Clinical Outcomes after Clozapine Discontinuation in Patients with Schizophrenia: A Systematic Review

Authors
Gentaro Miura[1], Kouhei Tanaka[2], Takashi Kemuriyama[3], Fuminari Misawa[2], Hiroyuki Uchida[4], Masaru Mimura[4], Hiroyoshi Takeuchi[4]

Affiliations
1 Oizumi Hospital, Tokyo, Japan
2 Yamanashi Prefectural Kita Hospital, Yamanashi, Japan
3 Asaka Hospital, Fukushima, Japan
4 Department of Neuropsychiatry, Keio University School of Medicine, Tokyo, Japan

Key words
cessation, clozapine, discontinuation, schizophrenia, treatment-resistant schizophrenia

received 24.01.2022
revised 12.03.2022
accepted 14.03.2022
published online 05.05.2022

Bibliography
Pharmacopsychiatry 2022; 55: 181–192
DOI 10.1055/a-1811-7318
ISSN 0176-3679

Georg Thieme Verlag, Rüdigerstraße 14,
70469 Stuttgart, Germany

Correspondence
Hiroyoshi Takeuchi, MD, PhD
Department of Neuropsychiatry
Keio University School of Medicine
35 Shinanomachi
Shinjuku-ku
160-8582 Tokyo
Japan
hirotak@dk9.so-net.ne.jp

ABSTRACT

Introduction Clozapine is the gold standard of treatment for patients with treatment-resistant schizophrenia. However, approximately 60 % of those patients do not respond to clozapine; moreover, clinical outcomes after clozapine discontinuation are unclear so far. Therefore, we conducted a systematic review to clarify the outcomes after clozapine discontinuation.

Methods A systematic literature search was conducted, using MEDLINE and Embase with the following keywords: (clozapine AND (cessation* OR cease* OR withdraw* OR discontinu* OR halt* OR stop* OR switch*) AND (schizophreni* OR schizoaffective)).

Results A total of 28 clinical studies from 27 articles were identified and included in this systematic review. Three randomized controlled trials reported worsening of psychiatric symptoms. In 10 single-arm studies, the results of worsening and improving psychiatric symptoms were inconsistent. In one large retrospective cohort study, clozapine rechallenge, olanzapine, and antipsychotic polypharmacy had lower rehospitalization rates compared to no medication after clozapine discontinuation. In the other 14 retrospective studies, the vast majority showed worsening of clinical status after clozapine discontinuation. Among five studies on clinical outcomes after clozapine rechallenge, four reported improvements in clinical status in more than half of patients who rechallenged clozapine. The remaining study reported that the clozapine discontinuation-rechallenge group had a worse remission assessment score than the clozapine discontinuation-no rechallenge group.

Discussion Clinical outcomes generally worsen after clozapine discontinuation. Clozapine rechallenge and olanzapine may be considered following clozapine discontinuation. The outcomes after clozapine discontinuation in clozapine non-responders remain inconclusive; therefore, well-designed studies are warranted.

Introduction

Approximately 30 % of patients with schizophrenia do not respond to antipsychotics, a condition called treatment-resistant schizophrenia (TRS) [1, 2]. TRS is not only a burden on the patient and caregiver but also a socioeconomic burden [3]. For TRS, clozapine is the gold standard of treatment [4, 5]; however, approximately 60 % of patients with TRS do not respond to clozapine [6], a condition referred to as clozapine-resistant schizophrenia (CRS). For CRS, augmentation strategies with other antipsychotics or electroconvulsive therapy (ECT) are currently recommended [7–10], which implies a continuation of clozapine treatment even for patients who fail to respond to clozapine. In the real world, however, a substantial number of patients discontinue clozapine treatment for various reasons, such as inefficacy, intolerance, physical complications, nonadher-

ence, and patient or clinician decision [11–13]. If outcomes after clozapine discontinuation are acceptable in patients with CRS, a clinician could choose to discontinue clozapine in a clinical setting. To assess whether clozapine should be discontinued if patients did not respond to clozapine, we conducted a systematic review of studies reporting clinical outcomes after discontinuation of clozapine treatment in patients with schizophrenia.

Methods

Literature search

A systematic literature search was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement, using MEDLINE (1946-) and Embase (1947-) through Ovid, and the following keywords were applied: (clozapine AND (cessation* OR cease* OR withdraw* OR discontinu* OR halt* OR stop* OR switch*) AND (schizophreni* OR schizoaffective)) and with limitations of "human" and "English" (last search: November 22, 2021).

Study selection

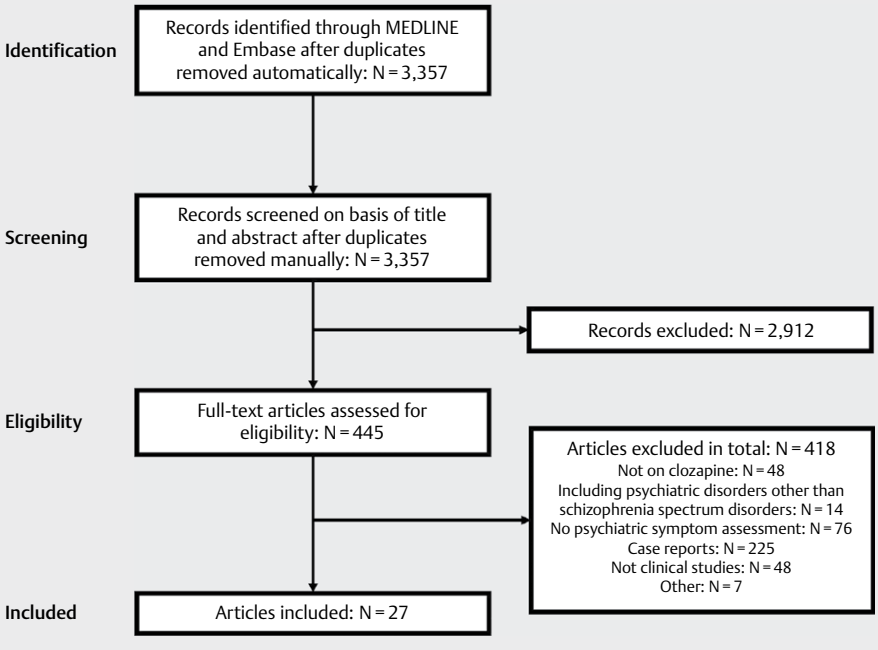
At least two of three authors (G.M., K.T., and T.K.) independently reviewed and selected clinical studies focusing on clozapine discontinuation. We included studies that reported clinical outcomes after clozapine discontinuation in patients with schizophrenia spectrum disorders (i. e., schizophrenia, schizophreniform disorder, and schizoaffective disorder). We excluded case reports and clinical studies that reported clozapine discontinuation but no clinical outcomes, such as psychopathological scales, suicidal activity, relapse, hospitalization, discharge, physical restrictions, and death. Any disagreements regarding the study selection were resolved by consensus with the senior author (H.T.).

