Barriers to stopping neuroleptic (antipsychotic) treatment in people with schizophrenia, psychosis or bipolar disorder

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Abstract: Most guidelines recommend long-term, indefinite neuroleptic (or antipsychotic) treatment for people with schizophrenia, recurrent psychosis or bipolar disorder, on the basis that these medications reduce the chance of relapse. However, neuroleptics have significant adverse effects, including sexual dysfunction, emotional blunting, metabolic disturbance and brain shrinkage, and patients often request to stop them. Evidence for the benefits of long-term treatment is also not as robust as generally thought. Short-term randomised trials show higher rates of relapse among those whose neuroleptic treatment is discontinued compared with those on maintenance treatment, but they are confounded by adverse effects associated with the withdrawal of established medication. Some longer-term studies show possible advantages of medication reduction and discontinuation in terms of improved social functioning and recovery. Therefore, there is a good rationale for supporting patients who wish to stop their medication, especially given the patient choice agenda favoured by The National Institute for Clinical Excellence (NICE). The major barrier to stopping antipsychotics is an understandable fear of relapse among patients, their families and clinicians. Institutional structures also prioritise short-term stability over possible long-term improvements. The risk of relapse may be mitigated by more gradual reduction of medication, but further research is needed on this. Psychosocial support for patients during the process of reducing medication may also be useful, particularly to enhance coping skills. Guidelines to summarise evidence on ways to reduce medication would be useful. Many patients want to try and stop neuroleptic medication for good reasons, and psychiatrists can help to make this a realistic option by supporting people to do it as safely as possible, with the best chance of a positive outcome.

Keywords: antipsychotics, bipolar disorder, de-prescribing, discontinuation, neuroleptic, schizophrenia, tapering, withdrawal

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Introduction
Drugs that we refer to as ‘antipsychotics’, ‘neuroleptics’ or, in the past, ‘major tranquillisers’ were introduced into psychiatry in the 1950s. Although they have always been associated most strongly with the treatment of psychosis, schizophrenia and bipolar disorder, they are also used widely in many other situations where their tranquillising or sedative effects could be useful, including agitation and challenging behaviour in people with dementia and learning difficulties, anxiety, depression, insomnia and some neuroleptic agents are used for rapid tranquillisation.

Neuroleptics are recommended and widely used both to reduce the symptoms of an acute psychotic or manic episode, and as a long-term treatment for people with a diagnosis of schizophrenia, another psychotic disorder or bipolar disorder. They were hailed as miracle cures when they were introduced in the 1950s.1 Most contemporary experts also believe that, despite their...
adverse effects, neuroleptics undoubtedly have ‘a favourable benefit-to-risk ratio’ for people diagnosed with schizophrenia, and that long-term, indefinite treatment should be recommended to everyone in this situation. Certain neuroleptic agents are among recommended long-term treatments for the prophylaxis of bipolar disorder and this is now among the most common indications for the use of these drugs.

Why stop neuroleptics?
So if neuroleptics are widely believed to be so effective, why might someone decide to stop taking them, and should clinicians ever support or encourage such a decision?

Although it is recognised that many people with long-term medical conditions do not adhere perfectly to medication regimes, when people with severe mental disorders stop medication they are often considered to have done so because they lack ‘insight’ into their disorder. Yet we know that neuroleptics produce serious physical complications and induce mental and behavioural alterations, such as sedation, emotional blunting and sexual dysfunction, that are often experienced as highly unpleasant by users. Despite early promises, second generation antipsychotics have proved no less harmful than their predecessors. In addition to previously recognised serious adverse effects such as tardive dyskinesia, neuroleptic malignant syndrome, weight gain, diabetes and sudden cardiac death, recent evidence suggests that neuroleptic treatment is associated with brain shrinkage. Although the evidence on whether this is linked to cognitive impairment is not entirely consistent, it is an obvious concern, especially as the reduction in brain volume was thought to be evidence of the toxic effects of schizophrenia itself, and therefore cited as one of the justifications for long-term neuroleptic treatment. Many qualitative studies show that some users experience the effects of neuroleptics as debilitating and harmful, and are sceptical or ambivalent about whether they confer any overall benefit. A decision to stop taking neuroleptics is not therefore necessarily irrational. It may be an understandable and rational response to the burden of adverse effects these drugs produce.

