Original Paper

Prevalence of treatment-resistant psychoses in the community: A naturalistic study

Journal of Psychopharmacology
1–6

DOI: 10.1177/0269881119855995
journals.sagepub.com/home/jop

Katherine Beck[1,2,3], Robert McCutcheon[1,2,3], Lucy Stephenson[2], Marcela Schilderman[2], Natasha Patel[2], Rosalind Ramsay[2] and Oliver D Howes[1,2,3]

Abstract

Background: Treatment-resistant schizophrenia (TRS) is a major cause of disability. Clozapine is currently the only antipsychotic medication licensed for its treatment. However, the rate of treatment resistance among outpatients with schizophrenia or other psychoses, and the rate of use of clozapine among them, is not known.

Aims: The aims of this study are (a) to determine the point prevalence of treatment-resistant psychosis in a community sample, and (b) to determine the number of patients with TRS who have never had a clozapine trial.

Method: Clinico-demographic data were extracted from the case notes for 202 patients from two community mental-health teams.

Results: We found that 56% (99/176) had a diagnosis of TRS, and 52% (51/99) of these patients had never been treated with clozapine. Patients of non-white ethnicity were less likely to have had a clozapine trial (p=0.009). The point prevalence of treatment resistance within the bipolar affective disorder sample was 19% (5/26).

Conclusion: These findings suggest that TRS is common in the community mental-health team, and a large proportion of these patients have not received clozapine. These findings indicate that identifying and treating treatment resistance should be a focus of community services for schizophrenia.

Keywords

Psychoses, antipsychotics, schizophrenia, bipolar disorder, psychopharmacology

Introduction

Schizophrenia is a serious mental illness characterised by positive, negative and cognitive symptoms. It has a prevalence of approximately 1% (Howes and Murray, 2014). Standard dopamine-targeting medications do not reduce symptoms in all patients, and are particularly poor at treating negative symptoms, which have been linked to poor functional outcomes (Rabinowitz et al., 2012). Non-response to standard antipsychotics is termed treatment-resistant schizophrenia (TRS). It is defined as an inadequate response to sequential treatment with two different antipsychotics at adequate dose and duration, and with adequate adherence (National Institute of Health and Care Excellence, 2014). These patients have worse quality of life, longer hospital admissions and higher treatment costs due to persistent poorly treated symptoms (Kennedy et al., 2014).

Previous studies have found a wide range in the prevalence of TRS, ranging from 14% to 60% of patients (Agid et al., 2011; Essock et al., 1996; Juarez-Reyes et al., 1995; Lally et al., 2016; Lieberman et al., 1993; Meltzer et al., 1997; Mortimer et al., 2010; Wimberley et al., 2016). The variation between studies may be dependent on settings (inpatient vs. outpatient), definition of treatment resistance and study method (Howes et al., 2017). Generally, studies including more patients with chronic schizophrenia report a higher prevalence (45–61%; Demjaha et al., 2017; Essock et al., 1996; Juarez-Reyes et al., 1995; Meltzer et al., 1997; Mortimer et al., 2010) relative to studies which specifically include first-episode patients, where prevalence estimates are 14–34% (Agid et al., 2011; Demjaha et al., 2017; Lally et al., 2016; Lieberman et al., 1993). These prevalence rates appear to reflect the nature of the population included, with low rates of treatment resistance occurring in first-episode patients in whom around 20% will not go on to develop a chronic illness (Robinson et al., 1999a). Studies conducted before have used inpatient tertiary services or location-based samples. To our knowledge, there has not been a study on the prevalence of TRS in a community sample that represents

[1]Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, UK
[2]South London and the Maudsley NHS Foundation Trust, London, UK
[3]MRC London Institute of Medical Sciences, Hammersmith Hospital Campus, London, UK

Corresponding author:
Oliver D Howes, Department of Psychosis Studies, Institute of Psychiatry, Psychology and Neuroscience, King's College London, De Crespigny Park, London, SE5 8AF, UK.
Email: oliver.howes@kcl.ac.uk

patients with schizophrenia commonly attending community mental-health teams (CMHTs).

