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Systematic Review-Meta-analysis

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Objective: No consensus exists on whether clozapine should be prescribed in early stages of psychosis. This systematic review and meta-analysis therefore focus on the use of clozapine as first-line or second-line treatment in non-treatment-resistant patients.

Methods: Articles were eligible if they investigated clozapine compared to another antipsychotic as a first- or second-line treatment in non-treatment-resistant schizophrenia spectrum disorders (SCZ) patients and provided data on treatment response. We performed random-effects meta-analyses.

Results: Fifteen articles were eligible for the systematic review ($N = 314$ subjects on clozapine and $N = 800$ on other antipsychotics). Our meta-analysis comparing clozapine to a miscellaneous group of antipsychotics revealed a significant benefit of clozapine (Hedges' $g = 0.220$, $P = 0.026$, 95% CI = 0.026–0.414), with no evidence of heterogeneity. In addition, a sensitivity analysis revealed a significant benefit of clozapine over risperidone (Hedges' $g = 0.274$, $P = 0.030$, 95% CI = 0.027–0.521).

Conclusion: The few eligible trials on this topic suggest that clozapine may be more effective than other antipsychotics when used as first- or second-line treatment. Only large clinical trials may comprehensively probe disease stage-dependent superiority of clozapine and investigate overall tolerability.

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Key words: schizophrenia; first-episode; antipsychotics; meta-analysis

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Summations

- As a first- or second-line treatment option clozapine outperforms other antipsychotics in schizophrenia spectrum disorders.
- Compared to first-line risperidone, clozapine is more effective in schizophrenia spectrum disorders.

Considerations

- Few studies have studied clozapine as a first- or second-line treatment modality in schizophrenia spectrum disorders.
- When including only randomized controlled trials, beneficial effects of clozapine over other antipsychotic drugs become insignificant, although the direction of effect (clozapine outperforming other antipsychotics) remains unchanged.

Introduction

In most countries, clozapine (CLZ) is the only registered drug for treatment-resistant schizophrenia (TRS). CLZ is also known to be one of the most effective antipsychotic agents (1–4). Up to 30% of TRS patients receive CLZ (5). CLZ is prescribed late in the course of illness (6), with an estimated time lag of ≥ 5 years (7). This delay may worsen outcome as increasing numbers of exacerbations of psychotic symptoms impair daily functioning (8–10). The ongoing debate about when to initiate CLZ could possibly explain the current underutilization.

A number of approaches have been applied in different study designs to investigate CLZ's superiority to other antipsychotics. In two observational studies, one in TRS and non-TRS patients (11) and the other in TRS patients only (12), improved treatment adherence for CLZ relative to other antipsychotics was demonstrated. Three randomized controlled trials in TRS patients point to better efficacy for CLZ (13–15), as well as better treatment adherence (14, 15), relative to other antipsychotics except for olanzapine (15). In four meta-analyses, two in TRS only (16, 17) and two in TRS and non-TRS patients (18, 19), CLZ performed better than other antipsychotics except for haloperidol (17), second-generation antipsychotics as a group (17), risperidone (19), and zotepine (19). A Cochrane review (including its later update) in TRS and non-TRS patients concluded that CLZ is more efficacious than first-generation antipsychotics, and the difference in efficacy compared to other antipsychotics turned out to be larger for TRS patients than for non-TRS patients (20, 21). In summary, previous findings regarding CLZ's efficacy compared to other antipsychotics are inconsistent. This could be explained by variable primary outcomes used in these trials, variable treatment designs, variable active comparators, variable disease stages studied, and by potential funding bias (16).

One may posit that CLZ works better when used earlier in the disease (8–10). This was investigated with a randomized treatment algorithm in early TRS patients (22–25). The results indicate that using CLZ early in treatment was effective (22–25). Meta-analyses on the same dataset demonstrate similar efficacy profiles across antipsychotics in first-episode psychosis (26, 27). However, it is currently unknown whether the efficacy of CLZ vs. other antipsychotics depends on stage of the disease.