Data extraction

The following information was extracted: study design, number of patients undergoing clozapine discontinuation, diagnosis, mean clozapine dose before clozapine discontinuation, mean clozapine treatment duration, reasons for clozapine discontinuation, strategy for clozapine discontinuation, follow-up duration after clozapine discontinuation, type of medication after clozapine discontinuation, clinical outcomes after clozapine discontinuation, clozapine rechallenge, and clinical outcomes after clozapine rechallenge. At least two of three authors (G.M., K.T., and T.K.) independently extracted the data. Any disagreements regarding the data extraction were resolved by consensus with the senior author (H.T.).

Results

A total of 28 clinical studies from 27 articles [11–37]were identified and included in this systematic review (▶ **Fig. 1**); these were three randomized controlled trials (RCTs) [13, 28, 37], 10 single-arm trials [11, 15, 21–23, 32, 33, 35–37], six retrospective cohort studies [17, 20, 24, 25, 31, 34], two mirror-image studies [26, 27], and seven retrospective studies [12, 14, 16, 18, 19, 29, 30] (▶ **Table 1**). The included studies were published between 1988–2021. The number of patients in each study was 106 in one RCT [13]; 190 in one retrospective study [12]; 1,008 in one mirror-image study [26]; 2,250 in one retrospective cohort study [17]; and small sample sizes (n < 100) for the remaining studies. All studies included



▶ **Fig. 1** PRISMA flow diagram of literature search.

▶ **Table 1** Summary of included studies: Clozapine treatment before discontinuation.

Author	Year	Study design	Number of patients receiving CLO DC	Diagnosis	Mean CLO dose before CLO DC	Mean CLO treatment duration	Reasons of CLO DC	Strategy of CLO DC
Tollefson et al.[13]	1999	Double-blind RCT	106	SSD	324 mg/day	NA	Inefficacy: n = 14/106 (13.2 %) Intolerance: n = 40/106 (37.7 %) Patient decision: n = 52/106 (49.1 %)	Tapering CLO at a maximum rate of 50 mg/day to a dose of 300 mg/day, and receiving either olanzapine 10 mg/day or placebo (2 to 12 days)
Lin et al.[28]	2013	Rater-blind RCT	35	SSD	NA	40.6 ± 25.5 months	Study design	Cross-titration (within 4 weeks)
Borison et al.[37]	1988	Open-label RCT	14	TRS	NA	6 weeks (fixed)	NA	Abrupt
Simpson et al.[21]	1974	Single-arm trial	9	SSD	NA	12 weeks	Study design	NA
Borison et al.[37]	1988	Single-arm trial	12	SSD	200 mg/day (fixed dose)	8 weeks (fixed)	NA	Abrupt
Kerepcic et al.[22]	1994	Single-arm trial	31	SSD	NA	average 18 months	Study design	NA
Meltzer et al.[11]	1996	Single-arm trial	83	SSD (n = 19), TRS (n = 64)	450 ± NA mg/day for SSD, NA for TRS	2 years for SSD (n = 7), 190 ± 158 days for SSD (n = 12), 438 ± 576 days for TRS (n = 14), 204 ± 21 days for TRS (n = 50)	Nonadherence: n = 10/19 (52.6 %) for SSD Intolerance: n = 2/19 (10.5 %) for SSD Study design: n = 7/19 (36.8 %) for SSD Nonadherence: n = 50/64 (78.1 %) for TRS Intolerance: n = 14/64 (21.9 %) for TRS	Tapering CLO without perphenazine, washout period, and then receiving APs: n = 9/19 (47.4 %) for SSD Tapering CLO with perphenazine, and then receiving APs: n = 8/19 (42.1 %) for SSD Abrupt: n = 2/19 (10.5 %) for SSD NA: n = 64/64 (100 %) for TRS
Still et al.[36]	1996	Single-arm trial	10	SSD	565 ± 156 mg/day	28.1 ± 14.8 months	Inefficacy or intolerance	Tapering CLO over ten days, and then receiving risperidone
Henderson et al.[35]	1998	Single-arm trial	19	SSD (n = 4), TRS (n = 15)	372 ± 160 mg/day	Olanzapine responder: 2.3 ± 1.3 years Olanzapine nonresponder: 3.9 ± 1.8 years	Inefficacy: n = 2/19 (10.5 %) Intolerance: n = 3/19 (15.8 %) Nonadherence: n = 1/19 (5.3 %) Patient decision: n = 13/19 (68.4 %)	Cross-titration
Littrell et al.[33]	2000	Single-arm trial	20	TRS	364 ± 160 mg/day	5.3 ± 2.5 years	Intolerance: n = NA Patient decision: n = NA	Cross-titration
Dossenbach et al.[32]	2000	Single-arm trial	45	TRS	426 ± 102 mg/day	244 days	Inefficacy: n = 41/45 (91.1 %) Intolerance: n = 11/45 (24.4 %)	Abrupt
Lindenmayer et al.[23]	2002	Single-arm trial	11	TRS	NA	NA	NA	Cross-titration (10 days)
Li et al.[15]	2013	Single-arm trial	68	SSD	NA	NA	NA	Cross-titration (2 to 4 weeks)
Dennis et al.[25]	1996	Retrospective cohort study	23	TRS	NA	NA	Inefficacy: n = 16/23 (69.6 %) Intolerance: n = 4/23 (17.4 %) Patient decision: n = 2/23 (8.7 %) Other: n = 1/23 (4.3 %)	NA

▶ **Table 1** Continued.

