

## Review Article

\*Joint last authors.

**Cite this article:** Griffiths K, Millgate E, Egerton A, MacCabe JH (2021). Demographic and clinical variables associated with response to clozapine in schizophrenia: a systematic review and meta-analysis. *Psychological Medicine* **51**, 376–386. <https://doi.org/10.1017/S0033291721000246>

Received: 24 September 2020  
Revised: 13 January 2021  
Accepted: 21 January 2021  
First published online: 19 February 2021

**Key words:**  
antipsychotic; psychosis; treatment resistant schizophrenia

**Author for correspondence:**  
Kira Griffiths, E-mail: [kira.griffiths@kcl.ac.uk](mailto:kira.griffiths@kcl.ac.uk)

# Demographic and clinical variables associated with response to clozapine in schizophrenia: a systematic review and meta-analysis

Kira Griffiths , Edward Millgate, Alice Egerton\* and James H. MacCabe\*

Institute of Psychiatry, Psychology & Neuroscience, King's College London, London, UK

## Abstract

Clozapine is the only licensed pharmacotherapy for treatment-resistant schizophrenia. However, response to clozapine is variable. Understanding the demographic and clinical features associated with response to clozapine may be useful for patient stratification for clinical trials or for identifying patients for earlier initiation of clozapine. We systematically reviewed the literature to investigate clinical and demographic factors associated with variation in clozapine response in treatment-resistant patients with schizophrenia spectrum disorders. Subsequently, we performed a random-effects meta-analysis to evaluate differences in duration of illness, age at clozapine initiation, age of illness onset, body weight and years of education between clozapine responders and non-responders. Thirty-one articles were eligible for qualitative review and 17 of these were quantitatively reviewed. Shorter duration of illness, later illness onset, younger age at clozapine initiation, fewer hospitalisations and fewer antipsychotic trials prior to clozapine initiation showed a trend to be significantly associated with a better response to clozapine. Meta-analysis of seven studies, totalling 313 subjects, found that clozapine responders had a significantly shorter duration of illness compared to clozapine non-responders [ $g = 0.31$ ; 95% confidence interval (CI) 0.06–0.56;  $p = 0.01$ ]. The results imply that a delay in clozapine treatment may result in a poorer response and that a focus on prompt treatment with clozapine is warranted.

## Introduction

Approximately one-third of patients with schizophrenia display suboptimal response to two trials of non-clozapine antipsychotic medication and are termed treatment resistant (Elkis, 2007; Howes et al., 2017). Treatment resistant patients face poorer prognosis and functioning than those whose symptoms respond to antipsychotic treatment (Iasevoli et al., 2016; Kennedy, Altar, Taylor, Degtiar, & Hornberger, 2014; Land et al., 2017). Consequently, management of this patient group consumes a disproportionately large share of the total cost of schizophrenia care (Andrews, Knapp, McCrone, Parsonage, & Trachtenberg, 2012; Kennedy et al., 2014). Clozapine is the only licensed pharmacotherapy for treatment resistant schizophrenia and is uniquely associated with better outcomes, although response to clozapine is variable (Kane, Honigfeld, Singer, & Meltzer, 1988; NICE, 2014; Siskind, McCartney, Goldschlager, & Kisely, 2016; Tiihonen et al., 2009).

Due to risk of adverse effects and monitoring requirements, and as the degree of therapeutic response to clozapine can only be determined through a trial of treatment, initiation of clozapine may be delayed in favour of poorly evidenced high dosage or polypharmacy strategies (Bachmann et al., 2017; Gee, Shergill, & Taylor, 2016; Kadra et al., 2016; Lally & MacCabe, 2015; Nielsen, Dahm, Lublin, & Taylor, 2010). According to almost all international guidelines, patients are defined as treatment resistant and thereby eligible for a trial of clozapine after failing to respond to at least two antipsychotics. These criteria can theoretically be met as soon as two months after illness onset, yet the average delay in clozapine initiation is estimated at approximately four years in the UK (Howes et al., 2012, 2017). Understanding the factors associated with variability in clozapine response could therefore help to optimise clinical treatment algorithms. This is particularly pertinent given evidence that (1) the majority of treatment-resistant patients have a suboptimal response to antipsychotic medication from illness onset (Lally et al., 2016); (2) when patients fail to reach remission after a first antipsychotic trial, switching to a second non-clozapine antipsychotic does not increase the likelihood of remission (Kahn et al., 2018) and (3) duration of inadequate treatment, and thereby active symptoms, is associated with poorer long-term outcomes (Marshall et al., 2005).

Accurate prediction of clozapine response holds potential for patient stratification in clinical trials of early clozapine use and clinical decision making. Currently, no biomarkers of clozapine response with sufficient reproducibility or predictive accuracy for clinical application have been identified (Samanaite et al., 2018). Clinical and demographic variables could

© The Author(s), 2021. Published by Cambridge University Press. This is an Open Access article, distributed under the terms of the Creative Commons Attribution licence (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted re-use, distribution, and reproduction in any medium, provided the original work is properly cited.

supplement biomarker data in the development of prediction models and inform biomarker research by highlighting confounding variables to be considered in analyses. A previous review found no consistent associations between clinical and demographic variables and clozapine response (Suzuki, Uchida, Watanabe, & Kashima, 2011). As this was performed almost a decade ago, an update of the literature is required. The aim of this review was to identify clinical and demographic factors associated with variance in response to clozapine.

## Methods

This review was performed and reported within PRISMA guidelines (Moher, Liberati, Tetzlaff, Altman, & PRISMA, 2009; online Supplementary materials 2), following a pre-registered protocol (PROSPERO: CRD42019138119).

### Search strategy

A PubMed search restricted to titles and abstracts was conducted on 20 March 2020 using search terms 'schizophrenia' or 'treatment-resistant schizophrenia' or 'treatment-refractory schizophrenia' and 'clozapine' and 'response' or 'outcome', with filters set to English language studies on human participants. Titles and abstracts returned from the search were screened for inclusion and exclusion criteria. Articles considered potentially eligible were full text screened. Reference lists of articles meeting inclusion criteria were hand-searched, and all non-duplicate potential papers were full text screened.

### Inclusion and exclusion criteria

Studies published in peer reviewed journals were included if they reported a relationship between any clinical or demographic variable and response to clozapine. Study designs using prospective, retrospective and cross-sectional ascertainment of clozapine response were all included if demographic and clinical measures were available from the time period immediately before clozapine initiation. To capture the complexity of therapeutic response, we included articles that used clinical, service use and functional measures of clozapine response, whether reported as categorical or continuous outcome variables. All-cause discontinuation of clozapine was not an eligible outcome measure because factors other than lack of efficacy may contribute to cessation of clozapine treatment (Legge et al., 2016; Üçok et al., 2019). The meta-analysis included a subset of articles where clozapine response was defined as symptomatic improvement on clinical rating scales (see Section 'Meta-analysis'). We included studies that allowed concurrent treatment with other pharmacological and non-pharmacological interventions, because this reflects clinical practice. Studies were excluded if treatment response was only compared between groups treated with clozapine *v.* clozapine-plus-augmentation.

Inclusion required that the publication reported on participants with a diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder and/or psychotic disorder (ICD-10 F20-F29). Studies were excluded if they focused on mood disorders (ICD-10 F30-F39) because the concept of treatment resistance in this cohort may involve resistant mood symptoms, as well as psychosis (Gitlin, 2001; Hui Poon, Sim, & Baldessarini, 2015). Studies were also excluded if their focus was on childhood onset schizophrenia (<18 years) due to

differential risk factors, relative rarity and frequent misdiagnosis of affective disorders within this patient cohort (Driver, Gogtay, & Rapoport, 2013; Driver, Thomas, Gogtay, & Rapoport, 2020; Rapoport & Gogtay, 2011). Studies were excluded if important data were omitted or insufficient methodological or statistical details were provided to be able to understand the results. For example, if the current authors were unable to determine whether the analysis performed was suited to the study design, or if it was unclear whether variables were recorded prior to clozapine initiation.

### Data extraction and quality assessment

Data on the study population, study design and duration, clozapine response definition, clozapine dose and/or plasma levels, analysis strategy, plus any demographic and clinical variables measured prior to clozapine initiation were extracted. Where articles reported the proportion of responders over multiple time-points, the longest time point was used, to provide maximal time for response. All data were extracted by one author (KG) and independently verified by another (EM). Overall study quality was assessed using the Newcastle-Ottawa Scale (NOS). Authors KG and EM independently rated each study and final ratings were a consensus (online Supplementary materials 2).

