Editorial

Psychotherapy and Psychosomatics

Psychother Psychosom 2019;88:129–140
DOI: 10.1159/000500151

Received: February 28, 2019
Accepted: April 4, 2019
Published online: May 14, 2019

Iatrogenic Factors in Psychopathology

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Introduction

The side effects and risks associated with the medical intervention are defined as iatrogenesis [1]. Adverse drug reactions, malpractice, medical error, and negligence constitute common iatrogenic complications [1]. Examples of important syndromes induced by medications are asthma caused by beta-adrenoceptor antagonists, pulmonary fibrosis associated with cytotoxic agents, gastric bleeding and complications with anti-inflammatory agents, torsade de pointes tachycardia with various drugs, abnormal glucose homeostasis with thiazide and corticosteroids, and osteonecrosis of the jaw with bisphosphonates [2].

In psychiatry, iatrogenesis has traditionally been concerned with medical complications of psychotropic drug treatment [3], such as tardive dyskinesia [4] and insulin resistance [5] with antipsychotic drugs, and cardiac and metabolic disturbances with antidepressant medications [6–8]. The complications may occur due to direct toxicity, drug-drug interactions, intoxication, or withdrawal from psychotropic medications [3]. In more recent years, attention has also been dedicated to the patient experience of negative effects of psychotherapy [9, 10], including the interactions between pharmacotherapy and psychotherapy [11, 12].

As it happened with medical therapy [13], psychiatric treatment has mainly been assessed and evaluated as to its capacity to improve psychiatric symptomatology. Side effects have been conceptualized as the unavoidable drawbacks of any form of medical therapy. Little attention has been paid to the adverse psychological and behavioral effects of psychiatric treatment on psychopathology and illness course. In view of the insufficient body of knowledge on the iatrogenic effects of psychological therapies [9, 10], we will only concentrate on the effects of psychotropic drug treatment. Many of the insights that have been gained in the past 25 years have originated in this journal.

The Changing Presentation of Psychiatric Disorders

Clinicians have always been aware of the fact that evaluation of a medicated patient requires consideration of psychotropic drug effects on the symptoms of the disorder. If a patient takes a hypnotic, for instance, he or she may fail to present with sleep disturbances that otherwise would have emerged in the clinical examination. The clinician would then adjust the use of diagnostic criteria accordingly, that is he or she would consider the fact that medications may simply cover symptoms that would otherwise be active. This is just a matter of clinical judgment,

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the neglected basic method of psychiatry [14]. In the nineties, however, the impact of pharmacopsychiatry on symptom configuration began to unravel its complexities. In 1996, the first comprehensive review on residual symptomatology in patients with mood and anxiety disorders who had been treated with psychotropic drugs and/or psychotherapy disclosed that most of the patients had residual symptomatology [15]. The review highlighted a wide spectrum of symptomatology that was inextricably linked to a past episode of depression or anxiety disorder, whether or not still under treatment, and the importance of taking into account the longitudinal development of the disorders [15]. Staging methods, which had so far been neglected in psychiatry [16], achieved an important connotation. How would we evaluate the presence of a limited number of depressive symptoms, not sufficient to formulate the diagnosis of a major depressive episode, in patients under long-term antidepressant treatment? In longitudinal relation to the past episode and its current drug treatment (using staging) or simply on the basis of cross-sectional current symptomatology regardless of treatment status?

In their book on *Modern Psychiatric Treatment*, Detre and Jarecki [17, p. 95] provided a model for relating prodromal and residual symptomatology to psychiatric illness, defined as the rollback phenomenon: as the illness remits, it progressively recapitulates, even though in reverse order, many of the stages and symptoms that were seen during the time it developed. The rollback phenomenon was later substantiated in research on mood and anxiety disorders [18, 19] and was the basic idea for developing the concept of sequential treatment [20]. If prodromal symptoms may have a pathophysiological role in affective disorders and some residual symptoms may progress to become prodromal symptoms of relapse, then reduction or disappearance of residual symptomatology may entail a more favorable long-term outcome of depression. A confirmation of this hypothesis was provided by two controlled therapeutic trials of our group [20, 21], and later by several independent investigations [22]. Sequential treatment was thus able to favorably affect the long-term course of depressive illness and the longitudinal development of symptoms (rollback phenomenon). Psychopathological assessment had thus not only to define the characteristics of a disorder at a particular point in time, but also the extent of progression and where a person was along the continuum of the course of illness [16].

However, in the nineties, the effects of drug treatment on illness configuration were essentially viewed in their capacity to relieve symptomatology [18, 19] and some questions about their potential for deterioration just started appearing [23].