As well as the burden of adverse effects, some features of the evidence base for long-term neuroleptic use mean the benefits that are usually attributed to this treatment are not as secure as usually believed. Maintenance treatment is recommended on the basis of discontinuation trials, whereby people who are already taking neuroleptics are randomised either to continue taking them or be switched to placebo. Although these trials demonstrate reduced rates of relapse with continuing drug treatment, it needs to be appreciated that they are discontinuation trials, rather than trials testing the difference between continuing treatment or placebo over the long-term. They all involve people who have already been established on neuroleptic treatment, indeed, often for years, beforehand. Therefore, the perceived benefits of continuous neuroleptic treatment in these studies may result from a prevention of adverse effects associated with ‘neuroleptic withdrawal’ rather than representing the benefits of long-term treatment in itself.

The fact that cessation of neuroleptics could lead to characteristic signs of withdrawal including agitation, anxiety, restlessness, insomnia and irritability, and occasionally psychotic symptoms that did not exist previously was recognized as far back as the 1960s, and has been explored in more detail recently. Withdrawal symptoms are relevant because they may be mistaken for relapse in randomised trials, especially where relapse is defined as a small increase in a broad range of symptoms and behaviours, as it often is.

Some case studies suggest that neuroleptic withdrawal may occasionally provoke the onset of psychotic symptoms in people who have never had them before, including people with no prior history of mental health problems. These case reports include new onset psychosis during the discontinuation of D2 blockers, such as metoclopramide and domperidone, that are used for other medical indications. Psychotic symptoms provoked by withdrawal will also be classified as relapse in randomised trials of long-term treatment.

The possibility that trials of maintenance neuroleptic treatment reveal the adverse effects of drug discontinuation has been highlighted by emerging evidence about the withdrawal effects of other prescription drugs, including antidepressants. In addition to withdrawal symptoms, some evidence suggests that neuroleptic discontinuation can increase vulnerability to a relapse of the underlying condition. We know from animal studies that antipsychotics induce changes in the brain’s dopamine system, for example, that
persist for some time after treatment is stopped.\textsuperscript{24,25} These changes may make people more susceptible to experiencing a psychotic episode when no longer opposed by the presence of the drug. In line with this hypothesis, the increased risk of relapse associated with discontinuing neuroleptic treatment is highest in the weeks and months following discontinuation, and declines with longer term follow up.\textsuperscript{13,26,27} In one study, for example, 50\% of relapses in the group who were switched to placebo occurred within the first 3 months.\textsuperscript{26}

Moreover, some studies suggest that gradual withdrawal is less likely to lead to relapse than abrupt withdrawal,\textsuperscript{27} although some analysis has not replicated this finding.\textsuperscript{13} The possibility that withdrawal of long-term medication may precipitate relapse has been clearly demonstrated in the case of lithium treatment in people with bipolar disorder, where it has been consistently shown that the risk of relapse is higher after stopping lithium than it was before people started.\textsuperscript{28–30} No comparable studies have been conducted with people on neuroleptics for psychotic disorders.

Therefore, the evidence from which the benefits of long-term neuroleptic treatment was deduced does not necessarily demonstrate the benefits of long-term treatment, and may, sometimes at least, merely reflect the difficulties of neuroleptic discontinuation. This realisation tilts the balance of considerations with regard to the long-term use of these drugs. It suggests that an increased risk of relapse in the short term following antipsychotic discontinuation does not need to be interpreted as a sign of the inevitable return of a chronic and worsening condition, but can be seen instead as a temporary hurdle to be traversed in the process of coming off these medications.

