Efficacy of clozapine versus second-generation antipsychotics in people with treatment-resistant schizophrenia: a systematic review and individual patient data meta-analysis

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Summary

Background Clozapine is recommended by national and international guidelines for people with treatment-resistant schizophrenia. However, available meta-analyses of randomised controlled trials have not shown superior efficacy of clozapine when compared with other second-generation antipsychotics, with heterogeneity identified between the original studies. We aimed to use individual patient data (IPD) to account for potential reasons of variability and to synthesise an adjusted estimate for the difference in efficacy between clozapine and other second-generation antipsychotics for treatment-resistant schizophrenia.

Methods In this systematic review and IPD meta-analysis, we searched the Cochrane Schizophrenia Group's Study-Based Register from inception to Jan 24, 2024, and previous reviews for blinded randomised controlled trials comparing clozapine with other second-generation antipsychotics in participants with treatment-resistant schizophrenia. Trials were eligible if they included patients with treatment-resistant schizophrenia and had a duration of at least 6 weeks. IPD were requested from trial investigators. The primary outcome was change in overall schizophrenia symptoms as measured by the Positive and Negative Syndrome Scale (PANSS) between clozapine and other second-generation antipsychotics after 6–8 weeks of treatment. The effect size measure for the primary outcome was mean difference with 95% credible interval (CrI). We fitted a Bayesian random-effects IPD meta-regression model that included duration of illness, baseline severity, and sex as potential prognostic factors or treatment effect modifiers. Confidence in the evidence was assessed using Grading of Recommendations, Assessment, Development, and Evaluation (GRADE). People with lived experience of mental illness were involved in this study. This study is registered with PROSPERO, CRD42021254986.

Findings We screened 13 876 references and included 19 studies with data for 1599 participants; IPD were available for 12 of 19 trials (n=1052; mean age 37·67 years [SD 11·24; range 10–66]; 348 [33·08%] women and 704 [66·92%] men). Data on ethnicity were not available. The estimated mean difference in change from baseline PANSS total score was –0·64 points (95% CrI –3·97 to 2·63; τ=2·68) in favour of other second-generation antipsychotics. Shorter duration of illness and higher baseline severity were prognostic factors associated with a larger reduction in symptoms, but neither those factors nor sex were found to modify the relative effect between clozapine and other second-generation antipsychotics. The confidence in the evidence was graded as very low.

Interpretation This IPD meta-analysis found a small and uncertain advantage of other second-generation antipsychotics, mainly olanzapine and risperidone, and so did not provide evidence for superior efficacy of clozapine compared with other second-generation antipsychotics in treatment-resistant schizophrenia. It is limited by unavailability of IPD for some studies, uncaptured sources of variance, and uncertainty due to premature study discontinuation. Given the side-effects of clozapine, the observed uncertainty regarding clozapine's superiority warrants prudent use and further research.

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Introduction

In up to a third of individuals with an acute episode of schizophrenia, standard antipsychotic treatment does not lead to sufficient improvement of symptoms.[1,2] Clinical guidelines[3–6] recommend the use of the antipsychotic clozapine in such cases, because it is considered more efficacious than other antipsychotics, especially in people with treatment-resistant schizophrenia (typically defined as insufficient response to two trials of different antipsychotics with adequate dose

Research in context

Evidence before this study

Clozapine is recommended by national and international clinical guidelines for treatment-resistant schizophrenia (typically defined as insufficient response to two trials of different antipsychotics with adequate dose and duration). We searched PubMed from database inception to June 12, 2024, for any meta-analyses of randomised controlled trials with an English language abstract, regardless of the full-text language, investigating efficacy of antipsychotic drugs in participants with treatment-resistant schizophrenia. We used the search terms: ("schizophrenia"[MeSH Terms] OR "schizophrenia"[All Fields]) AND ("resistant"[All Fields] OR "refractory"[All Fields] OR ("clozapine"[MeSH Terms] OR "clozapine"[All Fields])) AND ("antipsychotic"[MeSH Terms] OR "antipsychotic"[All Fields]) AND "meta-analysis". Our search yielded 243 articles, however, none were individual patient data meta-analyses. The available pairwise and network meta-analyses, which used aggregate data (ie, summary results per intervention group) from randomised controlled trials, indicated superior efficacy of clozapine versus first-generation antipsychotics, but superior efficacy compared with second-generation antipsychotics was not demonstrated. However, these meta-analyses identified heterogeneity in the summary estimates between studies and high variation in efficacy between participants.

Added value of this study

We used an individual patient data (IPD) meta-analysis to synthesise an adjusted estimate of the difference in efficacy between clozapine and other second-generation antipsychotics. We harmonised the measured outcomes across randomised controlled trials, and imputed missing data and accounted for differences in participant characteristics that might modify the treatment effect using IPD. No significant difference in efficacy was identified between clozapine and other second-generation antipsychotics (olanzapine, risperidone, zotepine, ziprasidone, or clinician-choice second-generation antipsychotics). Additionally, we found that shorter duration of illness and higher baseline severity were associated with a larger reduction in symptoms on both clozapine and other second-generation antipsychotics. However, neither duration of illness and baseline disease severity nor sex were associated with an increased response to clozapine compared with other second-generation antipsychotics. Two of the main limitations of our study were IPD not being available for all conducted studies and not being able to evaluate all potentially relevant patient variables (such as dose and plasma levels of clozapine).

Implications of all the available evidence

Based on meta-analyses of aggregate data and IPD from randomised controlled trials, there is no clear evidence for superior efficacy of clozapine in treatment-resistant schizophrenia. However, there are some indications from observational studies, individual randomised controlled trials in treatment-resistant schizophrenia, and meta-analyses of randomised controlled trials in non-treatment-resistant participants that clozapine might lead to a better outcome compared with other second-generation antipsychotics. Due to the lack of consensus regarding the superiority of clozapine and considering its multiple and potentially serious side-effects, cautious clinical use of clozapine seems warranted. This might include adequate previous treatment with other second-generation antipsychotics, a critical assessment of the outcome on clozapine, and its discontinuation in case of insufficient response. To specify clozapine's role in treatments for people with treatment-resistant schizophrenia, future studies should include participants with strictly defined treatment-resistant schizophrenia, monitor response and plasma concentrations, adapt the dose of antipsychotics in response to the therapeutic plasma range, and explore inter-individual variability in response to clozapine.

and duration). However, in meta-analyses of randomised controlled trials, which are the gold standard of evidence-based medicine, clozapine was mainly superior to chlorpromazine and haloperidol, whereas superior efficacy versus other second-generation antipsychotics was not demonstrated.[7–9] Another observation from these meta-analyses was the variation in treatment effects between participants (as evident by wide confidence intervals in the original studies) and the heterogeneity in results between studies (favouring clozapine in some trials and favouring other second-generation antipsychotics in others). This indicates that differences between participants, treatment regimens, and study methods influenced the treatment outcome.