The Concept of Behavioral Toxicity

In 1968, DiMascio et al. [24–26] specifically addressed the behavioral toxicity of psychotropic drugs. Such a concept referred to the pharmacological actions of a drug that, within the dose range in which it has been found to possess clinical utility, may produce alterations in mood, perceptual, cognitive and psychomotor functions, that limit the capacity of the individual or constitute a hazard to his/her well-being. The use of the term "toxicity" was not conventional, since it was not restricted to immediately dangerous clinical effects such as in overdose or to drugs with narrow therapeutic indices, such as lithium. DiMascio et al. [25] described two major drug-induced mood changes. "Paradoxical" drug effects are those alterations in mood in a direction opposite to the clinically desirable, such as increased anxiety and rage with benzodiazepines and deepening of depression with antidepressant drugs [25]. "Pendular" drug effects are those alterations that proceed in a desired direction however to a degree that the resultant state tends toward the opposite condition for which the drug was initially administered, such as euphoria with antidepressant drugs [25].

However, their formulation received scanty attention in the literature. Perl et al. [27], in 1980, reviewed the concept of behavioral toxicity of psychotropic medications. They illustrated that psychotropic drugs can cause behavioral toxicity through the extension of their primary therapeutic action and/or the onset of secondary actions as well as withdrawal, dependence and tolerance symptoms. Behavioral toxicity may be characterized by oversedation, depression, dystonia, akathisia with antipsychotic agents; impaired psychomotor and cognitive function, sedation, disinhibition and confusional states with benzodiazepines; fatigue, somnolence, restlessness and agitation with antidepressant drugs; and cognitive impairments with lithium [27].

In the same book, Hall et al. [28] reviewed the behavioral toxicity associated with drugs directed to medical conditions, such as antihypertensives, beta-blockers, corticosteroids, and oral contraceptives. Whitlock [29], in a review published the following year, noted that the past history of an affective or psychotic episode was the best predictor of a similar illness being precipitated by a particular medical drug. An important characteristic of

drug-induced affective disorders is the fact that they are unlikely to respond to antidepressant drugs [30].

The concept of behavioral toxicity has recently been revisited [31, 32]. Behavioral toxicity may ensue with any type of medical drug. At times, its effects on illness course are clear-cut. Examples are switching from unipolar to bipolar course with antidepressant drugs [6, 31] and supersensitivity psychosis, the onset of psychotic symptoms and co-occurring movement disorder with antipsychotic medications [4]. Paradoxical reactions may also occur, such as increased agitation, excitement, insomnia, and talkativeness with benzodiazepines, particularly in children and the elderly [33]. Other times, behavioral toxicity may entail subtle manifestations, which may be detected only with specific assessment strategies, such as with cognitive impairment associated with all psychotropic drugs [34] or with apathy related to the use of antidepressant drugs [35].

Withdrawal symptoms, which may follow discontinuation of psychotropic drugs, such as benzodiazepines [36], antipsychotic medications [4, 37], and antidepressant treatment [38–40], are also a form of behavioral toxicity. Discontinuation symptoms typically appear within 3 days of stopping antidepressant medication or initiating a medication taper. Untreated symptoms may be mild and resolve spontaneously in 1–3 weeks; in other cases, they may persist for months or even years [38–40]. Persistent postwithdrawal disorder has been described with different classes of psychotropic substances (e.g., mood fluctuations and anxiety disorders with antidepressant drugs, tardive dyskinesia and supersensitivity psychosis with antipsychotic medication, protracted insomnia for alcohol and benzodiazepine withdrawal, and major depression for cocaine and amphetamine withdrawal) [4, 38–40]. Events related to withdrawal with psychotropic drugs may thus be limited to the period of drug administration and/or persist long after their discontinuation. Similarly, other manifestations of behavioral toxicity related to tolerance, paradoxical effects, and resistance may occur months or years after the discontinuation of these medications [31]. The explanatory power of pharmacokinetics is limited for these phenomena, even if we take zero-order kinetics into account (only a fixed amount of drug is eliminated in a given interval of time because enzymes for biotransformation and elimination are saturated). Tapering does not appear to affect the occurrence of withdrawal reactions with antidepressant drugs [39, 40] and persistent postwithdrawal disorders months after discontinuation may occur [41]. Further, dosage increase is unlikely to restore response after loss of clinical effect [42].