Author	Year	Study design	Number of patients receiving CLO DC	Diagnosis	Mean CLO dose before CLO DC	Mean CLO treatment duration	Reasons of CLO DC	Strategy of CLO DC
Mortimer[24]	1997	Retrospective cohort study	15	TRS	NA	NA	Inefficacy: n = 3/15 (20.0 %) Intolerance: n = 1/15 (6.7 %) Nonadherence: n = 2/15 (13.3 %) Patient decision: n = 1/15 (6.7 %) Other: n = 8/15 (53.3 %)	NA
Dickson et al.[34]	1998	Retrospective cohort study	11	TRS	NA	NA	Inefficacy: n = NA Intolerance: n ≥ 2/11 Nonadherence: n = NA Patient decision: n = NA	NA
Baldacchino et al.[19]	1998	Retrospective study	16	TRS	NA	NA	Inefficacy: n = 1/16 (6.3 %) Intolerance: n = NA Nonadherence: n = NA	NA
Drew et al.[31]	2002	Retrospective cohort study	10	SSD	NA	NA	NA	NA
Seppala et al.[30]	2005	Retrospective study	28	SSD	329 ± 150 mg/day	95.3 ± NA days	Withdrawal of CLO from the market	Abrupt
Miodownik et al.[18]	2006	Retrospective case-control study	43	TRS	358 ± 22 mg/day	NA	NA	Abrupt
Kapsali et al.[29]	2011	Retrospective study	9	SSD	NA	NA	NA	Abrupt
Mustafa et al.[12]	2014	Retrospective study	190	SSD	NA	NA	Inefficacy: n = 6/190 (3.6 %) Intolerance: n = 48/190 (25.3 %) Nonadherence: n = 105/190 (55.3 %) Clinician decision: n = 10/190 (5.3 %) Death: n = 19/190 (10.0 %) Other: n = 2/190 (1.1 %)	NA
Shaker et al.[27]	2018	Mirror-image study	25	TRS	NA	532 ± 455 days	Intolerance: n = 10/25 (40.0 %) Nonadherence: n = 11/25 (44.0 %) Patient decision: n = 4/25 (16.0 %)	NA
Siskind et al.[26]	2019	Mirror-image study	Early cessation (n = 547), late cessation (n = 461)	SSD	NA	NA	NA	NA
Luykx et al.[17]	2020	Retrospective cohort study	2,250	SSD	NA	NA	NA	NA
Li et al.[20]	2021	Retrospective cohort study	78	SSD	288 ± 112 mg/day	25.7 ± 8.9 years	NA	Cross-titration (about 2–3 months)

▲ **Table 1** Continued.

Author	Year	Study design	Number of patients receiving CLO DC	Diagnosis	Mean CLO dose before CLO DC	Mean CLO treatment duration	Reasons of CLO DC	Strategy of CLO DC
Murata et al.[14]	2021	Retrospective cohort study	30	TRS	226 ± 181 mg/day	599 ± 795 days	Inefficacy: n = 2/30 (6.7 %) Intolerance: n = 17/30 (56.7 %) Patient decision: n = 9/30 (30.0 %) Other: n = 2/30 (6.7 %)	NA
Watanabe et al.[16]	2021	Retrospective cohort study	CLO responder (n = 13), CLO nonresponder (n = 16)	TRS	227 ± 151 mg/day*	NA	Intolerance: n = 20/29 (69.0 %)* Other: n = 9/29 (31.0 %)*	NA

* Obtained from the authors; Abbreviations: CLO = clozapine, DC = discontinuation, NA = not available, RCT = randomized controlled trial, S = significant, SSD = schizophrenia spectrum disorders, TRS = treatment-resistant schizophrenia.

patients with schizophrenia spectrum disorders, 12 [14, 16, 18, 19, 23–25, 27, 32–34, 37]exclusively included patients with TRS, two [11, 35] included both patients with TRS and non-TRS, and 14 [12, 13, 15, 17, 20–22, 26, 28–31, 36, 37] did not clearly state whether patients had TRS or non-TRS (▶ **Table 1**).

Clozapine treatment before discontinuation

Among the 12 studies [11, 13, 14, 16, 18, 20, 30, 32, 33, 35–37] that described the mean ± SD dose of clozapine before discontinuation, the doses ranged from 200 ± 0 mg/day to 565 ± 156 mg/day and relatively low doses (< 400 mg/day) of clozapine were used in nine studies [13, 14, 16, 18, 20, 30, 33, 35, 37] (▶ **Table 1**). The mean duration of clozapine treatment varied considerably from weeks to years. Among the 18 studies [11–14, 16, 19, 21, 22, 24, 25, 27, 28, 30, 32–36] that stated reasons for clozapine discontinuation, we classified the reasons into the following six categories: inefficacy, intolerance, nonadherence, patient or clinician decision, study design, and other. Among the 15 studies [11, 13, 15, 18, 20, 23, 28–30, 32, 33, 35–37] that described a clozapine discontinuation strategy, six studies [18, 29, 30, 32, 37] reported abrupt discontinuation and nine studies [11, 13, 15, 20, 23, 28, 33, 35, 36] reported gradual discontinuation (▶ **Table 1**).

Antipsychotic treatment after clozapine discontinuation

Regarding the length of follow-up period after clozapine discontinuation, there was considerable variation from weeks to years. Among the 17 studies [11–17, 19, 20, 22, 23, 28, 31–33, 35, 36] that described the type of non-clozapine antipsychotics used after clozapine discontinuation, olanzapine was the most frequently used, and six studies [13, 19, 23, 32, 33, 35] exclusively used olanzapine (▶ **Table 1**). In one large-scale retrospective cohort study [17], antipsychotic polypharmacy was most frequently used after clozapine discontinuation, followed by olanzapine monotherapy. In the 12 studies [13–16, 18–20, 28, 32, 33, 35, 36] that described the mean ± SD dose of antipsychotics after clozapine discontinuation, the doses were as follows: risperidone (one study) at 8.0 ± 1.4 mg/day; olanzapine (six studies) at 16.5 ± 4.9 mg/day to 31.4 ± 16.8 mg/day; ziprasidone (one study) at 131 ± 34 mg/day; zotepine (one study) at 397 ± 76 mg/day; paliperidone (one study) at 8.2 ± 3.8 mg/day; clozapine (rechallenge, one study) at 462 ± 20 mg/day; and total chlorpromazine equivalent dose of antipsychotics (one study) at 1031 ± 498 mg/day (▶ **Table 1**).

