

Review article

Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse

Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse.

Objective: To examine the evidence that discontinuation of long-term antipsychotic medication, including clozapine, may provoke a psychotic episode.

Method: Databases were searched and citations scrutinised.

Results: Evidence for a rapid onset psychosis (supersensitivity psychosis) following clozapine withdrawal was found and weaker evidence that this might occur with some other antipsychotic drugs. Some cases were reported in people without a psychiatric history. It appears that the psychosis may be a feature of drug withdrawal rather than the re-emergence of an underlying illness, at least in some patients. Meta-analyses of withdrawal studies have suggested that antipsychotic discontinuation may also increase the risk of relapse over and above the risk because of the underlying disorder, but not all individual studies show this effect. Mechanisms may relate to brain adaptations to long-term drug use but data are sparse.

Conclusion: These effects require further urgent research. Interventions to reduce morbidity after drug withdrawal need to be developed.

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Key words: antipsychotic agents; psychotic disorders;
schizophrenia; substance withdrawal syndrome

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Accepted for publication February 9, 2006

Summations

- Discontinuation of clozapine and possibly other antipsychotic drugs may provoke a rapid onset psychotic episode that may be distinct from the underlying illness in some patients.
- Concerns that withdrawal of antipsychotic drugs may increase risk of relapse above the risk associated with the underlying disorder need further investigation.
- Mechanisms are uncertain but interest has centred on brain adaptations to long-term drug use.

Considerations

- Evidence for rapid onset psychosis following drug discontinuation comes mainly from case studies and small withdrawal studies.
- Evidence for withdrawal-related relapse comes from meta-analyses of withdrawal studies, which are influenced by the variable quality and characteristics of the original studies.
- Distinguishing re-emergence of underlying illness from a new onset discontinuation-related episode is complex and has been paid little attention in the literature.

Introduction

Antipsychotic drugs are widely prescribed as long-term treatment for people with schizophrenia and other psychotic disorders. However, it is sometimes desirable to reduce or stop these drugs because of excessive dosing, side effects, long periods of stability, patient requests or non-compliance. Clinical practice is still dominated by the assumption that adverse effects following drug discontinuation are attributable to the re-emergence of the underlying illness. However, the consequences of withdrawing psychiatric drugs are complex and may relate either to the underlying illness, to the process of drug withdrawal itself, or to psychological or contextual factors. It is well established that antipsychotic drugs are associated with a physiological discontinuation syndrome. Other consequences of withdrawal have been described, including a rapid onset psychosis, sometimes called supersensitivity psychosis. In addition, some authors have suggested that the process of antipsychotic withdrawal may itself increase risk of relapse of schizophrenic or psychotic disorders, analogous to the increased risk of relapse demonstrated after lithium discontinuation in bipolar disorder (1).

I have preferred the term 'rapid onset psychosis' to 'supersensitivity psychosis' because the former is neutral about possible mechanisms. The term 'supersensitivity psychosis' refers to the proposal that chronic administration of dopamine-blocking drugs increases sensitivity of dopamine receptors in the mesolimbic system. These over-react to normalising levels of dopamine after drug discontinuation-producing psychotic symptoms, analogous to the proposed mechanism of tardive dyskinesia (2, 3). Chouinard and Jones (3) proposed criteria for identifying 'supersensitivity psychosis', which they believed included cases of psychosis, which deteriorated during continued drug treatment, as well as cases occurring after drug withdrawal. However, there is no consensus about the existence or mechanism of supersensitivity psychosis (4) and hence the criteria have not been generally applied.

The nature of any rapid onset psychosis also needs to be determined. So far, the literature is ambiguous about whether it is thought to be a recrudescence of the underlying illness or a new phenomenon. Although these situations may not be easy to distinguish, if the process of antipsychotic drug withdrawal is psychotogenic in itself, then the psychosis might be expected to have its own distinct and relatively consistent symptom profile. This might be similar to a stimulant-induced psychosis, if excessive dopaminergic

activity is involved. Drug withdrawal would also be expected, on occasion, to provoke a psychotic reaction in people taking long-term antipsychotic or related drugs without a psychiatric history. This scenario is also more plausible if the psychosis follows shortly after withdrawal and coincides with the onset of other withdrawal symptoms, determined by drug half-life, and if symptoms resolve rapidly on reinstatement of treatment. The origin of symptoms also likely depends on the stage and nature of the underlying illness. In acute stages, or in cases with chronic ongoing symptoms such as 'treatment resistant' cases, psychotic symptoms may indicate the return of temporarily suppressed symptoms. In a stable phase, they are more likely to indicate a new phenomena.

