Editorial

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Risks and Implications of Interrupting Maintenance Psychotropic Drug Therapy

A recent editorial by Dr. Giovanni Fava [1] in this journal posed the question of whether maintenance treatment with antidepressant or antianxiety drugs might contribute to worsening of the long-term course and symptomatic expression of affective disorders. There is insufficient information with which to answer his question with confidence, but the general topic of risks involved in the increasingly broad application of long-term maintenance treatment with psychotropic agents deserves continued consideration. My colleagues and I in an international consortium for research on bipolar and psychotic disorders have also raised questions which may be related to Dr. Fava's, including consideration of the risks and implications of *stopping* maintenance treatment with mood-altering or antipsychotic agents – particularly, abruptly.

We have been analyzing a growing body of data which support the impression that there is a substantial risk of early relapses in a variety of major mental illness in the weeks or months following discontinuation of maintenance drug therapy. In some disorders, relapse rates may be elevated above predictions based on their natural history, as best one can estimate this elusive variable. For example, direct comparison of episode intervals before and after abruptly stopping several years of successful lithium maintenance treatment in a small number of stable bipolar I manic-depressive patients showed a nearly 7-fold shorter time to first recurrence than was found in the shortest cycle before starting lithium [2]. Interpretation of these findings assumes that neither prodromal hypomanic denial nor worsening depressive nihilism contributed to the decision to stop successful long-term lithium treatment electively. We have attempted to avoid that potentially important source of artifact [3–5], but it remains a question.

With Sardinian and American collaborators, we have also developed preliminary evidence, which is being expanded, that the *rate* of removal of lithium predicts time to first recurrent episode in both bipolar I and II disorder, suggesting the contribution of pharmacodynamic factors [3]. These might include, for example, an altered functional state of neuronal mechanisms which had adjusted to the treatment and which may contribute to the pathophysiology involved [4].

Recently, we also found with Sardinian colleagues that the rate of fatal suicidal and

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potentially fatal parasuicidal behaviors in cases of bipolar I and II disorder rose from about 6 units (events per year per 1,000 persons at risk) during lithium maintenance treatment, to nearly 60 units in the 1st year after stopping lithium – again, electively and not in response to obvious prodromal illness. The rate off lithium was also nearly 3 times above that found prior to starting lithium treatment [5].

Additional analyses in schizophrenia indicate that the risk-by-time function after stopping oral neuroleptics is very similar to that found in bipolar patients coming off lithium, with a gross excess of relapses within the first 12 weeks and much lesser risk thereafter [4, 6, 7]. After stopping depot neuroleptics (with slow washout over at least 6 months), the level of risk was not only lower and delayed, but remained low into the 2nd year of follow-up, suggesting that risk was not only postponed, but perhaps actually avoided [6, 7]. A study carried out by colleagues in Boston [8] found further that removal of about 85% of an oral neuroleptic dose over 2 months led to a significantly lower 6-month relapse risk than stopping over only 2 weeks [4, 7, 8].

We are currently reviewing comparable data with antidepressants. An important University of Pittsburgh study of long-term maintenance treatment of major depression with imipramine and psychotherapy provides data which, again, indicate a high risk of recurrences within the several months after stopping, but much less at later times, even following several years of apparently successful maintenance treatment [9]. That group also found that decreasing the dose of imipramine by approximately 50% rather abruptly also led to a marked risk of recurrence, again within several months, but not thereafter [10].

Finally, experience with benzodiazepines indicates that their removal can lead not only to evidence of physiological dependence, but also to a high risk of rebound symptoms which are hard to distinguish clinically from the primary anxiety disorder being treated [11–13]. Several months may be required to become physiologically and psychologically 'dry' after stopping such agents as alcohol and heroin, and perhaps also benzodiazepines [11], suggesting that such periods may be required to reestablish a predrug level of neurophysiological and neuropsychological homeostasis.

Dr. Fava's editorial [1] interprets occasional loss of responsiveness to antidepressants over time as an indication of drug *tolerance*. This concept is a *description* of the loss of pharmacological or therapeutic response, often with the implication that a higher dose may temporarily restore response, without specifying a responsible pharmacodynamic mechanism. Moreover, a drug-dependence pharmacodynamic model also may be relevant to the reactions to discontinuing mood-altering or antipsychotic agents just summarized. Long-term exposure to centrally active neuropharmacological agents can induce adaptive physiological changes in the brain. Abrupt drug removal is associated with a variety of potentially untoward responses, including nonspecific malaise and autonomic symptoms, or even seizures in the case of some central depressants [14]. Some responses may be opposite to the drug-associated functional state and so contribute to the reemergence of the disorder being treated. A psychosomatic modification of this model, combining pharmacodynamic 'stressor' and vulnerably 'diathesis' factors, also may apply. These factors may determine what clinical response emerges in what kind of patient stopping what type of drug. For example, a hyperdopaminergic state may obtain in forebrain after abrupt removal of neuroleptics [15], but it is uncertain what may occur when lithium or other

mood-altering agents are removed, due to the complexity and subtlety of their neuropharmacology [14, 16]. 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 [14, 17, 18].

