Clozapine discontinuation withdrawal symptoms in schizophrenia

Graham Blackman and Ebenezer Oloyede

Abstract: Clozapine is an atypical antipsychotic used in treatment-resistant schizophrenia. Whilst clozapine is highly effective, there are some clinical scenarios, such as the emergence of severe side effects, that necessitate its discontinuation. There is an emerging literature suggesting that discontinuing antipsychotics, in particular clozapine, can cause an array of withdrawal symptoms. We review the evidence for the existence of clozapine-induced withdrawal symptoms, and in particular focus on withdrawal-associated psychosis, cholinergic rebound, catatonia and serotonergic discontinuation symptoms. To date, there has been surprisingly little clinical guidance on how to minimise the likelihood of withdrawal symptoms in patients who are stopped on clozapine abruptly or gradually. We discuss the key outstanding questions in this area and why there is a need for guidance on the management of withdrawal symptoms associated with clozapine discontinuation.

Keywords: clozapine, schizophrenia, psychosis, withdrawal

Introduction

Clozapine is an atypical antipsychotic that has been shown to reduce hospitalisation, mortality and risk of suicide in patients with treatment-resistant schizophrenia. Furthermore, studies – albeit mostly with relatively short follow up – suggest that clozapine is the only medication effective in treatment-resistant schizophrenia. Clozapine is an antipsychotic of the dibenzodiazepine class and has a complex pharmacological profile. It is a potent antagonist of H1, M1, 5-HT2A, 5-HT2C and α1 receptors; a potent inverse agonist of 5-HT2A receptors; and a relatively weak antagonist at D1, D2, D3 and D5 receptors, with higher affinity for D4 receptors.

Whilst clozapine is predominantly reserved for patients with treatment-resistant schizophrenia, there are several clinical indications where there is a necessity to stop clozapine. Perhaps most notable amongst these are the emergence of potentially life-threatening adverse drug reactions, such as neuroleptic malignant syndrome, agranulocytosis and myocarditis. Other indications for stopping clozapine include a lack of clinical efficacy, inadequate adherence to treatment or monitoring requirements and patient preference. In some circumstances, clozapine has been discontinued successfully after symptom remission.

Since the widespread use of clozapine, it has been recognised that stopping clozapine can lead to marked deterioration in clinical status in patients. Whilst this has been attributed largely to a relapse of the underlying mental disorder, it has become increasingly recognised that this may also be attributable to clozapine withdrawal symptoms. A wide spectrum of somatic and psychiatric symptoms have been reported (Figure 1), including psychotomatic, autonomic, gastrointestinal and psychomotor. Some of these withdrawal symptoms, such as nausea and vomiting, have been described in other antipsychotics, whilst others, such as catatonia, appear to be specific to clozapine. Whilst epidemiological evidence is limited, withdrawal symptoms have been reported most often in association with abrupt discontinuation. Furthermore, symptoms often appear as a cluster, and elucidating these groups may yield insights into the underlying mechanisms responsible. To date, there has not been an attempt to summarise the evidence on clozapine-induced withdrawal symptoms. We sought to address this through a narrative review of the literature.
Methods
The aim of this narrative review was to examine the evidence for specific groups of clozapine-induced withdrawal symptoms. To identify relevant studies, we searched the electronic database PubMed from inception to April 2020 using the search terms ‘clozapine’ AND ‘discontinuation’ OR ‘withdrawal’ OR ‘relapse’ OR ‘rapid onset psychosis’ OR ‘withdrawal-associated psychosis’ OR ‘dopamine supersensitivity’ OR ‘tardive psychosis’ OR ‘supersensitivity psychosis’. Eligibility required papers to be written in English and published in peer-reviewed journals reporting data on adult patients who were either decreased or discontinued on clozapine. Two researchers (GB and EO) performed the study search independently and in parallel. Where there were discrepancies, the researchers arrived at a consensus regarding eligibility. This was supplemented by searching the references of review articles on the topic. We then narratively summarised the evidence around the existence of distinct withdrawal symptom groups.

Withdrawal-associated psychosis
Clozapine discontinuation can precipitate the sudden emergence of psychotic symptoms that have been termed ‘withdrawal-associated psychosis’ or ‘supersensitivity psychosis’.

This phenomena has been described in several antipsychotics, but is particularly associated with clozapine where it is estimated to occur in up to 20% of cases.12 Early prospective studies on clozapine cessation suggest that withdrawal-associated psychosis typically occurs within 1 to 2 weeks of discontinuation; however, there is evidence of an excess risk of relapse several months after clozapine and other antipsychotics are discontinued, suggesting that neural adaptations persist.17

In a subgroup of patients, a ‘persistent post withdrawal psychosis’ has been described, whereby patients experience withdrawal-associated psychosis beyond the period typically associated with withdrawal symptoms.18 Persistent post withdrawal psychosis is characterised by an exacerbation of psychotic symptoms extending beyond 6 weeks after a decrease, discontinuation or switch of antipsychotics.13 Psychotic symptoms are often more severe than prior to treatment, may include new features and be less responsive to treatment.26,27

Withdrawal-associated psychosis is particularly related to the abrupt discontinuation of clozapine.14-16 Support for the existence of withdrawal-associated psychosis includes the evidence that symptoms are more severe than prior to starting clozapine in some patients.14,16 Furthermore, studies suggest that the dose required to achieve remission is often higher after restarting clozapine.22 As well as occurring in the context of discontinuation and dose reduction, withdrawal-associated symptoms have also been suggested to occur between doses of clozapine,13,29 particularly in patients on a once daily regime.30 With a mean half-life of 12 hours, clozapine plasma concentrations may fluctuate by over 50% within a patient on a stable dose; therefore, withdrawal symptoms between doses is plausible. Whilst further empirical research in this area is indicated, preliminary evidence supports this assertion.26

Patients with treatment-resistant schizophrenia are particularly vulnerable to symptom deterioration after clozapine discontinuation.28 Several studies support clozapine’s superiority over other antipsychotics, albeit with mostly short periods of follow-up.4,29 In contrast, there is a paucity of high-quality evidence exploring the most effective antipsychotic after clozapine discontinuation. No head-to-head studies have been reported, preventing direct comparisons. One randomised clinical trial found that switching from clozapine to the atypical antipsychotic zotepine led to a significant worsening of symptoms compared with clozapine continuation.30 The only randomised placebo controlled trial to date found that switching from clozapine to olanzapine led to a reduced likelihood of withdrawal-associated psychosis following abrupt discontinuation, compared with placebo.31