Aims of the study

Improving insight into the efficacy of CLZ in earlier disease stages than third-line may help

clinicians balancing CLZ's serious adverse reactions with its potential benefits in early disease stages. We therefore set out to systematically review and meta-analyze response to CLZ when used as a first- or second-line treatment in non-TRS SCZ patients.

Methods

We performed a literature search to identify all observational and interventional studies and case reports published until January 1, 2018, investigating the effect of CLZ on treatment response as a first- or second-line treatment in SCZ patients. This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) standards, except for prepublication of our protocol (28).

Inclusion and exclusion criteria

Studies were included in the systematic review if they: (i) investigated CLZ; (ii) included only adult human participants (≥ 18 years, with no upper age limit) with a diagnosis of schizophrenia, schizoaffective disorder, schizophreniform disorder, or psychosis not otherwise specified (clinician-based and/or using (semi-)structured interviews); (iii) investigated CLZ as a first-line or second-line treatment (so in non-treatment-resistant patients, who are generally defined as being refractory to at least two antipsychotics); (iv) had been written in English; and (v) when the full text was available. When a full text of an article was not available through our university library, librarians tried to retrieve the article from other sources, and the authors were contacted twice to request the articles. Controlled and non-controlled studies, as well as narrative reviews and case reports, were included. We excluded articles related to CLZ if the study population concerned TRS SCZ patients in whom CLZ was not used as a first- or second-line treatment or when no data were available about treatment response (defined as data on positive, negative, or total symptoms, for example, Positive and Negative Syndrome Scale (PANSS), Brief Psychiatric Rating Scale (BPRS), or Clinical Global Impression (CGI) data).

Resources and searches

Two independent reviewers (CP and EH) performed electronic searches using PubMed, EMBASE, Cochrane Central, and PsycINFO until January 1, 2018. The following search

terms were used: ‘Clozapine’ AND ‘schizophrenia spectrum and other psychotic disorders’ OR ‘schizophreni*’ OR ‘psychotic’ OR ‘psychosis’ OR ‘psychoses’ AND ‘naive’ OR ‘first response’ OR ‘first line’ OR ‘first treatment’ OR ‘second treatment’ OR ‘first episode’ OR ‘second line’. In addition, the reference lists of the retrieved articles and relevant review articles were screened for possible additional, eligible articles. Last, searches were done in www.clinicaltrials.gov and www.who.int/trialsearch to find additional (ongoing) trials. We thus identified two possibly relevant trials, but their results had not been published. The full search strings can be found in the Appendix S1.

Study selection

Abstracts of all articles identified by our search were independently examined by two of the authors (CP and EH); whenever eligibility was not clearly described in the abstract, full texts were examined. The lists of articles retrieved by the two authors were compared. Discrepancies were resolved during consensus meetings.

Meta-analysis

The selected articles were screened for eligibility for meta-analysis. The primary outcome was treatment response on CLZ vs. any other antipsychotic, as defined by the authors in changes in positive, negative, or total symptoms on the PANSS, BPRS, or CGI. In most of the studies included in this systematic review, response was defined as 50% change on BPRS (3, 29, 30), while other studies (also) defined response as a CGI of ‘mild’ or less (3, 29–32). One study used the Schedule for Affective Disorders and Schizophrenia – change (SADS-C) version to identify treatment response (32). Case reports were excluded for the meta-analysis part of the study, as well as articles without data on treatment response. Our first aim was to analyze CLZ vs. other antipsychotics. Only in the event three or more studies reported on outcomes in CLZ users vs. a specific active comparator, a sensitivity meta-analysis was planned. We identified articles including study populations overlapping with other studies by checking descriptions of study populations, author names, article titles, and cross-references. In such instances of overlapping study populations, the article with the highest quality score was selected, while the other was excluded. The quality of the articles was assessed using the CONSORT quality checklist (33). The meta-analysis test statistics were generated with

the program ‘Comprehensive meta-analysis’ version 2.2.064 (2011) from BioStat. A random-effects model was used with alpha set at 0.05. Heterogeneity was tested using a homogeneity test (Cochran’s Q test) and the I^2 statistic (34), with the absence of heterogeneity defined as $I^2 = 0.00$, while I^2 values of 0.25, 0.50, and 0.75 were considered indicative of low, moderate, and high degrees of heterogeneity. Publication bias was assessed using funnel plots.