Pathophysiological Mechanisms of Behavioral Toxicity

The likelihood of persistent pharmacodynamic changes after discontinuation of medications was suggested for antipsychotic drugs in 1978 [43] and for antidepressant and antianxiety medications in 1994 [23]. Commenting on the hypothesis that antidepressant drugs might increase chronicity [23], Ross Baldessarini [44], in this journal in 1995, noted that "the list of long-term pharmacodynamic actions of all psychotropic agents – not only at the level of receptor plasticity, transmitter synthesis rates, and neuronal firing levels, but perhaps even at the level of genetic control of neuronal functioning – is growing and provides many opportunities for theory construction" [44, p. 139]. He concluded his editorial by urging open-minded and serious clinical and research consideration [44]. Regrettably, such investigative efforts have been very limited, despite increasing awareness of the continually changing patterns of gene expression mediated by epigenetic mechanisms that may alter genomic stability associated with treatment and stress [45].

As a result, we still do not know whether and when the pharmacodynamic changes that occur with long-term psychotropic drug treatment return to a pretreatment condition: are they irreversible (and treatment is a one-way street) or do they take weeks, months, years? A pharmacodynamic consideration of the clinical phenomena related to antidepressant treatment was presented for the first time in this journal in 1995 [46] and was subsequently updated with an increasing number of studies supporting the model [41, 42, 47, 48]. According to the oppositional model of tolerance, continued drug treatment may recruit processes that oppose the initial acute effects of a drug. This may explain loss of treatment efficacy and the fact that certain side effects (such as increased appetite and weight gain) tend to ensue only after a certain time. These processes may also propel the illness to a more malignant and treatment-unresponsive course, as with bipolar manifestations or paradoxical reactions. When drug treatment ends, oppositional processes may encounter no more resistance, resulting in the appearance of new withdrawal symptoms, rebound symptomatology, persistent postwithdrawal disorders, hypomania, and resistance to treatment if it is reinstituted [41, 42]. In the long run, antidepressant drugs may increase chronicity, vulnerability to depressive disorders, and comorbidity.

The delayed effects of antidepressant drugs on serotonin function have long been established. If it is an adap-

tive response that mediates therapeutic actions at 2–4 weeks [49], it is also conceivable that further adaptive changes may occur at some later point in time. Such adaptive changes may take place through 5-HT1A autoreceptor activity [41], and/or be associated with the allosteric modulation of the serotonin transporter protein, which was recently detected with SSRIs such as paroxetine and escitalopram [50]. Genetic polymorphism in serotonin receptors such as 5-HT1A, 5-HT1B, and 5-HT2 may modulate the extent of opposing and compensatory processes to the initial effects of drugs [51]. However, factors such as duration and type of treatment, prior history of exposure to antidepressants, and augmenting and switch strategies may carry much more weight than genetic predisposition [42, 47, 48].

The Concept of Iatrogenic Comorbidity

Alvan Feinstein's [52] classic definition of comorbidity as "any distinct additional clinical entity that has existed or that may occur during the clinical course of a patient who has the index disease under study" also referred to antecedent pathological events that were judged to affect the current disease process. The cross-sectional nature of the classification systems in psychiatry has limited the use of the term "comorbidity" to what a patient may be currently experiencing. The term "iatrogenic comorbidity" refers to the unfavorable modifications in the course, characteristics, and responsiveness to treatment of an illness that may be related to previously administered therapies [31, 53]. Such vulnerabilities may manifest themselves during treatment administration and/or after its discontinuation. The changes are persistent and not limited to a short phase, such as in the case of withdrawal reactions. As a result, iatrogenic comorbidity is a persistent and particularly troublesome form of behavioral toxicity.

Two examples related to the use of antidepressant drugs may be particularly revealing. The first involves switching to a bipolar course in patients with unipolar depression. Treatment with antidepressant drugs has been associated with mania or other forms of excessive behavioral activation [54]. These responses may unveil unrecognized bipolar illness or may be drug-induced, since they may also occur in allegedly unipolar patients. A systematic review and meta-analysis concerned with excessive mood elevation and behavioral activation of children and adolescents disclosed that rates of excessive arousal-activation with antidepressants were very high both in anxiety (13.8%) and depression (9.8%), and much lower with placebos (5.2 vs. 1.1%, respectively) [55]. Furthermore, in almost half of pediatric patients who participate in antidepressant trials, such reactions occur in the absence of a family history of bipolar disorder [56]. Hence, the risk of developing behavioral activation may also occur with the use of antidepressants in anxiety disorders, particularly in younger patients, and symptoms do not necessarily subside upon discontinuation of these medications [54–56].