The pathophysiology of withdrawal-associated psychosis is not fully understood, and there is debate as to whether it reflects a relapse of the underlying psychotic disorder, or a distinct clinical phenomenon. Distinguishing between the two is challenging as most patients treated with clozapine have a psychotic disorder. However, there are case reports of withdrawal-associated psychosis occurring in patients discontinued on antipsychotics without a prior history of psychosis, suggesting that, at least in some patients, withdrawal-associated psychosis may represent a distinct clinical phenomenon.32,33 Meta-analytic evidence indicates that relapse rates in the 6 months following abrupt discontinuation of antipsychotics are significantly higher in patients with schizophrenia than would be predicted based on the natural course of the disorder.17 Furthermore, the abruptness of onset and the associated increased severity of symptoms (in some cases) are in keeping with...
### Table 1. Withdrawal-associated psychosis studies.

| Study | Patients discontinued on clozapine | Study design | Withdrawal symptom group | Withdrawal symptoms | Patients with withdrawal symptoms (%) | Highest clozapine dose/day (mg) | Clozapine dose before cessation (mg) | Time to onset of withdrawal symptoms | Withdrawal symptoms duration | Clozapine restarted | Symptoms resolved when clozapine restarted | Other medication to treat withdrawal symptoms |
|-------|-----------------------------------|-------------|--------------------------|---------------------|-----------------------------------------|-------------------------------|-----------------------------------|-------------------------------------|-------------------------------------|-----------------------|---------------------------------------------|-----------------------------------------------|
| Tollefson et al. (1999) | 106 | Double-blinded RCT | Withdrawal-associated psychosis | Delusions, hallucinations, hostility and paranoid delusions | 33 (25 placebo versus olanzapine) | 464 (mean) | <300 | 3 days | Unknown | Minimum 4 weeks | Yes | Yes | Olanzapine |
| Seppala et al. (2003) | 28 | Observational | Withdrawal-associated psychosis | Psychosis (3/28) | 46 | 100–600 | 100–600 | Unknown | Up to 1 year | 15–176 days | No | - | Anticholinergics |
| Meltzer et al. (1996) | 19 | Observational | Withdrawal-associated psychosis | Paranoid delusions, hallucinations, cognitive dysfunction, stereotypy, disorganisation, inappropriate affect, labile affect, suicidal thoughts, aggressive behaviour, insomnia, parkinsonism, akathisia, urinary retention | 5–58 | 150–550 | 50 | 3–14 days | Unknown | 2 years | No | - | Cyproheptadine |
| Durst (1999) | 3 | Case series | Withdrawal-associated psychosis | Abdominal pain, agitation, nausea and vomiting, hallucinations, delusions, suicidal ideation, insomnia | 100 | 300–400 | 100–425 | 2 days–1 week | 1–3 months | 3–6 months–1 year | Yes | Yes | None |
| Stanilla et al. (1997) | 3 | Case series | Withdrawal-associated psychosis | Agitation, hallucinations, delusions, delirium, diaphoresis, disturbed sleep, nausea and vomiting, nasal congestion | 100 | 250–400 | 50–250 | 1–5 days | Up to 3 weeks | 1–1.5 years | Yes | Yes | Benztropine |
| Ekblom et al. (1984) | 2 | Case series | Withdrawal-associated psychosis | Hallucinations | 100 | 300–450 | 300–450 | 1–2 days | Unknown | 1–2 years | No | - | None |
| Bastampillai et al. (2009) | 1 | Case report | Withdrawal-associated psychosis | Sleep disturbance, agitation, hostility, tangentiality, pressure of speech | 100 | 500 | 150–500 | Unknown | Unknown | 4 years | Yes | No | ECT |
| Wang et al. (2012) | 1 | Case report | Withdrawal-associated psychosis | Diaphoresis, difficulty swallowing | 100 | 450 | 250 | 1 day | 3 weeks | 3 months | Yes | Yes | None |

ECT, electroconvulsive therapy; EPSE, extrapyramidal side-effects; RCT, randomised controlled trial.
the suggestion that it is distinct from a relapse of the underlying psychotic illness (Table 1).12

**Cholinergic symptoms**

Cholinergic discontinuation symptoms, also known as ‘cholinergic rebound’, are characterised by a range of psychiatric and somatic clinical features including nausea, vomiting, confusion, insomnia and dystonia,35,36 which are thought to arise as a result of overactivity of the cholinergic system (Table 2). Several case reports have described the onset of cholinergic symptoms following clozapine discontinuation.31,34,35,37–41 These cases suggest that symptoms appear within a few days and continue for several weeks34,42–45; however studies in other antipsychotics suggest that symptoms may continue for longer.11 Furthermore, cholinergic rebound has been reported in patients on a range of doses of clozapine, including doses as low as 50 mg per day.37

Cholinergic rebound is not isolated to antipsychotics and has been associated with the discontinuation of a range of central nervous system medications, including tricyclic antidepressants and anti-parkinsonian drugs.36,42,46–50 Common to all the drugs associated with cholinergic rebound is a close affinity toward cholinergic receptors. The most likely mechanism underlying cholinergic rebound is the upregulation of muscarinic acetylcholine receptors due to prolonged exposure of clozapine, leading to super-sensitivity after discontinuation (Table 2).36,51

**Catatonia**

Catatonia is a psychomotor disorder characterised by a range of psychomotor features including stupor, posturing and echo phenomena.52 Catatonia is associated with a range of psychiatric disorders, such as depression and schizophrenia, as well as non-psychiatric disorders such as autoimmune encephalitis and withdrawal states. Several case reports have described the acute onset of catatonia following the withdrawal of clozapine (Table 3). This has typically been reported in the context of stopping clozapine abruptly.