Research on withdrawal-related relapse is complicated by difficulties of defining relapse in schizophrenia, which often involves 'fluctuation of symptom severity, not necessarily discrete episodes of illness' (5). Many withdrawal studies do not define relapse precisely or use a low threshold, such as small increase in rating scale score, which means that physiological discontinuation symptoms or psychological reactions to discontinuation might be mistaken for relapse (6, 7).

Aims of the study

This review sets out to examine the evidence for rapid onset psychosis and increased risk of relapse following antipsychotic withdrawal or reduction and to discuss the implications of these scenarios. Other features of the proposed supersensitivity concept such as worsening of symptoms during continued drug treatment and associations with other proposed indicators of supersensitivity have not been examined.

Material and methods

MEDLINE, Embase and PsychLit databases were searched using the following simple keywords: 'antipsychotic drugs' and 'neuroleptic drugs'. Each of these terms was combined with each of the following words: discontinuation, withdrawal, relapse and psychosis. Searches were also performed using the phrases 'supersensitivity psychosis,' 'tardive psychosis,' 'dopamine supersensitivity,' 'rebound psychosis' and 'rapid onset psychosis'. Reference lists of all relevant papers were scrutinised and two authors were asked if they knew of any recent relevant literature. Formal meta-analysis was not conducted because of the small number and heterogeneity of studies, but where numbers permitted, overall incidence rates of rapid onset

psychosis were calculated with confidence intervals (CI) according to formulae given in Prince et al. (8).

Results

Rapid onset psychotic reaction (supersensitivity psychosis)

The rapid emergence of psychotic symptoms within a few days or weeks of drug discontinuation or reduction has been described in relation to older antipsychotics and some atypical agents, notably clozapine. Ten papers were identified describing 42 individual cases of a suspected psychotic reaction after withdrawal or reduction of antipsychotic drugs excluding clozapine. These have been listed individually because little other data exist (Table 1).

A number of drugs were involved and discontinuation was usually gradual to some extent. In some cases onset was very rapid, within days of discontinuation. Of the symptoms noted, persecutory delusions and auditory hallucinations were the most frequent and visual hallucinations were described in two reports. Where it was described, all cases responded rapidly to restitution of antipsychotic drugs. Recent case reports concerning two elderly men on metoclopramide with no prior psychiatric history are particularly convincing because of the rapid onset of the psychotic symptoms after withdrawal and swift resolution after reinstatement of treatment. Both men had had cerebral vascular accidents 5–10 years earlier but were in a stable neurological condition and no neurological signs were reported at the time of the psychosis (15). One other case was traced involving a woman without a psychiatric history treated with reserpine for hypertension (9). Six cases were reported involving people with bipolar disorder with no previous psychotic symptoms (10, 12). Several cases involved atypical drugs, namely olanzapine and quetiapine (14, 16).

Seven studies were found that set out to investigate the incidence and prevalence of rapid onset psychosis or supersensitivity psychosis after withdrawal of conventional antipsychotics (Table 2).

These consisted of five prospective withdrawal studies. Three of these used placebo substitution to conceal the process of withdrawal to some extent (18, 21, 23, 24). One study randomised patients in a crossover design to periods of withdrawal and drug continuation (23). All involved people with schizophrenia or psychosis who were taking a variety of antipsychotic drugs. All but one of the studies was small and several only reported global psychopathology scores. Where any level of increase in symptom scores was reported, it is

impossible to be sure whether psychotic symptoms were involved or merely physiological withdrawal symptoms such as insomnia and agitation (20, 21). Two studies were conducted with treatment-resistant populations in which case symptoms may have represented re-emergence of temporarily suppressed chronic symptoms (21, 24). Therefore, these studies provide little data from which to assess the existence of a rapid onset psychosis and its frequency, and hence no attempt was made to calculate overall rates. Results also vary with one study reporting no cases (22) and one reporting a clinically significant deterioration in eight out of 20 patients (18). Four patients deteriorated and then improved within a 4-week drug-free period, which the authors hypothesised was the pattern consistent with the occurrence of supersensitivity psychosis (18).

