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# Neuroleptic discontinuation syndromes

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The existence of discontinuation syndromes following treatment with neuroleptic (antipsychotic) drugs was first outlined in the mid-1960s but the effects of such syndromes have been neglected since then. We have pursued evidence for the existence and nature of discontinuation syndromes following neuroleptics through reports of difficulties following the use of dopamine blocking anti-emetics, the use of chlorpromazine to treat tuberculosis, the use of antidepressant–neuroleptic combinations in affective disorders, the occurrence of tardive syndromes and studies designed to establish the existence of discontinuation syndromes in schizophrenia. Combined these bodies of data point strongly to the existence of discontinuation syndromes after cessation of treatment with neuroleptics which may involve features other than motor dyskinesias. There is at present little evidence on the relative frequency of such syndromes or predisposing factors. The area needs research input to establish the nature of the syndromes that may result, their frequency, predisposing factors and best methods of treatment.

**Key words:** discontinuation syndromes; drug dependence; pharmacologic stress syndromes; tardive dysthymia; withdrawal

## Introduction

In recent years there has been interest in the effects of withdrawal of neuroleptic medication, primarily in patients suffering from schizophrenia (Gilbert *et al.*, 1995; Carpenter and Tamminga, 1995; Greden and Tandon, 1995; Meltzer 1995; Nuechterlein *et al.*, 1995; Wyatt, 1995). There has also been a re-evaluation of the effects of withdrawal of lithium in manic–depressive disorders (Suppes *et al.*, 1991; Goodwin, 1994). In both cases meta-analytic and other studies have reviewed outcomes following abrupt and tapered discontinuation of treatment and have raised the possibility that treatment withdrawal may reveal two distinct populations, one with an uncomplicated withdrawal from treatment and another group who, especially after abrupt withdrawal, experience relapse rates that are temporarily greater than predicted in the ordinary course of the illness (Baldessarini and Viguera, 1995; Viguera *et al.*, 1997). To account for the latter effects, Baldessarini and colleagues introduced the notion of pharmacologic stress factors (Viguera *et al.*, 1997), by which they meant the neural adaptations that accompany long-term treatment which may in their own right have downstream effects on the disease process or other aspects of cerebral functioning.

Teasing apart the effects of pharmacologic stress factors and the natural course of an illness may not be easy. There are five possible relationships:

1. the emergence of a further episode of illness may stem from the underlying illness regardless of any withdrawal effects;
2. a new episode may be triggered by pharmacological stress factors consequent on the withdrawal of treatment;

3. a withdrawal syndrome could occur without further illness episodes but may be so problematic that it requires a resumption of treatment;
4. a combination of illness diathesis and pharmacologic stress factors may produce syndromes ordinarily not otherwise seen;
5. some combination of the above may occur.

While Option 1 has been the focus of some attention recently, Options 2–5 have been comparatively neglected. Searching *Medline*, using the following four search terms: Neuroleptic, Antipsychotic, Withdrawal and Discontinuation from 1970 through to 1997 yielded discussions of the wisdom of discontinuing neuroleptics in individuals with schizophrenia and isolated cases of akathisia emergent on withdrawal, but no reference to a distinct neuroleptic withdrawal or discontinuation syndrome in humans, apart from a possible rebound syndrome on clozapine discontinuation.

One reason for this neglect was the manner in which withdrawal syndromes were defined in the mid-1960s. Another was the dominance of the dopamine (DA) hypothesis of schizophrenia which biased perceptions of any problems emerging after treatment discontinuation, so that these were invariably seen as new illness episodes. A further reason was the recognition in the 1970s that a number of treatments, mainly involving receptor antagonists, can cause rebound symptoms, which are distinct from withdrawal syndromes as commonly understood, to which any difficulties halting neuroleptics could be ascribed. Typical examples are the rebound syndrome of increased heart rate and blood pressure that can occur following discontinuation of propranolol (O'Brien and McKinnon, 1972) or the cholinergic rebound

syndrome following discontinuation of anticholinergics characterized by nausea, vomiting, insomnia or dream-filled sleep, as well as restlessness and dyskinesias (Dilsaver *et al.*, 1983). While sometimes severe, these phenomena are relatively brief and generally not a problem. Given that neuroleptic agents block both D<sub>2</sub> and serotonin (5-HT<sub>2</sub>) receptors as well as adrenergic, cholinergic and histaminergic receptors, one might also predict rebound effects from the blockade of these receptors. All of these factors have served to obscure perceptions of other longer lasting discontinuation syndromes, distinct from simple rebound syndromes, regarding which there is in fact a considerable literature.