The prevalence of clozapine-withdrawal-induced catatonia is unknown; however, a recent systematic review identified 20 reported cases in the literature.59 It has been observed predominantly in patients treated with clozapine for several years and without a history of catatonia. Symptoms generally emerge within a week of clozapine discontinuation.59 Interestingly, catatonia is not associated with the discontinuation of other antipsychotics, which may suggest that the unique pharmacology of clozapine plays an important role. In contrast, withdrawal catatonia has been shown to occur with other medications, most notably benzodiazepines. The mechanisms underlying clozapine-withdrawal-induced catatonia are not fully understood; however, hypactivity of the GABAergic system is strongly implicated in the emergence of catatonia. Clozapine does not have a direct effect upon the GABA system (unlike benzodiazepines); however, prolonged use has been shown to lead to GABA receptor adaptation and a reduction in GABAergic effects (Table 3).60

**Serotonergic symptoms**

Serotonergic discontinuation symptoms (Table 4) including agitation, diaphoresis, clonus and hyperreflexia have been described in a small group of patients following the cessation of clozapine61,62; however, the incidence is unknown. Case report evidence suggests that clozapine-induced serotonergic symptoms can arise in the presence or absence of concomitant serotonergic medications.61–63 Symptoms have been described as typically appearing within a few days of clozapine discontinuation.62

Serotonergic discontinuation symptoms are not unique to clozapine and have been described in other antipsychotics, particularly those with 5-HT2A antagonistic properties, such as aripiprazole and quetiapine.64,65 However, serotonergic discontinuation symptoms appear to be associated more closely with clozapine, which may reflect the degree of affinity toward serotonergic receptors. The mechanism by which clozapine discontinuation induces these symptoms is not clear; however, it has been postulated to relate to clozapine’s direct effect on serotonergic receptors. Clozapine is a potent 5-HT2A antagonist and prolonged use may lead to an upregulation of serotonin receptors, resulting in super-sensitivity (Table 4).62

**Discussion**

A review of the literature suggests that clozapine discontinuation is associated with an array of withdrawal symptoms with important clinical implications. There is evidence for the existence of four groups of withdrawal symptoms:
Table 2. Cholinergic withdrawal symptom studies.

| Study                        | Patients discontinued on clozapine | Study design | Withdrawal symptom group | Withdrawal symptoms | Patients with withdrawal symptoms (%) | Highest clozapine dose/day (mg) | Clozapine dose before cessation (mg) | Time to onset of withdrawal symptoms | Withdrawal symptoms duration | Length of clozapine treatment | Clozapine restarted | Symptoms resolved when clozapine restarted | Other medications to treat withdrawal symptoms |
|------------------------------|----------------------------------|--------------|--------------------------|---------------------|---------------------------------------|---------------------------------|-------------------------------------|-----------------------------------|-----------------------------------|--------------------------------|---------------------|-----------------------------------------------|------------------------------------------------|
| Shiovitz et al. (1996)       | 28                               | Bioequivalence| Cholinergic withdrawal symptoms/ Withdrawal-associated psychosis | Agitation, headache, nausea, dystonia, vomiting, diarrhoea, psychosis | 60                                    | 200                              | 200                                | 1-2 days                          | Up to 7 days                      | 26 days             | No                               | -                                             |
| Ahmed et al. (1998)          | 4                                | Case Series  | Cholinergic withdrawal symptoms | Hallucinations, restlessness, diaphoresis, dystonia | 100                                  | 350-500                         | 250-500                            | 5 days – 2 weeks                  | Over 6 months                     | 2 months – 3 years | Yes                             | Yes                                           |
| Poyurovsky et al. (1998)     | 2                                | Case Series  | Cholinergic withdrawal symptoms | Vocal and motor tics, OCD | 50-100                              | 300-500                         | 150-300                            | 1-2 weeks                         | 2 weeks                          | 6 months – 3 years | Yes                             | Yes                                           |
| Delassus-Guenault et al. (1999) | 2                               | Case Series  | Cholinergic withdrawal symptoms | Nausea and vomiting, diaphoresis, hypertonia, bronchial obstruction, agitation, anxiety, enuresis | 100                                  | 700-800                         | 100                                | 2 days                            | 2 weeks                          | 3 – 4 years       | Yes                             | -                                             |
| Mondhekar and Duggal (2006)  | 1                                | Case report   | Cholinergic withdrawal symptoms | Oculogyric crisis | 100                                  | 300                             | 300                                | 2 days                            | 2 days                           | 6 weeks            | Yes                             | Yes                                           |
| Steed et al. (1996)          | 1                                | Case report   | Cholinergic withdrawal symptoms | Insomnia, restlessness, chills and chattering of teeth | 100                                  | 250                             | 75                                 | 1 day                             | 1 week                          | 2 years            | Yes                             | Yes                                           |
| Sarma et al. (2016)          | 1                                | Case Report   | Cholinergic withdrawal symptoms | Oculogyric crisis, limb-axial dystonia | 100                                  | 400                             | 400                                | 5 days                            | Unknown                         | 6 months           | Yes                             | Yes                                           |
| Galova et al. (2019)         | 1                                | Case report   | Cholinergic withdrawal symptoms/ Withdrawal-associated catatonia | Nausea, sweating, hypertension, tachycardia, catatonia | 100                                  | 50                              | 50                                 | 3 days                            | 20 days                         | 2 months           | Yes                             | Yes                                           |
| Berecz et al. (2000)         | 1                                | Case report   | Cholinergic withdrawal symptoms | Anxiety, nervousness, tension, hallucinations, nausea, sweating | 100                                  | 300                             | Unknown                            | 16 days                          | 26 days                         | 5 years            | Yes                             | None                                          |

OCD, obsessive compulsive disorder.
Table 3. Withdrawal catatonia studies.