### Meta-analysis

Studies were eligible for quantitative analysis if clozapine response was defined as  $\geq 20\%$  reduction in positive, negative or total score on the Brief Psychiatric Rating Scale (BPRS) or Positive and Negative Symptom Scale (PANSS) from baseline to follow-up. We chose a reduction in symptom severity as our primary outcome measure because it remains the most common criteria for treatment response since Kane's landmark study (Kane et al., 1988) and has greater reliability than measures of functional improvement. Percentage reduction in symptom severity from baseline may be the most appropriate measure for the treatment-resistant patient group, where absolute remission is rare (Suzuki et al., 2011). Furthermore, a threshold of 20% was chosen given evidence that this improvement corresponds to a clinically significant effect in treatment-refractory patients (Leucht et al., 2005a; 2005b). To be included in the meta-analysis, summary statistics (mean and standard deviation) of a variable had to be reported separately by clozapine responder status in at least three articles.

Meta-analyses were performed using the Jamovi statistical software package (v1.6.4; The Jamovi Project, 2020). A random effects model was used to determine overall effect size of mean group difference between clozapine responders and non-responders, with alpha set at 0.05. A Hedges *g* of 0 indicates no group difference, and a positive or negative Hedges *g* denotes higher or lower mean values in clozapine non-responders than clozapine responders. Between study heterogeneity was quantified using the  $I^2$  statistic where values of 0.25, 0.50 and 0.75 correspond to low, moderate and high degrees of heterogeneity (Higgins, Thompson, Deeks, & Altman, 2003). Publication bias was assessed by visual inspection of funnel plot symmetry, where an asymmetric funnel suggests the possibility of publication bias.

The primary analysis included all available studies. Secondary analysis was restricted to studies with a follow-up period of 12 weeks or longer, to align with the recommended minimum

amount of time to evaluate clozapine response (Howes et al., 2017).

## Results

Figure 1 shows a PRISMA flowchart. The database search returned 840 articles. Abstract screening identified 101 potentially eligible articles. On review of the full-text 29 of these were eligible for systematic review, and one additional eligible article was identified via handsearching references. In total, 30 studies met systematic review inclusion criteria (online Supplementary Table S1).

### Study characteristics

Twenty-one articles were prospective studies of clozapine response. Of these, twenty were observational studies where clozapine was administered as part of routine clinical care. The other article described a randomised clinical trial of clozapine *v.* haloperidol, where the clinical and demographic factors associated with clozapine response were reported. Eight articles collated data from medical records to determine clozapine response retrospectively. Of these, two articles included mirror image analyses, where outcomes before and after clozapine treatment were compared within-subjects. One article reported cross-sectional data where response to clozapine was determined based on persistence and severity of current symptoms at the time of study, although response status in approximately 10% of the sample was subsidised with retrospective information on change in symptom severity from a pre-treatment period.

Study sample sizes ranged from 18 to 502 participants, and included samples across Europe, North America, Asia and Oceania. The follow-up period to assess clozapine response ranged from 5 weeks to >7 years. The range in proportion of patients failing to respond to clozapine was 28–81% (online Supplementary Table S2), which varied according to the definition of response, indication for treatment and duration of treatment trial. Twenty articles (67%) reported clozapine dosage data and clozapine plasma concentration was reported in six (20%) (online Supplementary Table S3).

### Outcome measures of clozapine response

For the qualitative review there was substantial variation in outcome measures of clozapine response (Table 1), and six studies employed more than one definition.

Symptom severity rating scales were the most frequently used outcome measure ( $n = 22$ ), and included the BPRS ( $n = 12$ ), BPRS-psychosis ( $n = 1$ ) and PANSS ( $n = 3$ ). One study used the Scale for the Assessment of Positive Symptoms (SAPS) and the Scale for the Assessment of Negative Symptoms (SANS). The Clinical Global Impression (CGI) was the only scale used to assess treatment response in four studies, and a further four studies used the CGI in alongside the BPRS or PANSS. The clinical assessment scales used were not specified in one article (Üçok et al., 2015). Service use outcomes were used in seven articles and included the number and duration of psychiatric hospitalisations, time from clozapine initiation until rehospitalisation or discharge, and within-subject differences in hospital admissions before and during clozapine treatment. Functional definitions of clozapine response were used in eight studies, including improvements on the Global Assessment of Functioning (GAF), Health of the Nation Outcome Scales (HoNOS) and EQ-VAS, and employment status.

### Demographic and clinical variables associated with clozapine response

Twenty baseline variables were measured (online Supplementary Table S4). Associations with clozapine treatment response were evaluated by (1) comparisons of baseline variable between responder and non-responder groups, (2) associations between baseline variables and continuous measures of response or (3) comparison of response rates between different levels of a baseline variable. Statistical tests, effect sizes, confidence intervals (CIs) and  $p$  values are reported where available in online Supplementary Table S4. The following section describes variables significantly associated with clozapine response in at least two separate studies, with the same direction of effect.

