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Predictors of response to pharmacological treatments in treatment-resistant schizophrenia – A systematic review and meta-analysis

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ABSTRACT

Background: As the burden of treatment-resistant schizophrenia (TRS) on patients and society is high it is important to identify predictors of response to medications in TRS. The aim was to analyse whether baseline patient and study characteristics predict treatment response in TRS in drug trials.
Methods: A comprehensive search strategy completed in PubMed, Cochrane and Web of Science helped identify relevant studies. The studies had to meet the following criteria: English language clinical trial of pharmacological treatment of TRS, clear definition of TRS and response, percentage of response reported, at least one baseline characteristic presented, and total sample size of at least 15. Meta-regression techniques served to explore whether baseline characteristics predict response to medication in TRS.
Results: 77 articles were included in the systematic review. The overall sample included 7546 patients, of which 41% achieved response. Higher positive symptom score at baseline predicted higher response percentage. None of the other baseline patient or study characteristics achieved statistical significance at predicting response. When analysed in groups divided by antipsychotic drugs, studies of clozapine and other atypical antipsychotics produced the highest response rate.
Conclusions: This meta-analytic review identified surprisingly few baseline characteristics that predicted treatment response. However, higher positive symptoms and the use of atypical antipsychotics – particularly clozapine –was associated with the greatest likelihood of response. The difficulty involved in the prediction of medication response in TRS necessitates careful monitoring and personalised medication management. There is a need for more investigations of the predictors of treatment response in TRS.

1. Introduction

Treatment-resistant schizophrenia (TRS) is a severe yet highly prevalent form of schizophrenia (Kennedy et al., 2014). About 1% of the global population has schizophrenia and the percentage is even higher in some parts of the world, for example, Northern Finland, with its estimate of 1.8% (Perälä et al., 2008). One-fifth to one-third of all patients with schizophrenia present with a form of the illness resistant to treatment (Conley and Kelly, 2001).

The burden of TRS on patients and society is high. Many comorbidities are associated with the disease and the treatment. Unemployment and suicide risk are also notably increased. The healthcare costs of TRS are 3 to 11 times higher than schizophrenia in general (mainly due to the high number of hospitalizations), representing 60% to 80% of the

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total economic burden of schizophrenia (Kennedy et al., 2014).

Estimates of the proportion of treatment responders in TRS vary widely. Suzuki et al. (2011) reviewed 33 clinical trials of antipsychotics on TRS and the response rate varied between 0%–76%. In a systematic review of 65 trials, the average response rate was 41%, ranging from 0% to 74% (Kennedy et al., 2014).

Studies have examined the effects of antipsychotic medications and other treatments on the likelihood of response in TRS (Siskind et al., 2016). Meta-analyses on non-pharmacological predictors of response in TRS are rare (Okhuijsen-Pfeifer et al. 2020). A small number of original studies have examined predictors of response in TRS. Based on these studies, later age of illness onset (Semiz et al., 2007), shorter hospitalizations (Zito et al., 1993) and less severe symptoms at baseline (Hong et al., 1997; Zito et al., 1993; Wirshing et al., 1999) predict better treatment response. Remarkably, more severe positive or negative symptoms may also predict better treatment response (Wirshing et al., 1999). Shorter delay in clozapine initiation and fewer pre-clozapine hospitalisations have been associated with better clozapine response (Shah et al., 2019). Gender (Lieberman et al., 1994) and age at study initiation have not predicted treatment response (Zito et al., 1993; Hong et al., 1997; Lindenmayer et al., 2002; Semiz et al., 2007). In a meta-analysis of 34 articles, Okhuijsen-Pfeifer et al. (2020) analysed demographic and clinical predictors of clozapine response in schizophrenia. They found that lower age, lower PANSS negative score and paranoid schizophrenia subtype predicted better response to clozapine. To our knowledge, there are no systematic reviews or meta-analyses summarising predictors of response to any psychopharmacological treatment of TRS.

The goal of this systematic review and meta-analysis was to determine the average response rate and identify predictors of treatment response in patients with TRS in drug trials. We focused on putative predictors assessable at the start or switch of antipsychotic treatment – usually obtained during the baseline or pre-treatment phases in clinical trials. Based on previous literature, we hypothesised that later age of illness onset, shorter duration of hospitalisation and less severe symptoms at baseline will predict better treatment response. There is a negligible number of individual studies analysing whether patient characteristics predict treatment response. It is therefore not possible to perform a patient level meta-analysis. Thus, in this study, we analysed the associations at study level, i.e. we analysed the associations between patient and study characteristics and the response percentage in the corresponding study.

2. Methods

We followed the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) guidelines for systematic reviews and meta-analyses (Page et al., 2021) (see Online supplement appendix 1).

2.1. Search strategies

A comprehensive literature search was performed in November 2016 and updated in March 2019, using the electronic databases ISI Web of Science, PubMed (MEDLINE) and Cochrane CENTRAL (Cochrane Central Register of Controlled Trials). An information specialist (NH) conducted the search. The search strategy included the keyword 'schizophreni*' in the title of the article linked with an AND operator to a set of keywords describing treatment resistance ('treatment-resistan*', 'ultra-resistan*', 'treatment-refractory', 'clozapine') in the abstract and/or topic of the article. The search was restricted to articles in English and to clinical trials as a topic or publication type. There was no time restriction. See the online supplement Table 1 for a description of the search strategy for each database. Furthermore, articles were searched using a chaining method, i.e. finding interesting articles in the reference lists of included articles.

At least two authors (AS, EJ, JP) evaluated all search results based on the titles and abstracts of the articles. Subsequently, AS and JP evaluated full text articles. For studies that met the inclusion criteria, AS and JP extracted the data. When questions arose related to full text evaluation and data extraction, study authors (AS, JP, EJ, JM, and JS) resolved these by consensus.