Results

Studies included in the systematic review

Using our search methods, 1248 articles were found. Applying our inclusion and exclusion criteria reduced the number of relevant articles to fifteen (3, 29–32, 35–44), ten of which evaluated CLZ as a first-line treatment (3, 29, 31, 32, 35–40), while five were clinical reports that evaluated CLZ as a second-line treatment (Fig. 1) (30, 41–44). It is important to note that, from the articles excluded on the basis of criterion d1, nine articles (all published before 1990) seemed eligible at first sight because they investigated CLZ use in acutely psychotic patients (Fig. 1) (45–53). However, no information was available on whether they were first-episode patients or previous antipsychotic users.

Systematic review – Clozapine as a first-line treatment

There were two case reports (39, 40) and eight trials (3, 29, 32, 35–38) investigating CLZ as a first-line treatment. Detailed information about the outcomes mentioned in these papers can be found in the Supplementary Results. Both case reports concluded CLZ was effective (there was no active comparator). Four trials (50%) provided summary statistics in line with CLZ being equally effective to other antipsychotics (3, 29, 31, 32), while four trials (50%) pointed to increased efficacy of CLZ over other antipsychotics (35–38).

Systematic review – Clozapine as a second-line treatment

There were four case reports (41–44) and one trial investigating CLZ as a second-line treatment (30). Detailed information about the outcomes mentioned in these papers can be found in the Supplementary Results. All four case reports concluded CLZ was effective (there was no active comparator). The only trial that could be included also pointed to increased efficacy of

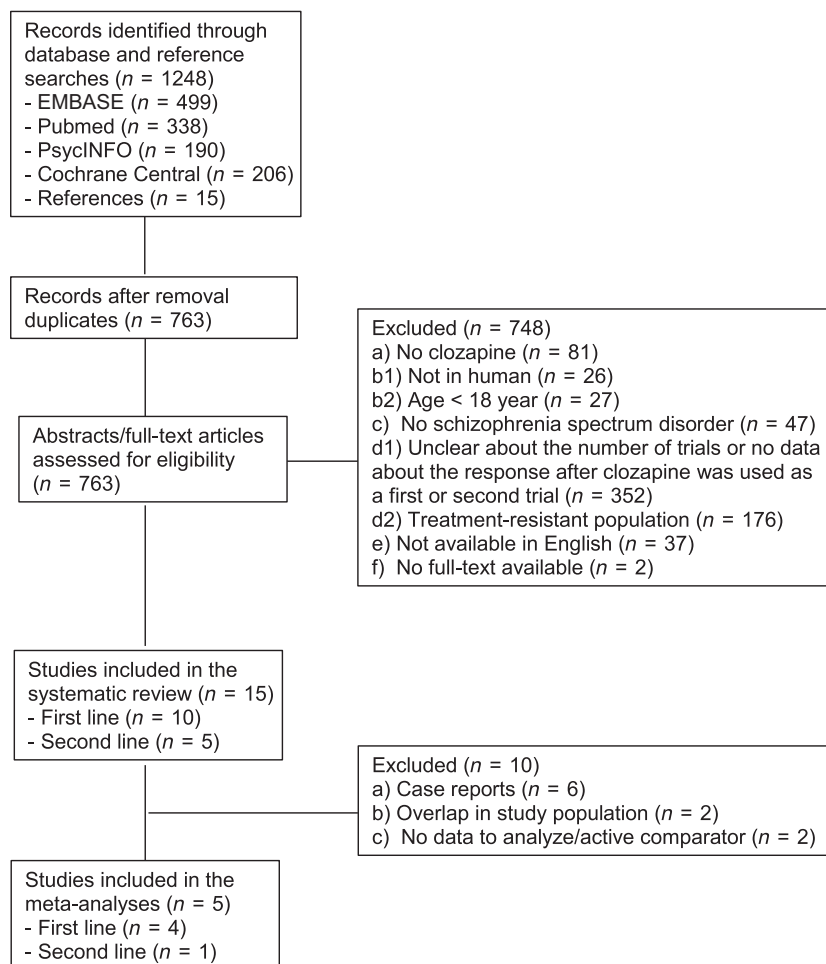


Fig. 1. Flow diagram of the systematic review and meta-analyses selection process.