Clozapine is the only treatment currently licensed for TRS, and is also used off-licence for treating treatment-resistant psychoses in other disorders. Evidence suggests that patients with TRS respond better to clozapine than they do to standard antipsychotics (Agid et al., 2011; Chakos et al., 2001), and its use is associated with lower rates of hospital readmission (Tiihonen et al., 2011) and reduced mortality (Tiihonen et al., 2009). Clinical guidelines advocate offering clozapine to those with TRS at the earliest opportunity (National Institute of Health and Care Excellence, 2014; Taylor et al., 2012; Tiihonen et al., 2009). Early treatment is important, given that it is possible that a longer duration of untreated symptoms could have a detrimental impact on prognosis (Black et al., 2001). Despite this, there are significant delays to clozapine initiation of four to five years, suggesting that it is underused (Howes et al., 2012; Taylor et al., 2003). Moreover, it has been suggested that monitoring requirements to initiate clozapine particularly limit its use in the community (Gee et al., 2014).

In view of this, we sought to determine what proportion of community patients with TRS were not treated with clozapine, and whether this differed between community patients identified as having high ongoing needs relative to a general community caseload. To investigate these questions and to calculate the point prevalence of TRS in patients in the community, we conducted a cross-sectional study of two CMHTs in the South London and Maudsley NHS Foundation Trust. The primary outcome was to identify the number of patients with TRS. The secondary outcomes were to determine (a) the number of patients with TRS who had never been treated with clozapine, (b) the number of treatment trials a patient with TRS had been given and (c) the number of patients with bipolar affective disorder (BPAD) with treatment-resistant psychosis.

Materials and methods

Participants

The total sample consisted of 202 patients from two CMHTs in the South London and Maudsley NHS Foundation Trust. We used two sampling strategies: (a) to select 100 consecutive patients, a strategy applied to one community team's caseload (the standard sample), and (b) to select all patients by the team as having ongoing or recurrent psychosis with high symptom burden and disability using the Health of the Nation Outcome Scale (HoNOS; Wing et al., 1998), a strategy applied to the other CMHT's case load (the high-needs community sample). The case notes for the standard sample were audited from January to September 2014, and the case notes for the high-needs community sample were audited from September 2014 to September 2015. Criteria for acceptance into these teams included (a) a primary diagnosis of a psychotic disorder, including mood disorder with psychotic symptoms; (b) chronic illness more than two years after diagnosis; (c) requiring a care programme approach and care coordination; and (d) age $<$65 years.

To be included in the study, a patient needed to have a diagnosis of: psychosis (ICD-10: paranoid schizophrenia F20.0; hebephrenic schizophrenia F20.1; undifferentiated schizophrenia F20.3; schizophrenia, unspecified F20.9; delusional disorder F22.0; schizoaffective disorder F25.0; or BPAD F31). Exclusion criteria for the study included: (a) evidence that psychotic symptoms were due to an organic cause, or (b) evidence of transient psychotic symptoms due to acute intoxication with drugs or alcohol. Study approval was given by the Psychosis Clinical Academic Group Audit committee at South London and Maudsley NHS Foundation Trust, London, UK.

Assessment of resistance

The criteria for diagnosing treatment-resistant psychosis were: persistent psychotic symptoms; functional impairment (including impairment of personal hygiene, communication, judgement, social functioning, family relations/interpersonal relationships, inability to work or attend school, suicidal acts); and at least two past adequate trials of different antipsychotics. An adequate treatment trial was defined as treatment dose (of either an oral or injectable antipsychotic) within the British National Formulary (www.bnf.org) therapeutic range for at least six weeks. Where treatment adherence was noted to be poor, the episode was considered inadequate. Treatment trials that were ended due to side effects of the medication were not considered an adequate treatment trial. In cases of polypharmacy, if a patient was taking two antipsychotics at the same time and both medications were given at adequate dose and length, as described above, this was considered as two treatment trials.