## Evidence for neuroleptic discontinuation syndromes

There are five sets of evidence in favour of the existence of discontinuation syndromes. One comes from populations taking anti-emetics. A second is a randomized double-blind placebo-controlled study of chlorpromazine withdrawal. A third is the evidence of difficulties terminating antidepressant-neuroleptic combinations in depressed subjects. A fourth is the existence of tardive syndromes. Finally, there were a series of controlled studies in psychotic patients in the 1960s that have disappeared from view.

### Anti-emetic withdrawal

Evidence of neuroleptic withdrawal syndromes would ideally come from populations not suffering from any nervous disorder. A number of such populations exist. One is groups of patients taking anti-emetics, such as metoclopramide and prochlorperazine, for lengthy periods of time who then discontinue treatment. To date seven cases of orobuccolingual dyskinesias following metoclopramide withdrawal have been reported (Grimes, 1981), one case of tardive dyskinesia (Patel, 1986) and two patients who have developed akathisia and depression which took 18 and 27 months to resolve (Shearer *et al.*, 1984).

Noll and Pinsky (1991) reported the case of a 41-year-old woman, who took 40 mg metoclopramide/day for 6 months. For 10 days when the dosage was reduced to 10 mg/day, previous side-effects of akathisia, tremor, difficulty concentrating, reduced libido and increased anxiety worsened and she began to experience sweating, nausea, rigidity and sensations of warmth. Complete withdrawal saw a worsening of these symptoms, the appearance of paraesthesiae in her arms and signs of 'depression'. Her symptoms had a diurnal pattern with akathisia lasting an hour in the morning and parkinsonism becoming more prominent in the afternoon. The patient continued to complain of anergia and irritability at 7 months post-withdrawal and of concentration and memory problems 14-months afterwards.

### Chlorpromazine withdrawal

One problem with these reports is that they are anecdotal. It is not clear that the problem does not stem from a pre-existing neurological diathesis. For this reason a placebo-controlled, randomized study is called for. It would be difficult to organize

such a study now but this was done in the past. In the late 1950s, it was discovered that chlorpromazine was tuberculo-static *in vitro*. Accordingly, it was given to patients with tuberculosis by Hollister and colleagues. Following 6 months of treatment with 300 mg chlorpromazine daily in a placebo-controlled double-blind protocol that produced little effect on the tuberculosis, treatment was discontinued. This led to a withdrawal syndrome in five of 17 subjects. The syndrome was characterized by nausea, vomiting, restlessness and sleeplessness; it could be mitigated by restarting chlorpromazine. This study was the first to show withdrawal effects to an agent that had no abuse potential and also the first to show withdrawal at therapeutic doses (Hollister *et al.*, 1960; Hollister and Healy, 1998).

### Neuroleptic discontinuation in affective disorders

A second non-schizophrenic group comprises patients taking combinations of antidepressants and neuroleptics such as Tryptafen (amitriptyline and perphenazine) and Parstelin (tranylcypromine and trifluoperazine) for mood disorders. These combinations are prescribed infrequently now but were common in the 1970s. The emergence of symptoms following the discontinuation of Parstelin is widely recognized. SmithKline Beecham, the manufacturer of Parstelin, recommend a conservative withdrawal regime spread over weeks but acknowledge that even then a range of symptoms may occur including anxiety, agitation, hallucinations, insomnia, headache, weakness, fatigue, nausea, nightmares, sweating, paraesthesiae and 'vaso-vagal' attacks and that these symptoms may be ameliorated by reinstatement of Parstelin. We describe below what we think may be a representative case, which illustrates the emergence of a novel syndrome stemming from the interaction of the mood disorder and pharmacologic stress factors following withdrawal of Parstelin.

