LEADING ARTICLE

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Pharmacotherapy of Mood Disorders and Treatment Discontinuation

Malcolm Lader

Institute of Psychiatry, King's College London, London, UK

Abstract

Depression is the most frequent and costly problem in primary care, where most of these patients are seen and treated. In many countries, the public regard antidepressant drugs as 'addictive', partly because of the withdrawal symptoms that can occur when they are discontinued. Indeed, discontinuation (withdrawal) symptoms can follow the stoppage of almost all classes of antidepressants, including selective serotonin receptor inhibitors (SSRIs). This is important because they are widely regarded as drugs of choice for both depression and the anxiety disorders. But is this true withdrawal or merely rebound? The antidepressant discontinuation syndrome is characterised by the time-locked emergence of new, clearly defined and quantifiable signs and symptoms that ensue on stopping or reducing the dose of an antidepressant. Thereby, it meets the criteria for a withdrawal syndrome. The symptoms are not usually severe or protracted. SSRIs vary in their propensity to be associated with a discontinuation syndrome: paroxetine appears to be the most likely. Patients should be warned of the possibility of developing such a reaction, but reassured that it is usually mild and self limiting. Tapering the dose, if practicable, is worthwhile. In severe cases, temporary reinstatement of the SSRI and slower tapering may be necessary. Escalation of antidepressant dosage, or 'street abuse', is rare with antidepressants. The use of antidepressants is generally beneficial, and efforts should be made to optimise our current use of these drugs as well as encouraging the development of newer, better and innovative compounds. To this end, physicians should educate themselves and the public about discontinuation and withdrawal, so that these clinical features can be put in a realistic context.

1. Introduction – Setting the Scene

Depression is a serious condition, with a substantial burden of morbidity and mortality. It was found to be the most frequent and costly mental health problem in primary care, where the vast majority of these patients are seen and treated.[1] The mainstays of treatment are pharmacotherapy and/or some form of psychotherapy, including counselling. Practice varies substantially from country to country: for example, counselling is the vogue in UK primary care, herbal remedies in Germany and psychotherapy is still popular in the US. Often the disorder is misdiagnosed, or even if diagnosed correctly, it is treated inappropriately with a tranquilliser or a sleeping tablet for the concomitant insomnia.

A major problem limiting the use of antidepressants in several countries, particularly the UK, is a perception upon the part of patients that these drugs are dependence-inducing or even 'addictive'. The fear appears to be that, once established on these

medications, one can never come off, or at the very least with difficulty. The 'Defeat Depression Campaign' was an attempt by the UK Royal Colleges of Psychiatrists and General Practice to try and reduce the stigma of depression, and to encourage patients to seek help earlier.[2] Three large-scale surveys of public attitudes and beliefs related to depression and its treatment were carried out in 1991, 1995 and 1997, before and after the campaign in 1992–6 (table I). Initially, antidepressants were much less favourably regarded as a treatment strategy than counselling, and a large majority of respondents regarded them as addictive. Over the 8 years, the antidepressants were regarded more favourably in terms of efficacy but were still regarded as addictive.

A more recent survey from Denmark used the Antidepressant Compliance Questionnaire.[3] It showed more positive attitudes to depression and to the effectiveness of the antidepressants. Nevertheless, 56% of respondents agreed that, 'Your body can become addicted to antidepressants'; the same percentage thought, 'When you have taken antidepressants over a long period of time it is difficult to stop taking them'.

That these adverse attitudes regarding stigma, in which addiction is a factor, impinge on compliance was shown in a study in which self-reported compliance with antidepressant treatment was associated with fewer perceptions that stigma is associated with mental illness and its treatment.[4] Nevertheless, prior exposure to antidepressant treatment improved the likelihood that a patient would adhere to treatment.[5] In turn, this lessens the likelihood of relapse and recurrence.[6] A series of studies by Demyttenaere and his colleagues[7-9] has established the extent of problems with compliance in depressed patients. Among the factors involved, concerns about addiction are important.[10] Professionals have also made assertions that antidepressants are associated with withdrawal reactions,[11,12] which have reinforced the public's fear that the antidepressants are drugs of 'addiction'; in effect, the tranquilliser saga is being re-played.