2.2. Study selection

We wanted to examine trials that studied response to medication in a TRS population. The articles included in the analyses were required to meet each of the following eligibility criteria:

1. The article detailed an original study of people diagnosed with DSM-III, DSM-III-R, DSM IV or ICD-9 or ICD-10 schizophrenia or schizo-affective disorder adjudged as treatment resistant.
2. The article presented clear criteria for treatment resistance (for further details, see 2.3).
3. The study included a sample size of at least 15 individuals at its initiation.
4. The study had at least a 6-week follow up period.
5. The article detailed a clinical trial analysing the effect of medications (mostly antipsychotics; in a few studies, mood stabilisers or antidepressants; and in a very few studies, other pharmacological treatment). Both naturalistic and controlled trials were included.
6. The article presented the response rate of the sample.
7. The study presented at least one baseline characteristic (i.e. predictor of response in this study).
8. The article presented the study characteristics and inclusion criteria of the sample.
9. The articles were in English.

The exclusion criteria included:

1. Studies analysing non-pharmacological treatments, for example, psychotherapies and ECT since these would be difficult to combine with pharmacological trials based on the different kinds of patient selection and methods.
2. Samples including children or adolescents (patients had to be at least 18 years of age at the study initiation).
3. Cross-over studies due to the inability to compare them with other studies.

2.3. Definition of TRS in this review

We included all the clinical trials that reported their sample as a TRS sample, and that defined TRS as a history of use of at least one trial of antipsychotics without response.

There are multiple operational definitions of TRS. The original Kane et al. (1988) criteria were very strict and the required medication dose was high. When developing a consensus for the definition of TRS, Howes et al. (2017) suggested a more specific definition with six points to consider, including use of a symptom questionnaire and performance evaluation. Table 1 summarizes various definitions of treatment-resistant schizophrenia.

We acknowledge that a consistent definition of TRS is important. However, in the studies identified, there was great variability in the operational definition of TRS and in reporting the definition. In order to capture all possible TRS samples, we chose to include all the clinical trials that reported their sample as a TRS sample, and that defined TRS as a history of use of at least one trial of antipsychotics without response. The review included a range of TRS definitions. For example, a broader definition from Scheepers et al. (2001): "All subjects were previously treated with at least one typical antipsychotic for a minimum of four weeks". In contrast, there was a narrower TRS definition from Dossenbach et al. (2000): "BPRS $\geq$ 45; Score $\geq$ 4 in 4 BPRS psychotic symptoms; non-response to $\geq$ 3 APs from different classes at $\geq$ 1000 mg

Table 1
Examples of definitions of treatment resistant schizophrenia.

Author	Definition
Kane et al., 1988	1. The patient should have manifested a failure to respond to three or more adequate trials of antipsychotic treatment within the last 5 years, including medication from two distinct classes with dosing at least the equivalent of 1000 mg per day of chlorpromazine. 2. There must be at least moderately severe continuous symptoms in certain psychosis symptoms (conceptual disorganization, suspiciousness, hallucinatory behaviour and unusual thought content). 3. There must be evidence of substantial current symptoms despite current optimized treatment to which the patient is adherent: defined as a score of greater than or equal to 45 on the Brief Psychiatric Rating Scale (BPRS) or 90 in the Positive and Negative Syndrome Scale (PANSS).
Suzuki et al., 2012	1. At least two failed adequate trials with different antipsychotics (at chlorpromazine-equivalent doses of ≥600 mg/day for ≥6 consecutive weeks) that could be retrospective or preferably include prospective failure to respond to one or more antipsychotic trials 2. Both a score of ≥4 on the Clinical Global Impression-Severity (CGI-S) and a score of ≤49 on the Functional Assessment for Comprehensive Treatment of Schizophrenia (FACT-Sz) or ≤ 50 on the Global Assessment of Functioning (GAF) scales
Howes et al., 2017	1. The patient should have at least moderate severity of symptoms for 12 weeks (using standardised scale) 2. At least moderate functional impairment measured using a validated scale. 3. At least two past treatments with different antipsychotic drugs for at least for 6 weeks with a dosage equivalent to 600 mg of chlorpromazine per day 4. Adherence is followed systematically, at least 80% of prescribed doses taken. Antipsychotic plasma levels monitored on at least one occasion. 5. In ideal cases, at least one antipsychotic drug trial to make sure of the treatment resistance 6. Criteria clearly separating responsive from treatment-resistant patients.

for ≥ 4 months; a history of hospitalization for ≥365 days; non-response (20% decrease in BPRS) to CLZ for ≥4 months or intolerance to CLZ". The sample also included studies using the Kane et al. (1988) criteria (see Table 1).

Most of the identified clinical trials defined TRS based on only the number of failed antipsychotic medication trials. Most studies did not report the dosage or treatment duration of each failed antipsychotic trial. Moreover, several were missing standard assessments of symptom severity (e.g. PANSS, BPRS) and the level of disability. Therefore, medication dosage and duration, symptom severity, and disability did not figure into our classification of TRS criteria. Rather, we classified the included studies into three subclasses based on the number of previous antipsychotic trials. We conducted the analyses in the total sample and conducted a sensitivity analysis including only studies in groups 2 and 3:

1. History of non-response to at least one adequate trial of antipsychotic treatment (broad criteria).
2. History of non-response to at least two adequate trials of antipsychotic treatment (average strict criteria).
3. History of non-response to at least three or more adequate trials of antipsychotic (narrow criteria).

2.4. Definition of response

There was also heterogeneity across studies regarding the definition of response. Howes et al. (2017) suggested the following criteria for adequate treatment response:

1.) Symptoms are rated no more than mild severity; 2.) Duration of response sustained for a minimum of 12 weeks; and 3.) Functional impairment rated as mild or better on a standardised scale such as the Social and Occupational Functioning Scale (SOFAS). In addition, whenever possible, they recommended that investigators ascertain response prospectively over at least six weeks and defined as at least a 20% improvement in symptom scores and meeting the absolute thresholds (symptoms rated at no more than mild severity). Suzuki et al. (2011) found that the most commonly used criteria for treatment response is at least a 20% reduction in PANSS or BPRS.

