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Demographic and clinical features as predictors of clozapine response in patients with schizophrenia spectrum disorders: A systematic review and meta-analysis

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ABSTRACT

Objectives: Clozapine (CLZ) is prescribed to (relatively) treatment-resistant patients with schizophrenia spectrum disorders. Currently, it is unknown what factors predict response to CLZ. Therefore, we performed meta-analyses to identify predictors of CLZ response, hence aiming to facilitate timely and efficient prescribing of CLZ.
Methods: A systematic search was performed in 'Pubmed' and 'Embase' until 1 January 2019. Articles were eligible if they provided data on predictors of CLZ response measured demographic and clinical factors at baseline or biochemical factors at follow-up in schizophrenia spectrum disorder patients.
Results: A total of 34 articles, total number of participants = 9386; N unique = 2094, were eligible. Factors significantly associated with better CLZ response were: lower age, lower PANSS negative score and paranoid schizophrenia subtype.
Conclusion: The results of our meta-analyses suggest that three baseline demographic and clinical features are associated with better clozapine response, i.e. relatively young age, few negative symptoms and paranoid schizophrenia subtype. These variables may be taken into account by clinicians who consider treating a specific patient with CLZ.

1. Introduction

In roughly one third of patients with schizophrenia spectrum and other psychotic disorders (SSD), response is not achieved after two consecutive antipsychotic trials (Lally and MacCabe, 2015). These patients are considered to have (relatively) treatment resistant schizophrenia (TRS) (Tandon, 2014; Tan and Van Os, 2014). TRS in turn is defined as achieving insufficient treatment response (i.e. persisting positive symptoms of at least moderate severity) after two or more antipsychotic trials from at least two different chemical classes at a recognized therapeutic dosage used for at least six weeks (Kane et al., 2003; Kreyenbuhl et al., 2010). Guidelines of the World Federation of Societies of Biological Psychiatry (WFSBP) and of other organizations advise that clozapine (CLZ) should be initiated in patients with TRS (Falkai et al., 2006; National Institute for Health & Clinical Excellence, 2010). CLZ is the only registered drug for TRS and one of the most effective antipsychotics (Tiihonen et al., 2017), with 30–60% of TRS patients responding to CLZ treatment (Hu et al., 1999; Kane et al., 1988; Meltzer et al., 2008). In addition, a recent meta-analysis demonstrated that CLZ, compared with second-generation antipsychotics, was associated with lower (re)hospitalization and lower all-cause discontinuation rates, as well as better outcomes regarding overall symptoms (Masuda et al., 2019). In clinical practice, WFSBP guidelines are not always followed and merely 30% of TRS patients receive CLZ treatment (Farooq and Taylor, 2011). The delay in initiation of CLZ pharmacotherapy, defined as the moment of meeting TRS criteria until initiating CLZ pharmacotherapy, is approximately 4–6 years (Taylor et al., 2003; Doyle et al., 2017; Howes et al., 2012). Delays in adequate treatment of SSD are clinically undesirable as increasing numbers of psychotic exacerbations impair daily and occupational functioning, thus negatively influencing quality of life of patients with SSD (Kahn et al., 2015; Harvey, 2009). Possible reasons for the underutilization of CLZ are the absence of personal prescribing experience by psychiatrists and psychiatry trainees, as well as patients' and mental health

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professionals' concerns about side effects and blood monitoring (Gee et al., 2014; Verdoux et al., 2018; Okhuijsen-Pfeifer et al., 2019). Although the majority of psychiatrists and psychiatry trainees are aware of the effectiveness of CLZ (Gee et al., 2014; Verdoux et al., 2018), many believe the possible complications and risks outweigh the benefits (Aringhieri et al., 2017). Importantly, clinicians might decide to initiate CLZ treatment with less of a delay when they have information at hand indicating what patient characteristics increase the odds of treatment response. Recently, a systematic review on biological predictors (e.g. neuroimaging, genetics and biochemistry) concluded that there are currently no biological predictors with sufficient accuracy available (Samanaite et al., 2018). The aim of the current study was therefore to focus not on biological predictors, but on demographical and, clinical and biochemical patient characteristics as potential predictors of CLZ response. To that end, we performed a systematic review and meta-analysis to examine which of those characteristics are most strongly associated with CLZ response.

