barriers (for an overview, see Lutz et al. 2021). Several examples of successful implementation and strategies to optimize adoption by therapists have also been documented, and we refer interested readers to a previously published collection of implementation-focused case studies (de Jong 2016).

Precision Mental Health Care

The debate about the development and implementation of personalized medicine (also called precision medicine) has also influenced psychotherapy (research) in recent years. Several new developments have emerged within this tradition of outcome prediction and monitoring, which can be summarized as precision mental health research. This branch of research is intertwined with the traditions and improvements in continuous outcome measurement (e.g., Delgadillo & Lutz 2020, DeRubeis et al. 2014, Huibers et al. 2015). The overarching goal is to use evidence-based strategies to support decision making in clinical practice (e.g., Bickman 2020, Chekroud et al. 2021, Cohen et al. 2021, Page et al. 2019, Zilcha-Mano 2019).

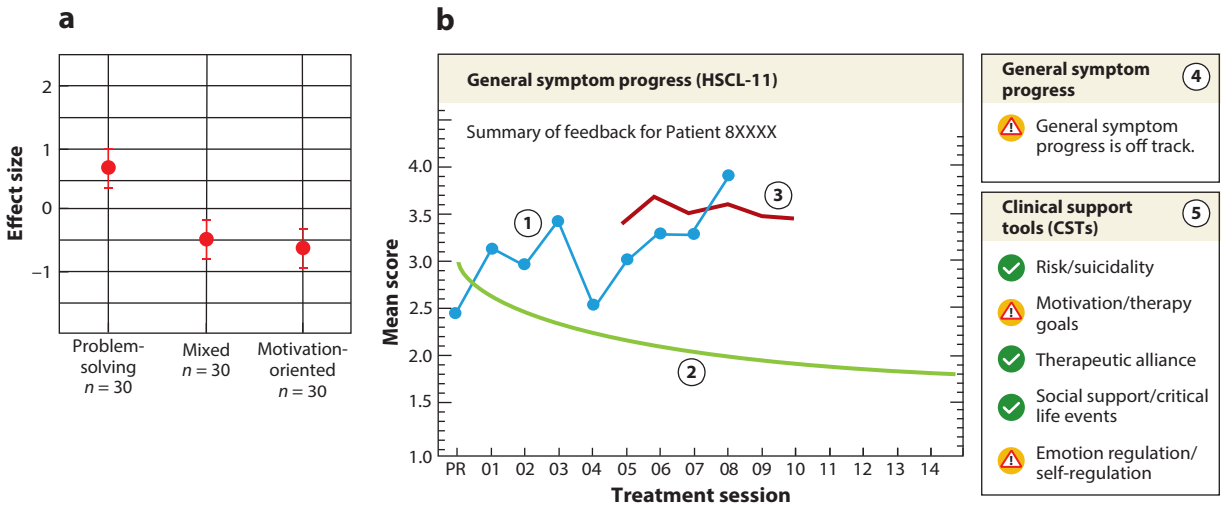

Figure 2

(*a*) Example of a patient-specific pretherapy strategy and (*b*) an adaptive personalized recommendation during treatment as displayed in the clinical decision-support system. (①) Patient scores at the beginning of each session, (②) expected recovery curve, and (③) failure boundary. (④) As soon as the patient's score exceeds the failure boundary on the HSCL-11, the therapist receives a warning signal, which is defined in more detail in the CSTs, and (⑤) CSTs are divided into five domains. The exclamation mark indicates the domains in which the patient has specific problems. The therapist is able to click on these icons to gain access to the activated tools. The check mark indicates that the patient has few or no problems in a given area. Abbreviations: CST, clinical support tool; HSCL-11, Hopkins Symptom Checklist-11; PR, preassessment.

One example of a comprehensive treatment selection and tracking system, which is also augmented by tools from e-mental health, is the Trier Treatment Navigator (TTN). This system includes a personalized treatment recommendation at the beginning as well as adjustments based on continuous outcome assessments during the course of treatment (Lutz et al. 2019, 2022). For each patient, the TTN generates individual predictions based on a large, previously treated patient sample for several important indicators—for instance, dropout risk and the optimal treatment strategy to start the treatment (see **Figure 2*a***). To predict the optimal treatment strategy, the most similar patients (based on the NN algorithm) who have already been treated are identified for an individual patient out of a large archival patient sample ($N = 1{,}234$). These NN groups of patients are generated for two treatment strategies or a combination of both (problem-solving-oriented, relationship- and motivation-oriented, or mixed approach in the first 10 sessions), and effect sizes for each group achieved in the first 10 sessions are generated. Effect sizes of the three treatment strategies and confidence intervals are then mapped, and the therapist can directly evaluate whether a particular treatment strategy is predicted to have a clear advantage for a given patient (i.e., the problem-solving approach for the patient example in **Figure 2*a***).

After the start of treatment, the navigation and monitoring system includes personalized treatment adjustment based on a dynamic risk index and CSTs. The system alerts therapists to the risk of an adverse treatment outcome. **Figure 2*b*** shows the course of treatment (session by session) and the visual feedback for a sample patient. The feedback graph is trained using data from the 30 most similar neighbors' average course of treatment and the above-described dynamic risk index. This risk index is also based on the ETRs of the most similar previously treated patients and is adaptively recalculated after each session. A patient progress score above the risk index indicates a significantly increased risk of a negative outcome. In such cases, therapists receive

a warning signal as in the example in **Figure 2*b***: "(!) General symptom progress is off track." In such cases, therapists also receive feedback on the potential problem area(s) (risk/suicidality, motivation/therapy goals, therapeutic alliance, social support/critical life events, and emotion regulation/self-regulation) in which the patient has indicated high scores. Furthermore, the system supports the implementation of helpful alternative clinical interventions by a number of support tools (e.g., videos on how to perform specific techniques, worksheets, audio files for download). In the example in **Figure 2*b***, the patient shows high scores in the areas of motivation/therapy goals and emotion regulation/self-regulation, and the feedback system advises the therapist to click on the support tools in these two areas.

Figure 2 shows the sample treatment of a 35-year-old, single male patient with major depressive disorder (single episode) and subthreshold personality disorder. At the beginning of therapy, the patient showed great ambivalence toward treatment and only started because of his friends' and family members' suggestions. He attributed all his problems to his environment, and, for example, in session 7 he was getting extremely upset about a friend who had canceled a vacation. This event led him to express strong doubts about whether therapy could help him at all. The navigation system proposed several techniques concerning doubts about treatment (CST motivation/therapy goals), and the therapist used these techniques to question the patient's perspective and attributions concerning the cause of his problems. Together, they developed alternative explanations for the origin of his problems and were able to strengthen his motivation for treatment by including additional motivational interviewing techniques.

In an RCT with 538 patients, the TTN was prospectively evaluated (Lutz et al. 2022). Patients showed an increased effect size of about 0.3 when therapists followed the recommended treatment strategy in the first 10 sessions. Moreover, the linear mixed models revealed therapist symptom awareness and therapist attitude and confidence as significant predictors of outcome as well as therapist-rated usefulness of feedback as a significant moderator of the feedback–outcome and the not on track–outcome associations. These results demonstrate the importance of prospective studies and the necessity of a high-quality implementation of digital decision-support tools in clinical practice.

Implementation

From the beginning, the integration of psychometric measures into clinical practice has been associated with barriers and implementation issues. Historically, psychotherapists have often been hesitant about or even critical of implementing measures on a routine basis (e.g., Boswell et al. 2015, de Jong 2016, Douglas et al. 2016). This phenomenon has been described as the scientist–practitioner gap in the psychological therapies (e.g., Lilienfeld et al. 2015). This contrasts with the patient perspective, from which outcome evaluation is usually well received. For example, when patients are asked whether they find it important to monitor the results of psychotherapeutic treatments, such as by using questionnaires, more than 90% seem to agree or partially agree (e.g., Lutz et al. 2021).

Furthermore, therapists' behavior and attitudes, perceived usefulness, and commitment to outcome measurement have some impact on the effectiveness of such measurement in clinical practice (e.g., de Jong et al. 2021, Lutz et al. 2022). Several factors contribute to the hesitant reception of outcome measurement in clinical practice. For example, the technical equipment, financial support, and necessary time might be not available in daily practice. Furthermore, therapists' general aversion to the use of technology in their practice has often been mentioned as a reason in the literature. In addition, clinicians might not trust the ecological validity of measures, thinking that empirical findings do not reflect their everyday practice (e.g., Boswell et al. 2015, Gilbody et al.

2002). Sometimes, measures can also be perceived as controlling, or concerns may arise with regard to data security (e.g., Mütze et al. 2021). All these factors culminate in an underuse of outcome monitoring in clinical practice, and clinicians lack the training and support necessary to make good use of the information (e.g., Boswell et al. 2015). As described throughout this review, in the future a cultural shift to measurement-based and data-informed psychological therapy including outcome measures as well as feedback and navigation systems is one of the most important steps to improve clinical services in mental health.

Summary

Measurement-based and data-informed psychological therapy evolved from efforts to extend the external validity of outcome research, which is traditionally based on efficacy research and RCTs. However, after a treatment effect has been established, observational, noninterventional designs and the monitoring of real-world applications are necessary to investigate implementation issues. The main focus of these Phase IV surveillance investigations is the transportability of a treatment into real-life conditions, as well as the identification of side effects, subgroup differences, and treatment failures (e.g., Suvarna 2010). The implementation of outcome monitoring supplemented by feedback and navigation systems takes this investigation a step further by not only monitoring real-world effects but also improving effects in real time.

CONCLUSION

Common to all endeavors described in this review is the idea of providing clinicians with personalized recommendations for their everyday clinical decision making based on continuous data collection. The generation of large practice-based data sets allows the development of new data disaggregation strategies to more precisely define relevant reference groups for each patient, thereby improving the applicability of information to the individual patient and supporting therapists in their clinical practice with an expert decision-support system.

So far, clinical judgment has been largely based on theory and intuition. However, we now have adequate assessment tools that are psychometrically reliable, brief, clinically useful, and sensitive to change (Lutz et al. 2021). Furthermore, feedback and decision-support tools are available that, when used, have been shown to lead to more evidence-based and effective treatments. Clinicians can make use of feedback to identify patients with a high likelihood of a negative treatment development and to obtain empirically supported recommendations about treatment strategies that could improve outcomes. In the future, further research efforts in this area should focus on implementation. Furthermore, the improvement of freely available and easy-to-apply measures remains a priority along with efforts to replicate results under large-scale routine care conditions. Of course, further improvements are also necessary in terms of item overlap and standardization of measures (e.g., Fried 2017). Important future research perspectives include (*a*) new statistical methods (e.g., machine learning) to analyze large cross-sectional as well as intensive longitudinal data sets, (*b*) improved research on processes and mechanisms of change, (*c*) better dissemination and cross-cultural adaptation (Kazdin 2018), and (*d*) better implementation and testing of clinical decision-support systems to identify and treat patients at risk for treatment failure.

Our vision for the future is to support clinical work not only with one algorithm but with multiple algorithms integrated into expert decision-support systems, which include algorithms and problem-solving modules to address several difficulties encountered in clinical practice, such as how to personalize the choice of treatment modality or techniques for the individual; how to predict and prevent dropout, symptomatic deterioration, and side effects; and how to predict and prevent relapse. The aim is to support human decision making, not to replace it with automated

interventions. Well-trained clinicians should receive empirically based support to solve the complex problems that are commonly encountered in the field of psychological therapy.

SUMMARY POINTS

1. Measurement-based and data-informed psychological therapy uses algorithmic decision tools to overcome some of the limitations of clinical judgment and intuition. This is enabled by the accumulation of large-scale routine clinical data sets.
2. Studies using longitudinal data show that the course of psychotherapy is influenced by patients' baseline characteristics as well as early symptomatic changes, and it often follows a nonlinear pattern. Furthermore, individual trajectories can deviate significantly from aggregated clinical population trends.
3. Intensive (i.e., daily) longitudinal assessments can improve the representation of high-frequency intrapersonal processes in patients' daily lives. However, because of their complexity and existing data analysis problems, less frequent session-by-session assessments are easier to implement and use in clinical practice.
4. Data-informed decision tools can guide treatment selection, monitoring of treatment progress, early detection of not-on-track patients, and adaptive recommendation of clinical strategies.
5. The effectiveness of measurement-based psychological therapy depends on therapists' behaviors and attitudes toward outcome measurement and feedback, as well as their use of technology. Therefore, to realize the full potential of data-informed therapy, future generations of psychotherapists need to be trained to understand psychometrics and to embrace technology as a means of making smarter and more effective decisions.

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Mental Pain in Eating Disorders: An Exploratory Controlled Study

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Abstract: Mental pain (MP) is a transdiagnostic feature characterized by depression, suicidal ideation, emotion dysregulation, and associated with worse levels of distress. The study explores the presence and the discriminating role of MP in EDs in detecting patients with higher depressive and ED-related symptoms. Seventy-one ED patients and 90 matched controls completed a Clinical Assessment Scale for MP (CASMP) and the Mental Pain Questionnaire (MPQ). ED patients also completed the Beck Depression Inventory-II (BDI-II), Clinical Interview for Depression (CID-20), and Eating Attitudes Test (EAT-40). ED patients exhibited significantly greater severity and higher number of cases of MP than controls. Moreover, MP resulted the most important cluster predictor followed by BDI-II, CID-20, and EAT-40 in discriminating between patients with different ED and depression severity in a two-step cluster analysis encompassing 87.3% (n = 62) of the total ED sample. Significant positive associations have been found between MP and bulimic symptoms, cognitive and somatic-affective depressive symptoms, suicidal tendencies, and anxiety-related symptoms. In particular, those presenting MP reported significantly higher levels of depressive and anxiety-related symptoms than those without. MP represents a clinical aspect that can help to detect more severe cases of EDs and to better understand the complex interplay between ED and mood symptomatology.

Keywords: mental pain; eating disorders; suicidality; assessment; depression

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1. Introduction

Mental pain (MP) is progressively gaining clinical relevance in the field of psychiatry and clinical psychology [1–4]. It could be described as a subjective, overwhelming, and unbearable experience characterized by a number of uncomfortable emotions—such as anguish, anger, emptiness, agitation, and guilt—which arises from negative self-evaluations and self-awareness of one's own inabilities and failures [1–4]. Over the past decades, it has also been present in the literature as suffering [5,6], psychic pain, psych-ache, emotional pain, psychological pain, social pain, emptiness, or internal perturbation [1,7–9]. There is growing evidence supporting the idea that MP may represent an independent condition with its own neurobiological characteristics [10]. However, it is significantly associated with several psychopathological conditions, such as suicidal ideation [2,7,11], depression [10,12,13], anxiety [14,15], borderline personality disorder [16], and emotion dysregulation [9].

More recently, based on the available literature stemming from the psychosomatic framework and clinical setting, Fava and colleagues [17] proposed an operationalization of the definition of MP as a transdiagnostic construct, supported by its association with several psychiatric illnesses, characterized by specific clinical features, such as feeling pain, feeling of being wounded, sense of hopelessness and helplessness, lack of localization in the body, persistence in time, lack of understanding of its occurrence, feelings of emptiness, loss of meaning, irreversibility of the pain, and suicidality. A clinimetric assessment tool was also empirically developed [18,19] and validated [20] and classified as a Patient-Reported Outcome (PRO), that is, any self-rated and "easy to use" report coming directly from

patients about how they perceive symptoms and how they function or feel in relation to a health condition [21–24]. Extending the assessment to PRO is increasingly necessary in psychiatry to identify at-risk patients as well as to detect the subjective impact and burden of symptoms on patients [25]. According to Fava and colleagues [17], MP should be incorporated into current psychiatric nosography as a specifier of the DSM-5 "clinically significant distress" caused by symptoms of a psychiatric disorder [26]. Indeed, MP has been found to be associated with worst levels of psychopathology and to distinguish between patients of diverse clinical populations [20]. In particular, higher levels of MP have been found in migraine outpatients with comorbid depression, suicidal tendencies, hopelessness, and guilt feelings [20]. In primary care, MP more frequently characterize patients with at least one psychiatric diagnosis based on the DSM-5 (in particular mood disorders) or with at least one syndrome based on the Diagnostic Criteria for Psychosomatic Research (DPCR) (in particular demoralization or irritable mood) [14].

Despite the clinical relevance of MP, there are some psychiatric populations in which it has not yet been investigated. Specifically in eating disorders (EDs), it is unexplored, although its inclusion may yield important clinical contributions to the standard assessment in this population. EDs are indeed not only characterized by a disturbance of eating and eating-related behaviors but are often comorbid with difficulties in tolerating negative emotional states [27,28], emotion dysregulation [29], and other psychiatric comorbidities, the most common being major depression [30,31], with suicide being one of the most frequently reported causes of death [32]. As these clinical features also characterize MP [2,7,9–11,33,34], adding the evaluation of MP in the assessment of EDs may support clinicians in better understanding the complex interplay between specific ED and non-specific ED symptomatology, in particular mood symptomatology. This is important considering that detecting ED patients at higher risk for depression and suicidality is increasingly urgent given the recent prevalence estimates of suicide attempts in U.S. adults with lifetime DSM-5 EDs, which range from 15.7% for anorexia nervosa restricting subtype (AN-R) and 22.9% in binge-eating disorder (BED) to 44.1% for anorexia binging-purging subtype (AN-BP) [35]. Moreover, since MP is considered a PRO, its measurement can offer a more in-depth look into the subjective experience of patients related to the burden of the ED illness [21–25].

Thus, to broaden the evaluation of psychological distress in EDs, the aims of the current study are to explore the presence of MP in patients with EDs when compared to controls and to examine the clinical utility of measuring MP in discriminating between ED patients in terms of eating and depressive symptomatology, including suicidality. We also aim to evaluate the presence of associations between MP, depressive symptomatology, and eating symptomatology and to compare ED patients with comorbid MP with those without MP in these variables.

2. Materials and Methods

2.1. Participants

Participants were enrolled in the frame of a larger study aimed at assessing psychological and psychosomatic features in ED patients [36]. Consecutively screened patients (n = 74), both inpatients and outpatients, who met diagnostic criteria for EDs (DSM-5; American Psychiatric Association, 2013), such as anorexia nervosa (AN), bulimia nervosa (BN), binge-eating disorder (BED), and other specified feeding or eating disorder (OSFED), were contacted from a specialized ED treatment center in Bologna, Northern Italy. With the exception of three patients who refused to participate, all invited patients took part in the study (n = 71) and were assessed before commencing treatment. Inclusion criteria were: (a) 18–65 years of age (b) with a diagnosis of AN, BN, BED, or OSFED (c) within one month of beginning treatment. The exclusion criteria were: (a) lack of capacity to consent for research, (b) ED diagnosis secondary to a physical health or metabolic condition, (c) comorbid drug/alcohol abuse, psychotic or neurocognitive disorders, and pregnancy. The socio-demographic and clinical data of the ED sample appear in Table 1.

Table 1. Socio-demographic characteristics of ED patients and controls.

Variables	Total ED Sample (n = 71) M ± SD	Control Sample (n = 90) M ± SD	p	Outpatients (n = 37) M ± SD	Inpatients (n = 34) M ± SD	p
Age	28.16 ± 11.29	29.36 ± 12.30	0.52 °	27.57 ± 12.57	28.82 ± 9.81	0.64 °
Education (years)	14.19 ± 3.21	15.40 ± 3.37	0.02 °	14.14 ± 3.05	14.25 ± 3.45	0.89 °
Marital status (% single)	86.96%	80.68%	0.34 #	94.59%	78.13%	0.09 #
Occupation % employed or student	74.63%	70.00%	<0.01+	94.44%	51.61%	<0.01+
% unemployed	23.88%	4.44%		2.78%	48.39%	
BMI						
AN (n, %)	(40, 56.3%) 15.28 ± 1.80			(16, 43.2%) 15.56 ± 1.77	(24, 70.6%) 15.09 ± 1.84	0.27 #
BN (n, %)	(13, 18.3%) 21.33 ± 1.91			(7, 18.9%) 21.69 ± 2.00	(6, 17.6%) 20.9 ± 1.87	0.31 #
BED (n, %)	(10, 14.1%) 36.20 ± 9.34			(8, 21.6%) 34.77 ± 10.27	(2, 5.9%) 41.21 ± 0.17	0.1 #
OSFED (n, %)	(8, 11.3%) 21.80 ± 9.62			(6, 16.2%) 18.03 ± 4.11	(2, 5.9%) 33.11 ± 14.93	0.051 #
Illness duration (months)	107.70 ± 110.18			77.14 ± 102.30	141.03 ± 110.24	0.01 °
Antidepressants (SSRI) use (%)	29.85%			23.53%	36.36%	0.25 +
Diagnosis of depression (MDD or PDD) (%)	55.88%			19.72%	33.80%	0.01 +

Notes: ° t-test for independent samples. + Pearson chi-Square. # Fisher's exact test.; Abbreviations: AN, anorexia nervosa; BN, bulimia nervosa; BED, binge eating disorder; M, mean; MDD, Major Depressive Disorder; OSFED, other-specified eating or feeding disorder; PDD, Persistent Depressive Disorder; SD, standard deviation; SSRI, selective serotonin-reuptake inhibitors.

Control participants matched for gender and age were recruited online from the adult general population and from university campuses in Northern Italy with the following inclusion criteria: (a) 18–65 years of age and (b) no prior diagnosis of any ED according to DSM-5 diagnostic criteria. Exclusion criteria were (a) lack of capacity to consent for research and (b) lifetime history of EDs according to DSM-5 diagnostic criteria either as primary diagnosis or in comorbidity to other mental health or due to a physical condition. The project was approved by University of Bologna Bioethics Committee and Department of Psychology Ethics Committee. Informed consent was obtained from all participants included in the study.

2.2. Procedures

The evaluation of ED patients was performed during the first intake visit before commencing treatment. ED diagnoses were established at intake by the consensus of a psychiatrist and a clinical psychologist independently using the Structured Clinical Interview for DSM-5 (SCID-5) [37]. Depressive disorder diagnoses were also established with DSM-5 criteria (SCID-5) [37] by independent raters. Each diagnostic interview was conducted and recorded by a clinical psychologist expert in assessment (E.T.) and subsequently reviewed by a consulting psychiatrist specialized in EDs who confirmed the diagnosis. Consent to be recorded while interviewed was obtained from all participants.

2.3. Measures

Both ED patients and controls were assessed before commencing treatment through the following instruments:

1. Mental Pain Questionnaire (MPQ) [18,19] to evaluate self-reported MP severity: the MPQ is a 10-item yes/no self-report questionnaire with a total score ranging from 0 to 10 developed to assess the experience of MP based on clinimetric properties. Ten aspects of MP in clinical settings have been identified on the basis of the literature and have been transformed into ten items that constitute the scale: (1) presence of mental pain; (2) feeling of woundedness, an aspect that is clearly defined by the expression "my heart is broken"; (3) the belief that it is not possible to receive any support or help by others (helplessness) and that the situation will not change in the future (hopelessness); (4) pain localization, which cannot be located in a specific part of the body and that is also defined as "central pain"; (5) pain duration; (6) association with specific events or situations that can be identified by the person as the exact moment in which suffering began; (7) feelings of emptiness; (8) loss of life meaning;

(9) irreversibility of pain, often accompanied by fears and suffering intolerance; and (10) association with suicidal ideation [17]. The Italian validation study of the MPQ showed good clinimetric properties with excellent reliability for mental pain intensity, especially for moderate/high levels of intensity, with a Cronbach's alpha of 0.77 [20].

2. Clinical Assessment Scale for Mental Pain (CASMP) (copyright Fava, Tossani, 2012 in Tossani, 2013) [9] to evaluate the presence of observer-assessed MP: this observer-assessed scale is used to assess MP experienced by patients based on their verbal expressions, which can give some information about the description, intensity, temporal patterns associated with physiological and behavioral processes related to the pain. Individuals are asked by a trained clinical psychologist to describe their MP and suffering and its duration (e.g., if it is experienced in specific moments, every day, or less frequently), to compare it to physical pain, if there is anything that ameliorates or that worsens the feeling, and if it is associated with a desire to die or if death is perceived as the only solution to stop MP. The structure of the questions and the ratings of such clinical assessment for MP are based upon the Clinical Interview for Depression (CID-20) [38,39] (see below in this section for more details), with a score ranging from 1 to 7 as follows: absent, very mild or occasional, mild (it comes at moments and then goes away), moderate (it tends to be steady), marked (it hurts all the time and does not get better), severe (it is unbearable), and extreme (it makes you feel like you want to die) [9]. As with the CID-20, a score of 3 or above in the individual items was considered the cut-off for presence of the experienced MP.

Only ED patients were also assessed through the following instruments:

3. Eating Attitudes Test-40 (EAT-40) [40] to assess self-reported ED symptomatology: a 40-items self-report screening measure identifying behaviors and cognitive patterns associated with eating disorders, where a greater total score indicates greater eating disorder severity. The measure yields a total score and three subscales' scores: dieting, bulimia and food preoccupations, and oral control. The measure shows excellent psychometric properties [40]. In this study, we used the Italian version of the EAT-40, which has been validated [41] and exhibits good psychometric properties, with reported Cronbach alphas of 0.80 for dieting subscale, 0.70 for food and bulimic preoccupations subscale, and 0.83 for oral control subscale.
4. Beck Depression Inventory-II (BDI-II) [42] to measure self-reported depression: a 21-item questionnaire. A total score ranging 0–63 is an index of depression severity, with higher total scores indicating more severe depressive symptoms. Composite scales of cognitive and somatic-affective symptoms were calculated. The measure exhibits excellent psychometric properties across clinical populations [43]. An average Alpha coefficient of 0.9 has been found, indicating a good internal consistency of the scale as well as a good retest reliability, with Pearson's r coefficients ranging from 0.73 to 0.96. Moreover, the BDI-II has a good convergent and discriminative validity, displaying a good capacity in discriminating between patients with and without depression [43] and between patients and nonclinical individuals [44]. In this study, we used the Italian version of the BDI-II [45].
5. Clinical Interview for Depression-20 item interview (CID-20) [38,39] to evaluate observer-assessed depression symptomatology severity: CID-20 is a dimensional observer-rated assessment instrument that consists of an expanded version of the Hamilton Rating Scale for Depression [46]. The interview covers 20 symptom areas/scales and is conducted by a trained clinical psychologist. Each area is rated on a 1–7 point scale, with 1 indicating absence of symptoms and 7 severe incapacitating manifestations. A score of 3 or above in the individual items was considered the cut-off for presence of the symptom. The scale encompasses a wide range of symptoms (such as irritability and phobic anxiety) compared to other scales and is particularly suitable to assess subclinical symptoms of mood disorders [25,39,47]. Summed total score and scores for anxiety and depression can be calculated, and individual items are also suitable for use as separate measures [39]. The CID-20 showed excellent

psychometric and clinimetric properties in terms of inter-rater reliability (Cohen k ranging from 0.81 to 0.82), discriminant validity, sensitivity to changes with treatment, test-retest reliability (depression r = 0.58; anxiety r = 0.59), and concurrent and divergent validity [38,39]. The Italian version showed clinimetric and psychometric properties consistent with the English version [48]. For the current study, CID-20 items pertaining to depressive symptoms with the highest frequency (>30%) in EDs were included [36]. Two items concerning appetite and weight gain/loss (items 12 and 13) were omitted due to the potentially confounding aspects of eating disorder-related symptomatology.

6. In ED patients, body mass index (BMI), illness duration in months, and use of antidepressant therapy were furthermore collected from updated medical records.

2.4. Data Analyses

Descriptive statistics were run for socio-demographic (age, education, level of occupation, marital status) and clinical characteristics (BMI, illness duration, use of antidepressants, ED diagnoses, depressive disorders diagnoses). Independent *t*-tests and chi-square tests were run to compare ED patients and control participants in MPQ and CASMP.

In the ED group, a two-step cluster analysis was also performed in order to organize the sample into two or more mutually exclusive groups of participants sharing common properties [49] and to see whether MP would be a significant cluster predictor. Variables included in the cluster analysis were MPQ, CASMP, CID-20, EAT-40, and BDI-II total scores. The log-likelihood distance measure was used, and no prescribed number of clusters was suggested a priori. The Bayesian Information Criterion (BIC) was used to judge the final cluster solution.