Of the 77 studies included in our review, 64 used a 20% reduction in symptoms as a definition of response, 18 studies used a 30% reduction, a single study used a reduction of 40% and 50%, and eight studies used the Kane 1988 criteria. Kane et al. (1988) defined response with ≥20% decrease in the BPRS total score, and either a post-treatment CGI-Severity score of ≤3 (i.e., better than mild) or BPRS of ≤35. Given that only one study used a 40% or 50% reduction, we combined the one study with those using the reduction of 30%. A small number of studies reported more than one response criteria. Based on these figures, we present the results for the response rate of studies using the following response definitions: 1.) reduction in 20% of symptoms, 2.) reduction in 30% of symptoms and 3.) the Kane criteria. Since most of the studies used a reduction in 20% of symptoms as the response criteria, we studied the associations between baseline and study characteristics and the percentage of response among these studies in a meta-analysis. In addition, as a sensitivity analysis, we performed the analyses in the total sample regardless of the response criteria.

2.5. Recorded variables and analysed predictors of response

Our team (AS and JP) recorded the following variables from each article: year of publication, original and final sample size, duration of follow-up, number of drop-outs, type of pharmacological treatment, proportion of males, mean age of participants, duration of illness, age of onset, age at first hospitalisation, number of hospitalisations, weight, BMI, ethnicity, inpatient/outpatient status, duration of current hospitalisation, years of education, baseline overall (PANSS, BPRS, or CGI) and positive and negative symptom (PANSS) severity, and proportion of response. BPRS positive and negative symptoms were not studied as those were reported only in a few studies.

2.6. Sensitivity analysis

We completed a sensitivity analysis by including only studies that used a more common definition of TRS, i.e. studies that included patients who had tried at least two different antipsychotic medications (i.e. studies using the average strict and narrow TRS criteria). Given that there are differences on the effects of different treatments, we also analysed the percentage of treatment response in subpopulations classified by the medication that was analysed in the trial. Further, we examined associations between predictors and treatment response in 1) studies that included only atypical or typical antipsychotics as a trial treatment and separately in 2) studies that included only atypical antipsychotics. Here, we combined the treatment categories in different trials regardless of the comparison treatment.

2.7. Statistical analysis

We divided predictor variables into three classes based on tertiles or into two classes based on median. Based on the expected heterogeneity of the treatment response percentage between studies, we used a random effects meta-analysis to pool overall estimates of response. In the random effects analysis, we weighted each study by the inverse of its variance and the between-studies variance. We used random effects meta-regression to explore the influence of potential predictor variables on response proportion. We assessed the heterogeneity of the studies using I^2 statistics, and adjudged the statistical significance of heterogeneity using a chi-square test. The values of I^2 ranged from 0% to 100%, reflecting the proportion of the total variation across studies beyond

chance. A value of 25% describes low heterogeneity, 50% moderate heterogeneity and 75% high heterogeneity or major excessive variation across studies (Higgins et al., 2003). We completed all analyses using Stata 13 (StataCorp, L, 2013).

3. Results

3.1. Search results

The initial literature search produced 1373 references, and after the removal of duplicates, 1148 unique publications were identified (Fig. 1). After inspecting the abstracts, 160 original articles were included for review against the above-mentioned eligibility criteria. 77 articles were included in the systematic review. The overall sample included 7546 TRS patients.

3.2. Study characteristics

In the included studies (online supplement Table 2), the median age at onset was 21.8 years (range 20.5–22.9), median baseline PANSS was 94.0 (81.6–104.4), BPRS 50.6 (42.6–57.5) and the majority 69.3% (62.0–74.0) of the samples were male. Table 2 includes a summary of the characteristics of included samples. 40 samples were from North America (35 from the USA), 20 from Europe, 17 from Asia, two from Africa and one from Australia. Three of the studies included patients from two different countries. Most of the studies had used DSM-IV as a diagnostic system ($n = 48$), 19 had used DMS-III-R, six studies DSM-III, two studies ICD-10 and two studies did not report the used diagnostic system. Regarding the strictness of the definition of TRS, 31 of the studies required a history of at least three antipsychotics, 29 of the studies required a history of at least two antipsychotics and 12 studies had a broad definition of history of at least one antipsychotic. It was not possible to classify the strictness of the definition of TRS for five studies. Nine studies also included schizoaffective patients in the sample and in six of them; the proportion of schizoaffective patients was less than 20% of the whole sample. The highest proportion of schizoaffective patients in an individual study was 40%.

3.3. Response percentage

In all the studies, 41.3% (95% CI: 36.8, 45.8) of the patients achieved response. When only analysing studies using a 20% reduction in symptoms as the response criteria ($n = 61$), 40.8% (36.1, 45.5) achieved response and 40.6% (31.9, 49.3) achieved response when the criteria was 30% of decrease of symptoms ($n = 18$). In studies using the Kane criteria for the response ($n = 8$), 35.0% (19.3, 50.7) of the patients experienced response. When only including studies using the most commonly used TRS criteria (groups 2 and 3, i.e. TRS history of at least 2 AP medications) ($n = 60$), 42.6% (37.4–47.7) achieved response. When using a 20% reduction in symptoms as the response criteria and excluding studies using the broad TRS criteria ($n = 44$), 42.6% (36.8–47.6) achieved response (Figs. 2–5).

3.4. Association between baseline and study characteristics and treatment response

Table 3 includes response percentages by baseline and study characteristic variables. Of the included variables only baseline positive symptoms associated statistically significantly with response ($p = 0.008$). Among those studies with highest mean of positive symptoms (highest tertile), median response was 50.0%, whereas in the lowest tertile response was 17.8%. None of the other baseline and study characteristics achieved statistical significance. In the studies of the youngest age at baseline, the median response rate was 50.7%, in the middle tertile the response rate was 44.4% and in the oldest tertile it was 39.4%. Among the studies in which the age at time of first hospitalisation was low, only 18.2% achieved response, whereas in the older group the rate was 59.0%. When the cumulative number of

Fig. 1. Flow diagram of the selection of studies.