Two prevalence studies were also retrieved, which attempted to identify if patients had ever had an episode that might be classed as supersensitivity psychosis, using Chouinard et al.'s criteria (3). Results varied from 22% of patients fulfilling criteria at some point (19) to only 5% classed as 'probable cases' (22). Both studies used criteria that were not restricted to cases following drug withdrawal or reduction. However, in the later study, all cases identified did follow drug withdrawal and it was reported that all improved within 4 weeks of drug reinstatement (22).

Early descriptions of the physiological withdrawal syndrome with antipsychotics may also provide some evidence. Although the studies did not specifically identify a new onset psychotic syndrome after withdrawal [see review in Lacoursiere (25)], some did report severe and rapid deterioration in some patients, compatible with rapid onset psychosis (26, 27). One also notes new onset hallucinations in some patients (28). Recent studies of antipsychotic withdrawal in patients with depression (29) and obsessive-compulsive disorder (27) did not record any cases of psychosis, although deterioration of obsessional symptoms was noted in most patients. Studies of reduction of antipsychotics in people with dementia have not documented psychosis, and have generally noted overall improvements in behaviour (30). However, only global results are reported and because the authors were not looking for it, deterioration which might have indicated a psychotic reaction would probably have been attributed to recurrence of the original problem.

Evidence on clozapine. Evidence for a rapid onset psychosis after clozapine withdrawal is most compelling. Eleven papers reporting individual

Table 1. Rapid onset psychosis case studies (excluding clozapine)

Study	Patient group	n	Drug	Timing of onset of symptoms after drug withdrawal	Rate of withdrawal	Symptoms	Outcome
Chouinard and Jones (1980) (3)	Schizophrenia	10	Depot fluphenazine and others	'Immediate' onset at end of injection interval	Gradual (depot)	Suspiciousness, delusions and hallucinations	Improved with increased antipsychotic dose
Kent and Wilber (1982) (9)	No psychiatric history	1	Reserpine	Within 3 days	Abrupt	New onset euphoria, sleeplessness, pressure of speech, visual hallucinations	Symptoms resolved within 1 week of reserpine being resumed
Witschy et al. (1984) (10)	Bipolar disorder	1	Fluphenazine	Within 3 days	Gradual	New onset paranoia and disconnected thoughts	Resolved within 48 h of restarting fluphenazine. Subsequently withdrawn successfully more gradually
Kahne (1989) (11)	Psychosis	1	Haloperidol	Within 1 week	Gradual	Grandiosity, delusions and tangentiality. Symptoms not clearly new	Responded within a week to reinstatement of medication. Subsequently successfully withdrawn even more gradually
Steiner et al. (1990) (12)	Bipolar disorder	5	Fluspiraline, pimozide and others unspecified	Not specified	Gradual	New onset auditory and visual hallucinations and paranoid ideation	Resolution of symptoms after antipsychotics reintroduced
Chouinard (1991) (13)	Schizophrenia	10	Various drugs	Within 6 weeks for oral and within 3 months for depot	Not given	Not reported	Not reported
Llorca et al. (2001) (14)	Schizophrenia	3	Olanzapine	Within 48 h	Sudden in two, not reported in one	Two had mania and grandiose delusions, one had auditory hallucinations and persecutory delusions. Symptoms not clearly new	Two improved within a week with restitution of antipsychotics. One improved but no timescale given
Lu et al. (2002) (15)	No psychiatric history	2	Metoclopramide (prescribed for nausea)	Within 3 days	Abrupt in one, not reported in other	New onset auditory and visual hallucinations, persecutory delusions	Improved rapidly on starting antipsychotics. Subsequently withdrawn gradually without recurrence
Margolese et al. (2002) (16)	Schizophrenia	4	Quetiapine	Within 6 weeks	Not reported	Not reported	Not reported
Fernandez et al. (2005) (17)	Parkinson's disease with drug-induced psychosis	5	Four quetiapine, one clozapine	Within 2 weeks to 2 months	Gradual	Three had new onset symptoms, namely auditory hallucinations and persecutory delusions (previously had benign visual hallucinations)	Not reported