Improved care for treatment-resistant schizophrenia is a top research priority in schizophrenia according to affected individuals,[10] and the question of whether clozapine is actually more efficacious than other second-generation antipsychotics is therefore of high clinical relevance. Moreover, clozapine causes multiple side-effects (eg, weight gain, sedation, anticholinergic effects, and sialorrhea), including rare but serious disorders such as agranulocytosis (occurring in ≥1 per 1000 patients to <1 per 100 patients), myocarditis (in ≥1 per 10 000 patients to <1 per 1000 patients), and seizures (in ≥1 per 100 patients to <1 per ten patients),[11] and should therefore be used with caution.

Previous evidence from randomised controlled trials was synthesised using aggregate data (ie, summary results per intervention group). By conducting an individual patient data (IPD) meta-analysis, we aimed to harmonise the outcomes from different studies, impute missing data, and account for differences in participant, treatment, and study characteristics using regression

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and sensitivity analyses at the participant level. We aimed to synthesise an adjusted estimate of the difference in efficacy between clozapine and other second-generation antipsychotics in treatment-resistant schizophrenia and to investigate the association between particular characteristics and treatment outcome.

Methods

Search strategy and selection criteria

This systematic review with IPD meta-analysis was approved by the ethics commission of the Technical University of Munich (612/21 S-NP), was registered on PROSPERO (CRD42021254986), and the protocol has been published previously,[12] with any necessary adaptations documented in the appendix (p 6). We report this systematic review and IPD meta-analysis in accordance with the PRISMA-IPD statement[13] (appendix p 1).

See Online for appendix

Briefly, two authors (JS-T and SD) independently searched the Cochrane Schizophrenia Group's Study-Based Register (appendix p 8) from inception to Jan 24, 2024 and the reference lists of previous reviews[7–9] for double-blind and single-blind randomised controlled trials comparing clozapine with other second-generation antipsychotics (as antipsychotic monotherapies) in people with treatment-resistant schizophrenia (as defined by the trial authors). Full search terms are in the appendix (p 8). We only included studies with a study population of at least 80% participants with schizophrenia or related disorders. We excluded studies with a duration of less than 6 weeks (because antipsychotics should be used at least 6 weeks before assuming treatment resistance[14]), studies from China (due to serious quality concerns[15]), and the second phase of crossover studies.

Data collection

We contacted the original investigators of eligible studies, including pharmaceutical companies, to invite them to collaborate and requested anonymised IPD for the trial. The IPD datasets that we received were brought into a common format using R and checked for unusual values and unlikely patterns of group allocation. The summary results that were calculated using IPD were then cross-checked with the aggregate data results from publications (extracted in duplicate by JS-T and SD). Additionally, two authors (JS-T and SD) extracted multiple study characteristics (eg, definition of treatment resistance applied and sponsorship), participant characteristics (eg, age, sex, and weight), and treatment characteristics (eg, antipsychotic dose and plasma concentration) that might affect the treatment effect (appendix p 10).

Outcomes

The primary outcome was the change in overall schizophrenia symptoms at 6–8 weeks of treatment as measured by the Positive and Negative Syndrome Scale (PANSS).[16] The PANSS is the most commonly used scale to assess symptoms of schizophrenia, with possible scores ranging from 30 to 210 points. Scores of 60, 75, 90, and 110 correspond to mildly, moderately, markedly, and severely ill, respectively, on the Clinical Global Impression-Severity (CGI-S) scale.[17] If the Brief Psychiatric Rating Scale (BPRS)[18] was used, we transformed the scores to PANSS scores using equipercentile linking.[19]

Secondary outcomes were the changes in BPRS positive and BPRS negative symptoms score (calculated from BPRS or PANSS items), the number of participants with at least a minimal response (defined as a ≥20% reduction in PANSS or BPRS scores), and the number of participants who discontinued treatment for any reason. All outcomes were assessed at 6–8 weeks of treatment (8 weeks preferred).

Data analysis

For analysis, we imputed missing data in outcomes and characteristics using multilevel joint modelling multiple imputations,[20] to generate ten complete datasets. Then, for each dataset, we fitted a Bayesian random-effects IPD meta-regression model including prognostic factors (ie, factors possibly associated with the outcome in both intervention groups) and treatment effect modifiers (ie, factors possibly associated with the difference in the treatment effect between interventions). Prognostic factors were duration of illness in years and baseline severity of symptoms on PANSS; treatment effect modifiers were duration of illness, baseline severity, and sex. These were selected from the extracted variables considering clinical importance, availability, redundancy, statistical power, and computational ease (details and rationale in the appendix p 10). Continuous outcomes were analysed by linear regression and effect size measures were presented as mean difference; binary outcomes were analysed using logistic regression with odds ratio (OR). The study-specific effect sizes and covariate effects were combined across studies using a random-effects meta-analysis model. The heterogeneity in treatment effects between studies was measured by their variance (τ^2). For two studies, IPD were only available in protected research environments.[21,22] Data from those two studies were analysed using the same linear and logistic regression models, and the resulting estimates of treatment effects and covariate effects were combined in a common-effects meta-analysis and used as informative priors for the analysis of the locally available IPD. The final results were derived from the analyses of the ten imputed datasets using Rubin's rule[20] (appendix p 17).