2. Methods

2.1. Search strategy and study selection

A systematic literature search was performed in the databases 'PubMed' and 'Embase' to find all studies investigating predictors of CLZ pharmacotherapy response in SSD patients. The following search terms were used: 'schizophreni*' AND 'clozapine' AND 'marker*' OR 'predict*' AND 'respon*'. The full search terms and details can be found in the Appendix, supplementary table 1. Publication date of the literature search was set until January 1, 2019 without further limitations. The snowball method was used by checking the references of the retrieved articles (including reviews) to identify potentially additional eligible studies for the current meta-analyses. Then, duplicates were removed. Articles were included only if (a) their study population consisted of SSD patients; (b) patients used CLZ and outcomes were given for the CLZ users group (if the article contained more information, i.e. about other antipsychotics, we required the outcomes for the CLZ group be given separately); (c) there was a quantitative measurement of CLZ response and non-response/relevant data; (d) age ≥ 18 years; (e) the full-text was available. When a full text of an article was not available through our university library, librarians tried to retrieve the article from other sources, and the authors were contacted twice to request the articles. Articles were excluded if: (f) an article was not available in English; (g) studies were not done in humans (such as computer model studies); (h) the independent variable of interest was not reported; (i) studies lacked (new) data; (j) studies were case reports; (k) insufficient statistics were provided, precluding meta-analysis. Two researchers (Y.S. and I.H.) independently selected articles. The lists of selected and excluded articles were compared and discrepancies were resolved during consensus meetings.

2.2. Assessment of treatment response

Response can be measured by using several rating scales assessing baseline symptoms and improvement of symptoms after starting a new treatment. The Positive And Negative Syndrome Scale (PANSS) and Brief Psychiatric Rating Scale (BPRS) are frequently used to measure response to antipsychotic drug treatment (Leucht, 2014). The PANSS is a semi-structured interview with 30 items rated on a 7-point scale, with 1 being "absent" and 7 being "extreme" (Kay et al., 1987). The BPRS is based on clinical observations and patient self-report. It has 18 items and is also rated on a 7-point scale, 1 being "not present" and 7 being "extremely severe" (Guy, 1976b). Both scales have been validated and show robust reliability and sensitivity (Leucht, 2014). Results of the PANSS and BPRS can be translated to the Clinical Global Impressions (CGI) scale to gain a better understanding of their clinical significance (Leucht, 2014; Hamann et al., 2006). The CGI-Severity (CGI-S) scale rates the current severity of illness on a 7-point scale, 1 meaning "normal, not at all ill" and 7 meaning "among the most severely ill" (Guy, 1976a). In all scales, a higher score is related to more severe illness. A reduction of 10 points in BPRS and 15 points in PANSS scores over time translate into a decrease of one point on the CGI-S (Hamann et al., 2006)]. Since these scales (BPRS, PANSS, CGI) have been validated for SSD patients and are intercorrelated all were allowed as response data input for the current meta-analyses. We thus conceded that the articles included in the meta-analysis used disparate rating scales for response.

2.3. Statistical analyses

We divided the patient characteristics into the articles in several categories; 1) Demographic and general factors; 2) Clinical factors and 3) Biochemical factors. We set a threshold of at least 3 articles per potential predictor to perform random-effects meta-analyses, because the included studies were expected not to be functionally equivalent and a common effect size across them could not be assumed (Borenstein et al., 2009). The test statistics were generated with the program 'Comprehensive Meta-Analysis' version 3.3.070 (2014) from BioStat. Alpha was set at 0.05. Hedges' g was used as a measurement of effect size. To quantify the degree of heterogeneity across the included studies we included, Cochran's Q test and the I^2 statistic were used. The Cochran's Q test was used to determine whether a single estimate of a variance was significantly larger than a group of variances. The I^2 statistic describes the degree of heterogeneity across studies' results, with the absence of heterogeneity being defined as $I^2 = 0\%$, whereas > 0 - 50%, > 50% and > 75% are indicative of low, moderate and high degrees of heterogeneity, respectively (Higgins et al., 2003). Publication bias was assessed using funnel plots.