A second example of iatrogenic comorbidity is concerned with resistance to a psychotropic drug that was previously effective [42, 57]. There is considerable confusion regarding the term "resistance" in mood disorders, since it is applied to either depressive illness (i.e., an episode which does not respond to drugs or psychotherapy) or to lack of response to a previously effective pharmacological treatment when it is started again after a drug-free period. The former use is the one which is prevalent, but also the latter is worthy of clinical attention. Indeed, lack of response after rechallenge was found to occur in at least a quarter of cases in clinical studies concerned with antidepressant drugs [42]. Further, the ill-defined concept of treatment resistance is based on the untested assumption that treatment was right in the first place and failure to respond is entirely shifted (and implicitly blamed) upon patient characteristics.

The concept of iatrogenic comorbidity may also apply to the persistence of side effects. For instance, several side effects of antidepressants are transient and may disappear after a few weeks following treatment initiation, but potentially serious adverse events may persist or ensue later. They encompass gastrointestinal symptoms (e.g., nausea, diarrhea, gastric bleeding, dyspepsia), hepatotoxicity, weight gain, and metabolic abnormalities, cardiovascular disturbances (e.g., heart rate, QT interval prolongation, hypertension, orthostatic hypotension), genitourinary symptoms (e.g., urinary retention, incontinence), sexual dysfunction, hyponatremia, osteoporosis and risk of fractures, bleeding, central nervous system disturbances (e.g., lowering of seizure threshold, extrapyramidal side effects, cognitive disturbances), sweating, sleep disturbances, affective disturbances (e.g., apathy, switches, paradoxical effects), ophthalmic manifestations (e.g., glaucoma, cataract), and hyperprolactinemia [6]. At times, such adverse events may persist after drug discontinuation, yielding iatrogenic comorbidity, such as with weight gain and sexual side effects [6]. Similar considerations apply to antipsychotic medications [4].

Cascade Iatrogenesis

In geriatrics, the concept of cascade iatrogenesis has been developed: the serial development of multiple medical complications that can be set in motion by a seemingly innocuous first event [58]. For instance, postoperative respiratory failure is common among elderly patients who underwent elective surgery or orthopedic treatment after a fracture; suffering an adverse event during hospitalization is strongly associated with a poorer prognosis following discharge [58]. The concept is highly relevant to psychiatric practice. Many cases of behavioral toxicity lend themselves to cascade iatrogenesis, as the following examples concerned with antidepressant drugs indicate.

First, when antidepressant drugs trigger a manic or hypomanic episode in allegedly unipolar disorders (i.e., a patient who has never had such episodes before), discontinuation of the medication is unlikely to entail a solution to the problem, which tends to persist and modify the entire course of illness in a cascade of affective episodes [32, 54–56].

Second, withdrawal symptoms are likely to be misunderstood as indicators of impending relapse and may lead to unnecessary reinstitution of treatment [41]. Even when the nature of symptoms is correctly interpreted, the renewed prescription of the same antidepressant drug or a switch to fluoxetine, which is less likely to induce withdrawal problems and is commonly suggested [59], may worsen the state of behavioral toxicity with subsequent episodes of refractoriness to treatment. Refractoriness to treatment, in turn, lends itself to the use of switching and/or augmenting strategies, which, as the Sequenced Treatment Alternatives to Relieve Depression Study (STAR*D) teaches [60], may propel depressive illness into a phase characterized by low remission, high relapse, and high intolerance to medications [48].

A third illustration of the appropriateness of the concept of cascade iatrogenesis to psychiatric settings is when psychotropic drugs are administered without indications that are based on controlled studies, for instance the use of paroxetine in a patient who has mild symptoms of depression, which can be subsumed under the rubrics of adjustment disorders or demoralization [42], where no evidence for the effectiveness of antidepressant drugs has been established [61]. This unnecessary prescription may lead to the development of dependence, onset of major depressive episode, withdrawal symptoms at discontinuation, persistent postwithdrawal disorder characterized by mood fluctuations and worsening of anxiety [41]. Carroll [62] warned about the inappropriate use of antidepressant drugs more than 3 decades ago: "we strongly suspect that many patients who are simply unhappy or dysphoric receive these drugs, with predictable consequences in terms of morbidity from side effects, mortality from overdose, economic waste, and irrational, unproductive clinical management" [62, p. 169].

These illustrations indicate that, particularly when symptoms of behavioral toxicity are misinterpreted or simply ignored, a cascade of events leading to illness deterioration may result from the choices of the clinician. Almost 40 years ago, Perl et al. [27] emphasized the need to consider the psychotropic medications that are being administered as a potential cause of psychopathology. "Unless recognized, these behavioral changes may prompt the use of increased amount of medication, thus further worsening the patient's condition" [27, p. 333].

