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Clozapine discontinuation withdrawal symptoms in schizophrenia

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***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 likeliness 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

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Introduction

Clozapine is an atypical antipsychotic that has been shown to reduce hospitalisation, mortality and risk of suicide in patients with treatment-resistant schizophrenia.[1–3] Furthermore, studies – albeit mostly with relatively short follow up – suggest that clozapine is the only medication effective in treatment-resistant schizophrenia.[4] Clozapine is an antipsychotic of the dibenzodiazepine class and has a complex pharmacological profile.[5] It is a potent antagonist of H_1, M_1, 5-HT_{2B}, 5-HT_{2C} and α_1 receptors; a potent inverse agonist of 5-HT_{2A} receptors; and a relatively weak antagonist at D_1, D_2, D_3 and D_5 receptors, with higher affinity for D_4 receptors.[6,7]

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.[8] Other indications for stopping clozapine include a lack of clinical efficacy, inadequate adherence to treatment or monitoring requirements and patient preference.[8] In some circumstances, clozapine has been discontinued successfully after symptom remission.[9,10]

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 psychotic, autonomic, gastrointestinal and psychomotor.[11] 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.[11] Whilst epidemiological evidence is limited, withdrawal symptoms have been reported most often in association with abrupt discontinuation.[11] 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.

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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'.[12,13] 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[14–16]; 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 likeliness 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	Length of clozapine treatment	Clozapine restarted	Symptoms resolved when clozapine restarted	Other medication to treat withdrawal symptoms
Tollefson *et al.*(1999)[31]	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.* (2005)[20]	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)[15]	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 *et al.* (1999)[34]	3	Case series	Withdrawal-associated psychosis	Abdominal pain, agitation, nausea and vomiting, hallucinations, delusions, suicidal ideation, insomnia	100	300-600	100-425	2 days-1 week	1 – 3 months	3 months-1 year	Yes	Yes	None
Stanilla *et al.* (1997)[35]	3	Case series	Withdrawal-associated psychosis	Agitation, hallucinations, delusions, delirium, diaphoretic, disturbed sleep, nausea and vomiting, nasal congestion	100	250-600	50-250	1-5 days	Up to 3 weeks	1-1.5 years	Yes	Yes	Benztropine
Ekblom *et al.* (1984)[23]	2	Case series	Withdrawal-associated psychosis	Hallucinations	100	300-450	300-450	1- 2 days	Unknown	1- 2 years	No	-	None
Bastiampillai *et al.* (2009)[24]	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)[25]	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 weeks[34,42–45]; 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, hypoactivity 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

Serotoninergic discontinuation symptoms (Table 4) including agitation, diaphoresis, clonus and hyperreflexia have been described in a small group of patients following the cessation of clozapine[61,62]; 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)[36]	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	-	Trihexyphenidyl Lorazepam
Ahmed *et al.* (1998)[39]	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	Benztropine, Trihexyphenidyl, Olanzapine, Lorazepam
Poyurovsky *et al.* (1998)[53]	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	None
Delassus-Guenault *et al.* (1999)[54]	2	Case Series	Cholinergic withdrawal symptoms	Nausea and vomitting, diaphoresis, hypersialorrhea, bronchial obstruction, agitation, anxiety, enuresis	100	700-800	100	2 days	2 months	3 – 4 years	No	-	Olanzapine, Trihexyphenidyl
Mendhekar and Duggal (2006)[55]	1	Case report	Cholinergic withdrawal symptoms	Oculogyric crisis	100	300	300	2 days	2 days	6 weeks	Yes	Yes	None
Staedt *et al.* (1996)[56]	1	Case report	Cholinergic withdrawal symptoms	Insomnia, restlessness, chills and chattering of teeth	100	250	75	1 day	1 week	2 years	Yes	Yes	None
Sarma *et al.* (2016)[57]	1	Case Report	Cholinergic withdrawal symptoms	Oculogyric crisis, limb-axial dystonia	100	400	400	5 days	Unknown	6 months	Yes	Yes	Promethazine
Galova *et al.* (2019)[33]	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	Biperiden
Berecz *et al.* (2000)[58]	1	Case report	Cholinergic withdrawal symptoms	Anxiety, nervousness, tensions, hallucinations, nausea, sweating	100	300	Unknown	16 days	26 days	5 years	Yes	Yes	None

OCD, obsessive compulsive disorder.

