Editorial

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Do Antidepressant and Antianxiety Drugs Increase Chronicity in Affective Disorders?

An extremely interesting book on pharmacology has recently been released [1]. It illustrates the 'antibiotic paradox': the best agents for treating bacterial infection are also the best agents for selecting and propagating resistant strains, which persist in the environment even when exposure to the drug is stopped. The need to minimize inappropriate use of new antibiotics as they are developed is thus emphasized [1]. At times, the cure may be worse than the disease. As a result, in clinical medicine the likelihood that drug treatment, while alleviating the symptoms of disease, may aggravate its course, is often evaluated. For instance, the issue as to whether early treatment of Parkinson's disease by levodopa may worsen its progression has been discussed [2]. Obviously, these problems are rather difficult to study and definitive answers may not be available. Nonetheless, these questions are always worth asking, at least for a better understanding of some side effects of therapy. In Parkinson's disease, depression [3] and panic attacks [4] have been regarded as long-term complications of levodopa therapy and their onset may call for substitution of levodopa with other drugs [3].

Within the field of psychopharmacology, practitioners have been more cautious, if not fearful, of opening a debate on whether the treatment is more damaging than the cure. This is due in part to the stigma which still surrounds psychiatric patients and has probably been exacerbated by the media and lay interest in such techniques as electroconvulsive therapy (ECT). However, I wonder whether the time has come for debating and initiating research into the likelihood that psychotropic drugs actually worsen, at least in some cases, the progression of the illness which they are supposed to treat. It is indeed rare to see such issues debated: is this because of some 'censorship' operated by medical journals, meeting organisers and certain pharmaceutical manufacturers [5]? Indeed, some associations (e.g., the American Psychological Association) have been concerned about the involvement of pharmaceutical manufacturers in the National Mental Health Association depression awareness campaign [6]. It is also possible, however, that researchers in the field are simply not aware of the possibility that psychotropic drugs, in some cases, may actually worsen the course of affective disorders.

The field of psychopharmacology has generally neglected the issue of potential sensitization of psychiatric disease to psychotropic

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drug use. A relevant exception is the concept of neuroleptic induced supersensitivity psychosis [7]. Chouinard and Jones [7] proposed that dopamine receptor binding sites could increase in the mesolimbic pathway in response to the chronic dopamine blockade operated by neuroleptics and that psychotic symptoms following withdrawal or decrease of neuroleptics could be the clinical expression of a mesolimbic dopamine postsynaptic receptor supersensitivity. The phenomenon of supersensitivity psychosis is still controversial [8, 9], yet the recent suggestion of treatment of supersensitivity psychosis by antiepileptic drugs [10] may be a direct, important and practical clinical consequence of such an investigative approach.

Do antidepressant drugs increase the likelihood of chronicity in mood disorders? The suggestion that the property of antidepressant drugs of inducing mania in susceptible individuals within the bipolar spectrum may potentially increase the frequency of recurrences and rapid cycling [11] is still controversial, not least because such an increased frequency over time was also observed in the predrug and pre-ECT days. It may ultimately lead, however, to a more cautious use of antidepressants in patients with bipolar genetic loading, to the same extent that the unsolved debate about the depressogenic properties of benzodiazepines [12] has led many specialists to limit their use in mood disorders. There also other clinical phenomena which call for closer research attention. Aronson and Shukla [13] reported on the clinical characteristics of 26 patients with major depression who repeatedly relapsed during or shortly after antidepressant tapering. They concluded that secondary axis I and axis II diagnoses in antidepressant–responsive depressed patients are associated with the need for long-term continuation treatment [13]. They also mentioned the possibility, however, that antidepressants might 'sensitize neural tissues, resulting in a dependence on their continued neurobiologic effects and, in fact, prolonging the syndrome' [ref. 13, p. 288]. Commenting on the development of endogenous depression in patients with panic disorder treated with therapeutic doses of antidepressants, Aronson [14] suggested the possibility that antidepressant medications may unmask a depressive diathesis. The loss of antidepressant effects during continuation therapy has been attributed to drug tolerance [15], since it responded to an increase in dosage [14, 15]. Even though a certain percentage of relapses might be due to the loss of nonspecific placebo effects [16] rather than to true drug effects, this clinical phenomenon is intriguing. Equally intriguing are the results of a naturalistic prospective survey, where low doses of antidepressants appeared to be less beneficial than either higher doses or clinical management without antidepressant drugs [17]. The latter two treatments yielded almost identical outcome. These findings parallel the follow-up results of the NIMH Treatment of Depression Collaborative Research Program, where there was a slightly better outcome of patients treated with placebo and clinical management compared to those who were given imipramine [18]. This latter study, however, had considerable methodological shortcomings, which are discussed in this issue of the journal [19].