RW was first depressed following a stillbirth in 1963. She was hospitalized and recovered on phenelzine 15 mg t.d.s. and chlorpromazine 25 mg t.d.s. Although well, she was left on this regime for 5 years. She became depressed again when her husband was made redundant. Both depressive episodes were characterized by melancholic features—*anergia*, *anhedonia*, *retardation*, *early morning wakening*, *diurnal mood variation*, *anorexia* and *suicidal ideation*. When her chlorpromazine and phenelzine were stopped, she became weepy and complained of paraesthesia in her arms and a churning in her stomach. This new state proved unresponsive to six electroconvulsive therapy sessions but subsequently responded to Parstelin 1 tablet b.d. She spent 29 years on Parstelin and low-dose benzodiazepines. She made eight attempts to halt, on two occasions on anaesthetic advice prior to surgery and on six at the prompting of her General Practitioner (GP). On all occasions she suffered problems which she attributed to influenza but which cleared up when Parstelin was recommenced. Her longest period off treatment was 2 weeks. Following one of these efforts to discontinue Parstelin, she was referred to us.

We continued her on tranylcypromine 10 mg b.d., halting the trifluoperazine 1 mg b.d. component of her Parstelin over 2 weeks. Following the first reduction she became shaky and nauseated. After halting completely she had severe shakiness for a month, a weakness of her legs, a shortness of breath (she asked whether she was developing asthma; this may have been a respiratory dyskinesia—see Kruk *et al.*, 1995), trembling of her tongue and a churning of her stomach. In addition she became weepy. The episodes of weepiness came on abruptly without obvious accompanying thoughts—'as though someone pressed a button'. During this period, however, her sleep and appetite were normal and after the first 2 weeks she had normal levels of energy and interest. After 8 weeks, she started mianserin 30 mg nocte and her symptoms began to ease. At 16 weeks episodes of weepiness, nausea and stomach trembling were much less frequent and shorter in duration. At 24 weeks the syndrome had cleared completely. It reappeared in a milder form over a further 8 weeks while her mianserin was discontinued.

### Tardive syndromes

Tardive syndromes including tardive dyskinesia offer a further compelling reason to believe that there may be discontinuation syndromes following neuroleptic withdrawal. While tardive dyskinesia is not simply a discontinuation syndrome as a similar syndrome may occur in drug-naïve states and can be observed in the ordinary course of treatment, it is exacerbated by reduction in dosages and is often most obvious following neuroleptic discontinuation. This is a syndrome which clearly, in some sense, results from pharmacologic stress leading to a disturbed neural balance, the result of which may be a syndrome, not commonly otherwise observed, that may last for months following treatment discontinuation. The risk of developing within-treatment and withdrawal tardive dyskinesia increases with age, female gender, mood disorders, a history of mood disorders in first degree relatives, organic brain dysfunction, diabetes mellitus and the occurrence of early extrapyramidal side-effects with neuroleptics (Jeste and Caligiuri, 1993). An association has been noted between intermittent neuroleptic treatment and both an increased risk of tardive dyskinesia and higher rates of psychotic and dysphoric-neurotic symptoms (Jeste and Caligiuri, 1993).

In addition to the emergence of tardive dyskinesia following treatment discontinuations, tardive akathisia can also develop and while tardive dyskinesia appears to have no effect in precipitating relapses, withdrawal akathisia may, plausibly, in some cases contribute to illness relapses (Sachdev, 1995). The argument in this review, however, is that tardive dyskinesia and discontinuation akathisia are only two syndromes among a range of potential syndromes that can occur following long-term treatment with and discontinuation from neuroleptics. The case of RW points to the possibility of tardive or discontinuation dysthymia, in that treatment discontinuation led to a relatively long-lasting affective syndrome that was atypical for this patient.

