

## Editorial

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# Holding On: Depression, Sensitization by Antidepressant Drugs, and the Prodigal Experts

In his latest essay, Milan Kundera [1] outlines a new character, the 'danseur'. The dancer (or news-courtier) is an ever-present intellectual in the media (newspapers, magazines, radio and especially TV). He is always ready to offer his valiant comments devoid of doubt on whatever happens in the world. What really matters to the 'danseur' is being on the news and imposing his presence. It is difficult not to apply this characterization to the medical field and to miss the similarities between Kundera's 'danseurs' and the prodigal experts who afflict our field [2]. Inevitably sponsored by the pharmaceutical industry, the prodigal experts move from one meeting to the other, providing optimism and continuity (same talk, same slides). In psychiatric terms this translates into a constant dismissal of psychotherapeutic modalities, that are overshadowed by the pharmacological (at times only pharmaceutical) approach. This is particularly evident in the field of anxiety disorders (e.g., panic), where the superiority of psychotherapeutic tools, both in the short and long term [3, 4], is not achieving adequate currency.

In this setting, 1 year ago, this journal raised the issue as to whether the use of antidepressant drugs in depression might be beneficial in the short term, but worsen the progression of the disease in the long term, by increasing the biochemical vulnerability to depression and decreasing its likelihood of subsequent response to pharmacotherapy [5]. The editorial was largely speculative and the clinical and biochemical evidence for this hypothesis was equivocal at best. It sparked however a debate that had been until then avoided (or censored?) [6]. Despite a largely critical response from three prominent psychopharmacologists (William Potter, Donald Klein and Robert Post), it was deemed to have raised some legitimate issues [6]. Ross Baldessarini [7], in this journal, extended these issues to the risks and implications of interrupting maintenance psychotropic drug therapy in bipolar disorder and schizophrenia. Long-term exposure to centrally active neuropharmacological agents can induce adaptive physiological changes in the brain [7], that may include genomic effects in addition to those which they elicit on amine reup-

take [8]. Abrupt drug removal is associated with a variety of potentially untoward responses, in a complex, multifactorial model encompassing various interlocking processes at the biochemical and experiential levels [7]. Massimo Biondi [9] attempted a psychosomatic synthesis of such processes. He also provided a sound justification for a psychosomatic journal being the ideal forum for this discussion.

The neurobiological framework of sensitization phenomena in depression is provided by the concept of tolerance. Dispositional (pharmacokinetic) tolerance, which reduces the concentration of a drug or its duration of action, is often confused with functional (pharmacodynamic) processes which change sensitivity to a drug [10]. Continued drug treatment may recruit processes that oppose the initial acute effects of a drug or of receptor alterations. When drug treatment ends, these processes may operate unopposed, at least for some time [10]. Reference to the fine tuning and integration of different serotonin receptors [11] may provide a potential relevance of these processes to the use of antidepressant drugs in depression. Changes in postreceptor signal transduction, in intraneuronal signaling pathways, in neuronal architecture, connections or sensitivity to neurotransmitters, in neurotransmitter synthesis and distribution are possible [10]. If these changes had to occur, a number of clinical issues would emerge.

*Inappropriate Use of Antidepressant Drugs.* The effectiveness of antidepressant drugs is established only in major depressive disorders [12]. However, there is a growing tendency to use them also in the setting of a collection of dysphoric complaints or demoralization. This tendency has been considerably increased by the introduction of the selective serotonin reuptake inhibitors (SSRI), because of their better tolerability compared to the tricyclics.

Carroll [12] warned about the inappropriate use of antidepressant drugs more than a decade 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'. To the same extent that awareness of tardive dyskinesia has limited inappropriate use of antipsychotics, or antibiotics should not be routinely prescribed with minor, viral ailments, the use of antidepressant drugs below the severity threshold provided by the diagnosis of major depressive disorder may lead to sensitization without any clear benefit. Similar considerations may apply to the use of antidepressants in chronic pain.

*Dependence versus Sensitization.* The issue of dependence has shifted drug treatment of anxiety disorders from use of benzodiazepines to antidepressant drugs. Biondi [9], for instance, expresses his orientation toward long-term imipramine or MAO inhibitor treatment. Once again, let us assume that sensitization by antidepressants exists. Such treatment would increase the vulnerability to depression. A simple way of exploring this research question would be to compare the long-term incidence of depression in patients randomly assigned to antidepressant drugs or benzodiazepines. Paradoxically, benzodiazepines might be reevaluated. If I had to choose between potential dependence to benzodiazepines and increased vulnerability to depression, I would go for the former.

*Full versus Subtherapeutic Dosage of Antidepressants.* There is increasing consensus about the advantage of maintaining patients at the acute treatment dosage [13]. The rationale for this choice would be the insufficient protective effects of subtherapeutic doses. Keeping a patient on low-dose antidepressants for a long time (a very common practice,

particularly by nonpsychiatric physicians, in Europe) would expose the patients to the risks of sensitization.