The effectiveness of antidepressant drugs in the treatment of depression has been substantiated by a large number of well-designed and well-conducted clinical trials [20, 21], which cannot be challenged by the meta-analysis of studies employing inadequately sensitive self-rating scales [22]. As a result, two hypotheses are worthy or research attention. One is based on the concept of tolerance [15]. Yet if tolerance were the only problem, it could be solved by an increase in dosage, whereas this is not always the case [15]. In our

Affective Disorders Program, it is not uncommon to encounter depressed patients who are treated with long-term subtherapeutic doses of antidepressant medications (below the equivalent of 100 mg of amitriptyline daily). A major fault in the treatment of depression by nonpsychiatrists lies in fact in using doses which are too low [3]. It is our practice then, when dealing with first-generation antidepressants, to simply increase the dosage. In a consecutive series of 18 such patients with DSM-III-R major depression, the increase was effective in 14 of these patients, whereas for the remaining patients a switch to another antidepressant was necessary (e.g., from imipramine to amitriptyline). We failed to detect clinical characteristics (e.g. duration of antidepressant treatment) which might explain the different responses to dosage increase. Another hypothesis then needs to be considered: do antidepressant drugs sensitize to depression? Such a question is most relevant to the vexing clinical problems of relapse and recurrence following successful treatment of major depression. Post [23] recently observed that a large body of evidence documents a greater role for psychosocial stressors in association with the first episode of major depression than with subsequent episodes. He postulates that both sensitization to stressors and episode sensitization occur and become encoded at the level of gene expression. In particular, stressors and the biochemical concomitants of the episode can themselves induce the proto-oncogene c-*fos* and related transcription factors, which then affect the expression of transmitters, receptors, and neuropeptides that alter responsiveness in a long-lasting way [23]. This extremely interesting conceptual model fails to contemplate, however, the possibility that use of antidepressant drugs might also trigger such a sensitization process while the episode is being treated not unlike the clinical phenomena related to the use of antibiotics in infectious disease [1]. The comparison with infectious disease may suggest another consideration. The presence of residual symptoms after completion of drug treatment has been correlated with poor long-term outcome and it has been suggested that some residual symptoms of major depression may progress to become prodromal symptoms of relapse [24]. Indeed, in a recent investigation [25], the majority of residual symptoms was found to occur in the prodromal phase of illness and reduction of residual symptoms by cognitive-behavioral therapy resulted in a lower, even though not significant, relapse rate at a 2-year follow-up compared to a control group. This may parallel the importance of treating residual foci of infection in bacterial disease, as outlined in this issue [19]. Stassen et al. [26] found that the time course of improvement among responders to amitriptyline, oxaprotiline and placebo was independent of the treatment modality, and thus identical in all three groups. Once triggered, the time course of recovery from illness became identical to the spontaneous remissions observed under placebo. Antidepressants, therefore, may not change the pattern of the natural course of recovery from depression, but simply speed the recovery and change the boundary between 'responders' and 'nonresponders' [26]. As a result, their effects may be dependent on the stage of major depression [27]. In the acute phase, antidepressant drugs may trigger the recovery [26]; in the postacute phase, they may have a protective effect upon the progression of residual symptoms to relapse or recurrence. Such protective action is conceivable, because of the neurotransmitter effects of antidepressants upon anxiety and irritability, the most important prodromal symptoms [28]. However, long-term use of antidepressant drugs may also increase the biochemical vulnerability to depression and decrease its likelihood of subsequent response to pharma-

cological treatment. In this vein, with low-dose antidepressant treatment the disadvantages of this sensitization may outweigh the benefits. Nonpharmacological therapeutic methods may prove more suitable in the subacute stage of illness [19, 25, 27].