3. Results

3.1. Study selection

A total of 556 articles were initially identified using the standardized search terms and the snowball method. Then, all duplicate articles, n = 110, were removed, reducing the number of articles to 446. The abstracts, and wherever needed, full-texts, of these 446 articles were assessed for eligibility. 405 articles were excluded based on the exclusion criteria. 7 articles had to be excluded because the variable under investigation was found in less than 3 articles, making a meta-analysis impossible. The factors described in the remaining 34 articles were divided in the following categories: 1 Demographic and general factors at baseline; 26 articles, n = 3656 participants 2 Clinical factors at baseline; 28 articles, n = 3949 participants, and 3 Biochemical factors during follow-up; 19 articles, n = 1781 participants. We allowed for a single article to target multiple categories and subcategories of factors and the same participants were therefore used for multiple factors. In total, 34 articles N total = 9386 participants, of whom N = 2094 unique participants were included in the meta-analyses Fig. 1).

3.2. Factors that might predict CLZ response

3.2.1. Demographic and general factors at baseline

A significant result was found for age, indicating that lower age is associated with better CLZ response (N = 1247 participants, Hedges' g = 0.142, 95% CI = 0.021 – 0.263, P = 0.022; Fig. 2a) with a low degree of heterogeneity (Q = 24.376, I^2 = 9.747). The funnel plot was examined and did not result in suspicion of publication bias (Supplementary Fig. 1a). We calculated the mean age of the participants in the included 23 articles for the responders and the non-responders and found that responders have a mean age (standard deviation) of 35.9 (8.4) and non-responders of 37.2 (9.3) years. For the following factors no significant results were found: gender, smoking, weight, years of

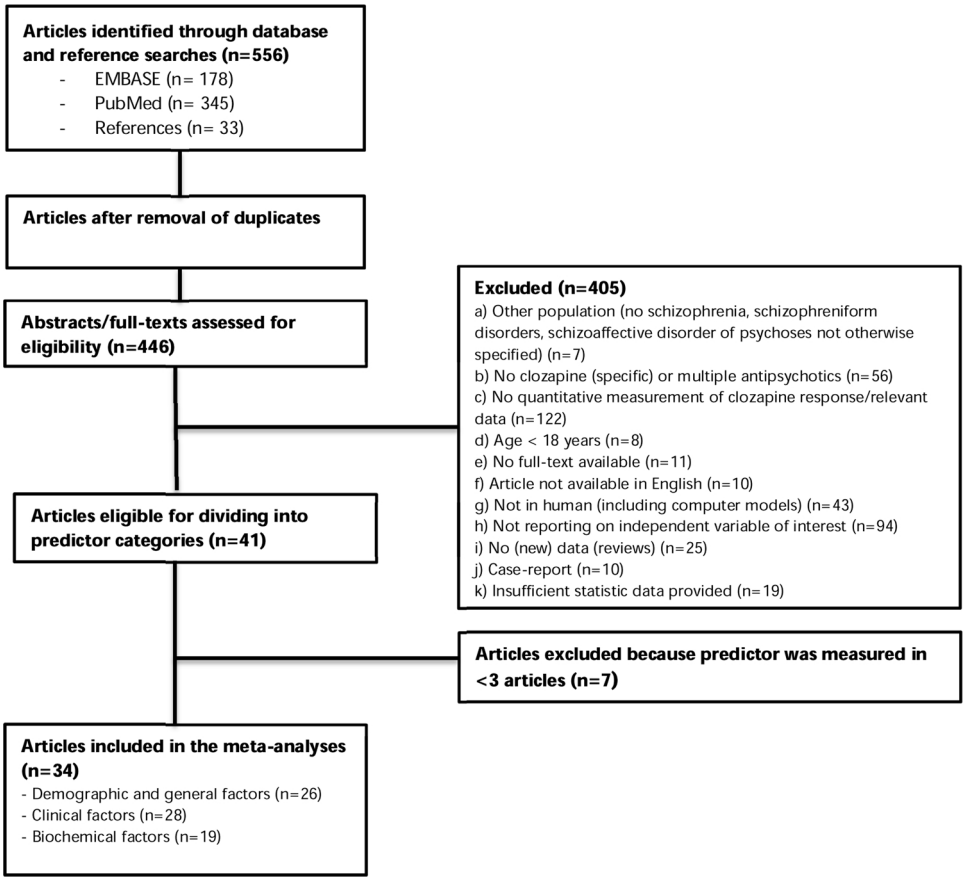

Fig. 1. Flow chart of the meta-analyses selection process. The articles included per category (n = 26, n = 28, n = 19) do not add up to the total number (n = 34) because articles could be used in multiple categories.

education, marital status. All statistical details can be found in Supplementary table 3.

