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META-ANALYSIS

Clozapine levels as a predictor for therapeutic response: A systematic review and meta-analysis

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Abstract

Objectives: Clozapine levels may be a more useful predictor of therapeutic response than the dose, given the variability in clozapine metabolism between individuals. We therefore systematically reviewed and meta-analysed the impact of clozapine levels on response and/or relapse to provide guidance on optimal clozapine levels.

Methods: We systematically searched PubMed, PsycInfo and Embase for studies exploring clozapine levels and response and/or relapse. Our primary meta-analysis was rates of response above and below clozapine level thresholds of 350 ng/ml and 600 ng/ml. Secondary analyses were undertaken of mean clozapine levels, dose and concentration/dose (C/D) ratio and response and/or relapse. A meta-regression by study duration was conducted.

Results: Twenty studies met inclusion criteria. Clozapine levels above 350 ng/ml were associated with statistically significantly higher rates of response (OR 2.27 95% CI 1.40–3.67, $p < 0.001$), but not above 600 ng/ml (OR 1.40 95% CI 0.85–2.31, $p = 0.19$). Higher mean clozapine levels were associated with better rates of response (SMD 0.24, 95% CI 0.00–0.49, $p = 0.05$), and lower rates of relapse (SMD −0.72, 95% CI −1.26 to −0.19, $p = 0.008$). By contrast, neither clozapine dose nor C/D ratio was associated with differing rates of response. Similarly, study duration did not affect outcome.

Conclusions: Our findings are in keeping with current guidelines that recommend targeting clozapine levels above 350 ng/ml before augmentation is considered. As some clozapine associated ADRs are dose dependent, levels above 600 ng/ml may have an unfavourable risk-benefit ratio.

KEYWORDS
clozapine, levels, meta-analysis, relapse, response

1 | INTRODUCTION

Treatment-resistant schizophrenia (TRS), defined as ongoing psychotic symptoms and functional deficits despite two adequate antipsychotic trials,[1] affects between 25% and 33% of people with schizophrenia.[2]

For people with TRS, clozapine is the most effective treatment for reducing positive symptoms,[3] hospitalisations[4] and overall mortality.[5] However, only 40% of people with TRS will have an adequate response to clozapine.[6] One possible strategy in this situation is augmentation but the quality of data in clozapine-resistant schizophrenia is limited,[7] with the strongest evidence for antipsychotic augmentation, notably aripiprazole[8] and electro-convulsive therapy (ECT).[9]

One of the challenges in understanding clozapine-resistant schizophrenia is disentangling pseudo- from true resistance to clozapine. In a systematic review of clinical trials in people with clozapine-resistant schizophrenia, many studies did not define the clozapine levels of participants prior to randomisation to intervention or control.[10] This is despite expert guidelines opinion on the treatment of clozapine-resistant schizophrenia recommending clozapine levels be optimised and psychotic symptoms re-evaluated prior to commencement of any augmentation therapy.[11]

There is a lack of clarity in the literature of the optimal minimum clozapine level above which treatment response may be expected. A clozapine level of 350 ng/ml has previously been reported as a minimum cut-off for therapeutic effect, and a level of 600 ng/ml as a level above which there is limited additional therapeutic benefit.[11,12] However, there has been no systematic review of the literature on minimum and maximum effective therapeutic clozapine levels.

We therefore undertook a systematic review and meta-analysis of clinical studies examining the relationship between clozapine levels and therapeutic response among people with schizophrenia, including if there was a threshold level of benefit.

Summations

- Clozapine levels above 350 ng/ml were associated with higher rates of response reinforcing the need to optimise clozapine levels before commencing augmentation strategies.
- Although some individual patients may respond at clozapine levels above 600 ng/ml higher levels may lead to higher rates of adverse drug reactions and as such may be associated with more risk to the patient than benefit.

Limitations

- We are unable to comment on whether clozapine level therapeutic thresholds differ between men and women

2 | METHODS

This systematic review conforms to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[13] A review protocol was prospectively submitted to PROSPERO CRD42021242181, an international database of prospectively registered systematic review protocols.