### Discontinuation studies in psychotic conditions

A surprising feature of recent discussions of neuroleptic withdrawal is the failure to note a series of studies conducted during the 1960s pointing to the existence of a withdrawal syndrome that in the opinion of the authors appeared to be distinct from illness relapse (Gallant *et al.*, 1964; Melnyk *et al.*, 1965; Simpson *et al.*, 1965; Greenberg and Roth, 1966; Battegay, 1966, 1967). The Battegay study is representative of the series. He and colleagues withdrew neuroleptic treatment in a placebo-controlled double-blind fashion from 81 patients. Emergent symptoms were recorded in 55 of 81 patients. Withdrawal dyskinesia only accounted for 11 of the 55 cases. Two others had dystonic syndromes. Thirty-nine patients had a syndrome involving sweating and alternating feelings of warmth and coldness, vertigo, a tendency to collapse and tachycardia (see Noll and Pinsky, 1991). Eight had headaches, 26 had nausea and vomiting and 16 had insomnia. It was difficult to judge the duration of the disturbances as in 46 of the 55 the problem was so severe that within a week drug treatment had to be re-administered. This led to the immediate disappearance of the syndrome. Battegay noted that older women were especially susceptible to

these discontinuation syndromes, an observation that anticipated subsequent findings from tardive dyskinesia research.

The other studies produced similar findings. Figures of up to 50 percent of subjects affected by withdrawal seemed standard. One explanation offered was that these effects stemmed from the cessation of cholinergic blockade (Simpson *et al.*, 1965). Quite clearly there is a cholinergic rebound syndrome which can also be noted following discontinuation of treatment with antidepressants. This, however, would not seem to cover the full range of disturbances reported by Battegay. While nausea and vomiting may occur following the discontinuation of anti-cholinergic agents, it seems just as likely that their occurrence following the discontinuation of neuroleptics is a consequence of the relief of DA blockade which is anti-emetic (Dilsaver, 1990).

In these studies, withdrawal was abrupt and from doses of the order of chlorpromazine 400 mg/day. The Hollister study indicates that these syndromes are not dependent on tolerance leading to an escalation of dose. They might, therefore, occur in response to even lower therapeutic doses sustained over a longer period of time and problems discontinuing Parstelin are consistent with this. AC's case may further illustrate the implications of this point.

In the early-1970s AC, a 36-year-old woman with no history of mental illness, suffered a psychotic breakdown in stressful family circumstances. She was diagnosed as having a paranoid psychosis, hospitalized for 2 weeks and treated with Stelazine 10 mg t.d.s. and Disipal 100 mg t.d.s. which on discharge was reduced to Stelazine 5 mg b.d. and Disipal 50 mg b.d. and at 6 months to Stelazine 5 mg and Disipal 50 mg/day. Her GP, however, deciding she had schizophrenia, maintained her on treatment indefinitely, despite evidence of superior functioning—she obtained a First Class Honours Degree and entered research. She complained that the side-effects of lethargy, weight gain and dysphoria significantly detracted from her abilities to achieve more and at 16 months stopped medication but experienced nausea, stiffness, pain, headaches and acute nervousness. She recommenced treatment which cleared these symptoms immediately. Her GP left her with the impression that this was a recurrence of her illness. Twenty years later, a second effort at withdrawal resulted in a similar outcome.

A year later, she was referred to us. Halting her Disipal produced an acute nervousness and light sleep, which cleared up after 48 h. Her Stelazine was then reduced by 1 mg every 2 weeks. Reduction to 4 and 3 mg produced stiffness and headaches. Reductions beyond 2 mg produced nausea, nervousness, tremor, hyperalgesia (pain on brushing her hair for instance), severe pains especially praecordially, mood instability, a sensitivity to either emotional or physical stress, disturbed sleep and concentration. After 2 drug-free weeks she returned to Stelazine 1 mg/day which produced a modest relief of the symptoms. Stemetil 5 mg t.d.s. alleviated her problems entirely. Two years later under further domestic stress, she attempted to reduce her Stemetil and suffered an apparent breakdown which responded within 72 h to sulpiride 400 mg b.d. A subsequent effort to reduce sulpiride by 100 mg increments/week led to a similar set of symptoms to those previously experienced which again responded to Stemetil 5 mg t.d.s. on which she remains. She has now, however, developed breast cancer (she has no family history). It is unclear what role hyperprolactinaemia may have played in this (see Goode *et al.*, 1981) or might play in her progress post-operatively (Wang *et al.*, 1995).

