

## Effect of age on the relative efficacy of clozapine in schizophrenia

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## Systematic Review Or Meta-Analysis

## Effect of age on the relative efficacy of clozapine in schizophrenia

Jones R, MacCabe JH, Price MJ, Liu X, Upthegrove R. Effect of age on the relative efficacy of clozapine in schizophrenia.

**Objective:** Early treatment of schizophrenia improves outcomes. Clozapine appears to have unique benefit when other antipsychotic medication has failed. This systematic review and meta-analysis aims to assess clozapine's superiority over alternative antipsychotic medication and examine whether earlier use is associated with additional benefit.

**Method:** Systematic retrieval of blinded, randomized controlled trials comparing clozapine with alternative antipsychotics in adults with schizophrenia. The effect of mean age on relative clozapine response was examined using random effects meta-regression, and multiple linear regression on available patient data.

**Results:** A total of 276 studies were retrieved. Thirty-four studies were included in the meta-analysis. Clozapine was significantly more effective than alternative antipsychotics in reducing psychotic symptoms and increasing response. However, meta-regression failed to show a more significant effect in younger patients (age on effect size (total psychotic symptoms) 0.00,  $P = 0.79$  CI  $-0.03$  to  $0.03$ ). Individual patient data were available for two studies, the larger of which showed a significant interaction between younger age and superiority of clozapine.

**Conclusion:** The results support clozapine's superiority over other antipsychotics. A convincing effect of age on this effect was not demonstrated, although this was suggested in one study. In view of the age of many of the included studies, and changes in reporting practice over time, new clozapine RCTs, which include age of illness onset as well as age at trial time, would be welcome in order to provide meta-analysable data for future use.

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Key words: early intervention; schizophrenia; antipsychotics

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## Summations

- Clozapine is more effective than other antipsychotics both in terms of reducing psychotic symptoms and increasing rate of response.
- It is unclear whether clozapine's relative effectiveness is greater when started earlier in the course of illness.

## Considerations

- Results need to be interpreted with caution in view of the heterogeneity of the data, narrow age range and the use of age as a proxy measure for duration of illness.
- There is an inherent risk of aggregation bias in meta-regression.

## Introduction

Schizophrenia has a peak age of onset in adolescence and young adulthood, and early and effective treatment is crucial to limit long-term disability—it has been acknowledged for some time that ‘the course of psychosis is the most stormy at its onset and early in its manifest course...the first three years of treated or untreated illness offer a window of opportunity to prevent, or limit the potential decline in outcome’ [1]. This concept of a ‘critical period’ of illness in schizophrenia [2,3], during which the future course of illness can be modified, is supported, albeit with qualification, by the literature. Studies have shown a clear association between shorter duration of untreated psychosis and more favourable clinical outcome [4-6]. Prospective studies of ‘services providing enhanced care’ for first episode psychosis compared to ‘treatment as usual’ have also shown early clinical benefits [7,8] although longer term follow-up has cast doubt on the degree to which these benefits are retained [9,10].

Whilst the majority of people who develop schizophrenia respond well to standard antipsychotic medication, up to one third show treatment resistance [11-13], typically defined as failure to respond adequately to two trials of antipsychotic medication of adequate dose and duration [14]. The concept of treatment resistance in schizophrenia remains incompletely understood. A recent study of a first episode schizophrenia sample by Demjaha et al. [12] found a high percentage of treatment-resistant cases (84%) to be treatment-resistant from the outset. However, a minority of cases had shown a previous good response to antipsychotic medication but had subsequently developed treatment resistance. Studies have demonstrated that patients in the early stages of psychotic illness require lower doses of antipsychotic medication [15], and have much higher rates of treatment response [16], compared to patients with multiple episodes of illness. These findings suggest that delay in effective treatment can increase the risk of treatment resistance.