We did several sensitivity analyses of the primary outcome using baseline severity of positive symptoms and negative symptoms as separate prognostic factors and effect modifiers; and with exclusion of single-blind studies, studies at high risk of bias, studies that included

participants with intolerance to previous antipsychotics in addition to participants who were treatment-resistant to previous antipsychotics, studies that included participants with intolerance to previous antipsychotics and studies that used relaxed criteria for defining treatment resistance (ie, we included studies with participants resistant to at least two previous antipsychotics only), and studies sponsored by pharmaceutical companies. Additionally, we analysed the primary outcome after 12–15 weeks and after 24–30 weeks of treatment, instead of 6–8 weeks. We also adjusted for differences in clozapine doses applied, and we excluded studies of low doses of clozapine (according to the highest dose allowed and the mean dose used, because individual participant's doses were not suitable for analysis; appendix p 6). To present the underlying data transparently and as post-hoc sensitivity analyses, we conducted standard frequentist random-effects meta-analyses of the primary outcome at study endpoint using published data, at 6–8 weeks (ie, observed cases), at the timepoint nearest to 6–8 weeks (similar to last-observation-carried-forward), and at 6–8 weeks using data generated by multiple imputation for second-generation antipsychotics as a group and for each specific antipsychotic versus clozapine separately; this analysis was additionally conducted with Bayesian methods. We also conducted a frequentist IPD meta-regression analysis, and finally, to combine and compare results of studies with IPD available and not available, we conducted random-effects Bayesian and frequentist pairwise meta-analyses of all identified studies with subgroups by IPD availability.

For interpretability of results, we transformed mean differences to standardised mean differences by dividing them by the observed standard deviation or conducted additional meta-analyses with standardised mean difference, where applicable.

The statistical analysis was performed using R. Multiple imputations were done using the jomo-function from the mitml package; Bayesian IPD meta-regression analyses were done using self-programmed routines in rjags; frequentist meta-analyses were done using meta; and frequentist regression analysis was done using the stats package.

For the primary outcome, we assessed the risk of within-study bias using Cochrane's risk of bias 2 tool,[23] the possibility of reporting bias by visual inspection of a contour-enhanced funnel plot and an Egger-test (Pustejovski-method),[24] and the confidence in the estimate using GRADE.[25]

People with lived experience of mental illness were involved in identifying and shaping the research question, choosing outcome measures and potential prognostic factors and effect modifiers, and interpreting the results. They will also be involved in writing and disseminating a summary of the findings in plain language.

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Our search identified 13 876 articles for screening, of which 4991 full-text articles were assessed for eligibility. 19 eligible trials met the inclusion criteria (1599 participants; figure), of which 12 studies[21,22,26–35] (n=1052) had IPD available and seven studies[36–41] (n=547) had only aggregate data. Additional data from clinical study reports were provided by the original authors of three studies that had only aggregate data.[36–38]

The summary characteristics of all included studies are shown in table 1 and the characteristics of individual studies are in the appendix (p 19). Since ethnicity data were not available, the region of origin for each study is presented. No substantial differences in participant, treatment, and study design characteristics were identified between studies for which IPD were available and those with only aggregate data. Five (26%) of the 12 studies with IPD and two (29%) of the seven studies with aggregate data only were judged at high risk of bias (appendix p 23).

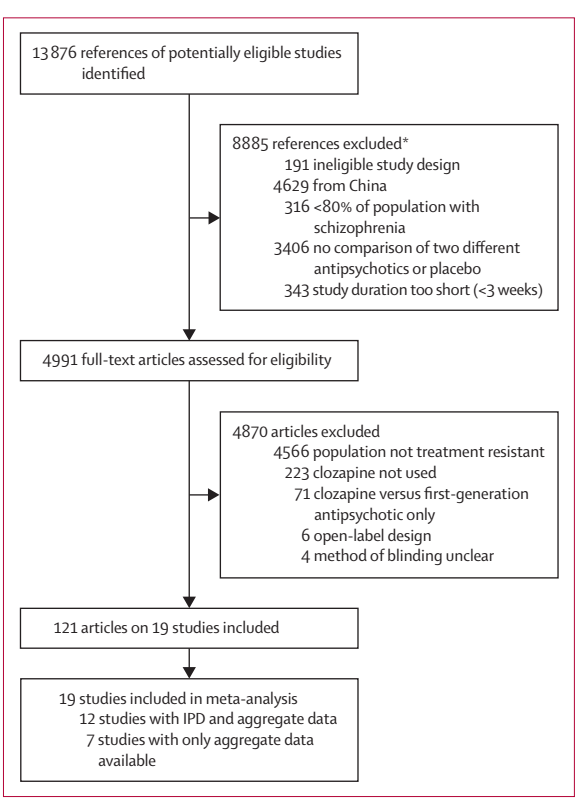

Figure: **Study selection**

IPD=individual patient data. *Our research group categorises studies according to their duration into <3 weeks, 3–13 weeks (3 months), and >13 weeks. For this review, studies shorter than 6 weeks were not eligible[12] and therefore we excluded the references for studies with a duration of less than 3 weeks as a category.

	Studies with IPD available	Studies with only aggregate data available
Studies, n	12	7
Participants, n	1052	547
Participants using clozapine, n	504	273
Study authors (publication year)	Sacchetti et al (2009);[21] Tollefson et al (2001);[22] Bondolfi et al (1998);[26] Conley et al (2003);[27] Kumra et al (2007);[28] Lewis et al (2006);[29] Meltzer et al (2008);[30] Meyer-Lindenberg et al (1997);[31] Naber et al (2005);[32] Schooler et al (2016);[33] Volavka et al (2002);[34] and Wahlbeck et al (2000)[35]	Bitter et al (2004);[36] Azorin et al (2001);[37] Kluge et al (2007);[38] Breier et al (1999);[39] Moresco et al (2004);[40] Shaw et al (2006);[41] and Daniel et al (1996)[42]
Study years	1997–2016	1996–2007
Studies with a double-blind design, n/N (%)	10/12 (83%)	6/7 (86%)
Median study duration, weeks (IQR; range)	16 (10–26; 6–52)	8 (6–10; 6–18)
Studies using different definitions of treatment resistance, n/N (%)*	Relaxed (2/12 [17%]); intermediate (9/12 [75%]); strict (1/12 [8%])	Relaxed (3/7 [43%]); intermediate (3/7 [43%]); strict (1/7 [14%])
Studies including participants who were intolerant to previous antipsychotics or whose symptoms were non-responsive to previous antipsychotics, n/N (%)	4/12 (33%)	4/7 (57%)
Studies sponsored by pharmaceutical companies, n/N (%)	7/12 (58%)	5/7 (71%)
Region of origin, n/N (%)	USA (5/12 [42%]), western Europe (6/12 [50%]), western Europe and South Africa (1/12 [8%])	Eastern Europe and South Africa (1/7 [14%]), USA (3/7 [43%]), western Europe (2/7 [29%]), western Europe and Canada (1/7 [14%])
Second-generation antipsychotic used as comparator, n/N (number of participants)†	Clinician's choice (1/13 [n=69]); olanzapine (6/13 [n=234]); risperidone (4/13 [n=147]); ziprasidone (1/13 [n=73]); zotepine (1/13 [n=25])	Olanzapine (4/7 [n=114]); risperidone (3/7 [n=160])
Median average dose of clozapine, mg/day (IQR; range)	365·4 (300·5–416·5, 209·4–564)	326·2 (281·4–384·5, 216·2–642)
Median average age of participants, years (IQR; range)	37·4 (35·7–38·9; 15·6–42·2)	35 (34·3–36·9; 12·3–38·8)
Median average duration of illness, years (IQR; range)	14 (11·5–16·0; 3·5– 20·5)	11·1 (5·8–12·5; 3·2–15·8)
Median average baseline severity on PANSS (IQR; range)‡	102·1 (90·5–106·7; 79·7–122·0)	101·8 (97·9–105·0; 71·1–110·9)
Median average proportion of women, % (IQR; range)	34·3% (30·4–40·0; 13·0– 46·2)	37·2% (32·2–40·1, 28·9–60·0)
Median average proportion of men, %, (IQR; range)	65·7% (60·0–69·6; 53·8–87·0)	62·8% (59·9–67·8; 40·0–71·1)