Table 2
Summary characteristics of the included studies ($n = 77$).

	n	%
Country[a]		
US	35	45.5
Canada	5	6.5
Europe	20	26.0
Asia	17	22.1
South-Africa	2	2.6
Australia	1	1.3
Time of the publication		
Before 1990	2	2.6
1990–1999	22	28.6
2000–2009	41	53.2
2010 or later	12	15.6
Design of the study		
Double blind RCT	51	66.2
Open label study or descriptive/naturalistic study	26	33.8
Size of the sample		
Under 50	44	57.1
50–99	17	22.1
100–199	7	9.1
200–299	6	7.8
Over 300	3	3.9
Used diagnostic system		
DSM-III	6	7.8
DSM-III-R	19	24.7
DSM-IV	48	62.3
ICD-10	2	2.6
Not reported	2	2.6
Studies reported to include also schizoaffective patients		
Yes	9	11.7
No	68	88.3
Length of the study		
6 weeks	10	
>6 weeks–8 weeks	10	
>8–12 weeks	24	
>12–20 weeks	13	
>20–50 weeks	9	
>50–100 weeks	8	
Over 100 weeks	2	
Used scale for analysing response[b]		
BPRS	43	55.8
PANSS	39	50.6
CGI	9	11.7
SANS	3	3.9
SAPS	2	2.6

BPRS = Brief Psychiatric Rating Scale.
PANSS = Positive And Negative Syndrome Scale.
SANS=Scale for the Assessment of Negative Symptoms.
SAPS = Scale for the Assessment of Positive Symptoms.
[a] Three of the studies included patients from two different continents, why the total percentage exceeds 100%.
[b] Some studies used several different scales for analysing response, why the total percentage exceeds 100%.

hospitalisations was lower, the median response rate was 27.6%, and when it was higher, it was 46.2%. In studies with low proportion of inpatients at baseline, the response rate was 44.0%, and in studies with higher proportion of inpatients, it was 31.9%. In the samples with shorter duration of current hospitalisation, 41.2% achieved response, whereas in the samples with longer duration, only 23.9% achieved response. There was no trend in response rates regarding year of publication. Using the TRS classification previously described, in the studies with a broad definition of TRS, 37.4% achieved response, in studies with a moderately strict definition, 45.2% achieved response and in studies with a narrow definition, 46.7% achieved response.

In the sensitivity analysis, when only studies that used a more common definition of TRS were included, i.e. studies that included patients who had tried at least two different antipsychotic medications, the results did not change: Only positive symptoms achieved statistical significance and there was no other statistically significant associations between any of the baseline and study characteristics and percentage of treatment response.

We also analysed the response percentage in the baseline and study characteristic variables in all 77 studies, i.e. including studies with variable response criteria. Only higher positive symptom score at baseline was associated with higher response percentage, and no other statistically significant associations occurred (see Table 2 in the Supplement).

3.5. Response in subpopulations to antipsychotic medication

Table 4 summarizes the proportion of responders to antipsychotic medications in several subpopulations. Of patients using typical antipsychotics, 25.0% achieved response whereas of those using atypicals, 41.5% achieved response. Patients using clozapine monotherapy had the highest response rate, 50.0%, and patients on chlorpromazine had the lowest, 10.3% (although the number of studies was low). There were no significant associations in baseline or study characteristics and the response rate in subgroups by type of medication (analysed separately for 1: studies including both typical and atypical antipsychotics and 2: studies including atypicals only).

4. Discussion

4.1. Main results

In this systematic review of medication trials of TRS, 41% of patients achieved response defined as a 20% reduction in symptoms. Rather surprisingly, none of the baseline or study characteristics other than positive symptoms predicted response. Studies of clozapine and other atypical antipsychotics produced the largest proportion of responders. Given that there were no significant difference in the percentage of responders by publication year, we can assume that the efficacy of medications for TRS has remained unchanged for 30 years.

There was no statistically significant association between the number of hospitalisations and treatment response. However, there were some differences in the response percentages. Surprisingly, samples with a higher cumulative number of hospitalisations had better treatment response (46% compared to a response rate of 28% in samples with a lower number of hospitalisations). One possibility is that patients with a fewer hospitalisations had more severe symptoms; thus, they may have spent longer periods in hospital and long-stay institutions and had fewer discharges. It is also possible that patients with fewer hospitalisations received less follow-up care.

Response rates varied relatively little by the strictness of TRS criteria, nor by different response criteria. However, among studies using the Kane et al. (1988) criteria, the response percentage was slightly lower than in other studies (35% vs. 41%).

When analysed in strata by antipsychotic drugs, the highest response rate was in studies with patients using clozapine. The response percentage was also high in studies analysing injections, although the results remains unsure due to the very low number of studies ($n = 3$). The difference in response rate between typical and atypical antipsychotic drugs was notable, whereas response rates did not vary greatly among individual atypical antipsychotic agents.

4.2. Comparison with previous results and clinical implications

The current meta-analysis obtained a response rate (40.8%) equivalent to Kennedy et al.' (2014) estimate of 41%. The response rates were very similar regardless of TRS criteria, which supports the reliability of the result. As a comparison, in general schizophrenia the response rates range from 23%–51% (Haddad and Correll, 2018).

The association between higher baseline positive symptom score and higher probability of response did not support our hypothesis of lower symptoms at baseline and better response. However, the result that higher positive symptoms specifically, but not negative symptoms,