2.1 | Searches

We undertook systematic searches of PubMed, PsycINFO and EMBASE from database inception up to 9 April 2021 using the search terms (Clozapin* OR Clozaril OR Zaponex OR Denzapin* OR Clopine OR Norclozapine OR Desmethylclozapine) AND (level OR levels OR concentration OR concentrations OR ratio OR ratios) AND (blood OR serum OR plasma) (Table S1). Following removal of duplicates, the titles and abstracts of all electronically identified articles were independently screened by two reviewers (MP, MS). Full text articles were screened by two of three reviewers (EP, MP, MS), with adjudication by DS. Reference lists of included articles were screened for any additional studies. Clozapine researchers were contacted about unpublished datasets.

2.2 | Inclusion and exclusion criteria

We included cohort studies, case series, case-control studies and randomised and non-randomised controlled trials. Single case reports were excluded. There were no language restrictions. To be included, studies had to report information on mean (and SD) clozapine levels among people with schizophrenia or schizoaffective disorder, and a measure of response and/or relapse.

2.3 | Study quality

A modified Newcastle-Ottawa Scale[14] was used to rate study quality (Table S4). The maximum score of the scale was 5. Studies with a score of ≥3 points were deemed to be of high quality with a low risk of bias. The following domains were considered: sample representativeness, sample size, comparability between responders and non-responders, ascertainment of clozapine levels, quality of reporting.

TABLE 1 Included studies

Author (year)	Country	Setting	Data collection	Diagnosis	Diagnostic tool	Number of participants (total (male)) meeting criteria in response/non-response group[a]
Non-Response						
Chong (1997)	Singapore	Inpatient	Prospective	Schizophrenia	DSM-III-R	8 (3)/6 (1)
Dettling (2000)	Germany	Inpatient and outpatient	Prospective	Schizophrenia	DSM-III-R	21 (13)/13 (5)
Fabrazzo (2002)	Italy	Inpatient and outpatient	Prospective	Schizophrenia	DSM-IV	23 (15)/9 (6)
Hasegawa (1993)	US	Inpatient and outpatient	Prospective	Schizophrenia	DSM-III-R	30/29
Hussein (1999)	Saudi Arabia	Unknown	Prospective	Schizophrenia	Not stated	11 (8)/15 (1)
Kronig (1995)	US	Inpatient	Prospectve	Schizophrenia or schizoaffective disorder	DSM-III	15/22
Llorca (2002)	France	Inpatients	Prospective	Schizophrenia	DSM-IV	19 (16)/18 (12)
Mauri (2004)	Italy	Inpatient	Prospective	Schizophrenia	DSM-IV	22/8
Perry (1991)	US	Inpatient	Prospective	Schizophrenia	DSM-III-R	11 (8)/18 (12)
Pickar (1992)	US	Inpatient	Prospective	Schizophrenia or schizoaffective disorder	DSM-III-R	8 (5)/13 (8)
Potkin (1994)	US	Inpatient	Prospective	Schizophrenia	DSM-III-R	15/35
Siskind, unpublished	Australia	Inpatient and outpatient	Prospective	Schizophrenia or schizoaffective disorder	DSM-V	3 (2)/9 (8)
Spina (2000)	Italy	Inpatient and outpatient	Prospective	Schizophrenia	DSM-IV	18 (15)/27 (20)
VanderZwaag (1996)	US	Inpatient	Prospective	Schizophrenia	DSM-III-R	30/56
Wong (2006)	Hong Kong	Inpatient	Prospective	Schizophrenia or schizoaffective disorder	DSM-IV	22 (14)/29 (24)
Yada (2021)	Japan	Inpatient	Retrospective	Schizophrenia	ICD-10	79 (45)/52 (28)
Yuanguang (1998)	China	Not stated	Prospective	Schizophrenia	CCMD	131/45