BPRS=Brief Psychiatric Rating Scale. IPD=individual patient data. PANSS=Positive and Negative Syndrome Scale. *A relaxed definition of treatment resistance was being non-responsive to at least one previous antipsychotic; an intermediate definition of treatment resistance was being non-responsive to at least two previous antipsychotics; and a strict definition of treatment resistance was being non-responsive to previous antipsychotics and to prospective testing. †Among the studies with IPD, one trial (Volavka et al)[34] compared risperidone versus olanzapine versus clozapine, therefore the number of studies for this category is 13 instead of 12. ‡Baseline severity was reported on different scales (PANSS, BPRS-18, or BPRS-24) in the different studies. We transformed all BPRS-18 values to PANSS using equipercentile linking. For BPRS-24, equipercentile linking with PANSS is not possible, therefore one study that provided aggregate data only (Shaw et al [2006][41]) that used BPRS-24 was not used for the calculation of baseline severity.

Table 1: **Summary study characteristics**

The results of the primary IPD meta-regression model with informative priors are presented in table 2. Data were centralised so that the relative treatment effects refer to the median participant: male, with baseline PANSS total score 91·50, and an illness duration of 12·46 years. Overall, across different second-generation antipsychotics used as comparators, the point estimate for the mean difference in change of overall symptoms was –0·64 PANSS points (95% credible interval [95% CrI] –3·97 to 2·63), indicating a small (corresponding to a standardised mean difference of –0·03 using the observed SD of 23·63 across IPD studies) but uncertain benefit with other second-generation antipsychotics, close to the value of no difference (mean difference of 0).

In terms of specific antipsychotics, none had a clear and substantial difference in efficacy versus clozapine: the mean differences ranged from –1·82 for olanzapine (95% CrI –6·79 to 3·00) to 0·59 for clinician's choice second-generation antipsychotic (–6·26 to 7·29), and there was uncertainty in the estimates as shown by wide 95% CrIs.

In terms of prognostic factors, shorter duration of illness and higher baseline symptom severity were associated with larger improvement in overall symptoms after 6–8 weeks, as indicated by 95% CrIs that excluded 0. The point estimates indicate that the expected reduction in symptoms is 2·90 points (95% CrI 1·00 to 4·70) smaller for every 10 years of illness and that participants who were severely ill (ie, baseline PANSS 110)[17] had a larger reduction in symptoms (by a mean of 9·20 PANSS points [–11·20 to –7·40]) compared with patients who were moderately ill (ie, PANSS 90), since the estimate in

table 2 corresponds to a –4·6 point reduction for every 10 additional points [ie, –9·2 point reduction for every 20 points] on the PANSS scale at baseline).

In terms of treatment effect modifiers (duration of illness, baseline disease severity, and sex), we were not able to draw clear conclusions due to the uncertainty of the results. However, the point estimates did not suggest strong effects, with changes in the mean difference of –1·20 PANSS points (95% CrI –5·80 to 3·40) for 20 years' duration of illness, 1·80 (–0·6 to 4·2) for a 20-point difference in PANSS score at baseline (eg, PANSS score of 110 *vs* 90), and 2·95 (–0·48 to 6·37) for female sex versus male sex (table 2).

The informative priors and the results from IPD meta-regression with approximately non-informative priors are in the appendix (p 25).

No certain and substantial differences in secondary efficacy outcomes were identified between clozapine and other second-generation antipsychotics (table 3). The mean difference in change of negative symptoms was –0·08 (95% CrI –0·72 to 0·56), which translates to a standardised mean difference of 0·03 when divided by the observed SD of 3·12, indicating a negligible effect in favour of other second-generation antipsychotics. The mean difference in change of positive symptoms was 0·47 (–0·53 to 1·44), which translates to a standardised mean difference of 0·11 when divided by the observed SD of 4·16, indicating a negligible advantage with clozapine. The average numbers of participants with a minimal response and with premature study discontinuation were numerically lower with clozapine than with other second-generation antipsychotics (OR 0·61 [95% CrI 0·22 to 1·62] for minimal response; 0·79 [0·43 to 1·40] for premature study discontinuation). However, all 95% CrIs for all secondary outcomes included the possibility of opposite effects given that the 95% CrIs crossed 0 (for effects estimated as mean difference) and crossed 1 (for effects estimated as ORs).

On the basis of the point estimates for the sensitivity analyses, no substantial benefit was observed with either clozapine or other second-generation antipsychotics: the average treatment effects ranged from a mean difference in PANSS total score points of –1·06 to 0·41, and all estimates were uncertain with 95% CrIs crossing 0, meaning that the direction of the effect was unclear (table 4). The study level meta-regression on clozapine dosage yielded unstable results (due to the sparsity of information) and could not account for possible dose effects.

