



Why is it so difficult to stop psychiatric drug treatment? It may be nothing to do with the original problem

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Summary In this paper, I argue that the problems that occur after discontinuation or reduction of long-term psychiatric drug treatment may be caused by the process of drug withdrawal itself, rather than representing the course of the underlying illness. Adverse effects induced by discontinuation of psychiatric medication include: (1) a somatic discontinuation syndrome that includes psychological symptoms which may be mistaken for relapse, (2) a rapid onset psychotic reaction after withdrawal of both conventional neuroleptic drugs and some atypicals, notably clozapine (sometimes referred to as supersensitivity psychosis), (3) a psychological reaction to withdrawal, which may be mistaken for relapse or may itself precipitate relapse, (4) a genuine relapse of the underlying condition precipitated by the process of withdrawal. The implications of these effects include the possibility that much of the research on maintenance treatment is flawed and that the recurrent nature of psychiatric conditions may sometimes be iatrogenic. If withdrawal induced adverse effects could be effectively managed, the success of drug discontinuation might be much greater than usually assumed and might outweigh the disadvantages of continued treatment.

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Introduction

Although long-term drug treatment is recommended for most patients with schizophrenia, bipolar disorder, recurrent depression and many other psychiatric conditions, there are many reasons to stop or reduce this medication. Firstly, patients may request to do so. Secondly, doses may be excessive. Evidence concerning neuroleptics, for example, suggests that patients often receive

doses that exceed the maximally effective range [1]. Thirdly, it has long been believed that some patients with psychosis do not need long-term drug treatment, especially those with good prognostic features [2], and some authors have suggested that most patients do not benefit from such treatment [3]. Elsewhere I have suggested that antidepressants do not have specific effects on depression that warrant their short or long-term use [4,5].

My clinical experience suggests that even small reductions in drug treatments are frequently problematic. This is usually attributed to the re-emergence of the underlying disorder in the absence

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of treatment and used to justify the need for recommencing or increasing drugs. However, there is a considerable body of research that suggests that there are intrinsic problems related to the process of withdrawal from long-term psychotropic drug treatment.

Hypothesis

This paper suggests that the problems that occur after withdrawal of psychiatric drugs may often be related to the process of withdrawal of that medication, rather than the natural course of the underlying condition. If this is the case, then the recurrent nature of psychiatric disorders may be partially attributable to the iatrogenic effects of psychiatric drugs. In addition, it calls for re-interpretation of the trial evidence that forms the basis of recommendations for long-term treatment in psychiatric disorders. If withdrawal related problems could be effectively managed, it also means that there may be no need to resume long-term treatment and stopping drugs would more often be successful.

Adverse outcomes caused by medication withdrawal or reduction

Somatic discontinuation syndromes (also known as withdrawal or rebound reactions)

These syndromes refer to physiological and psychological manifestations of the biological effects caused by the withdrawal of a regularly administered drug. These syndromes have been conceptualised as a result of the biological adaptations to continued drug exposure, which become suddenly unopposed when drugs are withdrawn. It is now recognised that discontinuation or withdrawal syndromes occur with many classes of drugs, not just drugs of abuse, including antidepressants [6,7] and neuroleptics [8]. Reactions to lithium withdrawal have been described less frequently [9]. Tranter and Healy noted the occurrence of persistent symptoms after discontinuation of neuroleptics in some cases [10]. Withdrawal reactions have also been reported to occasionally persist for long periods after benzodiazepine withdrawal [11].

For the purposes of this argument, the importance of withdrawal symptoms is that they include psychological and behavioural symptoms such as anxiety, restlessness and impaired sleep, which

may be misinterpreted as early signs of relapse. The criteria suggested by Lader [12] that withdrawal syndromes consist of physical and psychological symptoms not previously complained of by patients may not be straightforward to apply in people with longstanding psychiatric problems. In addition, the rapid suppression of withdrawal symptoms by "reinstitution of discontinued medication" may be mistaken for effects of drugs on the underlying illness.