Mean age (SD) in response/non-response groups[a]	Illness duration in years (SD) in response/non-response group[a]	Study duration	Antipsychotic co-medications	Non-response criteria	Participants. met treatment resistance classification[b]
31.6 (4.3)/34.5 (4.7)	15.4 (4.8)	12 weeks	None	>20% reduction in BPRS score and either a CGI-severity score ≤3 or BPRS score ≤35)	Yes
31.5 (10.2)/37.4 (10.5)	Not stated	10 weeks	None	>20% reduction in BPRS score	Yes
35.1 (11.3)/36.3 (10.5)	11.9 (7.2)	52 weeks	None	>20% reduction in BPRS score, or a post-treatment BPRS score >47	Yes
33.4 (10.2)/36.4 (11.0)	Not stated	24 weeks	None	>20% reduction in BPRS score	Yes
33.0 (6.3)/34.1 (11.1)	Not stated	2–41 months	None	>20% reduction in PANSS score	Yes
27.9 (6.2)	8.7 (5.7)	6 weeks	None	>20% reduction in total BPRS score and either a CGI-severity score ≤3 or BPRS-A score ≤35)	Yes
32.1 (8.4)/37.6 (11.8)	8.0 (4.3)	18 weeks	None	>20% reduction in PANSS score	Yes
Not Stated	Not stated	8 weeks	None	>20% reduction in BPRS score	Yes
34.2 (7.5)/32.6 (8.1)	13.6 (5.9)/13.3 (6.4)	4 weeks	None	>20% reduction in BPRS and a BPRS score ≤34)	Yes
31.8 (6.8)/28.0 (5.4)	10.8 (8.1)/11.7 (5.4)	27 weeks	None	>20% reduction in total BPRS, a BPRS score <36 or Bunney-Hamburg Global Psychosis Rating ≤ 6	Yes
Not stated	Not stated	12 weeks	None	>20% reduction in total BPRS score and either a CGI-severity score ≤3 or BPRS-A score ≤35)	Yes
30.0 (12.1)/35.9 (12.9)	Not stated	24 weeks	Cross taper from prior antipsychotic	>20% reduction in BPRS score	Yes
37.7 (8.8)/38.4 (11.5)	Not stated	12 weeks	None	>20% reduction in BPRS score and a BPRS score ≤35)	Yes
38 (range 21–56)	16 (–)	12 weeks	None	>20% reduction in total BPRS score	Yes
34.5 (7.4)/40 (8.9)	16.1 (7.4)/20.6 (7.9)	12 weeks	None	>20% reduction in BPRS score and either a CGI-severity score <3 or BPRS score <35)	Yes
40.1 (11.5)/39.9 (12.5)	18.7 (10.3)/18.4 (12.3)	12 weeks	None	>20% reduction in total BPRS score	Yes
Not Stated	Not stated	6 weeks	None	Not clear	Not stated

(Continues)

TABLE 1 (continued)

Author (year)	Country	Setting (i.e., inpatient)	Type of study (i.e., retrospective, prospective)	Diagnosis	Diagnostic tool	Number of participants (total (male)) meeting criteria in relapse/non-relapse group[a]
Relapse						
Gaertner (2001)	Germany	Outpatient	Prospective	Schizophrenia	ICD-10	10/13
Stieffenhofer (2011)	Germany	Outpatient	Prospective	Schizophrenia	ICD-10	6 (1)/18 (5)
Xiang (2006)	China	Outpatient	Prospective	Schizophrenia	ICD-10	33 (19)/69 (33)

Note: CCMD = Chinese Classification of Mental Disorders the second edition of the diagnostic criteria for schizophrenia.

[a]Data for entire cohort provided where disaggregated data not available.

[b]TRS criteria adapted from Kane et al (1988): two 6 week trials of different antipsychotics with a chlorpromazine equivalent >600 mg/day.

2.4 | Data extraction

Data were extracted by three reviewers (EP, MP, MS) and validated by DS. The following data wee extracted for participants, with disaggregation by response vs non-response and relapse vs non-relapse groups where available.