CLZ over other antipsychotics. A more detailed overview can be found in the Supplementary Results.

Meta-analyses

Fifteen articles were screened. Six case reports (39–44), two articles with overlapping study populations (29, 36), and two articles without data to analyze/no active comparator (32, 38) were excluded. From the five articles that remained, three compared clozapine vs. risperidone (31, 35, 37), one compared clozapine vs. chlorpromazine (3), and one compared clozapine vs. thioridazine (30). An overview of the studies can be found in Table 1.

The first meta-analysis was performed to assess whether CLZ as a first- or second-line treatment has a benefit over a miscellaneous group of antipsychotics. This analysis revealed a significant benefit of CLZ over other antipsychotics (Hedges' $g = 0.220$, $P = 0.026$, $CI = 0.026–0.414$; Fig. 2a), with no evidence of heterogeneity ($Q = 2.118$, $I^2 = 0.00$). Inspection of the funnel plot did not

give rise to suspicion of publication bias, although the numbers of studies were too low for thorough assessments because this method is based on symmetry (Figure S2a).

Then, a sensitivity meta-analysis was performed on CLZ vs. risperidone (RISP) as this antipsychotic was most often compared with CLZ. All these data concerned CLZ vs. RISP as a first-line treatment. This meta-analysis revealed a significant benefit of CLZ over RISP (Hedges' $g = 0.274$, $P = 0.030$, $CI = 0.027–0.521$; Fig. 2b), with no evidence of heterogeneity ($Q = 0.472$, $I^2 = 0.00$). Inspection of the funnel plot did not give rise to suspicion of publication bias, although the number of studies was low (Figure S2b).

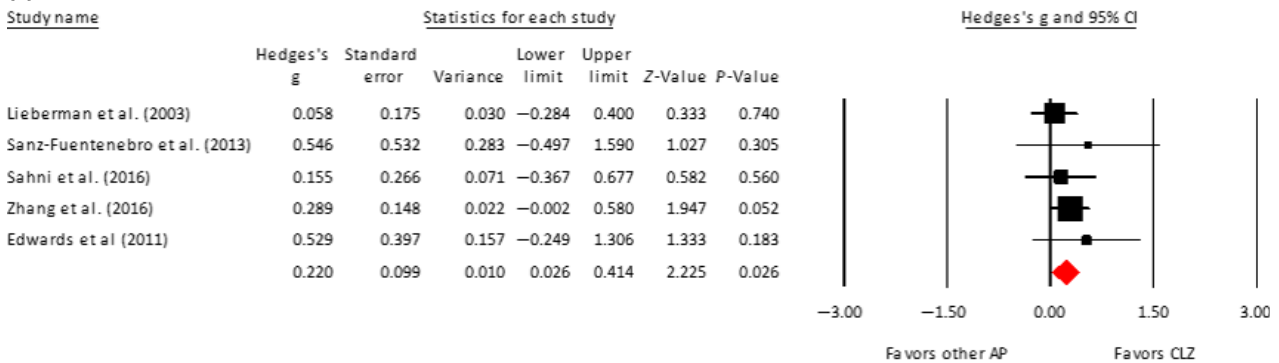
We found that two studies (31, 37) included in our meta-analysis were naturalistic. Another sensitivity analysis was therefore performed on CLZ vs. other antipsychotics only including randomized controlled trials (3, 30, 35), revealing no significant benefit of CLZ over the other antipsychotics (Hedges' $g = 0.169$, $P = 0.271$, $CI = -0.131–0.468$; Figure S3, with no evidence of heterogeneity, $Q = 1.729$, $I^2 = 0.00$). Another sensitivity