Clinical outcomes after clozapine discontinuation

All three RCTs reported worsening of psychiatric symptoms. In 10 single-arm studies, six [11, 21, 22, 35–37] reported worsening of psychiatric symptoms, three studies [15, 32, 33] reported improvement of psychiatric symptoms, and one study [23] did not report clear results; thus, overall results showed a worsening trend of psychiatric symptoms after clozapine discontinuation (▶ **Table 2**). In one large retrospective cohort study [17], clozapine rechallenge, olanzapine, and antipsychotic polypharmacy had lower psychiatric ward readmission rates than no antipsychotic medication after clozapine discontinuation. Similarly, aripiprazole long-acting injection, clozapine, and olanzapine had lower treatment failure rates than no antipsychotic medication after clozapine discontinuation.

Additionally, clozapine rechallenge, antipsychotic polypharmacy, quetiapine, and olanzapine had lower mortality rates than no antipsychotic medication after clozapine discontinuation. In one retrospective study [16], clinical outcomes worsened after clozapine discontinuation in clozapine responders and improved in clozapine non-responders. In one mirror-image study [26], early and late clozapine discontinuation were compared and were found to be associated with prolongation and shortening of bed days, respectively, albeit not significantly. In the other 12 retrospective studies [12, 14, 18–20, 24, 25, 27, 29–31, 34], eight studies [14, 18, 25, 27, 29–31, 34] clearly showed worsening of clinical status after clozapine discontinuation (▶ **Table 2**).

Clozapine rechallenge

Clozapine rechallenge was performed in 11 studies [11–14, 17, 18, 20, 24, 31, 33, 35] (▶ **Table 2**). Among the five studies [11, 13, 17, 18, 31, 35] that reported clinical outcomes after clozapine rechallenge, four [11, 13, 31, 35] reported clinical improvement in more than half of patients who rechallenged clozapine. The remaining study reported that the clozapine discontinuation-rechallenge group had a worse remission assessment score compared to the clozapine discontinuation-no rechallenge group, and the clozapine dose was higher after clozapine rechallenge than before clozapine discontinuation.

Discussion

The findings of the current systematic review of studies reporting clinical outcomes after discontinuation of clozapine are summarized as follows: (1) patients generally showed worsening of psychiatric symptoms after clozapine discontinuation; (2) patients showed good response to clozapine rechallenge; and (3) patients showed poor response to antipsychotics other than olanzapine after clozapine discontinuation.

Although psychiatric symptoms generally worsened following the discontinuation of clozapine, the current systematic review identified only one study that reported clinical outcomes after clozapine discontinuation based on response to clozapine [16]. This study reported clinical outcomes separately for clozapine responders, who reported worsened outcomes, and clozapine non-responders (i. e., CRS), who reported improved outcomes after clozapine discontinuation. However, this study, which had various limitations such as a retrospective design, lack of symptom assessments, and small sample size, was considered insufficient to answer to our clinical question of whether or not clozapine should be discontinued if patients did not respond to clozapine. Therefore, there is an urgent need to further examine clinical outcomes after clozapine discontinuation in patients with CRS, because current evidence recommends augmentation strategies with other antipsychotics or ECT for this population [7–10]. In addition, given that it is likely that patients responded to clozapine and then discontinued it due to poor tolerability, clinical outcomes should be examined not only by the response to clozapine but also by reason for clozapine discontinuation. However, none of the articles included in the current systematic review reported clinical outcomes based on the reason for discontinuation. Future studies are needed to examine clinical outcomes separately in terms of the reason for clozapine discontinuation.

Clozapine rechallenge improved clinical outcomes overall. Interestingly, however, one of the included studies showed that it led to a deterioration in remission quality [18] and required an increase in the clozapine dose when rechallenge was attempted. This is an analogue of a previous study [38], which showed that treatment response decreased with a higher dose of the same antipsychotic for the second episode compared to the first episode in patients with schizophrenia. It may be desirable to avoid discontinuing clozapine whenever possible if a patient responds to clozapine, as worsening of symptoms after clozapine discontinuation can induce resistance to clozapine.

Previous studies showed ECT as an effective treatment option for patients with TRS [39–41]. In addition, an RCT included in one of those previous meta-analyses demonstrated that ECT plus ziprasidone was not inferior to clozapine plus ziprasidone [40]. Although ECT is a potential alternative to clozapine, none of the included studies evaluated ECT as a post-clozapine discontinuation treatment. Therefore, we could not conclude if ECT could be an effective treatment after clozapine discontinuation.

Olanzapine was the most-used alternative antipsychotic after clozapine discontinuation. While there was a general trend toward worsening of symptoms with the use of non-clozapine antipsychotics, the rate of worsening was relatively low for olanzapine compared to the other antipsychotics. Specifically, two of six studies in which olanzapine was used as a post-clozapine discontinuation antipsychotic showed clinical improvement on average, and another study reported an improved outcome in 37.5 % of patients. Moreover, in the large retrospective cohort study, psychiatric ward readmission risk was the second-lowest for olanzapine, following clozapine rechallenge, after clozapine discontinuation. These findings are consistent with a recent network meta-analysis, which showed no significant difference in efficacy between clozapine and olanzapine in patients with TRS [42]. The doses of olanzapine in studies included in that network meta-analysis were relatively high (> 20 mg/day), which also aligns with the studies included in the current systematic review that switched from clozapine to olanzapine. Specifically, studies with improved outcomes after clozapine discontinuation used higher doses of olanzapine, while studies with worse outcomes used less than 20 mg/day of olanzapine. Taken together, these results suggest that a high-dose olanzapine treatment could be an alternative treatment after clozapine discontinuation for patients who are not candidates for clozapine rechallenge.