Data extraction

The following data were extracted from the clinical records: the primary diagnosis (according to ICD-10 criteria; World Health Organization, 1992), age, ethnicity, symptom status and treatment history. Information on demographics, diagnosis, psychotic symptom status and medication history (past antipsychotic use, medication adherence, primary reason for medication discontinuation/switch and clozapine treatment) was derived from clinical descriptions in the case notes, completed by members of the clinical team reviewing the patients. The data extraction was completed by four researchers (K.B., L.S., M.S. and N.P.). K.B. checked 25% of each data extraction to ensure that the inclusion criteria were followed appropriately and in a uniform manner.

Statistical analysis

Descriptive data are reported as means and standard deviations as appropriate. Chi-square tests were used to determine if there were differences in treatment resistance or clozapine treatment by sex, diagnostic or ethnic group. Chi-square tests were also used to determine if there were differences between the high-needs community and standard community samples in treatment resistance or clozapine treatment. Independent two-tailed *t*-tests were used to determine if there was a difference in the groups by age after checking for normality using the Shapiro–Wilk test.

Results

The sample comprised 202 patients (118 males) with a mean age of 48.2 years (*SD*=11.3 years). Diagnoses included schizophrenia (*n*=140), schizoaffective disorder (*n*=28), other psychotic disorder (*n*=8) and BPAD (*n*=26; see Supplementary Table 1). When

Table 1. Demographic and clinical characteristics of patients with treatment-resistant schizophrenia compared to non-resistant schizophrenia.

	Treatment-resistant schizophrenia (*n*=99)	Non-resistant schizophrenia group (*n*=77)	*p*-Value
Age (years), mean (*SD*)[a]	48.0 (11.0)	47.6 (11.2)	0.84
Male (%)	61%	57%	0.64
White (%)	29%	25%	0.50
Diagnosis (%)			
Schizophrenia	83%	75%	0.39
Schizoaffective disorder	14%	18%	
Other	3%	6%	

[a]Independent *t*-test (two-tailed). All other statistical tests are chi-square test.
SD: standard deviation.

Table 2. Demographic and clinical characteristics of treatment-resistant patients treated with clozapine compared to those never treated with clozapine.

	Treatment-resistant schizophrenia currently treated with clozapine or past history of clozapine trial (*n*=48)	Treatment-resistant schizophrenia never treated with clozapine (*n*=51)	*p*-Value
Age (years), mean (*SD*)[a]	48.0 (11.9)	48.0 (10.4)	1.0
Male (%)	54%	67%	0.20
White (%)	42%	18%	0.009[b]
Diagnosis			
Schizophrenia	85%	80%	0.77
Schizoaffective disorder	13%	16%	
Other	2%	4%	

[a]Independent *t*-test (two-tailed). All other statistical tests are chi-square test.
[b]Chi-square statistic 6.89, *p*=0.009.

patients with BPAD were excluded, the sample consisted of 176 patients (104 males), and of these, 56% (*n*=99) were defined as having a diagnosis of TRS. Of those 99 individuals diagnosed with TRS, 52% (*n*=51) were identified as having never taken clozapine. The point prevalence of TRS was similar between the high-needs community (62%) and standard community sample (49%; *p*=0.08), as was the rate of clozapine treatment (47% and 59%, retrospectively; *p*=0.24). The average number of antipsychotic trials in patients with TRS who had never been treated with clozapine was 3 (range 2–7; see Supplementary Table 1). The point prevalence of treatment resistance within the BPAD sample was 19% (*n*=5), and none of these patients had had a clozapine trial.

The demographic and clinical characteristics of the treatment-resistant and non-resistant groups are shown in Table 1, and those for the clozapine-treated resistant group and never clozapine-treated group are shown in Table 2. There were no significant differences between age and sex in either of the group comparisons. There was a significant difference in ethnicity for those treated with clozapine compared to those never having clozapine treatment, with non-white patients more likely never to have been treated with clozapine (*p*=0.009).

Discussion

Our main finding is that TRS is common in community mental-health services, being seen in 56% of patients in a general community service, 52% of whom had never received clozapine. Our findings extend previous studies by showing for the first time that there is a high rate of treatment resistance in the community setting.