To investigate the line of evidence going from aggregate data (ie, from publications) to the adjusted IPD (ie, our primary results), we conducted post-hoc sensitivity analyses using aggregate data (appendix p 26). On the basis of published data, there were no differences identified in efficacy between clozapine and other second-generation antipsychotics. Using observed cases, when PANSS change scores were analysed, an advantage was observed with clozapine (standardised mean difference 0·15 [95% CI 0·00 to 0·30]); however, this is below what is considered a small difference according to Cohen's rule,[43] and no difference was observed with endpoint scores (standardised mean difference 0·06 [–0·12 to 0·24]). This suggests that differences in baseline severity are relevant in unadjusted analyses and likely explain the discrepancy in the two previous reviews.[8,9,44] Using last-observation-carried-forward or multiple imputation, there were only negligible differences between clozapine and other second-generation antipsychotics. When comparing clozapine with specific antipsychotics, particularly the differences compared with olanzapine and risperidone were small. The results of the frequentist IPD meta-regression analysis were similar to the primary analysis (appendix p 37).

IPD were not available for seven studies.[36–40,42] It was not possible to combine IPD studies and studies with aggregate data only in a three-level hierarchical model because too few aggregate data were available (appendix p 6). Therefore, we compared and combined IPD studies and studies with aggregate data only using standard meta-analysis (appendix p 39). Using the pooled aggregate data of studies for which IPD were not

	Change from baseline in PANSS total score, estimate (95% CrI)
Mean difference in the outcome between antipsychotics as a group and clozapine*	–0·64 (–3·97 to 2·63)
Change in the outcome per unit of prognostic factor†	
Duration of illness, years	0·29 (0·10 to 0·47)
Baseline symptom severity (defined by PANSS total score)‡	–0·46 (–0·56 to –0·37)
Change in the mean difference in the outcome per unit of treatment effect modifier§	
Duration of illness, years	–0·06 (–0·29 to 0·17)
Baseline symptom severity (defined by PANSS total score points)‡	0·09 (–0·03 to 0·21)
Female sex	2·95 (–0·48 to 6·37)
Mean difference in the outcome between specific antipsychotics and clozapine*¶	
Clinician's choice second-generation antipsychotic	0·59 (–6·26 to 7·29)
Olanzapine	–1·82 (–6·79 to 3·00)
Risperidone	–0·71 (–5·27 to 3·79)
Zotepine	–1·22 (–9·19 to 6·72)
Heterogeneity, τ	2·68 (0·18 to 6·90)

95% CrI=95% credible interval. PANSS=Positive and Negative Syndrome Scale. *Values <0 indicate a larger reduction in symptoms with other second-generation antipsychotics than clozapine. †Values <0 indicate a larger reduction in symptoms with higher values of the prognostic factor. ‡PANSS severity is a continuous variable ranging from 30 to 210. §Values <0 indicate more reduction with other second-generation antipsychotics than clozapine with higher values of the effect modifier. ¶The treatment effect of ziprasidone versus clozapine was only investigated in one study (mean difference –2·06 [95% CrI –12·01 to 8·00]); however, the data were only available on the Vivli data sharing platform and thus could not be included in the individual patient data meta-analysis.

Table 2: **Results of the primary analysis**

For the **Vivli data sharing platform** see www.vivli.org

	Change in BPRS positive subscore, estimate (95% CrI)	Change in BPRS negative subscore, estimate (95% CrI)	Participants with at least a minimal response, estimate (95% CrI)*	Participants leaving the study early for any reason, estimate (95% CrI)*
Number of studies	11	11	12	12
Participants, n	961	961	1011	1019
Difference in the outcome between antipsychotics as a group and clozapine†‡	MD 0·47 (–0·53 to 1·44)	MD –0·08 (–0·72 to 0·56)	OR 0·61 (0·22 to 1·62)	OR 0·79 (0·43 to 1·40)
Change in the outcome per unit of prognostic factor§				
Duration of illness, years	0·06 (0·02 to 0·1)	0·02 (–0·01 to 0·05)	0·96 (0·94 to 0·99)	1·00 (0·97 to 1·03)
Baseline symptom severity (defined by PANSS total score)	..	..	1·03 (1·02 to 1·04)	0·99 (0·97 to 1·00)
Baseline symptom severity (defined by BPRS positive subscore)	–0·45 (–0·55 to –0·35)	..	..	..
Baseline symptom severity (defined by BPRS negative subscore)	..	–0·49 (–0·57 to –0·4)	..	..
Change in the difference in the outcome per unit of treatment effect modifier†¶				
Illness duration, years	–0·02 (–0·07 to 0·03)	–0·02 (–0·06 to 0·01)	1·02 (0·99 to 1·04)	0·96 (0·92 to 0·99)
Baseline symptom severity (defined by PANSS total score)	..	..	0·99 (0·97 to 1·00)	1·02 (1·01 to 1·04)
Baseline symptom severity (defined by BPRS positive subscore)	0·06 (–0·06 to 0·18)	..	..	..
Baseline symptom severity (defined by BPRS negative subscore)	..	0 (–0·1 to 0·11)	..	..
Female sex	0·16 (–0·6 to 0·92)	0·09 (–0·45 to 0·63)	0·82 (0·52 to 1·28)	1·19 (0·7 to 1·99)
Difference in the outcome between specific antipsychotics and clozapine†‡				
Clinician's choice second-generation antipsychotic	1·19 (–1·11 to 3·41)	–0·27 (–1·71 to 1·15)	0·24 (0·04 to 1·55)	0·57 (0·05 to 6·89)
Olanzapine	0·23 (–0·92 to 1·4)	–0·33 (–1·11 to 0·51)	0·89 (0·33 to 2·61)	0·75 (0·22 to 3·19)
Risperidone	0 (–1·27 to 1·23)	0·35 (–0·49 to 1·12)	0·76 (0·29 to 2·29)	0·82 (0·16 to 2·61)
Zotepine	..	..	0·84 (0·04 to 15·8)	1·13 (0·10 to 12·94)
Heterogeneity, τ	0·66 (0·03 to 1·91)	0·35 (0·01 to 1·18)	1·93 (1·07 to 5·99)	2·08 (1·04 to 9·21)

The results for the secondary outcomes positive symptoms and negative symptoms were centralised to participants with a baseline severity subscore of 15 on the positive BPRS and 9 on the negative BPRS, respectively. For secondary outcomes with the relative treatment effect presented as ORs, the estimates for prognostic factors and effect modifiers should be multiplied with and not added to the odds and the ORs of the outcome, respectively. BPRS=Brief Psychiatric Rating Scale. 95% CrI=95% credible interval. MD=mean difference. OR=odds ratio. PANSS=Positive and Negative Syndrome Scale. *Analysis conducted with logOR but transformed to OR for presentation. †Difference refers to MD or OR. ‡MDs of <0 and ORs of <1 indicate larger reductions in symptoms and lower event rates, respectively, with other second-generation antipsychotics than with clozapine. §Values of <0 for change in positive and negative symptoms and values <1 for the number of participants with response or premature discontinuation indicate larger reductions in symptoms and lower odds for events, respectively, with higher values of the prognostic factor. ¶Values of <0 for change in positive and negative symptoms and values of <1 for the number of participants with response or premature discontinuation indicate a larger reduction in symptoms and lower odds of having the event with other second-generation antipsychotics than clozapine with higher values of the effect modifier.