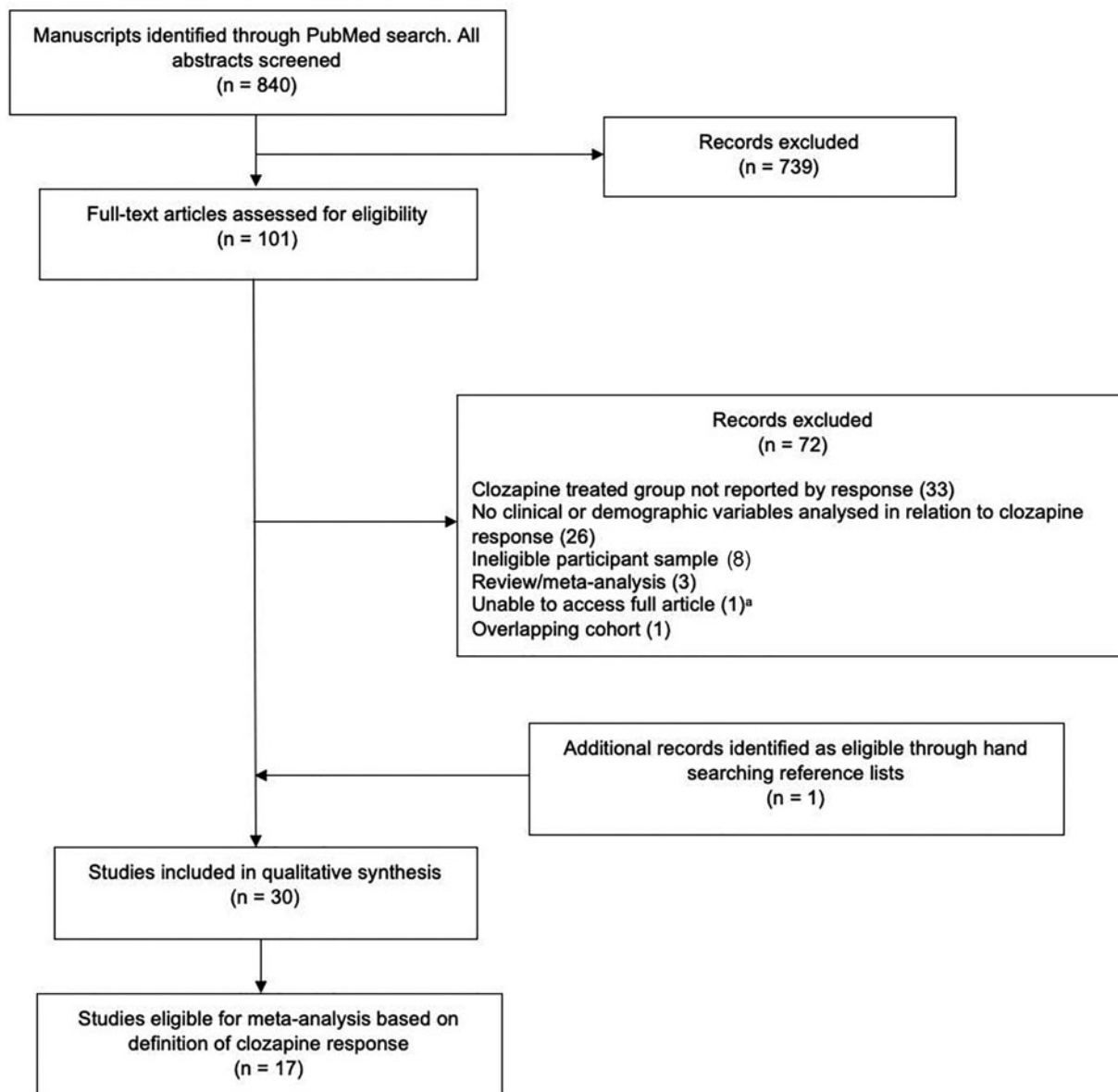
#### Age at clozapine initiation

Of the 21 studies testing for an effect of age, six reported an association between younger age and a better response to clozapine. Between group comparisons of clozapine responders and non-responders was assessed in three prospective studies with follow-ups ranging from 6 weeks to 12 months. All three found clozapine responders were younger than non-responders (Conley, Carpenter, & Tamminga, 1997; Hofer et al., 2003; Wong et al., 2006). Conley et al. (1997) also reported age was the only variable significantly associated with percentage change in CGI improvement in a multiple linear regression model. This finding was replicated in a retrospective chart review, which found those displaying good response to clozapine were significantly younger than those with minimal or no response (Üçok et al., 2015). Gee et al. (2016) compared outcomes during pre- and post-clozapine treatment periods within subjects and found the reduction in hospital admission days was greater in younger patients when compared to the older clozapine-treated group. In another study, younger age was associated with higher likelihood of employment after 1 year of treatment (Kaneda, Jayathilak, & Meltzer, 2010).

In contrast, one study found that younger patients had higher rates of rehospitalisation after clozapine initiation compared to older patients (Kelly, Gale, & Conley, 2003).

#### Age of onset of psychosis

Of 15 studies that examined age at onset of psychosis, three found a significant association between older age of onset and a good response to clozapine. No studies reported the opposite pattern of association. When clozapine response was defined as  $\geq 20\%$  improvement on BPRS and total score  $\leq 35$  at a 16-week follow-up, one study reported an older age of onset in responders (Semiz et al., 2007). Furthermore, older age of onset predicted better response to clozapine in a logistic regression model controlling for gender, age, weight gain, diagnosis subtype, baseline BPRS and baseline SAPS scores. The same response criteria (plus follow-up CGI score  $\leq 3$ ) was applied in an earlier study looking at cumulative percentage of patients who responded to clozapine at 12, 24 and 52 weeks (Lieberman et al., 1994). Here, age of onset was dichotomised to above or below 19 years. Those with an age of onset >19 years reached response status in a shorter amount of time in survival analysis. Preserving age of onset as a continuous variable, Nielsen and colleagues found that later age of onset was associated with longer time to psychiatric hospitalisation when readmission did occur (Nielsen, Nielsen & Correll, 2012). Clozapine dose across the entire sample was dichotomised using a median split and there



**Fig. 1.** PRISMA flow diagram for study selection.

<sup>a</sup>Online archive search of *Annals of Clinical Psychiatry* performed; full article inaccessible (Moeller et al., 1995).

was a trend towards a later age of onset in the group treated with lower doses, suggesting that patients with later onset responded at lower doses.

### Duration of illness

Fifteen articles tested for an effect of duration of illness. Of these, six found an association between shorter duration of illness and better outcomes. No studies reported the opposite pattern of association.

When participants were categorised as responders or non-responders using clinical outcome scales, clozapine responders had a shorter duration of illness (Wong et al., 2006). Üçok et al. (2015) similarly found a shorter duration of illness for those in the good response group compared to those in the minimal or no improvement groups ( $13 \pm 8$  v.  $18 \pm 8.9$  years). Another study reported time taken for symptoms to decrease by

at least 20% was greater for those who had been unwell for a longer period, and overall odds of reaching response criteria reduced as illness duration increased (Lieberman et al., 1994). Furthermore, one study reported a negative correlation between length of illness and percentage change in BPRS scores (Manschreck, Redmond, Candela, & Maher, 1999). In the same study, hospitalised non-responders also had longer duration of illness than both non-responders who had been discharged and all responders. This was interpreted by authors as a longer duration of illness being associated with the most severe form of illness overall. Köhler-Forsberg, Horsdal, Legge, MacCabe, and Gasse (2017) found an association between duration of illness and the probability of reaching substantial improvement on GAF in women only. Here, the chance of improvement decreased by 15% with each year of delay. Shorter duration of illness was also associated with increased likelihood of employment at 12 months in a separate study (Kaneda et al., 2010).

**Table 1.** All study definitions of clozapine response

First author (year)	Clozapine response definition(s)
Buckley <i>et al.</i> (1994)	≥20% reduction BPRS from baseline <sup>a</sup>
Conley <i>et al.</i> (1997)	≥20% reduction in BPRS from baseline and total BPRS ≤ 35 or CGI ≤ 3 <sup>a</sup>
El-Badri <i>et al.</i> (2011)	Number of hospitalisations and length of hospital stay post clozapine; item score changes on HoNOS from baseline
Fabrazzo <i>et al.</i> (2002)	≥20% reduction in BPRS from baseline and total ≤47 <sup>a</sup>
Gee <i>et al.</i> (2016)	Net change in number of hospital admissions and net change in days of admission, comparing figures before and after clozapine initiation within each participant
Hofer <i>et al.</i> (2003)	≥2-point reduction in CGI score from baseline or total ≤3 <sup>a</sup>
Kaneda <i>et al.</i> (2010)	Employment status at follow-up (employed <i>v.</i> unemployed)
Kelly <i>et al.</i> (2003)	Time to rehospitalisation after clozapine initiation
Kelly <i>et al.</i> (2006)	Change in BPRS score across clozapine treatment, measured as a continuous variable; time to hospital discharge.
Kelly <i>et al.</i> (2010)	≥20% reduction in BPRS from baseline <sup>a</sup>
Kim <i>et al.</i> (2013)	≥20% reduction in PANSS from baseline and ≥2-point reduction in CGI <sup>a</sup>
Köhler-Forsberg <i>et al.</i> (2017)	No further hospitalisations due to schizophrenia; GAF-F improvement where moderate improvement = GAF-F increase ≥10 and substantial improvement = GAF-F increase ≥20 plus total GAF-F ≥50
Krivoy <i>et al.</i> (2018)	≥20% PANSS from baseline or two or less PANSS-positive item scored as moderate (4) <sup>a</sup>
Lieberman <i>et al.</i> (1994)	≥20% reduction in BPRS from baseline and total ≤36 and CGI ≤3 <sup>a</sup> ; time to reach 20% reduction in symptoms and likelihood of meeting 20% reduction in symptoms
Llorca <i>et al.</i> (2002)	≥20% reduction in PANSS score from baseline <sup>a</sup>
Manschreck <i>et al.</i> (1999)	Discharged <i>v.</i> hospitalised at follow-up
McEvoy <i>et al.</i> (1999)	≥33.33% reduction in BPRS from baseline <sup>a</sup>
Nielsen <i>et al.</i> (2012)	Psychiatric hospitalisation during clozapine treatment; time to hospitalisation from clozapine initiation
Rodriguez <i>et al.</i> (1998)	≥50% reduction in global SANS plus SAPS from baseline and CGI ≤3
Semiz <i>et al.</i> (2007)	≥20% reduction in BPRS from baseline and total <35 <sup>a</sup>
Shah <i>et al.</i> (2020)	Follow-up CGI-global or CGI-positive ≤2. Participants also classed as non-responders if taking another antipsychotic with clozapine or undergoing electroconvulsive therapy
Spina <i>et al.</i> (2000)	≥20% reduction in BPRS from baseline and total ≤35 <sup>a</sup>
Stern <i>et al.</i> (1994)	1-point reduction CGI score from baseline
Sumiyoshi <i>et al.</i> (1997)	≥20% reduction in BPRS from baseline <sup>a</sup>
Szymanski <i>et al.</i> (1996)	≥20% reduction in BPRS from baseline <sup>a</sup>
Üçok <i>et al.</i> (2015)	Improvement in symptoms classified as remarkable moderate or no response based on scores symptom severity and collective opinion of patient, carers and clinician
Umbricht <i>et al.</i> (2002)	≥20% reduction in BPRS-psychosis from baseline <sup>a</sup>
Usall <i>et al.</i> (2007)	≥2-point reduction in CGI from baseline; item score changes on EQ-5D after baseline, measured as a continuous variable
Wong <i>et al.</i> (2006)	≥20% reduction in BPRS from baseline and total ≤35 or CGI total ≤3 <sup>a</sup>
Yoshimura <i>et al.</i> (2017)	≥40% reduction in BPRS from baseline <sup>a</sup>

<sup>a</sup>Eligible for meta-analysis (see online Supplementary Table S5 for complete meta-analysis screening).

