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Potential Sensitising Effects of Antidepressant Drugs on Depression

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Abstract

The possibility that antidepressant drugs, while effectively treating depression in the short term, may worsen its course through a sensitisation process has been proposed. Although this hypothesis has not been extensively tested, a number of clinical findings point toward this possibility: the very unfavourable long term outcome of major depression when treated by pharmacological means; paradoxical (depression-inducing) effects of antidepressant drugs in some patients with mood and anxiety disturbances; antidepressant-induced switching and cycle acceleration in bipolar disorder; the occurrence of tolerance to the effects of antidepressants during long term treatment; the onset of resistance upon rechallenge with the same antidepressant drug in some patients; and withdrawal syndromes following discontinuation of mood-elevating drugs.

The occurrence of a process of sensitisation in susceptible individuals may be explained on the basis of the oppositional model of tolerance. Continued drug treatment may recruit processes that oppose the initial acute effects of a drug. When drug treatment ends, these processes may operate unopposed, at least for some time. This hypothesis is, however, substantially untested and its scientific exploration is likely to encounter considerable methodological and ideological difficulties. It needs to be verified by epidemiological studies, controlled clinical trials, follow-up studies and psychobiological investigations.

The clinical implications of the sensitisation hypothesis in depression are considerable. The treatment of depression with antidepressant drugs would not be questioned, but its modalities and applications may undergo important changes. A number of current practices would need to be re-examined such as the (inappropriate) use of antidepressant drugs in minor mood disturbances, the treatment of anxiety disorders with antidepressants, the use of suboptimal dosages of antidepressant drugs, the application of antidepressants as prophylactic agents, and modalities of discontinuation. A cost-benefit appraisal of psychotherapeutic versus pharmacological treatment would also need to be considered.

Even though the hypothesis of sensitising effects of antidepressant drugs, at present, has no empirical support, it is important enough to deserve extensive studies and debate.

In clinical medicine, the likelihood that a specific treatment, while alleviating the symptoms of disease, may aggravate its course, has often been evaluated. It is best illustrated by the 'antibiotic paradox':[1] the most appropriate agents for treating bacterial infections are also the agents most effective in selecting and propagating resistant strains, which persist in the environment even when expo-

sure to the drug is stopped. The need to minimise inappropriate use of new antibiotics is thus emphasised.[1]

Other examples exist in different branches of medicine. The issue of whether early treatment of Parkinson's disease with levodopa may worsen disease progression has been discussed.[2] Both preclinical (neurotoxicity in tissue cultures) and clinical (gradual decrease of therapeutic response, refractoriness, and the onset of dementia which was not seen before the introduction of levodopa therapy) findings prompted this hypothesis.[2] Similar concerns have been raised about the long term treatment of asthma with inhaled β-agonists[3] which have been associated with tolerance[4] because of the loss of bronchodilator effect with time.

Obviously, these problems are rather difficult and complex to study and definitive answers may not be available. Nonetheless, these questions are always worth asking, at least for a better understanding of the adverse effects of therapy and of therapeutic choices.

The possibility that antidepressant drugs might unfavourably affect the outcome of depression was formulated in a specific hypothesis in 1994.[5] I suggested that long term use of antidepressant drugs may increase – in some cases – the biochemical vulnerability to depression and worsen its long term outcome and symptomatic expression, decreasing both the likelihood of subsequent response to pharmacological treatment and the duration of symptom-free periods. This largely speculative hypothesis was subsequently extended to the risks and implications of interrupting maintenance psychotropic drug therapy[6] and developed in neurobiological terms.[7]

The aim of this paper is to update and complete the original, tentative formulation,[5] by reviewing the clinical literature which may suggest the potential occurrence of sensitising phenomena related to antidepressant drug use and discussing the neurobiological framework for such events. In sections 3 and 4, some suggestions for further research in this neglected area and its clinical implications are presented.

1. Clinical Phenomena Suggestive of Sensitising Effects of Antidepressants

A number of clinical observations scattered throughout the psychiatric literature provide a potential basis for postulating – at least in some patients – sensitisation by antidepressant drugs. Many of these data are derived from uncontrolled clinical observations and bear limited implications if they are considered on their own, but achieve meaning and raise important questions if they are examined in the light of a unifying hypothesis.