Table 3: **Secondary outcomes**

available, clozapine had higher efficacy than pooled second-generation antipsychotics (standardised mean difference 0·24 [95% CI 0·04 to 0·43]), which led to a pooled estimate indicating a small to negligible advantage with clozapine when combined with unadjusted IPD (standardised mean difference 0·12 [95% CrI –0·02 to 0·26]) but not when combined with published results of IPD studies (standardised mean difference 0·02 (95% CI –0·10 to 0·14]). This observation raises the question of whether IPD were made available selectively, but from our communication with the original authors we have no indication for such a bias (appendix p 41).

A higher number of small studies in favour of clozapine (particularly studies with no IPD available) than other second-generation antipsychotics were published, which could indicate a small trial or publication bias, although the Egger test did not provide statistical evidence for it (p=0·66; appendix p 43).

The unavailability of IPD for some studies and the potential risk of small trial or publication bias, the frequent and partly differential premature study discontinuation of participants, and the fact that four trials included patients intolerant of previous antipsychotics led us to downgrade the confidence in the estimate of the primary outcome to very low (appendix p 45).

Discussion

To our knowledge, this is the first meta-analysis of randomised controlled trials comparing clozapine with other second-generation antipsychotics using IPD to homogenise outcomes, impute missing data, and

	Baseline severity of positive and negative symptoms separately	Double-blind studies only	Treatment-resistant participants only	Only treatment-resistant participants according to intermediate and strict criteria	Excluding studies at high risk of bias	Excluding studies that did not allow high clozapine doses (>700 mg per day)*	Excluding studies with low mean doses of clozapine (<350 mg per day)*	Excluding studies sponsored by pharmaceutical companies	Outcome after 12–15 weeks	Outcome after 24–30 weeks
Studies, n	11	10	8	7	7	4	4	5	12	12
Participants, n	961	894	618	492	665	321	259	276	1011	1011
Mean difference in the outcome between antipsychotics as a group and clozapine†	−0·02 (−3·34 to 3·21)	−1·06 (−4·73 to 2·56)	0·41 (−3·09 to 3·83)	0·07 (−4·11 to 4·17)	−0·94 (−4·63 to 2·74)	0·35 (−4·58 to 5·29)	−2·75 (−8·17 to 2·68)	−0·11 (−4·35 to 4·01)	0·04 (−2·06 to 2·07)	0·23 (−3·22 to 3·65)
Change in the outcome per unit of prognostic factor‡										
Duration of illness, years	0·21 (0·02 to 0·39)	0·24 (0·03 to 0·45)	0·24 (0 to 0·48)	0·28 (0·01 to 0·55)	0·19 (−0·09 to 0·46)	0·20 (−0·09 to 0·50)	0·4 (−0·04 to 0·84)	0·35 (−0·12 to 0·83)	0·30 (0·10 to 0·5)	0·52 (0·24 to 0·80)
Baseline symptom severity (defined by PANSS total score)	..	−0·45 (−0·56 to −0·34)	−0·43 (−0·55 to −0·30)	−0·36 (−0·49 to −0·24)	−0·51 (−0·64 to −0·38)	−0·45 (−0·71 to −0·19)	−0·48 (−0·75 to −0·21)	−0·39 (−0·59 to −0·20)	−0·45 (−0·55 to −0·35)	−0·40 (−0·55 to −0·25)
Baseline symptom severity (defined by BPRS positive subscore)	−1·29 (−1·75 to −0·8)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Baseline symptom severity (defined by BPRS negative subscore)	−0·89 (−1·62 to −0·17)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Change in the mean difference in the outcome per unit of treatment effect modifier§										
Illness duration, years	−0·03 (−0·27 to 0·20)	−0·06 (−0·31 to 0·20)	−0·07 (−0·34 to 0·20)	−0·09 (−0·4 to 0·23)	0·03 (−0·27 to 0·33)	−0·04 (−0·42 to 0·34)	−0·12 (−0·62 to 0·39)	−0·02 (−0·46 to 0·40)	−0·09 (−0·33 to 0·16)	−0·27 (−0·6 to 0·05)
Baseline symptom severity (defined by PANSS total score)	..	0·12 (−0·01 to 0·25)	0·1 (−0·04 to 0·24)	0·08 (−0·08 to 0·23)	0·1 (−0·06 to 0·26)	0·16 (−0·14 to 0·45)	0·23 (−0·05 to 0·51)	0·01 (−0·19 to 0·21)	0·10 (−0·03 to 0·23)	0·10 (−0·06 to 0·27)
Baseline symptom severity (defined by BPRS positive subscore)	0·28 (−0·3 to 0·85)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Baseline symptom severity (defined by BPRS negative subscore)	−0·12 (−0·95 to 0·73)	NA	NA	NA	NA	NA	NA	NA	NA	NA
Female sex	3·4 (−0·11 to 6·91)	3·85 (0·03 to 7·65)	3·38 (−0·51 to 7·29)	3·72 (−0·72 to 8·15)	2·24 (−2·16 to 6·69)	3·49 (−1·58 to 8·56)	2·85 (−2·98 to 8·68)	1·96 (−3·45 to 7·35)	3·62 (−0·06 to 7·3)	0·95 (−3·47 to 5·33)
Mean difference in the outcome between specific antipsychotics and clozapine†										
Clinician's choice second-generation antipsychotic	1·24 (−5·51 to 7·81)	NA	0·08 (−6·56 to 6·71)	0·49 (−7·13 to 8)	NA	4·23 (−2·96 to 11·41)	NA	0·73 (−6·6 to 7·86)	3·79 (−3·08 to 10·07)	1·65 (−5·67 to 8·68)
Olanzapine	−1·11 (−5·98 to 3·67)	−2·32 (−7·48 to 2·63)	0·02 (−5·08 to 5·03)	0·1 (−6·48 to 6·72)	−1·72 (−6·87 to 3·4)	−1·12 (−16 to 13·76)	−1·12 (−16 to 13·76)	−1·08 (−8·34 to 6·39)	−2·35 (−7·05 to 2·47)	−0·31 (−5·5 to 4·94)
Risperidone	−0·19 (−4·84 to 4·32)	0·62 (−4·19 to 5·44)	1·13 (−4·3 to 6·1)	−0·38 (−7·26 to 6·3)	0·37 (−4·42 to 5·16)	−1·12 (−16 to 13·76)	−1·59 (−10·34 to 7·16)	0 (−6·72 to 6·49)	−0·52 (−4·98 to 3·89)	−0·31 (−5·78 to 4·98)
Zotepine	NA	−1·48 (−9·6 to 7·13)	NA	NA	−1·45 (−9·62 to 6·83)	NA	NA	NA	−0·79 (−8·79 to 7·1)	−0·12 (−8·75 to 8·38)
Heterogeneity, τ	2·69 (0·15 to 6·97)	2·65 (0·13 to 6·74)	2·89 (0·14 to 7·49)	4·9 (0·78 to 10·22)	2·48 (0·12 to 6·92)	1·79	0·00	3·84 (0·21 to 9·57)	2·26 (0·11 to 5·93)	3·39 (0·38 to 7·80)