Clozapine has been the gold standard intervention for treatment-resistant schizophrenia (TRS) since the seminal trial by Kane and colleagues in the 1980s [17], and its use has generally been reserved for this indication due to its risk of agranulocytosis and the need for stringent blood monitoring. However, clozapine’s superiority in TRS has been questioned with some studies finding other second-generation antipsychotics to be as effective [18,19], and meta-analyses producing inconsistent results [20-23]. One recent meta-

analysis of randomized controlled trials (RCTs) [22] comparing clozapine to any other antipsychotic medication found in favour of clozapine in reducing total psychotic symptoms in short-term follow-up studies (standardized mean difference (smd)  $-0.39$ , 95% confidence interval (CI)  $-0.61$  to  $-0.17$ ), but in longer term follow-up studies the evidence was unclear (smd  $-0.11$ , 95% CI  $-0.31$  to  $0.09$ ). For the same outcome, a wider network meta-analysis of all antipsychotic comparison data (9 comparators) for TRS [23] did not find clozapine superior overall with effect estimates ranging from  $-0.02$  ( $-0.44$  to  $0.4$ ) for clozapine compared to ziprasidone to  $-0.4$  ( $-0.74$  to  $-0.04$ ) for clozapine compared to sertindole. There is, though, a sizeable evidence base for clozapine not included in these meta-analyses. Two large non-industry-funded trials, the CATIE phase 2 E study [24] and the CuTlaSS trial [25], have shown clear benefit of clozapine, as has evidence from observational data, suggesting improved clinical outcomes [26] such as hospital admission [26,27] and reduced mortality rates [28-31] in people who had been prescribed clozapine compared to those prescribed alternative antipsychotics.

If duration of illness is associated with degree of antipsychotic response, then it is reasonable to hypothesize that if clozapine is used earlier in TRS, it may be even more effective compared to other antipsychotic medication than when given later in the illness course. There is some research to suggest that starting clozapine early in the course of TRS is beneficial compared to delaying clozapine [32-37]. However, these findings are confined to retrospective data and do not assess the relative effectiveness of clozapine compared to alternative antipsychotics at different stages of illness.

## Aim

To identify and synthesize RCT data comparing clozapine to any other antipsychotic medication in patients with schizophrenia and to evaluate whether they provide evidence that earlier use of clozapine is associated with greater efficacy. As previous definitions of treatment resistance used in clozapine trials have been broad, with only the more recent trials following the Kane criteria [17], we elected to include all trials of adult-onset schizophrenia, other than those of predominantly treatment naïve patients, rather than to rely on reported treatment resistance, in order to provide as large a sample as possible for analysis. We hypothesized that, in studies that included adult participants with a younger age (suggesting shorter

illness duration), improved response rates relative to alternative antipsychotics will be seen.

## Material and methods

The systematic review protocol was registered with Prospero (CRD42017077910) in September 2017, and an updated literature search was conducted covering the period up to 9 July 2018.

Standard methods for systematic review following the PRISMA checklist were used.

Searches were carried out of PubMed, Embase and the Cochrane Schizophrenia Group's Trials Register and the WANGFANG database of Chinese medical literature.

The PubMed search terms used were randomized controlled trial OR controlled clinical trial OR randomized OR placebo OR drug therapy OR randomly OR trial OR groups OR randomised (<http://work.cochrane.org/pubmed>). The Embase search terms used were crossover procedure OR double-blind procedure OR randomized controlled trial OR single-blind procedure OR random\* OR factorial\* OR crossover\* OR (cross adj1 over\*) OR placebo\* OR (doubl\* adj1 blind\*) OR (singl\* adj1 blind\*) OR assign\* OR allocat\* OR volunteer\* (<http://work.cochrane.org/embase>).

The search terms used for clozapine were clozapine\* OR clozaril OR zaponex OR denzapin\* OR clopine OR leponex.

Secondary searches were carried out by examining references lists from included studies, past systematic reviews, citation searching of included studies, checking online trial databases, hand-searching key journals and contacting authors who have published previously on clozapine and are recognized to be experts in the field.

Trials in Chinese identified from the searches were screened at abstract level; then, full-text review of suitable studies was carried out by XL who also conducted the search of the WANFANG database.

## Type of study

Any single- or double-blind RCT comparing clozapine to one or more other antipsychotic drug. Only studies published in English or Chinese were included. In studies employing a crossover, design data were included for the first but not the crossover phase of the study.