Correlation analyses using Pearson's r were run to observe the association between MPQ and CASMP and BDI-II, CID-20, and EAT-40 subscales.

Independent *t*-tests and chi-square tests were run to compare ED patients with comorbid MP with those without in socio-demographic and clinical characteristics. Multivariate Analyses of Variance (MANOVA) with Bonferroni corrections were conducted to compare ED patients with comorbid MP with those without in CID-20, BDI-II, and EAT-40 subscales while controlling for age, BMI, and illness duration.

Prior to performing all statistical analyses, normal distribution of all variables was tested by using the Shapiro–Wilk test. All variables showed a normal distribution, so statistical analyses were performed.

In all analyses, the level of significance was set at $p < 0.05$ (two-sided). The Statistical Package for Social Sciences (SPSS; IBM Corp., Armonk, NY) was used for all calculations.

3. Results

3.1. ED Patient Sample

The patient response rate was high, with 95.95% (n = 71) of ED patients out of 74 agreeing to participate. The 71 ED patients were all females, with a mean age of 28.16 ± 11.29 years and mean educational years of 14.19 ± 3.21. In all, 56.3% (n = 40) had a diagnosis of AN, 18.3% (n = 13) of BN, 14.1% (n = 10) of BED, and 11.3% (n = 8) of OSFED. A total of 52.1% (n = 37) of the patients were outpatients, and the remaining 47.9% (n = 34) were inpatients. ED outpatients and inpatients did not differ significantly in the main socio-demographic characteristics, that is, age, education, or BMI (Table 1). They differed significantly in illness duration (t(67) = −0.2.49, p = 0.015), with inpatients reporting longer length of illness (141.03 ± 110.24 months) compared to outpatients (77.14 ± 102.30 months) and lower level of occupation ($\chi^2(14) = 82.48$, $p < 0.01$). About a third (n = 20, 29.85%) of patients were currently on antidepressants, more specifically on selective serotonin-reuptake inhibitors (SSRI). A total of 55.88% (n = 38) of ED patients had a comorbid diagnosis of depression, including major depressive disorder (MDD) and persistent depressive disorder (PDD), whereas 44.12% (n = 30) did not; inpatients reported significantly higher cases of comorbid depression, as shown in Table 1.

3.2. Control Sample

Ninety participants from the general population matched for age and gender constituted the control sample of the study. The control group was all female, with a mean age of 29.36 ± 12.30 and mean educational years of 15.40 ± 3.368. Significant differences were found between ED patients and controls in the levels of education (t(151) = −2.22, $p = 0.02$) and occupation ($\chi^2(7) = 44.53$, $p < 0.01$) (Table 1).

3.3. Comparisons between ED Patients and Controls in Mental Pain

ED patients and controls significantly differed in the number of MP cases assessed through the CASMP (cut-off point >3) [20,36,39] ($\chi^2(1) = 33.872$, $p < 0.01$). In particular, a considerable portion of ED patients reported MP ($n = 31$, 43.66%), while half of the ED sample did not ($n = 40$, 56.34%). In the control sample, only a small number of participants reported MP ($n = 5$, 5.6%), whereas the majority of them did not ($n = 85$, 94.4% of the sample). ED patients exhibited also significantly higher scores in MP assessed through the MPQ and the CASMP compared to controls (Table 2).

Table 2. Comparisons between ED patients and controls in mental pain using *t*-test for independent samples.

Measure (Range)	ED Patients ($n = 71$) M ± SD	Controls ($n = 90$) M ± SD	t(df)	*p*	Cohen's d
MPQ	4.11 ± 2.61	1.68 ± 2.11	6.37 (133.15)	<0.01	1.04
Clinical assesment scale for mental pain	2.21 ± 1.37	0.56 ± 1.02	8.43 (124.18)	<0.01	1.39

Abbreviations: ED, eating disorders; M, mean; MPQ, Mental Pain Questionnaire; SD, standard deviation.

3.4. Two-Step Cluster Analysis in the ED Sample

Two-step cluster analysis performed in the ED sample resulted in two clusters (BIC = 231.858) encompassing 87.3% ($n = 62$) of the sample, with nine outliers. MP assessed with MPQ and with the CASMP emerged as the most important cluster predictors, followed by BDI-II, CID-20, and EAT-40 in discriminating between ED patients (Figure 1). The first cluster had 50% of cases ($n = 31$) and contained ED patients with low MP (MPQ = 2.52 ± 2.00; CASMP = 1.23 ± 0.62), low depression (CDI = 39.19 ± 10.50; BDI-II = 17.71 ± 11.36), and low ED symptomatology (EAT-40 = 41.35 ± 26.30). The second cluster had 50% of cases ($n = 31$) and included ED patients with high MP (MPQ = 5.74 ± 2.34; CASMP = 3.29 ± 1.16), high depression (CID-20 = 53.81 ± 11.64; BDI-II = 31.42 ± 9.21), and high ED symptomatology (EAT-40 = 86.48 ± 46.50), Table 3.

Table 3. Cluster clinical characteristics and differences calculated with *t*-tests.

Variables	Cluster 1 ($n = 31$) M ± SD	Cluster 2 ($n = 31$) M ± SD	$t_{(df)}$	*p*
CASMP	1.23 ± 0.62	3.29 ± 1.16	$5.191_{(60)}$	<0.0001
MPQ	2.52 ± 2.00	5.7 ± 2.24	$5.220_{(60)}$	<0.0001
CID-20	39.19 ± 10.50	53.81 ± 11.64	$5.990_{(60)}$	<0.0001
BDI-II	17.71 ± 11.36	31.42 ± 9.21	$8.747_{(60)}$	<0.0001
EAT-40	41.35 ± 26.30	86.48 ± 46.50	$4.704_{(60)}$	<0.0001

Abbreviations: BDI-II, Beck Depression Inventory-II; CASMP, Clinical Assessment for Mental Pain, CID-20, Clinical Interview for Depression; EAT-40, Eating Attitudes Test-40; MPQ, Mental Pain Questionnaire.

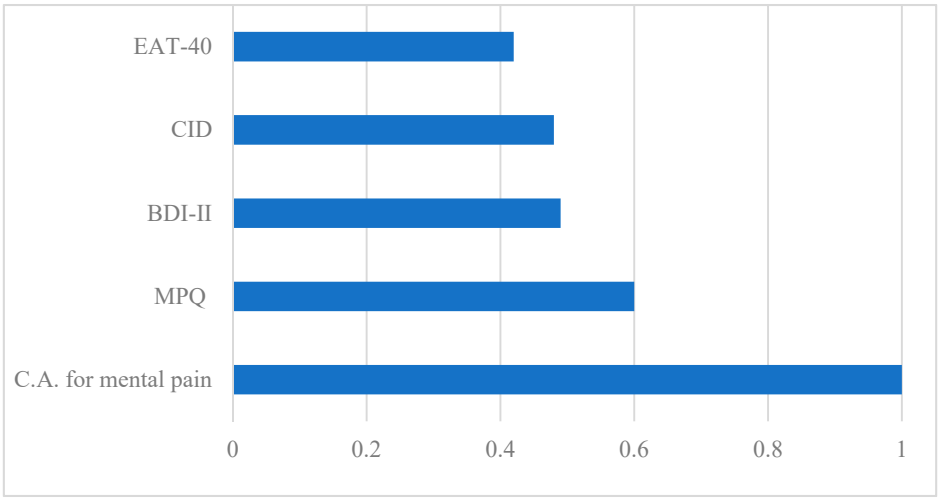

Figure 1. Predictor importance of the variables used in the cluster analysis. Abbreviations: BDI-II, Beck Depression Inventory-II; C.A., Clinical Assessment; CID-20, Clinical Interview for Depression-20 items; EAT-40, Eating Attitudes Test-40; MPQ, Mental Pain Questionnaire.

3.5. Correlations between MP, ED, and Depressive Symptomatology in ED Patients

Regarding ED symptomatology, only a significant correlation emerged between the CASMP total score and EAT-bulimia and food preoccupations subscale (r = 0.329, p = 0.007). Regarding self-rated depressive symptomatology, both somatic-affective (r = 0.340, p = 0.005) and cognitive (r = 0.308, p = 0.013) subscales of the BDI-II correlated significantly with CASMP scores but not with MPQ. However, as can be observed in Table S1, observer-rated depressive symptoms (CID-20), primarily CID-20-depressed mood (MPQ: r = 0.341, p = 0.004; CASMP: r = 0.400, p = 0.001), CID-20-suicidal tendencies (MPQ: r = 0.493, p < 0.001; CASMP: r = 0.292, p = 0.015), CID-20-work and interests (MPQ: r = 0.262, p = 0.030; CASMP: r = 0.290, p = 0.016), CID-20-general anxiety (MPQ: r = 0.297, p = 0.013; CASMP: r = 0.460, p < 0.001), CID-20-somatic anxiety (MPQ: r = 0.332, p = 0.005; CASMP: r = 0.407, p = 0.001), and CID-20-early insomnia (MPQ: r = 0.276, p = 0.022; CASMP: r = 0.403, p = 0.001), were found to present similar correlations with both CASMP and MPQ (Table S1).

3.6. Comparisons between ED Patients with Comorbid MP and without Comorbid MP in Sociodemographic and Clinical Characteristics

ED patients with comorbid MP (n = 31) (CASMP score >3) compared to those without MP (n = 40) (CASMP score <3) did not differ significantly in the main sociodemographic and clinical characteristics, such as BMI, illness duration, antidepressant use, and being outpatients or inpatients (Table 4). However, among patients considering specific ED diagnoses, AN patients reported significantly more frequent rates of MP (F = 9.457, p = 0.02). Moreover, while roughly a third of the clinical sample presented both MP and a concurrent depressive disorder (Major Depression Disorder or Persistent Depressive Disorder), a third was unaffected by either, and a portion of the sample (10.29%, n = 7) reported MP in absence of a depressive disorder. Additionally, 22.06% (n = 15) did not report MP despite receiving a diagnosis of a depressive disorder, Table 4.

Table 4. Sociodemographic characteristics of ED patients with and without comorbid mental pain.

Variables	Mental Pain Presence (n = 31) M ± SD	Mental Pain Absence (n = 40) M ± SD	p
Age	28.70 ± 10.93	28.13 ± 11.58	0.83 °
Education (years)	14.12 ± 2.89	14.41 ± 3.32	0.72 °
Marital status (% single)	83.33%	89.47%	0.89 #
Occupation % employed or students	72.41%	62.16%	0.75 #
% unemployed	27.59%	24.32%	
BMI	18.27 ± 7.39	21.38 ± 9.08	0.13 °
Illness duration (months)	118.03 ± 115.38	102.16 ± 107.18	0.56 °
Antidepressants use (%)	27.59%	32.43%	0.67 +
ED diagnoses (%)			
AN	32.9%	22.9%	
BN	7.1%	11.4%	0.02 #
BED	1.4%	12.9%	
OSFED	2.9%	8.6%	
Outpatients (%)	17.14%	34.29%	0.058 +
Inpatients (%)	27.14%	21.43%	
Depressive disorder absence (%)	10.29%	33.82%	0.002 +
Depressive disorder presence (%)	33.82%	22.06%	

Notes: ° t-test for independent samples.+ Pearson chi-Square. # Fisher's exact test.; Abbreviations: AN, Anorexia Nervosa; BED, Binge Eating Disorder; BMI, Body Mass Index; BN, Bulimia Nervosa, OSFED, Other Specified Feeding or Eating Disorders; M, Mean; SD, Standard Deviation.

3.7. Comparisons between ED Patients with Comorbid MP and without Comorbid MP in Eating and Depressive Symptomatology

Three multivariate analyses of variance (MANOVA) were conducted in order to compare patients with comorbid MP (n = 31) and patients without MP (n = 40) in ED symptomatology and in depressive symptomatology controlling for age, BMI, and illness duration. Given the high numbers of comparisons, Bonferroni correction was performed, and new p values were set (see Table S2).

MANOVA showed no significant differences between the two groups in EAT-40 scales (Table S2). ED patients with MP presented significantly greater BDI-II somatic-affective (F = 9.910, p = 0.003) and cognitive depressive (F = 6.210, p = 0.016) symptoms and CID-20 depressed mood (F = 10.713, p = 0.002), CID-20 general anxiety (F = 17.630, p = 0.0001), and CID-20 early insomnia (F = 10.216, p = 0.002) than ED patients without comorbid MP (Table S2).

4. Discussion

MP has, to the best of our knowledge, never been explored in EDs before. Therefore, the present study was carried out in order to explore the presence of MP in patients with EDs when compared to controls and to examine whether MP can discriminate between ED patients in terms of eating and depressive symptomatology. Associations between MP, depressive symptomatology, and eating symptomatology were also evaluated in the ED sample along with differences between ED patients with comorbid MP and those without MP in these variables. Our findings suggest that MP does not only characterize ED patients when compared to controls but can also represent an important clinical marker for discriminating, within ED patients, subgroups of patients with different levels of depressive and ED-related symptomatology. Significant associations were found especially between MP and disinhibited eating behavioral aspects, such as bulimic symptoms, and between MP and many aspects of depressive-symptomatology, such as suicidal tendencies, general and somatic anxiety, and insomnia. When comparing ED patients with comorbid MP to those without comorbid MP, only higher levels of depressive symptomatology and general anxiety have been found to be different between the groups.

Compared to controls, ED patients reported greater intensity and significantly higher number of cases of MP, confirming previous studies in which higher levels of MP have been established in clinical populations when compared to healthy controls, such as in patients with a major depressive episode [50] or who met the criteria for medically serious suicide attempts [51,52]. The higher cases and levels of MP in EDs compared to controls may be related to the specific difficulties of ED patients in recognizing, regulating, and communicating emotions. As described by patients themselves [53], dysfunctional eating behaviors are often used as a strategy to regulate or avoid uncomfortable emotions and deal with psychological pain. Moreover, alexithymia [54,55], interoceptive awareness deficits [56,57], and emotional dysregulation [58,59], widely known clinical features of EDs, are associated with MP as well [13,33,60].

MP does not only characterize ED patients when compared to controls, but it has been found to be a significant cluster predictor in discriminating two subgroups of ED patients with different levels of severity in depressive and ED symptomatology. Consistently, the group of patients with higher levels of MP also reported higher levels of depressive and ED symptomatology. On the one hand, such findings support the well-known association between MP and depression [10,12,13], depression severity, cognitive depressive symptoms [2,14,50], and suicide among different clinical samples [12,34,50,61,62]. On the other, our results are in line with those studies in which MP emerged to be associated with worst levels of psychopathology among patients in diverse clinical populations [14,20]. However, our study is the first that supports empirically, using a cluster analysis, the specific discriminating role of MP as a specifier of different severity of symptoms. This confirms its clinimetric role as a specifier of "clinically significant distress" associated with symptoms of a psychiatric disorder, as Fava and colleagues recently suggested [17].

Consistently, when looking at correlation analysis, a significant relationship was found between observer-assessed MP and ED-core symptomatology and depressive symptoms. In terms of ED-related symptomatology in particular, greater disinhibited eating aspects, such as bulimic behaviors, have been found to be related to greater levels of MP when observer rated. The relationship between bulimic behaviors and higher emotion regulation difficulties is well known in the ED literature [63,64], making findings of the present study coherent with previous results finding an association between MP and emotional dysregulation and suppression [13,60]. Bulimic behaviors, such as binging and purging, have been found to be associated with worst quality of life, increased psychological distress, negative physical and psychological consequences, medical burden [65–68], and increased risk of suicide in EDs [69–72]. However, no significant difference in ED-core symptomatology was found when comparing ED patients with comorbid MP to those without MP. This result might be also due to an insufficient sample size or to other methodological issues (e.g., the high number of comparisons lowering statistical power).

Considering the specific evaluation of depressive symptoms, several associations emerged in ED patients between MP and a wide set of symptoms related to the depressive symptomatology. The joint use in our study of a comprehensive clinical interview for depression (CID-20) [38] with the DSM-5 diagnostic criteria for depressive disorders yielded important clinical insights into depressive disturbances associated with MP in our ED sample. Higher levels of MP showed a significant association not only with higher levels of severity of depression but also with greater suicidal tendencies. Depression in EDs is not only associated with the severity of eating symptomatology [73], but it is one of the major risks associated with suicidal ideation and attempts [74,75]. In this clinical population, suicidality may represent an escape from emotional pain [76] and is furthermore strongly related with interoceptive awareness deficits, making the individuals "out of touch" with their body [77] (p. 53) and helping them shift the attention from psychological pain to physical pain [33]. Although this association was not confirmed when comparing levels of suicidal ideation between patients with comorbid MP and patients without comorbid MP, the relationship between increased levels of MP and increased risk of suicide has been supported by the literature, and such correlation has been found independently of

the severity of depressive condition, but at the same time, MP alone did not significantly predict suicide lethality [34]. For this reason, including the assessment of MP along with the evaluation of mood symptomatology is particularly warranted in this clinical population.

When comparing ED patients with MP to ED patients without MP, some significant differences emerged. ED individuals with MP more frequently reported a diagnosis of AN. This finding may be due, in part, to the majority of AN cases in our sample, but it might also be related to the greater severity characterizing AN compared to other ED diagnoses. Indeed, serious medical and psychological symptoms present in AN frequently persist even after recovery [78,79], and their underweight state is often accompanied by depression symptoms, such as depressed mood, social withdrawal, and irritability [26].

ED patients who reported MP also presented a more frequent comorbid diagnosis of depression according to the DSM-5 [26] when compared to those without MP and higher depressed mood symptoms (CID-20), supporting the well-known association between MP, depression, and suicidality [10,12,13,34] and, similarly, the well-established association between eating symptomatology and depression [31,36,80–82].

Furthermore, ED patients with comorbid MP also reported greater somatic-related depressive symptoms using CID-20 and BDI-II, supporting the overlap between MP and somatic pain [9,83,84] and the tendency of ED patients to express painful emotions through their body, turning the body into a "battleground" for unexpressed and unwanted emotions [53] (p. 17). Moreover, ED patients with comorbid MP reported higher levels of BDI-II cognitive depressive symptoms, such as guilt, self-criticism, and sense of failure [85], coherently with previous studies, which have found an association between MP and cognitive symptoms of depression [2]. This is also in line with the conceptualization of MP as a psychological condition arising from self-awareness of inadequacy and failure [11,86]. Lastly, ED patients with comorbid MP reported greater levels of general anxiety and insomnia measured by CID-20. Such association may also be due, even when not directly tested in our study, to the high degree of comorbidity with anxiety disorders present in EDs in which negative thinking, such as worry, co-occurs [87] together with body anxiety, eating, and avoidance behaviors related to food, body, and interpersonal situations [88–90].

While the well-known association between MP and depression was supported by our findings, it is also of clinical interest to remark that a subgroup of ED patients reported it also in the absence of a comorbid mood disorder—even though less frequently—confirming that MP may be considered as a distinct and isolated psychological condition from depression [2,10]. Further studies should target such important clinical aspects.

4.1. Implications

The presence of MP should be considered and included when assessing and treating patients with EDs due to its potential role as a specifier for DSM-5 "clinically significant distress" associated with ED diagnoses, paving the way for a more in-depth assessment that goes beyond the mere presence or absence of diagnostic symptoms as they are recognized in the standard psychiatric classification (DSM-5) [26]. An assessment that conversely considers the centrality of subjective phenomena (such as MP) may therefore demarcate clinical differences between ED patients [91], leading to a more individualized treatment [36]. Considering our results altogether, including the evaluation of MP in the assessment of individuals with EDs might help clinicians to identify patients experiencing higher distress that goes beyond ED core-related symptomatology, yielding incremental data to better evaluate the complex interplay between EDs and depression and the tendency to somatize emotions that characterize ED psychopathology through the body [53]. In particular, the assessment of MP in the context of eating disorders may have its clinical utility in the assessment of depression symptoms, which is particularly complex in this group of patients due to the overlap between somatic and physical symptoms that the two conditions have in common [36,80,92] and furthermore in detecting patients at higher risk for suicidal behaviors. Due to the high rate of suicide in ED individuals and the comorbidity with other

psychiatric conditions [26,93], such distinction is clinically warranted in order to initiate targeted interventions and prevent significant morbidity.

4.2. Limitations and Future Directions

The reported findings should be interpreted in light of the limitations of the present study, namely the small sample size, the use of a mixed-ED sample, and the failure to not include a specific assessment of common psychiatric comorbidities, such as anxiety and personality disorders. The assessment of physical conditions (e.g., migraine or thyroid-related problems) that might influence the presence and severity of MP in ED patients was not included in the study [20], and patients and controls were not matched for social status and education. Moreover, depression in EDs, besides being one of the most common psychiatric comorbidities, shows a number of overlapping symptoms and similar cognitive features with EDs (e.g., weight loss, over-eating, sleep disturbance, fatigue, irritability, perfectionism, harm avoidance, etc.) [36,80,94–96], which makes differential diagnosis difficult [36].

Future research including a larger sample size is needed in order to further explore MP in ED individuals. Exploring MP in non-mixed ED samples (e.g., AN- or BN-only samples) is also warranted in order to observe how MP might present differently across different ED diagnoses. Longitudinal designs could also be used to investigate the role of MP in treatment response.

Supplementary Materials: The following are available online at https://www.mdpi.com/article/10.3390/jcm10163584/s1, Table S1: Correlations between MPQ- mental pain, CID-20-mental pain item, EAT-40 and BDI-II and the CID-20-depression items in ED patients, Table S2: MANOVAs comparing ED patients with comorbid mental pain and ED patients without mental pain in EAT-40, BDI-II and CID-20 scores.

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Data Availability Statement: Due to the nature of this research, participants of this study did not agree for their data to be shared publicly, so supporting data are not available.

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The *Lancet Psychiatry* Commission on psychological treatments research in tomorrow's science

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Executive summary

Background

Psychological treatments occupy an important place in evidence-based mental health treatments. Now is an exciting time to fuel treatment research: a pressing demand for improvements is poised alongside new opportunities from closer links with sister scientific and clinical disciplines. The need to improve mental health treatment is great; even the best treatments do not work for everyone, treatments have not been developed for many mental disorders, and the implementation of treatments needs to address worldwide scalability. Psychological treatments have yet to benefit from numerous innovations that have occurred in science, particularly those that have emerged in the past 20 years, and arguably vice versa. This Commission comprises ten parts that each outline an area in which we see substantial opportunity and scope for advancements that will move psychological treatments research forward.

Part 1: How do existing treatments work? Making the case for the mechanisms of psychological treatments

Beyond knowing that an intervention is efficacious, research initiatives are needed that clarify the key mechanisms through which interventions work. An experimental psychopathological approach enables the identification of mechanisms. Research on these mechanisms has considerable scope to facilitate treatment innovation.

Part 2: Where can psychological treatments be deployed? Research to improve mental health worldwide

We outline a number of factors to facilitate worldwide access to psychological treatments. Future research initiatives need to continue to develop and assess the efficacy of brief and flexible interventions that can be adapted to meet the needs of individuals across cultural contexts, and delivered and disseminated in a sustainable way.

Part 3: With what? The potential for synergistic treatment effects—using and developing cross-modal treatment approaches

The combination of psychological and pharmacological treatments needs to be better understood, both in terms of the clinical effect and the underlying shared and different mechanisms. Efforts to develop and investigate the efficacy of novel cross-modal treatments could contribute to treatment innovation.

Part 4: When in life? Psychological science, prevention, and early intervention—getting the approach right from the start

The social and economic tolls of mental health problems early in life make the development of effective prevention and early intervention approaches a priority. A preventive focus and a developmental approach are needed to identify risk factors for psychopathology, and identification of the optimal time at which to offer prevention approaches is needed to increase the likelihood of vulnerable young people growing up with positive mental health.

Part 5: Technology—can we transform the availability and efficacy of psychological treatment through new technologies?

New technologies provide exciting and timely means by which to disseminate and extend the efficacy and global reach of evidence-based interventions. eHealth and mHealth approaches that use information technology (eg, the internet, virtual reality, serious gaming) and mobile and wireless applications (eg, text messaging, apps) are examples of how technology has been harnessed to innovate psychological treatments and their availability and evaluation.

Part 6: Trials to assess psychological treatments

The findings of randomised controlled trials that assess psychological therapies inform policy and practice. Accordingly, the design and conduct of these trials warrants scrutiny and ongoing efforts for quality improvement (eg, reporting standards, specification of protocols, inclusion and exclusion criteria, choice of outcome measures, measurement of adverse effects, and prevention of bias in design and analysis). We outline several opportunities for further improvement that should enhance the credibility and quality of future trials.

Part 7: Training—can we cultivate a vision for interdisciplinary training across mental health sciences to improve psychological treatments?

Early examples of collaboration between basic scientists and clinicians translated into historical steps in the innovation of psychological treatment. Such synergy has become less apparent in the past few years. The improvement in links between clinical psychology, psychiatry, and basic research has the potential to deliver more advances in psychological treatments. We propose opportunities to improve training in interdisciplinary mental health sciences. This training approach would be the first step toward forging links between scientists and

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clinicians in the next generation and bridging the gap between clinical practice and the basic research programmes that underpin psychological treatments.

Part 8: Whom should we treat, for what, and with what? Embracing the complexity of mental disorders from personalised models to universal approaches

Mental disorders are inherently complex (eg, heterogeneity in symptoms across disorders, high rates of comorbidity) and evidence-based treatments must address this complexity. Potential solutions include considering both highly individualised (ie, personalised) approaches and so-called universal or transdiagnostic approaches that target common mechanisms. A goal of future research will be to examine whether these approaches improve treatment effectiveness.

Part 9: Target: suicidal behaviour—protecting lives

Suicidal behaviour is one of many areas in which advances are needed. Despite developments in the understanding of risk factors that predict the likelihood of suicide attempts, and the treatment and prevention of suicidal behaviour, many questions remain. We specify areas for future research—eg, use of new technologies, the role of culture, input from individuals with lived experience of suicidal behaviour, and using a team-based approach in the development, assessment, and dissemination of prevention efforts.

Part 10: Active innovation and scrutiny of future psychological treatments research

The task of improving psychological treatments is an exciting prospect for scientists and clinicians with an interest in the so-called science of mental life. Clinicians, researchers, service users, carers, funders, commissioners, managers, policy planners, and change experts all have a part to play in improving psychological treatment. Some long-held ideas need examination, from the branding of psychological treatment types, to considering what people actually want treatment for. Scrutiny of new ideas should be rigorous and yet encourage innovation.

Introduction

Psychology and psychological treatments

Psychology from its inception was defined as "the science of mental life".[1] Psychological treatments have developed to occupy a key place in evidence-based treatments for mental health. Many pivotal techniques used in evidence-based psychological treatments arose from psychological research on processes in the 1950s and 1960s, with basic and clinical researchers often in the same department. During the past few decades, the psychological treatment field has drifted away from its scientific roots, while mechanistic studies have drifted away from treatment issues. Now is the time for greater synergy between basic and clinical researchers to invigorate psychological treatment research.[2] Psychological treatments offer great promise for continued innovation, not least because of the development of scientific methods and perspectives from many allied fields.

While researchers and industry struggle to produce new drugs for mental disorders, psychological treatments research might have the potential to deliver acceptable, effective, and safe treatment options more quickly.[3] Building bridges between psychological treatment and other modalities—eg, via combination approaches—could also benefit many service users, but will not be an easy task. New trials of psychological treatments are met with not only enthusiasm, but also controversy. Questions are constantly being asked about trial design, implementation, and interpretation. Do trial populations reflect real clinical populations? What is an appropriate control group? At what point should trial evidence be translated into day-to-day practice? How can an inter-vention be disseminated nationally and internationally? Existing assumptions are also being queried, for instance, is single-session therapy feasible? Is one consistent therapist an optimal or even necessary component of psychological treatment? How can new technologies best be harnessed?

We note that in the wider literature many terms are used, including mental health disorder, psychological disorder, psychiatric disorder, mental health problem, and other forms of terminology associated with psychological treatments, such as mental health difficulties and behavioural difficulties. In line with *Lancet Psychiatry* terminology and for consistency, the term mental disorder is used in this Commission.