### Delay in clozapine initiation

Three of four studies found shorter delay in clozapine initiation after fulfilment of treatment resistance criteria was associated with a more favourable response. The fourth article found no effect of length of clozapine delay on subsequent length or number of inpatient admissions (Gee *et al.*, 2016).

Shah *et al.* (2020) found clozapine responders had a significantly shorter delay in clozapine initiation than non-responders, and delay in clozapine initiation was a significant predictor of clozapine response in regression analysis. Here, age at clozapine initiation was not significantly associated with clozapine response

and therefore unlikely to be driving this effect. Üçok *et al.* (2015) instated a logistic regression model where the dependent variable was level of improvement on clozapine treatment (good *v.* none or minimal). Delay in clozapine initiation was identified as the only baseline variable contributing to symptomatic improvement. Furthermore, patients in the good response group had been prescribed clozapine after a shorter delay from treatment resistance onset compared to those in the non-response group.

Similarly, Yoshimura and colleagues found that delay in clozapine initiation was the only significant predictor of symptomatic improvement on the BPRS and BPRS-psychosis in two multiple

linear regression model, after controlling for age, sex, illness duration and number of previous hospitalisations (Yoshimura, Yada, So, Takaki, & Yamada, 2017). In the same sample, receiver operation curve analysis indicated 2.8 years as the best predictive cut-off value (area under curve = 0.78, sensitivity = 0.66, specificity = 0.84). Patients with a delay in clozapine initiation longer than 2.8 years displayed significantly poorer response on the BPRS compared those with a delay in clozapine initiation less than 2.8 years.

### Hospitalisations prior to clozapine initiation

Less time spent in psychiatric hospital prior to clozapine initiation was consistently associated with better response to clozapine. Of the five studies measuring length of hospitalisation prior to clozapine initiation, two found clozapine responders had spent significantly less time in hospital (Conley et al., 1997; Köhler-Forsberg et al., 2017), and one other reported clozapine responders had a significantly shorter length of current hospital admission (Wong et al., 2006). The remaining two studies reported no difference in length of current (Manschreck et al., 1999) or previous (Stern, Kahn, Davidson, Nora, & Davis, 1994) hospitalisations between clozapine responders and non-responders.

Nine studies assessed the number of hospitalisations prior to clozapine treatment and four found an association between fewer pre-clozapine hospital admissions and better outcomes. Three articles reported fewer pre-clozapine hospitalisations over the total duration of illness in clozapine responders than non-responders (Nielsen et al., 2012; Semiz et al., 2007; Üçok et al., 2015). Nielsen et al. (2012) also reported the same effect when analysis was limited to hospitalisations in the year preceding clozapine treatment. The fourth article reported a greater number of hospitalisations prior to clozapine initiation was identified as a significant predictor of poor outcome in regression analysis (Shah et al., 2020).

### Previous antipsychotic trials

Three of four studies found that fewer previous antipsychotic trials were associated with better clozapine response. Nielsen et al. (2012) reported an association between fewer pre-clozapine antipsychotic trials and lower risk of rehospitalisation although on clozapine treatment. When relapse did occur, those with fewer pre-clozapine antipsychotic trials had a longer time to readmission after clozapine initiation. This finding was replicated twice. Üçok et al. (2015) reported patients demonstrating the best response to clozapine response had fewer adequate antipsychotic trials before clozapine compared to those with minimal or no clinical response. Shah et al. (2020) also found clozapine responders had fewer antipsychotic trials prior to clozapine initiation than clozapine non-responders, despite the duration of non-clozapine antipsychotic treatment not differing between groups. The fourth study reported no association between the number of antipsychotic trials prior to clozapine initiation and the net change in number or length of hospital admissions after clozapine was initiated (Gee et al., 2016).

### Sex

Four of 23 articles reported a sex difference in clozapine response although the direction of effect was inconsistent.

Usall, Suarez, and Haro (2007) reported females were more likely to respond to clozapine treatment when response was

measured using clinical symptom rating scales, but not when response was measured using scales rating overall quality of life.

In contrast, Conley et al. (1997) found a larger proportion of males responded to clozapine over a 12-month trial. Similarly, Nielsen et al. (2012) reported males were less likely to be hospitalised during clozapine treatment compared to females. When hospitalisation did occur, males were generally hospitalised after a longer time period than females, suggesting better symptom management or less frequent relapse. Szymanski et al. (1996) calculated cumulative proportion of patients not responding to clozapine over a 12 week treatment period and found more males responded than females. Males were also less likely to withdraw from the study due to failure to improve. However, significantly more males had a paranoid diagnosis subtype, which was associated with better clozapine response in the same study.

### Demographic and clinical variables not associated with clozapine response

Variables reported in two or more articles and not reproducibly associated with clozapine response were body weight, diagnosis subtype, years of education, ethnicity, relationship status, premorbid functioning, smoking, substance abuse and presence of side effects from non-clozapine antipsychotics. Workforce, level of deprivation, IQ and comorbid conditions were each measured once (online Supplementary Table S4).

### Meta-analysis

Online Supplementary Table S5 lists all articles eligible for inclusion in the meta-analysis. The variables available for meta-analysis, reported in at least three of these studies, were age, age of onset, duration of illness, years of education and body weight.

Results from all meta-analyses are detailed in Table 2. There were no significant differences in mean age, age of onset, years of education or body weight between clozapine responders and non-responders. Corresponding forest and funnel plots are presented in online Supplementary Fig. S1. In a total sample of 313 participants (50% non-responder), the mean duration of illness (years) was significantly longer in those displaying poor response to clozapine (Fig. 2a;  $g = 0.31$ ; 95% CI 0.06–0.56;  $p = 0.01$ ). Between study heterogeneity was moderate ( $Q = 8.26$ ,  $I^2 = 10.08\%$ ,  $p = 0.23$ ). The relative symmetry of the corresponding funnel plot suggests publication bias is unlikely, although one study does fall outside the funnel area (Fig. 2b).

When analysis was limited to studies with a minimum follow-up period of 12 weeks, no additional significant findings were apparent (Table 2). Online Supplementary Fig. S2 displays forest and funnel plots for all sensitivity meta-analyses performed. The difference in duration of illness between responder *v.* non-responder groups remained significant and overall effect size increased ( $g = 0.42$ ; 95% CI 0.17–0.67;  $p < 0.001$ ). Between study heterogeneity was low ( $Q = 3.52$ ,  $I^2 = 0\%$ ,  $p = 0.62$ ). Visual inspection of the funnel plot suggests publication bias is unlikely, with the prior outlying study no longer included.

### Discussion

Both the systematic review and meta-analysis found consistent evidence that a longer duration of illness before clozapine initiation is associated with a worse clinical response to clozapine. The systematic review also found that a poorer response to clozapine is

**Table 2.** Meta-analyses results

Random effects model								
Variable	<i>N</i> studies	<i>N</i>	CR	CNR (%)	SMD (Hedges <i>g</i> )	s.e.	95% CI	<i>p</i>
Age	12	676	349	327 (48)	0.15	0.09	−0.03 to 0.33	0.10
Age of onset	7	370	197	173 (47)	−0.09	0.12	−0.30 to 0.12	0.39
Duration of illness	7	313	158	155 (50)	0.31	0.13	0.06–0.56	0.01*
Years of education	3	157	73	84 (54)	0.05	0.17	−0.27 to 0.38	0.75
Weight (kg)	3	133	59	74 (56)	−0.29	0.18	−0.64 to 0.07	0.11
Random effects model, datasets with follow-up less than 12 weeks excluded								
Age <sup>a</sup>	9	452	234	218 (48)	0.16	0.10	−0.03 to 0.36	0.10
Duration of illness <sup>b</sup>	6	273	143	130 (48)	0.42	0.13	0.17–0.67	<0.001*

*N*, total number of participants; CR, clozapine responders; CNR, clozapine non-responders; SMD, standardised mean difference; s.e., standard error.

\**p* < 0.05.

<sup>a</sup>Datasets excluded *n* = 3: Krivoy et al. (2018), follow-up = 8 weeks; Hofer et al. (2003), follow-up = 6 weeks; Kim et al. (2013), follow-up = 8 weeks.