Assessing Iatrogenic Psychopathology

In the past 2 decades, the use of psychotropic medications has dramatically increased: 1 out of 6 US adults is reported to take psychiatric drugs at least once during a year and in 8 out of 10 cases it is for long-term use [63]. Antidepressant drugs lead the ranking of medications [63]. A further issue has to do with the frequent practice of polypharmacy in medicine [64] and psychiatry [65]. Polypharmacy is simply not addressed by the literature and yet it is commonly encountered in clinical reality. Assessing medication burden and polypharmacy [64] is thus another important factor in modern psychiatric assessment, since it is likely to affect presentation of symptoms.

Current diagnostic methods in psychiatry, both DSM-5 [66] and the forthcoming ICD-11 [67], refer to patients who are drug-free and do not take the issue of iatrogenic comorbidity into adequate consideration. They are suited for a patient who no longer exists: most of the psychiatric cases that are seen in clinical practice receive some forms of psychotropic drug treatment at the time of the first psychiatric or psychological assessment and require evaluation of iatrogenic factors.

There is insufficient emphasis on collecting information related to previous treatment in psychiatric and psychological assessment. For instance, the Third Edition of the Practice Guidelines for the Psychiatric Evaluation of Adults of the American Psychiatric Association [68] does mention the importance of reviewing prior psychiatric treatment, either with open-ended questions or with a detailed inquiry about each treatment in sequence. How-

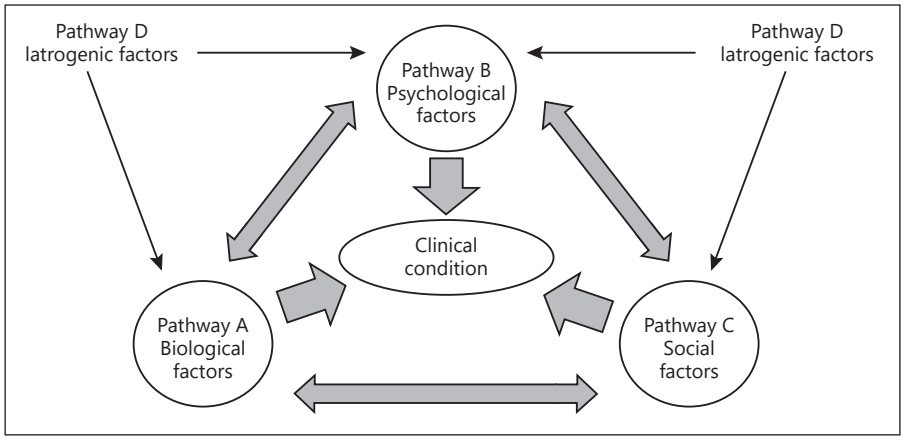

Fig. 1. Concentric model: multiple interconnected pathways contribute to the presentation of a clinical condition.

Table 1. Key points for assessing behavioral toxicity of psychotropic medications

1.	Documenting the individual sequence of psychotropic drugs that were administered (duration, dosages, adherence). Particular attention should be given to the concurrent use of medical drugs and to the occurrence of substance abuse
2.	Were there any paradoxical effects with any of these medications or their combinations (e.g., increased depression with antidepressant drugs, increased agitation with antipsychotics or benzodiazepines)?
3.	Was there any switching to an opposite condition (e.g., hypomania or mania with antidepressant drugs) both during or immediately after treatment?
4.	Was there any loss of clinical effects, despite adequate adherence, with long-term psychotropic drug treatment?
5.	Was there any lack of response to a previously effective pharmacological treatment when it was started again after a drug-free period?
6.	Did any withdrawal syndromes occur upon discontinuation of psychotropic drugs? Any persistent post-withdrawal disorders?

ever, it does not provide any specific indication as to the type of information that can be particularly meaningful.

A first crucial point is to collect data about previous treatments not only as to their efficacy [68], but also as to the occurrence of phenomena of behavioral toxicity, as suggested in Table 1. It is very important not to limit information to psychotropic medications, but to extend it to drugs directed to medical conditions, with particular reference to those which may induce psychiatric syndromes [28–30, 69].

Once data about behavioral toxicity have been obtained, the problem is to place them within the context of psychiatric, as well as medical, morbidity. Both psychiatric [14] and medical [70] assessments appear to be necessary and may include physical examination, laboratory tests, brain imaging techniques, neurophysiological testing and therapeutic drug monitoring [71].