1.1 Long Term Outcome of Pharmacologically Treated Major Depression

There has been increasing awareness of the bleak long term outcome of depression, in terms of relapse and recurrence.[8-10] Such an outcome is exemplified by a recent 2-year prospective follow-up study on the course of depression with respect to remission and relapse.[11] Remission after treatment with antidepressants was rapid, with symptoms in 70% of patients remitting within 6 months and those in only 6% of patients failing to do so by 15 months. However, 40% of patients relapsed over the subsequent months, with all relapses occurring during the first 10 months.

The poor outcome found in follow-up studies may be explained on the basis of several distinct yet ostensibly related phenomena. Firstly, it may reflect the inadequate treatment which patients may sometimes receive.[9] Secondly, it may reflect the partial nature of this treatment, even in specialised centres, leaving a substantial amount of residual symptomatology, which is probably the most powerful predictor of subsequent relapse.[12,13] Thirdly, it may derive from the chronic and increasing drive of depressive illness. Fourthly, it may be due to the loss of nonspecific placebo effects rather than the loss of true drug effects.[14]

But, it may also be a result of antidepressant drug treatment. In a naturalistic prospective study,[15] low doses of antidepressants appeared to be less beneficial than either higher doses or clinical man-

et al.[25,26] deserve credit for raising the issue that antidepressant-induced mania may not simply be a temporary and fully reversible phenomenon, but that it triggers complex biochemical mechanisms of illness deterioration.

Despite initial denial, the view that use of antidepressant drugs may worsen the course of bipolar disorder has achieved wide currency.[23] The possibility, however, that antidepressant drugs may induce episode acceleration in unipolar depression has not been adequately studied. Goodwin[27] has illustrated how this could occur. If both depressive and manic episodes tend naturally to evolve toward remission (either into a euthymic phase or an episode of opposite polarity) and antidepressant drugs accelerate this natural tendency, drug treatment may accelerate the next sequence in the natural course (i.e. the onset of a manic episode instead of euthymia): 'If the natural sequence of recurrent unipolar illness goes from depression to recovery and then eventually to the next episode, treatments that accelerate recovery of the index depression could also accelerate the onset of the next episode'.[27]

1.4 Tolerance to Antidepressants

Several clinical observations point to the existence of tolerance phenomena during antidepressant treatment.[6] Some studies[28,29] point to dispositional (pharmacokinetic) tolerance, which reduces the concentration of a drug or its duration of action. For instance, patients who relapsed while receiving fluoxetine (20 mg/day) responded to an increased dosage of the same drug (40 mg/day).[29]

Other studies, however, suggest the likelihood of pharmacodynamic processes which change sensitivity to the drug. Mann[30] described the loss of antidepressant effect with long term monoamine oxidase (MAO) inhibitor (MAOI) treatment without the loss of MAO inhibition. Lieb and Balter[31] described the development of tolerance to antidepressant effects which was refractory to dosage increase.

Probably the best exemplification of tolerance, however, comes from the Pittsburgh Maintenance

ally responded fully to imipramine relapsed while receiving full-dose imipramine. The return of depressive symptoms during maintenance antidepressant treatment was found to occur in 9 to 57% of patients in published trials, as examined in detail in a recent review.[33] These results bear strong resemblances to the progressive loss of effects which have been observed with both antidepressant and anti-anxiety drugs in anxiety disorders.[34] They have also been defined as 'fading' (a progressive decrease of therapeutic effects refractory to dosage increase, after non-immediate symptomatic improvement).[35]

1.5 Resistance to Antidepressants

In 1984, Lieb and Balter[31] described the refractoriness of symptoms in some patients to antidepressant drugs which had been effective in previous depressive episodes. A change to another antidepressant drug yielded clinical benefits, but was followed by refractoriness as well. 10 years later, I described similar phenomena and related them to long term low-dose antidepressant treatment.[5]

Lieb and Balter[31] defined this refractoriness as 'tachyphylaxis' (the increasing tolerance to a drug that develops following repeated administration). In bipolar disorder, it has repeatedly been observed[36-38] that patients who responded well to lithium do not always regain the same degree of initial responsiveness with lithium reinstitution. In a 6-year outcome study of unipolar depression,[39] patients who relapsed while drug-free were prescribed the same antidepressant that was effective in the initial episode. Resistance occurred in 4% of cases.