There were several limitations to the current systematic review. First, this review included only 13 prospective studies, accounting for less than half of the total number of studies analyzed, and only three RCTs, of which only one was conducted in a double-blind fashion. Second, although a large retrospective cohort and a large mirror-image study were included, the sample sizes of the other studies were relatively small. Third, because clozapine was used with a relatively low dose in the included studies, post-clozapine discontinuation outcomes in patients treated with a high dose of clozapine (> 600 mg/day) remain unknown. Fourth, in only one included study, clinical outcomes after clozapine discontinuation were re-

▶ **Table 2** Summary of included studies: Clinical outcomes after clozapine discontinuation.

Author	Follow-up duration after CLO DC	Type of APs after CLO DC	Mean dose of APs after CLO DC	Outcomes after CLO DC	CLO rechallenge after CLO DC	Outcomes after CLO rechallenge
Tollefson et al.[13]	9 weeks 3–5 days	Olanzapine or placebo	16.5 ± 4.9 mg/day	Worsened: PANSS, + 1.4 for olanzapine (n = 53) (NS), + 4.9 for placebo (n = 53) (NS)	n = 9 **	Improved: n = 6/9 (66.7 %) Not changed or worsened: n = 3/9 (33.3 %)
Lin et al.[28]	12 weeks	Zotepine	397 ± 76 mg/day	Worsened: BPRS, + 4.7 for zotepine (n = 35) vs. -1.3 for CLO (n = 24) (S)	None	NA
Borison et al.[37]	2 weeks	None	NA	Worsened: BPRS, 42.6 to 50.5 (NA)	None	NA
Simpson et al.[21]	4 weeks	None	NA	Worsened: Global Psychiatric Evaluation, 1.1 to -0.7 (NA)	NA	NA
Borison et al.[37]	1 week	None	NA	Worsened: BPRS, 20.8 to 32.0 (NA)	None	NA
Kerepcic et al.[22]	14–60 days	Prazine or flufenazine	NA	Worsened: BPRS, 24.2 to 29.0 (n = 15/31), 21.7 to 53.6 (n = 16/31), (NA)	NA	NA
Meltzer et al.[11]	12 months for SSD (n = 19), NA for TRS (n = 64)	Tapering without perphenazine: haloperidol (n = 1), loxapine (n = 4), perphenazine (n = 1), risperidone (n = 2), NA (n = 1) Tapering with perphenazine: loxapine (n = 1), risperidone (n = 7) Abrupt: risperidone (n = 2)	NA	Worsened: BPRS, 12.1 to 12.6 for slow taper without perphenazine for SSD (n = 8) Worsened: BPRS, 7.25 to 11.8 for slow taper with perphenazine for SSD (n = 8) Not changed: BPRS, 17.0 to 17.0 for abrupt stop for SSD (n = 1) Death: n = 1 for abrupt stop for SSD NA: n = 1 for slow taper without perphenazine for SSD Worsened: relapsed for TRS (n = 21) NA: n = 43 for TRS	n = 8 for SSD n = NA for TRS	Improved: BPRS, 34.6 to 16.3, n = 7/8 (87.5 %) for SSD NA: n = 1/8 (12.5 %) for SSD NA: n = NA for TRS
Still et al.[36]	12 weeks	Risperidone	8.0 ± 1.4 mg/day	Worsened: PANSS, NA (S); BPRS, NA (S)	None	NA
Henderson et al.[35]	NA	Olanzapine	17.1 ± 6.3 mg/day	Worsened: BPRS, 36.6 to 46.6 (S)	n = 11	Improved: n = 7/11 (63.6 %) NA: n = 4/11 (36.4 %)
Littrell et al.[33]	6 months	Olanzapine	21.7 ± 3.3 mg/day	Improved: PANSS, 79.8 to 62.5 (S)	n = 2	NA
Dossenbach et al.[32]	18 weeks	Olanzapine	22.0 ± 4.7 mg/day	Improved: PANSS, -14.2 % (S); BPRS, -20.2 % (S)	None	NA
Lindenmayer et al.[23]	10 weeks 4 days	Olanzapine	NA	Improved: PANSS, NA, n = 1/11(9 %); BPRS, NA, n = 1/11(9 %) Not changed or worsened (n = 10/11): PANSS, NA, n = 10/11(91 %); BPRS, NA, n = 10/11(91 %)	None	NA
Li et al.[15]	24 weeks	Ziprasidone	131 ± 34 mg/day	Improved: PANSS, NA (S)	None	NA

▶ **Table 2** Continued.

Author	Follow-up duration after CLO DC	Type of APs after CLO DC	Mean dose of APs after CLO DC	Outcomes after CLO DC	CLO rechallenge after CLO DC	Outcomes after CLO rechallenge
Dennis et al.[25]	NA	NA	NA	Worsened: hours of restraint/seclusion per 2 weeks, 10.1 to 5.4 for CLO DC (n = 23) (NS) vs. 10.3 to 1.0 for CLO CO (n = 89) (S); number of incidents of restraint & seclusion per 2 weeks, 0.59 to 0.58 for CLO DC (n = 23) (NS) vs. 0.86 to 0.12 for CLO CO (n = 89) (S); hours of authorized leave per 2 week, 0.12 to 0.79 hours for CLO DC (n = 23) (NS) vs. 5.1 to 8.5 hours for CLO CO (n = 89) (S); number of incidents of authorized leave per 2 weeks, 0.5 to 0.5 for CLO DC (n = 23) (NS) vs. 0.14 to 0.28 for CLO CO (n = 89) (S)	None	NA
Mortimer[24]	NA	NA	NA	Worsened: n = 1/15 (6.7 %) Not changed: n = 1/15 (6.7 %) NA: n = 13/15 (86.7 %)	n = 1	NA
Dickson et al.[34]	NA	NA	NA	Worsened: death/suicide, n = 3 (27.3 %)/2 (18.2 %)/11 for CLO DC vs. n = 0 (0 %)/0 (0 %)/15 for CLO CO and interrupted	NA	NA
Baldacchino et al.[19]	NA	Olanzapine	31.4 ± 16.8 mg/day for olanzapine CO (n = 7), 18.9 ± 6.0 mg/day for olanzapine DC (n = 9)	Improved: n = 6/16 (37.5 %) Not changed: n = 1/16 (6.3 %) Not changed or worsened: n = 3/16 (18.8 %) Worsened: n = 1/16 (6.3 %) Other: n = 5/16 (31.3 %)	None	NA
Drew et al.[31]	NA	Risperidone: n = 1 NA: n = 9	NA	Worsened: a larger percentage admitted to hospital, NA (S); admitted to hospital more frequently, NA (S); more time spent in hospital, NA (S)	n = 2	Improved: n = 2/2 (100 %)
Seppala et al.[30]	5 months	NA	NA	Worsened: CGI-S, 3.5 to 3.9 at 1 month and 3.8 at 5 months (S)	None	NA
Miodownik et al.[18]	NA	CLO	462 ± 20 mg/day	–	n = 43	Worsened: Remission Assessment Score, 5.8 for CLO DC vs. 6.5 for CLO CO (S); dose of CLO (mg/day), 358 before CLO DC to 462 after CLO rechallenge (S)
Kapsali et al.[29]	NA	NA	NA	Worsened: Aggression Scale, increased in all patients (NA)	NA	NA