In addition, several naturalistic studies that involve follow up of people with a first episode of psychosis or schizophrenia find, in contrast to short-term randomised trials, that people who avoid taking ongoing neuroleptic medication show better outcomes over long-term follow up of 10–20 years.\textsuperscript{31–34} However, confounding by underlying prognosis may explain these results, partially at least. In contrast, a study of prevalent cases in rural China found that people who had never had antipsychotic treatment were less likely to be in remission than people who had received treatment.\textsuperscript{35,36} However, this study has been criticised for comparing unlike groups – the treated group consisted of younger, married and educated urban patients while the untreated group consisted of older, unmarried, chronic, rural and uneducated patients.\textsuperscript{37} A study using data from a national registry reported higher mortality and readmission to hospital among people who were non-users or who discontinued antipsychotics compared with long-term users,\textsuperscript{38} but it has been criticised for inadequate control of confounders and likely omission of many deaths.\textsuperscript{39} Naturalistic studies of outcomes of people with bipolar disorder in the early 20th century cast doubt on the effectiveness of prophylactic drug treatment for this condition.\textsuperscript{40,41}

Two randomised controlled trials of antipsychotic maintenance treatment have reported on long-term outcomes, both involving people with a first episode of psychosis. One was an open trial that evaluated a gradual and supported reduction of neuroleptic treatment compared with maintenance treatment.\textsuperscript{42} This suggested that even though people allocated to antipsychotic reduction were more likely to deteriorate in the short term compared with people allocated to maintenance treatment, in the long term they were twice as likely to show improved social functioning and recovery. Rates of relapse, though raised to begin with, evened out with longer follow up.\textsuperscript{42} The other trial consisted of a placebo-controlled trial of quetiapine maintenance that lasted initially for up to a year; 10-year follow-up data suggested that more people originally randomised to placebo initially showed a poor outcome that consisted of a composite of suicide or clozapine treatment or a deterioration in symptoms.\textsuperscript{43} No individual outcome measure differed between the randomised groups, however, and a fifth of the sample was included by using their last observation during the actual trial rather than follow-up data.\textsuperscript{39} It should also be noted that, unlike in the Wunderink study, in this latter trial there was no difference in dose of medication at the end of long-term follow up between patients in the discontinuation and maintenance groups. Therefore, the study did not necessarily evaluate the effect of dose reduction in the long term. Its results may be explained by the short period over which quetiapine was discontinued (6 weeks) provoking relapse or withdrawal and resulting in the recommencement of antipsychotic medication. Since both these long-term follow ups involved people with a first episode of psychosis, there is still a lack of data on the long-term outcomes of reducing and discontinuing antipsychotic medication in people with recurrent psychosis or
schizophrenia. A study is currently underway with this population.44

Consistent with this account, some patients may reasonably articulate a preference to experience greater functional capacity (being alert enough to work or volunteer, engage in relationships) at the ‘cost’ of a greater burden of symptoms such as hallucinations or a greater risk of relapse.45 Although many people fear the experience of relapse, for some, risking relapse is preferable to the continuous debilitation produced by neuroleptics.46–48 The balance of the harms and benefits of treatment may also shift over time, especially as some patients develop a greater ability to tolerate symptoms of their illness, as a portion of patients do.49

Hence, helping people to try and stop neuroleptic medication may be justified in some circumstances and is consistent with a framework of enabling patient choice recommended by the National Institute of Health and Clinical Excellence (NICE).50 It may reduce the burden of adverse effects, reflect patient preferences and lead to functional improvement in the long-term despite an increased risk of relapse or deterioration in the short-term. Moreover, evidence for the benefits of long-term treatment is not as robust as is often presented. Even if people are not successful in stopping neuroleptics completely, a supported process of gradual reduction may enable them to achieve a lower dose, which will mitigate some adverse effects and may make the treatment more tolerable and compatible with a reasonable quality of life. In situations where patients and clinicians disagree about the wisdom of stopping medication, supporting patients to reduce medication gradually may avert the risks associated with covert and abrupt discontinuation.

Relapse

Barriers to the simplification of complex medication regimes are now well-recognised,51 but stopping neuroleptics presents particular problems.