Prevalence rates can vary greatly across different patient populations and settings (14–60%; Agid et al., 2011; Essock et al., 1996; Juarez-Reyes et al., 1995; Lally et al., 2016; Lieberman et al., 1993; Meltzer et al., 1997; Mortimer et al., 2010; Wimberley et al., 2016). Studies with first-episode patients find a lower prevalence of treatment resistance, ranging from 14% to 34% (Agid et al., 2011; Demjaha et al., 2017; Lally et al., 2016; Lieberman et al., 1993). The majority of these studies include patients recruited from the community and so may represent less unwell patients. However, one study which only included inpatients also found a low prevalence of treatment resistance (14%; Lieberman et al., 1993). First-episode studies are interesting because they suggest that some patients may be resistant to treatment from an early stage in their illness (Demjaha et al., 2017; Lally et al., 2016), highlighting the need to monitor and manage this early. However, they may be unrepresentative of the general schizophrenia population, since around 20% will not go on to develop a chronic illness (Robinson et al., 1999a). Studies including more chronic patients generally find a higher prevalence of treatment resistance (45–61%; Essock et al., 1996; Juarez-Reyes et al., 1995; Meltzer et al., 1997; Mortimer et al., 2010). Within this group, the study focussing on an inpatient population finds one of the highest prevalence rates (Essock et al., 1996; Meltzer et al., 1997). The wide range in the

prevalence of treatment resistance may also reflect the significant variation in the criteria used to define TRS, a problem highlighted by Howes et al. (2017).

The prevalence of TRS found in this study falls within the range found in previous studies, albeit at the higher end. The most recent studies identify prevalence rates of 34% and 23% (Demjaha et al., 2017; Lally et al., 2016). These two studies also included patients from mental-health teams in South London and had similar TRS criteria. However, these studies included first-episode patients, which may account for the lower prevalence of TRS. Interestingly, Lally et al. find a similar rate of patients who have TRS but who have never been treated with clozapine: 53% compared to the 52% found in our study. We found no difference in age, sex or ethnicity between the resistant and non-resistant groups. However, some studies have found that males are more likely to have a poorer response to medication (Lieberman et al., 1993; Robinson et al., 1999b).

The finding that 52% of patients with TRS had never been treated with clozapine is disappointingly low. However, this finding is similar to national audit findings in England and Wales (Patel et al., 2014), and is consistent with the low prevalence of clozapine prescribing internationally (Bachmann et al., 2017) and more specifically in high-income countries in Europe – around 10% of patients with schizophrenia (Nielsen et al., 2012). This low rate of clozapine prescribing in this patient population is concerning, given the body of evidence supporting its use. It suggests that clinicians are either struggling to identify patients with TRS or are having reservations about starting clozapine in the identified patients (Gee et al., 2014) – or perhaps both. It is also possible that patients are reluctant to try clozapine because of inpatient admissions for titration, blood tests and worries about adverse side effects (Gee et al., 2017). Our findings suggest that patients with TRS often receive more than two treatment trials instead of switching to clozapine, as guidelines suggest. We find that patients with TRS are given an average of three treatment trials with different antipsychotic drugs. This was not as high as identified by Howes and colleagues (Howes et al., 2012), who found that patients received on average five treatment trials prior to being prescribed clozapine. However, our sample of patients had not yet started clozapine, and so it is possible that they might receive further treatment trials prior to starting clozapine.

Patients of non-white ethnicity were less likely to have had a treatment trial of clozapine. One possible contributing factor may be the rates of benign ethnic neutropenia in individuals of non-white ethnicity, which may have discouraged clozapine prescribing. Approximately 25–50% of people of African descent and some ethnic groups in the Middle East have benign ethnic neutropenia, in which healthy individuals in these ethnic groups appear to have neutropenia, as defined in the white population. However, clozapine can be prescribed in these patient groups, and this should not be a barrier to treatment. This study finding may indicate that clinicians need more education in this area. There is evidence that African American patients are more likely to have clozapine discontinued than non-African American patients (Kelly et al., 2006; Moeller et al., 1995), and in one study, it was found that this group of patients had a significantly lower baseline white blood cell count, which may have contributed to clozapine discontinuation (Moeller et al., 1995). It is also possible that this group was less likely to have a clozapine trial because of concerns about adherence. There is some evidence to suggest that adherence may be lower in patients of non-white ethnicity, which may deter clinicians from prescribing clozapine to this patient group (Valenstein et al., 2004).