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Table 2. Rapid onset psychosis withdrawal and prevalence studies with conventional antipsychotics

Study	Design	<i>n</i>	Onset	Rate of withdrawal	Results
Weinberger et al. (1981) (18)	Prospective withdrawal study with placebo substitution	20	Deterioration occurred within 2 weeks	Abrupt (2–3 days in most subjects)	Eight patients deteriorated (> 40% increase in BPRS scores), four deteriorated and then improved
Chouinard et al. (1986) (19)	Retrospective prevalence study	227	Within 6 weeks for oral medication, 3 months for depot	Varied	Fifty (22%) fitted criteria for supersensitivity psychosis (3)
Diamond and Borison (1986) (20)	Prospective withdrawal study	11	Within 5 days	Gradual	Increase in BPRS scores of > 20% in two of seven patients withdrawn from thioridazine. Four patients withdrawn from haloperidol showed overall significant increase in BPRS scores.
Borison et al. (1988) (21)	Prospective withdrawal study	13 (treatment-resistant patients, all on chlorpromazine)	Within 14 days	Abrupt	No overall statistically significant difference between scores before and after withdrawal. Eight patients show any deterioration in BPRS scores
Hunt et al. (1988) (22)	Retrospective prevalence study	256	Within 6 weeks for oral medication, 3 months for depot	Varied	Twelve (5%) classed as probable cases of supersensitivity psychosis (3)
Singh et al. (1990) (23)	Prospective withdrawal crossover study with placebo substitution	10	Within 2 weeks	Abrupt	No overall statistically significant difference in BPRS ratings before and after withdrawal
Apud et al. (2003) (24)	Prospective withdrawal study with placebo substitution	118 treatment-resistant patients	Within 4 weeks	Not reported	Overall statistically significant worsening of BPRS behavioural symptoms, verbal symptoms, paranoia, deficit symptoms and mannerisms

BPRS, Brief Psychiatric Rating Scale.

cases were found. These have not been detailed as several withdrawal studies with prospective or retrospective follow-up were also identified, several of which also described symptom profiles (Table 3). None of these used placebo substitution to conceal withdrawal but some studies involved switching to other medication (31, 32). One randomised patients to olanzapine or placebo substitution (33).

Again, it is difficult to interpret results that only detail any increase in symptoms on a rating scale (21) and many studies, as to be expected, were conducted with treatment-resistant patients. The studies show widely varying prevalence rates, but overall suggest that a rapid onset psychosis occurs in a proportion of patients after clozapine withdrawal. In the large withdrawal study and randomised controlled trial of olanzapine substitution, increase in at least one psychotic symptom occurred in 25% of patients withdrawn rapidly from clozapine to placebo compared with 11% of patients switched to olanzapine (33). In all, 8% patients had a full-blown psychotic episode. However, it is not specified whether patients were treatment resistant or not. The data from treatment responsive patients presented by Meltzer et al. (34) are also convincing, especially in view of the fact that the protocol had to be changed to allow the administration of concomitant antipsychotics during the withdrawal phase because of the unexpected frequency of psychotic symptoms. The

low rates found by Shiovitz et al. (31) may be because of the fact that subjects were only taking clozapine as part of pharmacokinetic studies for 28 days at a relatively low dose (200 mg daily) and the patient's previous antipsychotic was restarted after 2 days. Several studies described that severity of psychopathology after clozapine withdrawal exceeded that recorded prior to clozapine initiation (20, 21, 34).