Table I. Public attitudes to the treatment of depression in the UK[2]

Statement	Percentage endorsing statement		
	1991	1995	1997
Counselling effective	85	86	86
Antidepressants effective	46	51	60
Antidepressants addictive	78	78	74

The public seek help for what they report as withdrawal symptoms.[13] In a study of telephone calls to a national medication helpline at the Maudsley Hospital in London between 1997 and 2005, 22 422 calls were received, of which 1753 (7.8%) concerned antidepressant discontinuation symptoms. Of these, 39% related to paroxetine and 14% to venlafaxine. The calls regarding paroxetine were grossly inflated following a television programme (Panorama) that raised alarm concerning the 'addictive' nature of paroxetine. Even so, the number of calls per million prescription items was highest for the monoamine oxidase inhibitors (MAOIs) such as tranylcypromine.

These dire warnings about adverse effects such as withdrawal problems are concatenated with scepticism concerning the efficacy of these drugs in trials and in real clinical practice.[14] As a result, many patients with diagnostic symptoms of persistent low mood, reduced energy and enjoyment of life are reluctant to start effective medication because of mistaken beliefs about the 'addictive' potential of antidepressants.[15]

In this leading article, just one topic is addressed, namely, that of discontinuation or withdrawal reactions, magnified as publicly perceived 'addiction'. All the main issues are discussed, but a formal comprehensive literature review is not included.

2. Discontinuing Antidepressants

2.1 Definitions

Symptoms arising on discontinuation of antidepressants have been recognised since the development of tricyclic antidepressants. The phenomenon has been postulated to be associated with rebound symptoms such as return of depression following abrupt discontinuation. Discontinuation symptoms are now known to be associated with most classes of antidepressants, if medication is stopped without

appropriate down-tapering of dose and/or dose frequency. The phenomena associated with stopping almost all antidepressants including the SSRIs are believed to result not from true dependence but from a reduction in intra-synaptic serotonin levels following receptor down-regulation. Secondary effects on associated neurotransmitters, such as noradrenaline (norepinephrine) and acetylcholine, ensue and impinge on a background of individual predisposition.[16]

In contrast to the withdrawal syndrome seen with alcohol or sedative hypnotics, antidepressant withdrawal is not associated with either psychological dependence or drug-seeking behaviour. According to the most comprehensive evaluations of clinical trials, published literature and spontaneous case reports from clinicians and patients to date, there is no evidence that antidepressants are associated with the risk of a dependence liability, a formal dependency syndrome, or abuse.[17] For these reasons, some clinicians emphasise that the most appropriate term is 'discontinuation' describing the operational process of stopping medication.[18,19] Others maintain that the discontinuation syndrome has the hallmarks of true withdrawal phenomena.[20] Whatever the semantic gymnastics entered into by various authorities, two issues remain important. Do patients translate 'withdrawal' but not 'discontinuation' to denote dependence and addiction? We do not really know and there may be major differences in emphasis across countries. Secondly, what are the practical clinical implications of the discontinuation syndrome?[21]

I shall use the two terms 'discontinuation' and 'withdrawal' interchangeably, despite attempts by some clinicians and drug manufacturers to avoid the implications of the term withdrawal. As section 2.2 shows, newly emergent symptoms, a *sine qua non* of withdrawal, certainly occur on the discontinuation of SSRIs.

2.2 Symptoms

Symptoms of the antidepressant discontinuation syndrome have been well documented.[22,23] They typically include flu-like symptoms, insomnia, nausea, imbalance, sensory disturbances and hyperarousal (the 'FINISH' syndrome).[24] Depending on the symptom pattern, it can be difficult to distinguish a withdrawal reaction from any relapse in depression, which often follows premature treatment discontinuation. Despite this, accurate diagnosis of a discontinuation syndrome is clinically imperative, because the discontinuation-related adverse events are highly preventable.[25] Accurate and timely diagnosis can avoid potentially disabling symptoms, which if misdiagnosed, can lead to inappropriate management decisions that exacerbate symptoms and worsen adherence to future antidepressant therapy, as well as incurring unnecessary healthcare costs.

The antidepressant withdrawal syndrome is characterised by the time-locked emergence of new, clearly defined and quantifiable signs and symptoms, which develop on cessation or reduction of an antidepressant that has been taken for more than a few weeks.[18] With some antidepressants even single missed doses may be followed by mild symptoms. Typically, however, patients describe transient symptoms that begin and peak within 1 week of treatment interruption, are mild in severity and follow a finite time-course, usually lasting between 1 day and 3 weeks.[25] Tapering is recommended; this lessens but does not entirely obviate the symptoms.[26] Patients with manageable symptoms can usually be reassured that the discomfort will be temporary. Reinstating the drug rapidly usually eliminates the symptoms and this strategy can be used in severe cases, followed by down-tapering of the dose at a slower rate with symptomatic relief.[27,28] Data from the published literature show marked variation in the incidence of these mild, self-limiting adverse reactions.[25] According to a post-marketing survey conducted in 1996, the incidence is generally <5%.[29] However, confounding factors such as treatment duration and rates of taper, as well as the study methods used to detect and define withdrawal reactions, influence the results. Overall, it is now accepted that a severe and disabling withdrawal syndrome occurs in up to 5% of patients: this

requires prompt modification of the management strategy.[30]