Our sample included two different patient populations. Patients in the high-needs community sample included patients identified by a structured symptom scoring scale (HoNOS) as having ongoing or recurrent psychosis with high symptom burden and disability. The patients in the standard community sample were not selected based on symptom severity. Although the point prevalence was higher in the high-needs sample at 62% compared to 49%, the prevalence of TRS was not significantly different, and overall both samples appeared to have a high level of TRS. There was no significant difference in the rate of clozapine treatment between the two groups. It might be expected that using a structured symptom questionnaire such as the HoNOS might help to alert clinicians to patients who might have TRS, and identify the need to provide a treatment review for that patient. However, this questionnaire does not have a question about past medications, and it is possible that structured symptom questionnaires could be adapted to include a few simple questions about past medications and treatment adherence to facilitate the routine identification of resistant patients.

We found that 19% (n=5) of the BPAD sample had a resistant illness. There is evidence that clozapine can improve symptoms for patients with BPAD (Goodwin et al., 2016; Li et al., 2015), and guidelines advocate its use (Goodwin et al., 2016). None of the patients with BPAD had received a trial of clozapine in this study.

There are a number of limitations to this study. First, clinicians may have considered clozapine but ruled it out due to concerns about physical health problems. However, it could be argued that there are very few absolute contraindications to clozapine (Beck et al., 2014) and that most people could be offered a treatment trial of clozapine with appropriate levels of care (including input from medical specialists if required) if their psychiatric illness requires it. Second, it is possible that patients identified as treatment resistant in this study were in fact covertly non-adherent (McCutcheon et al., 2015, 2018). We were unable to check antipsychotic levels, and so these could not be used to identify non-adherent patients. However, even if antipsychotic levels had been measured, these are often difficult to interpret, and because of this, most studies rely on verbal confirmation of medication adherence. Third, it is possible that patients were switched from an antipsychotic because of side effects rather than treatment non-response, running the risk that a treatment trial could have been identified as failed due to non-response when it was really due to intolerance of the medication. To try to guard against this, notes describing the reasons for the medication change were read, and where it was indicated that the change in treatment was due to side effects, the medication trial was not considered a full trial. However, it is possible that clinicians did not document this clearly. Fourth, it is possible that there is an overestimation of response, as patients who do not show overtly disruptive behaviour may be described by clinicians as ‘stable’, even if they are still symptomatic. It is also possible that negative symptoms are not documented as frequently, as they are often more chronic and not always as acutely clinically challenging, possibly reducing the ability to identify TRS in patients with predominantly negative symptoms. A clozapine trial was identified by documentation in the electronic notes. This included documentation in the progress notes/medication chart, and/or uploaded documentation of the registration form to the relevant monitoring body. It is unlikely that a patient had a clozapine trial without this documentation.

However, we cannot exclude this possibility. Another important limitation is the small sample size, particularly of the BPAD group. Finally, due to the naturalistic retrospective nature of the study, our definition of treatment resistance deviated slightly from the definition recommended in recent guidelines (see Supplementary Table 2 for a comparison; Howes et al., 2017). While our definition of treatment resistance included two treatment trials (both longer than six weeks) and evidence of decreased functioning, it was not possible to use rating scales to assess symptom severity.

Implications

We found that TRS is common in the CMHT and that a large proportion of patients have not received clozapine. This is despite clozapine being the only licensed antipsychotic for TRS, and numerous guidelines around the world proposing this treatment (Barnes and Schizophrenia Consensus Group of British Association for, 2011; National Institute of Health and Care Excellence, 2014; Taylor et al., 2012). The guidelines suggest that after two failed antipsychotic treatment trials, clozapine should be prescribed, but the results of this study suggest that clinicians are opting to try a greater number of antipsychotic trials instead of prescribing clozapine. Furthermore, we found that patients of non-white ethnicity were more likely not to have had a treatment trial of clozapine.

Acknowledgements

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR or the Department of Health.