Antidepressant withdrawal phenomena have been described [29]. They may include gastrointestinal and general somatic distress often in association with anxiety and agitation, sleep disturbances, movement disorders and withdrawal-related hypomania or mania. Some symptoms may simply suggest an early recurrence of a depressive syndrome [29]. Other symptoms, however, may be due to cholinergic overdrive, a consequence of the supersensitivity of muscarinic systems induced by tricyclic treatment [29, 30]. Is supersensitization of noradrenergic and serotonergic systems by antidepressant drugs possible? The question is worthy of research attention. The hypothesis of a potential sensitization to depression by antidepressant drugs can fail to be confirmed by research evidence. Yet, its current denial may help very little. This prospect may shed some new light on research findings which are already available. For instance, the results of the Pittsburgh Study of Maintenance Therapies in Recurrent Depression, indicating that antidepressant medication at the dosage used to treat the acute episode provides prophylaxis superior to the traditional reduced-dose maintenance strategies, and the poor outcome of the switch to placebo after 3 years [31] would be consistent with an inadequate effect of low-dose antidepressants upon residual symptoms and with a sensitization to depression leading to the inability to withdraw after 3 years. In addition, the issue of residual symptoms in depression – even though these were also found to occur after cognitive-behavioral therapy and to be predictive of relapse (32) – lends itself to the possibility of drug-related changes. 'Not anxious but not at ease; not incapable of working but not capable of working well; not tormented by children, but not able to enjoy them; willing to be made love to, but not actively loving; neither tense nor relaxed, neither cheerful nor tearful, neither ill nor well, more depressing than depressed ...' this is the description of the 'antidepressed personality' by a clinician [ref. 33, p. 349]. Is it a picture of incomplete recovery [34] or are there any potential drug-related characterological changes? The anticholinergic and antihistaminic effects of traditional tricylic antidepressants (amitriptyline and dothiepin) in impairing memory and cognitive function and general cognitive abilities might not be simply countertherapeutic, but a major inhibition to recovery from depressive illness.

I previously raised the issue as to whether antianxiety drugs may be depressogenic [12]. A more fundamental question, however, remains: *do benzodiazepines sensitize to anxiety?* The recent publication of the London-Toronto study of alprazolam and exposure in panic disorder with agoraphobia [35], whose main findings were anticipated in this journal [36], sparked a controversy on this issue. The study involved 154 patients who had 8 weeks of alprazolam and exposure (combined treatment), or alprazolam and relaxation (a psychological placebo), or placebo and exposure, or placebo and relaxation (double placebo). During taper and follow-up, gains after alprazolam were lost, while gains after exposure were maintained. Combining alprazolam with exposure marginally enhanced gains during treatment, but impaired improvement thereafter; that is, patients treated with exposure and placebo had a better long-term outcome. There are several likely explanations for these findings. First, there could be an adverse interaction of alprazolam with psychological treatment [35, 36]. What animals learn while on benzodiazepines or barbitu-