<sup>b</sup>Datasets excluded *n* = 1: Kim et al. (2013), follow-up = 8 weeks.

more likely in patients who are older at clozapine initiation, have an earlier illness onset and a longer delay in clozapine initiation after the identification of treatment resistance. More previous hospitalisations and antipsychotic trials prior to treatment with clozapine were also associated with poorer response. No consistent associations with clozapine response were found for sex, ethnicity, years of education, body weight, body mass index, smoking, pre-morbid functioning, relationship status, substance abuse or diagnosis subtype. Together, this supports the view that initiation of clozapine earlier in illness may be beneficial (John, Ko, & Dominic, 2018).

The main finding is that a longer duration of illness is associated with poorer response to clozapine. Our meta-analysis included studies categorising patients as clozapine responders or non-responders and found that non-responders had been unwell for significantly longer, with small to moderate effect size. This finding became more marked when analysis was restricted to studies with a follow-up of at least 12 weeks. When clozapine response was evaluated more broadly and in larger cohort studies, the same association between longer illness duration and poor clozapine response was found, suggesting this is a consistent finding. No articles reported an opposite effect, although null effects were reported in some smaller studies.

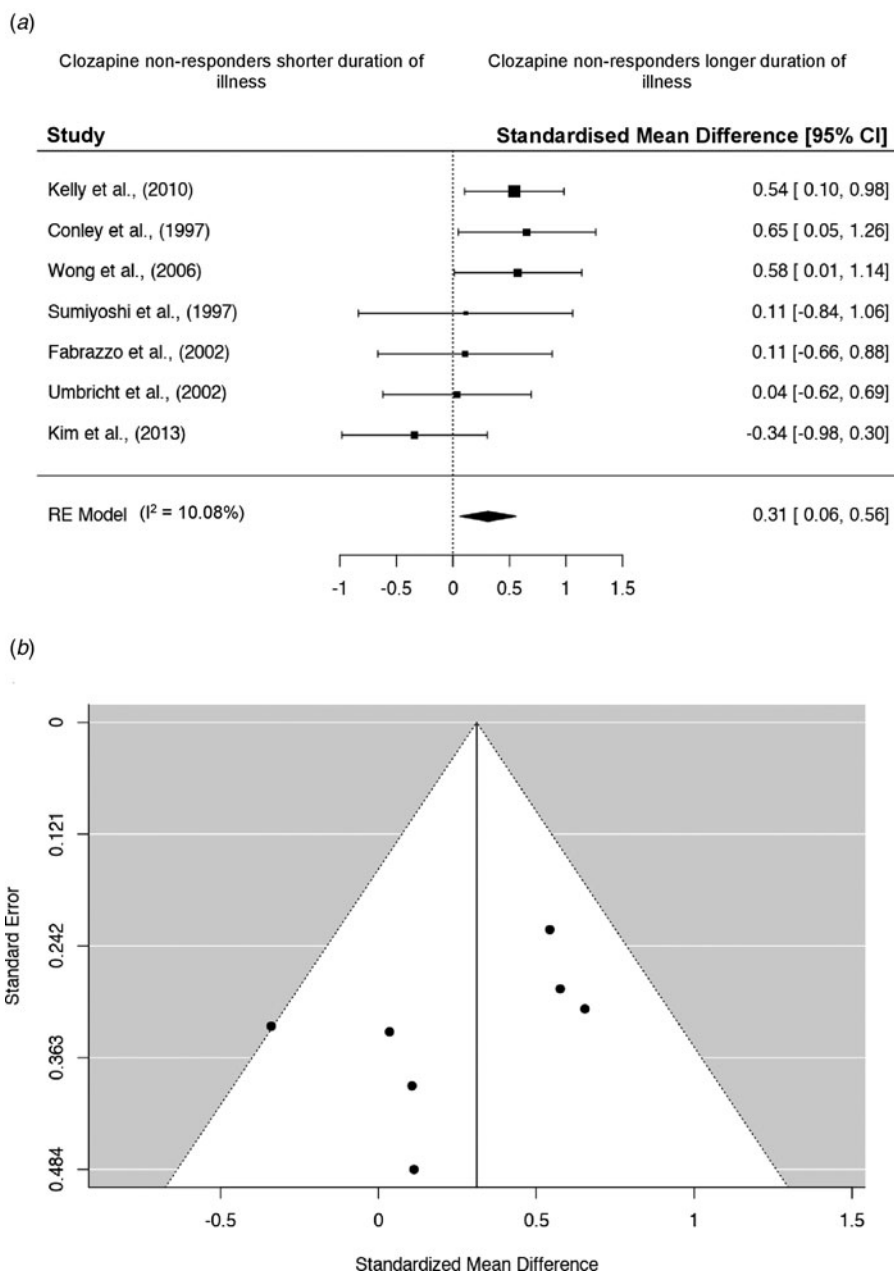
The systematic review found delay in clozapine prescription, more pre-clozapine hospitalisations and more antipsychotic trials were associated with poorer outcomes, which may reflect the presence of more severe illness and a longer duration of active symptoms prior to clozapine initiation. Neurobiological integrity, social functioning and self-care are all likely affected by sustained active symptoms (Jobe & Harrow, 2005; Mitelman & Buchsbaum, 2007), although the precise impact of prolonged ineffective treatment on subsequent response to clozapine requires further investigation. It is also possible that factors associated with a more severe illness will delay the point at which clozapine can be safely initiated for these patients, such as concerns of poor adherence, comorbid substance abuse, a more chaotic presentation, impaired insight and poor therapeutic alliance (Acosta et al., 2009; Baier, 2010; Farooq, Choudry, Cohen, Naem, & Ayub, 2019; Hudson et al., 2004; Löffler, Kilian, Toumi, & Angermeyer, 2003; Olfson, Marcus, Wilk, & West, 2006; Velligan et al., 2009).

Our review also found that older age at clozapine initiation, younger age at illness onset and longer delay in clozapine initiation after established treatment resistance were associated with worse response to clozapine. These variables are not independent from one another and longer duration of illness may be a common factor driving their associations with poor clozapine response. Older age at first clozapine prescription has been correlated with longer delays in clozapine prescription (Najim, Heath, & Singh, 2013; Tang et al., 2007) and higher likelihood of relapse (Altamura, Bobo, & Meltzer, 2007), which could account for the observed association between older age and worse therapeutic response. Significant associations between increased age of patients and delays in starting clozapine have also been reported (Üçok et al., 2015; Yoshimura et al., 2017).

### Strengths and limitations

This topic was previously reviewed almost a decade ago (Suzuki et al., 2011). Our updated search identified nine more recent publications and we were able to investigate some of the most frequently reported variables using meta-analysis for the first time. Study samples only included diagnoses of schizophrenia spectrum disorders, meaning patient cohorts were comparable and strengthen the clinical relevance of findings to those with treatment-resistant schizophrenia. We also included varied definitions of clozapine response to capture broad outcomes concerning patient quality of life, illness management within the community and economic burden. Although this limits study comparability, our meta-analysis adopted more stringent inclusion criteria centred on symptomatic response to clozapine.

The duration of illness prior to clozapine initiation was often long (9–25 years in the meta-analysis), which may reflect clinical practice (Üçok et al., 2019), and limits inference about the clinical and demographic predictors of clozapine response when initiated in earlier stages of illness. There was large variation in the number of patients identified as clozapine non-responders, which may be due to variation in clozapine response definition and duration of follow-up. We were unable to assess the effect of clozapine plasma concentration on outcome due to lack of data, meaning subtherapeutic clozapine dosage or poor compliance may have been incorrectly interpreted as non-response to clozapine in some



**Fig. 2.** Meta-analysis for duration of illness. (a) Forest plot for duration of illness meta-analysis. Square sizes represent the sample size of each study. Diamonds indicate overall effect size of the meta-analysis. (b) Accompanying funnel plot for duration of illness meta-analysis.

cases (McCutcheon et al., 2015; Potkin et al., 1994). Future research should record treatment adherence and plasma concentrations to address this potential confound (Tang et al., 2007). Finally, restricting our search to English language articles may have introduced bias towards studies performed in western populations.