▶ **Table 2** Continued.

Author	Follow-up duration after CLO DC	Type of APs after CLO DC	Mean dose of APs after CLO DC	Outcomes after CLO DC	CLO rechallenge after CLO DC	Outcomes after CLO rechallenge
Mustafa et al.[12]	NA	CLO: n = 23 LAIs: n = 14 Oral - LAI polypharmacy: n = 15 Oral monotherapy: n = 38 Oral polypharmacy: n = 27 None: n = 4 NA: n = 50	NA	Death: n = 25/171 (14.6 %)	n = 23	NA
Shaker et al.[27]	1 year	NA	NA	Worsened: days of inpatient/home treatment stay, 29.7 to 62.6 days (NS); total antipsychotic dose, 50.1 % of BNF limits to 60.5 % (NS); number of alternative antipsychotics prescribed, 1.28 to 1.80 (NS); number of hospital/home treatment episodes, 0.20 to 0.44 (NS)	None	NA
Siskind et al.[26]	24 months	NA	NA	Worsened for early cessation: bed days, 26.1 to 26.4 (NS); admissions 2.2 to 2.3 (NS) Improved for late cessation: Bed days, 28.0 to 26.4 (NS); admissions 2.2 to 1.7 (S)	NA	NA
Luykx et al.[17]	5.4 years	Oral polypharmacy: n = 409* Aripiprazole: n = 186* Levomepromazine: n = 52* Olanzapine: n = 344* Quetiapine: n = 210* Risperidone: n = 80* LAIs: n = 60*	NA	1) Risk of psychiatric ward readmission: adjusted HR, 0.58 for olanzapine 2) Risk of treatment failure: adjusted HR, 0.61 for olanzapine 3) Risk of all-cause mortality: adjusted HR, 0.26 for olanzapine * For use of APs compared with non-use of APs after CLO DC	n = 379	1) Risk of psychiatric ward readmission: adjusted HR, 0.58 for CLO 2) Risk of treatment failure: adjusted HR, 0.49 for CLO 3) Risk of all-cause mortality: adjusted HR, 0.18 for CLO * For use of APs compared with non-use of APs after CLO DC
Li et al.[20]	NA	Paliperidone	8.2 ± 3.8 mg/day	Continuation of paliperidone: n = 40/78 (51.3 %) Switch to CLO: n = 38/78 (48.7 %)	n = 38	NA
Murata et al.[14]	1 year	CLO: n = 1 Olanzapine: n = 3 Other oral monotherapy: n = 6 Polypharmacy: n = 14 LAIs: n = 5 NA: n = 1	Total chlorpromazine equivalent dose of antipsychotics: 973 ± 503 mg/day	Worsened: patient clinical status, 2.50 to 2.34 (NS)	n = 1	NA

▲ **Table 2** Continued.

Author	Follow-up duration after CLO DC	Type of APs after CLO DC	Mean dose of APs after CLO DC	Outcomes after CLO DC	CLO rechallenge after CLO DC	Outcomes after CLO rechallenge
Watanabe et al.[16]	1 year	Olanzapine: n = 5 (responder, n = 2; nonresponder, n = 3) Other oral monotherapy: n = 4 (responder, n = 2; nonresponder, n = 2) Polypharmacy: n = 20 (responder, n = 9; nonresponder, n = 11)	Total chlorpromazine equivalent dose of antipsychotics: 1031 ± 498 mg/day	Worsened: CGI-S, 5.3 to 5.5 (NA); CLO responder 4.6 to 5.7 (S), CLO nonresponder 5.9 to 5.4 (S)	NA	NA

*Most frequently initiated first antipsychotics during the first year after clozapine discontinuation. **CLO was temporally used; Abbreviations: APs = antipsychotics, BNF = British National Formulary, BPRS = Brief Psychiatric Rating Scale, CGI-S = Clinical Global Impressions - Severity scale, CLO = clozapine, CO = continuation, DC = discontinuation, ECT = electroconvulsive therapy, GAF = Global Assessment of Functioning, LAI = long-acting injectable, NA = not available, NS = not significant, PANSS = Positive and Negative Syndrome Scale, RCT = randomized controlled trial, S = significant, SSD = schizophrenia spectrum disorders, TRS = treatment-resistant schizophrenia.

ported separately for clozapine responders and non-responders. Fifth, no included studies reported clinical outcomes after clozapine discontinuation separately for each reason for clozapine discontinuation. Sixth, cross-over studies could not be included in this study due to the lack of detailed clinical outcomes for each arm, for instance, the study by Salganik et al. [43]. Seventh, it is difficult to differentiate between withdrawal symptoms and worsening psychiatric symptoms, and this review did not include withdrawal symptoms in the clinical outcomes. Eighth, the definition of TRS varied across the studies included in this review. Lastly, some studies were excluded from this review because they included patients with mood disorders, for instance, the studies by Atkinson et al. [44] and Modestin et al. [45]. However, the findings of these studies are similar to the results summarized in this review.

In conclusion, the evidence suggests that clozapine should be continued in patients with TRS when possible because of the potential for worsening clinical outcomes. When clozapine is discontinued, clozapine rechallenge or olanzapine may be considered, depending on patients' candidacy for clozapine rechallenge. Further studies are warranted to investigate clinical outcomes after clozapine discontinuation, specifically in clozapine non-responders (i. e., CRS), and to examine the efficacy of ECT after clozapine discontinuation.