## Population

Studies including predominantly treatment non-naive ( $\geq 60\%$ ) participants with diagnosis of

schizophrenia or schizoaffective disorder. Studies of childhood-onset schizophrenia, or studies of clozapine to treat tardive dyskinesia symptoms, comorbid substance misuse or aggression were excluded.

## Intervention and comparator

Comparison between clozapine and one or more other antipsychotic drug.

## Outcomes

*variables chosen for meta regression.* The two primary outcomes were (i) the effect on total psychotic symptoms as measured by a validated clinical scale, either the PANSS (Positive and Negative Syndrome Scale) total score or BPRS (Brief Psychiatric rating scale) total score and (ii) response rate. Response was defined variably across the studies; therefore, for the purpose of this review broad criteria were used, with response defined as at least a 20% reduction in PANSS or BPRS total score or by a CGI (clinical global impression) rating of improved or very much improved. Studies were included in the meta-analysis providing data could be extracted on either or both of the primary outcomes.

Secondary outcomes were as follows:

1. positive symptoms of psychosis (PANSS or BPRS positive subscale score)
2. negative symptoms of psychosis (PANSS or BPRS negative subscale score or SANS score)
3. CGI-severity scores
4. all-cause discontinuation rate
5. discontinuation rate due to lack of efficacy

Variables chosen for meta-regression.

Data were collected for both age and duration of illness when available. However, due to a lack of consistency in how the latter was defined, age was chosen for the primary analysis, with duration of illness as a secondary variable.

## Study selection

References were screened at title and abstract level by RJ. Full-text review was completed by RJ with discussion of any uncertain articles with RU. Consensus was reached on all papers included in the final list.

## Data extraction

Data extraction was carried out by RJ with input from RU. If data were only presented in graph form, values were measured by both RJ and RU with the

mean of the two data points recorded. In addition, RU independently extracted data on a random sample of 20% of papers. Missing data for standard deviations in a small number of early papers were inputted by taking the average values from the first half of studies (pre 2000) included in the review.

Data were extracted on the following: setting, interventions, number in each treatment arm, age, duration of illness, study duration and results of validated outcome measures.

For studies in which clozapine was compared to several comparator groups, the total number of patients and events in each clozapine group was divided by the number of comparison groups in the study and rounded down to the nearest integer, to ensure that the effect size of clozapine was not given extra weight [38].

For rating scales, change scores were used when possible. When standard errors for change scores were missing, these were estimated from p values when available. Otherwise, missing standard deviations were either inputted using methods referenced in the Cochrane handbook [38], or final scores were used instead. Standardized mean differences for each continuous outcome were used in the meta-analysis. For dichotomous outcomes, proportions of responders were used.

For the meta-regression, data were extracted for mean age prior to commencement of clozapine. Four studies reported medians and ranges for these values rather than means and standard deviations. For these studies, means were inputted from medians as per methodology reported by Hozo et al. [39]. In 3 of these studies, the sample size was sufficient to input medians directly for means. In the fourth study which was smaller, the mean was estimated from the median.

#### Study quality

The Cochrane risk of bias tool [38] was used to assess the quality of the included studies.

#### Solicitation of Individual Patient Data (IPD)

Individual patient data were requested by email from the corresponding authors of all papers published during or since the year 2000.

#### Statistical Analysis

Statistical analysis was conducted using STATA version 15 [40]. Meta-analyses were carried out using the metan command. A random effects model was chosen in view of the known heterogeneity of the data, with comparisons between

different drugs and dosages and studies of different durations. Heterogeneity was assessed using the  $I^2$  statistic [41].

Sensitivity analyses were performed to exclude:

1. Studies rated at high risk of bias in any category of the Cochrane risk of bias tool.
2. Non-intention-to-treat studies.
3. Industry conducted or sponsored studies.
4. Studies with inputted standard deviations.

Funnel plots were used to assess evidence of small study effects for both primary outcomes.

Random effects meta-regression models were fitted using the metareg command to look for possible effects of age/duration of illness on relative treatment effects for each outcome measure.