A core role for psychological treatments in the future requires a research agenda

The burden of mental disorders is enormous, and yet pharmacological and psychological treatments scarcely reduce the disease burden. Since most patients prefer psychological treatments over pharmacological treatments,[4] increased research efforts are required to develop psychological treatments to a point at which they will have a substantial effect upon the mental disease burden worldwide. To realise the development of psychological treatments, a research agenda is needed that can guide the field for the coming years. For example, a 2014 commentary[2] on improving psychology treatments stated: "By the end of 2015, representatives of the leading clinical and neuroscience bodies should meet to hammer out the ten most pressing research questions for psychological treatments. This list should be disseminated to granting agencies, scientists, clinicians, and the public internationally. Mental-health charities can help by urging national funding bodies to reconsider the proportion of investments in mental health relative to other diseases."[2]

Mental disorders are widespread and costly

Every year almost one in five people worldwide develops a mental disorder,[5] and more than 750 000 people die by suicide.[6] In 2010, mental and substance-use disorders

accounted for 183·9 million disability-adjusted life-years,[7] with most of the disease burden caused by depressive disorders, anxiety disorders, and substance-use disorders. These numbers are likely to be an underestimation since these calculations assume that mental disorders are not associated with excess mortality, except suicide. However, people with mental disorders have a considerably higher risk of dying earlier than those without mental disorders.[8]

Apart from the personal suffering of affected patients and their families, mental disorders pose enormous economic challenges to communities and societies, in terms of production losses and health and social care expenditures.[9–11] The global cost of mental health conditions in 2010 has been estimated at US$2·5 trillion, and these costs are expected to grow to $6·0 trillion by 2030.[12] For this reason, conceptualisations of mental health need to expand beyond the notions of disease or infirmity to functionally related outcomes or, more broadly speaking, the ability to adapt and self-manage.[13]

Treatments make a small contribution to the reduction of the disease burden

Several evidence-based biological and psychological treatments are available for a range of mental disorders. However, these treatments are estimated to be able to reduce the disease burden by only about 40%, and only under optimal conditions and when all patients with a mental illness receive evidence-based treatment.[14] Globally, coverage (ie, the proportion of people who receive a consultation for a mental disorder) is typically much lower than 100%, with coverage well below 50% for some disorders (eg, eating disorders) in most regions,[15] and for some disorders (eg, alcohol-related disorders) coverage is below 10%.[16] The 2014 Adult Psychiatric Morbidity Survey,[17] noted a welcome increase in the number of people with common mental disorders who are receiving treatment. This increase has been largely attributed to the use of psychotropic medication.[17] Unfortunately, most patients who are treated for mental disorders do not receive evidence-based treatments, but instead receive a wide array of treatments including interventions that are not evidence based.[18]

Patient preference for psychological treatment options alongside restricted availability

In the USA, psychotherapy has assumed a less prominent role in mental health care than have treatments with medication.[19] For example, in the USA, antidepressant use almost doubled between 1996 and 2005, from 13 to 27 million individuals, whereas the percentage of people among antidepressant users who underwent psychotherapy declined from 31·50% to 19·87%.[20] In an office-based clinical practice, between 1999 and 2010, on average 8·6% of visits made by adults with depression included the prescription of a second-generation antipsychotic drug,[21] and the frequency of use doubled from 4·6% in 1999–2000 to 12·5% in 2009–10. By contrast, most patients seem to prefer psychotherapy over medication. A meta-analysis[4] of patients with a range of mental disorders (eg, depression, anxiety, insomnia, bipolar disorder, schizophrenia, substance-related disorders, eating disorders, and personality disorders) estimated that approximately 75% of patients prefer psychotherapy as their treatment as opposed to medication. However, some patients do prefer pharmacological treatment, whereas others might have no preference. In this Commission we do not seek to reinforce what we believe to be a misplaced dichotomy between biological and psychological approaches (see Part 3), instead we seek a research agenda that is open to multiple perspectives, does not neglect one perspective at the expense of another, considers links between both perspectives, is informed by patient preferences, and ultimately leads to the greatest clinical effect.

Although most patients prefer psychotherapy to medications,[4] the availability of such treatment is a major problem in many countries.[22] This paucity of availability is attributable to a range of factors, including financial constraints or the scarcity of trained psychotherapists who can deliver the evidence-based treatments. Therefore, psychotherapy is mostly delivered in high-income countries to those who can afford it and know how to find a therapist. In low-income and middle-income countries, psychological treatments are scarce—although notable exceptions exist (see Part 2).[23]

Several approaches are being developed to increase access to psychological services, such as the Increasing Access to Psychological Treatment (IAPT) programme in the UK, in which low-intensity psychotherapies are made available on a large scale and high-intensity therapies are available for those who do not respond to low-intensity therapies.[24] Internet-based interventions (see Part 5) can help in making psychotherapies available to those who need them since these interventions can be offered relatively inexpensively and with a low threshold for access. Another important development to make therapies more accessible is to use so-called lay health counsellors (see Part 2).

Psychological treatment research in tomorrow's science

Improved psychological treatments are needed to help reduce the burden of mental disease worldwide. The landscape of psychological treatment research is ready for innovation, offering exciting and auspicious opportunities for research in the mental health sciences. Insights from different fields of science might allow us to "stand on the shoulders"[25] of existing evidence-based psychological treatments and see further to improve psychological interventions. Greater collaborative endeavours between clinical and basic researchers of many disciplines will help in this regard.[2]

In this Commission, we discuss opportunities to focus future research efforts to improve worldwide mental health. Suitable areas of inquiry for future research

include: understanding the mechanisms that underlie psychological treatments, increasing worldwide access to treatments, developing cross-modal treatment approaches, and enhancing preventive and developmental approaches. To address each of these themes, new tools will be needed, which will be provided by new technologies, improved trial methodologies, and improved training in interdisciplinary mental health sciences, to name but a few sources. In this Commission, we discuss how the goals of people developing and delivering psychological treatments should be to embrace challenging areas, such as the inherent complexities of mental disorders and issues such as suicide prevention. The array of challenges ahead to which a psychological perspective can contribute will require fresh innovation.

Research into these areas will require ideas to be tested, and rejected or developed in line with scientific methods and challenges of mental health of the time (as opposed to therapeutic habit and allegiance to a specific manner of clinical training, or science focused inwardly on itself rather than on genuine application); therefore, attitudes within mental health science will need to change. To illustrate, we make an analogy with a British contemporary art initiative that is engaged with Trafalgar Square's empty plinth in London, UK. Statues are on three of the four plinths in the corners of Trafalgar Square and the fourth plinth stood empty for over a century (figure 1). Now, the so-called Fourth Plinth Programme[26] invites world-class artists to make "astonishing" new artworks for the centre of the capital city. Commissions create a rolling programme of temporary artworks rather than settling permanently on one figure or idea. The resultant sculptures tend to be shown for a year, although sometimes only for a few months, and sometimes the plinth is empty for a period of time; however, the momentum of the programme and scrutiny over the choice of statues continues. Some artworks stand the test of time, whereas some might not. Associated initiatives encourage projects and creative thinking around past and present artworks displayed on the fourth plinth. However, the best use of the fourth plinth remains a subject of debate and discussion in the public, media, and art world.

Figure 1: **The fourth plinth in Trafalgar Square, London, UK**

Like the Fourth Plinth Programme, psychological treatments research needs innovation, rotation of ideas, and robust critical debate as a clear part of advancing research. Although the objects of inquiry might change, the principles of seeking to improve research efforts towards improved mental health will persist. Instead of being prescriptive regarding the future of psychological treatments research, this Commission sets out various suggestions and principles to guide research that should apply across different mental disorders and transdiagnostic processes, approaches, countries, and, indeed, to the new and future generations of mental health researchers. These principles might change over time and how best to strengthen psychological treatments should be a subject of research, debate, and discussion, involving the fields of both psychological treatments and mental health science, and many fields beyond these.

When considering the traditional delivery method of psychological treatments, the changes that can come about from two people talking with each other for a matter of hours during therapy sessions are fascinating, sometimes remediating years of mental distress. Although clearly the presence of another person can be helpful, evidence-based psychological treatments involve far more than just skills that boost therapeutic alliances. Therapeutic effects are now known to be achievable without a therapist being physically present (eg, via internet therapy, see Part 5) and some psychological techniques can be effective when delivered by lay workers with modest training (see Part 2). Moreover, neuroscience continues to reveal how efficiently the mind can work under various parameters (eg, in modulating memory) by a range of techniques that may or may not require another person to be present. The emotional, behavioural, and social changes rendered through therapy pose mechanistic questions for mental health science—eg, how do effective psychological treatments work? The identification of specific targets for mechanistic questions might be facilitated not only by quantitative methods but also by qualitative methods—eg, detailed narratives of individuals' experiences as they undergo psychological treatments. Once potential targets have been identified in this way, they could be subjected to experimental investigation to establish causality for therapeutic change.

We now focus and elaborate on the ten key themes that we see as instrumental to consider in the development of an agenda to progress mental health treatment research. These themes, which were decided as part of a consultation meeting in December, 2015 (panel 1), are not exhaustive and many more are to be welcomed for future scrutiny.

Part 1: How do existing treatments work? Making the case for mechanisms of psychological treatments

Introduction

Although some psychological treatments are effective, little is known about the processes through which therapeutic change occurs. As Alan Kazdin stated in his 2007 review,[27] many evidence-based therapies are available but little understanding exists of the mechansims of change or precisely how they work. Understanding mechanisms of action is essential to derive and hone treatment strategies to directly target the mechanisms, remove irrelevant strategies, and develop novel approaches that are more expeditious and effective than current treatments. Knowledge of mechanisms also allows improved precision in matching psychological treatments to the needs of individuals to improve outcomes compared with current methods.

Research into the mechanisms of treatments offers an exciting opportunity for psychological treatment research. However, most studies in psychopathology have simply described differences between groups of individuals with and without a diagnosis and identified a mechanism of action by use of these differences—an approach that cannot identify causal mechanisms. To move the field toward understanding causality, research on mechanisms should be optimised by framing research within the context of clinical treatment to understand how existing treatments work, and derive new and improved treatments.

What is a mechanism of psychological treatment?

Mechanisms of psychological treatment are defined as "the steps or processes through which therapy (or some independent variable) actually unfolds and produces the change. Mechanisms explain how the intervention translates into events that lead to the outcome."[27] A mechanism is an explanatory construct and not simply an intervening variable that explains the statistical association between an intervention and an outcome. For example, the finding that changes in a patient's perceived self-efficacy and outcome expectancy statistically mediates the subsequent changes in anxiety and functioning[28] does not explain how the changes in self-efficacy and outcome expectancy lead to those outcomes. The underlying changes responsible for symptom improvement could involve multiple processes, including, but not limited to, neural systems, other physiological systems, cognitions, emotions, and behaviours.

The processes through which psychological treatments produce change often overlap with or complement mechanisms that are responsible for the onset or, in particular, the maintenance of psychopathology (hereafter referred to as mechanisms of psychopathology). The US National Institute of Mental Health (NIMH) Research Domain Criteria (RDoC) initiative is directing the search for mechanisms of psychopathology away from the constraints of categorical diagnostic criteria and towards dimensions of observable behaviour and neurobiological measures.[29] The RDoC initiative aims to "elaborate a set of psychological constructs linked to behavioral dimensions for which strong evidence exists for circuits to implement these functions, and relate the extremes of functioning along these dimensions to specified symptoms (i.e., impairment)."[30] Essentially, the RDoC framework aims to identify biopsychological explanations or so-called process constructs for clinical events; these same process constructs could explain change in clinical events throughout treatment. The provisional list of RDoC explanatory constructs includes negative valence systems, positive valence systems, cognitive systems, systems for social processes, and arousal or modulatory systems, with each construct comprising more specific subconstructs.[30] The constructs are assessed with measures that represent at least seven levels called units of analysis: genes, molecules, cells, neural circuits, physiology, behaviour, and self-report. Identifying a mechanism using one unit of analysis does not exclude mechanisms identified using other units of analysis.

Mechanisms of psychopathology vary from being predominantly distal (eg, effects of early life adversity upon inflammatory markers for depression that might not become apparent until many years later[31]) to predominantly proximal (eg, ongoing biases in autobiographical memory for depression;[32] see Roiser's 2015 article[33] for a discussion of these ideas). Mechanisms of psychopathology also vary from being predominantly fixed (eg, within genes, albeit with variations in expression) to predominantly malleable (eg, negative interpretation bias for ambiguous stimuli). Psychological treatments generally target the predominantly proximal and malleable mechanisms of psychopathology—eg, attention bias

Panel 1: **Methodology and approach used in preparing this Commission**

- This Commission arose from an initial consultation meeting in December, 2015, in which researchers from a variety of backgrounds with interests or expertise in psychological treatments research met to discuss challenges in the field, and to lay out possibilities for a future research agenda for advancing the science of psychological treatments
- The group's common interest was captured by Kazdin's call to arms to "reboot psychotherapy research and practice to reduce the burden of mental illness"[22]
- Attendees' backgrounds in terms of subject disciplines included clinical psychology, psychiatry, neuroscience, experimental psychology, and pharmacology
- The language of the meeting was English, and attendees were from the UK, Europe, and the USA; in this Commission we have only cited papers that have been published in English
- The Commission expresses the authors' collective views about some of the key areas in which we see scope for improvements in the field; our goal was not to provide an exhaustive literature review, or a systematic review of specific topics; rather, we have cited sources that are relevant to the issues that we have discussed in the context of each of the ten themes
- We note that many important topic areas and perspectives continue to develop, and that this Commission is a start for necessary and continued discussion

modification training for anxious individuals who have selective attention bias towards threat-relevant stimuli.[34] Alternatively, psychological treatments can target factors that differ from mechanisms of psychopathology but compensate for them—eg, compensatory cognitive training for psychosis.[35] Although less commonly targeted, distal mechanisms can be particularly good targets for prevention efforts. Notably, not all treatment mechanisms are directly tied to mechanisms that are responsible for the onset or maintenance of psychopathology; some treatments work through independent processes—eg, applied behavioural analysis techniques for individuals with autism.[36]

What is the state of the field?

Pivotal evidence-based psychological treatments have evolved by specifically targeting identified mechanisms of psychopathology, one example of which is the treatment of panic disorder. Through a series of experimental investigations and animal modelling, interoceptive conditioning (ie, acquired fear of visceral or other internally generated stimuli due to pairing with an aversive outcome, such as pairing an elevated heart rate with the possibility of a heart attack) and catastrophic misappraisal (ie, misinterpretations of interoceptive stimuli as harmful or threatening) were recognised as mechanisms underlying the fear of bodily sensations that characterises panic disorder.[37–39] Psychological treatments for panic disorder were developed to target specific mechanisms in the form of interoceptive exposure[40] (ie, repeated exposure to interoceptive stimuli in the absence of aversive outcomes) and cognitive restructuring[41] (ie, reasoning skills to replace catastrophic interpretations with evidence-based interpretations). This type of treatment has been shown to be particularly effective for panic disorder, and more effective than non-targeted supportive psychotherapy (Hedges' g 0·35, 95% CI 0·04–0·65).[42] Similarly, the conceptualisation of instrumental reinforcement of compulsions led to a treatment for obsessive compulsive disorder known as exposure and response prevention.[43] In this conceptualisation, the distress-reducing effects of compulsive washing in response to obsessive thoughts of being contaminated act to reinforce and therefore increase compulsive washing with each subsequent obsessive thought. The treatment combines exposure of the individual to reminders of the obsessive thoughts (eg, a dirty piece of clothing) or the thought itself (eg, the thought of being covered in germs) with the prevention of washing. This approach is very effective for patients with obsessive compulsive disorder, and more so than non-targeted psychological control conditions, such as relaxation training (1·29, 0·76–1·81).[44] Another example is behavioural activation therapy, which targets deficits in positive reinforcement as a contributing factor for depression.[45] This approach aims to increase access to positively rewarding stimuli and achieve actions that are value driven and overcome task-related avoidance.[46] In a meta-analysis of behavioural activation treatments for depression,[47] this form of treatment was found to be highly effective compared with comparison-control interventions, which included wait-list and non-targeted psychological control conditions (0·87, 0·60–1·15 when collapsed across control conditions).

Overall, the development of psychological treatments via a mechanistic approach has resulted in more precise, efficient, and effective treatments than those that do not target specific mechanisms. However, the largest effect sizes come from comparisons with non-treatment or wait-list control conditions, with the wait-list control conditions potentially inflating the effect sizes;[48] some of the findings of meta-analyses mentioned earlier included wait-list control conditions.[47] The observation that comparisons of mechanistic treatment approaches with usual care typically yield lower effect sizes than comparisons with non-treatment or wait-list controls[49] could be an indication of the importance of common factors that are relevant to all psychotherapies—eg, goal consensus, therapeutic alliance, empathy, expectations, and therapist effects.[50] Notably, common factors do not obviate the importance of mechanistic research but rather imply the value of taking common factors into account when assessing the mechanisms of specifically targeted therapeutic approaches.

However, despite purported treatment mechanisms, little evidence exists on the precise mechanisms through which psychological treatments actually work. Although mechanistic developments in neuroscience have sparked interest in the psychopathology community, most studies to date have not investigated mechanisms of treatment. Even the study of mediation is often hindered by insufficiently rigorous methodology.[27] For example, although good evidence supports the efficacy of interoceptive exposure and cognitive restructuring for panic disorder, and that the extinction of the fear of interoceptive cues and reduction in catastrophic appraisals occur as a result of treatment, little direct evidence exists that the treatments work through the extinction of the conditional fear of interoceptive cues or reduction of catastrophic appraisals—a claim that requires that the changes in the purported mechanisms explain the subsequent changes in the symptoms. Similarly, although behavioural activation for depression might lead to changes in reward processing, no evidence is apparent that the treatment works through changing neural and behavioural sensitivity to reward.

To make matters worse, the focus of psychological research has slowly shifted away from mechanistically informed approaches toward modifying or adapting existing manualised psychological treatments, sometimes superficially, for different populations and settings. This approach of modification most commonly applies to cognitive and behavioural therapies. Although this shift in focus has been valuable for the advancement of treatment implementation in different settings, it has resulted in a

regrettable divorce from the foundations of mechanistically informed psychological treatments that in turn has impeded the investigation of their mechanisms of action.

Why is it important to understand the mechanisms of psychological treatments?

Without an understanding of the mechanisms of psychological treatments, pathways to intervention development and refinement remain restricted. With a knowledge of how change occurs as a result of treatment, therapeutic strategies can be developed that are more direct, precise, and effective.[51] Also, those therapeutic strategies that do not affect the crucial processes can be removed, making treatments more efficient and effective.[51] Moreover, by refuting a claimed mechanism, research attention can be redirected toward investigating alternative mechanisms and the development of novel treatments that are effective and efficient (panel 2).

Understanding the mechanisms of psychological treatment might uncover moderators of treatment outcome, and thereby lead to improvements in the precision of matching treatments to the needs of individuals.[51] For example, initial interest in training for attention bias modification for anxious individuals waned as a result of mixed findings and small effect sizes.[52] Subsequent research has provided some indication that the effects of training attention bias are larger for individuals with a greater attention bias at baseline,[34] and for those with low-expressing forms of the serotonin-transporter-linked polymorphic region (5-HTTLPR) of the serotonin-transporter gene (*SLC6A4*),[53] than for those with high-expressing forms of 5-HTTLPR. As another example, extinction-based exposure therapy to trauma cues for individuals with post-traumatic stress disorder (PTSD) have been suggested to function in part by enhancing prefrontal cortex inhibitory regulation over the responses of the amygdala.[54] Neuroscientists have identified that some individuals with PTSD fit into subtypes, with the majority showing hyperactivation of the amygdala and hypoactivation of the prefrontal cortex when exposed to trauma reminders, and about 30% showing the reverse pattern of hypoactivation of the amygdala and hyperactivation of the prefrontal cortex.[55] If exposure therapy can be established to work at least partially through enhancing the prefrontal cortex regulation of the amygdala, then exposure therapy might be more effective for the former set of individuals with PTSD than the latter. These examples show ways in which the field of psychological treatment could progress. Conclusive findings will depend upon replication of these results within substantially larger samples.

Not only is the identification of such mechanistic moderators valuable for precision in matching treatment to individuals, but it also improves the elucidation of psychological treatment mechanisms.[51] To follow the previous example of individuals with PTSD, by studying the entire sample (ie, those showing amygdala hyperactivation and those showing amygdala hypoactivation) the extent to which change in amygdala activation serves as a treatment mechanism is likely to be nullified. By recognising baseline differences between individuals, differential mediational pathways could be uncovered—eg, the possibility of amygdala deactivation for those who initially present with hyperactivation, and activation for those who initially present with amygdala hypoactivation. These are illustrative examples, but a mechanistic approach to moderation avoids the default approach of trial and error that assumes that a given psychological intervention strategy works through the same mechanisms for everyone. Another example of a speculative mechanistic hypothesis is the theory that behavioural activation for depression,[46] which involves scheduling activities that are rewarding, leads to symptom improvement for some individuals through enhancing approach motivation or initial responsiveness to reward within positive-valence systems, whereas for other individuals the treatment might reduce threat or potential threat within negative-valence systems or even modulate arousal systems through regulating sleep–wake cycles.

Additionally, psychological treatments with a mechanistic focus can be turned into training in everyday habits that pertain to prevention of and recovery from mental ill health—eg, training in mindfulness techniques to reduce affective memory bias and development of, or relapse into, depressive ruminative states.[56] Another example is the delivery of cognitive behavioural therapy (CBT) as an adjunct to usual primary care for individuals who are depressed and have not responded well to medication alone. In one study,[57] short-term focused CBT was associated with significantly reduced depression 3–5 years after treatment compared with usual care alone. Similarly, another study[58] found that cognitive therapy decreased the recurrence of depression over a 10-year interval in patients with remitted depression who had a history of recurrent depression compared with usual treatment. Together, these data suggest that CBT and cognitive therapy provided patients with skills that were embedded into their daily lives and led to sustained long-term improvements.

***Panel 2:* Reasons for understanding the mechanisms of psychological treatments**

- To hone treatments to target the processes that are responsible for change more directly and efficiently
- To uncover essential moderators of treatment outcomes and improve precision in treatment matching
- To develop training programmes for the prevention of and recovery from psychopathology
- To eliminate wasteful and inefficient treatments
- To provide evidence for specificity in treatment beyond non-specific factors that are responsible for the so-called dodo-bird effect

Not understanding the mechanisms of psychological treatments could be detrimental—eg, the development of novel and effective treatments could be hindered by the continued modification of the procedural elements of existing treatments without fully understanding the processes that lead to change. We encourage the development of a larger evidence base of critical processes for therapeutic change and, specifically, of which psychological treatments—existing and newly developed—affect which processes. This evidence base should include common and specific factors of psychotherapies.[30] Additionally, knowing the psycho-logical treatments that exert their effects primarily through common non-specific factors rather than through more targeted specific factors, would be informative, as well as whether the common and specific factors are of greater relevance to one mental disorder or individual than another. Such an evidence base would offer the potential to move the field beyond the long-standing debate of whether all psychological treatments are equally effective (ie, the dodo-bird hypothesis[59]) and whether differential treatment effects exist.[60] We have the opportunity to assess whether matching treatments that are mechanistically focused to individual patients with underlying dysregulation leads to superior outcomes when compared with targeting non-specific factors that are common across psychological treatments. Of course, applying personalised treatments that are mechanistically focused and understanding the role of common factors are not the only ways in which psychotherapy can improve outcomes; other factors that warrant consideration include the personal resources and social context of those in need, and the service delivery systems by which treatments are delivered.

Experimental psychopathology

Understanding mechanisms of psychopathology involves substantial explanatory specificity, and hence is driven by theory.[27] The mechanisms are elaborated through plausible and coherent reasoning on the basis of integration with broader scientific knowledge, and at the same time the explanation provided must be specific in how change in the mechanism accounts for change in the outcome.[27] Once theoretical mechanisms have been elaborated, investigators in the field of experimental psychopathology then assess the validity of the mechanism's causal influences upon selected outcomes (panel 3).

Showing that experimental manipulation of a proposed mechanism leads to symptom change is a powerful method for validation. Experimental studies of this kind in human participants can identify key processes that maintain or change aspects of psychopathology. These studies can also elucidate which of the processes' underlying psychopathology can (or cannot) be modified, and can therefore identify appropriate treatment targets. Burgeoning interest in the mechanisms that underlie psychopathology has been fuelled by advances in cognitive science and neuroscience.[51] For example, an increased activation in affective brain networks and a decreased activation in cognitive control and social cognitive networks has been seen in the brains of young people when they listen to criticism from their mothers, and this activation has been identified as a potentially key mechanism in emotional development.[61] These findings could inform strategies aimed at increasing effective parenting to reduce the risk of mental health problems in offspring.

The direct application of identified mechanisms of psychopathology to mechanisms of psychological treatment is well represented in fear learning and exposure therapies for anxiety disorders—eg, pharmacological drugs that facilitate the consolidation of fear-extinction learning (eg, d-cycloserine) have been shown to have beneficial effects in the context of exposure therapy;[62] although some mixed effects have been reported, possibly due to mechanistic moderators.[63] Another study[64] has shown that retrieving memories that are already stored induces a process of reconsolidation. Once retrieved, the memory has to be rewritten into a long-term memory, which requires neurochemical processes (de novo protein synthesis) in the brain. These processes give rise to the fascinating possibility of changing memories post factum during the period of reconsolidation on retrieval. One study[65] found that engaging an individual with a highly visually absorbing computer game after a memory-reminder cue interrupted the reconsolidation of intrusive visual memories induced by experimental trauma. Pharmacological drugs (eg, propranolol) and behavioural techniques (eg, extinction) have been shown to interrupt the reconsolidation process in human beings, albeit with mixed results,[66] restricting boundary conditions and conceptual challenges.[67]

Evidence that disturbances in autobiographical memory can be potential mechanisms of depression has led to novel therapeutic strategies for depression, including memory specificity training and positive memory elaboration.[32] Additional mechanistic research is needed, and particularly in young people for whom innovative psychological treatments are needed that can precisely target narrowly specified mechanisms that

***Panel 3*: Recommendations for identifying potential mechanisms of psychological treatments**

- Develop a model of explanatory specificity
- Experimental investigation of an explanatory construct to establish causal validity
- Human studies to show that manipulation of a proposed construct leads to symptom change (experimental psychopathology)
- Animal studies to allow more precision and elucidation of targets that cannot be studied in human beings
- Reverse-translation models by use of clinical research to inform models that will be tested in animals
- The flow of iterative and reciprocal information between experimental psychopathology studies in human beings and animals

are consistent with developmental models of causality (see Part 4).

Purported mechanisms can be tested in animals with much more precision with regards to measurement and causality than is possible in human beings. Animal studies are invaluable for identifying basic processes and mechanisms that are not possible to address in human beings because of practical or ethical constraints. Indeed, the first clinical applications of d-cycloserine for exposure therapy and disruption of reconsolidation for fear memories were derived from careful experimentation in animals.[64,68] Animal studies have also elucidated the potential value of disruption of reconsolidation in the treatment of substance abuse or dependence.[69] Ongoing animal work is examining pharmacological drugs that regulate the stress response via inhibition of the renin–angiotensin system (eg, losartan) as another method for enhancing consolidation of extinction learning.[70] Furthermore, advances in understanding the neurobiology of rodent self-grooming could identify potential treatment mechanisms for repetitive behaviours such as compulsions.[71]

In reverse-translation approaches, clinical research informs models to be tested in animals—eg, paradigms for assessing depressive cognitive styles, such as pessimism, that have been validated in human studies have now been reverse translated into paradigms that measure judgment bias in rodents.[72] Similarly, drawing from human-based studies on reward systems, paradigms have been developed to assess decision making in rodents between cues that predict reward versus cues that predict punishment.[73]

Despite these examples of the iterative flow of reciprocal information between experimental studies in human beings and animals, for the most part a huge gap exists between basic and clinical researchers. This gap hinders the development of more refined animal models of psychopathology and treatment and their translation to clinical populations. The reverse and forward translation of advances in basic science and clinical science is essential.

Assessment of mechanisms

Once a mechanism has been identified through careful experimentation, it can be assessed within the context of adequately powered clinical trials. To reach this stage requires measures of the purported mechanisms that are reliable, valid, and sensitive to change, since these measures will become the mediators that are assessed statistically. A major contribution to this effort will be funding to establish a list of candidate mechanisms that explain therapeutic change (based on evidence that the experimental manipulation influences only selected outcomes in animal or human studies) and a list of measures for each candidate mechanism. The RDoC notion of units of analysis provides a helpful framework for choosing measures from multiple modalities.