Data are estimate (95% CrI). All studies used operationalised criteria to diagnose schizophrenia and therefore no sensitivity analyses were conducted in this regard. In the sensitivity analyses regarding dose effects, Bayesian modelling did not yield stable estimates and the vague priors set for dose effects (assuming no dose effect) remained unchanged. Thus, using the available information, it was not possible to account for the role of dosage and the estimates of all other parameters did not change. Therefore, these results were omitted from this table but are reported in the appendix (p 54). BPRS=Brief Psychiatric Rating Scale. MD=mean difference. NA=not applicable. PANSS=Positive and Negative Syndrome Scale. *Median clozapine doses across studies of 700 mg (maximum allowed value) and 350 mg (mean value) per day were used as criteria for excluding studies, analysed based on individual patient data locally available to the authors using frequentist methods identical to those in the appendix (p 37), thus no 95% CrIs are provided for the heterogeneity parameters for these analyses. †The outcome for sensitivity analyses was the primary outcome of change from baseline in PANSS total score; values <0 indicate a larger reduction in symptoms with other second-generation antipsychotics than clozapine. ‡Values <0 indicate a larger reduction in symptoms with higher values of the prognostic factor. §Values <0 indicate more reduction with other second-generation antipsychotics than clozapine with higher values of the effect modifier.

Table 4: **Sensitivity analyses**

account for differences in participant characteristics between studies and study arms. Overall, we found no indication for superior efficacy of clozapine, since the point estimate of the primary analysis yielded an estimate close to 0. Moreover, none of the multiple sensitivity analyses, the secondary outcomes, or the comparisons between clozapine and specific second-generation antipsychotics indicated a substantial difference between clozapine and other second-generation antipsychotics. Furthermore, there was no indication that this difference is associated with participants' duration of illness, baseline severity, or sex.

Thus, similar to previous pairwise and network meta-analyses using aggregate data from randomised controlled trials,[7–9] this IPD meta-analysis did not provide evidence for superior efficacy of clozapine in treatment-resistant schizophrenia when compared with other second-generation antipsychotics. In contrast, in meta-analysis of randomised controlled trials in participants who were not treatment resistant,[45] clozapine was the top-ranked drug based on efficacy, superior to all other second-generation antipsychotics, albeit based on a small sample size (n=270). In meta-analysis of observational studies,[46] in which potential systematic differences between patients receiving clozapine or other drugs (eg, regarding compliance or monitoring) prevent causal conclusions, clozapine use was associated with lower risk of hospitalisation and all-cause discontinuation in populations with treatment-resistant and non-treatment-resistant symptoms compared with other second-generation antipsychotics. However, in comparison with individual second-generation antipsychotics, there was clear evidence of superior efficacy to only aripiprazole and quetiapine, weak evidence of superiority to risperidone, and no indication of a difference to olanzapine. In a network meta-analysis of open-label and blinded randomised controlled trials, the efficacy of olanzapine in treatment-resistant schizophrenia was found to be comparable to the efficacy of clozapine.[47]

The findings of no clear effect modification by duration of illness, baseline severity, or sex is consistent with an analysis of variability in the treatment effect,[48] in which the authors concluded that results do not support the hypothesis that there is a subtype of patients whose symptoms specifically respond to clozapine.

When interpreting the finding that shorter duration of illness and higher baseline severity were associated with a greater reduction in symptoms in both treatment groups, it should be noted that shorter duration of illness is not necessarily a prognostic factor of better response to antipsychotic treatment, but that it could also be a general marker of favourable prognosis (eg, in response to other medical and social benefits of participating in a trial) and that, inherently, participants with higher baseline scores have more potential for improvement. The limitations of evidence from randomised controlled trials in treatment-resistant schizophrenia discussed for previous aggregate-data meta-analyses,[49] such as selection of patients with a better prognosis (due to less severity of illness and more insight with regard to their illness) and clozapine doses that were possibly too low (effective dose unknown[50]) used in some randomised controlled trials also apply in principle for the studies in our IPD dataset. However, our point estimate for baseline severity as a treatment effect modifier suggests that extremely ill patients (ie, those with a PANSS of 130)[17] might have a reduction of symptoms of only 2·83 PANSS points more on clozapine than on other second-generation antipsychotics. Regarding dose effects, the individual patient's dose could not be used for analysis because it was adapted after randomisation to the participant's needs according to the flexible dose design applied in 11 of 12 studies. The fact that outcome-adapted dosing in flexible dose studies can be problematic for evaluating dose effects is shown by the paradoxical observation that participants treated with higher doses of either treatment had smaller reductions in symptoms than participants treated with lower doses (appendix p 48). The sensitivity analyses adjusting for maximum and mean clozapine doses did not converge but, notably, the sensitivity analyses that were restricted to studies of higher doses of clozapine did not indicate better efficacy of clozapine.

For similar methodological reasons and because the information was only available in two studies, we could not account for the effect of plasma levels of clozapine;[51] however, in the few studies with data available, higher plasma levels were not associated with a larger reduction in symptoms (appendix p 48).

The inability to account for the effects of clozapine concentrations (which are associated with dose but with high inter-individual variability[52]) at the participant level is an important limitation of the original studies and of our analysis. Randomised controlled trials that monitor clozapine concentrations—and in case of non-response increase the concentration to 350 ng/mL (the concentration with optimised sensitivity and specificity regarding response[51]) or higher (in case of ongoing non-response, if tolerated) in patients with treatment-resistant symptoms—are warranted.