The picture following clozapine discontinuation is particularly complicated. Clozapine is the neuroleptic least likely to cause tardive dyskinesia and might accordingly have been thought to be less likely to produce other discontinuation syndromes and perhaps even to be useful in their management. This, however, may not be the case as relapse following its discontinuation appears particularly likely (Baldessarini *et al.*, 1995; Meltzer *et al.*, 1996). Whether this is owing to the severity of the conditions being treated or to discontinuation

effects is uncertain. Meltzer, however, has recently reported some success in mitigating the problems by using cyproheptadine in combination with other neuroleptics (Meltzer, 1997), a strategy that seems based on the same reasoning we employed in the case of RW.

## Discontinuation syndromes: boundaries and implications

A number of features suggest that the difficulties that have faced AC and RW and were apparent in studies during the 1960s are discontinuation syndromes rather than new illness episodes. Chief among these is the early onset of difficulties. A rash of new illness episodes in the week following discontinuation is improbable. Second, the rapid clinical response to the reinstatement of treatment is in favour of a discontinuation syndrome as clinical experience suggests that illness relapse may often be initially refractory to the reinstatement of treatment.

The pattern fits the definition of a withdrawal syndrome offered by Lader (1983): 'a well-defined syndrome with a predictable onset, duration and offset of action containing psychological and bodily symptoms not previously complained of by the patients. It can be suppressed by the reinstatement of discontinued medication'. This definition, although broad enough to encompass changes following agents that do not cause tolerance or craving, was offered in the context of agents which produce dependence. Given three decades of the use of the term withdrawal syndrome in this context, it may make sense to talk about discontinuation syndromes in the context of neuroleptic agents or perhaps to refer to them as pharmacologic stress syndromes, as while these syndromes arise most obviously when treatment is discontinued, the example of tardive dyskinesia raises the possibility that in a number of cases they may arise in the course of treatment and be exacerbated on discontinuation.

The features that occur on neuroleptic discontinuation can be divided into acute and chronic motor and non-motor syndromes. Within the motor sphere there may be acute dystonias, dyskinesias and akathisia and the subsequent establishment of chronic tardive dyskinesia or akathisia. Within the neurovegetative sphere, the initial withdrawal period is dominated by nausea, insomnia and anxiety which can also appear following even slight reductions in dosage, beyond a critical level, in susceptible individuals. Further reductions or a longer drug-free period give rise to paraesthesias, disturbances in temperature regulation and hyperalgesia. The chronic features include dysthymias and concentration problems that may persist for months. Viguera *et al.* (1997) point to experimental data that support the possibility that withdrawal syndromes may last up to 6 months and the natural history of tardive dyskinesia would support this.

Given the present evidence, it is difficult to state with confidence which subjects are more likely to be affected by neuroleptic discontinuation, although older women appear more at risk. It is also difficult to decide whether particular agents are more likely to cause problems, although the early

literature implicated compounds with prominent anticholinergic effects and the co-administration of anticholinergic agents.

The several lines of evidence we have offered raise the question of why syndromes which had been relatively well described in the 1960s should have been eclipsed. Two contemporary developments may have contributed to this. First, descriptions of neuroleptic discontinuation syndromes were put forward at a time when withdrawal syndromes were being defined in a manner that all but ruled out the possibility of a neuroleptic withdrawal syndrome. According to the World Health Organization position paper in 1965, withdrawal syndromes would only be expected of drugs that were liable to abuse and would be most likely in drugs leading to tolerance. Withdrawal after very low doses of drugs, liable to cause dysphoria rather than craving, was not expected.