3.2.2. Clinical factors at baseline

Schizophrenia paranoid subtype was found to be significantly predictive of good CLZ response (N = 424 participants, Hedges' g = 0.259, 95% CI = 0.006 – 0.513, P = 0.045; Fig. 2b) with no evidence of heterogeneity (Q = 4.690, I^2 = 0.000). The funnel plot was examined and did not result in suspicion of publication bias (Supplementary Fig. 1b). As other subtypes may be predictive of response as well, we performed a sensitivity analysis on all subtypes, paranoid vs undifferentiated and paranoid vs disorganized subtype using the same articles we used for the paranoid subtype, if they contained data on other subtypes. For each subtype we found the following numbers: 1) paranoid subtype: total n = 176, 63.1% responders; 2) undifferentiated subtype: total n = 17, 64.7% responders; and 3) disorganized subtype: total n = 36, 52.8% responders. A X^2 test on all subtypes indicated no significant differences between the three subtype (p = .493). X^2 tests between paranoid vs undifferentiated subtype, and paranoid vs disorganized indicated no significant differences (p = .894 and p = .248 respectively) either. Secondly, lower PANSS negative subscores at baseline were associated with better CLZ response (N = 133 participants, Hedges' g = 0.719, 95% CI = 0.036–1.401, P = 0.039; Fig. 2c), with a moderate degree of heterogeneity (Q = 6.079, I^2 = 67.102) and without suspicion of publication bias (Supplementary Fig. 1c). For the following factors, no significant results were found: age at SSD onset, age at first hospitalization, number of hospitalizations, duration of illness, length of stay during hospitalizations, BPRS baseline score, CGI baseline score, PANSS total score at baseline, and PANSS positive subscore at baseline (Supplementary table 3).

3.2.3. Biochemical factors during follow-up

None of these characterisics were associated with clozapine response: serum and plasma concentrations of CLZ and norclozapine (NCLZ), and mean daily CLZ dose (Supplementary table 3).

4. Discussion

By performing the first meta-analysis on patient characteristics at baseline as potential predictors of clozapine response, we found relatively young age, a low burden of PANSS negative symptoms and paranoid schizophrenia subtype to be significantly associated with better CLZ response. No effects were found for gender, smoking, weight, years of education, marital status, age at SSD onset, age at first hospitalization, number of hospitalizations, duration of illness, length of hospitalizations, overall disease severity, positive symptoms, blood level concentrations or dosing of CLZ. A possible explanation for the finding that younger age is associated with better CLZ response may be that young patients generally have a relatively short duration of illness and thus less persistent symptoms and as a result may be less resistant to treatment (Spellmann et al., 2012). Although we cannot check this within the current data, in an earlier meta-analysis, which has shown that CLZ prescribed as a first or second-line agent is more efficacious than other antipsychotics (Okhuijsen-Pfeifer et al., 2018), the mean age in all studies was lower (Lieberman et al., 2003; Sahni et al., 2016; Sanz-Fuentenebro et al., 2013; Edwards et al., 2011; Zhang et al., 2016) than in the study used for the market authorisation of CLZ (Kane et al., 1988). Furthermore, most likely, the association between younger age and better treatment response is not CLZ-specific. Interestingly, for 14 out of 23 studies, the mean age for responders was lower than non-responders (some were significant on their own, some were not), 8 out of 23 found an opposite effect and 1 study found equal results. The