The small number of studies available for meta-analysis meant we were unable to explore sources of heterogeneity with meta-regression or statistically assess publication bias. Total number of patients in the meta-analysis of illness duration was also small, as were sample sizes within the wider reviewed literature. We identified few prospective observational studies in large cohorts, but research spanning long time periods within naturalistic settings is generally lacking. Although studies using

population registry data have access to larger patient cohorts and therefore higher statistical power, missing data and retrospective recall biases are limitations to consider. It is also important to note that final study samples risk being biased towards higher functioning patients given that (1) only patients who are relatively compliant and willing to take oral medication are successfully started on clozapine, and (2) higher drop-out of non-responders due to worse functioning and symptom severity. Variables were quantitatively evaluated by defining response on the PANSS or BPRS, but not on the CGI. The PANSS and BPRS are well suited to prospective designs while the CGI may be preferable for retrospective evaluation of response (Howes et al., 2017). Predictors of clozapine response as assessed on the CGI could be evaluated further in future research.



## Conclusions and future directions

The association between longer duration of illness and poor outcomes has substantial clinical importance given the modifiable nature of this variable. Specifically, our finding supports identifying cases of treatment resistance earlier in the illness course and initiating clozapine as soon as possible for these patients. Further research on the mechanism(s) driving the association between duration of illness and clozapine response may better our understanding of the pathophysiology of treatment-resistant schizophrenia, and lead to improved treatment strategies.

**Supplementary material.** The supplementary material for this article can be found at <https://doi.org/10.1017/S0033291721000246>

**Financial support.** KG is in receipt of a Ph.D. studentship funded by the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. The views expressed are those of the author and not necessarily those of the NHS, the NIHR or the Department of Health and Social Care.

**Conflict of interest.** JHM has received research funding from H Lundbeck, unrelated to this study.

## References

- Acosta, F. J., Bosch, E., Sarmiento, G., Juanes, N., Caballero-Hidalgo, A., & Mayans, T. (2009). Evaluation of noncompliance in schizophrenia patients using electronic monitoring (MEMS) and its relationship to sociodemographic, clinical and psychopathological variables. *Schizophrenia Research*, 107(2–3), 213–217. doi: 10.1016/j.schres.2008.09.007.
- Altamura, A. C., Bobo, W. V., & Meltzer, H. Y. (2007). Factors affecting outcome in schizophrenia and their relevance for psychopharmacological treatment. *International Clinical Psychopharmacology*, 22(5), 249–267. doi: 10.1097/YIC.0b013e3280de2c7f.
- Andrews, A., Knapp, M., McCrone, P. R., Parsonage, M., & Trachtenberg, M. (2012). Effective interventions in schizophrenia: the economic case. A Report Prepared for the Schizophrenia Commission. Rethink Mental Illness: London. Retrieved from <https://rethink.org/media/2628/lost-generation-rethink-mental-illness-report.pdf>.
- Bachmann, C. J., Aagaard, L., Bernardo, M., Brandt, L., Cartabia, M., Clavenna, A., ... Taylor, D. (2017). International trends in clozapine use: A study in 17 countries. *Acta Psychiatrica Scandinavica*, 136(1), 37–51. doi: 10.1111/acps.12742.
- Baier, M. (2010). Insight in schizophrenia: A review. *Current Psychiatry Reports*, 12(4), 356–361. doi: 10.1007/s11920-010-0125-7
- Buckley, P., Thompson, P., Way, L., & Meltzer, H. Y. (1994). Substance abuse among patients with treatment-resistant schizophrenia: Characteristics and implications for clozapine therapy. *The American Journal of Psychiatry*, 151(3), 385–389. doi: 10.1176/ajp.151.3.385
- Conley, R. R., Carpenter, W. T., & Tamminga, C. A. (1997). Time to clozapine response in a standardized trial. *The American Journal of Psychiatry*, 154(9), 1243–1247. doi: 10.1176/ajp.154.9.1243
- Driver, D. I., Gogtay, N., & Rapoport, J. L. (2013). Childhood onset schizophrenia and early onset schizophrenia spectrum disorders. *Child and Adolescent Psychiatric Clinics of North America*, 22(4), 539–555. doi: 10.1016/j.chc.2013.04.001
- Driver, D. I., Thomas, S., Gogtay, N., & Rapoport, J. L. (2020). Childhood-onset schizophrenia and early-onset schizophrenia spectrum disorders: An update. *Child and Adolescent Psychiatric Clinics of North America*, 29(1), 71–90. doi: 10.1016/j.chc.2019.08.017
- El-Badri, S., & Mellsop, G. (2011). Clozapine use and outcomes among patients with treatment resistant schizophrenia. *Australasian Psychiatry*, 19(5), 410–414. doi: 10.3109/10398562.2011.602078
- Elkis, H. (2007). Treatment-resistant schizophrenia. *Psychiatric Clinics of North America*, 30(3), 511–533. doi: 10.1016/j.psc.2007.04.001.

- Fabrazzo, M., La Pia, S., Monteleone, P., Esposito, G., Pinto, A., De Simone, L., ... Maj, M. (2002). Is the time course of clozapine response correlated to the time course of clozapine plasma levels? A one-year prospective study in drug-resistant patients with schizophrenia. *Neuropsychopharmacology*, 27(6), 1050–1055. doi: 10.1016/S0893-133X(02)00319-6.
- Farooq, S., Choudry, A., Cohen, D., Naeem, F., & Ayub, M. (2019). Barriers to using clozapine in treatment-resistant schizophrenia: Systematic review. *Bjpsych Bulletin*, 43(1), 8–16. doi: 10.1192/bjb.2018.67.
- Gee, S. H., Shergill, S. S., & Taylor, D. M. (2016). Factors associated with changes in hospitalisation in patients prescribed clozapine. *Journal of Psychopharmacology*, 30(8), 819–825. doi: 10.1177/0269881116642745.
- Gitlin, M. J. (2001). Treatment-resistant bipolar disorder. *Bulletin of Menninger Clinic*, 65(1: Special Issue), 26–40. doi:10.1521/bumc.65.1.26.18709.
- Higgins, J. P., Thompson, S. G., Deeks, J. J., & Altman, D. G. (2003). Measuring inconsistency in meta-analyses. *BMJ*, 327(7414), 557–560. doi: 10.1136/bmj.327.7414.557.
- Hofer, A., Hummer, M., Kemmler, G., Kurz, M., Kurzthaler, I., & Fleischhacker, W. W. (2003). The safety of clozapine in the treatment of first- and multiple-episode patients with treatment-resistant schizophrenia. *International Journal of Neuropsychopharmacology*, 6(3), 201–206. doi: 10.1017/S1461145703003456.
- Howes, O. D., McCutcheon, R., Agid, O., de Bartolomeis, A., van Beveren, N. J., Birnbaum, M. L., ... Correll, C. U. (2017). Treatment-resistant schizophrenia: Treatment response and resistance in psychosis (TRIP) working group consensus guidelines on diagnosis and terminology. *The American Journal of Psychiatry*, 174(3), 216–229. doi: 10.1176/appi.ajp.2016.16050503.
- Howes, O. D., Vergunst, F., Gee, S., McGuire, P., Kapur, S., & Taylor, D. (2012). Adherence to treatment guidelines in clinical practice: Study of antipsychotic treatment prior to clozapine initiation. *The British Journal of Psychiatry*, 201(6), 481–485. doi: 10.1192/bjp.bp.111.105833.
- Hudson, T. J., Owen, R. R., Thrush, C. R., Han, X., Pyne, J. M., Thapa, P., & Sullivan, G. (2004). A pilot study of barriers to medication adherence in schizophrenia. *The Journal of Clinical Psychiatry*, 65(2), 211–216. doi: 10.4088/jcp.v65n0211.
- Hui Poon, S., Sim, K., & Baldessarini, R. J. (2015). Pharmacological approaches for treatment-resistant bipolar disorder. *Current Neuropharmacology*, 13(5), 592–604. doi:10.2174/1570159x13666150630171954.
- Iasevoli, F., Giordano, S., Balletta, R., Latte, G., Formato, M. V., Prinziavalli, E., ... de Bartolomeis, A. (2016). Treatment resistant schizophrenia is associated with the worst community functioning among severely-ill highly-disabling psychiatric conditions and is the most relevant predictor of poorer achievements in functional milestones. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 65, 34–48. doi: 10.1016/j.pnpbp.2015.08.010.
- The jamovi Project. (2020). jamovi. (Version 1.6) [Computer Software]. Retrieved from [www.jamovi.org](http://www.jamovi.org).
- Jobe, T. H., & Harrow, M. (2005). Long-term outcome of patients with schizophrenia: A review. *Canadian Journal of Psychiatry*, 50(14), 892–900. doi: 10.1177/070674370505001403.
- John, A. P., Ko, E. K. F., & Dominic, A. (2018). Delayed initiation of clozapine continues to be a substantial clinical concern. *The Canadian Journal of Psychiatry*, 63(8), 526–531. doi: 10.1177/0706743718772522.
- Kadra, G., Stewart, R., Shetty, H., Downs, J., MacCabe, J. H., Taylor, D., & Hayes, R. D. (2016). Predictors of long-term ( $\geq 6$  months) antipsychotic polypharmacy prescribing in secondary mental healthcare. *Schizophrenia Research*, 174(1–3), 106–112. doi: 10.1016/j.schres.2016.04.010.
- Kahn, R. S., Winter van Rossum, I., Leucht, S., McGuire, P., Lewis, S. W., Leboyer, M., ... Wilson, D. (2018). Amisulpride and olanzapine followed by open-label treatment with clozapine in first-episode schizophrenia and schizophreniform disorder (OPTiMiSE): A three-phase switching study. *The Lancet Psychiatry*, 5(10), 797–807. doi: 10.1016/S2215-0366(18)30252-9.
- Kane, J., Honigfeld, G., Singer, J., & Meltzer, H. (1988). Clozapine for the treatment-resistant schizophrenic. A double-blind comparison with chlorpromazine. *Archives of General Psychiatry*, 45(9), 789–796. doi: 10.1001/archpsyc.1988.01800330013001.
- Kaneda, Y., Jayathilak, K., & Meltzer, H. (2010). Determinants of work outcome in neuroleptic-resistant schizophrenia and schizoaffective disorder: Cognitive impairment and clozapine treatment. *Psychiatry Research*, 178(1), 57–62. doi: 10.1016/j.psychres.2009.04.001.