- Country of study
- Setting (inpatient or outpatient)
- Prospective of retrospective collection of data
- Diagnostic criteria and diagnoses
- Number and sex of participants
- Age of participants
- Mean (and standard deviation) serum Clozapine levels (ng/ml)
- Mean (and standard deviation) Clozapine dose (mg)
- Number of participants per study who responded and/or relapsed with serum Clozapine levels >350 ng/ml and >600 ng/ml
- Illness duration of participants
- Study duration
- Antipsychotic co-medications
- Criteria for non-response and relapse
- Whether participants met criteria for treatment refractory schizophrenia adapted from Kane et al.[15] 1988 (two 6-week trials of different antipsychotics with a chlorpromazine equivalent >600 mg/day)

2.5 | Data synthesis and analysis

The primary outcome was a meta-analysis of response rates at clozapine levels above and below 350 ng/ml, assessed as an odds ratio. Secondary analyses included odds ratios of response at clozapine levels above and below 600 ng/ml, as well as assessing the association between response and mean clozapine levels, dose, concentration to dose ratios (C/D ratios), norclozapine levels and clozapine to norclozapine ratio as measured by the standardised mean difference. The C/D ratio is a proxy measure for fast or slow clozapine metabolism. We repeated the above analyses for the effects on relapse. Finally, we investigated any differences in gender or mean age between responders/non-relapsers and non-responders/relapsers. We used the random-effects model throughout as we could not definitively exclude between-study variation even in the absence of statistical heterogeneity. A number needed to treat was calculated for the primary outcome.

Meta-analyses were conducted using Revman (Version 5.4). Meta-regressions, Kendall's Tau, Egger's regression and Funnel Plot were conducted using Comprehensive Meta-Analysis (Version 3.3). Heterogeneity was assessed using the I^2 statistic, providing an estimate of the variability due to heterogeneity rather than chance, with >50% suggesting possible heterogeneity and >75% suggesting high heterogeneity. As the primary studies were observational, and expected levels of heterogeneity were high, a random-effects model was used throughout. Significance was set at $\alpha < 0.05$.

2.6 | Sensitivity analyses

Sensitivity analyses were undertaken on study quality and ethnicity (Asian versus non-Asian participants) given the literature suggesting slower clozapine metabolism among Asian populations.[16] Meta-regression was undertaken by study duration.

Mean age (SD) in relapse/non-relapse groups	Illness duration in years (SD) in relapse/non-relapse groups[a]	Study duration	Antipsychotic co-medications	Relapse criteria	Remission criteria at time of recruitment
40, 13	9.9 (7)	46 months	None	One of the BPRS psychosis factor scores exceeding 4	Score ≤ 9 on seven BPRS items on four successive occasions
34.5, 4.6	Not stated	21 months	One in three patients on another antipsychotic	Rehospitalisation	Not stated
34.6, 5.8	8.7 (6.1)/8.7 (6.0)	12 months	None	>20% increase in total or self-injury or hospitalisation	BPRS ≤ 30

2.7 | Publication bias

For the primary meta-analysis, we tested publication bias with Kendall's Tau and Egger's regression, where low p-values suggest publication bias, and a Funnel Plot.

3 | RESULTS

Following removal of duplicates, 7219 studies were identified in the database search. One unpublished dataset was identified.[17] Of these, 6954 studies were excluded at the title and abstract level. Of the 265 articles reviewed at full text level, 20 met inclusion criteria.[17–36] A PRISMA Flow Chart is provided as Figure S1, and a Table of Excluded Studies as Table S6.

3.1 | Study characteristics

The 20 included studies included data on 1019 participants (Table 1 Table of Included Studies). Studies were from Europe ($n = 7$), North America ($n = 6$), Asia ($n = 6$) and Australia ($n = 1$). Nine studies had data on inpatients, three on outpatients, five on a combination of inpatients and outpatients and in two studies this was unclear. Diagnostic classifications for the diagnoses of schizophrenia and schizoaffective disorder included DSM-III, DSM-IV, DSM-V, ICD-10 and Chinese Classification of Mental Disorders (CCMD). Mean clozapine levels ranged from 211 ng/ml to 791 ng/ml, while doses ranged from 306 mg to 481 mg, and C/D ratios from 0.66 to 2.69. Clozapine levels were undertaken from serum in five studies, with the remaining 15 from plasma (Table S6); however, clozapine levels in serum and plasma clozapine are comparable.[37] The reported mean durations of illness ranged from eight to 18.7 years. Mean study duration was 32 weeks (SD 43, range 4–184). Fifteen studies with data on response reported no antipsychotic co-prescribing, one reported cross tapering of the previous antipsychotic. Only one of the three studies with data on relapse reported antipsychotic co-prescribing in one third of included participants. All studies of response reported that included participants met criteria for treatment resistant schizophrenia. (Table 1 Included Studies).