Tentative overall incidence rates were calculated including only studies where a clinical diagnosis was made. There were 46 possible cases recorded in 229 patients, giving an overall incidence rate of 20.1% (CI: 14.9–25.3%). Within 7 days or shorter periods of observation, there were 18 possible cases among 136 patients giving an incidence rate of 13.2% (CI: 7.5–18.9%). There were 15 possible cases among 74 treatment-resistant patients giving a rate of 20.3% (CI: 11.1–29.4%), although this figure is subject to the reservations about diagnosing a rapid onset psychosis in treatment-resistant populations. The only study providing a clinical diagnosis in treatment responsive patients found a very high incidence of 68.4% (CI: 47.5–89.3%) but the sample was small and CI wide (34).

Symptoms described are numerous but paranoid delusions, hallucinations and hostility are consistently reported and these are also described in case studies (33, 35, 36). Onset after abrupt discontinuation was reported to be typically within 24–48 h (33).

Table 3. Clozapine withdrawal studies

Study	Design	Number of patients	Onset	Speed of withdrawal	Outcome	Symptoms
Diamond and Borison (1986) (20)	Prospective withdrawal study	Twelve stable chronic schizophrenia	Within 7 days	Abrupt	Four patients showed > 20% worsening of BPRS scores. For six patients scores were statistically significantly worse than preclozapine scores	Not reported
Borison et al. (1988) (21)	Prospective withdrawal studies	Twelve treatment responsive patients Fourteen treatment resistant	Within 14 days	Abrupt	Six patients showed some increase on BPRS. They had statistically significantly higher BPRS scores after withdrawal compared with preclozapine scores Nine patients showed statistically significant increase in BPRS scores compared with scores on clozapine	Not reported
Meltzer et al. (1996) (34)	Prospective withdrawal study. Some patients received treatment with other antipsychotics during withdrawal Retrospective study of naturalistic withdrawal	Nineteen treatment responsive patients Sixty-four treatment resistant	Within 14 days	3 weeks Abrupt	Thirteen patients developed psychotic symptoms (clinical diagnosis). Ten patients developed a psychotic episode (clinical diagnosis of relapse)	Paranoid delusions, auditory, visual and olfactory hallucinations and disorganised thinking
Shiovitz et al. (1996) (31)	Prospective switch from clozapine to previous neuroleptic treatment (with 2. days gap)	Thirty treatment responsive and treatment-resistant schizophrenia	Within 7 days	Abrupt	One developed psychotic episode (clinical diagnosis)	Aggression, auditory hallucinations, grandiosity, elation and agitation. Took 63 days to stabilise
Still et al. (1996) (32)	Prospective switch from clozapine to risperidone	Ten treatment-resistant schizophrenia	First assessment at 6 weeks	Tapered over 10 days	Five patients had "clinically significant" worsening of symptoms	Not reported
Tollefson et al. (1999) (33)	RCT of placebo vs. olanzapine substitution for clozapine discontinuation	One hundred and six schizophrenia	Three to five days observation	Abrupt	Seventeen patients had increase of at least one psychotic symptom. Nine had full psychotic episode (clinical diagnosis)	Paranoia, delusions, hallucinations, hostility and agitation

RCT, randomised-controlled trial; BPRS, Brief Psychiatric Rating Scale.

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Mechanism of rapid onset psychosis. Animal studies have shown that chronic administration of antipsychotic drugs induces dopamine receptor changes that result in increased behavioural sensitivity to dopamine mimetic drugs (37). Positive Emission Tomography studies confirm that humans also show increased dopamine₂ receptor binding after long-term antipsychotic drug use (38), and this is thought to play a role in the development of tardive dyskinesia (37). However, the association with psychosis has been little investigated in humans or animals. One small study with 12 schizophrenic patients did not show increased psychotic symptoms with amphetamine administration after pimozide withdrawal compared with amphetamine administration in a previous drug-free state, although this drug-free state was only 3–7 weeks after withdrawal of previous antipsychotic treatment (39). In addition, proposed associations with other presumed manifestations of dopamine supersensitivity such as tardive dyskinesia and prolactin elevation have not been consistently demonstrated (4, 24). Supersensitivity of cholinergic, serotonergic and GABAergic systems (40) have also been suggested and multiple system involvement and interaction has been proposed (41).