Declaration of conflicting interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: O.D.H. has received investigator-initiated research funding from and/or participated in advisory/speaker meetings organised by Astra-Zeneca, Autifony, BMS, Eli Lilly, Heptares, Jansenn, Lundbeck, Lyden-Delta, Otsuka, Servier, Sunovion, Rand and Roche. Neither Dr Howes nor his family have been employed by or have holdings/a financial stake in any biomedical company. K.B., R.M., L.S., M.S., N.P. and R.R. declare no conflicts of interest.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship and/or publication of this article: This study was funded by Medical Research Council-UK (no. MC-A656-5QD30), Maudsley Charity (no. 666), Brain and Behavior Research Foundation, and Wellcome Trust (no. 094849/Z/10/Z) grants to ODH and the National Institute for Health Research (NIHR) Biomedical Research Centre at South London and Maudsley NHS Foundation Trust and King's College London. It was also funded by grants to KB from the Royal College of Psychiatrists, Rosetrees Trust and the Stoneygate Trust.

ORCID iD


Katherine Beck https://orcid.org/0000-0003-2769-8237

Supplemental material

Supplemental material for this article is available online.

References

Agid O, Arenovich T, Sajeev G, et al. (2011) An algorithm-based approach to first-episode schizophrenia: response rates over 3 prospective antipsychotic trials with a retrospective data analysis. *J Clin Psychiatry* 72: 1439–1444.

Bachmann CJ, Aagaard L, Bernardo M, et al. (2017) International trends in clozapine use: a study in 17 countries. *Acta Psychiatr Scand* 136: 37–51.

Barnes TR and Schizophrenia Consensus Group of British Association for Psychopharmacology (2011) Evidence-based guidelines for the pharmacological treatment of schizophrenia: recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 25: 567–620.

Beck K, McCutcheon R, Bloomfield MA, et al. (2014) The practical management of refractory schizophrenia – the Maudsley Treatment REview and Assessment Team service approach. *Acta Psychiatr Scand* 130: 427–438.

Black K, Peters L, Rui Q, et al. (2001) Duration of untreated psychosis predicts treatment outcome in an early psychosis program. *Schizophr Res* 47: 215–222.

Chakos M, Lieberman J, Hoffman E, et al. (2001) Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. *Am J Psychiatry* 158: 518–526.

Demjaha A, Lappin JM, Stahl D, et al. (2017) Antipsychotic treatment resistance in first-episode psychosis: prevalence, subtypes and predictors. *Psychol Med* 1–9.

Essock SM, Hargreaves WA, Dohm FA, et al. (1996) Clozapine eligibility among state hospital patients. *Schizophr Bull* 22: 15–25.

Gee S, Vergunst F, Howes O, et al. (2014) Practitioner attitudes to clozapine initiation. *Acta Psychiatr Scand* 130: 16–24.

Gee SH, Shergill SS and Taylor DM (2017) Patient attitudes to clozapine initiation. *Int Clin Psychopharmacol* 32: 337–342.

Goodwin GM, Haddad PM, Ferrier IN, et al. (2016) Evidence-based guidelines for treating bipolar disorder: revised third edition recommendations from the British Association for Psychopharmacology. *J Psychopharmacol* 30: 495–553.

Howes OD, McCutcheon R, Agid O, et al. (2017) Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) Working Group consensus guidelines on diagnosis and terminology. *Am J Psychiatry* 174: 216–229.

Howes OD and Murray RM (2014) Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet* 383: 1677–1687.

Howes OD, Vergunst F, Gee S, et al. (2012) Adherence to treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. *Br J Psychiatry* 201: 481–485.

Juarez-Reyes MG, Shumway M, Battle C, et al. (1995) Effects of stringent criteria on eligibility for clozapine among public mental health clients. *Psychiatr Serv* 46: 801–806.

Kelly DL, Dixon LB, Kreyenbuhl JA, et al. (2006) Clozapine utilization and outcomes by race in a public mental health system: 1994–2000. *J Clin Psychiatry* 67: 1404–1411.

Kennedy JL, Altar CA, Taylor DL, et al. (2014) The social and economic burden of treatment-resistant schizophrenia: a systematic literature review. *Int Clin Psychopharmacol* 29: 63–76.