rates is retained less well in the drug-free state [37]. Golombok et al. [38] found that patients taking high doses of benzodiazepines for long periods of time perform poorly on tasks involving visual-spatial ability and sustained attention, consistent with deficits in posterior cortical cognitive function. Some benzodiazepines, however, show a better profile as to sensorimotor and cognitive functioning [39, 40] and these differences between molecules may be important at the clinical level. Another possibility involves the attribution of treatment gains to medication rather than to one's personal effort. Patients who attributed their gains to medication during treatment did significantly worse at posttaper than those who believed their improvement was a result of their personal efforts during psychological treatment [36]. Conviction that benzodiazepines may lead to the resolution of problems and conflicts is likely to discourage patients from attempting these tasks [41]. In a recent study [42], benzodiazepines were discontinued in 16 patients who had recovered from panic disorder with agoraphobia after exposure treatment. Drug discontinuation yielded a paradoxical decrease in state anxiety as measured by a self-rating scale free of observer bias, a finding which had already been reported [43]. It also yielded, however, a highly significant drop in anxiety sensitivity – the tendency to believe that anxiety has undesirable consequences aside from its immediate unpleasantness [44] – and harm avoidance – a tendency to respond intensely to aversive stimuli and to learn to avoid punishment, novelty and nonreward passively [45] – both also assessed by self-rating scales. It is thus possible that benzodiazepines, by suppressing and preventing anxiety, may increase a patient's fears of anxiety, and thus anxiety sensitivity [42]. A patient who gets used to suppressing all anxiety, even 'tolerable doses', may become fearful of paying the price for behavioral changes (in terms of temporary apprehension, pain or frustration) and his or her ability for self-assertion may become impaired [41]. This is thus another likely explanation for the findings of the London-Toronto Study. Benzodiazepines, however, might also sensitize to anxiety directly, in addition to the intermediate step of anxiety sensitivity. Chronic benzodiazepine administration is associated with the development of tolerance and dependence [43]. To evaluate the cellular mechanisms for these phenomena, Miller [46] developed a mouse model of chronic benzodiazepine exposure and showed a temporal association between the development of tolerance discontinuation syndromes and receptor modulation. In particular, $GABA_A$ receptor upregulation was found to occur after drug discontinuation and might be due to enhanced receptor synthesis. Conversely, receptor downregulation occurred during chronic administration of benzodiazepines [46]. Panic disorder was associated with functional subsensitivity of the GABA-benzodiazepine supramolecular complex [47], even though such a finding might also be related to chronic use of alcohol and/or benzodiazepines [48]. It is then possible that in a subgroup of patients with anxiety disorder (panic disorder), long-term administration of benzodiazepines may result in receptor modulation sensitizing to anxiety. It cannot be excluded that these receptor changes may also affect the liability of patients with panic disorder to developing major depression at some point during the course of illness. Such liability was observed in patients maintained on tricyclic drugs, benzodiazepines or drug-free [14, 49, 50] and can hardly be attributed to drug treatment only, even though the issue is still largely unexplored. A surprising finding of a long-term follow-up (2–9 years) study [51] of 81 patients who became panic free after behavioral treatment based on exposure, was the extremely

low percentage of patients who developed major depression (3.7%). It is possible that successful behavioral treatment of panic disorder may also decrease the vulnerability to depression in these patients, as found in major depression [25].

The clinical observations that I have summarized here should not be viewed as voices adding to the narrow-minded damnation chorus against psychotropic drugs [52]. Ananth [53], in a review published in this journal, has outlined the improvements in quality of life and clinical course of illness which may derive from the use of psychotropic drugs in the medical setting. And the underutilization of antidepressant drugs in the medically ill is quite unwarranted [3]. Yet, with psychotropic drugs – as with any drugs [1] – it is important not to be blind to certain effects in order to optimize their clinical use, particularly when they are employed in conjunction with psychotherapy. Lipowski [54] remarks that 'after a period marked by one-sided emphasis on psychodynamics and social issues, or what could be called 'brainless' psychiatry on account of its relative neglect of cerebral processes, we are witnessing an opposing trend towards extreme biologism or 'mindless' psychiatry' [p. 249]. The distinguishing feature of psychosomatic medicine is its equal concern with subjective experience (the mind) and with the body (including brain function), which together constitute a person, the clinician's proper focus of inquiry and intervention [54]. As a result, psychosomatic medicine, and this journal which is uniquely devoted to both psychotherapy and psychosomatics, is the ideal forum for a comprehensive understanding of the role of psychotropic drugs and psychotherapy in affective disorders.

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