Customary clinical taxonomy, however, does not include consideration of iatrogenic factors related to behavioral toxicity and an adequate level of integration is required [14]. When the psychiatrist approaches patients' complaints, he or she should consider different pathways, interconnected in a sort of concentric model (Fig. 1), where all may contribute to the presentation of a clinical condition. These pathways include biological, psychological, and social factors of iatrogenic nature, whose consequences (syndromes, symptoms and any sort of problem) may be considered as potentially counter-therapeutic [72].

In order to establish the relationship between co-occurring problems and where treatment should begin in the first place, one helpful method is macroanalysis [14]. It starts from the assumption that, in most cases, there are functional relationships among problem areas, and that the targets of treatment may vary during the course of disturbances. It may include the various manifestations of tolerance we described.

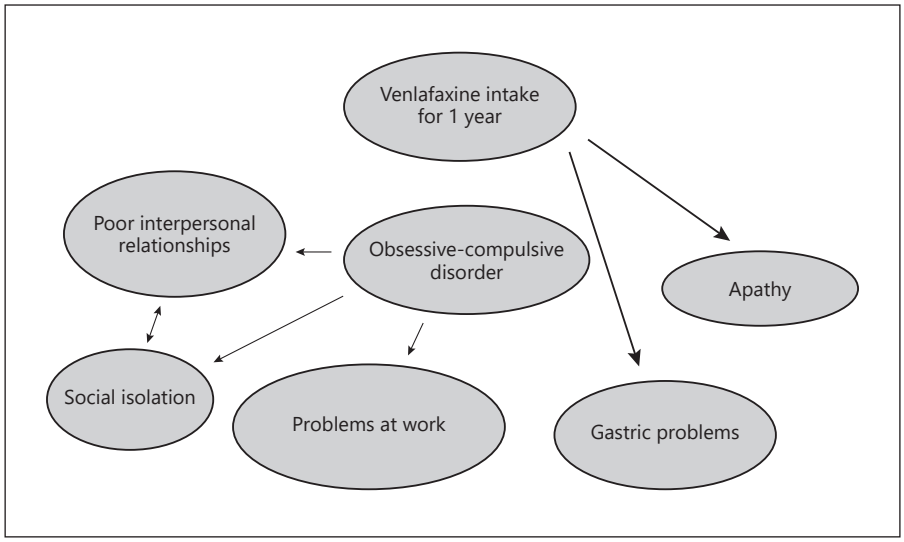

Fig. 2. Macroanalysis at the first assessment.

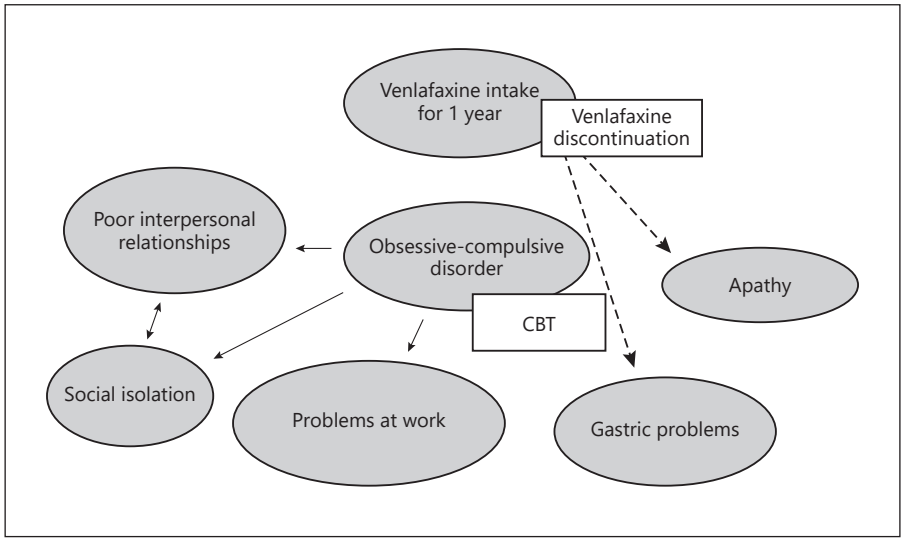

Fig. 3. First line of treatment.

Figure 2 illustrates how macroanalysis can be accomplished. Sylvia is a 27-year-old woman who works as a secretary in a factory. She started having obsessive-compulsive symptoms about a year before, which affected her work. Also, her interpersonal relationships, including the one with her boyfriend, have deteriorated and Sylvia spent a lot of time by herself ruminating, thus resulting in social isolation. She was treated with venlafaxine up to 150 mg per day with a modest decrease in symptomatology. In the past few months, she developed a profound sense of apathy [35]. She also complained of gastric disturbances.