The problem of refractory depression is attracting increasing attention,[40,41] yet the specific contribution of resistance in inducing refractoriness is unknown. Donaldson[42] described 3 patients with major depression who relapsed while receiving phenelzine and who developed a severe chronic depression that was refractory to other treatments.

The issues of tolerance and resistance may be related, and point to a common underlying mecha-

1.6 Withdrawal and Dependence

Withdrawal symptoms following discontinuation of antidepressant treatment were recognised soon after the introduction of these drugs.[43] The symptoms have been described with all types of antidepressants[44] but particularly MAOIs and SSRIs.[45-48]

One of the first potential explanations involved cholinergic rebound; however, this hypothesis is unlikely to explain the serotonergically mediated withdrawal syndromes of SSRIs.[49] The exact meaning of these syndromes is unclear, as is their relationship with post-treatment discontinuation recurrence risk.

There are some data which may suggest an inverse relationship between duration of maintenance antidepressant treatment and time to recurrence of treatment.[50] This raises concern about potential circularity, in the proposition that recurrence of illness after interrupting treatment proves the need for more treatment, and suggests the possibility of an addiction model, whose most immediate clinical manifestations are withdrawal symptoms.

2. The Sensitisation Hypothesis

In an attempt to view the clinical phenomena described in section 1 under a unifying light, it is necessary to refer to the concept of tolerance. Decremental pharmacodynamic models of tolerance, which focus on processes that change the number or properties of drug-sensitive receptor populations, have a very limited explanatory power in terms of the clinical phenomena described. The oppositional model of tolerance,[51] however, seems to entail several important implications.

According to this model, continued drug treatment may recruit processes that oppose the initial acute effects of a drug or of receptor alterations. This may explain the onset of tolerance in some patients. Use of antidepressant drugs may also propel the illness to a more malignant and treatment-unresponsive course, as was suggested in bipolar disorder. When drug treatment ends, oppositional processes may operate for some time, resulting in the appearance of withdrawal symptoms and increased vulnerability to relapse. As Baldessarini[61] remarks, the assumption that such physiological processes will readjust after a withdrawal phase is not supported by current awareness in the field of drug dependence.[52]

The type of oppositional processes that can be recruited and/or sensitised by antidepressant drugs is open to question. Several mechanisms may be postulated. They may include:

- interactions between different types of serotonin receptors[53,54]
- the complex balance of different neurotransmitter systems[53]
- interactions between neurotransmitter balance and the hypothalamic-pituitary-adrenal (HPA) axis[55-57]
- cross-sensitisation between antidepressant drugs and behavioural and cognitive phenomena.[58]

Another potential neurobiological mechanism may involve direct sensitisation. Neurophysiologists have used the term sensitisation, as opposed to habituation, to refer to the long-lasting increment in response occurring upon repeated presentation of a stimulus that reliably elicits a response at its initial presentation.[59] Psychostimulants such as amphetamine and cocaine have been found to induce sensitisation. Antidepressant therapy may induce time-dependent sensitisation.[60]

3. Testing the Hypothesis

Verifying the occurrence of potential sensitising effects of antidepressant drugs in depression is associated with considerable methodological difficulties. A basic problem is that antidepressants have been used so widely that it is difficult to recruit clinical populations who have never been exposed to them.

Further, in clinical studies many variables which are difficult to control for may potentially influence the verification of the sensitisation hypothesis, leading to spurious results. For instance, there is increasing evidence that cognitive behaviour therapy (CBT) reduces the risk of depressive relapse and may have a more durable effect than pharmacotherapy alone.[61,62] However, the differences may

be due to some protective effects of CBT more than to the occurrence of sensitising effects due to the use of antidepressants. There is some preliminary evidence suggesting that CBT may reduce residual symptomatology,[63-66] which is probably the most powerful risk factor for relapse in unipolar depression.[12] It should thus be demonstrated that the combination of psychotherapy and pharmacotherapy is inferior – in terms of relapse prevention – to psychotherapy alone. In a recent study,[67] patients with recurrent depression were allocated to 3 groups: (i) short term and maintenance (2 years) treatment with antidepressant drugs; (ii) CBT in the short term and maintenance phases; and (iii) antidepressant use in the short term phase and CBT for maintenance. CBT displayed a similar prophylactic effect to that of maintenance medication. The long term outcome of the group receiving both short term and maintenance treatment with CBT was slightly better than that of the group which received pharmacotherapy followed by psychotherapy.[67] In addition, an additive effect of combination therapy has not been shown.[68] However, all results may be affected by the presence of patients who had been previously treated with antidepressant drugs.