One of the principle barriers to stopping neuroleptic treatment is the issue of relapse.51 The risk of relapse may be minimised by reducing medication gradually,27 although evidence is sparse and inconsistent on this point.13 Nevertheless, it should be acknowledged that relapse is a risk of discontinuing neuroleptics. Relapse may occur because the prophylactic effect of the drugs has been removed, it may occur because stopping the drugs increases the individual’s vulnerability to having a relapse that may not otherwise have occurred at that point, or it may unmask ongoing psychotic symptoms that were effectively suppressed by the drug. It is difficult to tease apart these possibilities or to fathom which explanation applies in individual cases.

Relapse means different things to different people,51 and there is no agreed or consistent definition.17 The term may be used to refer to an increase in non-specific or psychotic symptoms, which may, in some instances, represent normal fluctuations for the individual, or may be the consequence of withdrawal. In other cases, however, relapse can be severe, and may lead to hospitalisation and all the disruption that goes with that. Having a relapse may be made even more distressing because it can be interpreted as a sign of failure and an indication that lifelong treatment is now the only option. This is linked with the assumption that relapse always represents the resurfacing of the underlying condition, rather than an episode related to the discontinuation process itself. This is the frequent perception of mental health professionals, who are therefore sometimes reluctant to support people’s wishes to discontinue neuroleptic medication.

For some people relapse may be important to avoid at all costs, especially when previous episodes have involved the individual becoming violent towards themselves or the people around them.48 Yet others may be prepared to run the risk of having a relapse in order to have a chance of avoiding the adverse effects of neuroleptic medication and have a better quality of life in the long run. This would be consistent with findings from the recovery literature that many people prioritise quality of life and functioning above the presence or absence of symptoms.52 Those people with a diagnosis of bipolar disorder and others who recover completely from psychotic episodes, in particular, may logically prefer to tolerate a higher risk of relapse rather than endure the adverse impact of taking neuroleptics in between episodes. On the other hand, families, carers and clinicians may be reluctant to take the risk of having to endure another relapse, and this makes the process of withdrawal even more difficult, since many people report that they benefit from having support from other people when they try to reduce medication.46,53–57
Institutional factors
Societal and institutional forces are ranged against any strategy that could increase the risk of a relapse of a severe mental disorder. The short-term costs of someone having a relapse can be high. People may sometimes behave in ways that are disturbing and socially disruptive when they are in the midst of a psychotic episode, and this can be frightening and upsetting for other people. People may also need to stop work, or become unable to fulfil other duties. They may need care, so that someone else needs to stop work in order to look after them. They may need hospitalisation, which, if involuntary, can be traumatising, and is costly.

Hence there are economic and social pressures to avoid relapse in the short term that may, in practice, trump any potential long-term benefit of discontinuing neuroleptics. This is exacerbated by the reduction in psychiatric inpatient beds that has accelerated over recent years in order to contain health service budgets. What this means is that short-term stability is prioritised by health services at the cost of potential improvements in quality of life, health and independent functioning in the long-term.

Although there is political support for involving all patients in decisions about their care, including those with severe mental disorder, older paternalistic attitudes persist. The idea that someone with a mental disorder could make a rational decision that should be respected is still not universally embraced, especially when that decision involves a rejection of medical treatment. Medical professionals find the rejection of treatment difficult in general, and therefore when the individual has a mental disorder it is easy to blame the disorder as a way of disguising the difference in values. It has been shown that clinicians have negative views about reducing medication in people diagnosed with schizophrenia, and can react punitively against people who do not adhere to treatment recommendations. When someone relapses, this is often interpreted as a lesson that the individual was not fit to make decisions and long-term treatment is presented as the only really rational option, despite whatever harmful and unwanted effects it provokes. Indeed, there is often a moral tenor to judgements about medication and relapse. Taking long-term treatment is viewed as a moral responsibility and refusal of it as foolish or even immoral behaviour.