A second development was the emphasis on a DA hypothesis of schizophrenia. An inevitable consequence of this was that episodes consequent on DA supersensitivity were interpreted as new illness episodes—supersensitivity psychoses (Chouinard and Jones, 1980). While it is incontestable that the primary locus through which neuroleptics exert their therapeutic effects is the DA system, a DA hypothesis of schizophrenia is no longer supported even by its former proponents some of whom for instance see the primary lesion as more likely to lie in the glutamate system (Carlsson *et al.*, 1993). These developments make it possible to reinterpret changes in mental state consequent on the relief of DA blockade as potentially something other than new illness episodes.

## Implications

The possibility of a discontinuation syndrome has implications for risk-benefit assessments of the utility of treatment. In clear cut cases of schizophrenia and manic-depressive disorder, the benefits of treatment in pharmacotherapy responsive cases remain overwhelmingly in favour of proceeding with treatment in compliant patients, even for individuals prone to discontinuation syndromes. But in some cases where the longer term prognosis may be favourable, as in an acute reactive psychosis, the possibility of a discontinuation syndrome with prolonged treatment might favour an early taper of medication following an initial clinical response.

The possibility of discontinuation effects also has implications for the interpretation of studies which have employed intermittent dosing strategies in schizophrenia and for prophylactic studies in both the affective disorders and schizophrenia, especially those that have employed a cross-over design. Conventional estimates of the likelihood of relapse following the cessation of neuroleptic treatment may need to factor out the influence of discontinuation effects. In other words, if the correct agent is used or the optimal discontinuation strategy adopted, the benefits that can be gained in terms of postponement of further episodes of either affective disorders or schizophrenia may be greater than studies have indicated. Equally, however, where prophylactic benefits have been calculated on the basis of emergence of difficulties on withdrawal of treatment, these may have been overestimated. There are, furthermore, implications for clinical trial designs that would infer efficacy from relapse on halting

treatment. Future trials looking at the effects of longer term administration of neuroleptics which include a discontinuation arm have the power to address these issues. The proportion of deteriorations occurring within 2 weeks of halting treatment compared with later decompensations and any differential in symptom profiles between the two 'relapses', broken down according to treatment agent, would, if collected systematically over time, offer insights into the pathogenesis of discontinuation effects and the mechanisms by which they may interact with the index disease.

With regard to further research, an immediate question is to establish which patients are most susceptible to neuroleptic discontinuation effects. This is likely to be a fruitful area for pharmacogenetic research. Initial impressions from the published literature are that older women are particularly susceptible to the effects of neuroleptic withdrawal. Early indications from the antidepressant literature are that not all selective serotonin reuptake inhibitors are equally likely to produce these effects (Coupland *et al.*, 1996) and that agents with a longer plasma elimination half-life seem less likely to lead to withdrawal effects. Work on animals has pointed to differences in the propensity of neuroleptics to trigger withdrawal effects (Antkiewicz-Michaluk *et al.*, 1995); pimo- zide seems much less likely to cause discontinuation effects than haloperidol for instance.

A number of possible treatments can be suggested. There are indications that some cases of tardive dyskinesia may respond to clozapine. The risks of agranulocytosis may appear too dangerous to warrant its usage for other discontinuation syndromes in the absence of a clear theoretical rationale or evidence of efficacy, but the use of other novel antipsychotics might be worth considering for this purpose. Indeed, if any of the newer antipsychotics could be shown to be less likely to produce discontinuation effects, this would be a strong argument in favour of their wider use and would clearly justify the increased costs of treatment.

There is some evidence from the case cited here and others cited by Meltzer (1997) that 5-HT receptor antagonists, such as cyproheptadine or mianserin, may be of some benefit in a proportion of cases. Whether there are particular syndromes that respond is an issue that remains to be established. There are also indications that calcium entry blockers may have a utility in some cases of tardive dyskinesia (Barrow and Childs, 1986) and accordingly verapamil or other agents in this group might also be considered in these other discontinuation syndromes. Animal work further supports this possibility in that pimo- zide which has significant calcium-channel blocking properties seems much less likely to trigger discontinuation effects (Antkiewicz-Michaluk *et al.*, 1995).

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