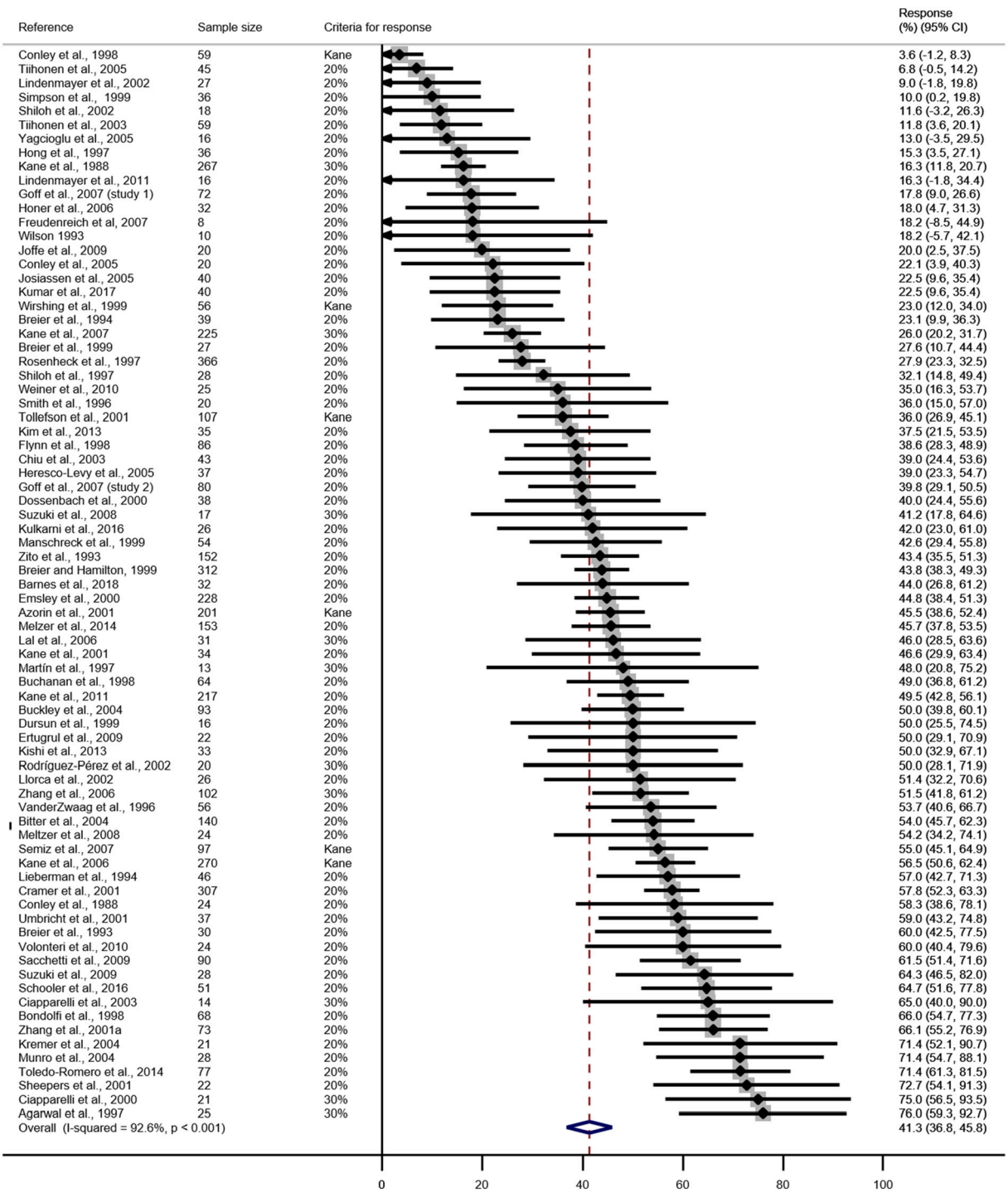

Fig. 2. Percentage of response in all studies.
20%: reduction in 20% of symptoms in PANSS or BPRS, 30%: reduction in 30% of symptoms in PANSS or BPRS, Kane: ≥20% decrease in the BPRS total score, and either a post-treatment CGI-Severity score of ≤3 (i.e., better than mild) or BPRS of ≤35.

predicts better response is understandable, since antipsychotics are effective in the treatment of positive, but less so in the treatment of negative symptoms. Earlier meta-analysis of clozapine response had somewhat different results, showing that fewer negative symptoms predicted clozapine response, but positive symptoms were not statistically significant (Okhuijsen-Pfeifer et al., 2020). The differences in our study and the study by Okhuijsen-Pfeifer et al. (2020) may be explained by differences in the inclusion criteria, and the differences in the characteristics (e.g. symptom severity at baseline, analysed medications) of included samples. More severe positive symptoms at baseline have been associated with better treatment response also in original study with treatment-refractory schizophrenia patients (Wirshing et al., 1999).

We found no statistically significant difference between patient gender or age at the study moment and response. This result is similar to previous original studies that analysed the associations at patient level (Zito et al., 1993; Lieberman et al., 1994; Hong et al., 1997; Lindenmayer et al., 2001; Semiz et al., 2007). Age of illness onset, length of hospitalisation did not predict response either, and similar results were found in previous original studies (Semiz et al., 2007; Hong et al., 1997; Zito et al., 1993; Wirshing et al., 1999). Predicting response in TRS using