Assessment failed to detect symptoms of a major depressive disorder that could be associated with apathy. The clinician thus interpreted apathy as a behavioral side effect of venlafaxine treatment. Since gastric symptomatology did not follow the somatic patterns typical of anxiety disturbances, venlafaxine was also suspected as a iatrogenic cause [6]. The clinician decided to taper and eventually discontinue venlafaxine, while at the same time starting cognitive-behavioral treatment of obsessive-compulsive disorder (Fig. 3). Sylvia was very compliant with homework assignments and did very well with cognitive-behavioral treatment. Despite slow tapering of

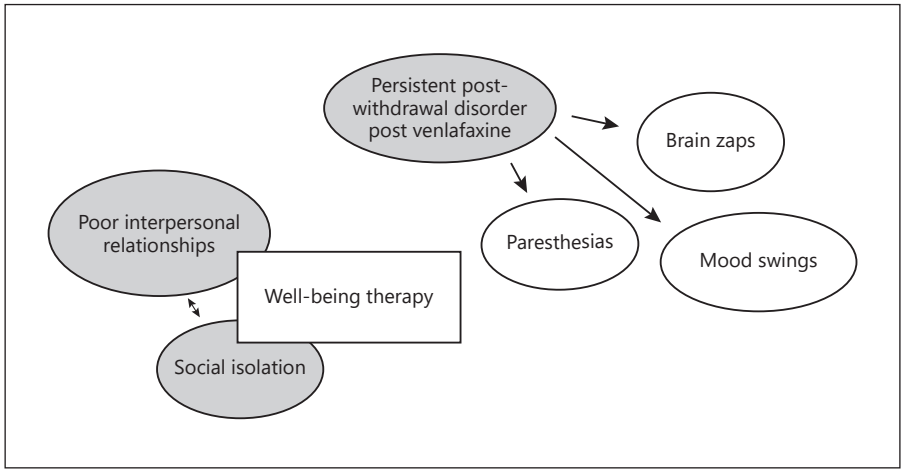

Fig. 4. Macroanalysis at the second assessment 1 year later.

venlafaxine over months, she suffered from a withdrawal syndrome which then developed into a persistent post-withdrawal disorder, according to the criteria of Chouinard and Chouinard [38]. One year after discontinuation of venlafaxine, Sylvia was troubled by brain zaps, paresthesias, and mood swings which she had never experience before the use of venlafaxine. Obsessive-compulsive symptomatology was greatly reduced after cognitive-behavioral therapy, which positively affected her performance at work. Poor interpersonal relationships, however, persisted, as well as social isolation. Apathy and gastric symptomatology greatly improved after venlafaxine discontinuation. After the first line of treatment, Well-Being Therapy [73] for addressing impairments in well-being was thus performed as a second line of treatment and yielded positive relations with others, satisfactory degrees of self-acceptance, and personal growth (Fig. 4). Persistent postwithdrawal symptomatology slowly faded, but was still present 18 months after discontinuation of venlafaxine.

The Renaissance of Psychopathology

Assessment of iatrogenic factors and its incorporation in the overall assessment of a patient are a complex task that requires considerable clinical skills in differential diagnosis, as illustrated in the clinical example that we provided. A few areas of application deserve brief comment.

1. Withdrawal symptoms can easily be misinterpreted as signs of relapse; their differential diagnosis requires careful collection of new symptoms which were not part of the previous symptomatology [38]. Indeed, trial designs that assess the effects of discontinuing antidepressant drugs for inferring efficacy (i.e., a significant increase in depressive symptoms in the patients whose medications are discontinued and switched to placebo compared to those who continue with treatment) are flawed by lack of consideration and proper assessment of withdrawal events [74]. The clinical difficulty is increased by the fact that relapse and withdrawal syndromes may coexist [41].
2. It is important to discriminate nonresponse to a new treatment from tolerance to a previously administered therapy (refractoriness) or onset of loss of response during maintenance therapy [42].
3. Robins and Guze [75] 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 identification of secondary or symptomatic affective disturbances appears to have important implications with drug-induced psychiatric syndromes [28–30, 69]. As Hall et al. [28] remarked: "polypharmacy places patients at risk as, as has been discussed, increases the incidence of drug-induced psychiatric symptoms, which may mimic many primary psychiatric disorders. Whenever psychiatric symptoms appear in a patient taking medical agents known to be associated with the production of psychiatric symptoms, the physician safest posture is to consider the syndrome as drug-related until proven otherwise. In the majority of instances, discontinuation of as many medications as possible is the most spe-

cific and salutary intervention that can be made" [28, p. 346].