Table 1. Summary of study characteristics

Study	AP line	Comp. AP	Outcome	Duration (weeks)	Mean CLZ dose (mg/day)	Mean Comp. AP dose (mg/day)	Result	N CLZ	N total
Lieberman et al. (2003) (3)	1 st	CPZ	BPRS	52	300*	400*	#	68	130
Sanz-Fuentenebro et al. (2013) (35)	1 st	RISP	PANSS	52	220.45	5.43	+	9	14
Sahni et al. (2016) (37)	1 st	RISP	PANSS	26	289.28	6.85	+	28	55
Zhang et al. (2016) (31)	1 st	RISP	PANSS	52	Data missing	Data missing	#	84	183
Edwards et al. (2011) (30)	2 nd	THR	CGI	24	364.65	148.55	#	14	25
Total								203	407

AP line, use of CLZ as a first- ('1st') or second-line ('2nd') antipsychotic; Comp. AP, comparator antipsychotic; CPZ, chlorpromazine; RISP, risperidone; THR, thioridazine; PANSS, Positive and Negative Syndrome Scale; CGI, Clinical Global Impression; N CLZ, Number of patients on clozapine; N total, Number of patients on CLZ and on Comp; AP, '+' = favoring CLZ; '#' = CLZ equally effective as Comp; AP, *median dose.

(a)



(b)

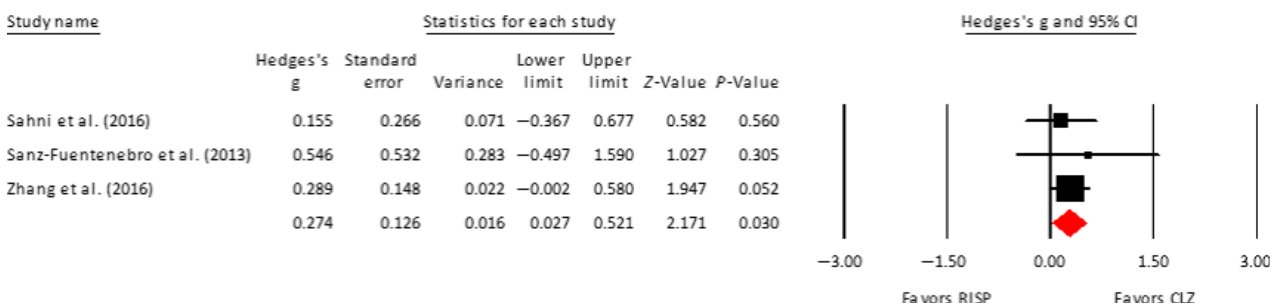


Fig. 2. (a) Forest plot showing meta-analytic results of response to clozapine vs. other antipsychotics. Squares (whiskers represent 95% confidence intervals) indicate the effect sizes of the individual studies. The size of the squares reflects the sample size of each individual study. Diamonds represent summary statistics. CI, confidence interval; other AP, risperidone/chlorpromazine/thioridazine; CLZ, clozapine. (b) Forest plot showing meta-analytic results of response to clozapine vs. risperidone. Squares (whiskers represent 95% confidence intervals) indicate the effect sizes of the individual studies. The size of the squares reflects the sample size of each individual study. Diamonds represent summary statistics. CI, confidence interval; RISP, risperidone; CLZ, clozapine. [Colour figure can be viewed at wileyonlinelibrary.com]

analysis only including blinded RCTs (3, 30) did not reveal a significant benefit of CLZ over the other antipsychotics either (Hedges' $g = 0.159$, $P = 0.411$, $CI = -0.219-0.537$; Figure S4). However, the directions of effect remained identical for all these sensitivity analyses, favoring CLZ.

Discussion

Despite a scarcity of studies on this topic, we found increased efficacy of clozapine as a first- or second-

line treatment in schizophrenia spectrum patients compared to other antipsychotic medication, in particular, relative to risperidone. This finding suggests that CLZ might be superior to other antipsychotics when used earlier than as a third step. However, our study was not designed to investigate CLZ's overall tolerability, and therefore, we cannot recommend it as a first-line treatment for SCZ. On the other hand, our findings may contribute to recent recommendations of CLZ as a second-line treatment in certain SCZ patients (54).