Acknowledgments

We sincerely thank Kelley Cortright for her assistance in writing the manuscript.

Conflicts of Interest

Dr. Miura has received speaker's fees from Janssen, Meiji Seika Pharma, Otsuka, and Yoshitomiyakuhin. Dr. Tanaka has received speaker's fees from Janssen, Meiji Seika Pharma, Otsuka, and Sumitomo Dainippon Pharma. Dr. Kemuriyama has no conflicts of interest. Dr. Misawa has received speaker's fees from Eli Lilly, Janssen, Novartis Pharma, Otsuka, Pfizer, and Sumitomo Dainippon Pharma. Dr. Uchida has received grants from Daiichi Sankyo, Eisai, Meiji Seika Pharma Mochida, Otsuka, and Sumitomo Dainippon Pharma; speaker's fees from Eisai, Meiji Seika Pharma, Otsuka, and Sumitomo Dainippon Pharma; and consultant fees from Sumitomo Dainippon Pharma. Dr. Mimura has received grants from Daiichi Sankyo, Eisai, Mitsubishi Tanabe Pharma, Pfizer, Shionogi, Takeda, and Tsumura; and speaker's fees from Bayer, Daiichi Sankyo, Eisai, Eli Lilly, Fujifilm RI Pharma, Hisamitsu, Janssen, Kyowa, Mochida, MSD, Mylan EPD, Nihon Mediphysics, Nippon Chemipher, Novartis Pharma, Ono Yakuhin, Otsuka, Pfizer, Santen, Shire, Sumitomo Dainippon Pharma, Takeda, Tsumura, and Yoshitomiyakuhin. Dr. Takeuchi has grants from Daiichi Sankyo and Novartis Pharma; speaker's fees from EA Pharma, Kyowa, Janssen, Lundbeck, Meiji Seika Pharma, Mochida, Otsuka, Sumitomo Dainippon Pharma, Takeda, and Yoshitomiyakuhin; and consultant fees from Janssen, Mitsubishi Tanabe Pharma, and Sumitomo Dainippon Pharma.

References

[1] Lally J, Ajnakina O, Di Forti M et al. Two distinct patterns of treatment resistance: Clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. Psychol Med 2016; 46: 3231–3240. doi:10.1017/S0033291716002014

[2] Demjaha A, Lappin JM, Stahl D et al. Antipsychotic treatment resistance in first-episode psychosis: Prevalence, subtypes and predictors. Psychol Med 2017; 47: 1981–1989. doi:10.1017/S0033291717000435

[3] Kennedy JL, Altar CA, Taylor DL et al. The social and economic burden of treatment-resistant schizophrenia: A systematic literature review. Int Clin Psychopharmacol 2014; 29: 63–76

[4] Warnez S, Alessi-Severini S. Clozapine: A review of clinical practice guidelines and prescribing trends. BMC Psychiatry 2014; 14. doi:10.1186/1471-244X-14-102

[5] Bachmann CJ, Aagaard L, Bernardo M et al. International trends in clozapine use: A study in 17 countries. Acta Psychiatr Scand 2017; 136: 37–51. doi:10.1111/acps.12742

[6] Siskind D, Siskind V, Kisely S. Clozapine response rates among people with treatment-resistant schizophrenia: Data from a systematic review and meta-analysis. Can J Psychiatry 2017; 62: 772–777. doi:10.1177/0706743717718167

[7] Siskind DJ, Lee M, Ravindran A et al. Augmentation strategies for clozapine refractory schizophrenia: A systematic review and meta-analysis. Aust N Z J Psychiatry 2018; 52: 751–767. doi:10.1177/0004867418772351

[8] Wang G, Zheng W, Li X Bin et al. ECT augmentation of clozapine for clozapine-resistant schizophrenia: A meta-analysis of randomized controlled trials. J Psychiatr Res 2018; 105: 23–32. doi:10.1016/j.jpsychires.2018.08.002

[9] Wagner E, Löhrs L, Siskind D et al. Clozapine augmentation strategies – a systematic meta-review of available evidence. Treatment options for clozapine resistance. J Psychopharmacol 2019; 33: 423–435. doi:10.1177/0269881118822171

[10] Shimomura Y, Kikuchi Y, Suzuki T et al. Antipsychotic treatment strategies for acute phase and treatment resistance in schizophrenia: A systematic review of the guidelines and algorithms. Schizophr Res 2021; 236: 142–155. doi: 10.1016/j.schres.2021.07.040

[11] Meltzer HY, Lee MA, Ranjan R et al. Relapse following clozapine withdrawal: Effect of neuroleptic drugs and cyproheptadine. Psychopharmacology 1996; 124: 176–187. doi:10.1007/BF02245619

[12] Mustafa FA, Burke JG, Abukmeil SS et al. Schizophrenia past clozapine: Reasons for clozapine discontinuation, mortality, and alternative antipsychotic prescribing. Pharmacopsychiatry 2014; 45: 11–14. doi:10.1055/s-0034-1394397

[13] Tollefson GD, Dellva MA, Mattler CA et al. Controlled, double-blind investigation of the clozapine discontinuation symptoms with conversion to either olanzapine or placebo. J Clin Psychopharmacol 1999; 19: 435–443. doi:10.1097/00004714-199910000-00007

[14] Murata T, Negishi T, Yuki K et al. Post-clozapine in a clinical setting: A retrospective case note review in Kumamoto, Japan (2009–2019). Asian J Psychiatr 2021; 65. doi:10.1016/j.ajp.2021.102845

[15] Li CH, Shi L, Zhan GL et al. A twenty-four-week, open-label study on Ziprasidones efficacy and influence on glucolipid metabolism in patients with schizophrenia and metabolic disorder. Eur Rev Med Pharmacol Sci 2013; 17: 2136–2140

[16] Watanabe M, Misawa F, Miura G et al. Clinical outcomes after clozapine discontinuation in responders versus nonresponders: A retrospective chart review. Int Clin Psychopharmacol 2021; 36: 188–192. doi:10.1097/YIC.0000000000000361