- Kelly, D. L., Dixon, L. B., Kreyenbuhl, J. A., Medoff, D., Lehman, A. F., Love, R. C., ... Conley, R. R. (2006). Clozapine utilization and outcomes by race in a public mental health system: 1994–2000. *The Journal of Clinical Psychiatry*, 67(9), 1404–1411. doi: 10.4088/JCP.v67n0911.
- Kelly, D. L., Feldman, S., Boggs, D. L., Gale, E., & Conley, R. R. (2010). Nonresponse to clozapine and premorbid functioning in treatment of refractory schizophrenia. *Comprehensive Psychiatry*, 51(3), 298–302. doi: 10.1016/j.comppsy.2009.07.003.
- Kelly, D. L., Gale, E. A., & Conley, R. R. (2003). Clozapine treatment in patients with prior substance abuse. *The Canadian Journal of Psychiatry*, 48(2), 111–114. doi: 10.1177/070674370304800208.
- Kennedy, J. L., Altar, C. A., Taylor, D. L., Degtiar, I., & Hornberger, J. C. (2014). The social and economic burden of treatment-resistant schizophrenia: A systematic literature review. *International Clinical Psychopharmacology*, 29(2), 63–76. doi: 10.1097/YIC.0b013e32836508e6.
- Kim, J. H., Yi, S. H., Lee, J., & Kim, Y. S. (2013). Effects of clozapine on heart rate dynamics and their relationship with therapeutic response in treatment-resistant schizophrenia. *Journal of Clinical Psychopharmacology*, 33(1), 69–73. doi: 10.1097/JCP.0b013e32831827d14e3.
- Köhler-Forsberg, O., Horsdal, H. T., Legge, S. E., MacCabe, J. H., & Gasse, C. (2017). Predictors of nonhospitalization and functional response in clozapine treatment: A nationwide, population-based cohort study. *Journal of Clinical Psychopharmacology*, 37(2), 148–154. doi: 10.1097/JCP.0000000000000649.
- Krivoy, A., Hochman, E., Sendt, K. V., Hollander, S., Vilner, Y., Selakovic, M., ... Taler, M. (2018). Association between serum levels of glutamate and neurotrophic factors and response to clozapine treatment. *Schizophrenia Research*, 192, 226–231. doi: 10.1016/j.schres.2017.05.040.
- Lally, J., Ajnakina, O., Di Forti, M., Trotta, A., Demjaha, A., Koliakou, A., ... Murray, R. M. (2016). Two distinct patterns of treatment resistance: Clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychological Medicine*, 46(15), 3231–3240. doi: 10.1017/S0033291716002014.
- Lally, J., & MacCabe, J. H. (2015). Antipsychotic medication in schizophrenia: A review. *British Medical Bulletin*, 114(1), 169–179. doi: 10.1093/bmb/ldv017.
- Land, R., Siskind, D., McArdle, P., Kisely, S., Winckel, K., & Hollingworth, S. A. (2017). The impact of clozapine on hospital use: A systematic review and meta-analysis. *Acta Psychiatrica Scandinavica*, 135(4), 296–309. doi: 10.1111/acps.12700.
- Legge, S. E., Hamshere, M., Hayes, R. D., Downs, J., O'Donovan, M. C., Owen, M. J., ... MacCabe, J. H. (2016). Reasons for discontinuing clozapine: A cohort study of patients commencing treatment. *Schizophrenia Research*, 174(1–3), 113–119. doi: 10.1016/j.schres.2016.05.002.
- Leucht, S., Kane, J. M., Kissling, W., Hamann, J., Etschel, E., & Engel, R. R. (2005a). Clinical implications of BPRS scores. *The British Journal of Psychiatry*, 187(4), 363–371. doi: 10.1192/bjp.187.4.366.
- Leucht, S., Kane, J. M., Kissling, W., Hamann, J., Etschel, E., & Engel, R. R. (2005b). What does the PANSS mean? *Schizophrenia Research*, 79(2–3), 231–238. doi: 10.1016/j.schres.2005.04.008.
- Lieberman, J. A., Safferman, A. Z., Pollack, S., Szymanski, S., Johns, C., Howard, A., ... Kane, J. M. (1994). Clinical effects of clozapine in chronic schizophrenia: Response to treatment and predictors of outcome. *The American Journal of Psychiatry*, 151(12), 1744–1752. doi: 10.1176/ajp.151.12.1744.
- Llorca, P. M., Lancon, C., Disdier, B., Fariuse, J., Sapin, C., & Auquier, P. (2002). Effectiveness of clozapine in neuroleptic-resistant schizophrenia: Clinical response and plasma concentrations. *Journal of Psychiatry and Neuroscience*, 27(1), 30–37. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/11836974>.
- Löffler, W., Kilian, R., Toumi, M., & Angermeyer, M. C. (2003). Schizophrenic patients' subjective reasons for compliance and noncompliance with neuroleptic treatment. *Pharmacopsychiatry*, 36(3), 105–112. doi: 10.1055/s-2003-39985.
- Manschreck, T. C., Redmond, D. A., Candela, S. F., & Maher, B. A. (1999). Effects of clozapine on psychiatric symptoms, cognition, and functional outcome in schizophrenia. *Journal of Neuropsychiatry and Clinical Neurosciences*, 11(4), 481–489. doi: 10.1176/jnp.11.4.481.
- Marshall, M., Lewis, S., Lockwood, A., Drake, R., Jones, P., & Croudace, T. (2005). Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: A systematic review. *Archives of General Psychiatry*, 62(9), 975–983. doi: 10.1001/archpsyc.62.9.975.
- McCutcheon, R., Beck, K., Bloomfield, M. A., Marques, T. R., Rogdaki, M., & Howes, O. D. (2015). Treatment resistant or resistant to treatment? Antipsychotic plasma levels in patients with poorly controlled psychotic symptoms. *Journal of Psychopharmacology*, 29(8), 892–897. doi: 10.1177/0269881115576688.
- McEvoy, J. P., Freudenreich, O., & Wilson, W. H. (1999). Smoking and therapeutic response to clozapine in patients with schizophrenia. *Biological Psychiatry*, 46(1), 125–129. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/10394482>.
- Mitelman, S. A., & Buchsbaum, M. S. (2007). Very poor outcome schizophrenia: Clinical and neuroimaging aspects. *International Review of Psychiatry*, 19(4), 345–357. doi: 10.1080/09540260701486563.
- Moeller, F. G., Chen, Y. W., Steinberg, J. L., Petty, F., Ripper, G. W., Shah, N., & Garver, D. L. (1995). Risk factors for clozapine discontinuation among 805 patients in the VA hospital system. *Annals of Clinical Psychiatry*, 7(4), 167–173. doi: 10.3109/10401239509149622.
- Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., & Group, P. R. I. S. M. A. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, 6(7), e1000097. doi: 10.1371/journal.pmed.1000097.
- Najim, H., Heath, D., & Singh, P. (2013). Antipsychotic prescribing before clozapine in a community psychiatric hospital: A case note review. *Psychiatry Danubina*, 25(Suppl 2), S165–S170. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/23995168>.
- NICE. (2014). Psychosis and schizophrenia in adults: Treatment and management: updated edition 2014.
- Nielsen, J., Dahm, M., Lublin, H., & Taylor, D. (2010). Psychiatrists' attitude towards and knowledge of clozapine treatment. *Journal of Psychopharmacology*, 24(7), 965–971. doi: 10.1177/0269881108100320.
- Nielsen, J., Nielsen, R. E., & Correll, C. U. (2012). Predictors of clozapine response in patients with treatment-refractory schizophrenia: Results from a Danish Register Study. *Journal of Clinical Psychopharmacology*, 32(5), 678–683. doi: 10.1097/JCP.0b013e328318267b3cd.
- Olfson, M., Marcus, S. C., Wilk, J., & West, J. C. (2006). Awareness of illness and nonadherence to antipsychotic medications among persons with schizophrenia. *Psychiatric Services*, 57(2), 205–211. doi: 10.1176/appi.ps.57.2.205.
- Potkin, S. G., Bera, R., Gulasekaram, B., Costa, J., Hayes, S., Jin, Y., ... Gerber, B. (1994). Plasma clozapine concentrations predict clinical response in treatment-resistant schizophrenia. *The Journal of Clinical Psychiatry*, 55(Suppl B), 133–136. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/7961557>.
- Rapoport, J. L., & Gogtay, N. (2011). Childhood onset schizophrenia: Support for a progressive neurodevelopmental disorder. *International Journal of Developmental Neuroscience*, 29(3), 251–258. doi: 10.1016/j.ijdevneu.2010.10.003.
- Rodriguez, V. M., Catalina, M. L., García-Noblejas, J. A., & Cuesta, P. (1998). Schizophrenic syndromes and clozapine response in treatment-resistant schizophrenia. *Psychiatry Research*, 77(1), 21–28. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/10710171>.
- Samanaite, R., Gillespie, A., Sendt, K. V., McQueen, G., MacCabe, J. H., & Egerton, A. (2018). Biological predictors of clozapine response: A systematic review. *Frontiers in Psychiatry*, 9, 327. doi: 10.3389/fpsy.2018.00327.
- Semiz, U. B., Cetin, M., Basoglu, C., Ebrinc, S., Uzun, O., Herken, H., ... Ates, A. (2007). Clinical predictors of therapeutic response to clozapine in a sample of Turkish patients with treatment-resistant schizophrenia. *Progress in Neuropsychopharmacology and Biological Psychiatry*, 31(6), 1330–1336. doi: 10.1016/j.pnpbp.2007.06.002.
- Shah, P., Iwata, Y., Brown, E. E., Kim, J., Sanches, M., Takeuchi, H., ... Graff-Guerrero, A. (2020). Clozapine response trajectories and predictors of non-response in treatment-resistant schizophrenia: A chart review study. *European Archives of Psychiatry and Clinical Neuroscience*, 270(1), 11–22. doi: 10.1007/s00406-019-01053-6.