Chouinard and Jones (3) first proposed that supersensitivity psychosis would be most readily provoked by drugs with short half-lives such as metoclopramide, a suggestion supported by recent case reports (15). Other drugs in this class such as sulpiride and amisulpiride also have relatively short half-lives (although not as short as clozapine's) and may therefore also be particularly potent for this reaction. Baldessarini et al. (42) have suggested that the effects of clozapine could be attributable to its short half-life, especially its rapid elimination from brain tissue. It has also been proposed that the loose attachment of clozapine to D₂ receptors and rapid detachment from them after withdrawal are relevant and this would also apply to quetiapine (43).

Is rapid onset psychosis a relapse or a new phenomenon? Symptom profiles of psychoses related to older antipsychotic and clozapine withdrawal appear fairly consistent with each other and consistent with descriptions of stimulant psychoses (44), suggesting it may be a new onset phenomenon provoked by withdrawal, at least in some cases. The rapid resolution of symptoms frequently reported on reinstatement of treatment would also support this possibility. However, the symptoms reported are common and there has been no systematic comparison with symptoms in previous episodes or in other acutely psychotic patients.

Case reports in people without psychiatric histories and descriptions of new onset symptoms in psychiatric patients also suggest that it is a new phenomenon. However, the paucity of such reports and the fact that research with some other diagnostic groups is negative suggests that it is probably rare other than with clozapine. The timing of the onset of the psychosis for clozapine is consistent with it being a manifestation of the withdrawal process itself and it coincides with the timing of the somatic discontinuation syndrome (40). The relation between onset and physiological withdrawal is less clear for other drugs on current evidence.

Discontinuation-induced relapse

The idea that withdrawal of long-term psychiatric medication might provoke or bring forward a relapse of an underlying disorder has been proposed in a separate body of literature. This suggestion has been made in relation to both antipsychotics and lithium and is based on three strands of evidence: i) The observation that the increased incidence of relapse following drug withdrawal is concentrated in the first few months and tails off thereafter. The contention is that if drug withdrawal was simply revealing the natural history of the underlying condition then the proportion relapsing would be constant. ii) The observation that the rate of relapse is reduced after gradual drug discontinuation compared with abrupt discontinuation. iii) There are some studies of bipolar disorder that demonstrate that the rate of recurrence after lithium withdrawal exceeds the rate of episodes prior to initiation of lithium therapy (45, 46).

It is now generally accepted that lithium discontinuation increases the risk of relapse of bipolar disorder above the risk associated with the natural history of the condition (1, 47).

Evidence identified relating to antipsychotic withdrawal consisted of two meta-analyses and some individual withdrawal studies that provided data on relapse rates over time. Both meta-analyses included data from prospective uncontrolled withdrawal studies and randomised-controlled trials comparing placebo substitution with drug continuation. They both showed that excess risk of relapse was concentrated in the first few months after discontinuation (6, 48). In one, based on 66 discontinuation studies involving 4365 patients with schizophrenia (6, 48), 50% of patients relapsed within the first 3 months, with little additional risk thereafter (5). In 28 studies using randomised or matched controls, risks in patients

whose drugs were discontinued appeared to converge over time with risks in patients whose medication was maintained (6). A subsequent meta-analysis of data from 1210 patients from 13 studies, mostly blinded randomised-controlled trials, found 25% relapse risk within 10 weeks of abrupt discontinuation and 50% risk within 30 weeks. Few further relapses occurred after 6 months after discontinuation. In all 54% patients relapsed in the first year after discontinuation compared with a further 2% in the following year (48). Comparison of abrupt vs. gradual discontinuation across studies showed only weak and non-statistically significant differences. However, comparison within three blinded-randomised withdrawal studies based on 107 patients did reveal substantial and statistically significant differences with 32% of patients withdrawn gradually relapsing in 6 months compared with 65% of patients withdrawn abruptly.