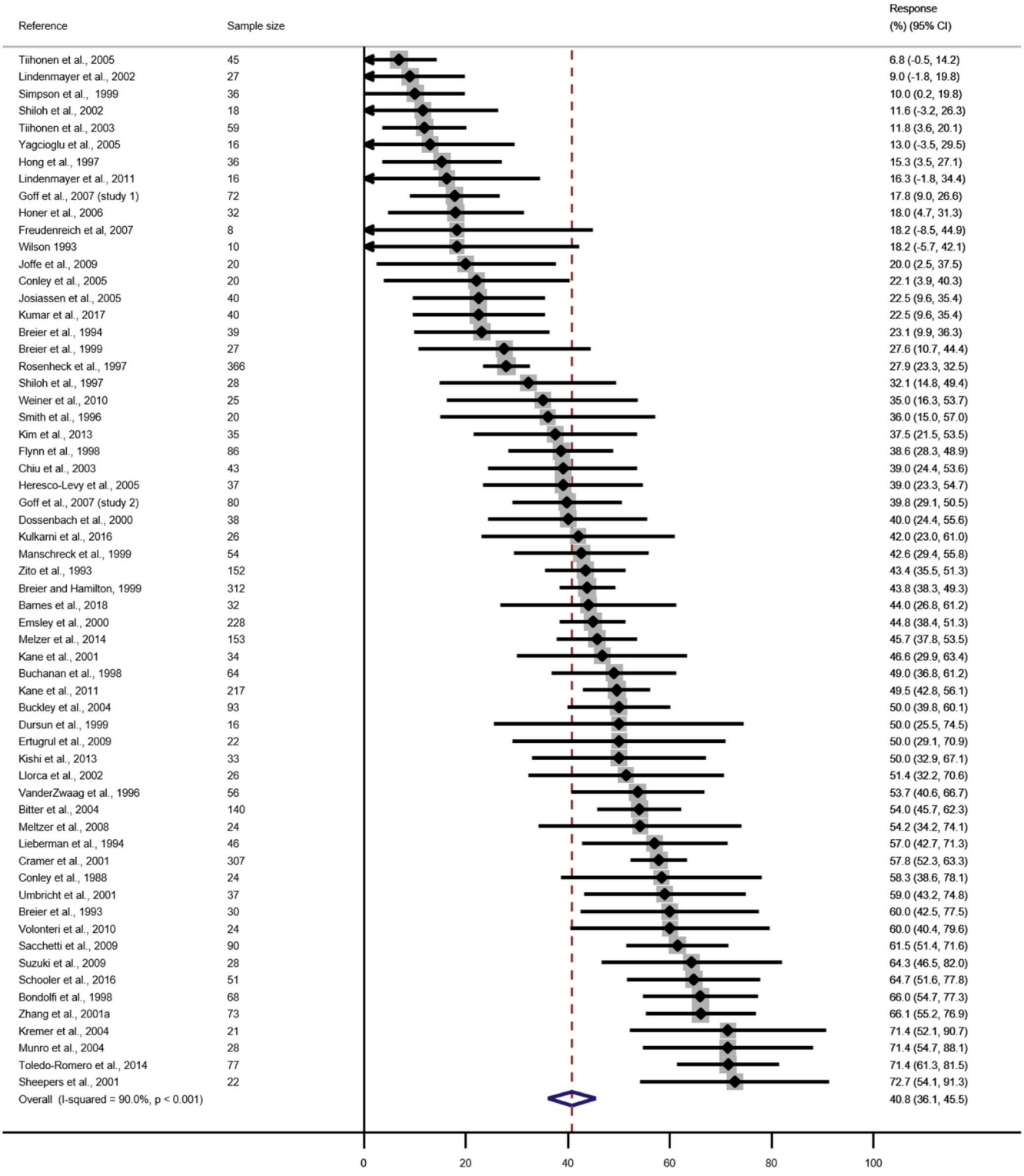

Fig. 3. Percentage of response in studies using 20% of decrease of symptoms as response criteria.

patient characteristics is challenging. In comparison, in first-episode psychosis, being female, antipsychotic-naïve, having a more severe illness and shorter duration of illness at baseline predicted a higher response rate (Zhu et al., 2017).

It may be that TRS has a complex nature with multiple factors affecting the course of the illness. Thus, identifying associations between certain patient characteristics and response is challenging. There has been some tentative evidence of etiological differences between treatment-resistant and non-treatment-resistant schizophrenia (Gillespie et al., 2017). Treatment-resistant patients have shown a lack of dopaminergic abnormalities but rather show glutamatergic abnormalities, a significant reduction in brain gray matter, and higher familial loading compared to treatment-responsive patients (Gillespie et al., 2017). Okhuijsen-Pfeifer et al.'s (2020) meta-analysis showed that younger age (35,9 years in responders, 37,2 in non-responders), few negative symptoms, and paranoid schizophrenia subtype were

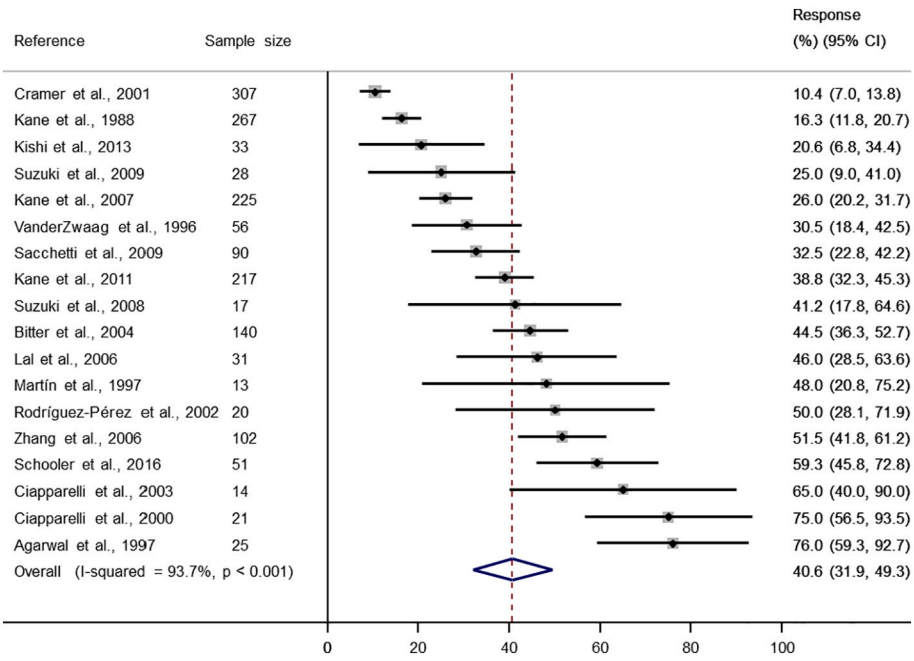

Fig. 4. Percentage of response in studies using 30% of decrease of symptoms as response criteria.

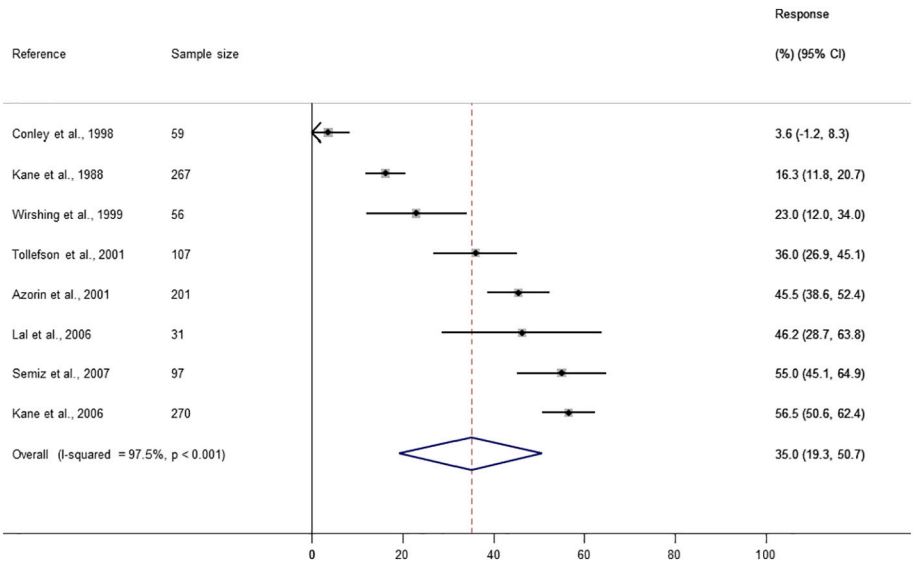

Fig. 5. Percentage of response in studies using Kane criteria as response.

associated to better clozapine response. It may be that the more homogenous sample of their study (only clozapine users) associated to the fact that significant predictors were found.