Anxiety and indifference
All mental health problems can be frightening, and people are particularly worried about the possibility that they might recur. Anxiety is therefore a common accompaniment to the process of reducing and stopping a psychiatric medicine. This is compounded by the narrative that mental disorders like schizophrenia are lifelong conditions, even though we know that a significant proportion of people who have had one or two psychotic episodes will make a complete recovery, regardless of treatment, and that many others will have significant periods of good mental health. For this reason, it can be particularly disorienting for people to hear that discontinuing their neuroleptic medication may be a sensible option to consider when they have been told otherwise all their lives, and have built their identity around being a long-term patient who needs medication.

The rebound emotions that people can experience while reducing neuroleptic drugs or after stopping them, are likely to compound this anxiety. Neuroleptics are recognised to suppress emotional reactions, producing a state of emotional blunting or indifference. From experience with other drugs such as selective serotonin reuptake inhibitors (SSRIs), which also blunt emotions and can cause rebound emotional lability after discontinuation, it is likely that people who are withdrawing from neuroleptics will experience heightened emotions. Although people often welcome the return of feelings after years of emotional suppression, still they may need to learn how to manage a normal range of emotions, and this task is complicated further by the intensity of rebound emotions following drug withdrawal.
Since fear of relapse is associated with a higher risk of relapse, it has also been suggested that anxiety about medication withdrawal, coupled with anxiety precipitated by the process of withdrawal itself, may increase the individual’s vulnerability to relapse and may be one of the mechanisms whereby medication withdrawal itself precipitates relapse.

The lethargy and indifference that neuroleptics induce may also discourage people from trying to stop or reduce their medication in the first place. These effects may be superimposed on motivational deficits associated with conditions like schizophrenia, and compounded by the social marginalisation of the mentally ill, which can leave people feeling powerless and ineffective. People often give up hope of ever resuming normal activities and settle instead for a constrained lifestyle with limited opportunities.

**Overcoming the barriers to neuroleptic discontinuation**

Any intervention that reduces the risk of relapse associated with discontinuing neuroleptics would help people who want to try this option. It would reduce the anxiety associated with the process of medication reduction for patients, carers and professionals alike.

There is some evidence that gradual reduction of neuroleptics prior to cessation may reduce the risk of relapse. A meta-analysis by Viguera et al. found that people relapsed earlier following abrupt discontinuation compared with slower discontinuation. A research survey also found an association between gradual tapering over a period of 4 weeks or more and self-reported successful discontinuation and absence of relapse. However, another meta-analysis of discontinuation studies did not find any difference in overall relapse rates between studies using abrupt versus gradual discontinuation, also using a definition of gradual as 4 weeks or more (or when depot injection was abruptly stopped). This suggests that this may not be not gradual enough. Research demonstrating hyperbolic receptor occupancy patterns suggests that reduction needs to be done in a similarly hyperbolic fashion. This involves making proportional reductions at each stage, so that reductions get smaller and smaller in terms of absolute dose. At lower doses, reductions are increasingly small, hence reduction could be spread over years. A small naturalistic study which tapered neuroleptics over a period of up to 5 years showed that dose reductions could be achieved without increasing rates of hospitalisation.

Appreciating that at least a proportion of relapses or deteriorations following neuroleptic discontinuation may have been induced by the process of discontinuation is also important in enabling patients and professionals to move beyond the relapse and consider all the pros and cons of neuroleptic treatment. If some relapses are the consequences of discontinuation, then it implies that once the body has re-adjusted to the absence of the drug, stability may be achievable. Instead of regarding relapse as the proof that life-long neuroleptics are a necessity, relapse could be regarded as a blip on the course to a drug-free state. Although relapse may require drugs to be reinstated at least temporarily, once symptoms have settled down, further attempts could be made to reduce medication, maybe progressing more gradually (and to lower final doses) than before. Much as addicts may take several detoxification attempts to get clean, the process of getting off neuroleptics may be drawn out and punctuated by set-backs, but this does not mean it should automatically be abandoned at the first hurdle. Even if people do not succeed in stopping neuroleptics altogether, attempting to discontinue can be worthwhile by leading to lower doses and reduced adverse effects.