Multiple linear regression was carried out on results from studies which reported individual patient data to look for evidence of interaction between age/duration of illness and treatment arm on outcome.

## Results

The initial search yielded 5575 studies for screening. A further 15 studies were identified by secondary search methods. Of these, 276 papers were selected for full-text review.

Full-text review identified 40 studies which met the review inclusion criteria [17-19,25,42-77], but of these, 6 did not have any usable statistics [52,54,64,66,72,77]; therefore, 34 studies were included in the statistical analyses (see Table S1 in supplementary information for characteristics of included studies).

The PRISMA flow diagram for the literature review is shown in Fig. 1.

#### Characteristics of included studies

The majority of studies were reported as double-blind (35 out of 40 studies) with sample sizes ranging from 10 to 423 participants. Most studies were of clozapine versus a single comparator group, with 5 studies having 2 or more comparators and one comparing clozapine to an alternative antipsychotic at two different dosages. Twenty-six of the 40 studies (24 of the 34 included in the statistical analyses) referred to patients being treatment-resistant, though definitions of treatment resistance varied between studies.

#### Risk of bias review

Using the Cochrane risk of bias tool, ten out of the 40 studies (six out of the 34 studies included in the

## Effect of age on relative efficacy of clozapine

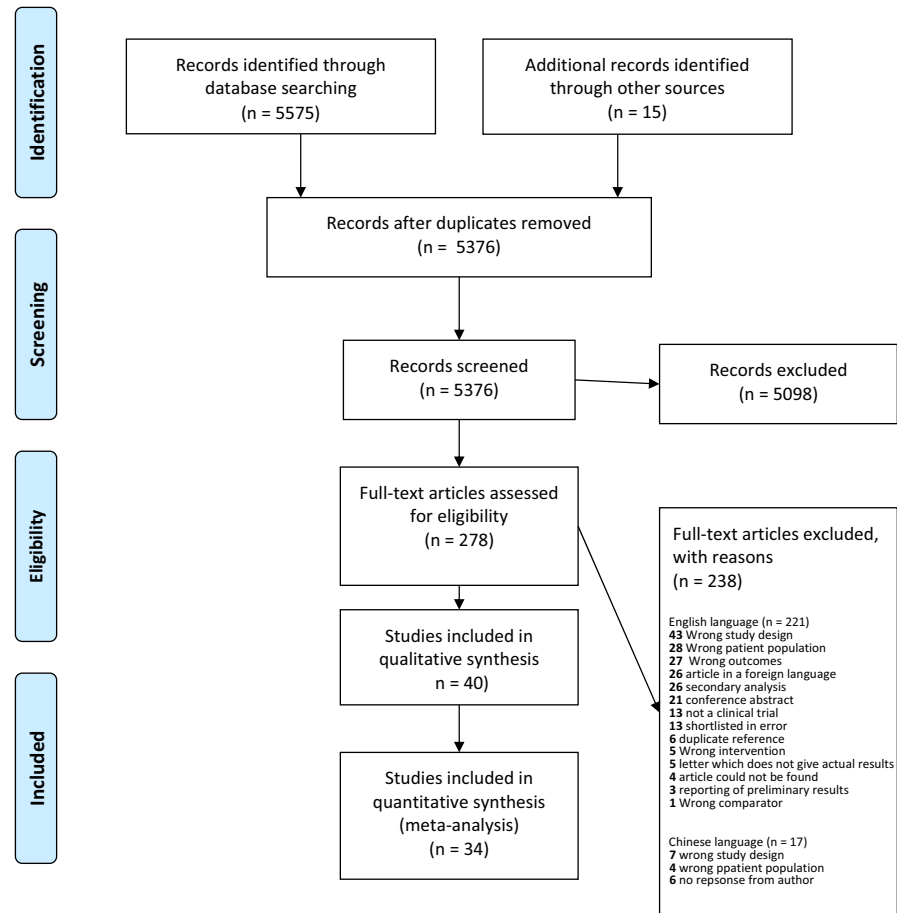


Fig. 1. PRISMA 2009 Flow Diagram.

meta-analysis) scored high on at least one domain. Few of the studies were recent, and 50% were published before the year 2000. The reporting of methodology was limited in the majority of studies (see Table S2 in supplementary information for Cochrane risk of bias table).