All included studies compared separate groups of participants who met either response versus non-response criteria, or relapse versus non-relapse criteria. Sixteen studies provided data on participants who did or did not meet response criteria, while three studies provided data on participants who relapsed or did not relapse.

Response criteria were reported to be >20% reduction in PANSS or BPRS in all but one of the 17 studies on response, with eight of these studies also requiring a BPRS threshold of at least 34 or a CGI of 3 or more. Relapse criteria ranged from rehospitalisation to change in BPRS score.

Overall study quality was good, with all but one study rated to be of high quality (Table S5 Risk of Bias). Over half ($n = 13$) of the studies had less than 50 participants, while seven did not provide sufficient data to compare the sex and age of participants with response/non-relapse and non-response/non-relapse.

There was no statistically significant difference between the response/non-relapse and non-response/relapse groups in terms of age and gender (Figure S7 and

Figure S8). There was insufficient data to compare rates of smoking between participants with response/non-relapse and non-response/relapse groups.

3.2 | Meta-analyses

3.2.1 | Response

Twelve studies (eleven high quality) of 380 participants provided data on a response above and below clozapine levels of 350 ng/ml.[17,18,20,23–25,28–30,32,35,36] (Figure 1) Participants with a clozapine level above the threshold were 2.27 times more likely to meet response criteria (95% CI 1.40–3.67, $p < 0.001$, I^2 36%). This corresponds to a number needed to treat of 5. By contrast, using a threshold of 600 ng/ml, there was no significant difference in rates of response using data from 6 studies of 166 participants (OR 1.40 95% CI 0.85–2.31, $p = 0.19$, I^2 0%), with a number needed to treat of 8.4. Sensitivity analysis by ethnicity or study quality did not alter the overall significance of the results. There was no statistically significant difference by study duration in a meta-regression (Table S2).

Fourteen studies (13 high quality) with 696 participants had data on mean clozapine levels and whether participants met response criteria.[17,18,23–25,28,35] (Figure 2) An analysis of continuous clozapine levels found that higher clozapine levels were associated with lower rates of relapse (SMD 0.24, 95% CI 0.00–0.49, $p = 0.05$, $I^2 = 49\%$). Sensitivity analysis by study quality did not impact the overall significance of the results, although when the meta-analysis was restricted to either only studies with Asian or non-Asian participants, it failed to reach statistical significance.

Eight high-quality studies with 358 participants had data on clozapine dose as well as C/D ratio, with no difference between lower or higher clozapine dose or C/D ratio and response.[17,18,20,23,24,26,30,35] (Figure S3 and Figure S4). Nine high-quality studies with data on 426 participants had data on mean norclozapine level, and clozapine/norclozapine ratio and response.[17,20,23,27,28,30,33,35,26] Norclozapine levels were statistically significantly higher in participants who responded (SMD 0.30, 95%CI 0.03 to 0.56, $p = 0.03$,