Lally J, Ajnakina O, Di Forti M, et al. (2016) Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. *Psychol Med* 46: 3231–3240.

Li XB, Tang YL, Wang CY, et al. (2015) Clozapine for treatment-resistant bipolar disorder: a systematic review. *Bipolar Disord* 17: 235–247.

Lieberman J, Jody D, Geisler S, et al. (1993) Time course and biologic correlates of treatment response in first-episode schizophrenia. *Arch Gen Psychiatry* 50: 369–376.

McCutcheon R, Beck K, Bloomfield MA, et al. (2015) Treatment resistant or resistant to treatment? Antipsychotic plasma levels in patients with poorly controlled psychotic symptoms. *J Psychopharmacol* 29: 892–897.

McCutcheon R, Beck K, D'Ambrosio E, et al. (2018) Antipsychotic plasma levels in the assessment of poor treatment response in schizophrenia. *Acta Psychiatr Scand* 137: 39–46.

Meltzer HY, Rabinowitz J, Lee MA, et al. (1997) Age at onset and gender of schizophrenic patients in relation to neuroleptic resistance. *Am J Psychiatry* 154: 475–482.

Moeller FG, Chen YW, Steinberg JL, et al. (1995) Risk factors for clozapine discontinuation among 805 patients in the VA hospital system. *Ann Clin Psychiatry* 7: 167–173.

Mortimer AM, Singh P, Shepherd CJ, et al. (2010) Clozapine for treatment-resistant schizophrenia: National Institute of Clinical Excellence (NICE) guidance in the real world. *Clin Schizophr Relat Psychoses* 4: 49–55.

National Institute of Health and Care Excellence (2014) Psychosis and schizophrenia: treatment and management. *Clinical guideline 178*. Available at: www.nice.org.uk/guidance/cg178 (accessed 6 March 2019).

Nielsen J, Roge R, Schjerning O, et al. (2012) Geographical and temporal variations in clozapine prescription for schizophrenia. *Eur Neuropsychopharmacol* 22: 818–824.

Patel MX, Bishara D, Jayakumar S, et al. (2014) Quality of prescribing for schizophrenia: evidence from a national audit in England and Wales. *Eur Neuropsychopharmacol* 24: 499–509.

Rabinowitz J, Levine SZ, Garibaldi G, et al. (2012) Negative symptoms have greater impact on functioning than positive symptoms in schizophrenia: analysis of CATIE data. *Schizophr Res* 137: 147–150.

Robinson DG, Woerner MG, Alvir JM, et al. (1999a) Predictors of relapse following response from a first episode of schizophrenia or schizoaffective disorder. *Arch Gen Psychiatry* 56: 241–247.

Robinson DG, Woerner MG, Alvir JM, et al. (1999b) Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiatry* 156: 544–549.

Taylor D, Paton C and Kapur S (2012) *The Maudsley Prescribing Guidelines in Psychiatry*. 11th ed. Hoboken, NJ: John Wiley, p.682.

Taylor DM, Young C and Paton C (2003) Prior antipsychotic prescribing in patients currently receiving clozapine: a case note review. *J Clin Psychiatry* 64: 30–34.

Tiihonen J, Haukka J, Taylor M, et al. (2011) A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. *Am J Psychiatry* 168: 603–609.

Tiihonen J, Lonnqvist J, Wahlbeck K, et al. (2009) 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet* 374: 620–627.

Valenstein M, Blow FC, Copeland LA, et al. (2004) Poor antipsychotic adherence among patients with schizophrenia: medication and patient factors. *Schizophr Bull* 30: 255–264.

Wimberley T, Stovring H, Sorensen HJ, et al. (2016) Predictors of treatment resistance in patients with schizophrenia: a population-based cohort study. *Lancet Psychiatry* 3: 358–366.

Wing JK, Beevor AS, Curtis RH, et al. (1998) Health of the Nation Outcome Scales (HoNOS). Research and development. *Br J Psychiatry* 172: 11–18.

World Health Organization (1992) *The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines*. Geneva, Switzerland: World Health Organization.