### Meta-analyses

**Primary outcomes.** Analysis of the complete set of 34 studies (40 treatment comparisons) showed that clozapine was on average superior to alternative antipsychotics for both the primary outcomes. The effect size for total psychotic symptoms was a standardized mean difference of  $-0.207$  (CI  $-0.33$ ,  $-0.06$ )  $I^2$  65%. The effect size for response rate was a relative risk of 1.22 (CI 1.03, 1.44)  $I^2$  55% (see Fig. 2a and b).

### Secondary outcomes

There were significant differences in favour of clozapine in both reduction in CGI-S scores and lower discontinuation rates for lack of efficacy. Results for other secondary outcomes (positive

psychotic symptoms, negative psychotic symptoms and all-cause discontinuation rate) were not significant (see Table S3 supplementary information).

### Sensitivity analyses

The results for the four planned sensitivity analyses are shown in Figure S1 supplementary information. Effect sizes were broadly similar across the analyses and ranged from 0.18 to 0.21 for total psychotic symptoms and 1.19 to 1.38 for response rate.

Funnel plots for both primary outcomes showed no obvious evidence of small study effects (Figure S2a and b in supplementary information).

### Meta-regression

The median of the mean ages reported across the studies was 37 years (range 21–65 years), with an inter-quartile range of 34–40 years.

Random effects meta-regressions did not show evidence of a relationship between age and clozapine response relative to alternative antipsychotic medication as measured by both primary and secondary outcomes. Neither was a relationship