To our knowledge, the current study is the first systematic review and meta-analysis comprehensively probing the use of CLZ in early disease stages. Relatively high efficacy of CLZ may stem from its important effects on psychotic features. However, as the main outcome was general improvement on total PANSS, BPRS, or GCI measures, other aspects of CLZ – such as its beneficial effects on aggressive behavior (55), suicidality (56), and substance abuse (57) – may also have contributed. In clinical settings, the decision to start a specific antipsychotic is not only based on efficacy, but also on tolerability and safety, which may be lower for CLZ compared to other antipsychotics. Nevertheless, lower mortality rates have been found in CLZ users compared to all other antipsychotics (58, 59) and compared to former CLZ users (60) and to users of other antipsychotics (59), suggesting long-term good physical tolerability of CLZ. Another factor possibly explaining our results is that patient characteristics independent of disease stage may partially explain CLZ treatment response: Some research hints that factors such as abundant negative symptoms, a longer duration of untreated psychosis (61), young age at onset (61, 62), and disorganized subtype of SCZ (63) might predict TRS early in the disease.

The prime limitation of our method is the relative paucity of available studies comparing CLZ to active comparators in early disease stages, likely explaining the non-significant results when considering only RCTs or blinded RCTs. However, our inclusion of naturalistic studies in the main analysis has most likely resulted in conservative estimates of CLZ's efficacy as CLZ may be preferred for patients with relatively severe symptomatology compared to other antipsychotics, who in turn may be more difficult to treat. Alternatively, one may reason that, in treatment-compliant patients, CLZ may be preferred over depot antipsychotics since CLZ is unavailable as long-acting injectable and CLZ requires mandatory blood tests. This could in turn have resulted in overestimated effect sizes of CLZ vs. other antipsychotics. In addition, although the effect sizes we found in our meta-analyses were relatively small (0.155–0.546), possibly such effect sizes may reflect a proportion of patients responding well (e.g., hedge's $g = 0.5$), while some receiving CLZ in early disease stages may respond more poorly (e.g., hedge's $g = 0.05$). The fairly large standard deviations for treatment response found in the studies we base our meta-analysis on (31, 35, 37) hints at variable response rates on CLZ in early disease stages. Furthermore,

our observation that the directions of effect in all sensitivity analyses do not change compared to our main analysis may be indicative of lack of power rather than lack of benefit of CLZ. On a general note, the relative scarcity of studies limits statistical power and extrapolation to other active comparators than risperidone. A potential caveat of two studies (6, 57) is their use of baseline data including subjects lost to follow-up. However, considering the absence of heterogeneity and the overall identical effect sizes between the studies included in our meta-analysis, it is unlikely that such participants have influenced the results. Moreover, in our analyses, lower sample sizes excluding drop-outs were used, likely rendering our method relatively conservative.

Future, large, randomized controlled clinical trials may elucidate whether prescribing CLZ as a first- or second-line treatment to patients with schizophrenia spectrum disorders may indeed improve compliance, quality of life, and treatment response. Such trials may also shed light on patient characteristics associated with CLZ efficacy in variable disease stages and should also consider CLZ's safety profile relative to other antipsychotics.

Author contributions

CO and JL conceived the study; CO and EH performed the statistical analyses; CO, EH, and JL wrote the first draft; JL and AH supervised the project; AH and SL provided methodological advice; and all authors were involved in the writing and critical appraisal of methods and approved the final manuscript.

Conflict of interest

In the last 3 years, SL has received honoraria for consulting or lectures from LB Pharma, Lundbeck, Otsuka, TEVA, LTS Lohmann, Geodon Richter, Recordati, Boehringer Ingelheim, Sandoz, Janssen, Lilly, SanofiAventis, Servier and Sunovion. RSK declares personal fees for consultancy from Alkermes, Minerva Neuroscience, Gedeon Richter, and Otsuka; and personal (speaker) fees from Otsuka/Lundbeck. AH has been on the advisory boards of and has received speaker fees from Janssen-Cilag, Lundbeck and Otsuka. The other authors report no conflicts of interest.

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Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. Methods.

Figure S1. CONSORT selection overview.

Figure S2. Funnel plot showing standard error by hedge's g, regarding meta-analysis 1.

Figure S3. Forest plot showing meta-analytic results of response to clozapine vs. other AP, only considering RCTs.

Figure S4. Forest plot showing meta-analytic results of response to clozapine vs. other AP, only considering blinded RCTs.