*Acute versus Prophylactic Effect of Antidepressants.* The full-dose continuation treatment strategies, however, endorse a hidden conceptual model: that what is effective acutely in depression is also the best option for continuation treatment. The stages of development of a disorder would be unimportant in guiding the treatment. There is evidence, however, to call such views in question [14]. Different stages of illness may require different types of treatment. For instance, drugs that act primarily as 5-HT<sub>2</sub> antagonists (such as ritanserin or mianserin) may prove more suitable for continuation treatment, whereas traditional antidepressants may be more suitable in the acute phase. 5-HT<sub>2</sub> antagonists, in fact, may act against the enhanced 5-HT<sub>2</sub> receptor function prodromal to onset or relapse of depression [15].

*Fading of Treatment Effects.* A loss of antidepressant effect with long-term treatment has been repeatedly observed both in mood [16] and anxiety disorders [17]. Mann [16], for instance, observed such a phenomenon with MAO inhibitors without loss of MAO inhibition. Probably its best exemplification comes from the Pittsburgh Maintenance Study [13]. This study is simply viewed, because of the deformation entailed by the quest for statistical significance, as an investigation showing the superiority of high-dose antidepressant treatment versus other modalities. However, if one looks at the study carefully, one may discover that about 18% of patients who initially fully responded to imipramine relapsed while being on full-dose imipramine. Since other patients dropped out, the percentage of patients in the medication clinic and active imipramine group who did not relapse was only about 60%. (Interestingly it was 84% with the combination of interpersonal psy-

chotherapy and pharmacotherapy.) Would a clinician be satisfied with a strategy that loses 1 patient out of 5 every 3 years, from a pool that has already been decreased by compliance issues? Why does a previously drug-responsive patient stop being so? I have termed this clinical phenomenon fading (progressive decrease of therapeutic effects refractory to dosage increase, after nonimmediate symptomatic improvement) [18]. Is fading related to sensitization? Why does it not occur in every patient?

*Discontinuation of Antidepressant Drugs.* Baldessarini [7] described the risks and implications of interrupting abruptly maintenance drug therapy and the clinical advantages of a gradual decrease. It is astonishing how little we know about very practical issues such as discontinuation of antidepressant drugs. In a planned, controlled discontinuation of antidepressants in 40 depressed patients [14], we did not observe any clear-cut withdrawal reactions [19]. However, most of our patients were on tricyclics and decreases were very slow (25 mg of amitriptyline or its equivalents every other week). We lack good, controlled studies of different schedules of antidepressant reduction. Similarly, there is insufficient biologic exploration of antidepressant withdrawal [19]. Are antidepressant withdrawal phenomena related to sensitization? Are some drugs more likely than others to induce these phenomena – for instance SSRI [20]? What is the relationship between duration of treatment and sensitization? In clinical terms this would translate as follows: how long should we treat patients with antidepressants before sensitization becomes a risk?

*Temporary versus Irreversible Receptor Modifications.* Withdrawal phenomena are generally viewed as adverse effects occurring within 2–3 weeks from drug discontinuation [19]. A hidden conceptual requirement, however, is the fact that full receptor regulation

balance is regained after the acute withdrawal phenomena. Baldessarini [7] suggests that 'several months may be required to become physiologically and psychologically 'dry' after stopping such agents as alcohol and heroin, and perhaps also benzodiazepines (...), suggesting that such periods may be required to reestablish a pre-drug level of neurophysiological and neuropsychological homeostasis'. As to depression, this would translate into a potentially vulnerable postdrug period (extending over a few months). Some epidemiologic evidence as to relapse would be consistent with this view. As a result, together with acute and clinically evident symptoms of withdrawal from antidepressant drugs, there might be subtle and subclinical symptoms of subacute withdrawal. In other words, if antidepressant drugs increase vulnerability to depression, this may occur in a specific phase. This appraisal could pave the way for specific relapse-preventing strategies. Receptor changes may be irreversible, however, such as in tardive dyskinesia. A prolonged benzodiazepine withdrawal syndrome has been described [21]. Kukopulos et al. [22] observed how treatment by antidepressant drugs may contribute to changes of course from unipolar to bipolar illness, and to increased frequency of cyclicity. They thus deserve credit in raising the issue that antidepressant-induced mania may not simply be a temporary and fully reversible phenomenon, but trigger complex biochemical mechanisms of illness deterioration. A case of tricyclic-induced mania in a 60-year-old woman, with a long-standing history of unipolar depression (that was followed by rapid cycling refractory to lithium), illustrates the hormonal implications of such mechanisms [23].

*Psychotherapeutic versus Pharmacologic Changes.* Biondi [9] emphasized how both acute stressors and psychotherapy can induce biological modifications at the central level

and how psychotropic drugs and psychological interventions are probably acting on common neurotransmitter pathways. The extent and type of action, however, may be different and from such differences differential therapeutic efforts may ensue. For instance, both exposure and imipramine may share the same neurochemical mechanism in severe cases of panic disorder with agoraphobia [24]. However, what they do not share (the fact that changes are generally long-lasting after exposure and short-lived after imipramine) may be as important [4].

Are all or some of these issues worthy of research attention? The reader may judge for himself or herself. Certainly researchers working along these lines are likely to encounter tremendous difficulties in performing their studies and getting them funded and published. As Klein [6] wisely pointed out: 'The industry is not interested, NIMH is not interested, and the FDA is not interested. Nobody is interested.' Our journal is interested. I hope our readers will be interested as well and support in any possible way this independent journal, at the present time alone in its battle for opening a new research paradigm.

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