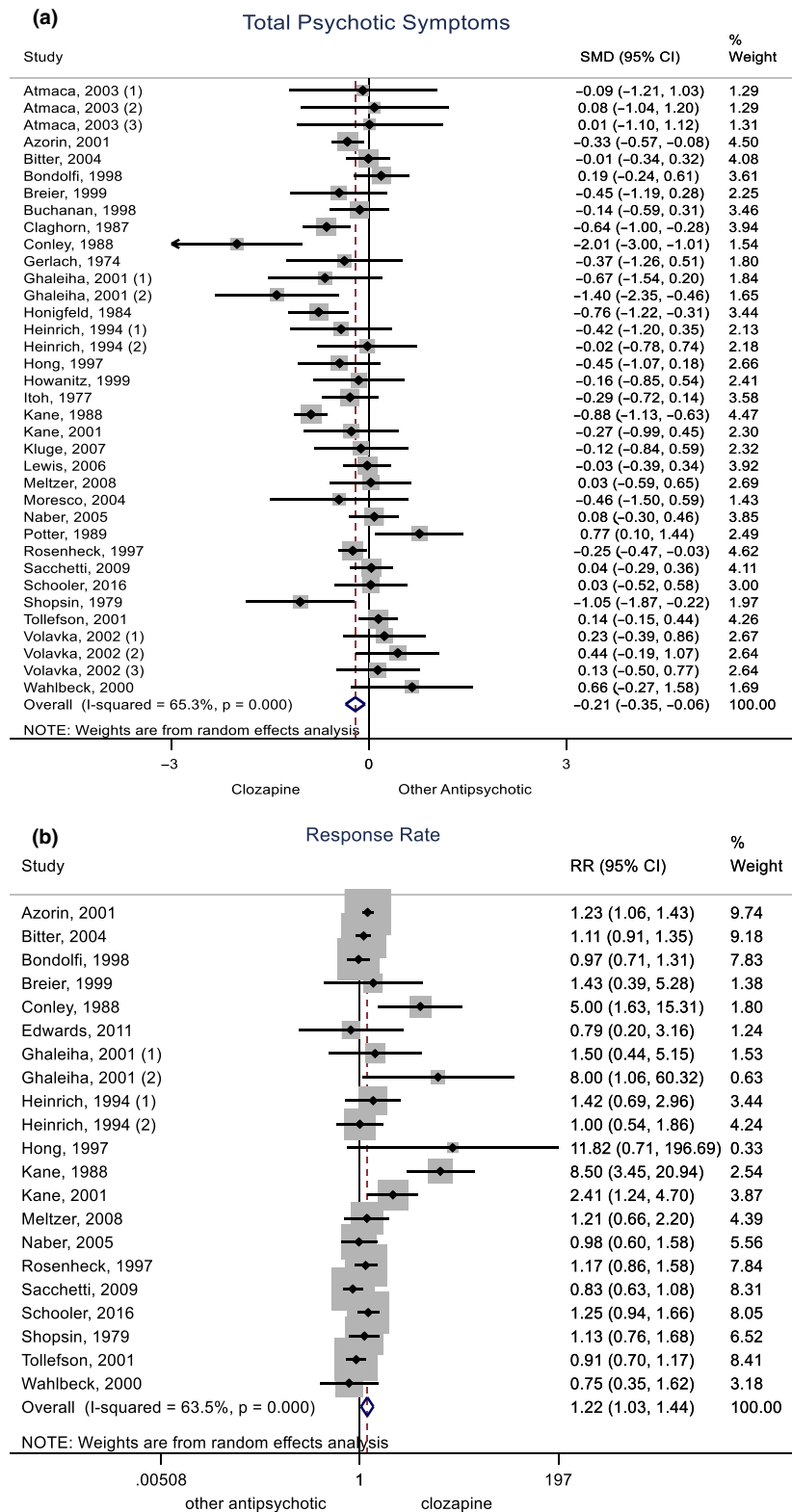


Fig. 2. (a) Forest plot showing effect of clozapine compared to other antipsychotic medication on total psychotic symptoms. SMD, standardized mean difference; 95% CI, 95% confidence intervals. (b). Forest plot showing effect of clozapine compared to other antipsychotic medication on response rate. RR, relative risk; 95% CI, 95% confidence intervals.

between duration of illness and relative response observed (Table 1). The results of the meta-regression for total psychotic symptoms are shown as a scatter plot in Figure 3.

Individual patient data

Two studies (Hong 1997 and Wahlbeck 2000) reported individual patient data. Requests for

## Effect of age on relative efficacy of clozapine

individual patient data from other authors did not yield any additional data.

Hong et al. [58] reported a 12-week study of 40 treatment-refractory patients comparing clozapine (mean dose 543 mg) with chlorpromazine (mean dose 1163 mg) in a double-blind randomized controlled study design. Six clozapine patients (28.6%) improved by more than 20% reduction in BPRS scores during the study, as compared to none from the chlorpromazine group. The percentage reduction in scores for BPRS, PANSS and PANSS positive and general psychopathology subscales were all significantly greater with clozapine than chlorpromazine. The effect of drug on PANSS negative subscale scores was not significant.

Wahlbeck et al. [76] was a single-blind (raters only) trial of clozapine versus risperidone for 10 weeks. Mean doses were 385 mg for clozapine and 7.8 mg for risperidone. The study found no significant differences between the two groups in terms of PANSS total scores, positive and negative subscale scores, global scores or social functioning scores.

Multiple linear regression using age and drug as co-variables with the dependent variable as change in BPRS score showed significant interaction between age and drug in the Hong et al. [58] study, with younger age associated with greater symptom reduction in the clozapine group. The results for the Wahlbeck et al. [76] study were not significant (Table 2).

Similar results were found when duration of illness rather than age was used in the regression (see Table S4 supplementary information).