Rapid onset psychosis (rebound psychosis, supersensitivity psychosis)

I have recently summarised the evidence for the occurrence of a psychotic episode shortly after discontinuation of long-term treatment with neuroleptic drugs [13]. The evidence is strongest for clozapine, where numerous case studies and withdrawal studies demonstrate this effect in patients with treatment resistant and treatment responsive psychosis. Several convincing case reports suggest it may also occur with some other drugs. Onset is usually within days and symptoms are fairly consistent, including auditory hallucinations, paranoid delusions, hostility and occasionally visual hallucinations, grandiosity and elation. Three cases were reported in people without prior psychiatric histories. Several further cases documented new onset psychotic symptoms in patients previously diagnosed with manic depression and other psychotic disorder.

Some evidence points to the possibility that this psychotic reaction is distinct from the underlying disorder and represents an iatrogenic syndrome. The occurrence in people without a previous psychiatric history is the strongest evidence to this effect and the new onset of certain symptoms reported in many other cases. The relative consistency of symptoms also points towards this possibility and it is interesting to note that they are also consistent with symptoms of stimulant psychosis, which is attributed to over-activity of dopamine and noradrenalin systems [14]. The rapidity of onset suggests that the phenomenon may be a manifestation of the withdrawal process and in the case of clozapine it is clear that the onset coincides with onset of the somatic discontinuation syndrome.

It is difficult to know how common the syndrome is. It is reported most commonly after clozapine withdrawal, possibly due to clozapine's very short elimination half-life. With drugs with a longer half-life a withdrawal psychosis may more easily be mistaken for a naturally occurring relapse, since

its onset will not so rapidly follow withdrawal. The following case vignette illustrates the difficulty of distinguishing a withdrawal related episode from ongoing symptoms.

Mr. A was in his mid 30s when he was admitted to hospital for the first time with a one week history of acute agitation and increasingly distressing auditory hallucinations after reduction of quetiapine (by half from 100 to 50 mg daily) and stopping venlafaxine. He had a 9 years history of contact with psychiatric services with chronic fluctuating symptoms consisting of depression, apathy, social withdrawal and occasional reports of possible auditory hallucinations, ideas of reference and suspiciousness. The acute psychosis improved within two weeks on an increased dose of quetiapine but he remained apathetic and withdrawn. He was changed from quetiapine to amisulpiride and transferred to a rehabilitation ward. There he engaged well but complained of drowsiness, confirmed by nursing staff, which he attributed to the amisulpiride. After a period of leave he reported that he had stopped taking the amisulpiride. On return to the ward he was elated in mood, laughing inappropriately and apparently uncontrollably, he expressed grandiose delusions and was observed frequently responding to auditory hallucinations. He was prescribed chlorpromazine 50 mg, which was all he would accept, but over the next few days his behaviour remained bizarre. He became agitated and aggressive and smashed a window in the ward. He was recommenced on amisulpiride three days after his return to the ward and 2 days later he was settled. No further episodes of elation, grandiosity or aggression were observed during the further 3 months of his admission or in the community over the next 12 months to date. He did complain intermittently of auditory hallucinations, associated with low mood, but he was not subsequently observed to be responding to them.

In Mr. A's case there appear to be two withdrawal related episodes, one on admission, which may relate either to cessation of venlafaxine or reduction of quetiapine, and one subsequently on stopping amisulpiride. The episodes were qualitatively different from other presentations, they were both short lived and appeared to respond rapidly to reinstatement or increase of neuroleptic medication. However, some of the symptoms, namely the auditory hallucinations, were present previously and subsequently. It is clear that such episodes may occur when a patient stops medication without professionals' knowledge, in which case the link will be particularly difficult to determine.

Psychological reaction and misattribution

Withdrawal or reduction of a drug may theoretically induce a psychological reaction analogous to the inverse of the placebo effect, sometimes called the "nocebo effect". This term refers to the situation in which expectations of illness induce illness. Numerous studies demonstrate that people can become physically ill and psychologically distressed through suggestion [15]. In the current case, the "nocebo effect" is the idea that the outcome of withdrawal may be influenced by negative expectations of patients or others involved in their care. This effect may be stimulated either by the somatic experience of drug withdrawal or reduction or simply by the knowledge that a drug is being reduced. Conceptually it can be distinguished from psychological symptoms that are produced directly by the biological effects of drug withdrawal but in practice this may be difficult. A psychological reaction might be less consistent in its symptom profile and onset than withdrawal symptoms. Anxiety is likely to be a prominent feature.