4. In a recent longitudinal epidemiological study [76], mood disorders were found to be associated with an increased risk of developing other mental disorders. A possibility that needs to be explored, and was not entertained by the authors, is that antidepressant treatment, more than depression itself, might have caused persistent postwithdrawal disorders and be, at least in part, responsible for the increased secondary comorbidity. Such studies are now feasible since diagnostic criteria are available [38]. Similarly, how epidemiological findings may be inflated by iatrogenic factors remains to be explored.
5. Richardson and Doster [77] have suggested consideration of three dimensions in the process of evidence-based medical decision: *baseline risk* of poor outcomes from an index disorder without treatment, *responsiveness* to the treatment option, and *vulnerability* to the adverse effects of treatment. A rational approach to treatment should take into account the balance between potential benefits and adverse effects applied to the individual patient [42]. However, appropriate information about vulnerabilities needs to be available [78, 79] and should include iatrogenic psychopathology. Exclusive reliance on diagnostic criteria has impoverished the clinical process and does not reflect the complex thinking that underlies decisions in psychiatric practice [14]. Clinical assessment in psychiatry and psychology is currently viewed as a historic relic, to be substituted by biomarkers and neuroscience methods [80]. This position is clearly the reflection of an intellectual crisis in psychiatry, which can be attributed to a decline of clinical observation as the source of fundamental scientific challenges [81].

Adequate evaluation of iatrogenic factors calls for a renaissance of psychopathology as a unified theoretical basis of clinical psychiatry [82], which may lead to an overdue critical scrutiny of current conceptual models that clash with clinical reality [14, 79]. Such renewed attention highlights the importance of the newly established discipline of clinical pharmacopsychology, which encompasses the clinical benefits of psychotropic drugs, the characteristics that predict responsiveness to treatment, the vulnerabilities induced by treatment (side effects, behavioral toxicity, iatrogenic comorbidity), and the interactions between drug therapy and psychological variables [83].

Conclusion

Current classification systems in psychiatry fail to consider the iatrogenic components of psychopathology related to behavioral toxicity. Affective disturbances caused by medical drugs, as well as paradoxical effects, manifestations of tolerance (loss of clinical effect, refractoriness), withdrawal and postwithdrawal disorders, are increasingly common due to the widespread use of psychotropic drugs in the general population. Such neglect is serious, since manifestations of behavioral toxicity are unlikely to respond to standard psychiatric treatments and may be responsible for the wide spectrum of disturbances subsumed under the generic rubric of treatment resistance. The term "iatrogenic comorbidity" refers to the unfavorable modifications in the course, characteristics, and responsiveness to treatment of an illness that may be related to previously administered therapies [31, 53]. Such modifications may also lead to a serial development of multiple medical and psychiatric complications (cascade iatrogenesis).

The notion of psychiatric disease is no longer in line with the changed spectrum of health and the complex interplay of biological, iatrogenic and psychosocial factors [14]. Consideration of iatrogenic factors challenges most of the current practices of prescription of psychotropic drugs [4, 42, 84–86]. Recognition of iatrogenic factors in psychopathology runs counter major commercial interests, and not surprisingly is censored in mainstream medical journals, scientific meetings, and guidelines [41]. Currently, the prescribing physician is driven by evidence-based medicine and guidelines, the marketing arm of pharmaceutical industry [79], to an overestimated consideration of potential benefits, little attention to the likelihood of responsiveness and neglect of potential vulnerabilities to the adverse effects of treatment [78].

In the fifties, a sociologist, Harvey L. Smith [87], defined the psychiatrist as the marginal man of the medical profession. Psychiatry has been struggling against this marginality, but current emphasis on the role of biomarkers that should compensate the clinical inadequacies of psychiatrists are likely to reinforce this process further. Actually, psychiatrists, in their clinical practice, use sophisticated forms of clinical judgment, master techniques of interviewing and history taking, are geared to capture the iatrogenic components of psychopathology. Fascinating vistas for psychiatrists who are skillful in differential psychopathology and have a strong background in clinical pharmacology and internal medicine are opening up. They should be welcome to all those who are disillusioned

with the modest practical results of decades of mainstream psychiatric research and should become the preferred channel of funding and attention. Long-term outcomes of psychiatric disorders may be unsatisfactory not because technical interventions are missing, but because our conceptual models that ignore iatrogenic forms of psychopathology are inadequate.

Disclosure Statement

The authors have no conflict of interest to disclose.

Funding Sources

This paper was supported in part by a grant from Compagnia di San Paolo, Torino, Italy, to Dr. Rafanelli.

Author Contributions

Both authors conceived and drafted the manuscript.

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