## Discussion

The results of this systematic review and meta-analysis showed clozapine to be on average superior to alternative antipsychotics in the

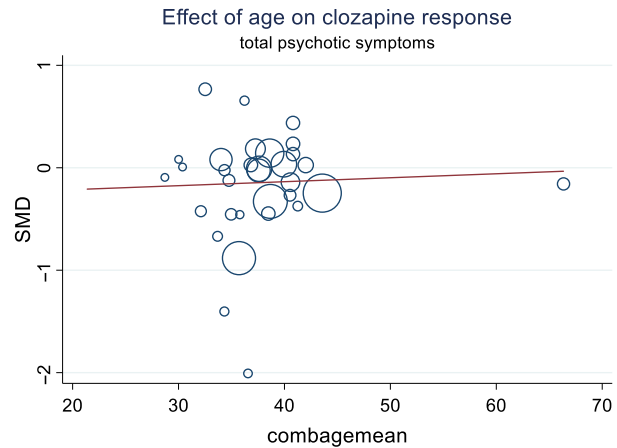


Fig. 3. Scatter plot showing the effect of age on relative clozapine response as measured by total psychotic symptoms. SMD, standardized mean difference; combagemean, combined mean age in studies.

treatment of non-treatment naïve schizophrenia in adults. These findings were consistent across a range of general measures of treatment response, but not in specific clusters of symptoms. The results were robust in sensitivity analyses. The results of the meta-regression found no evidence of an effect of mean age on the relative effectiveness of clozapine. Individual patient data were only available from two studies, and multiple regression of age against drug effect yielded mixed results, with the larger trial showing an association between age and treatment arm.

In the light of recent meta-analyses of clozapine RCT data reporting contrasting results [22,23], the current review helps provide clarity that clozapine has unique benefit for patients who have not responded to first-line treatment. As regards timing of clozapine, the findings of the review do not provide an answer to our hypothesis as to whether earlier use of clozapine is beneficial. Individual patient data meta-analysis would be the optimum method for interrogating the question but

Table 1. Random effects meta-regression of the effect of age/duration of illness on measures of clozapine response relative to alternative antipsychotics

Outcome measure	Age			Duration of illness		
	Mean age/treatment interaction coefficient	P-value	95% confidence interval	Mean duration of illness/treatment interaction coefficient	P-value	95% confidence interval
Total psychotic symptoms	0.00	0.79	−0.03 to 0.03	−0.01	0.51	−0.04 to 0.02
Response rate	0.00	0.86	−0.03 to 0.04	0.01	0.75	−0.03 to 0.04
CGI-S	−0.01	0.35	−0.04 to 0.02	−0.02	0.12	−0.05 to 0.01
Positive symptoms	0.01	0.44	−0.02 to 0.03	0.01	0.66	−0.02 to 0.03
Negative symptoms	0.00	0.78	−0.03 to 0.02	0.00	0.89	−0.02 to 0.03
All-cause discontinuation	−0.03	0.08	−0.06 to 0.00	−0.02	0.11	−0.03 to 0.00
Discontinuation due to lack of efficacy	−0.09	0.06	−0.18 to 0.00	−0.05	0.10	−0.11 to 0.01

CGI-S, clinical global impression-severity scale.

Table 2. Multiple linear regression of interaction between age and treatment arm on change in BPRS scores from studies reporting individual patient data

Change in BPRS total score	Hong et al. [58] $n = 38$ Adj $R^2 = 0.34$			Wahleck et al. [76] $n = 19$ Adj $R^2 = 0.40$		
	Regression coefficient	<i>P</i> -value	95% Confidence interval	Regression coefficient	<i>P</i> -value	95% Confidence interval
Clozapine/comparator drug	−68.95	0.00	−110.71 to −27.20	14.78	0.58	−40.80 to −70.34
Age	−1.30	0.00	−2.08 to −0.52	−0.84	0.1	−1.86 to 0.19
Drug/age interaction	1.38	0.01	0.33 to 2.42	−0.02	0.97	−1.51 to 1.45

BPRS, Brief psychiatric rating scale.

unfortunately this was not available in sufficient quantity for this review.

This study has several strengths, in particular the larger number of studies than previous reviews. The removal of a criterion of treatment resistance increased the number of eligible studies without obviously increasing heterogeneity. The review by Siskind et al. [22] included 21 randomized controlled trials of clozapine and that of Samara et al. [23] twenty. All of the clozapine studies from the Samara et al. clozapine analysis were included in this review, but six studies from the Siskind et al. review were excluded, three because they were studies of childhood-onset schizophrenia, one as it was the phase two of the CATIE study [78], in which the clozapine arm was not blind, and two Chinese studies on the basis that they were either not considered to meet inclusion criteria or we were unable to contact the authors for further information. Cochrane reviews were also of smaller study numbers and were limited to either comparing clozapine to typical [20] or atypical [21] antipsychotics. The inclusion of Chinese language studies is an additional strength, as most English-language reviews include only trials published in English.