This IPD analysis had additional limitations. First, despite extensive efforts, we were unable to obtain IPD from seven studies (equating to a third of all included participants; appendix p 41). Among those, four small studies (30 participants or fewer in each; two studies sponsored by public institutions and two sponsored by an olanzapine manufacturer) and one larger study[37] (n=249, sponsored by a clozapine manufacturer) indicated an advantage with clozapine, and one larger study[36] (n=140; sponsored by an olanzapine manufacturer) identified no difference between olanzapine and clozapine. It remains unclear whether the unavailability of these IPD is indicative of bias against clozapine because we cannot rule out selective withholding of IPD that were not consistent with published results or have other biases with full certainty, and because the possibility of small study or publication

bias introduced by the four small studies (appendix p 43) must be considered. Additionally, as observed in studies with IPD available (appendix pp 26, 37), harmonisation of the outcomes, imputation of missing data, and adjustments in IPD meta-regression can lead to deviations from published results. Nonetheless, the exploratory unadjusted meta-analysis combining studies with and without IPD only indicated a small to negligible effect size (standardised mean difference 0·12) in favour of clozapine (appendix p 39). Furthermore, it cannot be ruled out that industry-supported studies exist that have not been published because they did not show the expected effect for the sponsored drug.

A second limitation is that we could not investigate all potentially interesting prognostic factors and treatment effect modifiers due to unavailability of data and limited statistical power to analyse multiple coefficients (appendix p 10). Specifically, the effects of ethnicity could not be explored and given that the majority of studies were conducted in the USA and western Europe, the representativeness of the study population is likely to be limited.

Third, four IPD studies included participants who had not tolerated previous antipsychotics in addition to treatment-resistant participants, but this was not coded for in the original datasets. Therefore, it was not possible to select only treatment-resistant participants for inclusion in this meta-analysis and as a result, we downgraded the GRADE assessment. Additionally, the included studies used multiple criteria to define treatment resistance, each not covering all criteria of the recent consensus.[14] However, sensitivity analyses excluding studies admitting participants who were intolerant to previous antipsychotics and studies with comparably relaxed definitions of treatment resistance showed no evidence of superior efficacy of clozapine.

Fourth, some outcome data were missing due to premature study discontinuation or missing study visits at 6–8 weeks, leading to uncertainty regarding the actual study outcome. Instead of using observed case or last-observation-carried-forward data, which imply strong assumptions, we imputed missing data by multiple imputation. This method incorporates the uncertainty introduced by missing data in the estimation of confidence or credible intervals and thereby provides a more realistic scenario of uncertainty in the results.

Fifth, uncertainty in the results arises from the fact that symptoms of schizophrenia (or their rating) fluctuate, which is a direct source of variance and also leads to uncertainty in imputation (appendix p 60), and that our adjustment for differences in duration of illness, baseline severity, and sex only incompletely explained the variance in results. These limitations, although partly mitigated by the use of IPD, led to a GRADE assessment of very low quality of evidence.

It is noteworthy that an IPD meta-analysis of randomised controlled trials, which is methodologically considered a high standard of evidence, did not provide evidence for the preferential use of clozapine in treatment-resistant schizophrenia and therefore uncertainty remains regarding superiority of clozapine. Thus, considering the multiple side-effects of clozapine and the risk of serious adverse events, we suggest that other second-generation antipsychotics (particularly olanzapine or risperidone; in agreement with the summary of product characteristics,[11] should first be used in sufficient dose, duration, and adherence, eventually even in a long-acting injectable formulation to rule out non-adherence.[14] In case of disabling symptoms despite adequate treatment with other second-generation antipsychotics, clozapine might then be considered, since other evidence suggests an advantage with clozapine.[53] However, clinicians and patients should bear in mind that the superiority of clozapine in treatment-resistant schizophrenia is not certain, and therefore the outcome on clozapine should be critically evaluated (preferably using a validated brief rating scale applicable for busy clinical practice, such as the Brief Evaluation of Psychosis Symptom Domains[54] or the Clinical Global Impression–Schizophrenia Scale[55]) and its discontinuation (with slow down-titration to prevent withdrawal effects) should be considered in case of insufficient response.

Regarding further research, to support the evidence underlying the current guideline recommendations, an adequately powered controlled trial in individuals with strictly defined treatment-resistant schizophrenia in which doses are adapted according to response and plasma concentrations is needed. Reasons for inter-individual differences in response to clozapine might be explored in future studies.

Contributors

StL obtained the funding and supervised the study. SS, JS-T, TH, IB, SD, JMD, GS, and StL designed the systematic review and meta-analysis. JS-T and SD screened the literature search. PB, RC, JC, DK, MK, SK, ShL, HM, DN, NS, JV, and KW prepared and provided the original individual patient data (IPD) datasets. JS-T, SS, and SD harmonised and checked the IPD datasets and extracted aggregate data. TH, KC, and GS conducted the statistical analysis. W-PH and ES provided the patients' perspective when designing the study and interpreting the results. JS-T, TH, KC, SS, StL, GS, JMD, and JP interpreted the results. JS-T, SS, GS, and SL drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final manuscript. JS-T, SS, and SD had access to and verified the individual patient and aggregate data of randomised controlled trials. JS-T and StL were responsible for the decision to submit the manuscript.

Declaration of interests

SL has received honoraria for advising or consulting, or for lectures or for educational material from Angelini, Boehringer Ingelheim, Eisai, Ekademia, Gedeon Richter, Janssen, Karuna, Kynexis, Lundbeck, Medichem, Medscape, Mitsubishi, Neurotorium, Otsuka, NovoNordisk, Recordati, Rovi, and Teva. RC is the Chief Science and Chief Medical Officer of Beckley Psytech; owns stocks in Eli Lilly; and is on the medical advisory board of Autobahn Therapeutics. DK served on the advisory board for Janssen, Alkermes, and Karuna. HYM has received grant support from ACADIA. NS has served on advisory boards for Boehringer Ingelheim and on a grant review committee for Alkermes. All other authors declare no competing interests.

For the **online data sharing platform** see vivli.org

Data sharing

Individual patient data and aggregate data (including a data dictionary) can be made available from the study authors or, for two studies, from the Vivli online data sharing platform on reasonable written request.

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