Kazdin[27] has carefully outlined the steps necessary to establish that a measure is a mediator of a psychological treatment. As an initial step, a strong association must be shown between the psychological treatment and the hypothesised mediator (ie, the mediator changes over the course of treatment), and between the mediator and therapeutic outcome (ie, change in the mediator is related to clinical outcomes). Kazdin lists several methods that allow greater attribution of causality to the mediator—ie, the underlying mechanism. One method is temporal precedence, since mediation cannot be presumed unless changes in the purported mediators occur before, and then predict changes in, the outcomes. Temporal precedence necessitates repeated measurement of mediators and of outcome variables throughout treatment, ideally in every treatment session.

Causality can be attributed to a mechanism more confidently when a single mechanism is specifically associated with a single outcome. Even more convincing than the identification of a single mediator is when the purported mediator of a specific psychological treatment can predict patient outcomes more accurately than a mediator of a different mechanism that has no theoretical association with the treatment. Specificity can also be shown by a stronger mediation via a proposed mediator for a treatment with which it has a theoretical association, compared with a treatment to which it is not theoretically relevant. Evidence for dose–response effects, in which stronger doses of the proposed mediator are associated with greater changes in symptoms than weaker doses, also strengthens the argument for a causal link. The consistency of the associations observed across independent replications is another validator. Although for some mechanistic questions appropriately powered experimental studies of small samples can be informative, validation of the mechanism will require large samples. Collaborative multisite studies will be needed, which will require a strong investment from funders and collaboration among researchers focusing on common goals.

Finally, the field would be advanced by listing the various therapeutic elements that constitute psychological therapies; an effort that has already been initiated.[74] Psychological treatments are mostly packages of different elements, such as cognitive restructuring, self-monitoring, problem solving, relaxation training, or assertiveness training. The more elements that are combined in a psychological treatment, the harder mechanistic specificity is to establish. Improved precision is likely to come from assessing the mechanisms of particular procedural elements rather than combinations of elements (panel 4).[75] Increased collaboration between clinical researchers and basic scientists, combined with new methods and technologies, will help the field of psychopathology to make substantial progress in understanding the mechanisms of change in evidence-based psychological treatments.

Part 2: Where can psychological treatments be deployed? Research to improve mental health worldwide

Introduction

Little or no access to efficacious psychological treatments is not only a major problem for people in low-income and middle-income countries, but is also problematic for many people in high-income countries. Brief, flexible, modular, and efficacious treatments that are derived from mechanistic research could enable the efficient adaptation of such treatments to different cultural contexts. Furthermore, the adaptation of treatments could be of help in the training of lay people who could implement such interventions within a framework of low-intensity treatment using modern techniques on a large scale in low-income, middle-income, and high-income countries. To achieve this goal further work is needed, including: the development of such treatments and adapting them to the local needs, priorities, traditions, and cultural norms of different environments; education and training for lay people to acquire proficiency to deliver such treatments as counsellors in a sustainable way; and the development of delivery models for mental health care with long-term sustainability.

Psychological treatments from an international perspective

As discussed in Part 1, mental disorders constitute a substantial part of the burden of disease worldwide.[7,76] Mental disorders also interact with other serious health conditions—eg, cardiovascular diseases, ischaemic stroke, and HIV—increasing the risk of premature death.[77] Efficacious psychological treatments for a wide range of mental disorders have mainly been developed in North America or Europe, and are typically designed for delivery through one-to-one psychotherapy by highly trained professionals. However, at a global level, 90% of individuals with mental disorders do not receive treatment.[78] Little success will be achieved in decreasing the prevalence and incidence of mental illness without a major shift and expansion in clinical practice and intervention research.[22]

A scarcity of skilled human resources (ie, therapists) and low acceptability of psychological treatments across cultures have been suggested as the two major barriers to increasing access to evidence-based psychological treatments in low-income and middle-income countries.[79] WHO estimated a shortage of 1·18 million mental-health-care workers across 144 low-income and middle-income countries.[80] Other key barriers include prevailing public health priority agendas and inadequate investment in mental health care, stigma associated with accessing mental health care, and challenges in using primary-care settings for implementation of mental health care.[81]

Panel 4: **Recommendations for the assessment of mechanisms of psychological treatments**

- Assess within the context of adequately powered clinical trials
- Develop measures of mechanisms that are reliable, valid, and sensitive to change, and that represent multiple units of analysis (eg, genes, molecules, cells, circuits, physiology, behaviour, cognition, self-report); mechanisms are explanatory constructs, whereas measures are mediators that explain the statistical association between an intervention and an outcome
- Once a mechanism has been identified through experimental work, it can be assessed within clinical trials (see text)
- Establish mediation by showing change in the mediator over the course of treatment, and that change in the mediator precedes and predicts clinical outcomes
  - Temporal precedence (ie, change in the mediator precedes and predicts subsequent change in symptoms); value of repeated measurement
  - Specificity of mediation to a single or restricted number of mediators
  - Specificity of mediation to a theoretically relevant mediator versus an irrelevant mediator for a given treatment, or specificity of a theoretically relevant mediator versus one treatment relative to another treatment to which it does not have theoretical relevance
  - Dose–response relationship between degree of change in mediator and degree of clinical improvement
- Consistency in independent replication
- Assess mediation for elements or specific therapeutic strategies rather than packages of treatment elements

Research to improve worldwide access to psychological treatments

Global access to psychological treatments could become a reality if adequate global and local political support is given and a research agenda is compiled that includes, but is not limited to, the following conditions (panel 5). Psychological treatments that could be scaled up successfully would be brief, flexible, modular, efficacious, and streamlined to remove any unnecessary complexities. Such treatments should be aided by research into mechanisms of action in psychological treatments (see Part 1), and a consideration of the core psychopathology of mental disorders. Large and complicated psychological treatment packages can be delivered only by highly trained professionals and to the minority of people who can afford the high costs that are associated with such treatments. Simplified and clearly defined treatments could be more readily adapted to local needs and delivered by lay mental-health-care workers on a larger scale, and as low-intensity treatments—eg, via the internet. Mechanistically informed treatments could also afford flexibility—eg, shaping treatment to align with local cultural norms and conditions. For example, if one of the major maintaining factors in depression concerns a paucity of positive reinforcement in daily life (see Part 1) then treatment strategies to increase positive reinforcement can be formed in many different ways depending on what is the most relevant, acceptable, and affordable option in the specific context or culture—eg, via various cognitive, behavioural, or psychosocial

techniques. Such treatments could each have flexible forms, but be identical in function.

In low-income and middle-income countries, the development of psychological treatments has typically focused on improving availability and accessibility, and researchers have taken a pragmatic approach to treatment development itself; however, future research efforts should harness scientifically driven developments. Developing psychological treatments on the basis of sound psychological theories and empirical knowledge gained from research on the processes of action in treatment could afford opportunities for cultural adaptation and psychological treatment across international contexts. Research that has tested theories about the mechanisms of action of various exposure therapies for anxiety disorders has provided invaluable knowledge,[82] leading to the enhanced flexibility of exposure therapy, which in turn could be tailored for global adaptation. The findings of research on basic mechanisms will hopefully show the potential for brief and highly efficacious psychological treatments.[2] Future research will need to progress this work into the development of intervention formats and modules that are acceptable and efficacious cross-culturally, and that can be delivered on a wider scale.

The traditional models of one-to-one delivery of psychological treatments by skilled psychotherapists who have had many years of training need to be reconsidered, and new efficient methods of treatment delivery explored.[22,83] Given the small number of highly skilled and trained professionals internationally, a shift towards collaborative models of care delivery has been proposed in which novel strategies, such as task shifting (eg, educating lay people with no previous experience of the mental-health services to become lay counsellors; panel 5), have been successfully used to deliver streamlined treatment of mental disorders with promising results.[79,84,85] Nevertheless, empirical questions remain such as: how best to train people to become lay counsellors in a sustainable way? And what barriers might exist to such sustainability? One solution is the delivery of therapy to a group of patients rather than one-to-one.

Other research questions include: how many training, supervision, and booster sessions will be needed to ensure the high-quality delivery of treatments? Most studies in which potential treatment group leaders have received brief training (1–4 weeks) have shown effective outcomes,[86] but more research is needed in this context. These strategies of task shifting and training the trainer have been pioneering in the global context of mental health, as well as in developed countries. For example, the IAPT programme[24] resembles an advanced form of task shifting, rapidly educating a new category of mental-health professionals called psychological wellbeing practitioners, and the strengths and limitations of the programme can be of use to help in the improvement of future large-scale endeavours. How can technologies be used to train health-care workers on a large scale and maintain the reliability of treatment delivery? Primary-care clinics in the USA have used computerised guides to train inexperienced clinicians to give psychological treatments, albeit on a much smaller scale than IAPT.[87] The outcome and long-term follow-up data from such endeavours will yield many lessons on how to increase access to psychological treatments worldwide.

***Panel 5:* How can access to psychological treatments be increased worldwide?**

- Develop low cost, simple, specific, and effective treatments
- Task shifting: educate people who have not worked within the mental-health services to deliver psychological interventions
- Low-intensity intervention: self-help interventions comprising the most potent components of effective psychological treatments that can be provided through books, CDs or DVDs, the internet, or other media, combined with brief support—usually remote via e-mail or phone—over the course of a few weeks
- Cultural adaptation: rooting the treatment in the sociocultural context (eg, traditions, expectations, cultural norms, symbols) to make sure that it is perceived as intended

Technology is another important tool that can improve the availability of psychological treatments (see Part 5).[83] Providing psychological treatments via the internet or mobile phones, combined with minimal individual support through e-mail or telephone, has shown highly promising results in many studies in high-income countries;[88] however, few studies have tested such interventions in low-income and middle-income countries.[89] Further research is required, particularly since mobile phones are rapidly becoming available worldwide, and the availability of the internet is increasing.[90]

Low-intensity treatments delivered by computerised or mobile-based guided self-help technologies are an ideal early option in a stepped-care model of treatment. National guidelines are starting to propose the use of low-intensity treatments as a first option to improve the availability of efficacious treatments (eg, for bulimia nervosa and binge eating disorder[91]). Countries such as Sweden and Australia have led the way in research on internet-based treatment and the implementation of low-intensity treatments, with examples from eating disorders[92] to parent training[93] (for a meta-analysis of mental and somatic disorders see Anderson et al[94]). Work such as this provides models and lessons that can be used or developed to improve access to care worldwide—eg, the internet could offer enhanced possibilities for long-term follow-up after a standard course of psychological treatment has ended and the implementation of booster sessions.

Contextual factors have an essential role in any efforts to increase access to psychological treatments and are a topic for future implementation research. The involvement of all stakeholders is a key factor in scaling up services to ensure support and to facilitate sustainability.[95] Initiatives to improve mental health in low-income and middle-income countries need to be rooted in the local society to assure sustainability, and to inform ways to maximise and achieve this goal. Methods

to improve societal involvement could include engaging the local government, considering local legislations and traditions, involving patient organisations, and creating conditions for continued education and mutual exchange. One area that needs further research is the effort to help people who are refugees from war and persecution;[96] for these individuals, not only is the development of treatments essential, but particular contextual factors require investigation—eg, moving populations, multiple trauma experiences.

The stigma related to mental health problems is another barrier to improved access to treatment that requires further research. Understanding and addressing the association between religious or cultural beliefs and attitudes towards mental health is a crucial factor. The potential of media, such as radio and television, to combat the stigma related to mental health problems and seeking treatment for mental health problems warrants investigation. As an example, stigma is clearly associated with talking openly about family planning among people living in poor communities in some low-income and middle-income countries. The successful use of a well designed television series to improve family planning and to reduce fertility rates in Mexico is a good example of the effective application of such strategies to reduce stigma.[97] The Headspace initiative in Australia provides a model that could be adapted to different cultural contexts with the goal of decreasing the stigma of mental illness and facilitating access to treatment.

For the **Headspace initiative** see https://www.headspace.org.au

The economic aspects of international efforts to improve mental health should also be subject to more rigorous research. Evidence from the UK[98] suggests that psychological treatment approaches—eg, early intervention for psychosis, conduct disorder, and suicide prevention—can have a cost-effectiveness ratio higher than 10 (ie, for every £1 invested in such an intervention, there will be more than £10 of benefit). Future research designs should include cost-effectiveness analyses regarding the broader provision of psychological treatments in resource-limited settings, both in developed and developing countries.

Panel 6: **Example directions for future research to improve access to psychological treatments worldwide**

- Build brief, flexible, modular, and efficacious treatments that are streamlined on the basis of knowledge from research on mechanisms of action in psychological treatments
- With knowledge of the mechanisms of action of psychological treatments, derive treatments aligned with the local needs, priorities, traditions, and cultural factors, which will be specific to the environment in which the treatment will be given
- Investigate how much education and training is needed for people without or with little previous experience of work within mental health care to acquire proficiency to give basic psychological treatments as lay counsellors in a sustainable way
- Investigate how models of delivery of psychological treatments can be scaled up in a sustainable way
- Investigate the use of media such as television, radio, and the internet to combat the stigma related to mental disorders

Research collaboration and exchange between cultures

The best way to enable the improvement in psychological treatments would be by an international mutual exchange of knowledge, experience, and expertise between disciplines (panel 6). Opportunities for students and professionals—both scientific and clinical—from different parts of the world to visit one another and learn about conditions for, and challenges in, improving access to psychological treatments in different contexts could prove to be a key factor in creating the enthusiasm and lasting collaborations needed to develop sustainable interventions (see Part 7). Such exchanges could also facilitate cross-cultural comparisons that might contribute to understanding and more efficient prevention and treatment of mental disorders.

Work needs to continue towards increasing global access to psychological treatments, both for individuals in low-income and middle-income countries and those in high-income countries. Research into psychological treatments will allow the psychiatric community to continue to develop and assess the efficacy of brief and flexible interventions, which could be focussed on precise mechanisms of action, that could in turn be adapted to meet the needs of individuals in different cultural contexts. Training lay people to deliver such interventions, and scaling treatments for delivery in a manner that is sustainable in the long-term, are two key directions for future work.

Part 3: With what? The potential for synergistic treatment effects—using and developing cross-modal treatment approaches

Introduction

Both pharmacological and psychological interventions are commonly recommended as first-line treatments in psychiatry and the potential for enhancing treatment action through combination approaches has started to attract research interest. However, the optimal method for treatment combination is far from clear and requires dedicated research in preclinical studies, experimental medicine models, and randomised controlled trials. We advocate that such an approach should consider the potential for synergy between key mechanisms of action across different treatment modalities and consider these different treatment methods within the same research framework. The potential for negative effects from treatment combinations should be included in future research programmes.

Creating synergy and avoiding harm with combination treatments

An individual with a mental disorder or comorbid mental disorders is likely to receive a combination of different treatment approaches as part of his or her care, often

including psychological therapies, different types of medication, and social interventions (panel 7). However, clinical guidelines include little about combination treatments and the vast majority of research focuses on single treatments, often with the presence of another treatment as an exclusion criterion to participation in randomised controlled trials; although, some meta-analyses have been completed of existing studies on combination treatments.[101,102] The generalisation of research based on single treatments to the typical clinical reality of combination treatments is not always valid in practice. Therefore, exciting basic and clinical science questions arise about what happens when a psychological treatment is combined with other therapeutic approaches.

Empirical studies suggest that combination treatment might have small benefits over single treatments—eg, when a psychological treatment, such as CBT, and a pharmacological treatment, such as a selective serotonin-reuptake inhibitor (SSRI), are combined in the acute treatment of emotional disorders, including depression.[103] However, the longevity of effects after treatment discontinuation could actually be reduced in some cases compared with each single treatment alone. For example, in the treatment of anxiety disorders, post-treatment relapse has been reported to be higher in patients who also received benzodiazepine or antidepressant treatment during CBT than in those who received CBT alone or in combination with a placebo.[100,104] Findings such as these emphasise the importance of capturing clinical effects after treatment ends and during the acute response phase, and also of focusing on potential mechanisms that could underlie these differential outcomes (panel 7).

Mostly, combination treatments in the clinic are driven pragmatically—eg, an individual might receive two effective treatments, often with each from a different practitioner, such as a clinical psychologist and a psychiatrist. This sort of approach contrasts with attempts to combine treatments on the basis of a mechanistic understanding or model. The hope is that scientifically informed combination treatments have the potential to create synergy and to support a better therapeutic response than either treatment offered alone. This scientifically informed approach could be of use to potentiate the mechanisms that are hypothesised to support a therapeutic effect or to overcome the limitations or barriers to a particular mechanism applied on its own (see Part 1). Interventions that are given together with psychological treatments could include the addition of drugs, neuromodulation, social, nutritional, or other forms of psychological intervention such as computerised training (eg, cognitive bias modification).

Boosting psychological interventions by use of contemporary cognitive neuroscience research

Developments in neuroscience and experimental psychology[82] have been used by researchers who are focused on boosting the effects and retention of psychological treatments. Understanding the molecular basis of memory processes provides targets that might be manipulated to facilitate learning and the extinction and reconsolidation of memories, which are key components of many psychological treatments for a number of mental disorders.[64,105]

Augmentation of existing psychological treatments

A growing area of interest is the use of drugs that target the glutamatergic system (eg, d-cycloserine) to facilitate underlying processes of extinction and retention during exposure therapy for anxiety disorders such as agoraphobia, social anxiety, and PTSD.[63] However, identifying the factors that might moderate this benefit is challenging, and a 2015 Cochrane review[99] found no evidence that d-cycloserine versus placebo conferred any advantage overall when combined with CBT in the treatment of anxiety disorders. Techniques that directly stimulate the brain (eg, transcranial magnetic stimulation) applied over the medial prefrontal cortex have been reported to modulate conditioned fear learning and extinction in healthy volunteers.[106] Hopefully, add-on treatments that affect the underlying mechanisms of learning and memory might speed up overall treatment effects, reduce the number of treatment sessions needed, or even prolong treatment effects. However, better understanding is needed of the best methods to facilitate learning in an area about which much is still unknown. For example, the optimal parameters to support learning pharmacologically or through neuromodulatory devices are elusive and require dedicated strategic focus to support preclinical work in healthy volunteers and animal models (see Part 1).[63]

A focus on mechanistically derived combinations also requires an understanding of and the ability to predict the effects of a psychological treatment alone and in combination with other treatments—eg, enhancing learning by pharmacological means in an exposure

***Panel 7*: What is a combination treatment?**

Combination treatment

The application of two or more types of intervention that have been specifically assessed for efficacy in combination.

In this Commission, the combination of psychological treatments is referred to with other types of interventions across modalities, including the addition of drugs, neuromodulation, social, nutritional, or other forms of psychological intervention such as computerised training.

Synergistic *vs* harmful combination treatments

Some treatments might work well together and have greater efficacy than either applied on its own—eg, the use of a drug to improve learning has been hypothesised to enhance retention of the benefits of CBT;[63] however, no tested drugs exist that relaibly do this.[99]

By contrast, some treatments could impair efficacy in combination—eg, patients who receive benzodiazepines during psychological treatment can show reduced long-term benefits of CBT after drug discontinuation.[100]

CBT=cognitive behavioural therapy.

treatment that has failed, or in which extinction has not occurred, would be expected to have counterproductive effects, strengthening poor outcomes. These complexities underscore the necessity and potential effects of understanding the mechanisms of treatments in isolation and in combination.

The need for better preclinical models

These observations of the potential outcomes of combination treatment highlight the crucial role of preclinical and experimental medicine models in understanding both the key processes and mechanisms that are important for combination treatments and assessing early signals of efficacy for future clinical testing. Animal models are commonly of use in the pharmaceutical industry to screen novel drugs, but are rarely of use in a combination approach—ie, by testing the effect of a drug together with a psychological intervention. This single-treatment approach could lead to the early rejection of a drug that might have weak effects on its own, but which could be clinically useful in an adjunctive role with psychological treatments. Strategic focus and funding are needed for mechanistically informed approaches to treatment combination in animal and human models. The back translation of findings from the clinic to these models needs to be enhanced, and increased interest is needed in using combination models to assess novel treatments, including as part of drug development within the pharmaceutical industry. Research in this area needs to incorporate measures that can assess and predict when and for whom combination treatment will be helpful. Regulatory support for this approach from the US Food and Drug Association and the European Medicines Agency, linked to approval and licensing of drugs, will be required to allow pharmaceutical companies to develop and test these kinds of combined treatments, both to facilitate potentially beneficial combinations and to reduce potentially harmful ones.

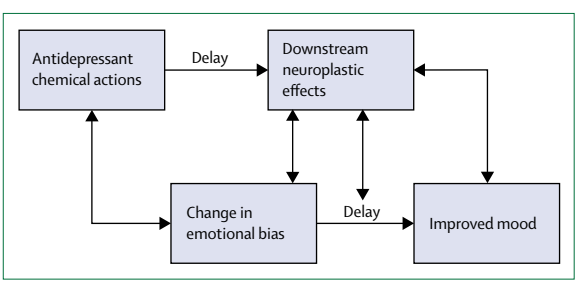

Figure 2: **Combining antidepressant drugs and psychological interventions to speed up the therapeutic effects**
Antidepressant drugs are hypothesised to work via early changes in negative affective bias—ie, by reducing the influence of this key maintaining factor in depression.[108] This theory raises the possibility that psychological treatments could be used in combination with chemical actions to boost the effect of antidepressants on negative affective bias, avoid delays in action, and facilitate the translation of effects on bias into clinical action—ie, improved mood. Reproduced from Harmer et al,[108] with permission from Elsevier.

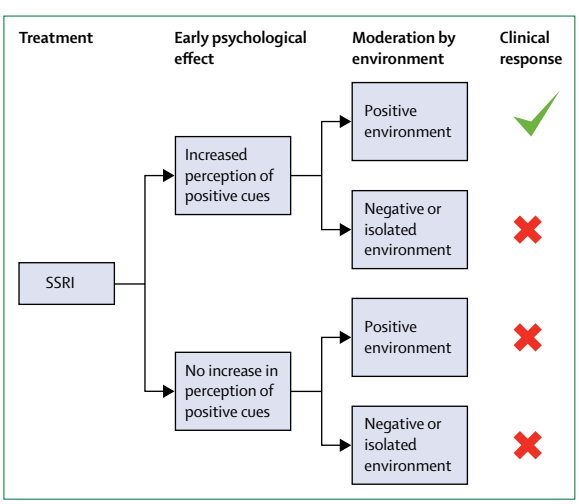

Figure 3: **Effect of patient environment on the clinical efficacy of antidepressant drugs**
Increased perception of positive cues has been associated with delayed clinical response with SSRI treatment, but this effect is moderated by environmental and social factors. Therefore, increased positive bias is only associated with improvements in depression in the context of a relatively supportive or positive environment. In the absence of changes in emotional bias, the patient's environment has little effect.[111] SSRI=selective serotonin-reuptake inhibitor.

Unifying approaches and measures across treatment research

Treatment combination across different treatment modalities can be restricted by barriers between researchers, clinicians, and funders. These barriers include different frameworks, languages, focus, and outcome measures, making it difficult to see natural synergy between the fields. However, exploring treatments using a common framework could help to overcome these barriers and lead to novel hypotheses that could not be predicted by a single approach alone. For example, studies have used measures across scientific fields to understand treatment effects, such as neuroimaging to understand and predict therapeutic response to psychological treatments,[107] and psychological outcome measures to explore the effects of drug treatment.[108]

As an example, efforts to understand the mechanism of an antidepressant drug usually focus on the molecular, cellular, or chemical interactions, but evidence is increasing that antidepressants affect core psychological processes that are important in depression before therapeutic effects are observed, which could help explain their delayed clinical actions in depression (figure 2).[108] Antidepressants increase the relative processing of positive versus negative information early in treatment, which could be important in the recovery process from depression since the patient has more positive feedback and reinforcement, countering the negative biases that are hypothesised to play a key role in maintaining the disorder.[109,110]

A key barrier to the successful translation of these effects into clinical benefit is the need for interaction with the environment. If a patient is socially isolated or in a socially detrimental environment, then increased

positive bias and processing would be expected to have only a small effect. Shiroma and colleagues[111] reported that increased positive bias, induced by treatment with antidepressant drugs, interacted with interpersonal support in the patients' environment to predict the therapeutic response (figure 3). This kind of interdisciplinary approach to treatment has the potential to generate new hypotheses concerning combination treatment that would not have been predicted from either approach alone. Using this example, the combination of early phase treatment with an antidepressant drug in combination with a psychological intervention is predicted to increase the patient's interaction with the environment (eg, behavioural activation), and could remove a barrier to successful treatment with an antidepressant drug (figure 2).[108]

To facilitate interdisciplinary combination approaches to treatment, increased communication and translation are key. Greater collaboration and joint meetings, the use of similar assessments and measures, and joint funding initiatives will help support this aim to improve combination treatments in the future. These improvements will require organisations, funding bodies, and researchers to work together, but the results will no doubt be exciting. An example of this collaborative approach to treatment occurred following a joint symposium and was presented at two very different meetings; the British Association for Psychopharmacology and the British Association for Behavioural and Cognitive Psychotherapies. The joint symposium, supported by the charity MQ: Transforming Mental Health, focused on the divide between psychological and biological treatment development and stimulated approaches to start to bridge the gap and align research strategies between psychopharmacology and psychotherapy.[112] Researchers in the field need to build on this exciting initiative, call researchers across all mental-health fields, and get strategic funding to strengthen this promising endeavour.

Testing the efficacy of combination treatments

Developing and assessing the efficacy of combination treatment also creates complexities in trial design and methodology (see Part 6). Treatment trials that compare active treatment with control treatment often require large sample sizes to have sufficient statistical power to isolate true effects from demand or placebo effects. Exploring interaction effects in comparison with individual treatments can require even larger sample sizes, depending on the study design. In particular, the effects of two treatments will often be assessed in isolation, as well as in combination, leading to a factorial design with four groups. Mechanistic studies also need to consider possible state dependency of learning—ie, that memory will be enhanced if tested in the same state versus a different state, including internal states produced by a drug.[113] The field of combination treatments will therefore benefit from a variety of approaches and from testing the effects of treatment at different time points and under multiple conditions.

Experimental medicine can be used to test hypotheses in smaller controlled studies and using surrogate markers of treatment success. This approach has revealed key effects of both pharmacological[114] and psychological[115] treatments that are used for anxiety disorders on the same underlying cognitive processes, and it has been used to explore the effects of combined treatment. For example, the effects of pairing computerised training for cognitive bias modification with brain stimulation of the dorsolateral prefrontal cortex were assessed using reactivity to a stressor as a proxy marker of efficacy in healthy volunteers.[116] The effects of cognitive bias modification and SSRI treatment alone and in combination have been explored by use of the same outcome measure, along with effects on negative memory bias. The results of this study showed that the combined effects could be worse than either applied in isolation in healthy volunteers.[117] Early changes in these measures are associated with delayed therapeutic benefit in patients[111] and can therefore be of use to guide initial proof-of-principle studies for treatment combinations and to reject those that have little therapeutic promise. Combinations that appear to be successful with these surrogate markers can be put forward for the next stage of clinical assessment, typically in a randomised controlled trial. This approach might be supported by big-data approaches in which the data are collected under more naturalistic conditions (eg, large-scale analysis of medical records or prescribing patterns; figure 4). Promising treatment combinations and timing of treatment combinations might be isolated by pattern analysis from large datasets. To facilitate this analysis, assessment and treatment elements must be standardised (see Part 8). The triangulation of experimental medicine, randomised controlled trials, and big-data analysis will be necessary to develop, assess, and understand combination approaches of the future.