To our knowledge, this is the first systematic study of the predictors of response to any pharmacological treatment in TRS. The number of individual investigations of predictors of treatment response in TRS is rather few. It was therefore not possible to perform a patient-level meta-analysis. Thus, in this study, we analysed the associations in a study level, as did Okhuijsen-Pfeifer et al. (2020). We examined the associations between sample and study characteristics and the response rates in the corresponding study using a relatively crude method. Our meta-analysis generally did not support the few previous findings in which baseline characteristics predicted treatment response.

In our study, of patients using typical antipsychotics, 25.0% achieved response, whereas among patients using atypicals (not including clozapine), the response rate was 41.5%. In a meta-analysis of 15 antipsychotic medications, Leucht et al. (2013) found only minor differences in efficacy in schizophrenia patients. They identified 212 trials involving 43,049 participants. All drugs were significantly more effective than placebo. Their findings challenge the straightforward classification of antipsychotics into typical and atypicals and the idea that atypical antipsychotics are more effective than typicals. Our finding of different response percentage between typicals and atypicals is interesting. Despite criticism for classifying antipsychotics into typicals and atypicals, it may be that TRS patient response differently to these two classes and one reason behind this could be differences in etiology of the illness in TRS and schizophrenia in general.

Samara et al. (2015) found no major differences in the efficacy of different antipsychotic agents in TRS, or when comparing clozapine with other atypicals. However, clozapine was more effective than typical antipsychotics. Several studies that support the efficacy of clozapine in the treatment of TRS, and the earlier initiation of clozapine may improve

Table 3
Percentage of response in subpopulations. Among studies using 20% of decrease of symptoms as criteria for response.

Predictor	Number of studies	Median response %	IQR	Statistical test
Proportion of males in the sample	57			
Less than 64%	19	37.5%	18.2–50.0	$t = -0.27$, $p = 0.79$
64–73%	20	49.5%	42.0–60.3	$t = 1.75$, $p = 0.09$
More than 73%	18	39.2%	18.2–57.8	Ref.
Publication year	61			
Before year 2000	19	42.6%	27.6–53.7	$t = -0.82$, p = 0.41
2000–2009	30	42.4%	18.2–57.8	$t = -0.83$, $p = 0.41$
2010 or later	12	44.8%	36.3–55.0	Ref.
Proportion of white persons in the sample	19			$t = -0.11$, $p = 0.91$
Less than 66%	9	45.7%	36.0–54.2	
Equal or more than 66%	10	45.3%	27.9–57.0	
Age at baseline	46			
Under 38 years	18	50.7%	27.6–60.0	$t = 0.87$, $p = 0.39$
38–40 years	18	44.4%	32.1–49.5	$t = -0.04$, $p = 0.97$
41 years or older	20	39.4%	21.1–59.5	Ref.
Age of onset	26			$t = 0.34$, $p = 0.74$
Under 20 years	13	42.6%	22.5–49.0	
20 years or older	13	43.8%	27.6–57.8	
Age at time of first hospitalisation	10			$t = 2.24$, $p = 0.06$
Under 23 years	5	18.2%	18.2–22.5	
23 Years or older	5	59.0%	46.6–64.7	
Duration of illness	32			$t = 0.08$, $p = 0.94$
16 or under	16	50.0%	22.8–55.6	
Over 16	16	44.1%	21.3–58.7	
Cumulative number of hospitalizations	17			$t = 0.78$, $p = 0.45$
Under 7	7	27.6%	16.3–60.0	
7 or over	10	46.2%	22.1–53.7	
Proportion of inpatients of the sample at baseline	9			$t = -1.13$, $p = 0.30$
Under 43%	5	44.0%	42.6–71.4	
43% or more	4	31.9%	19.1–46.9	
Proportion of outpatient of the sample at baseline	10			$t = 0.12$, p = 0.91
Under 59%	5	43.8%	20.0–50.0	
59% and over	5	42.6%	23.1–60.0	
Duration of current hospitalisation	8			$t = -1.27$, $p = 0.25$
Under 6.4 months	4	41.2%	28.6–57.4	
6.4 and over	4	23.9%	10.9–43.0	
Baseline total PANSS	36			
Under 88	12	40.9%	15.4–53.9	$t = -0.71$, $p = 0.48$
88–101.9	12	43.9%	32.7–47.8	$t = -0.41$, $p = 0.69$
102 and over	12	39.5%	21.3–57.8	Ref.
Baseline total BPRS	21			
Under 43	7	49.0%	27.6–71.4	$t = 0.60$, $p = 0.56$
43–51	7	36.0%	22.5–57.0	$t = -0.23$, $p = 0.82$
Over 51	7	43.4%	22.1–58.3	Ref.
Baseline CGI	23			$t = 0.28$, $p = 0.78$
Under 5	11	44.8%	20.0–54.0	
5 and over	12	44.2%	22.3–60.8	
Baseline positive PANSS				
Under 19.4	7	17.8%	12.0–42.0	t = 3.20, p = 0,008
19.4–24.0	8	39.4%	18.5–57.1	t = 1.10, p = 0.29
Over 24.0	7	50.0%	37.5–66.0	Ref.
Baseline negative PANSS				
Under 22.1	7	37.5%	16.3–45.7	t = 0.91, p = 0.38
22.1–25.7	7	48.5%	13.0–60.0	t = -0.05, p = 0.96
Over 25.7	7	39.0%	20.0–66.0	Ref.
Weight	9			$t = -0.43$, $p = 0.68$
Under 79 kg	4	50.7%	32.7–61.4	
79 kg or over	5	49.0%	22.1–49.5	
BMI	8			$t = -0.72$, $p = 0.50$
Under 30	4	46.0%	32.1–60.7	
30 or over	4	40.3%	25.7–49.9	
TRS classification	72			
Has used at least 1 AP	12	37.4%	18.0–46.9	$t = -1.13$, $p = 0.26$
Has used at least 2 APs	24	45.2%	25.0–56.0	$t = -0.22$, $p = 0.83$
Has used at least 3 APs	20	46.7%	27.6–58.7	Ref.
Attrition	57			$t = 1.28$ $p = 0.207$
Under 15.4%	28	38.1%	21.3–53.7	
15.4% or over	29	44.8%	36.0–57.8	

IQR, inter quartile range.