Those involved in patients' care may also feel substantial anxiety about changes in medication, particularly reductions in long-term drug treatments. These feelings may be transmitted to patients and precipitate or exacerbate psychological reactions in patients. These reactions are illustrated by the case of Mr. B.

Mr. B was in his 40s and had spent many years in hospital with a diagnosis of paranoid schizophrenia and a history of anxiety and aggressive behaviour. He had been discharged to supported accommodation where he was coping well, despite occasional incidents of paranoid ideation and arguments with staff. Therefore, I suggested he could reduce his neuroleptic medication, which consisted of zuclopenthixol decanoate 500 mg fortnightly and olanzapine 20 mg daily. At first he was reluctant to do so, but later he changed his mind and the zuclopenthixol was reduced from 500 to 200 mg fortnightly over the next seven months. At this point it was suggested he was well enough to move to less supported accommodation. He then became anxious, reported paranoid ideas and became increasingly argumentative with staff at his accommodation. The staffs were concerned about his behaviour and attributed it to the medication changes, which they communicated to Mr. B. He became increasingly anxious, had reduced sleep and also began to worry about the reduction of his medication. He eventually asked for it to be increased again.

A related scenario is that normal longstanding fluctuations in a patient's condition are misattributed to the effects of drug discontinuation by patients or others anxious about effects of medication reduction or discontinuation. In my experience, this is a very common situation, which occurs especially where some clinical staff are opposed to the decision to reduce or stop medication. In this situation all negative events that occur after the change in drug regimen are attributed to it, regardless of their previous occurrence or the plausibility of a connection. The case of Mr. C is one of numerous such examples from my own practice:

Mr. C was in his 50s and a long-term hospital resident. He was diagnosed as having schizophrenia, which had been treatment resistant at first but he had been stable for many years. He had some residual delusions concerning having no "insides" and not being able to eat, if he was questioned directly, but these did not interfere with his functioning. When I took over his care he was prescribed three types of neuroleptics: zuclopenthixol decanoate 300 mg fortnightly, olanzapine 20 mg daily and chlorpromazine 150 mg daily. In order to reduce his neuroleptic load, and according to his preference, his olanzapine was reduced to 15 mg. Shortly after this nursing staff reported that he was expressing his delusional beliefs more frequently than usual, he was shouting and disruptive at mealtimes and he appeared agitated. They linked this to the reduction in his olanzapine, which was subsequently increased. A few months later the same symptoms and behaviour recurred without any medication changes and nursing staff reported that this was in fact a longstanding pattern of behaviour that had occurred sporadically prior to the reduction of his medication as well as subsequently.

Psychological reactions are an important concept, because, like physiological discontinuation syndromes, they may be mistaken for relapse, or may themselves contribute to relapse of a psychotic or affective illness. My clinical experience suggests they are a substantial impediment to rationalising drug regimens.

Relapse of an underlying condition

This situation refers to the relapse or exacerbation of an underlying illness, in contrast to the onset of a novel drug withdrawal or discontinuation syndrome. The relationship between reduction of medication and relapse or exacerbation is complex [10]. Firstly, a relapse may occur after medication

withdrawal due to the removal of the beneficial prophylactic effect of the medication. Secondly, the process of withdrawal may itself induce or bring forward a relapse that would not otherwise have occurred at that time in the natural course of the disorder. Thirdly, a relapse may occur coincidentally. The difficulties of distinguishing these situations are illustrated by the case of Mr. D.

Mr. D was first admitted with a paranoid psychotic episode in his late teens and had 5 further episodes over the next 15 years. Recent relapses were not associated with non-compliance, or any medication changes. After repeated requests to reduce his long-term depot zuclopenthixol due to perceived drowsiness, it was reduced from 400 mg fortnightly to 350 mg. Six weeks later he was admitted to hospital with reduced sleep and agitation that rapidly escalated into a full blown relapse, with all the characteristics of previous episodes. He was treated and discharged after three months.