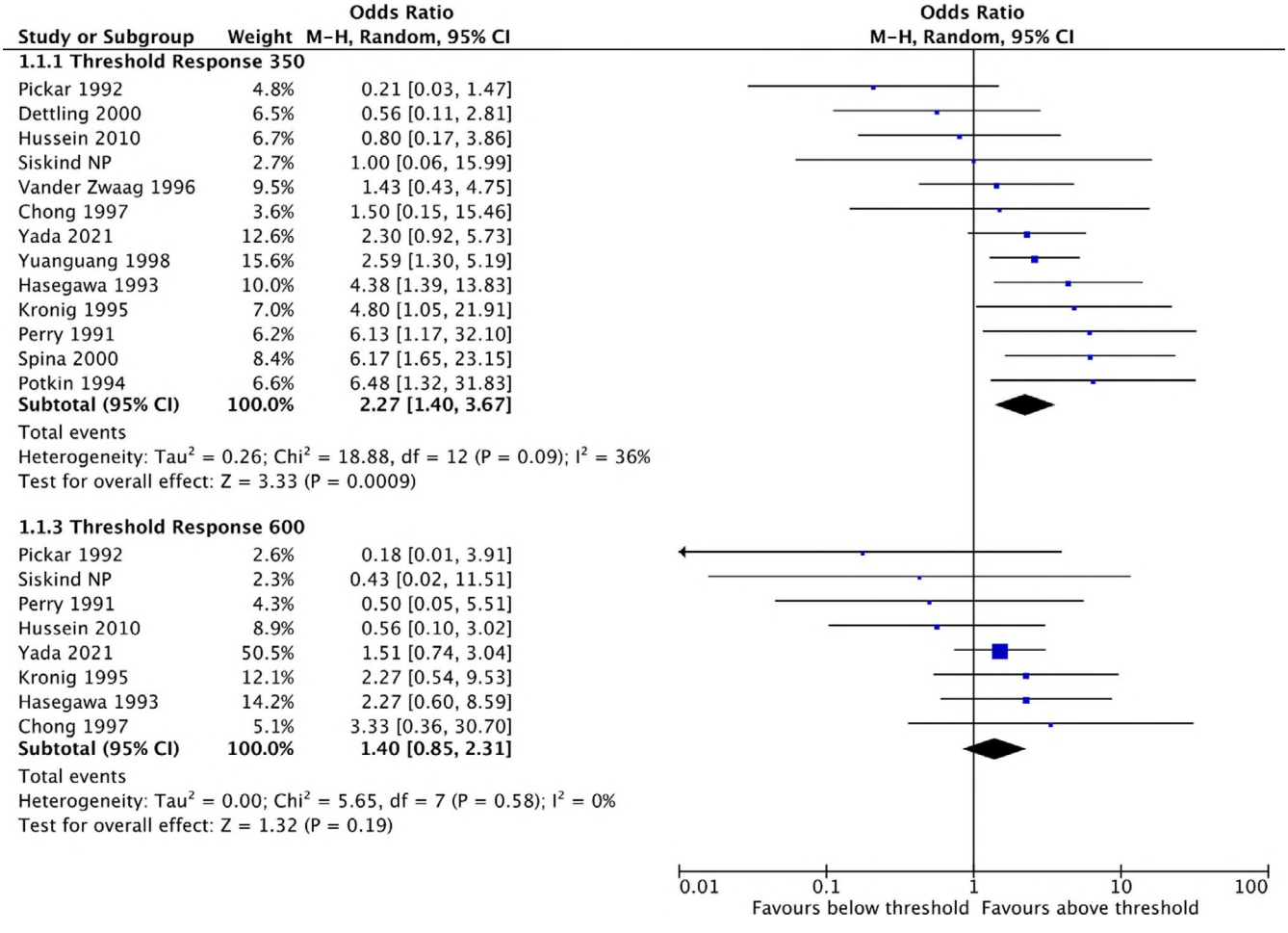

FIGURE 1 Forest plot of response at clozapine level thresholds of 350 ng/ml and 600 ng/ml. For the analysis of clozapine response at 350 mg/ml, some studies provided data for slightly different clozapine thresholds: Dettling 2000 (threshold of below 350 ng/ml and above 450 ng/ml) and Potkin 1994 (above and below 420 ng/ml)