| Study                        | Patients withdrawn on clozapine | Study design | Withdrawal symptom group | Withdrawal symptoms                                      | Patients with withdrawal symptoms (%) | Highest clozapine dose/day (mg) | Clozapine dose before cessation (mg) | Time to onset of withdrawal symptoms | Withdrawal symptoms duration | Length of clozapine treatment | Clozapine restarted | Symptoms resolved when clozapine restarted | Other medications to treat withdrawal symptoms |
|------------------------------|--------------------------------|--------------|---------------------------|-----------------------------------------------------------|---------------------------------------|-----------------------------------|------------------------------------|---------------------------------------|-------------------------------------|-------------------------------|--------------------------|-------------------------------------------|--------------------------------------------------|
| Parsa et al. (1993)          | 1                              | Case report  | Withdrawal-associated catatonia/Withdrawal-associated psychosis | Catatonia, hallucinations, diaphoresis, fever, hypertension, tachycardia, tachypnoea | 100                                  | 400                                | 225                                | 1 week                                | 6 weeks                             | 5 months                    | No                       | -                                        | Meliperone, Loxapine                                   |
| Lee and Robertson (1997)     | 1                              | Case report  | Withdrawal-associated catatonia/Withdrawal-associated psychosis | Catatonia, thought disorder                               | 100                                  | 350                                | 350                                | 1.5 days                              | 3 weeks                             | 14 months                   | Yes                      | Yes                                      | None                                               |
| Yeh et al. (2004)            | 1                              | Case report  | Withdrawal-associated catatonia/Serotonin withdrawal symptoms | Catatonia, hallucinations, diaphoresis, facial flushing, bradycardia, tachycardia | 100                                  | 400                                | 400                                | <1 week                               | 1 week                              | 6 years                     | Yes                      | Yes                                      | Trihexyphenidyl                                                 |
| Hung et al. (2006)           | 1                              | Case report  | Withdrawal-associated catatonia/Withdrawal-associated psychosis | Catatonia, hallucinations, delusions                      | 100                                  | 500                                | 500                                | 2 weeks                               | Unknown                             | Unknown                     | Yes                      | Yes                                      | None                                               |
| Kalogeropoulou et al. (2007) | 1                              | Case report  | Withdrawal-associated catatonia/Withdrawal-associated psychosis | Catatonia, disorganized speech and behaviour, fever       | 100                                  | 350                                | 350                                | <1 week                               | Unknown                             | 10 years                    | Yes                      | Yes                                      | None                                               |
| Bastianpillai et al. (2009)  | 1                              | Case report  | Withdrawal-associated catatonia/Serotonin withdrawal symptoms | Catatonia, fever, diaphoresis, fluctuating blood pressure | 100                                  | 150                                | 150                                | 3 days                                | Unknown                             | 4 years                     | No                       | -                                        | ECT                                                |
| Thanasan and Jambunathan (2010) | 1                              | Case report  | Withdrawal-associated catatonia/Serotonin withdrawal symptoms | Catatonia, hallucinations, delusions, fever, fluctuating blood pressure, tachycardia | 100                                  | 200                                | 200                                | 1 week                               | 12 days                             | 5 years                     | No                       | -                                        | Bromocriptine, anticholinergic, diazepam          |
| Wadekar and Syed (2010)      | 1                              | Case report  | Withdrawal-associated catatonia | Catatonia                                              | 100                                  | 550                                | 550                                | 5 days                                | 1 week                              | Unknown                     | Yes                      | Yes                                      | None                                               |
| Dhillon et al. (2011)        | 1                              | Case report  | Withdrawal-associated catatonia/Withdrawal-associated psychosis | Catatonia, psychosis                                     | 100                                  | 400                                | 400                                | Unknown                              | Unknown                             | 16 years                    | No                       | -                                        | ECT, Aripiprazole                                              |
| Kanagasundram and Chengappa (2011) | 1                              | Case report  | Withdrawal-associated catatonia/Withdrawal-associated psychosis/Cholinergic withdrawal symptoms | Catatonia, hallucinations, delusions, fever              | 100                                  | 400                                | 400                                | Unknown                              | Unknown                             | 7 years                     | No                       | -                                        | Amisulpride                                                   |
| Kumar et al. (2011)          | 1                              | Case report  | Withdrawal-associated catatonia | Catatonia                                              | 100                                  | 250                                | 250                                | 2 days                                | Unknown                             | 3 months                   | No                       | -                                        | Lorzapam, ECT                                              |
| Cerit et al. (2012)          | 1                              | Case report  | Withdrawal-associated catatonia/Cholinergic withdrawal symptoms | Catatonia, hallucinations, delusions, fever tachycardia | 100                                  | 200                                | 200                                | 5 days                                | 7 days                              | 10 years                    | Yes                      | Yes                                      | Lorzapam                                                   |
### Table 3. (Continued)

| Study | Patients discontinued on clozapine | Study design | Withdrawal symptom group | Withdrawal symptoms | Patients with withdrawal symptoms (%) | Highest clozapine dose/day (mg) | Clozapine dose before cessation (mg) | Time to onset of withdrawal symptoms | Withdrawal symptoms duration | Clozapine re-started | Symptoms resolved when clozapine re-started | Other medications to treat withdrawal symptoms |
|-------|-----------------------------------|-------------|--------------------------|---------------------|--------------------------------------|-------------------------------|----------------------------------|--------------------------------------|--------------------------------------|-------------------------------|-----------------------------------------------|------------------------------------------------|
| Wang et al. (2012) | 1 | Case report | Withdrawal-associated catatonia/Withdrawal-associated psychosis | Catatonia, hallucinations, delusions | 100 | 200 | 200 | Unknown | Unknown | 8 years | Yes | Yes | None |
| Erol et al. (2013) | 1 | Case report | Withdrawal-associated catatonia/Serotonin withdrawal symptoms | Catatonia, hallucinations, delusions, fever, tachycardia, labile blood pressure, diaphoresis | 100 | 225 | 150 | 5 days | Unknown | 4 years | No | - | ECT |
| Koch et al. (2013) | 1 | Case report | Withdrawal-associated catatonia/Withdrawal-associated psychosis | Catatonia, hallucinations, fever | 100 | 250 | 250 | 14 days | 4 weeks | 6 months | No | - | Olanzapine, Lorazepam, ECT |
| Ariyasinghe and Abeyasinghe (2014) | 1 | Case report | Withdrawal-associated catatonia | Catatonia | 100 | 400 | Unknown | Unknown | 4 weeks | 10 years | Yes | Yes | None |
| Saddawi-Konefka et al. (2014) | 1 | Case report | Withdrawal-associated catatonia | Catatonia | 100 | Unknown | Unknown | 7 days | 2 weeks | Unknown | No | - | ECT |
| Koychev et al. (2016) | 1 | Case report | Withdrawal-associated catatonia | Catatonia | 100 | 300 | 300 | 4 days | 1 week | 5 weeks | No | - | Lorazepam |
| Ingole et al. (2017) | 1 | Case report | Withdrawal-associated catatonia | Catatonia, autonomic instability | 100 | 200 | 200 | 7 days | 4 weeks | Unknown | No | - | Lorazepam |
| Bilbily et al. (2017) | 1 | Case report | Withdrawal-associated catatonia | Catatonia | 100 | 400 | 400 | 10 days | 3 months | 7 years | Yes | Yes | Lorazepam |
| Kapulsky et al. (2019) | 1 | Case report | Withdrawal-associated catatonia | Catatonia, tachycardia, diaphoresis | 100 | Unknown | Unknown | 1 day | 4 days | 2 years | Yes | Yes | ECT, benzodiazepines |
| McGuire and Ruilly (2019) | 1 | Case report | Withdrawal-associated catatonia | Catatonia, mutism | 100 | Unknown | Unknown | Unknown | Unknown | 13 years | No | Yes | Lorazepam |