Mr. D's clinical team, who had been mostly opposed to the change in medication, attributed the relapse to the surfacing of the underlying illness due to the reduction of medication. Another possible explanation is that the relapse was brought on by the medication reduction, although it seems uncertain that this size of reduction of a long-acting preparation would have such a rapid effect. Alternatively, the relapse may have been co-incident, and consistent with the prior pattern of the illness. The anxiety of the clinical team may also have been relevant.

Despite some earlier doubts, there is now a consensus that discontinuing lithium increases the risk of relapse of manic depression over and above the levels associated with the natural course of the disorder [16]. The evidence consists of the fact that the increased risk of relapse is concentrated in the first few months after discontinuation and tails off thereafter [17], that higher rates of relapse are observed after rapid compared with gradual withdrawal [18,19], and that the rate of recurrence after lithium withdrawal exceeds the rate of episodes prior to lithium's initiation [17,20]. It is still uncertain whether only manic relapses are increased or all relapses. In a recent study manic relapses predominated in the early months after discontinuation, but risk of depression was also increased [21].

There is some suggestion that lithium discontinuation may induce an episode of mania in unipolar depressed patients without a prior history of mania. In an open label study of lithium augmentation for resistant depression, relatively rapid double blind lithium withdrawal led to 2 out of 15

patients developing mania within 4 months of withdrawal [22]. Faedda et al. [23] pointed out that this rate of switching is far higher than that expected from the natural history of unipolar depression. However, the authors of the study suggested that the continued use of antidepressants may have contributed, although the link between antidepressants and mania is uncertain. The fact that patients had been taking lithium for only 8–10 weeks in this study is interesting and may suggest that only short term treatment is required before the relapse inducing effect of lithium occurs.

Baldessarini et al. [24] have proposed that withdrawal of neuroleptic drugs may also induce or bring forward relapse. Meta-analyses have demonstrated that the excess risk of relapse after neuroleptic discontinuation is concentrated in the first few months [25,26]. Differences from people whose drugs are maintained fall gradually on longer follow up and appear to converge [25]. Like lithium, risks are substantially lower with gradual versus abrupt discontinuation [25,26]. Recent evidence that first episode patients, whose exposure to neuroleptics is likely to have been relatively short, showed lower relapse rates than multiple episode patients during a targeted treatment trial may be further evidence of a discontinuation effect [27].

However, the concept of “relapse” is less clear in schizophrenia than it is in bipolar disorder, and as suggested above, other discontinuation related phenomena may be mistaken for relapse. It is difficult to rule out this possibility since in many studies patients are immediately put back onto neuroleptic medication if any increase in symptomatology is observed [28].

It has also been suggested that discontinuation of antidepressants may increase risk of relapse. In a meta-analysis of long-term studies mostly involving randomised double blind withdrawal of some patients to placebo, the excess risk of relapse was concentrated in the first few months after withdrawal, as in the neuroleptic discontinuation studies, and diminished thereafter in a logarithmic fashion [29]. The authors also noted that the risk of relapse remained constant regardless of the previous duration of antidepressant treatment. That is, relapse risk was increased by the same amount on withdrawal to placebo after less than 3 weeks or 4 years of prior maintenance treatment [30]. The authors suggest this may indicate that a withdrawal related effect can override the reduction of risk that would normally be associated with several years of stability. However, some of the excess risk of relapse may be

accounted for by discontinuation syndromes and psychological reactions.

Mechanisms of withdrawal related disorders

Two possible mechanisms for withdrawal related disorders are suggested by the preceding evidence.