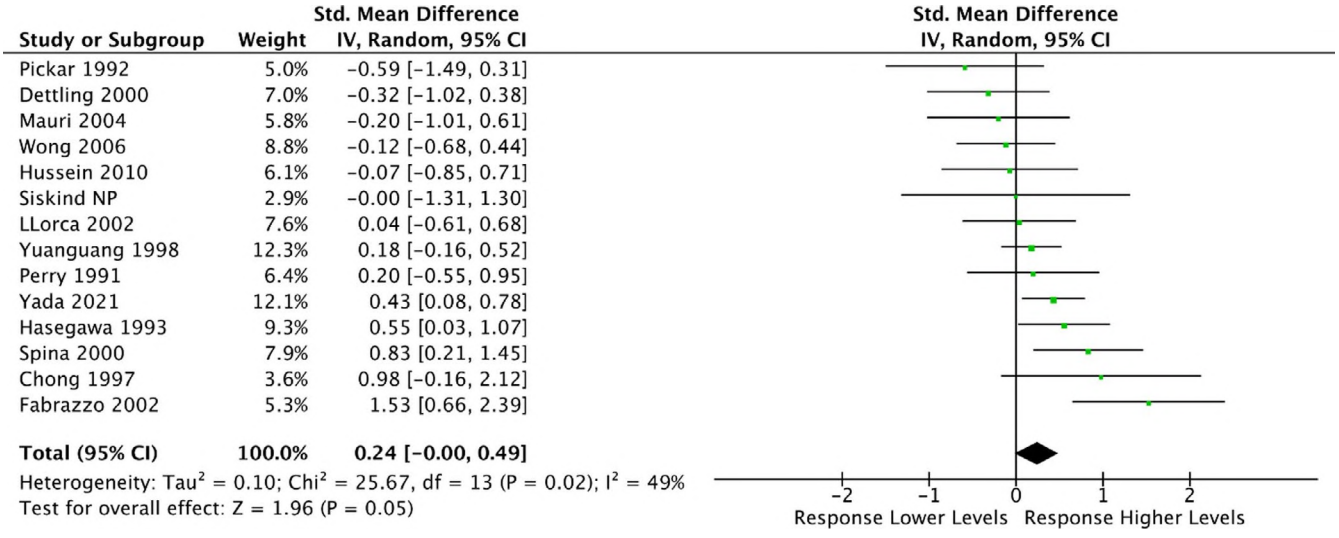

FIGURE 2 Forest plot of response and mean clozapine levels

I^2 = 36%), while there was no statistically significant difference reported in clozapine/norclozapine ratio. Figure S5 and Figure S6 The overall significance was not impacted by sensitivity analysis by ethnicity of participants.

3.2.2 | Relapse

There was insufficient data to examine relapse above and below thresholds of 350 ng/ml or 600 ng/ml. Three high-quality studies of 149 participants found lower clozapine levels were associated with higher rates of relapse (SMD −0.72, 95% CI −1.26 to −0.19, p = 0.008, I^2 = 42%).[22,31,34] (Figure S2) These results remained significant when only data from the one study with Asian participants was included, but not when it was excluded. Using data from two studies with 126 participants, the clozapine dose was not statistically significantly different between participants who did or did not relapse; however, the C/D ratio was lower among those who relapsed (SMD −0.70, 95% CI −1.09 to −0.31, $p < 0.001$, I^2 = 0%). (Figure S4).[31,34] There were insufficient studies to do meaningful sensitivity analysis.

Using the primary analysis of odds ratio of response above and below clozapine levels of 350 ng/ml, neither the Kendall's Tau nor Egger's regression showed evidence of publication bias (Table S3). The funnel Plot is provided as Figure S9.

4 | DISCUSSION

This is the first study to comprehensively meta-analyse the impact of clozapine levels on response and relapse. We found that clozapine levels above a threshold of 350 ng/ml were associated with higher rates of response among people with schizophrenia. However, we did not find evidence of additional benefit of levels above 600 ng/ml. Overall, higher clozapine levels were associated with higher rates of response and lower rates of relapse.

These findings are in keeping with current consensus guidelines on the use of clozapine, which recommend that for people with inadequate response to clozapine, the first step should be to optimise clozapine levels to between 350 ng/ml and 600 ng/ml before considering augmentation of clozapine.[11,38] This is to ensure that pseudo-resistance to clozapine is excluded prior to adding further treatments. Although the evidence for augmentation of clozapine is limited, with there is the most evidence for augmentation with second-generation antipsychotics, ECT and cognitive-behavioural therapy.[7,8,11,39]

We found that higher clozapine levels were associated with higher rates of response. However, higher rates of adverse drug reactions from clozapine have been also been found to be associated with higher clozapine levels,[40] especially tachycardia and dyslipidaemia.[40] Risk of seizures are also increased with clozapine levels above 1000 ng/ml.[41] As such, our finding that clozapine levels above 600 ng/ml were not associated with statistically significantly higher rates of response is worth reflecting on. Although higher levels of clozapine may be of benefit to certain patients, the potential harms to patients may outweigh the benefits.