In contrast, Davis and Andriukaitis (49) found constant rates of relapse at different follow-up points in three placebo controlled-randomised withdrawal studies, although two of these lasted less than six months. A recent follow-up study of 53 recent onset patients with schizophrenia showed a constant incident rate of relapse after drug withdrawal over an 18-month period for both minor signs of relapse and hospitalisation. However, withdrawal was gradual and medication was re-instated rapidly after minor increases in symptoms (7). Another uncontrolled individual study of withdrawal from long-acting depot medications [only partially included in the Gilbert et al. (6) meta-analysis] showed a high incidence of relapse in the first year after withdrawal falling off sharply in subsequent years (50).

The failure of intermittent antipsychotic regimes may be further evidence of withdrawal-related relapse (51). Recent evidence suggests that first episode patients have lower relapse rates than multiple episode patients under targeted treatment (52). Withdrawal-related relapse may partly account for the poorer outcome in the multiple episode group, whose exposure to antipsychotics is likely to have been more prolonged.

Suggested mechanisms. Explanations for increased risk of relapse of a mental condition after drug withdrawal have focused on the concept of 'pharmacodynamic stress' and overlap with explanations for withdrawal syndromes and rapid onset psychosis. The idea is that pharmacodynamic adaptations to long-term treatment may act as a stressor when no longer opposed by treatment (48). Gradual discontinuation is less problematic because brain

changes have time to revert to normal. Dopamine receptor supersensitivity has been suggested as one such possible adaptation (48). The fact that excess risk of relapse lasts for months after discontinuation might appear to contradict this hypothesis. Alternatively, it might suggest that adaptations persist. Animal studies confirm that repeat dosing prolongs adaptive responses (53), but the effects of years of treatment have not and probably could not be studied in animals. Psychological mechanisms have not been discussed in the literature but might also be relevant. There is often an intense anxiety about stopping or even reducing long-term medication, which may increase vulnerability to relapse. This may plausibly combine with pharmacodynamic mechanisms, with removal of effects of antipsychotic drugs increasing anxiety still further.

Discussion

The existence of psychiatric disorders caused by withdrawal of psychiatric drugs is difficult to investigate. Technically, there is the problem of distinguishing the natural history of the underlying disorder from effects related to drug withdrawal. Ethically, it is difficult to justify experimental studies involving rapid discontinuation of drugs and the understandable tendency to re-establish drug treatment rapidly with even minor increases in psychopathology obscures the natural history of events after withdrawal. Although Chouinard and Jones (3) tried to draw up diagnostic criteria, such as onset within 6 weeks and suggested that symptoms might be new or more severe, existing studies have generally failed to draw comparisons with prior psychopathology and timing of reactions is not always clear. Withdrawal studies have mostly been uncontrolled and only a few have attempted to blind participants or observers by use of placebo substitution. Research has also been complicated by the concept of supersensitivity psychosis as it elides a proposed clinical syndrome with a presumed mechanism, neither of which has been established. Research on withdrawal-induced relapse relies heavily on meta-analytic reviews with the associated problems of heterogeneity, data selection and varying quality of the original data. Relapse rates may have been inflated by use of broad criteria.

Despite these difficulties, the implications of a possible relation between drug discontinuation and occurrence of psychosis mean that existing research needs to be considered carefully. Although there is greater difficulty demonstrating a new onset condition in treatment-resistant patients, the rapidity and consistency of the reaction has convinced many

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commentators that clozapine withdrawal induces a rapid onset psychotic reaction (54). Current evidence suggests an overall incidence of around 20%, but rates may be higher with longer follow-up and in treatment responsive patients. The symptom profile is consistent with that described in research on older antipsychotics. It is more difficult to be sure whether this syndrome occurs after withdrawal of other antipsychotic drugs. Withdrawal studies are difficult to interpret but some convincing case descriptions suggest that it may occur with some other drugs at least. It may also have been missed if its onset is less rapid than that associated with clozapine withdrawal. Current evidence seems to suggest, on balance, that it is a manifestation of drug withdrawal, rather than a withdrawal-induced re-emergence of an underlying illness, at least in some cases. Data on mechanisms are sparse. Although dopamine supersensitivity has been assumed to be involved, there is little direct evidence for this. A short half-life may be an important factor in the potency of clozapine for causing a psychotic reaction after withdrawal, or it may simply increase the visibility of the reaction.