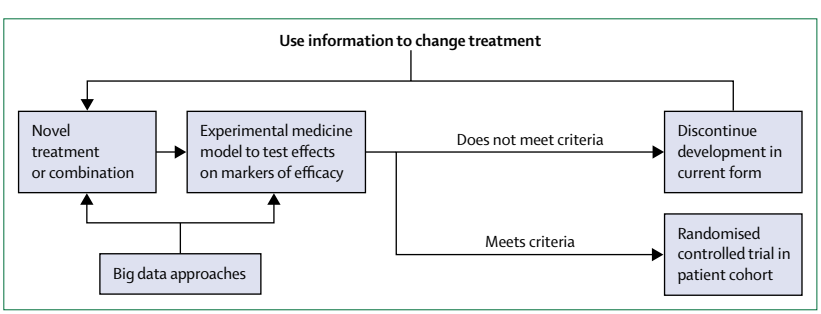

Figure 4: **Experimental medicine models for earlier assessment of efficacy of novel treatments and combinations**

Surrogate markers within experimental medicine models can be of use to screen new treatment combinations in small groups of patients or volunteers. This information is used to refine decision making for subsequent application in and design of randomised controlled trials. If insufficient evidence of efficacy is seen in the model, this information can be used to change treatment focus, the dose or duration, or the treatment target. If pre-set criteria are met, the efficacy of the treatment combination can be assessed using randomised trial designs. Approaches with big data can be useful to highlight particularly promising treatments or combinations and provide additional evidence of efficacy from naturalistic data-capture methods.

***Panel 8:* Potential future research directions in combination treatment**

- Development and validation of preclinical animal and human models for proof-of-principle studies and mechanistic focus in combination-treatment research
- Elucidating the optimal parameters for enhanced learning with drug-treatment approaches and the consideration of individual differences in this response
- Encouraging pharmaceutical companies to develop and assess novel drugs for a combinative role with psychological interventions; cultivate an understanding of this approach within the regulatory community
- Clinical studies informed by proof-of-principle work to test the efficacy of treatments alone and in combination across mental disorders
- Consideration of the potentially harmful effects of combination treatment for treatments that work well in isolation, including a focus on attribution bias and long-term outcomes
- Research the views and acceptability of combined treatments in mental disorders and the importance of patient preference and views about treatment for their clinical symptoms
- Patient preference needs to be considered in formal research programmes that attempt to bridge the psychological–pharmacological divide; the views, acceptance, and opinions of the individual receiving treatment can influence its effects
- Preclinical research using animal or human models is needed to understand key mechanisms and the effects of novel interventions before translation to clinical research programmes
- Back translation can be used to determine the success of translational research since success depends in large part on the validity of the experimental model that is used to mimic the disorder in the laboratory; back translation describes how evidence from clinical research and experience is used to drive, test, and refine the development and validation of animal and human preclinical models
- Experimental medicine and experimental psychopathology: investigators use models, typically human models in laboratory settings, to explore key mechanisms and processes that are hypothesised to be important for treatment action in psychiatry and psychology; these models can be of use for screening novel treatments and refining their application before full clinical testing

Breaking down barriers: from patient perspectives to research of the future

Finally, patient preference should be considered when assessing the effects of combination treatment. Individuals often express a preference for either psychological or pharmacological treatment, so the option of a combination of treatments might be a difficult choice for some. This view that a dichotomy exists between a psychological or biological view of mental disorders is challenged by evidence that psychological and biological treatments tap into the same core processes and represent different methods, rather than different concepts.[108] Challenging these assumptions and creating synergy at multiple levels (including among the public, clinicians, and scientists) will be a crucial step towards the optimal development of treatments. The ethical implications of combination treatments and their development should be incorporated within research strategies for these areas. Additionally, the attribution of treatment effects needs to be considered from the patient's perspective—eg, if any benefits from combined treatments are attributed to the medication, then the long-term advantage of CBT can be lessened.[118] Studies to characterise attribution bias in combined treatment approaches and consideration of the strategies that might be effective in reducing these effects are key priorities for future work (panel 8).

In summary, research to date that has tested the efficacy of combination treatments has shown great promise for the clinical utility of combining psychological and pharmacological approaches. However, many unanswered questions remain that need to be addressed regarding the optimal method for treatment combination in preclinical studies, experimental medicine models, and randomised controlled trials.

Part 4: When in life? Psychological science, prevention, and early intervention—getting the approach right from the start

Introduction

Opportunities for prevention and early intervention into mental health problems exist throughout a patient's lifespan; however, the early years of life are perhaps the best opportunity to set an individual on a path to good mental health. This process requires both population-based change and the accurate identification of those at risk, and for both approaches effective and safe interventions are needed. Many approaches have little or no scientific underpinning, and so the rigorous and sustained application of approaches that are based on psychological science to this area of practice is crucial and offers enormous promise. The focus of this section is primarily on children and young people.

Prevention and early intervention

The prevention of mental disorders is one of the main challenges for the future of mental health care because of their high burden of disease for individuals and societies, the relatively small effect of treatments to date, and the enormous societal costs of mental disorders once they have emerged.[119] The imperative to reduce risk factors across the population and to intervene at the earliest point when symptoms or precursors of mental distress occur makes sense on a human, societal, and economic level.[120,121] Psychological science can inform and underpin the development of early preventive interventions, even if the risk factors are social in origin.

The early years of life, from conception through to childhood and adolescence, are a good opportunity to set an individual on a path to good mental health. Most mental disorders have their origin or onset before the age of 18 years.[122] The greater plasticity of the brain during childhood and the nature of the emotional and behavioural responses of a child mean that the potential to intervene successfully and powerfully could be greater than at any other point in life. Nowadays, the potential role in early life for psychological approaches is greater than that of pharmacological and other physical interventions; however, many interventions remain under-researched, such as nutritional approaches. For psychological interventions to make progress into the

effective prevention of mental disorders, some key requirements and scientific and clinical challenges have to be met.[2]

Requirements and challenges for prevention and early intervention

Preventive approaches in childhood and adolescence (panel 9) require the identification of risk factors or at-risk groups (unless an intervention is going to be delivered to the whole population).[120] Key risk factors in early life include exposure to severe adversities, such as maltreatment, disturbed parenting, parental substance misuse, exposure to domestic and other violence, and loss events—eg, serious parental illness or death of a parent.[126] However, further research is needed into these and additional risk factors, as well as into the interactive effect of risk factors.

For change to occur, effective and acceptable interventions should be available. These interventions might target modifiable risk factors or use other theoretical approaches to affect change, including tackling key psychological mechanisms. However, many early interventions do not have sufficient evidence to be considered as effective. Developing and testing early interventions that might reduce the risk of psychological illness is a fundamental and largely unmet challenge.

Current research limitations regarding early interventions

Any kind of early intervention is often implicitly assumed to be better than no intervention, but this assumption is not correct. Almost any intervention that can do or change something has the potential to cause harm if applied in the wrong circumstances, as discussed by Carter and colleagues[127] regarding eating disorders. The possibility for harm is often overlooked and is probably one of the key blind spots in the field of prevention of psychological problems, particularly when translated into policy. Crucially, clincians and researchers need to acknowledge that not all interventions are the same; even those interventions that overlap in appearance or content can have different effects.[128]

A paucity of evidence on the effectiveness of psychological treatments exists in many areas of child and adolescent mental health practice, particularly for very young children. However, this area does hold promise since the differences in effectiveness for different treatments can be seen where high-quality evidence exists.[60,129] A related consideration is that an intervention might not have the same treatment effect in every setting or with all individuals equally (eg, the apparently contradictory findings for the Family Nurse Partnership intervention[130]). Disentangling these challenging problems is made more difficult if the components of a psychological intervention are not clearly specified or publicly available, perhaps because of some commercial or other protective reason.

***Panel 9:* Psychological treatments: what are preventive and early interventions?**

Prevention is often defined as those interventions that are done before people meet formal criteria for a disorder.[123]

Three types are described:

- Universal prevention, which is aimed at the general population or parts of the general population regardless of whether they have a higher than average risk of developing a disorder (eg, school programmes or mass media campaigns).
- Selective prevention, which is aimed at high-risk groups who have not yet developed a mental disorder (eg, the Nurse Family Partnership programme developed in the USA that initially aimed to prevent later adverse psychosocial outcomes for women and their children in socioeconomically deprived areas).[124]
- Indicated prevention, which is aimed at individuals who have some symptoms of a mental disorder but do not meet diagnostic criteria (eg, the intervention developed by Rapee[125] for parents of preschool-aged children who are at risk of anxiety disorders).

A further challenge is the paucity of understanding of the mechanisms by which an intervention occurs in many preventive and early interventions. As set out in Part 1, an understanding of the mechanism of action is crucial to the development of new and more effective methods of successful treatment. However, the mechanisms of action are likely to be more changeable in early life than at other points in life, complicating efforts to understand them in a preventive and developmental context. For example, different mechanisms could operate at different points in childhood, and each of these mechanisms could be different from those operating in adulthood, even for the same condition or problem that is presented (see Part 8). Although few well studied examples of this divergence between childhood and adult mechanisms seem to exist, studies are emerging—eg, Ewing and colleagues[131] found that children at risk of anxiety disorders do not have the specific cognitive biases for emotional stimuli that are seen in adults at risk of anixety disorders. For patients in early childhood, clinicians and researchers will need to go beyond the individualised mechanisms suggested in the RDoC explanatory constructs (see Part 1). Instead, other mechanisms existing in the social world of young children might open crucial pathways to help change precursors of psychopathology—eg, via the early relationships or attachments that children form to their parents or carers. Parental sensitivity has been shown to be a key mechanism of change (eg, in the context of attachment),[132] although the detailed processes which might then lead to the development of psychopathology remain to be elucidated.

Making interventions stick—persistence of effects

Another challenge for preventive and early intervention approaches, which is shared with many other forms of psychological intervention, is how to make interventions stick—ie, not only how to make the effects of psychological treatment last beyond the end of the treatment, but also how to make them generalise to other areas of functioning. Few psychological interventions have convincing evidence of sustained benefit.

Panel 10: **Examples of promising preventive and early intervention approaches**

Example 1: video feedback to promote positive parenting

During infancy, brief and focussed interventions, such as video feedback to promote positive parenting,[135] can improve parental sensitivity and the child's attachment relationship with their primary carer or parent; this technique draws on both attachment theory and social learning theory; some evidence of effects on child behaviour exist for this intervention, which are largely lacking for other video feedback parent-focused approaches to date.

Example 2: parental interventions for childhood anxiety

An intervention for parents of children aged 3-5 years who have an increased risk of anxiety disorders (identified by having high levels of behavioural inhibition) has been shown to reduce the risk of subsequent anxiety disorders within the child; this intervention was brief (six sessions), and used an educational approach with some behavioural components focussed on exposure; effects from the treatment were still seen 11 years later, although only convincingly in girls, and were shown to be cost-effective using Australian criteria for cost-effectiveness.[125]

Example 3: parenting programmes for child behavioural problems

Among school-age children (aged 3–7 years), consistent evidence has shown the benefit of parenting groups based on social learning theory, such as Scott and colleagues' Parenting Programmes to improve child behaviour;[136] longer-lasting benefits have been shown, and economic modelling studies point to societal, financial, and individual health gains.[137]

Panel 11: **Research questions in prevention and early interventions**

- When are the optimal times to intervene to prevent mental disorders?
- Who are the key at-risk groups that will most effectively respond to early or preventive treatment?
- What are the potential harmful effects of specific early-intervention approaches?
- How do we increase the so-called stickiness of treatment effects? How do we make them last beyond the end of treatment?
- How can we deliver interventions on the scale needed (including internationally) to reach at-risk children and young people?
- How can insights from mechanisms of change help prevent or delay disorders and reduce the recurrence of episodes?
- How can insights about prevention be applied across the human lifespan?

Developments are needed in psychological science to inform how to take psychological interventions outside of the therapy room—which could make interventions more widely available and acceptable, and make the effects of interventions more generaliseable to everyday life functioning. Technologies could help in this regard (see Part 5)—eg, by use of gaming and other technologies to prevent or treat early signs of depression.[133] A further approach is to take interventions into schools.[134] To date, both of these approaches have utilised primarily cognitive behavioural interventions, although other approaches, such as interpersonal therapy, also show promise for the treatment of depression in children and young people.

Positive examples for the future

Panel 10 contains three examples of intervention types for young children and their parents that have shown that preventive and early interventions are possible from very early in life, and that longer-lasting benefits are possible. All three interventions are derived from scientifically rigorous and sustained approaches to intervention development and are informed by theory. Other preventive or early interventions do exist, with varying levels of research evidence to support them, for a range of psychological and psychiatric conditions.

Prevention of mental disorders in adults

In the past two decades, randomised controlled trials have shown that preventing or at least delaying the onset of mental disorders is possible in adolescents and young adults, especially depression and psychotic disorders. Psychosocial preventive interventions, typically based on psychological treatments such as CBT or interpersonal psychotherapy, have been tested in at-risk populations and in people with subthreshold symptoms of depression or psychosis. Meta-analyses[138,139] confirm that these interventions effectively reduce the incidence of new cases of depressive disorders by about 20–25%, and prevent or delay the onset of about 50% of psychotic disorders in those at high risk for developing a psychotic disorder.[140,141] Preventing the onset of mental disorders is one of the most promising areas in which research on psychological interventions can help to reduce the disease burden of mental disorders.

The challenges ahead

Clearly, more research is needed to expand the repertoire of approaches and the range of mental disorders that can be treated. These approaches need to be theory driven and rigorously trialled (see Part 1 and Part 6).

Particular attention should be given to ensuring that interventions can produce effects with lasting benefits for children and adolescents, and substantial efforts need to be made to develop or adapt interventions so that they can be of use across a range of settings and accessible internationally (see Part 2).[142] Although preventive and early intervention approaches for mental disorders potentially have huge health benefits, they face particular challenges in terms of showing reliable efficacy and being applied consistently and thoughtfully in everyday practice in health care. The examples considered in this section provide optimism for future developments, but health-care professionals and researchers need to look carefully at the limits of effectiveness, and at the potential to cause harm (eg, potential negative effects of screening and classifying high-risk groups, offering unnecessary treatment to young people with only temporary distress or symptoms, or harmful side-effects of individual psychological treatments; panel 11). Knowledge of these benefits and harms should be pooled from patients of all ages. Although a lot of work still has to be done before effective methods of prevention for mental disorders are widely available, the rigorous and sustained application of psychological-science approaches to these areas of practice offers enormous promise.

Part 5: Technology—can we transform the availability and efficacy of psychological treatment through new technologies?

Introduction

Internet-based psychological treatments have been applied across a broad range of mental disorders. The rise of eHealth and mHealth approaches that use information technology (eg, the internet, virtual reality, serious gaming) and mobile and wireless applications (eg, text messaging, apps) marks a new era for psychological assessment and treatments. Technological innovations offer considerable possibilities to innovate psychological treatments, adjust them to daily life and the people using them, and improve access to treatment. Such knowledge could be of use to better understand how therapies work, make them easier to use, and enable more people to benefit from psychological treatments. Developments in technology-based treatments should be theory driven and properly assessed.

Internet-based psychological treatments

Most research into psychological treatments has been done with somewhat traditional internet interventions. In these interventions, patients work through self-help materials on a computer, learning how to apply a psychological treatment to themselves with the help of a coach or psychologist.[143] Such self-help materials have often been very close in content to face-to-face psychological therapy (eg, CBT). Accordingly, the materials are as if a hard-copy paper manual has been converted into a computerised form, sometimes with simple additional content such as video clips. Direct comparisons between face-to-face interventions and guided internet interventions suggest that no major differences are apparent in efficacy between the two treatment formats.[94] The efficacy of internet-based therapies (see appendix) has been shown for a broad range of mental disorders, including depression,[144] anxiety disorders,[145] sleep problems,[146] bulimia,[147] and alcohol problems.[148]

Internet interventions have many advantages, including saving time for therapists, reducing waiting lists, allowing patients to work at their own pace, removing the need to schedule appointments with a therapist, saving travelling time, reducing the stigma of going to a therapist, and facilitating psychological help for individuals who are hard of hearing.[149] Furthermore, internet interventions might reach patients who cannot be reached with more traditional forms of treatment (eg, because of distance or stigma). Interventions can be quite easily adapted to specific patient groups, with a wide range of attractive audiovisual information with voices giving instructions via a character of whichever gender or age, with whichever accent or language, or perhaps game format, the patient prefers. Internet interventions are probably more cost-effective than face-to-face treatments, but further economic research is needed to verify this.

From a research perspective, internet interventions have many advantages. One major advantage is that recruiting patients for randomised controlled trials of internet interventions is much easier and more cost-effective and efficient than doing trials of traditional face-to-face psychotherapies (see Part 6). Research into these interventions should stimulate further development of personalised treatments for mental disorders by allowing large-scale trials that are powered to examine complex questions (see Part 8) or test for weaker effects (eg, prevention trials).

However, internet interventions have limitations. The quality of interventions that are offered through the internet is not clear, and despite portals for evidence-based internet therapies, such as Beacon, the possibility that low-quality therapies are being offered remains a threat. Beacon is a webservice through which a panel of health experts categorise, review, and rate websites and mobile applications for internet-based psychological treatments. It is part of a suite of self-help programmes that have been developed and delivered by the National Institute for Mental Health Research at the Australian National University, although it is unfortunately not being updated. Drop-out rates are higher in internet-based interventions than in face-to-face therapies,[150] and it is unknown whether the condition of these patients gets worse as a result of the intervention, or in general, since they cannot be followed-up. Internet interventions might affect the therapeutic alliance between therapists and patients, but most evidence suggests that internet-based therapies are at least equivalent to face-to-face therapies in terms of therapeutic alliance.[151] Little research has focused on the long-term effects of internet interventions; however, the same is true for face-to-face psychological treatments. Furthermore, we acknowledge that internet interventions might have unknown disadvantages, such as misunderstandings due to reduced communication channels in unguided interventions and the potentially confusing depiction of content as graphs and schemes. Additionally, data security and privacy should be guarded for any intervention that is offered through the internet.

For **Beacon** website see https://beacon.anu.edu.au

See **Online** for appendix

Finally, despite increasing access, the internet is not yet accessible to many potential users around the world, and dissemination will depend on the attitudes of possible users and health-care professionals. However, even in low-income and middle-income countries, access to the internet and mobile phones is expanding (see Part 2), although creative solutions (eg, regarding literacy) might need to be taken into consideration where applicable.

Other technological opportunities

Interventions can increasingly be offered through smart phones and watches, Google glasses, virtual-reality headsets, and other kinds of innovative devices. Many of these devices have the advantage that they can be worn by the patient and collect information during daily life (ecological momentary assessment;[152] see Part 8). The

Panel 12: **Potential directions for future research with new technologies for psychological treatments**

- Treatment and theory development: health behaviour theory can be of use to inform technological treatment innovation across all areas of psychological treatments
- Treatment evaluation: trials to assess the effectiveness of new products such as apps
- Learning: maximising and innovating learning methods during psychological treatment by fresh means—eg, skills learning, habit change—such as via serious gaming
- Devices: the incorporation of new technologies—eg, avatars , smart watches, and other devices—into existing psychological treatments to facilitate delivery and improve outcomes
- Harnessing new technologies to advance methods of examining causal mechanisms, refine treatments, and derive treatment approaches that are mechanistically driven
- Health monitoring: enable large-scale data mining and data interpretation to predict the onset and course of mental disorders
- Personalisation of technology-based interventions
- Technologically aided preventive treatment approaches adapted across all age ranges and globally

information collected might considerably improve prediction models for individual patients and thus potentially improve and increase the effect sizes of existing treatments. Computerised adaptive-testing techniques assess symptoms online with greater sensitivity and specificity from fewer items than traditional forms of outcome monitoring—ie, pen and paper questionnaires.[153] Several virtual-reality treatments have been developed, mainly for anxiety disorders. Patients are not confronted with the real stimuli that provoke their anxiety but with their virtual counterparts using real-time computer graphics, body-tracking devices, and other sensory input devices.[154] This form of treatment has shown some effectiveness;[155] however, many of the trials have been small and of suboptimal quality. Many studies have shown that telephone-supported therapies are effective in the treatment of common mental disorders.[156]

The range of mental-health applications (ie, apps) available is rapidly growing, offering a range of psychological interventions;[157] however, most apps are not based on health behaviour theory and little evidence supports their effectiveness.[158] Future researchers should develop theory-driven interventions and assess their effectiveness, since only a few interventions have been tested in randomised controlled trials.[159,160] Specific adaptations to the design of a randomised trial might be needed because of rapid technological developments.[161] Widely available and untested products pose a risk to the public. Although the field of technology-based interventions is still young, and efforts to progress treatment development have started, international approaches are needed to develop regulated approaches and procedures.

The format of new technologies could allow new treatment techniques to be developed that are not part of existing face-to-face psychological treatments, offering novel information processing options (eg, virtual-reality exposure, and possibly interpretation of bias training). Serious gaming, such as the SPARX program, also opens opportunities for interdisciplinary research and new methods of treatment delivery.[133] Serious games refer to games with a purpose other than providing entertainment, which in this case is the delivery of a psychological treatment using game principles. SPARX is an interactive fantasy game designed to give CBT to adolescents seeking help for depression.

At some point, the automated support of these new technologies might replace the therapist altogether (ie, therapist-free therapy[162]), and lead to improved, personalised treatments (see Part 8). New technologies can also be of use in predicting the development and outcome of mental disorders. For example, mobile phone apps are available to monitor associations between psychological risk and suicidal ideation,[163] and evidence exists that the use of specific phrases and personal pronouns can, for example, predict an individual's depression status from their blog posts (see Part 9), although we acknowledge that such monitoring could raise ethical concerns.[163] Because of the huge quantities of data can be collected through mobile phones and other devices that can be connected with existing databases, data-mining techniques could be helpful to predict the onset and course of mental disorders. This data accumulation could aid the development of innovative psychological interventions that could be integrated into new technologies that become part of the daily lives of patients. However, to increase the likelihood of success, new technology and data accumulation alone will not suffice. A sound theoretical framework should be incorporated to drive hypothesis alongside clinical knowledge.

Finally, eHealth and mHealth approaches that use information technology and mobile and wireless applications are examples of ways that technology has been harnessed to innovate psychological treatments, their availability, and their assessment. Technology-based treatments need to improve with advances in psychological theory and understanding of mechanisms of change. Future technological innovations offer considerable possibilities to innovate psychological treatments (panel 12), including adjusting treatments to patients' daily lives and using the information gained to better understand how therapies work, improve the treatments, and improve the technology's ease of use, so that people across all age ranges and worldwide can benefit from psychological treatments.

Part 6: Trials to assess psychological therapies

Introduction

Several key issues in the design and conduct of clinical trials to assess psychological therapies must be addressed to develop therapies that are evidence based. These issues offer several opportunities for improvement and

some specific challenges, given the complexities of both the therapies being assessed and the populations who are receiving them. The challenges include more accurate reporting of clinical trials, eg, specification of therapy protocols and inclusion and exclusion criteria, choice of outcome measures, measurement of adverse effects, and prevention of bias in trial design and analysis. The opportunities include the increasing role of service users and carers in all aspects of trial design and conduct, the development of methodologies for achieving a consensus regarding research questions and outcome measures, the development of new methods for analysis of mediators and mechanisms, and innovations in the design of clinical trials (eg, adaptive trial designs and mixed methods approaches that incorporate nested qualitative studies).

These challenges and opportunities will be considered in this section of the Commission in the context of a feasibility study (the COMPARE trial, ISRCTN06022197) and the potential for a subsequent trial to assess CBT for people with psychosis. This subsequent trial would be a direct comparison of CBT, an antipsychotic medication, and as a combined treatment, which is a research recommendation in the UK National Institute for Health and Care Excellence guideline for the treatment of psychosis in children and young people (for additional information see appendix).[164]

The need to improve clinical trial methodology

Clinical trials are the cornerstone of evidence-based approaches to decisions about access to health care, but in the field of mental health such trials often have substantial methodological shortcomings that result in low-quality evidence. Many psychotherapy trials are not registered in an international database before recruitment starts,[165] therefore other researchers cannot be sure whether the outcomes that are reported were those originally intended, and raises the possibility of selective reporting of outcomes (ie, focusing on those results that were statistically significant), or that negative trials remain unpublished. A systematic review[166] found that many psychotherapy trials did not attempt to maintain blinding (ie, masking) in the people rating the treatment outcomes increasing the likelihood of bias. Additionally, treatment protocols were broad and not based on a specific model, which makes assessment of fidelity and replication problematic. These limitations could be overcome by ensuring linkage between experts in trial design and methodology and statisticians and innovators in psychological therapy development. Accredited clinical trials units, with their extensive experience of trial design and conduct, could coordinate with academic methodologists who are at the forefront of developments in trial statistics and methodologies.[167] In the past decade, substantial improvements in psychological treatment trials have been made, with more studies adopting clinical trial registration and pre-specification of primary outcomes, including application of Consolidated Standards of Reporting Trials (CONSORT) criteria (appendix). Such procedures are increasingly required by leading journals and ethical review boards. However, to apply these procedures to psychotherapy trials particular adaptations of both trial design and reporting guidelines will need to be developed—eg, around issues such as double-blinded studies, a trial design that cannot be maintained with a therapist-delivered psychological treatment. However, double-blinded studies can also be problematic for pharmacological treatments, since aspects of the treatments can become apparent despite the investigators' best intentions—eg, the rapid and dramatic weight gain and parkinsonian side-effects found with both first-generation and second-generation antipsychotics. Another possibility is that subjective cognitive effects[168] unmask participants.

Additionally, the potential negative effects of psychotherapy are increasingly being recognised, and unwanted effects and serious adverse events need to be documented and reported to ethics committees as part of safety monitoring. Historically, psychological therapy trials have been poor at both monitoring hypothesised side-effects and deterioration, and reporting serious adverse events.[169] Negative effects and adverse events that require documenting range from the worsening of existing symptoms, to issues such as novel symptoms, poor therapeutic relationship, and perceived coercion.[170] Such adverse events are possible in both traditional psychotherapy and internet-based interventions.[171] A procedural model and checklist are available for clinicians and researchers,[172] and the detection and management of adverse events in treatment trials is considered a sign of good practice. Formalised measures of possible harms (ie, side-effects) caused by trials should be the rule, rather than the exception, in psychotherapy research.[169]

To ensure that psychological therapy trials are credible, the minimum standards expected in other fields should be met (eg, those standards in pharmaceutical trials). However, psychotherapy researchers have an opportunity to develop their own standards, which could ensure superior trial design, conduct, and reporting, which other fields could aspire to meet.

A set of reporting standards specifically tailored to psychological therapy trials are being developed as an extension of the original CONSORT guidelines.[173] These reporting standards include recommendations to improve internal and external validity, address measurement issues (psychological therapy trials often have many measures, of which many assess latent constructs), improve reporting of recruitment processes and representativeness of participant groups, and increase contextual information—eg, factors that helped or hindered the interventions. Additionally, research on general trial methodology (eg, on how to deal with the issue of masking participants) will be an important area of future inquiry.

Conflicts of interest

Management of a clinical trial by the developer of a psychological therapy could be considered equivalent in terms of bias to a pharmaceutical company managing a drug trial, and investigator allegiance effects have been observed in psychological therapy trials.[174,175] The focus of investigations into this bias has been more on allegiance to a given type of psychotherapy than on financial interests. Steps can be taken to reduce bias, including the declaration of interests (ie, personal financial interests such as training fees, book royalties, and non-financial interests), registration of protocols, prespecification of plans for statistical analysis, and involvement of independent methodologists in the trial design and data analysis. Trial steering committees and data-monitoring committees with independent clinical, statistical, and service-user representation also increase study confidence and minimise bias. These committees can provide constructive criticism and protect the safety of participants and scientific integrity of the trial. Expertise in all relevant approaches is important for trials that compare two or more therapies—eg, the team for the COMPARE trial includes researchers with expertise in both CBT and antipsychotic medication.

Inclusion and exclusion criteria

The selection and justification of inclusion and exclusion criteria are crucial to good trial design. The criteria should be specific enough to allow the identification of suitable participants and replication of a trial, but broad enough to reflect real-world clinical settings and permit generalisability according to the purpose of the trial. Historically, many psychological therapy trials require a single diagnostic category or symptom as an entry criterion, not allowing those with several or at least specific comorbidities (eg, other mental disorders, physical health issues, drug or alcohol use). These exclusion criteria are difficult to justify when the clinical reality of a mental health difficulties is complex and comorbidities are the norm (see Part 8). Trials in the past two decades that have assessed CBT for psychosis have typically been good in terms of generalisability, allowing for inclusion of participants who meet broad criteria (which is also true for trials of psychological therapy for depression[176]). Even trials that have focused on mechanisms of change—eg, whether reducing worry processes results in a reduction in paranoid thinking—have allowed participants with comorbidities.[177] However, in these situations compromises might have been made between clinical pragmatism (ie, having broad entry criteria) and the ability to scrutinise specific mechanisms within the trial. Trials that attempt to address transdiagnostic processes by targeting a specific mechanism (eg, modification of attention biases or extended perseverative processing) or problem (eg, sleep difficulties or irritability) across diagnostic groups offer potential advantages in terms of recruitment, generalisability, and implementation in mental health care (for further discussion of these issues see Part 8).