Aside from the theory of what may be going on, the possible implications of the observations reviewed are also worth considering. The clinical implications for risk of morbidity and perhaps mortality following abrupt interruption of maintenance pharmacotherapies are clear and ominous enough. Additional matters of concern include the still-open question of possible 'retreatment resistance' or a proposed lack of responsiveness on restarting a previously interrupted pharmacotherapy [4, 19]. Moreover, it may be timely to reconsider the ethics and scientific interpretation of studies of maintenance treatments broadly, as well as the clinical risks involved.

The standard therapeutic experimental design is to treat an active phase of acute illness, to reestablish a degree of clinical stability in follow-up treatment, and then to randomize to at least two conditions, which may involve removal of some or all of the active treatment in longer-term follow-up. Studies of neuroleptics [4, 8], imipramine [10], and lithium [4, 20] suggest that even *partial* abrupt removal of a drug may be sufficient to induce an excess risk of relapse or recurrence of illness. Removal of all drug to a placebo condition would, presumably, carry an even greater risk of early relapse. The level of risk involved may be in excess of the natural history of untreated illness in some instances [2, 4]. If so, interpretation of the findings (as well as what should be included in consent information) in maintenance experimental therapeutics trials may be confounded by comparing *pharmacologically increased* placebo-associated risk with low risk on continued treatment.

If the concept of excess drug withdrawal-associated relapse risk is valid, it may be possible to minimize it by *slowing* the rate of removal of drug so as to permit gradual physiological-psychological readjustments to occur, as well as by excluding clinically unstable subjects [3, 4, 6, 7]. While this approach may be realistic, it implies a level of complication, prolongation, inconvenience and expense in the design of maintenance therapeutic protocols which may be difficult to carry out or to support. It would be of interest to consider, further, whether similar phenomena may also occur in general medicine, for example in the treatment of such disorders as hypertension, peptic ulcer, arthritis or other chronic inflammatory disorders. Abrupt withdrawal of beta-adrenergic antagonists lacking any intrinsic agonist activity can induce rebound hypertension and tachycardia, for example, with a potential risk of sudden death [21, 22].

Even broader suggestions that maintenance treatment per se may have a pathogenic or destabilizing effect [1] have received little serious scientific or clinical consideration. Among the examples proposed by Fava [1], the status of 'limbic' supersensitivity psychosis' during prolonged neuroleptic treatment remains particularly uncertain. This phenomenon is probably uncommon, and may be a manifestation of drug tolerance or of severe and relentless illness rather than *pharmacologically* based new risk of illness. On the other hand, supersensitive dopaminergic mechanisms in forebrain [15] might contribute to the high relapse risk found soon after stopping oral neuroleptic maintenance [7].

Drug-related destabilization in bipolar disorder, particularly by antidepressants, is a more likely phenomenon [14, 16, 23, 24].

However, data quantifying the risks involved are limited and inconsistent, and direct assessments of spontaneous versus drug-altered cycling and switching of moods in bipolar disorder based on placebo-antidepressant comparisons are rare [14, 24]. In addition, the effects of adding an antidepressant to a mood stabilizing regimen in bipolar disorder are complex: some patients do undergo more fluctuations per time, with more time in hypomania or mania, but may fluctuate less on lithium alone at the price of more time in depression rather than in euthymia [23]. Even monotherapy with lithium may lead to such paradoxical effects as a shortening of euthymic intervals between manic and depressive episodes in bipolar disorder, despite amelioration and shortening of illness episodes themselves [25].

A further extension to the induction of 'compromised states' [1], such as chronic semimisery on long-term antidepressant or anxiolytic therapy, should be accessible to controlled investigation. However, anticipation of their possible modification by psychological therapies [1] requires particular caution since combined psychological and pharmacological therapies have scarcely been seriously investigated yet in patients with severe forms of major psychiatric illnesses, and the most secure support for effectiveness and a favorable cost/benefit ratio has been developed for the maintenance pharmacotherapies [8, 14].

In conclusion, the editorial writer [1] is not alone in wondering about the risks involved in the long-term use of psychotropic agents, and particularly in their discontinuation. His question and the several related matters considered here are not pleasant to contemplate, and may seem paradoxical, but they now require open-minded and serious clinical and research consideration.

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