ECT, electroconvulsive therapy.
withdrawal-associated psychosis, cholinergic rebound, catatonia and serotonergic discontinuation symptoms. Furthermore, there is some evidence to suggest that these symptom groups are underpinned by distinct neural mechanisms. Clozapine has a complex pharmacological profile and induces a range of neuronal changes at the receptor level, especially when taken over an extended period. Evidence suggests that these neural adaptations underlie the emergence of withdrawal symptoms upon the discontinuation of clozapine.

What are the clinical implications of these findings? To date, there has been little guidance on how to safely discontinue clozapine to reduce the likeliness of withdrawal symptoms. This is likely to reflect, at least in part, a lack of awareness of this important topic alongside a sparse empirical basis. Clozapine discontinuation rates are estimated to be as high as 45% after 2 years. As such, there is a need for evidence-based guidelines on

---

**Table 4. Serotonin withdrawal symptom studies.**

| Study | Patients | Study design | Withdrawal symptom group | Other medications to treat withdrawal symptoms | Symptoms resolved when clozapine restarted |
|-------|----------|--------------|--------------------------|-----------------------------------------------|------------------------------------------|
| Zesiewicz et al. (2006) | 1 | Case report | Serotonin withdrawal symptoms | No | - |
| Srisuma et al. (2015) | 1 | Case report | Serotonin withdrawal symptoms | Cyproheptadine | No |
| Stevenson et al. (2013) | 1 | Case report | Serotonin withdrawal symptoms | No | Yes |
| Zerjav-Lacombe and Dewan (2002) | 1 | Case report | Serotonin withdrawal symptoms | None | No |

---

**Figure 1.** Clozapine withdrawal symptoms. A diverse range of symptoms have been reported; however, they can be broadly grouped according to the proposed underlying mechanism as (a) Withdrawal-associated psychosis, (b) Cholinergic discontinuation symptoms, (c) Serotonergic discontinuation symptoms and (d) Withdrawal-associated catatonia. Example symptoms within each group are listed. A patient may experience symptoms from one or more groups and symptom profile between groups may overlap.
the prevention and management of withdrawal syndromes associated with clozapine discontinuation.\textsuperscript{67,68} For example, in light of the evidence that withdrawal symptoms are likely to be underpinned by neuronal adaptions giving rise to receptor supersensitivity, when stopping clozapine, a slow taper (for example, over several months or years) may help to reduce the risk of withdrawal symptoms.\textsuperscript{69}

Guidelines would have at least two clear patient benefits. First, they would minimise the potential harms associated with clozapine withdrawal where discontinuation is indicated. Second, they may help to address clinicians’ reservations around offering clozapine to patients due to the risks associated with clozapine discontinuation. As a consequence, this may help reduce the underutilisation of clozapine in patients who may benefit.

Although withdrawal symptoms as a result of clozapine discontinuation have been described for over three decades,\textsuperscript{91} there remains a general lack of awareness of this phenomenon. This may result in clinicians misdiagnosing withdrawal symptoms for relapse of the underlying disorder.\textsuperscript{92} A potential consequence of this conflation is that it may lead to the conclusion that all patients should be maintained on clozapine indefinitely to prevent relapse. For example, it is plausible that some of the negative outcomes attributable to stopping clozapine\textsuperscript{1–3} are due to withdrawal-associated symptoms. Consequently, it may be that (at least in some patients) outcomes could be improved by simply optimising the discontinuation of clozapine to minimise the risk of withdrawal symptoms.

Further research is vital to better prevent, detect and treat clozapine withdrawal. Whilst there is evidence for withdrawal-associated psychosis, catatonia, cholinergic and serotonergic symptoms occurring as a result of clozapine cessation, there is a need for large prospective studies to further examine these withdrawal symptoms using standardised measures to address the many important outstanding questions. For example, from an epidemiological perspective, the prevalence of clozapine discontinuation withdrawal symptoms remains unknown. Risk factors for developing clozapine-withdrawal symptoms also remain largely unexplored. Whilst immediate cessation of clozapine is strongly associated with the emergence of withdrawal symptoms, to what extent other variables (such as clozapine dose, treatment duration and demographic variables) are important remains to be addressed. From a mechanistic perspective, it is not clear to what extent clozapine-induced withdrawal effects, such as withdrawal-associated psychosis and cholinergic rebound, overlap. From a preventative approach, the optimal tapering regime to minimise the risk of withdrawal symptoms has also not been explored empirically; however, studies are underway.\textsuperscript{93} Whilst a patient-rated scale to measure the success of antipsychotic and antidepressant discontinuation has recently been developed,\textsuperscript{94} the scale does not differentiate between the withdrawal symptoms described in this review, which may also be present with other psychotropics.\textsuperscript{11} Finally, the role of medication to prevent and treat clozapine-withdrawal symptoms is largely unknown. Such advances could greatly benefit patients at risk of developing withdrawal symptoms. Furthermore, the availability of such treatments would likely have the additional advantage of lowering the threshold for clinicians to trial clozapine in patients who may benefit.

Conflict of interest statement
The authors declare no conflict of interest.

Funding
This work was supported by the Psychiatry Research Trust.