[17] Luykx JJ, Stam N, Tanskanen A et al. In the aftermath of clozapine discontinuation: Comparative effectiveness and safety of antipsychotics in patients with schizophrenia who discontinue clozapine. Br J Psychiatry 2020; 217: 1–8. doi:10.1192/bjp.2019.267

[18] 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. doi:10.4088/JCP.v67n0805

[19] Baldacchino AM, Stubbs JH, Nevison-Andrews D. The use of olanzapine in non compliant or treatment resistant clozapine populations in hospital. Pharm J 1998; 260: 207–209

[20] Li D-J, Lin C-H, Chen C-C. Factors impeding switching from clozapine to paliperidone among patients with chronic schizophrenia – A retrospective cohort study. Exp Clinical Psychopharmacol 2021. doi:10.1037/pha0000434

[21] Simpson GM, Varga E. Clozapine: A new antipsychotic agent. Curr Ther Res – Clin Exp 1974; 16: 679–686

[22] Kerepcic I, Koludrovic M, Jurin M et al. Clozapine in treatment of schizophrenic heteroaggressive forensic patients. Psychiatria Danubina 1994; 6: 105–108

[23] Lindenmayer JP, Czobor P, Volavka J et al. Olanzapine in refractory schizophrenia after failure of typical or atypical antipsychotic treatment: An open-label switch study. J Clin Psychiatry 2002; 63: 931–935. doi:10.4088/JCP.v63n1011

[24] Mortimer AM. A clozapine cohort: Outcome and issues of concern. Hum Psychopharmacol 1997; 12: 361–363. doi:10.1002/(SICI)1099-1077(199707/08)12:4<361:AID-HUP875>3.0.CO;2-Q

[25] Dennis JL, McBride D, Peterson PD et al. Clozapine therapy in a state hospital: Patient care and policy implications. Adm Policy Ment Health 1996; 24: 39–52. doi:10.1007/BF02106482

[26] 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. Psychopharmacology 2019; 236: 1931–1935. doi:10.1007/s00213-019-5179-6

[27] Shaker A, 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. doi:10.1177/2045125317741449

[28] Lin CC, Chiu HJ, Chen JY et al. Switching from clozapine to zotepine in patients with schizophrenia: A 12-week prospective, randomized, rater blind, and parallel study. J Clin Psychopharmacol 2013; 33: 211–214. doi:10.1097/JCP.0b013e31828700c7

[29] Kapsali F, Rabavilas AD, Michopoulou A et al. Aggressive behaviour in schizophrenic patients after abrupt treatment discontinuation. Int J Psychiatry Clin Pract 2011; 15: 296–302. doi:10.3109/13651501.2011.589517

[30] Seppälä N, Kovio C, Leinonen E. Effect of anticholinergics in preventing acute deterioration in patients undergoing abrupt clozapine withdrawal. CNS Drugs 2005; 19: 1049–1055. doi:10.2165/00023210-200519120-00006

[31] Drew LRH, Griffiths KM, Hodgson DM. A five year follow-up study of the use of clozapine in community practice. Aust N Z J Psychiatry 2002; 36: 780–786. doi:10.1046/j.1440-1614.2002.01091.x

[32] 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. doi:10.1016/S0149-2918(00)80082-X

[33] Littrell KH, Johnson CG, Hilligoss NM et al. Switching clozapine responders to olanzapine. J Clin Psychiatry 2000; 61: 912–915. doi:10.4088/JCP.v61n1204

[34] Dickson RA, Thomas Dalby J, Williams R et al. Hospital days in clozapine-treated patients. Can J Psychiatry 1998; 43: 945–948. doi:10.1177/070674379804300911

[35] Henderson DC, Nasrallah RA, Goff DC. Switching from clozapine to olanzapine in treatment-refractory schizophrenia: Safety, clinical efficacy, and predictors of response. J Clin Psychiatry 1998; 59: 585–588. doi:10.4088/JCP.v59n1105

[36] Still DJ, Dorson PG, Crismon ML et al. Effects of switching inpatients with treatment-resistant schizophrenia from clozapine to risperidone. Psychiatr Serv 1996; 47: 1382–1384. doi:10.1176/ps.47.12.1382

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

[38] Takeuchi H, Siu C, Remington G et al. Does relapse contribute to treatment resistance? Antipsychotic response in first- vs. second-episode schizophrenia. Neuropsychopharmacology 2019; 44: 1036–1042. doi:10.1038/s41386-018-0278-3

[39] Thomas N, Sollychin M, Takács A et al. Right unilateral ultrabrief electroconvulsive therapy in the maintenance treatment of schizophrenia. Journal of ECT 2019; 35: E34–E35

[40] Sinclair DJM, Zhao S, Qi F et al. Electroconvulsive therapy for treatment-resistant schizophrenia. Cochrane Database Syst Rev 2019; 3: CD011847

[41] Choi KM, Choi S-H, Hong JK et al. The effects of continuation-maintenance electroconvulsive therapy on reducing hospital re-admissions in patients with treatment-resistant schizophrenia. Clin Psychopharmacol Neurosci 2018; 16: 339–342. doi:10.9758/cpn.2018.16.3.339

[42] Samara MT, Dold M, Gianatsi M et al. Efficacy, acceptability, and tolerability of antipsychotics in treatment-resistant schizophrenia. JAMA Psychiatry 2016; 73: 199. doi:10.1001/jamapsychiatry.2015.2955

[43] Salganik I, Modai I, Bercovici BR et al. Clozapine vs haloperidol therapy in elderly chronic schizophrenic inpatients – Preliminary results. A double-blind, cross-over randomized study. Int J of Geriatr Psychopharmacol 1998; 1: 185–187

[44] Atkinson JM, Douglas-Hall P, Fischetti C et al. Outcome following clozapine discontinuation: A retrospective analysis. J Clin Psychiatry 2007; 68: 1027–1030. doi:10.4088/jcp.v68n0708

[45] Modestin J, Dal Pian D, Agarwalla P. Clozapine diminishes suicidal behavior: A retrospective evaluation of clinical records. J Clin Psychiatry 2005; 66: 534–538. doi:10.4088/JCP.v66n0418