Evidence from some meta-analyses of withdrawal studies suggests that withdrawal of neuroleptic drugs may increase the risk of relapse of a schizophrenic illness above the risk associated with the underlying illness. However, evidence from individual studies is contradictory and a withdrawal-related rapid onset psychotic reaction might account for some of the early excess of episodes. Alternatively, the same mechanisms may plausibly give rise to both a new onset withdrawal psychosis and an increased risk of relapse of a pre-existing psychotic tendency.

There is an urgent need to clarify to what extent antipsychotics, including clozapine, induce rapid onset psychosis and whether risk of relapse is increased by withdrawal. Further controlled prospective trials of drug withdrawal are needed with careful description of emergent disorders and comparison with previous episodes. Criteria for the timing of rapid onset psychosis need to be developed for different drugs in association with further research into the mechanism for this reaction, including associations with half-lives of different drugs. The course of events after treatment of an acute discontinuation-related disorder needs to be charted.

Implications for research on efficacy of long-term treatment

It has been suggested that research evaluating the efficacy of maintenance drug treatment may be confounded by adverse effects associated with

discontinuation (48). Trials start with subjects who have been stabilised on drug treatment and one group is then randomised to have that medication withdrawn, usually fairly rapidly, and replaced by placebo. Hence a comparison with patients who continue on drug treatment reflects the difficulties of stopping treatment as well as the possible superiority of that treatment. Rapid onset psychosis or increased risk of relapse after withdrawal may increase the relapse rate in the placebo group, leading to an overestimate of the benefits of maintenance treatment. Gradual discontinuation schedules may help with this problem. However, what research really needs to address is whether outcomes for patients withdrawn from antipsychotic drugs are worse in the long term if acute treatment is given for early episodes, which may be discontinuation-related, without reinstating long-term treatment.

Clinical implications

It is important to acknowledge that despite possible adverse outcomes, some people do successfully stop antipsychotic drugs. In the meta-analysis by Viguera et al. (48) over 40% of patients did not relapse after 2 years even with abrupt discontinuation, although most other estimates of survival are lower. Clinicians should therefore be willing to help patients who request to reduce or stop their drugs. However, both parties need to be aware of the possibility that this process of withdrawal or reduction may itself provoke psychotic symptoms. This occurrence should not simply be taken as confirmation of the need for long-term treatment, although it may need treatment in its own right. Gradual reduction may reduce risk, but there is a need to develop and evaluate interventions for morbidity associated with drug withdrawal. Psychological interventions might be useful and/or temporary use of medication. A brief randomised trial showed that diazepam and fluphenazine were more successful than placebo in preventing exacerbation in patients who became symptomatic after antipsychotic withdrawal (55).

The possible risks associated with drug withdrawal suggest that more consideration should be given to not starting long-term drug treatment in the first place in some psychotic patients, especially as it is uncertain that all patients require long-term treatment (56). It would also be useful to re-examine the efficacy of targeted treatment in the light of knowledge about discontinuation effects and results of a trial with first episode patients are awaited (57).

In conclusion, there is evidence to suggest that the process of discontinuation of some antipsychotic drugs may precipitate the new onset or relapse of psychotic episodes. Whereas psychotic deterioration following withdrawal of antipsychotic drugs has traditionally been taken as evidence of the chronicity of the underlying condition, this evidence suggests that some recurrent episodes of psychosis may be iatrogenic. Clinicians may therefore want to re-evaluate the benefits of long-term treatment in some patients. There is an urgent need for research to clarify the risks. Strategies to manage withdrawal-related conditions that attempt to avoid the resumption of long-term treatment should be developed both to facilitate patient choice and to reduce the unnecessary exposure to drugs.

Acknowledgements

I would like to thank Professor Ross Baldessarini and Dr Philip Thomas for helpful comments on earlier drafts of this paper.

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