ORCID iD
Graham Blackman \textsuperscript{ID} https://orcid.org/0000-0001-7025-8670

References
1. Wimberley T, MacCabe JH, Laursen TM, et al. Mortality and self-harm in association with clozapine in treatment-resistant schizophrenia. \textit{Am J Psychiatry} 2017; 174: 990–998.
2. Cho J, Hayes RD, Jewell A, et al. Clozapine and all-cause mortality in treatment-resistant schizophrenia: a historical cohort study. \textit{Acta Psychiatr Scand} 2019; 139: 237–247.
3. Siskind D, Reddel T, MacCabe JH, et al. The impact of clozapine initiation and cessation on psychiatric hospital admissions and bed days: a mirror image cohort study. \textit{Psychopharmacology} 2019; 236: 1931–1935.
4. Kane J, Honigfeld G, Singer J, et al. Clozapine for the treatment-resistant schizophrenic. A double-
5. Hippius H. A historical perspective of clozapine. *J Clin Psychiatry* 1999; 60 Suppl 12: 22–23.

6. Masuda T, Misawa F, Takase M, et al. Association with hospitalization and all-cause discontinuation among patients with schizophrenia on clozapine vs other oral second-generation antipsychotics: a systematic review and meta-analysis of cohort studies. *JAMA Psychiatry* 2019; 76: 1052–1062.

7. Takeuchi H, Borlido C, Sanches M, et al. Adherence to clozapine vs. other antipsychotics in schizophrenia. *Acta Psychiatr Scand* 2020; 142: 87–95.

8. Meyer J and Stahl S. *The clozapine handbook: Stahl's handbooks*. Cambridge, UK: Cambridge University Press; 2019.

9. Atkinson JM, Douglas-Hall P, Fischetti C, et al. Outcome following clozapine discontinuation: a retrospective analysis. *J Clin Psychiatry* 2007; 68: 1027–1030.

10. Shaker A and Jones R. Clozapine discontinuation in early schizophrenia: a retrospective case note review of patients under an early intervention service. *Ther Adv Psychopharmacol* 2018; 8: 3–11.

11. Brandt L, Bschor T, Henssler J, et al. Antipsychotic withdrawal symptoms: a systematic review and meta-analysis. *Front Psychiatry* 2020; 11: 569912.

12. Moncrieff J. Does antipsychotic withdrawal provoke psychosis? Review of the literature on rapid onset psychosis (supersensitivity psychosis) and withdrawal-related relapse. *Acta Psychiatrica Scandinavica* 2006; 114: 3–13.

13. Chouinard G, Samaha AN, Chouinard VA, et al. Antipsychotic-induced dopamine supersensitivity psychosis: pharmacology, criteria, and therapy. *Psychother Psychosom* 2017; 86: 189–219.

14. Borison RL, Diamond BI, Sinha D, et al. Clozapine withdrawal rebound psychosis. *Psychopharmacol Bull* 1988; 24: 260–263.

15. Meltzer HY, Lee MA, Ranjan R, et al. Relapse following clozapine withdrawal: effect of neuroleptic drugs and cyproheptadine. *Psychopharmacology* 1996; 124: 176–187.

16. Diamond BI and Borison RL. Basic and clinical studies of neuroleptic-induced supersensitivity psychosis and dyskinesia. *Psychopharmacol Bull* 1986; 22: 900–905.

17. Viguera AC, Baldessarini RJ, Hegarty JD, et al. Clinical risk following abrupt and gradual withdrawal of maintenance neuroleptic treatment. *Arch Gen Psychiatry* 1997; 54: 49–55.

18. Cosci F and Chouinard G. Acute and persistent withdrawal syndromes following discontinuation of psychotropic medications. *Psychother Psychosom* 2020; 89: 283–306.

19. Kimura H, Kanahara N, Sasaki T, et al. Risperidone long-acting injectable in the treatment of treatment-resistant schizophrenia with dopamine supersensitivity psychosis: results of a 2-year prospective study, including an additional 1-year follow-up. *J Psychopharmacol* 2016; 30: 795–802.

20. Seppälä N, Koviö C and Leinonen E. Effect of anticholinergics in preventing acute deterioration in patients undergoing abrupt clozapine withdrawal. *CNS Drugs* 2005; 19: 1049–1055.

21. Suzuki T, Kanahara N, Yamamaka H, et al. Dopamine supersensitivity psychosis as a pivotal factor in treatment-resistant schizophrenia. *Psychiatry Res* 2015; 227: 278–282.

22. Miodownik C, Lerner V, Kibari A, et al. The effect of sudden clozapine discontinuation on management of schizophrenic patients: a retrospective controlled study. *J Clin Psychiatry* 2006; 67: 1204–1208.

23. Ekblom B, Eriksson K and Lindström L.H. Supersensitivity psychosis in schizophrenic patients after sudden clozapine withdrawal. *Psychopharmacol* 1984; 83: 293–294.

24. Bastiampillai T, Forooziya F and Dhillon R. Clozapine-withdrawal catatonia. *Aust N Z J Psychiatry* 2009; 43: 283–284.

25. Wang BZ, Gupta A, Bastiampillai T, et al. Recurrent clozapine and lorazepam withdrawal psychosis with catatonia. *Aust N Z J Psychiatry* 2012; 46: 795–796.

26. Chouinard G and Chouinard V-A. New classification of selective serotonin reuptake inhibitor withdrawal. *Psychother Psychosom* 2015; 84: 63–71.

27. Chouinard G and Chouinard VA. Atypical antipsychotics: CATIE study, drug-induced movement disorder and resulting iatrogenic psychiatric-like symptoms, supersensitivity rebound psychosis and withdrawal discontinuation syndromes. *Psychother Psychosom* 2008; 77: 69–77.

28. Dossenbach MRK, Beuzen JN, Avnon M, et al. The effectiveness of olanzapine in treatment-refractory schizophrenia when patients are nonresponsive to or unable to tolerate clozapine. *Clin Ther* 2000; 22: 1021–1034.
29. Mizuno Y, McCutcheon RA, Brugger SP, et al. Heterogeneity and efficacy of antipsychotic treatment for schizophrenia with or without treatment resistance: a meta-analysis. *Neuropsychopharmacology* 2020; 45: 622–6231.

30. Lin C-C, Chiu H-J, Chen J-Y, et al. Switching from clozapine to zotepine in patients with schizophrenia. *J Clin Psychopharmacol* 2013; 33: 211–214.

31. Tollefson GD, Dellva MA, Mattler CA, et al. Controlled, double-blind investigation of the clozapine discontinuation symptoms with conversion to either olanzapine or placebo. The Collaborative Crossover Study Group. *J Clin Psychopharmacol* 1999; 19: 435–443.