Table 3. Withdrawal catatonia 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
Parsa *et al.* (1993)[70]	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	-	Melperone Loxapine
Lee and Robertson (1997)[71]	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)[39]	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)[72]	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)[73]	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
Bastiampillai *et al.* (2009)[74]	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)[75]	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)[76]	1	Case report	Withdrawal-associated catatonia	Catatonia	100	550	550	5 days	1 week	Unknown	Yes	Yes	None
Dhillon *et al.* (2011)[77]	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)[78]	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) [79]	1	Case report	Withdrawal-associated catatonia	Catatonia	100	250	250	2 days	Unknown	3 months	No	-	Lorazepam, ECT
Cerit *et al.* (2012)[80]	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	Lorazepam

(Continued)

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	Length of clozapine treatment	Clozapine restarted	Symptoms resolved when clozapine restarted	Other medications to treat withdrawal symptoms
Wang *et al.* (2012)[25]	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)[81]	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)[82]	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)[83]	1	Case report	Withdrawal-associated catatonia	Catatonia	100	400	Unknown	Unknown	4 weeks	10 years	Yes	Yes	None
Saddawi-Konefka *et al.* (2014)[84]	1	Case report	Withdrawal-associated catatonia	Catatonia	100	Unknown	Unknown	7 days	2 weeks	Unknown	No	–	ECT
Koychev *et al.* (2016)[85]	1	Case report	Withdrawal-associated catatonia	Catatonia	100	300	300	4 days	1 week	5 weeks	No	–	Lorazepam
Ingole *et al.* (2017)[86]	1	Case report	Withdrawal-associated catatonia	Catatonia, autonomic instability	100	200	200	7 days	4 weeks	Unknown	No	–	Lorazepam
Bilbily *et al.* (2017)[87]	1	Case report	Withdrawal-associated catatonia	Catatonia	100	400	400	10 days	3 months	7 years	Yes	Yes	Lorazepam
Kapulsky *et al.* (2019)[88]	1	Case report	Withdrawal-associated catatonia	Catatonia, tachycardia, diaphoresis	100	Unknown	Unknown	1 day	4 days	2 years	Yes	Yes	ECT, benzodiazepines
McGuire and Reilly (2019)[89]	1	Case report	Withdrawal-associated catatonia	Catatonia, mutism	100	Unknown	Unknown	Unknown	Unknown	13 years	No	Yes	Lorazepam

ECT, electroconvulsive therapy.

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.

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.[66] As such, there is a need for evidence-based guidelines on

Table 4. Serotonin 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
Zesiewicz *et al.* (2006)[63]	1	Case report	Serotonin withdrawal symptoms	Myoclonus, tremor, rigidity, hyperreflexia, stupor, confusion, agitation, restlessness	100	50	37.5	1 day	1 day	10 years	No	-	Cyproheptadine
Srisuma *et al.* (2015)[90]	1	Case report	Serotonin withdrawal symptoms	Agitation, fever, diaphoresis, tremor, restlessness, clonus, spasticity	100	50	50	3 days	1 week	1 month	No	-	Cyproheptadine
Stevenson *et al.* (2013)[51]	1	Case report	Serotonin withdrawal symptoms	Coma, hypersalivation, hyperreflexia, clonus	100	100	100	5 days	1 week	Unknown	Yes	Yes	Cyproheptadine
Zerjav-Lacombe and Dewan (2002)[62]	1	Case report	Serotonin withdrawal symptoms	Agitation, sweating, shivering, tremor, confusion	100	600	Unknown	1 day	2 weeks	5 years	Yes	(symptoms resolved before clozapine restarted)	None

the prevention and management of withdrawal syndromes associated with clozapine discontinuation.[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.[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,[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.[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[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.[93] Whilst a patient-rated scale to measure the success of antipsychotic and antidepressant discontinuation has recently been developed,[94] the scale does not differentiate between the withdrawal symptoms described in this review, which may also be present with other psychotropics.[11] Finally, the role of medication to prevent and treat clozapine-withdrawal symptom 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

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