One of the problems with the evaluation of discontinuation syndromes is the assessment of discontinuation symptoms. Some scales have been developed, but they tend to be derived from those used for tranquillisers and many of the items are inappropriate. Nevertheless, a more formal diagnosis of antidepressant withdrawal can be made using the broader and generally adopted discontinuation-emergent signs and symptoms (DESS) checklist.[31] This is a 43-item clinician-rated list that covers signs and symptoms observed in association with interruption of antidepressants. The DESS is lengthy, which limits its use in some research and clinical settings. However, it remains the scale requested by most regulatory agencies.

Debate continues about certain aspects of discontinuation. Although discontinuation symptoms seem to follow abrupt cessation of antidepressants of every class, there remains uncertainty among many clinicians as to whether these are class- or drug-specific effects. Evaluation of the published literature demonstrates that even within drug classes there are marked differences between individual agents.[17,25] There seems to be quite consistent evidence that within the SSRI class, paroxetine is associated with a clinically significantly greater risk of discontinuation symptoms than the other SSRIs. This conclusion is based on data from adverse event spontaneous report databases, clinical trials and case reports. For example, the UK spontaneous adverse drug reaction database assessment reveals that paroxetine is associated with a significantly greater proportion of withdrawal reactions (≈5%) and more frequent reports of withdrawal compared with other SSRIs.[17] Such data have also been adduced in other countries.[25] Clinical trial data from double-blind, placebo-controlled active comparator studies further support differences among SSRIs in inducing discontinuation effects. The study by Rosenbaum and colleagues[31] showed that the incidence of discontinuation syndrome was higher in patients treated with paroxetine and sertraline compared with those receiving fluoxetine.

A study that evaluated the cognitive, psychomotor and symptomatic effects of interrupting treatment with SSRIs found paroxetine discontinuation to have the most effects, with deterioration in various aspects of health and functioning.[32] Similarly, in a double-blind, placebo substitution study that compared the brief interruption (3–5 days) of paroxetine and fluoxetine in 141 patients with major depression, designed to reproduce the effect of missing only a few doses, 29% of patients taking paroxetine experienced discontinuation symptoms versus 12% receiving fluoxetine.[33] The explanation for the difference most likely reflects the long half-life of the main metabolite of fluoxetine, thus acting as a natural taper.[34] The discontinuation syndrome is more likely to occur in patients who abruptly stop paroxetine than in those who taper the dose.[35] However, discontinuation symptoms on stopping an antidepressant do not seem to be inevitable: agomelatine, a melatonergic/serotonergic compound, showed little or no discontinuation features on abrupt cessation of treatment.[36]

A further question is whether the discontinuation reactions are specific to the particular indication in which the drug is being used. Antidepressants, particularly the SSRIs, are licensed for use in a range of conditions such as panic disorder, generalised anxiety disorder, social anxiety disorder and obsessive-compulsive disorder. Withdrawal reactions are similar both in incidence, nature and extent across all these indications.[37]

The influence of the duration of treatment has also been evaluated. From various studies, it appears that the duration of treatment does not predict discontinuation symptoms.[37]

Analogous to the benzodiazepine claims, some data have been adduced to assess the possibility of an SSRI withdrawal syndrome in neonates.[38] Analysis of a WHO database uncovered a total of 93 suspected cases, most following the administration of paroxetine to the pregnant mother.