Improved integration of research trials within clinical settings would facilitate the generalisability of results to the real world. One goal is for every individual who attends a hospital clinic because of a mental health problem, or engages with a community mental health team, or attends an appointment in primary care, to be offered participation in psychological therapy research (if willing and able to provide consent). For example, for interventions for which genuine uncertainties in treatment exist (eg, what dose of CBT for psychosis is required), all willing participants could be randomised into groups with different treatment durations.

Choice of control condition

Appropriate control conditions for psychological therapy trials are a matter of considerable debate—eg many argue that so-called treatment as usual is not appropriate since such conditions can be highly variable and at times include access to the treatment that is being provided in the experimental group. The use of an active control condition is often recommended, which reduces confounds such as non-specific factors (eg, attention, warmth, human relationships); however, inclusion of an active control condition could oversimplify the issue of therapeutic relationship—itself a topic of research and debate about its importance. The provision of an alternative therapy can raise other confounds, such as the so-called match between therapist and participant, and the ability of a therapist to switch between, and adhere to, different treatment protocols even though they probably have greater skill and allegiance to one protocol over another. Ways to deal with such issues include having multiple therapists who can provide each active condition, perhaps across trial sites, so that different trial sites can have different expertise but can provide all therapies (eg, a trial of CBT for psychosis compared with befriending).[178] Furthermore, mental health problems might differ in their response to psychological placebos—eg, the effects of non-directive supportive therapy are similar to CBT and interpersonal psychotherapy for depression,[179] although CBT is superior for patients with psychosis.[180]

Experts in clinical psychology trials, such as Alan Kazdin, have formulated models to guide the type of trial needed to address the type of question asked. In part, design solutions will depend on the specific research question. For example, if the pragmatic question is whether an intervention works better than the current provision, then a two-arm trial design would allow the comparison of the new intervention with a specified and defined treatment as usual that follows best practice—eg, CBT plus monthly engagement and monitoring of the participant's daily difficulties compared with monthly engagement and monitoring alone.[181] If the question is whether one form of psychotherapy is better than another, then a direct comparison might be required.

However, if the question is why a treatment works, or whether a specific element is necessary, then the comparator treatment should be a therapy that controls for specified factors (eg, human contact) but in which the active ingredient has been removed. Findings from meta-analyses suggest that wait-list controls should be avoided, since they can lead to inflated effects sizes for the experimental treatment, possibly because people abandon their efforts to solve their mental health problems or recover independently because they are waiting for therapy.[48]

Outcome measures

Most trial methodologists would recommend a single primary outcome and a single prespecified timepoint at which this main outcome should be measured (eg, total symptoms at final follow-up assessment). This method can sit uncomfortably with basic aspects of psychological assessment—eg, the need for multiple assessments of a construct for validity, and multiple timepoints for reliability, as well as tracking the time course of the response. Having more than one primary outcome is justified in some situations (eg, in psychosis studies clinicians prefer psychiatric symptoms whereas service users tend to prefer social outcomes).[182] However, multiple primary outcomes require larger sample sizes. Additionally, the use of data obtained at multiple timepoints can give the most accurate estimate of treatment effects over the full follow-up duration. This process can be done by specifying an analysis involving all available data for a particular measure, which might be preferable to anchoring judgements regarding efficacy to a single assessment timepoint.

The most important outcome can be a subject of debate. Clinicians often prefer clinical outcomes (eg, psychiatric symptoms) whereas service users might prefer social outcomes (eg, recovery, social functioning, and quality of life).[182] Consensus regarding outcome measures for a specific condition would enable individual participant data meta-analyses,[183–185] which could hopefully provide information about the moderators and mediators of the treatment response. Integration with and adoption of routinely collected service user outcome data would also facilitate understanding of mediators and moderators. As part of a UK initiative that aims to establish agreement about sets of core outcomes for particular health conditions (Core Outcome Measures in Effectiveness Trials [COMET]), work is underway to establish consensus about a set of core outcomes for assessments of interventions for people with psychosis.[186] Regarding reporting outcome measures, it is unclear whether having a detailed interviewer-administered rating scale, which could provide rich data and be more engaging for participants than self-administered rating, is preferable to a self-report measure, which could be more reliable since inter-rater reliability is not needed across sites and staff and it avoids rater bias. A combination of both approaches could be a reasonable solution that maximises the benefits of both, so long as they are clearly prespecified as dual primary outcomes. If a trial with dual primary outcomes shows consistency across these outcomes, then the confidence in the findings would be increased.

Another important consideration when selecting outcomes is the time required to complete all assessments. Psychological therapy trials often include numerous secondary outcome measures, which might be of substantial interest. However, a large assessment burden on participants is more likely to impair retention in the trial, subsequently resulting in missing outcome data and reducing the internal validity of the trial. Limiting the number of outcome measures is likely to minimise attrition, but it restricts opportunities for understanding the processes of change. Similarly, agreement on the frequency of assessments and the length of follow-up would facilitate the pooling of data and the capacity for comparisons across trials. A compromise usually needs to be made between collecting meaningful data that will permit identification of what approaches work for whom across a broad range of outcomes and that facilitate mediation and moderation analyses, and not jeopardising participant retention. The involvement of service users who would be eligible for trial participation in the design of the trial, and ensuring pilot and feasibility work has been done, are both likely to be useful strategies in achieving a balance between these factors. Another possibility for minimising the assessment burden and maximising ecological validity and multiple measurements of outcomes is by use of experience sampling methods or ecological momentary assessment data as outcomes. This approach would allow reporting of symptoms, emotions, and indicators of functioning (eg, use of time in daily life—how many hours are spent engaged in constructive activity such as employment, education, parenting, housework, and leisue) as primary outcomes in clinical trials (see Part 8).

In addition to the measurement of wanted effects, such as improvements in symptoms or quality of life, measuring unwanted effects and reporting serious adverse events to ethics committees are important to safety monitoring. Historically, trials of psychological therapies have been poor at both monitoring hypothesised side effects and deterioration and reporting serious adverse events.[169] Several trials[181,187] of CBT for psychosis have attempted to measure adverse effects via qualitative and quantitative approaches. Some critics have suggested an association between CBT for psychosis and increasing stigma, encouraging deterioration or destabilisation, leading to serious adverse events such as admissions to hospital. However, these trials[181,187] also showed the opposite effect when compared with control conditions. This result is surprising when the inbuilt detection bias inherent in the design and implementation of these studies is taken into account (ie, therapists might have

For **COMET** website see http://www.comet-initiative.org/about/overview

weekly contact with a participant, whereas raters might only have contact at baseline, end of treatment, and follow-up, which clearly reduces the likelihood of detection of serious adverse events).

Public and patient involvement

Public and patient involvement is another area that can help to improve how psychological therapy trials are run.[188,189] People with mental disorders can provide unique insights into clinical trials, including identification of the most important and relevant research questions and thus outcome measures. For example, a definitive trial comparing CBT with antipsychotic medication would need to decide whether the most important question is one of superiority (ie, is combination treatment superior to monotherapy), equivalence (which would enable choice), or non-inferiority (in which case choice might depend on adverse-effect profiles). The assessment of acceptability of psychological therapies and the exploration of potential adverse effects can be informed by embedded qualitative interviews and analyses that can be led by service users (eg, the COMPARE trial is incorporating such a study). Finally, the involvement of service users as staff and, ideally, coapplicants, and investigators, should ensure meaningful participation in all phases of the design of the trial, running the trial, and reporting (eg, COMPARE has two service users as co-investigators and two as grant holders).

Public and patient involvement can be via consultancy groups (which is the case for the COMPARE trial), via priority setting partnerships that identify and prioritise the top ten unanswered questions (the James Lind Alliance facilitate the development of such partnerships in the UK), which has been done for the treatment uncertainties related to a diagnosis of schizophrenia,[190] or by the use of Delphi methods to establish consensus on topics with experts with experience (the COMPARE trial is also informed by Delphi studies of people with psychosis for both defining recovery[191] and identifying treatment priorities and preferences[192]).

For the **James Lind Alliance** website see http://www.jla.nihr.ac.uk/

Mechanisms and mediators of change

Trial design should also attempt to facilitate the identification of potential mechanisms, mediators of change (see Part 1), and moderators of treatment effects to inform on how a treatment works, what components are necessary and sufficient, and what treatments work for whom. The identification of mechanisms could be built into all clinical trials, which would also allow pooling of data, although this pooling would require consensus among researchers about the instruments that should be included in the trials. When a specific research question involves testing a mechanism, the trial must have sufficient statistical power for the mechanistic hypotheses and any between-group predictions.

The identification of mediators and moderators requires considerable thought at the planning stage to ensure that the appropriate factors are measured at the appropriate timepoints. The development of new statistical methods for the analysis of mediation and moderation should help with the accurate identification of mechanisms of change and mediators of treatment outcome. Traditional approaches to mediation analysis[193] assume the absence of confounding due to an unmeasured variable being responsible for changes in both the mechanism and outcome. These approaches are problematic because the assumptions made are unrealistic in many instances, especially given the complexity of potential influences on mental health. Subsequent developments that might be better suited to mediation analysis include attempting to measure and adjust for all important confounders,[194] or attempting to adjust effectively for unmeasured confounders (hidden confounding) by use of instrumental variable-based methods analysed on the basis of principal stratification.[195] Examples that are relevant to CBT for psychosis include the finding that participants with a psychosocial causal explanation of their difficulties could be more likely to engage with and benefit from CBT than those with a biological explanation,[196] and that participants with a good therapeutic alliance with their therapist are likely to benefit from a high number of CBT sessions, whereas participants with a poor alliance might be more likely to be harmed as the number of sessions increase.[197]

Innovation in trial design and methodology

The wider context of an individual trial should be considered. The reliability and validity of the findings from meta-analyses that are used to inform policy, guidelines, and service recommendations are largely dependent upon the quality of the trials that are included and the suitability of the selection criteria (ie, whether the included trials were designed to answer equivalent questions). Designing high-quality trials with a long-term perspective provides an opportunity to improve such meta-analyses. Collaboration between research groups, investigators, and methodologists with regard to future pooling of data could be facilitated by establishing collective research groups that would be recognised by group authorship, which would incentivise such involvement and cooperation.

Sometimes, alternative approaches to the traditional two-arm randomised controlled trial are needed, such as multiarm multistage trials.[198]

New methodologies, including adaptive designs, preference trials, and sequential multiple assignment randomised trials (SMARTs), will permit better generalisability to routine practice and more ethical and efficient trial conduct than traditional approaches. For example, a SMART that permits investigators to re-randomise patients who do not respond to CBT or antipsychotic medication after a relatively short period of time into the other monotherapy group or the combination group would confer future clinical

advantages—eg, arriving at a suitable treatment for an individual faster than with traditional trial designs. A preference trial would maximise recruitment in a field in which both service users and clinicians can have strong treatment preferences and opinions about psychological therapy or medication that could jeopardise recruitment, generalisability, or adherence to allocation in a standard randomised controlled trial. An adaptive design with a planned and prespecified interim analysis could permit the early abandonment of a treatment group that proved to be inferior. The cohort multiple randomised controlled trial design[199] allows several randomised controlled trials to be done simultaneously within a large patient cohort. For each randomised trial, all people who are eligible in the cohort are identified, then some are randomly selected to be offered the experimental intervention. The outcomes in the randomly selected participants are compared with the outcomes in those who were eligible but not selected (ie, receiving standard care or treatment as usual). Such designs could overcome recruitment difficulties and increase statistical power, efficiency, representativeness of samples, and comparability between trials, as well as increasing knowledge about the natural course of mental disorders and the likelihood of collecting data on long-term outcomes. This approach would be ideally suited to mental disorders that are seen within specialist teams (eg, eating disorders or first-episode psychosis), especially when the teams are linked within a national or international network and routinely monitor outcomes in a standardised way.

Improvements in the detection of patients who can be classified as responders and non-responders could be achieved by the selection of appropriate measures, incorporation of experience sampling or momentary assessment in the early phases of a trial (see Part 5), use of improved inclusion and exclusion criteria, and the development of statistical methods for mediation, moderation, and consideration of individual response trajectories rather than aggregate effects.

Notably, researchers should recognise that identifying successful interventions is not just about randomised trials, and clinical trials should complement other types of research questions and evidence. For example, randomised trials need to include embedded qualitative studies to obtain rich data alongside quantitative outcomes to inform understanding of active treatment processes and generate new hypotheses that can be tested empirically. The COMPARE trial involves interviewing participants about their experiences of both CBT and medication, focusing on acceptability, credibility, and wanted and unwanted effects (these interviews are designed, completed, and analysed by researchers with lived experience of psychosis). The results of these interviews have the potential to inform the design of a definitive trial related to the selection and recruitment of participants, inclusion and exclusion criteria, outcome measures, and treatment protocols.

If all of the above improvements can be achieved, the ability of researchers to identify and answer the most important questions will improve, trials will be run with greater reliability and validity, and confidence in and acceptance of the findings of these trials will increase (panel 13). Meaningful involvement of service users and carers will allow the identification of appropriate research questions and methods, ensure the relevance of outcomes (including adverse effects), and improve the retention of participants. Additionally, creation of large-scale datasets will enhance the credibility of the results of clinical trials, either by consensus regarding design considerations and measures that enable pooling of data, developments in individual participant data meta-analyses, or by use of routinely collected service data. Psychological treatment trials should also benefit from advances in trials in other areas of medicine.

Part 7: Training—can we cultivate a vision for interdisciplinary training across mental health sciences to improve psychological treatments?

Introduction

In this section, we discuss why the field of mental health science should endeavour to improve links between

Panel 13: **Directions and priorities for future research in clinical trials of psychological treatments**

- Establish a consensus among stakeholders (ie, the innovators and developers of psychological treatments, service users, and methodologists) regarding outcome measures, appropriate scheduling of assessments, and the length of follow-ups
- Routinely build into the design of clinical trials the ability to analyse for mechanisms of treatment
- Engage with commissioners and providers of psychological services to maximise the likelihood that such services can facilitate the routine collection of data to contribute to the evidence base and include clinical trials as part of service delivery when uncertainty exists
- Ensure quality trial design and valid, reliable analysis of data by routine and early engagement with clinical trials units, registration for all trials (including production of prespecified statistical analysis plans), and ensure that data analysis adheres to plans and is done by independent specialists in trial statistics
- Involve service users in all aspects of trial design and conduct, from decisions regarding research questions and methods, through to involvement in trial management and governance, research administration, and interpretation and dissemination of findings
- Carefully match comparators to the specific research questions that trials are seeking to answer
- Measure unwanted and wanted effects and arrive at a consensus about how to measure and report adverse effects
- Increase the use of innovative trial designs that maximise value for money, value for participant input, and reflect clinical practice; such designs include adaptive trials, multiple trials within cohorts, SMARTs, and preference trials; different designs will be suited to different research questions and clinical contexts
- Encourage career paths for those focused on advancing methods in the methodology of psychological treatment trial design, statistics, and other areas that will aid in future research

clinical psychology, psychiatry, and basic research training, and make some proposals about how this aim might be achieved. We review some early successes in innovation in psychological treatments in which basic researchers and clinicians have worked together, and discuss the reasons that such productive interaction has decreased in the past several decades. We offer some recommendations to bridge the gap between clinical practice and basic research into psychological interventions.

Historical shifts in interdisciplinary training

In 1949, in Colorado, the American Psychological Association held the Boulder Conference on Graduate Education in Clinical Psychology to agree on a standard model for clinical psychology training in the USA. Heavily influenced by the ideas of David Shakow, the conference adopted a scientist–practitioner training framework that encouraged clinical psychologists to use scientific research to inform their practice.[200] This proposal facilitated the development of effective new psychological interventions, which was catalysed by clinicians who did basic research, and basic researchers who understood the principles of psychological treatments (see appendix). This confluence of expertise resulted in crucial insights into the mechanisms of onset, maintenance, and treatment of symptoms of mental disorders, and, in some cases, completely revolutionised the psychological treatments available.

By taking a scientist–practitioner approach, training in psychological treatment becomes far more than just learning how to deliver a treatment described in a manual. Understanding the principles on which a treatment was derived can help the practitioner to deliver the treatment well and adapt the treatment to a given situation or patient. An example of a situation in which basic training was important was the development of various types of exposure therapy (incorporating response prevention) for anxiety disorders, including phobias, PTSD, and obsessive compulsive disorder. This treatment was initially derived from research on fear extinction in rodents, which showed a reduction in Pavlovian responses to negatively conditioned stimuli when the aversive outcome was omitted (see Part 1).[201,202] Notably, the focus on response prevention—ie, encouraging patients with anxiety not to engage in their usual coping strategies when confronted with an anxiety-provoking stimulus (eg, avoidance for phobias, rituals for obsessive compulsive disorder)—came from the insight that these behaviours can maintain the conditioned association through preventing extinction.[203] This approach might seem counterintuitive to the patient because, acutely, the prevention of coping behaviours increases their anxiety in the short term, but leads to a reduction in anxiety in the long term. Since this approach can also be counterintuitive from the perspective of some other therapeutic approaches, understanding the principles behind exposure techniques is important. Another example of practitioners benefiting from understanding the underlying science via their training is in the context of depression—namely, the influential learned helplessness model,[204] and its later modifications associated with hopelessness.[205] The learned helplessness model originated from the finding that animals that were exposed to inescapable aversive stimuli subsequently failed to escape when they had the option to do so.[206] Learned helplessness theory has made notable contributions to the understanding of risk factors for depression, especially associated with the roles of attributional style and perceived controllability.[207] Moreover, this theory has inspired numerous animal models that remain the mainstay of testing procedures for new antidepressant drugs in preclinical research, and translational research in this field has yielded valuable insights into the basic cognitive and brain changes that underlie depressive symptoms and their response to treatment.[208]

Over the past several decades, the links between basic research, clinical psychology, and psychiatry have become weaker, the reasons for which could be numerous. One simple fact is that because of the rapid expansion of psychology, basic researchers and practitioners rarely work in the same building. This distance reduces opportunities for interaction and the sharing of ideas between researchers and practitioners. Another important issue is that basic researchers and clinical psychologists often do not read the same journals, or even attend the same conferences, meaning that opportunities for interaction are few.[2]

Renewing the links between basic research and psychological treatments

Clinicians providing psychological treatments need training in basic research

In most countries, little teaching of contemporary basic research (eg, experimental psychology, neuroscience, genetics, physiology, pharmacology, data science, social science, economics) is incorporated into the clinical syllabuses of clinical psychology or psychiatry, or of allied professional training in the treatment of mental disorders. Canada and the USA are notable exceptions, since many clinical psychologists in these countries complete a doctoral training programme lasting at least 5 years, which includes substantial teaching in basic research together with an extensive research-based thesis and clinical training. The basic science content of training courses for psychiatry trainees in the USA has been emphasised,[209] although professionals within the field recognise that further training in basic science would be desirable.[210,211] Other than these examples, the basic research content included in clinical psychology programmes is small, even at the doctoral level (eg, PsyD in Canada and the USA, which is completed by approximately half of all qualified clinical psychologists in these countries; DClinPsy in the UK). In other countries, in which a master's degree is the standard educational

qualification required to become a clinical psychologist (including most of the European Union, Australia, New Zealand, and South Africa), very little basic research is in the curriculum.

This paucity of basic research content in clinical psychology programmes raises a serious concern about the training of clinical mental health researchers of the future and the risk that they will not be equipped with the tools to understand, critically assess, and use basic research that might be relevant to the development of new treatments or preventive strategies. Psychological interventions might become stuck in the past—relying on outdated models that are not supported by contemporary research or theory. This disconnect between basic researchers and clinical psychologists hinders innovation, and slows the emergence of effective and truly novel psychological treatments. Unless clinical psychologists and psychiatrists have the skills to assess research on both risk factors (eg, genetic and socioeconomic influences) and proximal mechanisms (eg, cognitive and neural processing of information), improving preventive strategies and treatments will be difficult.

Basic researchers need training in clinical conditions and psychological treatments

Although most basic researchers are enthusiastic that their research might contribute to improved treatments for mental disorders, they tend to have only a vague idea of what standard psychological interventions entail, since clinical practice is not generally taught even in undergraduate psychology degrees. Specifically, many basic researchers have little knowledge of the evidence base that supports standard psychological treatments, and have little opportunity to interact with clinical psychologists, see therapy in action, or find out what the common techniques comprise. Indeed, in our experience, the view that psychological treatments are primarily given in the context of an antiempirical psychoanalytical couch tradition, and that they are not derived from solid scientific theory or supported by robust evidence from clinical trials, is worryingly prevalent among basic researchers.[2] To formulate relevant research questions, basic researchers who are interested in contributing to the development of psychological treatments need to understand what the symptoms of mental disorders are (and are not), what the most common evidence-based psychological interventions entail and how theoretical models guided their development, and what the key questions are that need to be solved in the future.

The future of interdisciplinary training

Training clinicians in basic research

How can we ensure that the next generation of research leaders, both clinical and basic, are able to bridge the growing divide between their fields? One priority is to provide extra opportunities for academic training to trainees and qualified practitioners, and to attract those with a strong aptitude for research. In the UK, although competition for places on professional doctoral courses in clinical psychology is intense, and they recruit students who are highly academically able, very few graduates subsequently have a career in clinical research. Funding opportunities for the academic training of qualified clinical psychologists are highly competitive. That said, some major UK research funding bodies, such as the National Institute for Health Research (NIHR) and the Medical Research Council, offer academic training pathways for clinicians. These training pathways offer clinically qualified, non-medical health-care professionals the chance to undertake a PhD, while covering a clinical-level salary, tuition, travel, training costs, and research consumables. This training provides a valuable springboard for a career in clinical research, but there is scope for uptake by more clinical psychologists than at present, in part because they might not be aware of these opportunities or have sufficient support or research experience to develop a strong application. Another way of improving academic training in clinical psychology would be to create longer training programmes specifically for those trainees with a strong aptitude for research. These courses could be similar to the North American PhD model, providing students with sufficient time to complete an extensive research project and teaching relevant scientific material alongside clinical skills. The Psychological Clinical Science Accreditation System model that has been developed in the USA, which emphasises the science of clinical psychology in training and internships, would also be an effective way of increasing opportunities for research training. A similar training model is offered at The University of New South Wales (UNSW), Sydney, Australia, in which students are enrolled in a clinical training programme and a PhD programme concurrently, and they are awarded both degrees at the conclusion of their course (eg, Master of Psychology [Clinical] and PhD).

Training pathways also need to be developed for mental health researchers that cultivate an interdisciplinary approach both between clinical psychology and psychiatry, and between disciplines of clinical mental health and a variety of relevant basic research. One possible way to achieve this interdisciplinary approach would be to encourage clinical psychologists to undertake internships or placements in basic-research settings across a range of relevant disciplines, from economics and social science, to neuroscience and genetics. Psychiatrists in the UK already have such an opportunity through the NIHR Academic Clinical Fellowships scheme, but no equivalent programmes seem to be available for clinical psychologists, in either the UK or other European countries. Multiskilled clinical academics, trained in an interdisciplinary environment, would have the advantage of being able to speak the languages of both clinical and basic research. They would also be best placed to develop the metaprofessional skills needed to do truly interdisciplinary

For more on the **UK National Institute for Health Research fellowship for research** see https://www.nihr.ac.uk/funding-and-support/funding-for-training-and-career-development/training-programmes/nihr-hee-ica-programme/nihr-hee-ica-programme-cdrf.htm

For more on the **UK Medical Research Council Clinical Research Training Fellowship** see http://www.mrc.ac.uk/skills-careers/fellowships/clinical-fellowships/clinical-research-training-fellowship-crtf/

translational research, and to use the knowledge derived from basic research to drive innovation in the development of psychological treatments.

Training basic researchers in psychological interventions

Basic researchers with an interest in understanding and contributing to the development of new psychological treatments need to be provided with the opportunities to do so. In the same way that a first-year neuroscience PhD student might learn about the principles and practice of neuroimaging analysis, and therefore be able to assess neuroimaging evidence more effectively because they understand the potential pitfalls (even though they might never use the technique), basic researchers need a route through which they can learn about what psychological treatments are used in practice and how they are hypothesised to work. This knowledge would provide a new generation of researchers who understand the basic principles underlying psychological interventions and could bring a fresh perspective on driving innovation. Even sitting in the same lectures and tutorials as clinical trainees would increase the opportunities for meaningful interaction, and encourage clinical and non-clinical students to value input from each other when developing collaborations. Although neuroscience and cognitive or experimental psychology students are obvious candidates for such an approach, students with backgrounds in a whole range of disciplines—from social science and economics, to computer science and mathematics, and molecular biology and genetics—might have an interest in psychological interventions and could contribute important ideas.

A culture change is needed to accept more crossover

To address these problems that are hindering interdisciplinary interaction several obstacles will need to be overcome, which will require bold changes in thinking within the health-care system. These obstacles exist for both clinical accreditation and funding. A huge number of mental health practitioners have research talents that are being underutilised, and perverse disincentives often discourage clinicians from entering academia, including a possible reduction in salary and a perception that research will not help in their career progression. Additionally, the procedures for obtaining funding for a research doctorate are not widely understood among trainees, and the opportunities to gain the research experience that would contribute to a competitive application are sporadic and invariably depend on locally available supervisors; therefore, the trainees with the most research potential might be overlooked. Furthermore, unlike for clinical training (at least in the UK), an absence of national recruitment is apparent for research training in clinical psychology.

These obstacles could be addressed through longer, targeted clinical academic programmes (like the PhD programme in North America) that include a substantial research component in the professional doctorate, alongside standard clinical training, and national recruitment to attract trainees with the greatest research potential. More substantial research projects than are completed nowadays in most clinical psychology courses would also help to address the concern that learning about techniques could be forgotten if they are not put into practice. Many European training programmes for clinical psychology successfully blend clinical training with basic research; however, the courses are at a master's level, and so do not have the requirement of a doctoral-level thesis, and therefore trainees do not receive the same quality of research training as those in the North American PhD model. For example, in the past decade a pioneering model for training clinical psychologists has been adopted by the Karolinska Institutet in Stockholm, Sweden. In this model, teaching is based within the Division of Psychology in the Department of Clinical Neuroscience, and within a medical university. This design has resulted in the students being exposed to both psychology and neuroscience, and encouraged awareness of the rich links between clinical psychology, neuroscience, psychiatry, and physical medicine. Almost all of the instructors are involved in research, and the majority have at least 50% of their time devoted to research. Although only a master's level qualification is required to become a clinical psychologist in Sweden, Karolinska students are poised as members of the new scientist–practitioner generation. The development of similar programmes elsewhere would be a positive step toward interdisciplinary training, as would an examination of the outcomes of different international models. To our knowledge, such an investigation has not been done to date, but would be extremely valuable.

Models of shared research supervision

Another major factor that restricts access to interdisciplinary training is that those trainees who do enter research training are often supervised only by clinicians, rather than by basic researchers. As discussed, this separation between clinical training and basic research affects both fields with very few opportunities available for trainees in basic research who are keen to understand psychological treatments, to find out what they entail, and the diverse approaches that they adopt. Such exposure to ideas, and understanding of how psychological interventions are actually administered, is an important first step for basic researchers to start to formulate valuable research questions. Therefore, allowing basic researchers to have an active part in the supervision of research projects of clinical psychology trainees would be desirable when possible, and vice versa. Encouraging joint doctoral supervision (whether for research or clinical students) between principal investigators within basic research and clinical

psychology would be a simple and valuable step in the right direction in this regard. Returning to the Australian example, at UNSW Sydney, students who are studying for a combined clinical and PhD degree often do their PhD research under the supervision of a basic researcher (eg, behavioural neuroscientists) and test questions with clear clinical relevance (eg, on topics such as fear extinction, and drug addiction), alongside their clinical training programme. Such a model of supervision facilitates a broad training experience and a unique opportunity for mentorship from both clinical supervisors and basic researchers.