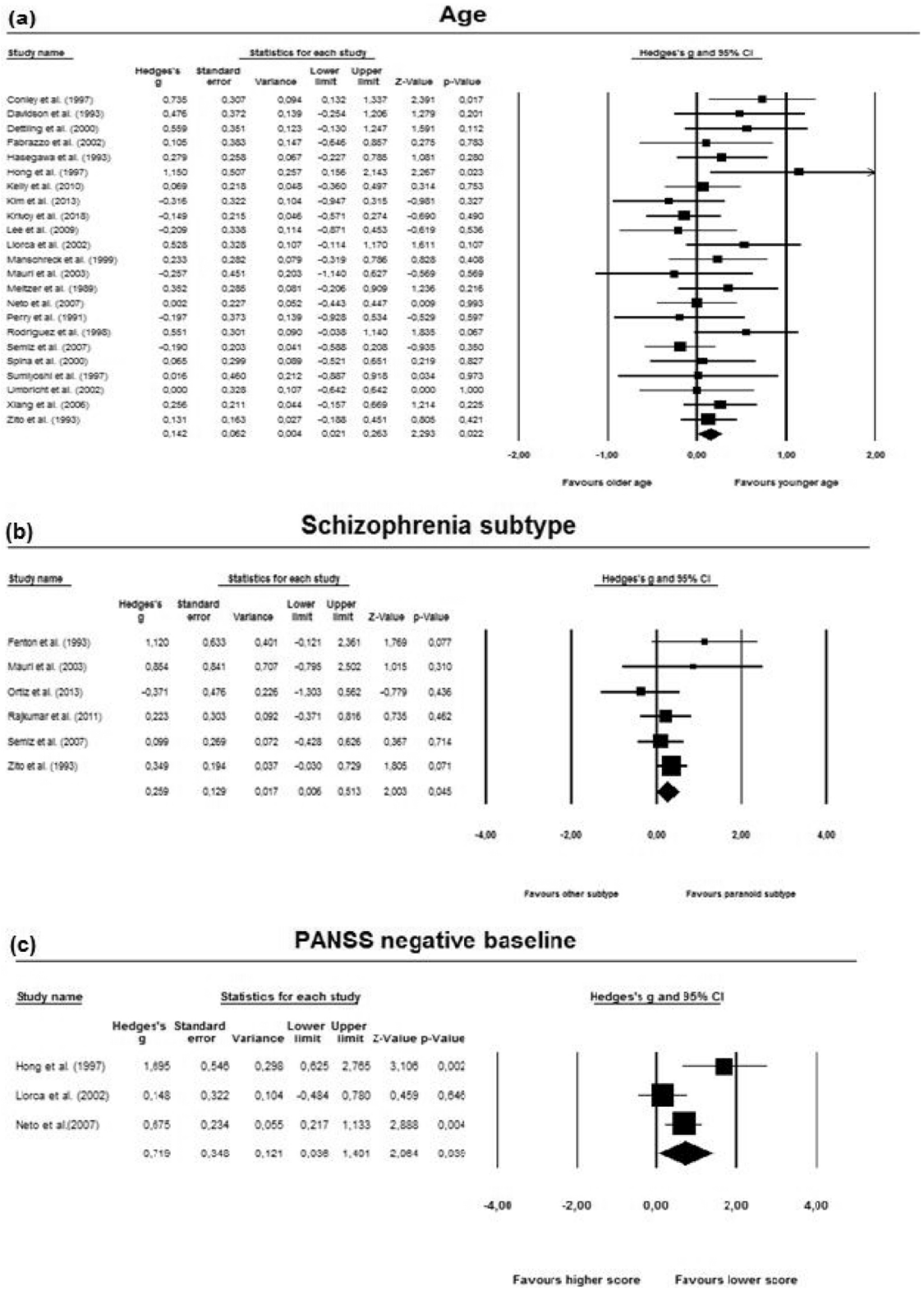

Fig. 2. Forest plots for clozapine response of (a) age, (b) schizophrenia subtype, and (c) PANSS negative subscore at baseline. Squares represent the effect size of each study and the size reflects the sample size. Squares are bounded by a 95 % confidence interval. The summary effect is shown on the bottom line (diamond).