A very detailed and authoritative account of discontinuation from a regulatory perspective is the Report of the Committee on Safety of Medicines Expert Working Group on the Safety of the Selec-

Table II. Recommendations of the Committee on Safety of Medicines working party[17]

Symptoms can emerge from discontinuation or tapering all SSRIs and, to a much lesser extent, tricyclic antidepressants
They comprise dizziness, numbness and tingling, nausea and vomiting, sweating, headache, anxiety and insomnia
They usually peak within 1 week of treatment interruption, are of mild to moderate severity, and follow a self-limiting course
Patients should be warned of the possibility of developing such a reaction, but reassured that it usually mild and self-limiting
Those experiencing such a reaction can usually be effectively helped by reassurance, support and brief symptomatic relief
Approximately 3–5% of patients experience more severe discontinuation reactions, usually following discontinuation of paroxetine and to a lesser extent venlafaxine
Tapering the drug dose prior to complete discontinuation is considered to be a useful way of reducing the likelihood and severity of such reactions
There is no clear evidence that the SSRIs and related antidepressants have a significant dependence liability … according to internationally accepted criteria
Wider public and patient education is a key feature in management

SSRI = selective serotonin receptor inhibitor.

tive Serotonin Reuptake Inhibitor Antidepressants.[17] They came to several conclusions as set out in table II. Adoption by the clinician of these guidelines should reinforce the message that antidepressants are not addictive and that certain SSRIs are less likely than others to cause withdrawal symptoms following treatment. This is likely to improve patient adherence and treatment outcome.

3. Overview

Discontinuation phenomena or withdrawal reactions led to a re-evaluation of the acceptability of the antidepressants. A similar review took place when the greater tolerability of the SSRIs over the tricyclic antidepressants became apparent. Since then, questions over the safety of the SSRIs, and related drugs such as venlafaxine, have prompted yet more discussion. Various meta-analyses challenged the basis for the acceptance of useful effect sizes of the antidepressants.[39] This led to an ongoing debate on efficacy.[40] All this brouhaha has taken place against the background of a general disillusionment with science in general, medicine as a component of science, and medications, in particular those used in psychiatry. Sustained campaigns have been waged against a range of psychotropic drugs, to some effect. The long shadow of the tranquilliser episode has promoted sceptical attitudes about other drugs used in psychiatry. The media are scornful about both mental illness and medication, disdainfully dismissing antidepressants as 'happy pills'.[41]

Set against this background, the problems with the antidepressants have been thrown into stark relief. All of the classes of drugs used in psychiatry have become somewhat suspect as various unwanted effects have become apparent, such as movement disorders and prolongation of the QT interval with the antipsychotic drugs. And yet similar considerations appertain to the whole ranges of medicaments that are used in other areas of therapeutics. What is different is the public sentiment that mental illness is not truly a set of medical disorders but falls into a different category. This has its historical roots in the medieval ideas that mental illness was punishment for sin of either the individual or his or her forebears. This was replaced by the ideas of inherent weakness and inexorable degeneration, and the area of eugenics encompassing mental disorders, culminating in the enormities of the Nazi atrocities. This influenced attitudes to the validity of the use of psychiatric remedies. Stigma still exists.[2] However, even where the medical concept of the disorders is acknowledged as valid, there persists a sense that the 'talking' therapies such as cognitive behavioural therapy and the analytic-based psychotherapies are all more appropriate for treating symptoms that are themselves manifested as psychological abnormalities.

Because of these various considerations, encouraging adherence to the use of medications such as the antidepressants was always going to be an uphill task. It is imperative that professionals and informed lay people strive continuously to maintain a proper

basis for the use of medications. This is not to gainsay the usefulness of most psychological treatments, but to set them into their context amid their relative merits and demerits. We should be devoting more resources now to establishing how the various forms of therapy can be combined and include a discontinuation phase for all these treatments,[42] rather than drawing up lists of positive and negative effects in order to rank the various treatments.

In addition, individuals have their own characteristics. At the biological level is an increasing emphasis on the genetic makeup of an individual, either in order to see whether there is a genetic predisposition to a particular condition or, more pragmatically, to determine whether a particular individual will respond optimally to a particular medication. By refining this approach, which has been quite assiduously applied in psychiatry, the use of drugs in medical practice can be made more acceptable.

Another less technical, but essential, part of the process is education of primary care physicians, particularly with respect to the diagnosis and management of withdrawal reactions.[43,44] Along that road, it is important that the benefits and risks of antidepressant drugs are carefully delineated so the effects of antidepressants in improving quality of life can be appreciated.[45] It is important to keep this problem in perspective, because if antidepressant usage declines under the obloquy of perceived major disadvantages, the properties of future antidepressants become irrelevant if no one can persuade depressive patients to use these drugs.[46] The pharmaceutical industry would be better advised to spend money on a continuous educational campaign using disinterested commentators and independent data, than on spending nearly a billion dollars each in developing antidepressants that will linger on the shelf.

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Correspondence: Dr *Malcolm Lader*, P 056, Institute of Psychiatry, Denmark Hill, London, SE5 8AF, UK.
E-mail: m.lader@iop.kcl.ac.uk