Pharmacodynamic adaptations

Long-term use of drugs that suppress certain neurotransmitters is thought to cause a compensatory increase in the number and/or sensitivity of the relevant receptors (the concept of supersensitivity). When these receptors are no longer opposed by drugs there is an over-activity of the neurotransmitter system or systems involved. This may result in the characteristic discontinuation syndromes, may cause rapid onset psychosis and may act a source of “pharmacodynamic stress” which increases vulnerability to relapse [26]. Research on rapid onset or supersensitivity psychosis has confirmed that animals and humans show changes in dopamine receptors after long-term administration of neuroleptic drugs. However, the relation between psychosis and dopamine receptor over-activity has not been investigated empirically and proposed associations with other presumed manifestations of dopamine supersensitivity such as tardive dyskinesia and prolactin elevation have not been consistently demonstrated [31,32]. Supersensitivity of other receptor systems and interaction between them has also been proposed in relation to clozapine [33].

Increased risk of relapse consequent on withdrawal has been attributed to the same theory of pharmacodynamic adaptations. The fact that abrupt withdrawal of lithium and neuroleptics appears to be associated with higher risks than gradual withdrawal would be consistent with this explanation, since there is less opportunity for adaptations to return to normal. However, some studies do not show this pattern [34]. The fact that these adaptations are present for weeks in animals after only one dose may explain why the increased risk of relapse persists for months after withdrawal [35].

Psychological mechanisms

A psychological reaction to drug withdrawal may cause symptoms in its own right, and may also increase vulnerability to deterioration or relapse.

The case studies illustrate these effects in people with psychosis, but psychological reactions might be even more important in people with depression. Psychological effects may also combine with pharmacodynamic mechanisms in a number of ways. For example, the removal of the sedating and intoxicating effects of drugs may increase anxiety in its own right, and also indirectly by reminding people of the fact that their medication is being withdrawn or reduced. In my experience, psychological reactions by patients, staff and carers are important determinants of the success or failure of drug discontinuation, a proposition that is open to empirical testing.

Implications for maintenance treatment

Since all the adverse effects outlined above may be mistaken for re-emergence of underlying illness, evidence on the value of maintenance drug treatment in psychiatry needs to be re-evaluated. Maintenance studies involve a group of people who have been taking medication for some time. Such people are then randomised either to continue medication or to have it withdrawn and replaced by placebo, usually quite rapidly. Hence, the placebo group are in reality a "medication withdrawal" group and are subject to all the adverse effects of medication withdrawal. However, since this fact has usually been overlooked, these effects have been attributed to the underlying illness and taken as evidence of the superiority of continued treatment. Where relapse is judged simply as any clinical deterioration, or as small increases in scores on rating scales, somatic discontinuation symptoms or anxiety induced by the process of discontinuation may be mistaken for relapse. In addition, some early psychotic relapses may not be relapses of the original disorder but a new phenomenon induced by the process of withdrawal. Some episodes that are genuine relapses may be induced by the process of withdrawal itself. This has been established for lithium and suggested for other drug classes.

I do not want to rule out that some problems following drug withdrawal may be genuine relapses that are due to the resurfacing of the underlying illness in the absence of treatment. However, the neglect of the adverse effects of drug withdrawal mean it is likely there are fewer cases of this than is generally assumed in clinical trials and practice. This adds support to those who question the benefits of long-term maintenance treatment in psychiatric conditions and suggests that the recurrent nature of psychiatric illness may sometimes be iatrogenic [3].

Implications for management of drug discontinuation

Research shows that a proportion of people even with severe psychotic disorders (somewhere between 20% and 40% [26,36]) can stop long-term drug treatment without difficulty. If withdrawal related morbidity could be managed effectively, then the outcome of drug discontinuation might be more successful. For psychotic episodes brought on by drug withdrawal some combination of short-term drug therapy, psychological therapy and social support might be necessary. For other problems, including the clinically significant problem of anxiety about withdrawal among patients and staff, changing attitudes to withdrawal may be what is needed. Research that looks at the long-term outcome after treatment of acute withdrawal related disorders is needed to ascertain the ultimate outcome of drug discontinuation. The fact that adverse effects of withdrawal have been neglected, and misinterpreted as evidence of the natural course of the underlying condition, has contributed to a climate in which there is intense anxiety and pessimism about the outcome of medication withdrawal in long-term psychiatric illness. This paper suggests that if withdrawal related disorders can be managed effectively, there may be cause to be more optimistic about the outcome of stopping psychiatric drugs.

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