difference in means (standard deviations) for responders and non-responders were 35.9 (8.4) and 37.2 years (9.3), respectively. This difference is quite small and the standard deviations quite high, so we believe we cannot recommend a certain age as a cut-off when a doctor considers prescribing clozapine, but we do believe age is something that should be taken into account when prescribing clozapine. The message we intend to convey is that younger patients respond better (on average), so when prescribing antipsychotics, it is best not waiting too long with clozapine, especially when have not responded well to other antipsychotics. The association between lower PANSS negative subscores at baseline and better CLZ response could be explained by the relative specificity of CLZ to target mainly positive symptoms – the

relatively disappointing efficacy of antipsychotics in general on negative symptoms has been demonstrated for most antipsychotics (Breier et al., 1994; Lieberman et al., 1994a). It is important to note that the PANSS negative subscore scale does not only include items about negative symptoms such as blunting of affect and loss of motivation, but also about cognitive symptoms. Therefore, it may be that that when patients have relatively preserved cognitive functioning, they respond to CLZ better. We did not find articles that related cognitive symptoms specifically to CLZ response, so we cannot check whether cognitive symptoms mediate or moderate the result that we found for the PANSS negative subscore. Interestingly, there was no significant difference between lower (or higher) PANSS positive or total subscores at baseline.

Patients with paranoid schizophrenia subtype showed better response, which is in line with earlier findings for CLZ (Lieberman et al., 1994a, Lieberman et al., 1994b) and first-generation antipsychotics (Fenton and Mcglashan, 1991). This could be explained by a previous observation that patients with the paranoid subtype are generally in earlier stages of the disease than patients with non-paranoid subtypes (Lieberman et al., 1994a). As another result in this meta-analysis was that younger age is associated with better response, it is possible that the paranoid subtype and younger age are correlated or even converge as one single factor. Our sensitivity analysis on the undifferentiated and disorganized subtype did not reveal significant effects, although this could be due to a lack of power since the number of participants for these subtypes was very low (n = 17 and n = 36 respectively).

It was unexpected that there was no association between response and CLZ blood levels, as nearly all guidelines define blood levels above 350 ng/ml as important for CLZ response. Most likely, the absence of effect can be explained by a lack of power, as the N was 208 and 252 for the serum and plasma blood level analyses, respectively. Alternatively, the included studies were observational, not randomized. We hypothesize that there may be patients who are sensible to side effects but respond to fairly low dosages and blood levels (e.g. < 300). Those patients would count toward the group of responders with low blood levels. Then, there may be patients who respond poorly but tolerate clozapine well. Clinicians will likely increase the dose to higher blood levels to try and achieve remission, which will work in some but not all patients. In summary, based on the current fairly low sample size and lack of randomized studies (randomizing between levels > 350 and < 350) we cannot definitely conclude what blood level gives the highest likelihood of response. There are some limitations of this study. First, there were varying definitions of response, CLZ dosages, treatment times and follow-up time across the studies we included for meta-analyses (Supplementary table 2 summarizes this). Earlier research has shown that approximately 40–50 % of the responders, respond to CLZ within 12 weeks (Rosenheck et al., 1999; Zito et al., 1993). In studies with relatively short follow-up, possibly not all responders had been identified at the end of study, which could have influenced our results if certain variables are more strongly associated with response in a relatively late stage of a trial than in early trial phases. Second, although the funnel plots did not lead to suspicion of publication bias, we cannot rule out the possibility of publication bias as some studies only reported significant results. Third, it is unclear whether non-responders had been put on therapeutical CLZ dosages as not all studies reported CLZ blood levels. Finally, the effect sizes of the significant factors were small (age: g = 0.14; paranoid subtype: g = 0.26) to medium (PANSS negative subscore: g = 0.72). No large effects were found. However, most sample sizes were relatively small, which could have led to the small effect sized and false negative results.

In conclusion, this meta-analysis suggests that three easily identifiable demographic and clinical variables (younger age, lower PANSS negative subscores and SCZ paranoid subtype) could aid to predict whether clozapine response is more or less likely. Potentially, younger age and the SCZ paranoid subtype converge as one factor, as the paranoid subtype is usually diagnosed at younger age than the other subtypes. Future, large (randomized) clinical trials also incorporating biological variables such as (epi)genetics and neuro-imaging will hopefully ascertain how easily identifiable variables and biological variables interact to influence CLZ response.

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Declaration of Competing Interest

RK declares personal fees for consultancy from Alkermes, Minerva Neuroscience, Gedeon Richter, and Otsuka; and personal (speaker) fees from Otsuka/Lundbeck. All other authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.neubiorev.2020.01.017.

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