By contrast, clozapine dose was not associated with response rates. One explanation is that clozapine metabolism differs between individuals, and so serum levels are a more accurate predictor of response than absolute dose. Clozapine

is metabolised by the cytochrome P450 (CYP) system, in particular through 1A2, with lessor contributions from 2D6 and 3A4.[42] Ethnicity can impact clozapine metabolism, with people of Asian and Amerindian ancestry requiring lower doses than Caucasians.[16,43] Medications such as fluvoxamine inhibit CYP1A2, leading to higher clozapine levels[44] while the polycyclic hydrocarbons in cigarette smoke induce CYP1A2, leading to lower clozapine levels.[45] As such, our findings that clozapine dose did not correlate with relapse or response rates are understandable. Of note, sensitivity analysis by Asian ethnicity did not impact the overall rate of response. Unsurprisingly, higher norclozapine levels were also associated with higher rates of response.

Similarly, there was no relationship between clozapine concentration to dose (C/D) ratio and response. This ratio is sometimes used to assess rate of clozapine metabolism, a lower ratio being associated with faster metabolism. There was a significant association between lower C/D ratio and relapse in a meta-analysis of two studies, but this was driven by one study where relapse was related to clozapine non-adherence,[34] and as such this finding should be interpreted with caution.

Our study had several limitations. Firstly, there were insufficient data to meaningfully meta-analyse rates of relapse at multiple clozapine level thresholds or to assess the impact of smoking on response rates and levels. This may be relevant given the high rates of tobacco use in this population and recent meta-analytic findings that clozapine levels in smokers were significantly lower than in non-smokers.[45] Furthermore, there were insufficient data to do sub-analyses by sex, and as such we are unable to comment as to whether clozapine response thresholds differ between men and women. Similarly, we could not analyse whether multiple clozapine level thresholds were associated with differing rates of relapse. There was insufficient information in the included studies to determine the duration that participants were at the reported clozapine levels, and as such some non-responders may have responded if they had been at therapeutic levels for longer. Response definitions were usually aligned with the criteria outlined by Kane et al 1988.[15] These criteria may not align with more recent definitions for response, which have a higher threshold.[46] We were only able to include data from 20 studies with just over 1000 participants, which may limit generalisability. The clozapine level thresholds selected reflected those provided by the published studies, and an analysis of response by specific clozapine levels was not able to be undertaken in this meta-analysis. There was a lack of consistent information on dosing schedules among the included studies. As such, it is possible that people who do not respond to clozapine may receive higher doses, leading to higher clozapine levels among non-responders. This may artificially suggest that people on higher doses are less likely to respond, making detection of an upper dose threshold more challenging. Finally, although the heterogeneity of our primary outcome was low, heterogeneity was higher for some of the secondary analyses, and as such these results should be treated with caution even though we tried to incorporate heterogeneity through the use of random-effects models.

Reassuringly, definitions of clozapine response were consistent between studies, and all studies reported that clozapine testing was done as a trough level.

5 | CONCLUSIONS

We found that clozapine levels above 350 ng/ml were associated with higher levels of response, while levels above 600 ng/ml did not increase response rates. This is in keeping with clozapine optimisation guidelines which recommend targeting clozapine levels above 350 ng/ml to rule out pseudo-resistance before augmenting clozapine. Overall, higher clozapine levels were associated with higher rates of response. Although certain individual patients may benefit from clozapine levels above 600 ng/ml, this must be weighed against a potential risk of dose dependent clozapine associated adverse drug reactions in a shared decision making approach with patients and their carers.

CONFLICTS OF INTEREST

There are no conflicts of interest to declare.

PEER REVIEW

The peer review history for this article is available at https://publons.com/publon/10.1111/acps.13361.

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 online in the Supporting Information section.

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