- Siskind, D., McCartney, L., Goldschlager, R., & Kisely, S. (2016). Clozapine v. first- and second-generation antipsychotics in treatment-refractory schizophrenia: Systematic review and meta-analysis. *The British Journal of Psychiatry*, 209(5), 385–392. doi: 10.1192/bjp.bp.115.177261.
- Spina, E., Avenoso, A., Facciola, G., Scordo, M. G., Ancione, M., Madia, A. G., ... Perucca, E. (2000). Relationship between plasma concentrations of clozapine and norclozapine and therapeutic response in patients with schizophrenia resistant to conventional neuroleptics. *Psychopharmacology*, 148(1), 83–89. doi: 10.1007/s002130050028.
- Stern, R. G., Kahn, R. S., Davidson, M., Nora, R. M., & Davis, K. L. (1994). Early response to clozapine in schizophrenia. *The American Journal of Psychiatry*, 151(12), 1817–1818. doi: 10.1176/ajp.151.12.1817.
- Sumiyoshi, T., Hasegawa, M., Jayathilake, K., & Meltzer, H. Y. (1997). Prediction of short-term changes in symptom severity by baseline plasma homovanillic acid levels in schizophrenic patients receiving clozapine. *Psychiatry Research*, 69(2–3), 113–121. doi: 10.1016/s0165-1781(96)02993-9.
- Suzuki, T., Uchida, H., Watanabe, K., & Kashima, H. (2011). Factors associated with response to clozapine in schizophrenia: A review. *Psychopharmacology Bulletin*, 44(1), 32–60. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/22506438>.
- Szymanski, S., Lieberman, J., Pollack, S., Kane, J. M., Safferman, A., Munne, R., ... Kronig, M. (1996). Gender differences in neuroleptic nonresponsive clozapine-treated schizophrenics. *Biological Psychiatry*, 39(4), 249–254. doi: 10.1016/0006-3223(95)00138-7.
- Tang, Y. L., Mao, P., Li, F. M., Li, W., Chen, Q., Jiang, F., ... Mitchell, P. B. (2007). Gender, age, smoking behaviour and plasma clozapine concentrations in 193 Chinese inpatients with schizophrenia. *British Journal of Clinical Pharmacology*, 64(1), 49–56. doi: 10.1111/j.1365-2125.2007.02852.x.
- Tiihonen, J., Lönnqvist, J., Wahlbeck, K., Klaukka, T., Niskanen, L., Tanskanen, A., & Haukka, J. (2009). 11-year follow-up of mortality in patients with schizophrenia: A population-based cohort study (FIN11 study). *The Lancet*, 374(9690), 620–627. doi: 10.1016/S0140-6736(09)60742-X.
- Üçok, A., Çikrikçili, U., Karabulut, S., Salaj, A., Öztürk, M., Tabak, Ö., & Durak, R. (2015). Delayed initiation of clozapine may be related to poor response in treatment-resistant schizophrenia. *International Clinical Psychopharmacology*, 30(5), 290–295. doi: 10.1097/YIC.000000000000086.
- Üçok, A., Yağcıoğlu, E. A., Yıldız, M., Kaymak, S. U., Saka, M. C., Taşdelen, R., ... Şenol, ŞH (2019). Reasons for clozapine discontinuation in patients with treatment-resistant schizophrenia. *Psychiatry Research*, 275, 149–154. doi: 10.1016/j.psychres.2019.01.110.
- Umbricht, D. S., Wirshing, W. C., Wirshing, D. A., McMeniman, M., Schooler, N. R., Marder, S. R., & Kane, J. M. (2002). Clinical predictors of response to clozapine treatment in ambulatory patients with schizophrenia. *The Journal of Clinical Psychiatry*, 63(5), 420–424. doi: 10.4088/jcp.v63n0508.
- Usall, J., Suarez, D., Haro, J. M., & SOHO Study Group. (2007). Gender differences in response to antipsychotic treatment in outpatients with schizophrenia. *Psychiatry Research*, 153(3), 225–231. doi:10.1016/j.psychres.2006.09.016.
- Velligan, D. I., Weiden, P. J., Sajatovic, M., Scott, J., Carpenter, D., Ross, R., ... Expert Consensus Panel on Adherence Problems in Serious and Persistent Mental Illness. (2009). The expert consensus guideline series: Adherence problems in patients with serious and persistent mental illness. *The Journal of Clinical Psychiatry*, 70(Suppl 4), 1–46. Retrieved from <https://www.ncbi.nlm.nih.gov/pubmed/19686636>.
- Wong, J. O., Leung, S. P., Mak, T., Ng, R. M., Chan, K. T., Hon-Kee Cheung, H., ... Wai-Kiu Tsang, A. (2006). Plasma clozapine levels and clinical response in treatment-refractory Chinese schizophrenic patients. *Progress in Neuropsychopharmacology & Biological Psychiatry*, 30(2), 251–264. doi: 10.1016/j.pnpbp.2005.10.008.
- Yoshimura, B., Yada, Y., So, R., Takaki, M., & Yamada, N. (2017). The critical treatment window of clozapine in treatment-resistant schizophrenia: Secondary analysis of an observational study. *Psychiatry Research*, 250, 65–70. doi: 10.1016/j.psychres.2017.01.064.