The main limitations of the study are firstly those of the methodology of meta-regression itself. Meta-regression is prone to aggregation bias when examining patient-level covariates and can produce misleading results. Thus, the lack of evidence of an effect of age in study-level data is not evidence of an absence of such an effect within studies, at the individual level. Indeed, where we were able to analyse individual patient data, we did see an effect of lower age on increased superiority of clozapine.

Secondly, the outcome in this meta-analysis is not response to clozapine, but the relative response compared to the comparator drug. The lack of a demonstrable effect of age on the superiority of clozapine compared to other antipsychotics does not mean that there is no effect of age on response rates to clozapine per se.

Thirdly, although the sample size of 35 studies is not atypical for meta-regression, the lack of

variability in the mean age means that the lack of evidence of an effect is not surprising. Using duration of illness prior to clozapine prescription as a variable for meta-regression, rather than age, would have been optimal but whilst this was often reported in studies it was not consistently defined. Another potential confounder of using age as a proxy measure for duration of illness is the overlap between adult and child onset schizophrenia, with the latter often carrying a poorer prognosis. For this reason, studies of childhood-onset illness were excluded. Other limitations of the clozapine RCT data in relation to potential methodological bias such as inadequate blinding and the uncertain role of industry funding are unlikely to influence data in relation to age as an effect modifier.

Whilst this study did not find a specific effect of age on differential response to clozapine, this does not argue against the pressing need to reduce delays in clozapine prescribing, which range in the literature from about 4 [14] to 10 years [79]. In the UK, despite the national roll-out of early intervention services, designed to optimize treatment of psychotic illnesses in the critical period of illness, clozapine is still only prescribed to less than half of those who are eligible [80]. Under-use of clozapine remains an issue internationally, particularly in younger patients [81]. The time until eligible patients receive a treatment trial of clozapine is marred by enduring psychotic symptoms and loss in social and occupational functioning. Risks during this period are high, including risk of self-harm or suicide [82]. Delay to clozapine prescribing has been shown to be associated with adverse outcomes in retrospective studies [83].

There is some support in the literature for the existence of a critical period for clozapine prescription. Whilst studies of first-line clozapine for treatment-naïve patients have been inconclusive [84–86], it has been suggested that lack of superiority of clozapine in the first episode population may be due to a ceiling effect, with response rates to antipsychotic medication as high as 90% reported [16]. However, bringing forward the use of clozapine to second line [87] or using clozapine earlier in the

course of a first episode of illness may be more effective [88]. It has also been shown that in first episode schizophrenia the response rate to a second antipsychotic drops dramatically then increases again with clozapine, suggesting that second-line use of clozapine may well be more appropriate than third line [16].

There are many reported barriers to clozapine prescribing, including concerns over need for blood testing and potential for side-effects but also clinician and patient attitudes to clozapine [89-91]. Recent authors have highlighted the need to review stringent blood monitoring requirements for clozapine, which can lead to unnecessary treatment discontinuation [92]. This review helps shore up the evidence base for the use of clozapine in schizophrenia, which has not responded to first-line treatment, and provides some qualified support for the hypothesis that using clozapine earlier in the course of illness is more effective, which it is hoped should help surmount some of these barriers.

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## Declarations of interest

None.

## Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Supporting Information

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

**Figure S1.** Results of planned sensitivity analyses for primary and secondary outcomes.

**Table S1.** Characteristics of Included Studies.

**Table S2.** Cochrane Risk of Bias Tool for included studies.

**Table S3.** Effect of clozapine versus alternative antipsychotics on secondary outcomes.

**Figure S2.** (a) Funnel Plot –total psychotic symptoms; (b) Funnel plot – response rate.