Mixing and mingling—the role of conferences

Finally, even among those clinical psychologists who do enter academia, few forums exist for exchanging ideas with researchers from other disciplines, since the journals they read and the conferences they attend are typically discipline specific (with some notable exceptions—eg, the MQ: Transforming Mental Health annual science meeting; the meeting on neuroscientific research into psychological treatments arranged by the European College of Neuropsychopharmacology;[212] and the annual meeting of the German Association for Psychiatry, Psychotherapy and Psychosomatics). Some clinical psychologists and neuroscience researchers have started to work together to produce new ideas for intervention. A good example is the adoption of ideas from the literature on the neuroscience of reconsolidation—the modification of old memories during their reactivation—in the formulation of new treatment approaches for PTSD.[213] Several studies have tested the possibility that reactivated memories could be disrupted through pharmacological intervention with propranolol,[214,215] with some preliminary indications of positive effects. Other studies[65,216,217] have tested whether the reconsolidation of established memories can be disrupted by use of simple psychological interventions based on cognitive science, with promising results. Engagement with a simple visuospatial task (the computer game Tetris) following memory reactivation was shown to substantially reduce subsequent intrusive memories of experimental trauma.[65] Although this line of research requires considerable further work to show robust clinical efficacy (see Part 6),[216,217] it is an intriguing example of the type of interdisciplinary innovation between basic and clinical research that holds promise for improved treatments in the future. Other good examples of interdisciplinary innovations have been found in the development of new psychological interventions for anhedonia (panel 14).

In the 1950s and 1960s, the development of new psychological interventions transformed the treatment of mental disorders, with the creation of effective treatments on the basis of novel, empirically testable models. Inspired by ideas that were drawn from cognitive psychology and behavioural neuroscience, interventions that were developed through collaborations between previous generations of basic researchers and clinicians have become the treatments of choice. Despite these successes, improvements in treatments are still needed since patient responses to psychological interventions are highly variable. However, in the past few decades the productive interaction between those who deliver psychological interventions and basic researchers has waned. The gap between these

For the **German Association for Psychiatry, Psychotherapy and Psychosomatics** website see https://www.dgppn.de/

***Panel 14:* Could understanding reward processing in the brain help in the development of new treatments for anhedonia?**

Over the past decade, interest has been renewed in a core symptom of depression, anhedonia, which is the loss of interest or pleasure in previously enjoyable activities; anhedonia is also an important component of many other mental disorders, including schizophrenia and addiction, as well as a prominent symptom in neurological disorders, such as Parkinson's disease.

In depression, anhedonia is associated with a more severe course of illness and poorer response to standard antidepressant drugs[218] and psychological treatments[15] than depression without anhedonia; clinicians appreciate that this symptom is an area in which treatments are inadequate.

Given that anhedonia is intrinsically related to an absence of motivation and hedonic response, researchers have proposed that this symptom could arise because of a disruption of the brain's reward circuits,[219] which have been characterised in extensive detail by neuroscience research over the past 30 years.

This idea is not new; in the 1970s Jeffrey Gray first proposed that symptoms of depression might be explained by changes in a behavioural activation system and a behavioural inhibition system,[220] although most researchers focused on the behavioural inhibition system and its association with neuroticism.

An important conceptual advance in this theory has been the notion that the reward system (the behavioural activation system) comprises several relevant cognitive processes: hedonic response to reward delivery, valuation of rewards, reward learning, propensity to exert effort, and decision making; these components at least partially dissociate, and are linked with activation in different brain circuits and neurochemical systems.[221]

This knowledge from neuroscience research has been exploited by clinical psychologists seeking to develop treatments specifically targeted at anhedonia—eg, positive affect treatment;[221] this treatment builds on behavioural activation therapy and positive event scheduling, which are both effective treatments for depression[222] that were originally motivated by ideas derived from behaviourism,[45] and that are known to increase responsivity in the brain's reward system.[223]

Drawing on the finding that reward processing comprises a diverse set of processes, the aim of positive affective treatment is to increase engagement in, attention to, and anticipation of enjoyable activities.[17]

From a complementary angle, another novel approach based on cognitive science (ie, the processes of mental imagery and interpretation bias) has been via positive imagery training; in trials with individuals with depression, post-hoc analyses show early indication of an effect on anhedonia;[224,225] this type of focussed approach could be developed into the wider package of positive affective training.

Although these novel interventions require further assessment, specifically in groups of individuals with anhedonia and depression, the research so far provides examples of how scientific discoveries are of use to fuel development of innovative psychological interventions.

Panel 15: **Example directions for the future of training and links between clinical and basic science**

- Opportunities for integrated clinical and academic training in psychology, through extended programmes that are targeted at those clinicians with the greatest research potential
- Training for basic researchers in psychological treatments, including hands-on experience of techniques and interactions with clinicians, so that they can formulate research questions that are relevant to psychological interventions
- An expectation of interdisciplinary research for psychological treatment researchers, including cosupervision of the research component of professional qualifications by clinical and non-clinical principal investigators
- The provision of seminars on the next steps, focused on academic training as a standard part of programmes for clinical training in mental disorders
- Improved dissemination of research internship and doctoral funding opportunities for clinical psychologists, such as that provided by the Society for a Science of Clinical Psychology
- Training programmes in which trainees in clinical psychology, psychiatry, and basic research can learn alongside each other
- High-level interdisciplinary meetings between basic researchers, clinical psychologists, psychiatrists, and others, including forums in which practitioners can propose questions that they think are important to basic scientists; with tangible outcomes such as papers, grant applications, and implementation work
- Use of the continuing professional development framework to enhance the understanding of basic science among psychological treatment practitioners

For **Society for a Science of Clinical Psychology** website see http://www.sscpweb.org/

disciplines impedes innovation in the development of new psychological treatments, both because basic researchers do not understand what psychological interventions entail, and because clinicians are not familiar with relevant advances. In this section, we have outlined a number of proposals for how to bridge this gap; these proposals should promote a much more extensive interdisciplinary interaction and dialogue than exists nowadays (panel 15).

Part 8: Whom should we treat, for what, and with what? Embracing the complexity of mental disorders from personalised models to universal approaches

Introduction

Most theoretical models and evidence-based psychological treatments have typically been designed for specific, categorically defined mental disorders—eg, major depressive disorder, social phobia, or PTSD. Leading clinical guidelines recommend specific treatments for each mental disorder, usually categorically defined by symptomatology.[226,227] However, mental disorders are more complex than these guidelines take into account, and are characterised by huge varieties between individuals with a given disorder.Heterogeneity in symptomatology across mental disorders is very common,[228] and many individuals have more than one mental disorder.[229,230] Additionally, many individuals have subsyndromal symptoms of other disorders, and could have symptoms that shift between disorders over time. Mental health researchers—and those in psychological treatment research specifically—need to embrace the complexity of mental disorders to make progress in reducing the burden of these disabling conditions. The complexity of mental disorders is a challenge for research and clinical practice. Treatment solutions to deal with this complexity include both highly individualised (ie, personalised) approaches, and so-called universal or transdiagnostic approaches that target common mechanisms. More studies are needed to examine whether these approaches improve the effectiveness of treatments for mental disorders.

Why are mental disorders so complex?

Unlike most areas of medicine, mental disorders are defined predominantly by their symptoms. A paucity of knowledge about the causes of mental disorders contributes to this approach. Symptoms are often considered as manifestations of an underlying latent factor (eg, sad mood and loss of interest are caused by an underlying major depressive disorder). However, these symptoms might not only serve as an output from so-called underlying processes, but could also mutually reinforce one another, as presumed by the network approach.[231] For example, in depression, insomnia might lead to concentration problems, which in turn might cause sadness and loss of pleasure, which in turn might lead to fatigue, feelings of guilt, and suicidal ideation, resulting in the full syndrome of major depressive disorder. Thus, whether these symptoms are indeed manifestations of an underlying factor is still uncertain.[231]

Mental disorders are dimensional, and yet most mental health researchers use a categorical model to study the effects of treatments. The Diagnostic and Statistical Manual of Mental Disorders-5 (DSM–5)[227] is a categorical nosology for classification, to identify, for instance, a depressive episode, and to study the effects of a disorder-specific treatment for depression, such as behavioural activation. In the past few years, initiatives have been taken—eg, the RDoC initiative[29]—to stimulate research on the dimensions of observable behaviour and neurobiological measures of mental disorders, instead of categorical diagnostic criteria (see Part 1).

An additional complicating factor is the differences between individuals and the specific characteristics of their psychopathology. Studies using network analyses have given new insights into the variation of psychopathology between patients.[228,232] These studies show that, although for some people—eg, those with a strongly connected network of symptomatology—the transition from feeling healthy to being fully depressed can be abrupt (categorical), for others—eg, individuals with a weakly connected network of symptoms—external stressors (such as not being able to pay rent) could lead to an increase in symptomatology; although these symptoms gradually decrease after the stressor is gone.[233] These differences in psychopathology could be explained

by a dimensional model of psychopathology—ie, that the individuals with strongly connected networks might be those with increased neuroticism. However, whether these differences between individuals can be explained by an underlying dimensional mechanism or categorical disorder remains unclear.

Mental disorders are complex to study because of the interplay between an individual's emotions, cognitions, physiology, and other factors, as well as how they interact with the environment, which can change over time or as a consequence of having a mental disorder (for the differentiation of mechanisms responsible for onset *vs* mechanisms that are responsible for maintenance of psychopathology see Part 1). For instance, for individuals with depression, major life events (eg, the death of a loved one) are consistent risk factors for the onset of the first episode, whereas for those who have had one or two previous depressive episodes, comparatively less stressful events (eg, getting a minor traffic ticket) are sufficient to trigger a subsequent depressive episode.[234] Huge differences have been found between individuals in how their emotions fluctuate—an important part of many mental disorders—and huge differences over time.[235]

Furthermore, at least 45% of people with mental disorders have more than one disorder (for definitions see appendix), while over half of people with a mental disorder have subsyndromal symptoms of other mental conditions.[229] The lifetime comorbidity of common mental disorders (ie, anxiety disorders with major depressive disorder) can be as high as 73%.[230] The Global Burden of Disease Study[236] estimated that comorbidities for mental disorders for 188 countries between 1990 and 2016 had risen substantially. Comorbid disorders are consistently associated with a greater demand for professional help, poorer prognosis, greater interference with everyday life, and a higher incidence of suicide than disorders without comorbidities.[237,238] An improved understanding of comorbid mental disorders is crucial to give insight into their causes and to improve psychological treatments for all mental disorders and other conditions.

Heterogeneity and comorbidity have been studied in some fields of mental health to explain the causes of mental disorders, including comorbid disorders.[239,240] Dimensional models have been proposed to explain the cause of comorbid disorders; most suggest shared factors for the concurrent disorders (eg, neuroticism),[241] and some add specific factors that differentiate among mental disorders.[242] For instance, the dimensional tri-level hierarchical model of anxiety and depression includes the following levels: a shared higher level factor for anxiety and depression (ie, general distress); two additional factors that are at an intermediate level in terms of specificity for anxiety and depression (ie, anxious misery; fears that explain covariation in positive affect, anhedonia, and sad mood; social fears and fears to explain covariation in social fears; and fears of specific stimuli and interoceptive sensations, and agoraphobic fears); and five further specific unique factors for depression and anxiety disorders (ie, depression, fears of specific stimuli, anxious arousal, social fears, and interoceptive or agoraphobic fears; figure 5).[243]

Alternatively, a network approach can be of use to explain comorbidities through spreading symptom activations. Comorbidities are hypothesised to result from direct associations between the symptoms of multiple disorders—ie, a symptom of one diagnostic category (eg, major depressive disorder) can evoke other symptoms that in turn evoke symptoms of another diagnostic category (eg, anxiety about several events, chronic anxiety or worry).[231] Thus, a comorbidity might be the result of shared symptoms across mental disorders, so-called bridge symptoms.

Figure 6 is an example of a dynamic network of symptoms of major depressive disorder that mutually reinforce other symptoms of the disorder and comorbid symptoms of generalised anxiety disorder.[228,231] For example, disturbed sleeping, which is a symptom of depression, could lead to fatigue, concentration problems, and irritability or agitation (bridge symptoms), as well as other specific generalised anxiety disorder symptomatology. The bridge symptoms are criteria of major depressive disorder and generalised anxiety disorder.[231,244] Additionally, between different individuals comorbidities can develop in different ways, resulting in many different paths to the comorbidity depending on the individual and their environment. However, the network approach does not explain why some individuals are more prone to developing comorbidities (ie, having more symptoms) than others.

Both the network model and the dimensional (hierarchical) model could contribute to the explanation of mental disorders, including comorbidities. These models emphasise the necessity of translating findings from group studies to specific individuals struggling with mental health problems. The role of symptoms, individual differences in symptoms and emotions, and potential underlying mechanisms as maintenance factors in mental disorders, are key elements that require further study.

Personalised models of mental disorders

Although some disorder-specific treatments have positive effects on comorbid disorders in addition to the specific presenting disorder (eg, CBT for specific anxiety disorders also reduces depressive symptomatology),[245] improvements in treatment outcomes are still needed for people with mental disorders, including those with comorbid mental disorders.

Research should embrace the complexity of mental disorders to make progress in psychological treatment research (panel 16). One way forward is to study both interindividual and intraindividual differences. An experience sampling method or ecological momentary assessment can be of use to develop personalised models of psychopathology.[246] The experience sampling method

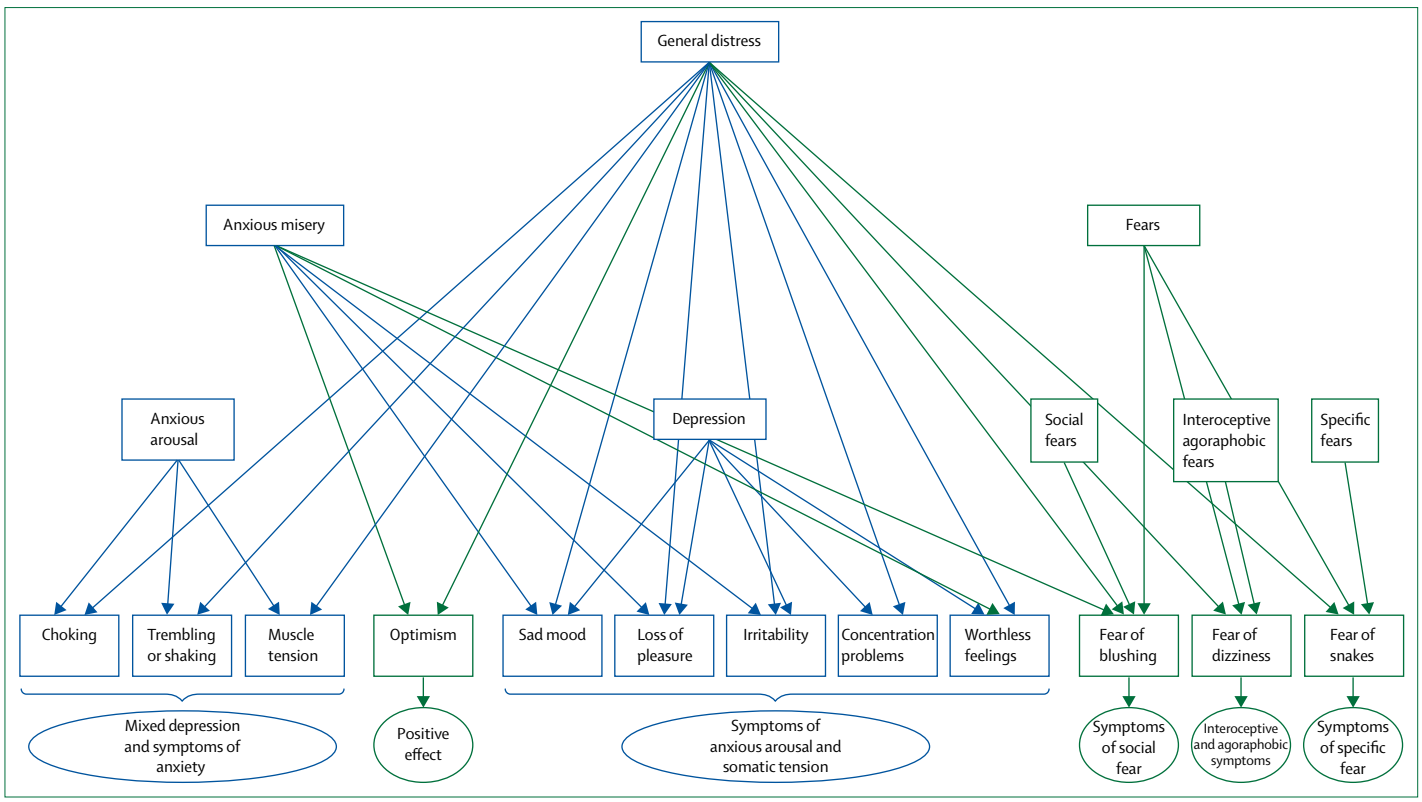

Figure 5: **Tri-level hierarchical model of the comorbidities associated with major depressive disorder and generalised anxiety disorder**
Blue and green boxes and lines show how factors and symptoms are associated with the major comorbidities. Adapted from Prenoveau et al,[243] with permission from Elsevier.

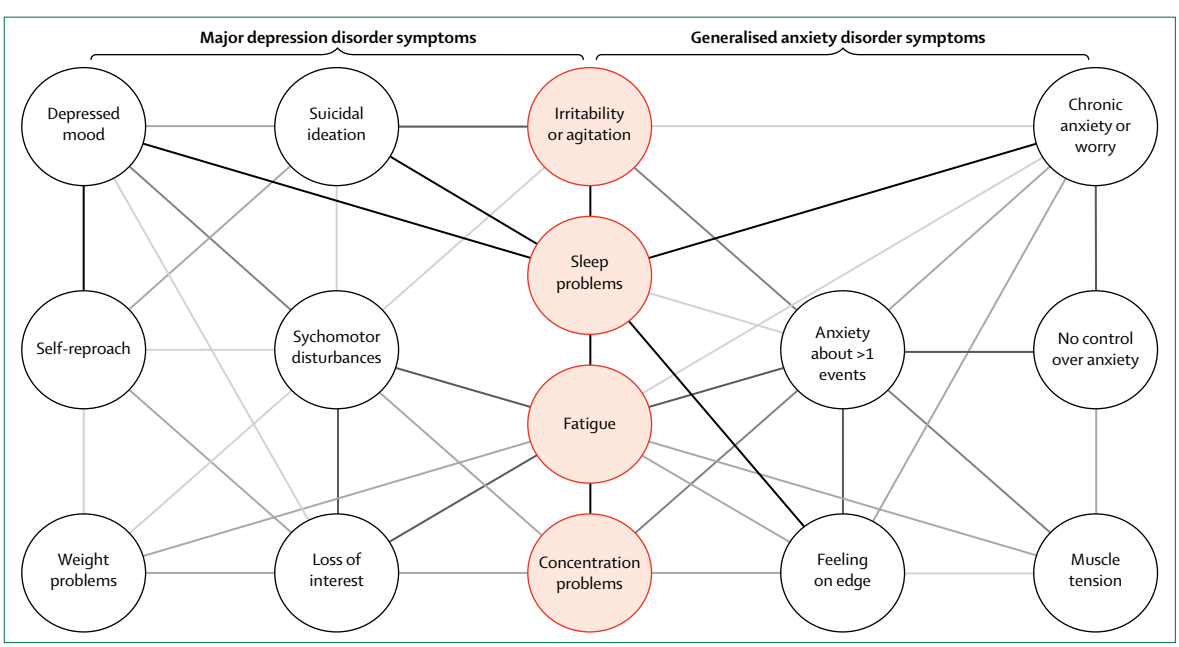

Figure 6: **Hypothetical dynamic network of the symptoms of major depressive disorder that mutually reinforce other symptoms of the disorder and comorbid generalised anxiety disorder symptoms**
Circles contain symptoms and the lines show the causal relationship between those symptoms. Darker lines indicate a stronger relationship between the symptoms. Red circles are bridge symptoms of major depressive disorder and generalised anxiety disorder. Adapted from findings in Borsboom et al[231] and Cramer et al.[228]

is a collection of research methods by which a service user reports on symptoms, affect, behaviour, and cognitions close to when they occurred in the service user's daily life—eg via an application on a mobile phone (see Part 5). Given that the experience sampling method can gather extensive data for each individual, individualised analyses can generate personalised models on the dynamics of each patient's network of psychopathology. Therefore, for instance, the centrality (or the strength) of a specific symptom or mechanism for a specific person can be defined—eg, a loss of interest might be a central symptom for one person with major depressive disorder, whereas the central symptom for another person with the same disorder could be sad mood.[246] This experience sampling method would offer new insights into mental disorders and personalised models of psychopathology. Systematic reviews have emphasised the value of the experience sampling method for assessing symptom fluctuations and interactions over time in anxiety disorders,[247] depressive disorders,[248] and substance use.[249] Studying the transient processes of emotions, cognitions, symptoms, and stress (and other relevant factors) in daily life can be done in prospective and experimental studies—eg, in a randomised controlled trial (see Part 6). In one study,[250] alongside a randomised trial of the effectiveness of three relapse-prevention treatments for depression, an ecological momentary assessment study was incorporated for a subset of patients who had remitted from recurrent depression. This momentary assessment study assessed the participants' emotions, cognitions, symptoms, and imagery-based processing ten times a day, 3 days a week, for 8 weeks, using the *Imagine your mood* application on a mobile phone.[250] Given these ecological momentary assessment studies involve self-reporting questionnaires, addition of physiological and behavioural measures might be useful for such investigations.

Personalised treatment approaches

Research on personalised models might disentangle the complexity of mental disorders, including comorbidities, and enable the optimisation of psychological treatments (appendix). The goal of the personalised medicine approach is to optimise the patient's response to treatment on the basis of their unique characteristics (ranging from genetic and neurobiological factors to symptoms) and underlying mechanisms (appendix). Ecological momentary assessment might improve insight into specific diagnoses[251,252] and offer valuable information that might improve matching treatments to patients. For instance, assessing daily fluctuations in positive and negative emotions by use of an experience sampling method for patients with depression predicts their response to treatment.[253] Assessing an individual's change in emotions (and other processes) over time as they are undergoing therapy might offer valuable empirical information on patterns and mechanisms of change during treatment.

An alternative route to improve the matching of patients to treatment is to use a machine-learning approach to identify the characteristics of an individual on the basis of group studies, which predict the patient's differential responses to existing treatments. An example of this technique is the calculation of a personalised advantage index score,[254] generated by comparing psychological treatments with pharmacological treatments for depression. Future studies should examine whether treatment matching can be improved for individuals with comorbid mental disorders. Similar approaches include clinical-risk scoring,[255] as is used in the field of medicine—eg, treatments for lung cancer are improved by molecular testing for targeted therapies that can overcome resistance to first-generation drugs.[256] Within the field of mental disorders, further studies are needed to examine the relevant variables of these index scores to optimise treatment matching and incorporate, for instance, machine learning.

Additionally, as discussed in Part 1, research on the mechanisms of psychological treatments might reveal crucial moderators of treatment outcomes that lead to better matching of patients to treatment, such as cognitive and biological markers.

Apart from enhancing treatment matching, feedback to the clinician and the patient on daily fluctuations might be of use to adapt treatment and thereby improve the treatment outcomes. Feedback on daily fluctuations via momentary assessment might enable clinicians to adapt interventions immediately—ie, within the session—by

Panel 16: Potential directions for future research regarding the complexities of mental disorders

- Embrace the complexity of mental disorders, including comorbidities, by studying interindividual and intraindividual differences in daily life, and investigate individual dynamics of emotions, cognitions, symptoms, and stress (and other relevant mechanisms) in prospective studies, and in experimental studies, such as randomised controlled trials
- Study models that explain comorbidities in mental disorders and treatment approaches for comorbid disorders
- Investigate whether psychopathological models can be personalised to the extent that treatments can be adjusted, and thereby improve treatment outcomes
- Investigate which patients should be treated, and with what; a disorder-specific treatment, a personalised treatment, or a transdiagnostic or universal treatment, or a combination of these approaches
- Examine the effects of transdiagnostic or universal treatments for several mental disorders, including the comorbid conditions, in comparison with evidence-based disorder-specific treatments

giving real-time feedback on progress to the clinician and the patient.[234] A randomised controlled trial[257] of 102 patients with depression showed that the efficacy of pharmacological treatment could be enhanced by the addition of feedback to the clinician and patient on the personalised patterns of positive affect via an experience sampling method. The collection of data from ecological momentary assessments, with comparable assessments within clinical settings on a patient's patterns of daily fluctuation of change over time while undergoing treatment, would be of great value in a large population with mental disorders (including outcomes after treatment; see Part 6). Mobile devices and applications could increasingly be of use for personalised and immediate interventions. In the future, researchers could make empirical data available to clinicians and patients, which could help them to work together on improving treatment outcomes. Close collaboration will be needed with computer scientists and mathematicians, drawing on advances in these fields (eg, areas of complexity, dynamical systems, and handling big data). Further research is needed on the dynamics of symptom outcomes, rather than just static assessments—eg, time-series analysis of data on mood in patients with bipolar disorder.[258] For now, studies are needed to examine whether personalised treatments are indeed more effective than traditional treatments. A crucial question is, can psychopathological models be personalised to the extent that treatments can be adjusted for the individual, and thereby improve outcomes (see Part 6)?

One size fits all or a universal approach?

Most traditional disorder-specific psychological treatments contain a package of several interventions that target underlying mechanisms of psychopathology (see Part 1). Another, approach is to consider common features between mental disorders via a so-called universal approach (appendix; panel 9)—eg, adverse life events are consistent predictors for the onset of most mental disorders.[259] A risk factor—eg, stress sensitisation—might prove to be a valuable target for treatment, since changing sensitisation might also influence other symptoms in the network, such as rumination or sleeping problems.[260] Alternatively, changing stress sensitisation might reduce a latent factor (eg, neuroticism) and thereby reduce symptomatology. Research efforts could be focussed on trying to identify universal underlying mechanisms across numerous mental disorders, and targeting these mechanisms by universal interventions (panel 16; see Part 4). This transdiagnostic approach has begun to give very promising results—eg, in the treatment of eating disorders.[261,262]

Another example of a transdiagnostic approach to psychological treatment is Barlow's unified protocol for the treatment of emotional disorders.[263] This approach targets transdiagnostic mechanisms that are hypothesised to be responsible for the development and maintenance of psychopathology broadly, rather than addressing disorder-specific mechanisms or symptomatology (especially studied in patients with a principal anxiety disorder). A more personalised approach is taken as part of this protocol than in most treatment protocols, including an assessment of how each patient's dysfunction is associated with the underlying mechanisms of their disorder. The patient's personal profile can then be used by a clinician to select additional interventions that are specific to the mechanisms underlying their symptomatology.[264] Further studies are needed that examine whether these unified approaches are indeed more effective than traditional disorder-specific treatments.

Finally, despite the apparent contrast between a personalised and a universal approach, we suggest that future research agendas embrace the complexity of mental disorders, including comorbidities, and consider both ends of the treatment spectrum—ie, examine approaches that could offer universal treatment and, if necessary, add disorder-specific interventions alongside personalised treatment solutions (panel 16). Solutions to the problems regarding the complexity of mental disorders need to consider both highly individualised approaches and universal or transdiagnostic approaches to target common mechanisms.

Part 9: Target: suicidal behaviour—protecting lives

Introduction

In this section, we discuss how many of the principles outlined earlier in the Commission could be applied to the development, assessment, and implementation of treatments to reduce suicidal behaviour. Although the causes of suicide and suicidal behaviour are complex, they are psychological at their core, since an individual who attempts suicide makes a decision to end their life. In the past 25 years, substantial advances have been made in understanding who is most at risk of death by suicide and what factors increase this risk in some individuals but not in others. Moving forward, the growing evidence base for psychological treatments can be built on to reduce the risk of suicidal behaviour. However, despite these advances, key gaps are apparent in the understanding of suicidal behaviour that require urgent attention. Addressing these gaps is an excellent opportunity to develop more effective treatments that can be replicated, are more precise than treatments to date, and can reach those who are most vulnerable irrespective of who they are or where they live.

Suicide and suicide attempts are the most tragic outcomes that result from an inability to effectively treat those with mental disorders. Suicide is a major public health concern, with at least 804 000 people dying by suicide globally each year.[265] Since suicidal behaviour is a transdiagnostic occurrence that is

associated with many mental disorders, we believe that it is an ideal test case of how the methods that have been discussed elsewhere in this Commission can be applied to a specific problem.