Addressing the reasons why relapse is feared so intently by all parties is also important. Relapse prevention planning with detailed contingency arrangements to intervene with early signs of relapse may help to allay patients’ and relatives’ fears, as well as close monitoring and access to help and advice in between scheduled appointments. Among staff, education about the rational motivations for stopping neuroleptics and the adverse effects precipitated by long-term treatment and withdrawal is important, as well as addressing attitudes that convey failure and blame when things go wrong.

Enhancement of personal resources for coping with unpleasant symptoms may also be useful during a period of discontinuing or reducing medication. People report using a variety of coping mechanisms to prepare for, and endure a period of, withdrawal including psychological, behavioural and medication-based strategies. People also seek support from a variety of sources, including clinicians, friends and personal
acquaintances. Several studies of non-pharmacological clinical interventions or strategies have been found to improve the outcomes for people who reduce, or wish to avoid, the use of medication. Indeed, a recent systematic review has found that patients with psychotic disorders who were randomised to certain psychosocial programmes as an alternative to usual antipsychotic treatment, had equal or, in some cases, better outcomes than those patients randomised to treatment as usual with antipsychotics.68 Hence strengthening individual coping mechanisms or offering other psycho-social interventions might help to reduce the risk of relapse or destabilisation associated with neuroleptic discontinuation.

Support from friends, family and professionals is also helpful for people trying to come off any drug that affects emotions and behaviour, and this is especially important with neuroleptic withdrawal given the risk of relapse.69 Although general attitudes towards medical treatment have changed significantly, and patients are no longer the passive recipients of medical beneficence nor doctors the final arbiters of what must be done, many psychiatrists remain nervous about helping patients to stop neuroleptics, fearing they will be blamed if something goes wrong. Yet others do support patients to reduce or stop neuroleptic treatment when they request it, and even encourage patients to consider this option who have not previously done so.56 Professionals cite the lack of guidance when surveyed about their attitudes towards deprescribing in general,51 and a desire to identify those patients who are likely to have a good outcome following antipsychotic reduction or discontinuation.30 Unfortunately, although some individual studies have identified various patient and treatment characteristics that predict subsequent relapse or functional outcome,42 meta-analyses have failed to confirm any consistent predictors of relapse.13,70,71 Few existing guidelines contain any guidance on how to help people stop taking a prescribed medicine. Although, as with other psychiatric drugs, standard evidence on how to reduce and stop neuroleptics is sparse, there is a wealth of evidence from the service user community and experienced clinicians on different approaches to stopping medication.51,72,73 These and other sources suggest that a flexible approach, involving continual self-reflection and adjustment of the tapering plan according to the individual experience of withdrawal is most likely to be successful and acceptable.53 Official guidance based on this experience would encourage clinicians to support people who wish to try and stop their neuroleptic medication. NICE is currently developing guidelines for stopping benzodiazepines, opiates and antidepressant drugs, and it is to be hoped that NICE, or a similar institution, will take up the challenge of providing guidelines for the withdrawal of neuroleptics in the future.74

Conclusion
Neuroleptic drugs reduce acute symptoms of psychosis and may be helpful in some people on a long-term basis to prevent relapse or suppress ongoing symptoms. They have serious and unpleasant adverse effects, however, and some research suggests that some people may have better overall outcomes in the long-term if they attempt to discontinue the medication and avoid or minimise long-term use. On current evidence, it is not possible to predict who these people will be. Therefore, helping people to reduce and stop neuroleptic medication can be justified as a legitimate treatment option. Fear of relapse is a realistic and significant hurdle, however, and professionals, relatives and services often prioritise short-term stability, possibly at the expense of longer-term benefits. The risk of relapse may be reduced by gradual reduction of medication with support from professionals, although further research is required on just how gradual this should be. Even if the increased risk of relapse cannot be mitigated, patients should have the right to make their own decisions about neuroleptic medication in most scenarios, following a full discussion about the pros and cons of taking neuroleptic medication. They should receive support to reduce and stop neuroleptic medication if this is what they decide to do, and should not be blamed or deemed irrational if they wish to try to have a better quality of life free of the burdens of neuroleptic drugs.

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