This is just an example of the difficulties that may be encountered in testing this hypothesis. So far, only one study has specifically attempted to verify the sensitisation hypothesis. Young et al.[69] investigated the response to desipramine treatment in relation to prior antidepressant treatment. Patients with past antidepressant treatments had more episodes of depression and a longer duration of illness; however, this may simply reflect the more severe course of their illness and not an antidepressant effect. Young et al.[69] failed to substantiate a relationship between prior antidepressant therapy and a lower response to further antidepressant therapy. Despite considerable methodological difficulties, several research strategies may yield some valuable information as to the sensitisation hypothesis.

3.1 Epidemiological Studies

An essential source of information may derive from epidemiological trials. Unfortunately, treatment of the depressed episode in itself may confound the results. However, studies reporting on the natural history of major depression tend to omit consideration of antidepressant drug use as a risk factor for recurrence.

3.2 Controlled Clinical Trials

Controlled clinical trials may provide valuable information, but only if they are associated with an adequate follow-up period (at least 2 years). These trials achieve considerable validity if they compare drug treatment and placebo or clinical management in patients who have had no previous exposure to antidepressant drugs.

Three types of trials appear to be particularly suitable: (i) those that involved children and adolescents, since these individuals are more likely to be at their first episode of major depression and in patients of this age group antidepressant drug treatment does not appear to be superior to placebo;[70] (ii) those which involved situations where there were no significant differences between drug and placebo in the short treatment (e.g. in minor depression);[71] and (iii) those that involved the use of antidepressants in anxiety disorders (particularly panic, social phobia and obsessive-compulsive disorder). It is possible, in fact, that, despite substantial clinical improvement in anxiety symptoms during active treatment, patients treated with antidepressant drugs may experience episodes of major depression once drug treatment has been discontinued more often than patients treated with placebo or benzodiazepines, although there are no data to confirm this.

3.3 Differentiating Refractoriness and Resistance

As discussed in section 1.5, it is not known how many of the patients who are judged to be refractory to antidepressant treatment actually display resistance to that treatment, i.e. they became refractory to an antidepressant therapy to which they initially responded. Valuable information may be provided by prospective studies, where rechallenge with the same drug upon relapse is performed.[39]

3.4 Biological Studies

The use of biological markers has provided important insights into the psychobiology of depression. Unfortunately, however, most of the studies have been cross-sectional and did not include longitudinal follow-up of patients. Nevertheless, very important clinical results have been achieved with this strategy. For instance, reversion to an abnormal response to the dexamethasone suppression test after its initial normalisation upon antidepressant drug treatment may either reflect the progression of illness or a delayed sensitising effect of antidepressant drugs on the HPA axis.[72] Positron emission tomography imaging of serotonin transporters may be another helpful modality for dissecting sensitising effects.

4. Clinical Implications of the Sensitisation Hypothesis

If the sensitisation hypothesis of antidepressants was substantiated, in part or in total, by research evidence, a number of clinical issues could emerge. Treatment of depression with antidepressant drugs would not be questioned *per se*, but a more informed use of pharmacotherapy may ensue.

4.1 Inappropriate Use of Antidepressants

The effectiveness of antidepressant drugs is firmly established in major depressive disorders.[71] However, there is a growing tendency to also use them in the setting of a collection of dysphoric complaints or demoralisation.[73] This tendency has been considerably increased by the introduction of the SSRIs, because of their better tolerability compared with the tricyclic antidepressants.[74,75] Carroll[76] warned about 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 the awareness that antibiotics should not be routinely prescribed for minor viral ailments, inappropriate use of antidepressant drugs may lead to sensitisation without any clear benefit.

4.2 Dependence versus Sensitisation

The issue of dependence has resulted in a shift in the drug treatment of anxiety disorders from benzodiazepines to antidepressants. If sensitisation by antidepressants is assumed to exist, the use of antidepressants to treat anxiety disorders could increase vulnerability to depression in anxious patients. Paradoxically, benzodiazepines might then be re-evaluated, since dependence could be regarded as the lesser of the two problems.