In addition to the personal tragedy associated with death by suicide, the economic cost of suicide is huge. For example, in countries in the European Union, the average lifetime cost associated with a suicide is approximately €2 million.[266] Although the science of suicide research is still relatively new compared with other mental health sciences, in the past few decades several welcome advances in the understanding, treatment, and prevention of suicidal behaviour have been made.[267] These advances include a better understanding of the common risk factors for suicidal behaviour,[268–271] evidence that some psychological treatments reduce suicidal ideation and behaviour,[272–279] and growing evidence that public health interventions are associated with reductions in suicide.[278,279] In this section, we discuss the advances that relate to psychological treatments for suicidal behaviour in more detail and identify a number of urgent calls to action (panel 17). We focus on psychological treatments, but clinicians and researchers should keep in mind how the principles outlined in this Commission can be applied to the primary prevention of suicide.

Although suicide most often occurs in the context of mental disorders,[280,281] the need to move beyond diagnostic categories to explain and treat suicidal behaviour is widely recognised,[282] as is the central role of psychological factors in the cause and course of suicidal behaviour.[271] Arguably, suicide is the cause of death that is most closely associated with psychological factors, given that an individual makes a decision to end their own life.[271] Despite advances in the knowledge of the risk factors associated with suicidal behaviour, the ability to predict who is most likely to die by suicide is poor because no markers of suicide risk are sufficiently specific—eg, although depression is the mental disorder most associated with suicide risk, less than 5% of people with depression die by suicide.[271,283]

New psychological models of suicide have been developed that have identified more proximal and specific markers for risk of suicide than previous models.[284–290] In addition to the theoretical importance of identifying proximal markers of the final common pathway to suicidal behaviour, proximal markers are crucially important for clinical practice and should be treatment targets. Specifically, constructs that are among the key predictors of suicide attempts include feelings of defeat, entrapment, not belonging, and being a burden, as well as future thinking, goal adjustment, reasons for living, and fearlessness of death;[271,286–288,291,292] therefore, these constructs should be targeted in psychological treatments and suicide prevention activities. To date, insufficient focus has been on these suicide-specific psychological proximal markers. Moreover, little is known about which factors are responsible for the observed effectiveness of approaches to suicide prevention (see Part 1). Trials of psychological treatments for suicidal behaviour should routinely assess theoretically derived mechanisms (both psychological and biological) that could explain the treatment effect. A concerted focus on potential biomarkers—eg, salivary cortisol or the serotonin metabolite 5-hydroxyindoleacetic acid—is also required, ideally tested in combination with other factors.[293,294]

Evidence for psychological treatments and their effect on suicidal ideation and behaviour

Psychological treatments reduce suicidal ideation and the frequency of suicide attempts,[272,274,295] although little evidence is available that such treatments have a marked effect on subsequent incidences of death by suicide.[296] Indeed, in 86 (50%) of the 172 WHO member states, between 2000 and 2012, the incidence of death by suicide either remained approximately the same, or increased by more than 10%.[265] Most people who die by suicide are not in contact with clinical services in the 12 months before death, so until the reach of psychological treatments can be expanded beyond those already in contact with clinical

***Panel 17*: Calls to action for research into psychological treatments for suicidal behaviour**

- More large-scale psychological treatment trials (including psychotherapeutic and brief-contact interventions) targeting suicidal ideation and behaviour are urgently required
- Establish whether psychological treatments work for different sociodemographic populations (eg, men *vs* women, adolescents *vs* older adults, individuals from different ethnic backgrounds) and in different settings (eg, primary or secondary care *vs* acute settings), patient groups (eg, treatment as an inpatient *vs* as an outpatient) and countries (eg, low-income and middle-income countries *vs* high-income countries)
- Rigorous investigation of those individuals at imminent risk of suicide
- Replication of psychological treatments by independent research groups
- Agree on common measures of core outcomes (ie, suicidal ideation and behaviour) and complete multicentre treatment studies and harness so-called big-data techniques to establish whether psychological treatments can prevent suicide
- Assess potential mechanisms derived from psychological theories that are hypothesised to account for treatment effects in all trials (risk and protective mechanisms) and moderators of the effects
- Use techniques derived from experimental psychopathology to establish whether hypothesised mechanisms account for changes in symptoms or wellbeing (see Part 1)
- Establish the active ingredients of psychological treatments, including the role of therapeutic alliance
- All psychological and social treatments trials (irrespective of whether suicidal ideation or behaviour is the target) should routinely include a measure of suicidal ideation or behaviour (even as a secondary outcome) that could be harvested in big-data analyses
- Ascertain the barriers to seeking treatment—particularly for males
- Investigate the extent to which new technologies might be of use to engage difficult to reach populations (eg, men, adolescents)
- Those with lived experience of suicidal behaviour (eg, bereaved by suicide or with personal experience) should be involved in all stages of psychological treatment research

services, these services are unlikely to have a direct effect on national suicide rates. Given the complexity of the risk factors for suicide, multilevel interventions offer the most promise.[279,297]

Nonetheless, meta-analyses show that CBT is effective in reducing suicidal behaviour in adults, although not in adolescents.[275] A systematic review and meta-analysis[275] of psychosocial interventions following self-harm in adults concluded that CBT "seems to be effective in patients after self-harm", and specific studies (which require replication) provide support for dialectical behaviour therapy (for individuals with borderline personality disorder),[298] psychodynamic interpersonal therapy,[299] and mentalisation-based therapy.[300] Efforts have also been made to establish whether the Collaborative Assessment and Management of Suicidal ideation and behaviour (CAMS) is feasible and clinically effective.[301] The Attempted Suicide Short Intervention Program (ASSIP), a brief intervention consisting of integrated therapy and personalised letters, showed encouraging findings in patients who have attempted suicide.[302]

A meta-analysis[303] of therapeutic interventions for attempted suicide and self-harm in adolescents found that therapeutic interventions are effective in reducing self-harm when it is treated as a global category that includes suicidal and non-suicidal self-harm, but that the effects are weaker when suicidal and non-suicidal behaviour are examined separately. This weaker effect when separately analysing suicidal and non-suicidal behaviour is consistent with the findings of a Cochrane review of interventions for children and adolescents who self-harm.[277] The authors of the review found only 11 trials, most of which were single trials, from which they concluded that therapeutic assessment, mentalisation, and dialectical behaviour therapy "warrant further evaluation"(see also Part 4).[277] Treatments that target depression are not effective in reducing suicidal thoughts or suicide attempts.[304] A marked heterogeneity is notable across treatment studies in the field, and many studies have small sample sizes and evidence of publication bias is clear since no published studies seem to report negative findings.[275] Replication of the existing treatments by independent groups is needed, as is the development of evidence-based assessment measures that are clinically useful in the field of treatment research for suicidal behaviour (see Part 6).

The development, assessment, and implementation of psychological treatments for suicidal behaviour should be prioritised. Moreover, the extent to which psychological treatments are effective for different sociodemographic populations needs to be established (eg, men *vs* women, adolescents *vs* older adults, individuals from different ethnic backgrounds), as well as in different health-care settings (eg, primary or secondary care *vs* acute settings) and patient groups (eg, psychiatric inpatients *vs* outpatients; see Part 8). The sex-specific research is especially important, because more men die by suicide than women in all countries worldwide,[265] but many more women participate in treatment trials for suicidal behaviour.[276] Additionally, the optimal time to give treatment interventions to reduce the risk of future suicidal behaviour among those who have attempted suicide is still unclear.

Psychological treatments are not a panacea. For those psychological treatments that are effective, the overall effect sizes are small.[276,305,306] Also, for many reasons, including access and suitability, psychological treatments reach only a minority of people who die by suicide or who are suicidal. Given the inequality gradient for suicide (ie, people from lower socioeconomic backgrounds are substantially more likely to die by suicide than people in a higher socioeconomic situation[307]), the structural inequalities (eg, poverty) that contribute to the excess in suicide mortality among those from low socioeconomic backgrounds needs to be challenged.

Most suicides occur in low-income and middle-income countries,[265] so the extent to which treatments that are developed in high-income countries are generalisable worldwide needs careful consideration (see Part 2). When developing and assessing treatment trials, consideration should be given to whether a tailored or modular approach is desirable and feasible, whether the treatment is based on principles or manualised (eg, a person-centered approach or an approach with a specified session plan), and whether the interventions account for different risk profiles and inequalities (see Part 8). Furthermore, as noted in Part 1, efforts need to be re-focussed to ensure that when treatment successes occur, the mechanisms responsible for them are understood (eg, does prevention of suicide depend on changes in reward sensitivity?). An appreciation of mechanisms will help explain why treatments that are expected to be effective are not.

Challenges and opportunities for research

Panel 17 highlights the key challenges and opportunities for treatment research for suicidal behaviour in the next decade and beyond. Since individuals who are at imminent risk of death by suicide are usually excluded from treatment trials, little is known about which treatments might be effective in this patient group. Similarly, most people who are suicidal do not receive treatment;[308] therefore, an understanding is needed of the barriers to seeking help and accessing treatment. One reason some people in distress are reluctant to seek psychological or psychiatric treatment could be for fear of stigma. Organisations such as Headspace in Australia (see Part 2) offer promising stepped-care treatment models that aim to remove the stigma of mental disorders, are set in the community, and provide people with a way to seek help for relatives and friends. Another challenge is that patients with suicidal behaviour or ideation are difficult to keep in treatment;[309] an understanding of the factors associated with

disengagement is needed, so that the treatment given can be maximised when patients are in health-care settings—eg, innovative brief-contact interventions have been shown to offer some promise in acute settings.[273,310–312] Maximised treatment approaches should be considered as adjuncts to existing treatments and could be effective in reducing the likelihood that individuals act on their suicidal thoughts.[310,311] Although some public health interventions for suicide prevention have a multilevel approach and explored synergies through a combination of interventions,[297,313] few examples exist in which interventions for suicide prevention have explored combining different psychological treatments (see Part 3). Given the heterogeneity of individuals who attempt suicide or die by suicide, exploring the efficacy of treatment combinations is likely to be a rewarding approach. However, potential iatrogenic effects should be monitored in such studies, as well as in monotreatment studies (see Part 6). The potential for harm during psychological treatments research has been highlighted in the Royal Australian and New Zealand College of Psychiatrists guidelines for deliberate self-harm.[305]

To facilitate the pooling of findings across treatment studies, we urge researchers of suicidal behaviour and ideation to agree on a common set of core outcome measures (see Part 6). In the USA, some movement has been made in this regard;[273] however, an international consensus would be ideal. Agreement on such a set of measures would be aided by the gathering of an international, interdisciplinary working group. We also call for all psychological treatment trials to include a measures of suicidal ideation and behaviour as an outcome measure. Although suicidal behaviour occurs transdiagnostically, the differential prevalence of suicidal ideation and behaviour across psychiatric categories needs to be considered to understand why, for example, individuals with bipolar disorder are at particularly high risk of suicide.[314] Research into psychological treatments needs to embrace the assessment of potential mechanisms to account for treatment efficacy, and establish the active ingredients of effective treatments for suicidal ideation and behaviour (see Part 1).

The extent to which new technologies could be useful to engage so-called difficult to reach populations (eg, men, adolescents) needs to be investigated.[315,316] For example, could gaming technology be harnessed to engage young people in seeking help and treatment? Mobile applications offer opportunities to monitor suicidal ideation and mood in real time and have the potential to enhance the ability to identify (and intervene) when individuals are at their most vulnerable; however, these applications should be developed with the same rigor as traditional methods of psychological treatment (see Part 5). Arguably, the field of suicide prevention has not given sufficient consideration to the cultural influences and pressures on men, women, and adolescents (eg, depictions of masculinity). Given the high incidence of death by suicide among male individuals, the improved integration of such factors into the understanding of suicide risk and suicide prevention efforts is crucial.[317–319]

Those with lived experience of suicidal behaviour (eg, individuals bereaved by suicide, and those with personal experience) should be involved in all stages of treatment development.[320] Since little is known about what protects vulnerable people from engaging in suicidal behaviour, research into potential buffering factors should be central to the development of treatment protocols (see Part 4).

Finally, multidisciplinary collaboration is key to the success of developing, assessing, and implementing psychological treatments to prevent suicide. Since suicide is an end product of the interplay between psychological, social, biological, clinical, and cultural factors, an interdisciplinary approach should be the norm in psychological treatment research (see Part 7). However, since an individual who attempts suicide makes a decision to end their life, in the context of a range of different risk factors, psychology needs to be at the centre of future developments in the field.

Now is an exciting time to be working in research for psychological treatments for suicidal behaviour, since the theoretical and empirical foundations are available for promising treatments. However, in the next decade and beyond, innovative thinking and practice will be needed to ensure that the promise of research into psychological treatments is realised and leads to a reduction in suicidal ideation and suicide attempts.

Part 10: Active innovation and scrutiny of future psychological treatments research

Inspecting ideas and making space for future ideas

Psychological treatments are highly effective for many patients, but a large proportion of patients either do not respond to existing therapies, or the therapies are inaccessible to them. New ideas are needed, and they should be critically inspected, with the progression and rejection of ideas via rigorous and high-quality research.

In the Introduction, we used the metaphor of the fourth plinth in London's Trafalgar Square. The plinth is a metaphor to make contemporary ideas visible and to give them critical consideration. Although some pieces that are displayed on the plinth will be preserved for posterity, others might not be. Some psychological treatments or research ideas should not stand on the plinth forever, whereas some might stand the test of time. Ideas for the plinth need to be generated, inspected, and replaced over time, all within the context of a science-driven framework. Psychological treatment is a relatively young field compared with some medical treatment fields, and the notion of innovation and turnover are crucial parts of its future.

How might this innovation work for psychological treatments? The wide range of potential topics would need to be considered, as well as how these topics could

be selected, where they would be used, how they could achieve visibility, in addition to the need for a repeated cycle of this endeavour, the ultimate aim of which would be to improve the discussion and debate of the pertinent issues to make a difference for mental health. Topics could include both longstanding challenges and novel ideas such as new findings that would benefit from constructive and rapid scrutiny (eg, therapeutic approaches that emerge from the findings of preclinical studies, new ideas from sister disciplines, and new technology and ethical issues). Exciting new directions that emerge in these and other contexts should be clearly formulated, considered, and reflected upon. The ideas would need to undergo rigorous debate within and beyond the field of mental health science, and empirical assessment in the context of scientifically sound studies—eg, well controlled randomised trials.

Open and constructive debate needs to be encouraged, without new ideas being too swiftly quashed by tradition and vested interests in maintaining a status quo. However, new ideas and trends in thinking must be scrutinised before being accepted into clinical practice. One problem for the field of psychological therapy is the need to promote the use of evidence-based treatments by practitioners, who might prefer to ignore the evidence and use techniques for which they have a personal preference. For example, exposure is a treatment technique that is theoretically driven with an excellent evidence base and there is a strong scientific understanding of the mechanisms that underlie its effectiveness;[82] however, in practice, a substantial proportion of therapists do not use this technique.[321] This reluctance and sparse uptake of empirically supported interventions, or aspects of them, among practitioners is an issue that needs to be understood and rectified.

The plinth metaphor also provides a way to question older ideas that are now taken for granted, but that would benefit from further examination. Many broad issues that affect the whole field of psychological treatment require discussion (eg, the diagnostic systems, the quantity of academic publications *vs* their capacity to affect patients, and funding issues specific to psychological treatments), in addition to many issues that are relevant to science generally—from reproducibility to open data. Psychological science is a young discipline compared with many other fields, and emphasis on the progression of psychological treatments over the past century could be beneficial to stimulate innovation. Parallels exist between some of our suggestions in this Commission and the Science in Transition initiative in the Netherlands, which calls for several key reforms in science with the goal of achieving reproducible outcomes.[322,323]

For the **Science in Transition** website see http://scienceintransition.nl/

How can topics be selected? In the art world, the Fourth Plinth Initiative is an open competition to artists and is subject to a review panel. For research into psychological treatments, an equivalent competition or selection process could be held, with specific calls for people to raise challenging ideas that can catalyse progress. This process would generate topics outside what can be imagined now, and potentially create a way to capture the concerns and questions of younger generations in the field (eg, why is neuroscience not being used in treatment research more?), or those of researchers with several decades of experience (eg, why have effect sizes for psychological treatments not improved?).

Such debates and discussions could be included in a dedicated session at conferences and cross-disciplinary meetings, in a specific type of journal article, and in electronic media and areas and settings that allow debate and scrutiny. The metaphor could be adapted to fit a range of outlets, and journal editors and conference organisers could be encouraged to provide space for it. To bring attention to the resulting ideas, an annual prize could be awarded for topics that have attracted attention and made constructive progress.

The empty plinth metaphor highlights the need for repetition in the process of innovation, so that novel ideas for psychological treatment would constantly be generated, tested, and disseminated. This iterative process would not only encourage innovation, but would also enable differentiation of the new treatments and ideas that can stand the test of time, and allow long-held assumptions to be questioned to bring about progress. Essentially, these processes all occur throughout the scientific process, but—as we have discussed throughout this Commission—because of the huge scale of mental disorders globally, progress needs to speed up within psychological treatments research. Borrowing an idea from the arts gives a metaphor for one way (among many needed) to start achieving this goal.

Mental disorders and psychological treatments provide crucial and demanding targets for research enquiry. Creative but realistic solutions require communication and meaningful multidisciplinary collaborations among researchers and funding agencies, and some so-called blue skies thinking from outside the field. Additional researchers from across all disciplines are needed within the psychological treatment field, since a vast range of important questions remain that need to be addressed. This need within the field poses a great opportunity for many early career scientists to make landmark contributions, and other researchers should be encouraged into the field.

Debatably, research has stagnated in some areas of psychological treatment. Outcomes for many mental disorders (ie, depression, obsessive compulsive disorder, schizophrenia, and bipolar disorders) have not improved since the original interventions were developed, and might even be declining.[324] Understandably, an emphasis has been put on increasing access to psychological treatments,[24] given the large unmet need and changing models of service delivery.[22,83,325,326] However, an equally

strong need exists for the development of innovative new psychological treatments for the large proportion of people who do not engage with or respond to existing interventions, or who relapse after a seemingly successful course of treatment. The proportion of people who are in one of these categories varies by disorder, age group, and research study, but it can be considered to be at least 50%.[327,328] We also see a pressing need for multiple solutions, given the scale of the challenge ahead. A range of approaches could be valuable in this endeavour, including the dissemination of evidence-based therapies and increasing the accessibility of evidence-based psychotherapies. Therefore, although we see the need for a multipronged approach to tackling mental disorders worldwide, we argue that the development of new psychological treatments is one of the most promising approaches, especially given the scale of the problem of mental disorders from a public health perspective.

What factors might encourage stagnation or innovation? Branding, communication, and funding

One obstacle to innovation in the field of psychological treatment research is branding of psychological interventions, with the accompanying restrictions due to intellectual property issues. Such branding prevents the dissemination and implementation of psychological therapies, and stifles innovation by implying ownership.[329] A sustainable, not-for-profit model for the development of psychological interventions is an alternative and potentially better model than the branding model. Some research groups are under increasing pressure from so-called knowledge transfer departments at universities to brand their work for uniqueness—this pressure needs to be resisted. Instead, departments and research groups should be in favour of developments in psychological therapies that are more open, that highlight shared common components, and that are described to an extent that they can benefit from examination by the wider psychological treatment community. The issue of sharing knowledge is clearly complex because of concerns regarding incent-ivising investment in psychological treatments from a range of sources, and the need for quality control within some interventions. The development of citizen science has the potential to counteract branding and provide a fertile ground for innovation.

Noticeably, as discussed in Part 7 about training, the majority of psychological treatment researchers stick to what they know. Such adherence is rewarded by strong CVs, grant funding, and in-depth knowledge of a specific field. However, this approach can also lead to insularity. Input from fields such as neuroscience, maths, pharmacology, and more diverse disciplines, such as medical geography,[330] could help clinical researchers and practitioners think differently. Jointly reviewing advances in areas such as cognitive and social science to identify which innovations might be relevant to improving psychological therapies is entirely feasible. Such an approach has substantial potential to facilitate the introduction of new, scientifically sound ideas into psychological treatment. Innovation can benefit from creativity, including taking ideas from one area and seeing if they apply to another for treatment benefits.

Improvements are needed in communication between service users, clinicians, and across the health services. Mental and physical health-care services are typically entirely separate services, with minimal overlap despite their close relationship in terms of pathology, service use, and cost to the health services around the world.[331] Improving communication between providers of these two health-care services via shared training, resources, or even co-location would be a fundamental step toward innovation, with scope to give substantial benefits to the entire health-care system. Drawing on multiple areas of expertise will be important—particularly, obtaining input from patients and carers, which is a topic that is receiving increasing attention,[188] but which requires further consideration.

The issues of innovation and improvement cannot be dissociated from those of dissemination and implementation. Innovations that stay localised will benefit some patients but the effect will be minimal (see Part 2). Furthermore, the time taken for a treatment to get from bench to bedside will continue to be unacceptably high (estimated to be 17 years, although some argue the development of psychological treatments is quicker than pharmacological treatments[3,332]) unless dissemination and implementation are part of the development plan from the outset. Communication between stakeholders is essential to ensuring the effects of innovations are as anticipated. Only through the development of meaningful networks can genuine collaborations be built—eg, joint training, conferences, and funding. Such joint networks need to be funded appropriately for the stage of development, with basic researchers and clinicians having a bidirectional conversation, initially by email but then face to face in a relaxed atmosphere with time to think creatively, discuss constructively, and develop testable hypotheses.

The role of funders in promoting or stifling innovation cannot be overemphasised. The NIMH's influence on funding has been profound, and inclusion of a category on the RDoC entitled "Other"—so that researchers are not restricted to only studying established research domains—encourages new ideas.[333] Although researchers understand that funding agencies tend to want to avoid risks, the funding of high-risk studies is fundamental to the development of new treatments. Agency support to fund proof-of-concept studies in psychological therapies could be especially important to the field. The extent of funding for international research into mental disorders, and psychological treatments in particular, is far too low;[334,335] increased funding is essential for progress and to take risks in new areas.

Globally, within large funding organisations, mental health is often included with other diseases or with, for example, neuroscience. Representation within these funding organisations of people with experience in mental health research can be minimal and people with genuine expertise in mental health are needed within the decision-making bodies of the major funding organisations. Clearer representation of expertise in psychological treatments would also be of benefit. A review of the international funding organisations that address mental health would be useful, including the extent to which psychological treatment research is accommodated. Some charities fund research, which is of course welcomed, but unfortunately many smaller charities often do not have the capacity for a rigorous research review process. The quality and effect of studies that do not benefit from peer review and scientific support is often suboptimal. Funding models whereby smaller charities that support mental health research are themselves supported by larger charities, with regard to their commissioning and execution of research, are likely to improve both the quality of research and the value for money of the research projects. The creation of a framework for peer review for mental health in general, and psychological treatment in particular, or even a possible outsourcing model for such processes, might help many organisations with funding initiatives in this area.

How can the effectiveness of efforts toward new treatments be assessed?

Broadly, our aim in undertaking this Commission was to identify the scope of advancing research efforts to improve mental health globally via improvements in the effectiveness and the global reach of psychological treatments. We have outlined an agenda of some of the areas in which we see real scope to improve treatment research and treatment delivery to enable more effective interventions and greater accessibility of such treatments to individuals with mental disorders than have been available to date. Treatment protocols that effectively treat and prevent the onset of mental disorders will have a key role as one of the many contributions that are needed to relieve the substantial worldwide burden of mental disorders.

The ability to assess in a tangible and meaningful way whether the goal of improving treatments for mental disorders has been achieved remains a challenge for the field. The initial indicator of success is within the outcomes of the treatment trial—ie, whether the effect sizes indicate improved efficacy of novel and refined psychological interventions. In the longer term, meta-analyses will outline whether new treatment approaches have improved effectiveness, and thus, in turn, contribute to reducing the prevalence and the burden of mental disorders. In the future, the findings of epidemiological studies that show changes in the prevalence of mental disorders over time will reveal the success of scalable treatment and prevention approaches. We acknowledge, however, that measurement in this field can be complicated and ambitious—eg, changes in the diagnostic classification systems over time complicate comparisons. We therefore see a need for research on how to define and quantify the burden of mental disorders globally and over time. We see scope for progress to be made, not only by examining changes in prevalence, but also by investigating improvements in the functional effect of mental disorders—from impairments in social and occupational functioning, through to quality of life. Such a suggestion aligns with our acknowledgment of the value of expanding ideas of mental disorders beyond the notions of disease and infirmity, to outcomes with broad functional relevance (eg, an individual's capacity to adapt, and self-manage; see Introduction).

Innovation to create new treatments—what ideas can be put on the plinth in the first round?

Increasing access to effective psychological treatments is a priority, but investment in innovations that will energise the research field of psychological treatment and improve therapeutic outcomes is equally important.[22,83] Many books and journal articles have been dedicated to the issue of innovation, and even an entire journal is devoted to this topic (*Healthcare: The Journal of Delivery Science and Innovation*), which commenced in June 2013. Innovation is clearly a challenging area and what is presented as an innovation can often be seen as old wine in a new bottle. Innovation needs to be put into a historical context, so that existing ideas are not repackaged with enthusiasm as an innovation.[336] Engagement is needed in the critical inspection, progression, and rejection of ideas through research. One approach is to change the nature of the questions being asked; here we begin with two examples.

What matters to patients?

Most clinical research has tended to focus on single diagnoses, despite many patients having multiple coexisting disorders.[230] Clinicians have guidelines for the treatment of specific diagnoses but almost no data to guide them with regard to evidence-based decision making for patients who have common co-occurring disorders—eg, anxiety and depression. Patients' difficulties can alternatively be considered in terms of the problem they are having rather than in diagnostic terms—eg, loneliness or betrayal.[337] Linking with social psychology and having a problem-based approach to the development of psychological treatments, instead of a disorder-based approach, is likely to lead to new ways of thinking about and addressing mental disorders, which was partly the intention of the RDoC initiative.[333] Such approaches could increase engage-ment in and the acceptability of therapies, but challenges would still

exist for agreeing operationalised definitions of the problem, and ensuring that such difficulties were affecting people's lives in ways they value and that could be viewed within a psychological framework.

What matters to researchers?

Many things matter to researchers, but most scientists are curious about what does not work, as well as what does. Data that do not obey the expected rules are essential to scientific progress. For psychological treatments research, defining non-responders, identifying which people relapse, and those who do not engage in treatment, are all necessary and crucial steps.[328] A thorough and focused analysis of the characteristics of those individuals who do not respond to existing treatments, and having dedicated funding for such research, are priorities that would have a positive effect and bring generalisable benefits to existing and new treatments. Additionally, in areas in which no existing treatments work adequately, the generation of novel treatments is essential.

What next?

We see mental health as a substantial global challenge, but at the same time we recognise that nowadays we are faced with an array of pressing priorities that demand global attention and action, including, but in no way limited to: climate change, international conflicts, famine, and the displacement of millions of people from their home countries. Notwithstanding that many such substantial problems exist in the world, in the domain of mental health, we call for increased research efforts to advance psychological treatments, so that more effective interventions will serve as an essential part of our set of approaches that are needed to make an impact upon the burden of mental disorders worldwide and improve lives.

We acknowledge that our call for developments in psychological treatments for mental disorders is but one endeavour in the context other similar timely initiatives. For example, Wykes and colleagues[338] have laid out six key priorities for a mental health research agenda for Europe and worldwide. Mental health is increasingly being recognised as an area that needs to move forward on a global scale. Furthermore, psychological interventions can be applied not only to mental disorders, but have been increasingly of use across a range of areas—eg, in changing health behaviour, managing the psychological aspects and effects of physical health problems (ie, pain management and somatic concerns, psycho-oncology), and instituting organisational change.

Clinicians, researchers, patients, carers, funders, commissioners, managers, policy planners, change experts, and the general public all have a part to play in innovating psychological therapies, and a focus on any one of the ideas presented in this Commission has the potential to bring about substantial and much-needed improvements. More ideas will be needed than just those included here. This Commission is not a specific roadmap, all relevant areas of research and mental health science need to be considered to gain traction in this endeavour. Innovations arising from thoughtful effort have genuine potential to transform the science and practice of psychological therapies, and the lives of all of those who are affected by mental disorders.

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