32. Lu ML, Pan JJ, Teng HW, et al. Metoclopramide-induced supersensitivity psychosis. 2002; 36: 1387–1390.

33. Kent TA and Wilber RD. Reserpine withdrawal psychosis: the possible role of denervation supersensitivity of receptors. *J Nerv Ment Dis* 1982; 170: 502–504.

34. Durst R, Teitelbaum A, Katz G, et al. Withdrawal from clozapine: the “rebound phenomenon”. *Isr J Psychiatry Relat Sci* 1999; 36: 122–128.

35. Stanilla JK, de Leon J and Simpson GM. Clozapine withdrawal resulting in delirium with psychosis: a report of three cases. *J Clin Psychiatry* 1997; 58: 252–255.

36. Luchins DJ, Freed WJ and Wyatt RJ. The role of cholinergic supersensitivity in the medical symptoms associated with withdrawal of antipsychotic drugs. *Am J Psychiatry* 1980; 137: 1395–1398.

37. Galova A, Berney P, Desmeules J, et al. A case report of cholinergic rebound syndrome following abrupt low-dose clozapine discontinuation in a patient with type I bipolar affective disorder. *BMC Psychiatry* 2019; 19: 73.

38. de Leon J, Stanilla JK, White AO, et al. Anticholinergics to treat clozapine withdrawal. *J Clin Psychiatry* 1994; 55: 119–120.

39. Yeh AW, Lee JW, Cheng TC, et al. Clozapine withdrawal catatonia associated with cholinergic and serotonergic rebound hyperactivity: a case report. *Clin Neuropharmacol* 2004; 27: 216–218.

40. Shiovitz TM, Welke TL, Tigel PD, et al. Cholinergic rebound and rapid onset psychosis following abrupt clozapine withdrawal. *Schizophr Bull* 1996; 22: 591–565.

41. Simpson GM, Lee JH and Shrivastava RK. Clozapine in tardive dyskinesia. *Psychopharmacology* 1978; 56: 75–80.

42. Dilsaver SC, Kronfol Z, Sackellaes JC, et al. Antidepressant withdrawal syndromes: evidence supporting the cholinergic overdrive hypothesis. *J Clin Psychopharmacol* 1983; 3: 157–164.

43. Ahmed S, Chengappa KN, Naidu VR, et al. Clozapine withdrawal-emergent dystonias and dyskinesias: a case series. *J Clin Psychiatry* 1998; 59: 472–477.

44. Vasile D, Vasiliu O, Gheorghe M, et al. Psychotropic drugs discontinuation syndromes in clinical practice. *BMJ* 2006; 9: 38–41.

45. Wang W, Wen H and Sheng J. Malignant syndrome or withdrawal reaction? *Shanghai Arch Psychiatry* 2016; 28: 227–229.

46. Xu L and Krishnaswamy S. Switch-associated adverse events: focus on olanzapine. *Australas Psychiatry* 2018; 26: 635–639.

47. Nayudu SK and Scheftner WA. Case report of withdrawal syndrome after olanzapine discontinuation. *J Clin Psychopharmacol* 2000; 20: 489–490.

48. Ganguli R, Brar JS, Mahmoud R, et al. Assessment of strategies for switching patients from olanzapine to risperidone: a randomized, open-label, rater-blinded study. *BMC Med* 2008; 6: 17.

49. Greenberg LM and Roth S. Differential effects of abrupt versus gradual withdrawal of chlorpromazine in hospitalized chronic schizophrenic patients. *Am J Psychiatry* 1966; 123: 221–226.

50. Melnyk W, Worthington A and Laverty S. Abrupt withdrawal of chlorpromazine and thioridazine from schizophrenic in-patients. *Can J Psychiatry* 1966; 123: 221–226.

51. Eppel AB and Mishra R. The mechanism of neuroleptic withdrawal. *Can J Psychiatry* 1984; 29: 508–509.

52. Rogers JP, Pollak TA, Blackman G, et al. Catatonia and the immune system: a review. *Lancet Psychiatry* 2019; 6: 620–630.

53. Poyurovsky M, Bergman Y, Shoshani D, et al. Emergence of obsessive – compulsive symptoms and tics during clozapine withdrawal. *Clin Neuropharmacol* 1998; 21: 97–100.

54. Delassus-Guenault N, Jegouzo A, Odou P, et al. Clozapine–olanzapine: A potentially dangerous switch. A report of two cases. *J Clin Pharmacol Ther* 1999; 24: 191–195.

55. Mendhekar DN and Duggal HS. Clozapine-induced tardive dyskinesia and hypothyroidism. *J Neuropsychiatry Clin Neurosci* 2006; 18: 245–246.
56. Staedt J, Stoppe G, Hajak G, et al. Rebound insomnia after abrupt clozapine withdrawal. *Eur Arch Psychiatry Clin Neuropsy* 1996; 246: 79–82.

57. Sarma S, Chetia D, Raha B, et al. Clozapine withdrawal emergent dystonia, oculogyric crisis and rebound psychosis in a single patient. *Ther Adv Psychopharmacol* 2016; 145–146.

58. Berecz R, Glaub T, Kellermann M, et al. Clozapine withdrawal symptoms after change to sertindole in a schizophrenic patient. *Pharmacopsychiatry* 2000; 33: 42–44.

59. Lander M, Bastiampillai T and Sareen J. Review of withdrawal catatonia: what does this reveal about clozapine? *Transl Psychiatry* 2018; 8: 139.

60. Hirjak D, Northoff G, Taylor SF, et al. GABA B receptor, clozapine, and catatonia—a complex triad. *Molecular Psychiatry*. 2020; 1–2. https://doi.org/10.1038/s41380-020-00889-y

61. Stevenson E, Schembri F, Green DM, et al. Serotonin syndrome associated with clozapine withdrawal. *JAMA Neurol* 2013; 70: 1054.

62. Zerjav-Lacombe S and Dewan V. Possible serotonin syndrome associated with clomipramine after withdrawal of clozapine. *Ann Pharmacother* 2001; 35: 180–182.

63. Zesiewicz TA, Borra S and Hauser RA. Clozapine withdrawal symptoms in a Parkinson’s disease patient. *Mov Disord* 2002; 17: 1365–1367.