4.3 Full versus Subtherapeutic Dosages of Antidepressants

There is increasing consensus about the advantage of maintaining patients on the dosage of antidepressant that was found to be effective as acute treatment.[32] The rationale for this approach is the insufficient protective effects of subtherapeutic doses. In addition, keeping a patient on low-dose antidepressants for a long time (a very common practice, particularly among nonpsychiatric physicians in Europe) could expose patients to the risks of sensitisation, without an adequate protective effect.

4.4 Acute versus Prophylactic Effect of Antidepressants

Despite their benefits, full-dose continuation treatment strategies endorse a hidden conceptual model, i.e. what is effective acutely in depression is also the best option for continuation treatment. This implies that the stages of development of a disorder should not be influential in guiding treatment. There is evidence, however, to call such views in question.[64,66] Different stages of illness may require different types of treatment. For instance, a hypothesis that has not been tested is whether drugs that act primarily as serotonin 5-HT_2 receptor antagonists (such as ritanserin or mianserin) may prove more suitable for continuation treatment, whereas traditional antidepressants may be more suitable in

the acute phase. Antagonists of 5-HT_2 receptors, in fact, may act against the enhanced 5-HT_2 receptor function prodromal to the onset or relapse of depression.[53] This, or a psychotherapeutic approach aimed at the residual phase of mood disorders,[64,66] may be particularly important if a vulnerability phase for sensitisation were to be discovered.

4.5 Discontinuation of Antidepressant Drugs

Baldessarini[6] described the risks and implications of abruptly interrupting maintenance drug therapy and the clinical advantages of a gradual decrease. It is astonishing how little is known about very practical issues such as discontinuation of antidepressant drugs. In a planned, controlled discontinuation of antidepressants in 40 patients with depression,[63] my colleagues and I did not observe any clearcut withdrawal reactions. However, most of our patients were receiving tricyclic antidepressants and decreases were very slow (25mg of amitriptyline or its equivalents every other week). The fact that withdrawal reactions, because of very slow tapering over several weeks, did not occur does not necessarily imply that sensitisation is avoided.

There is a lack of good, controlled studies of different schedules of antidepressants reduction. Similarly, there is insufficient biological exploration of antidepressant withdrawal.[44] However, the issue of withdrawal phenomena is getting increasing attention with the use of SSRIs.[45-49] Are withdrawal phenomena simply bothersome and self-limiting reactions, or are they a manifestation of an increased vulnerability to relapse once drug treatment has been discontinued? There is evidence that certain SSRIs are more likely to induce withdrawal reactions than others.[48] According to the sensitisation hypothesis, this would mean that they also facilitate (or fail to protect from) relapse once they are discontinued. This could explain the high rate of relapse upon switching from an SSRI to placebo,[77] which may be different from one drug to another and be disclosed by follow-up studies.

4.6 Psychotherapeutic versus Pharmacological Changes

Biondi[78] emphasised 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 this differential therapeutic efforts may ensue. For instance, both exposure therapy and imipramine may share the same neurochemical mechanism in severe cases of panic disorder with agoraphobia.[79] However, what they do not share (the fact that changes are generally long-lasting after exposure and short-lived after imipramine[34]) may be as important.[79]

Substantial evidence supports the efficacy of long term antidepressant medication in patients with recurrent depression.[77,80,81] Such evidence has been translated into practice guidelines for the treatment of major depressive disorders.[82] However, recent research[66,67] indicates that CBT may yield similar results in recurrent depression, whereas the role of such strategies in bipolar disorder is yet to be established.[83] If the sensitisation hypothesis were correct, nonpharmacological strategies for maintenance treatment would achieve even greater importance.

5. Conclusions

At present, there are no robust data to support the view that sensitisation to depression by antidepressant drugs exists and – if it does – whether it is a generalised or very limited phenomenon. However, various clinical phenomena reported in the literature provide a high degree of suspicion that sensitisation may exist. Also, there are no robust data to support the view that sensitisation does not take place.

The scientific study of sensitisation entails considerable methodological problems. Nevertheless, many important data have probably been inadvertently collected during clinical studies on depression (e.g. on resistance) and on antidepressants in

the setting of anxiety disorders. Given the clinical importance of the issues, the time has come to debate and explore them more fully.

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