Table 4
Response in subpopulations by antipsychotic medication. Among studies using 20% of decrease of symptoms as criteria for response.

	Number of Studies	Median percentage of persons meeting response criteria %	IQR
Medication class			
Typical	20	25.0	9.75–39.0
Atypical (excluding clozapine)[a]	36	41.5	24.0–52.0
Injection	3	45.8	45.5–60.0
Combination of two medications	4	45.6	38.1–59.5
Clozapine monotherapy	39	50.0	35.7–60.0
Clozapine combined to second medication	3	35.0	21.0–50.0
Risperidone	14	33.5	20.0–57.0
Chlorpromazine	6	10.3	0.00–31.6
Haloperidol	10	36.5	25.0–40.0
Olanzapine	11	45.0	38.0–50.0
Quetiapine	5	25.0	16.3–52.0
Other psychiatric medication than antipsychotic[b]	8	19.0	17.7–52.0
Other than psychiatric medication[c]	3	42.0	39.0–63.0
Placebo	16	11.5	6.50–27.5

[a] This class included studies analysing risperidone, amisulpride, aripiprazole, olanzapine, quetiapine, sertindole, ziprasidone.

[b] This class included studies analysing lamotrigine, lithium mirtazapine, valproic acid, topiramate, mianserin, topiramate, Lamotrigine, study subjects might have ongoing other antipsychotic treatment.

[c] This class included D-serine, ondansetron, raloxifene, study subjects might have ongoing other antipsychotic treatment.

the outcomes in TRS (Haddad and Correll, 2018). Early recognition and treatment of TRS are important because for as many as 84% of patients with treatment resistance may be present from the illness onset (Demjaha et al., 2017).

Our study revealed that the prediction of medication response in TRS is difficult to tease out. In such a situation, careful monitoring, follow-up and personalised medicine should be applied. In practice, this means tailored antipsychotic medication. When providers start, switch, taper or terminate antipsychotics, a one–three-month experimental period with well-planned medication management (Isohanni et al., 2020) is often useful. In practice this stresses good collaboration with the patient and relatives and follow-up of clinical responses and efficacies, side effects, and patients' experiences and beliefs about antipsychotics (Isohanni et al., 2018, 2020). TRS poses a challenge to the treatment system, where standard treatment recommendations and algorithms tend often to fail. Unfortunately, there are no anticipated breakthroughs in near future in antipsychotic medication efficacy of TRS. In such situation, non-pharmacological efforts designed by sophisticated professional team must be activated.

In addition, in TRS, especially in non-responders, it is important to ascertain diagnostic accuracy and the impact of comorbid conditions on response and efficacy. For instance, it is reasonable to consider the effect of neurological or metabolic disorders given that these may complicate the overall treatment course (Lally and Gaughran, 2019).

4.3. Strengths and limitations

There are several important caveats related to this review. The protocol of this study was not pre-published. We included only English language articles so we may have missed some non-English publications. We included studies with variable definitions of TRS and this may have caused some heterogeneity and noise in the results. On the other hand, the results did not change in sensitivity analyses restricted to studies that only had stricter TRS criteria. The broad inclusion of TRS studies was necessary, as we wanted to have a large number of studies in order to study potential predictors. There are multiple definitions of TRS as indicated in Online supplement Table 4. When developing a consensus for the definition of TRS, Howes et al. (2017) suggested a much more specific definition, including a symptom questionnaire and the evaluation of functioning capacity. However, studies have rarely adopted this TRS standard. We acknowledge that the field remains in a state of flux with respect to the conceptual validity of treatment resistance, as well as the definition of response.

It is important to consider pseudoresistance when analysing the response to treatment (Howes et al., 2017). Unfortunately, most of the studies included in this meta-analysis did not separately mention pseudo-resistant subjects, and this may have caused additional heterogeneity in the sample. In addition, we did not separate the ultra-resistant patients since this would have led to a small number of studies in the analyses.

77 studies were included. However, the eventual number of studies in the analyses of different predictors varied notably, and for some predictors the number of studies was very low. Studying these predictors at study level and not at patient level is not very powerful statistically and there is a need for original studies that focus on individual predictors. Our analyses on the response rate in the categories of used medications are crude and do not reflect a standard analyses of efficacy. Regarding analysing of response, it is possible that some original studies may have not correctly subtracted minimum points (30 in PANSS and 18 in some versions of BPRS) before calculating the response (Obermeier et al., 2010; Thompson et al., 1994). In other words some studies may have used e.g. the original 1–7 scale of PANSS without subtraction.

A strength of this study was that we were able to analyse predictors of treatment response by utilising a meta-analysis, which has not been done before. Several plausible predictors that could be utilized in clinical practice were included. Our search strategy included multiple search terms and databases, and was comprehensive enough to identify at least most of the published drug trials on TRS.

4.4. Conclusions

In this systematic review, we identified that higher positive symptoms at baseline predicts higher response, but no other baseline characteristics predicted treatment response in TRS. The response rate remained relatively similar across studies with different definitions of TRS and response criteria. It also appears that the percentage of responders has remained static from earlier to recent studies. Our results support the complex nature of TRS and the need for more effective pharmacological and non-pharmacological treatments of TRS. In future studies, it would also be important to study predictors of treatment response at patient level and studies should specifically focus on analysing predictors of treatment response and other outcomes in TRS. To help the future studies on this subject, the patient material should be more homogenous and researchers should rule-out pseudoresistance in clinical trials. The field would also benefit from coherent criteria for TRS and treatment response.

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CRediT authorship contribution statement

AS, JS, JM and EJ designed this study. NH performed literature search. AS, JP and EJ extracted the data. HL analysed data. AS wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript.

Declaration of competing interest

There are no conflicts of interests.

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