64. Sansone RA and Sawyer RJ. Aripiprazole withdrawal: a case report. *Innov Clin Neurosci* 2013; 10: 10.

65. Ahmad MT, Yip CW and Prakash KM. Reversible hyperkinetic movement disorder related to quetiapine withdrawal: a case report. *Proc Singapore Healthc* 2010; 19: 347–348.

66. Legge SE, Hamshere M, Hayes RD, et al. Reasons for discontinuing clozapine: a cohort study of patients commencing treatment. *Schizopr Res* 2016; 174: 113–119.

67. Breen EG. Clozapine withdrawal syndrome. *BJPsych Bull* 2017; 41: 366.

68. Cooper RE, Grünwald LM and Horowitz M. The case for including antipsychotics in the UK NICE guideline: “Medicines associated with dependence or withdrawal symptoms: safe prescribing and withdrawal management for adults”. *Psychosis* 2020; 12: 89–93.

69. Horowitz MA, Murray RM and Taylor D. Tapering antipsychotic treatment. *JAMA Psychiatry* 2021; 78: 125–126.

70. Parsa MA, Al-Lahham YH, Ramirez LF, et al. Prolonged psychotic relapse after abrupt clozapine withdrawal. *J Clin Psychopharmacol* 1993; 13: 154.

71. Lee JW and Robertson S. Clozapine Withdrawal Catatonia and Neuroleptic Malignant Syndrome: A Case Report. *Ann Clin Psychiatry* 1997; 9: 165.

72. Hung YY, Yang PS and Huang TL. Clozapine in schizophrenia patients with recurrent catatonia: Report of two cases. *Psychiatry Clin Neurosci* 2006; 60: 256–258.

73. Kalogерopoulou C, Leotsakou I, Fotara C, et al. Catatonia after abrupt discontinuation of chronic clozapine treatment. *Eur Psychiatry* 2007; 22: S120–S121.

74. Bastiampillai T, Juneja V and Nance MJ. Clozapine rebound mania. *Aust N Z J Psychiatry* 2014; 48: 98–99.

75. Thanasan S and Jambunathan ST. Clozapine withdrawal catatonia or lethal catatonia in a schizoaffective patient with a family history of Parkinson’s disease. *Afr J Psychiatry (Johannesbg)* 2010; 13: 402–404.

76. Wadekar M and Syed S. Clozapine-withdrawal catatonia. *Psychosomatics* 2010; 51: 355–355.e2.

77. Dhillon R, Bastiampillai T, Tee K, et al. Clozapine and associated QTc prolongation. *Aust N Z J Psychiatry* 2011; 45: 1098–1099.

78. Kanagasundram S and Chengappa K. Meningoencephalitis or clozapine withdrawal catatonia or both in a patient with schizophrenia. *Acta Neuropsychiatr* 2011; 23: 85–87.

79. Kumar S, Sur S and Singh A. Catatonia following abrupt stoppage of clozapine. *Aust N Z J Psychiatry* 2011; 45: 499–499.

80. Cerit C, Tuzun B, Akpinar E, et al. Clozapine withdrawal catatonia refractory to ECT: A case report. *Klinik Psikofarmakoloji Bülteni-Psychopharmacol Bull* 2012; 22: 275–277.

81. Erol A, Putgül G, Sert E, et al. Clozapin kullanıma bağlı nöroleptik malign sendrom ve ardından katatoni: Olgu sunumu [Clozapine-associated neuroleptic malignant syndrome followed by catatonia: A case report]. *Turk Psikiyatri Derg* 2013; 24: 140–144.

82. Koch A, Reich K, Wielopolski J, et al. Catatonic Dilemma in a 33-Year-Old Woman: A Discussion. *Case Rep Psychiatry* 2013; 2013: 3. https://doi.org/10.1155/2013/542303

83. Ariyasinghe D and Abeyasinghe R. Catatonia following abrupt discontinuation of clozapine. *Sri Lanka Journal of Psychiatry* 2014; 5: 27–28.
84. Saddawi-Konefka D, Berg SM, Nejad SH, et al. Catatonia in the ICU. An important and underdiagnosed cause of altered mental status. A case series and review of the literature. Crit Care Med 2014; 42: e234–e241.

85. Koychev I, Hadjiphilippou S, Lynch J, et al. Sudden-onset catatonia following clozapine withdrawal: A case report. J Clin Psychiatry 2016; 77: e899.

86. Ingole A, Bastiampillai T and Tibrewal P. Clozapine withdrawal catatonia, psychosis and associated neuroleptic malignant syndrome. Asian J Psychiatr 2017; 30: 96–97.

87. Bilbily J, McCollum B and de Leon J. Catatonia secondary to Sudden Clozapine Withdrawal: A case with three repeated episodes and a literature review. Case Rep Psychiatry 2017; 2017: 11. https://doi.org/10.1155/2017/2402731

88. Kapulsky L, Greiner MG, Daniels JE, et al. Clozapine Discontinuation and Malignant Catatonia: A Case Report. Psychosomatics 2019; 60: 75–79.

89. McGuire E, Reilly M. Clozaril Withdrawal Induced Catatonia. Ir Med J 2019; 112: 938.

90. Srisuma S, Hoyte CO, Wongvisavakorn S, et al. Serotonin syndrome precipitated by sertraline and discontinuation of clozapine, Clinical Toxicology 2015; 53: 840–841.

91. Shore D, Matthews S, Cott J, et al. NIMH activities: clinical implications of clozapine discontinuation: report of an NIMH workshop. Schizophr Bull 1995; 21: 333–338.

92. Moncrieff J, Gupta S and Horowitz MA. Barriers to stopping neuroleptic (antipsychotic) treatment in people with schizophrenia, psychosis or bipolar disorder. Ther Adv Psychopharmacol 2020; 10: 2045125320937910.

93. Moncrieff J, Lewis G, Freemantle N, et al. Randomised controlled trial of gradual antipsychotic reduction and discontinuation in people with schizophrenia and related disorders: the RADAR trial (Research into Antipsychotic Discontinuation and Reduction). BMJ Open 2019; 9: e030912.

94. Lincoln TM, Sommer D, Könemund M, et al. A rating scale to inform successful discontinuation of antipsychotics and antidepressants. Psychiatry Res 2021; 298: 113768.