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Gender disparities in clozapine prescription in a cohort of treatment-resistant schizophrenia in the South London and Maudsley case register

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ABSTRACT

Background: Gender disparities in treatment are apparent across many areas of healthcare. There has been little research into whether clozapine prescription, the first-line treatment for treatment-resistant schizophrenia (TRS), is affected by patient gender.

Methods: This retrospective cohort study identified 2244 patients with TRS within the South London and Maudsley NHS Trust, by using a bespoke method validated against a gold-standard, manually coded, dataset of TRS cases. The outcome and exposures were identified from the free-text using natural language processing applications (including machine learning and rules-based approaches) and from information entered in structured fields. Multivariable logistic regression was carried out to calculate the odds ratios for clozapine prescription according to patients' gender, and adjusting for numerous potential confounders including sociodemographic, clinical (e.g., psychiatric comorbidities and substance use), neutropenia, functional factors (e.g., problems with occupation), and clinical monitoring.

Results: Clozapine was prescribed to 77% of the women and 85% of the men with TRS. Women had reduced odds of being prescribed clozapine as compared to men after adjusting for all factors included in the present study (adjusted OR: 0.66; 95% CI 0.44–0.97; $p = 0.037$).

Conclusion: Women with TRS are less likely to be prescribed clozapine than men with TRS, even when considering the effects of multiple clinical and functional factors. This finding suggests there could be gender bias in clozapine prescription, which carries ramifications for the relatively poorer care of women with TRS regarding many outcomes such as increased hospitalisation, mortality, and poorer quality of life.

1. Introduction

Across healthcare, gender differences have been reported in treatment and outcomes. For example, women may be less likely to be offered joint replacement or admitted into intensive care (Foust and Kaspar, 2012; Govender and Penn-Kekana, 2008; Hamberg, 2008; Kent et al., 2012; Raine, 2000), and may have greater perceived unmet healthcare needs (Bryant et al., 2009; Socías et al., 2016). It is possible that pre-existing and often unconscious stereotyping of women may lead to disparities in the care of women and subsequent health outcomes (Dovidio and Fiske, 2012; Krieger, 2014).

In schizophrenia, gender differences have been noted within the clinical course of illness and response to psychopharmacology; with women noted to have a later onset of schizophrenia (Kirkbride et al., 2006), men reported to present with greater negative symptoms (Bobes et al., 2010; Ring et al., 1991; Seeman, 2018), and women responding better to antipsychotic medication, and requiring lower doses of antipsychotics (Seeman, 2018; Smith, 2010). Relatively little attention has been paid to gender differences in the treatment with clozapine, and those studies that have been undertaken rarely control for potential confounders such as severity of illness or other clinical factors.

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Service-users who have not adequately improved following the prescription of two courses (for at least 4–6 weeks) of antipsychotics, including at least one second generation antipsychotic, are considered to have treatment-resistant schizophrenia (TRS) (Conley and Kelly, 2001; Mistry and Osborn, 2011). TRS is estimated to affect one third of people with schizophrenia (Essali et al., 2009; Meltzer, 1997). Despite National Institute for Health and Care Excellence (NICE) guidelines recommending clozapine for individuals with TRS (NICE, 2016, 2014), it is estimated that fewer than half of service-users with TRS are prescribed clozapine (Beck et al., 2019; Manuel et al., 2012; Mistry and Osborn, 2011; Stroup et al., 2014). This may be due to concerns about side effects, particularly agranulocytosis (Farooq et al., 2019; Legge et al., 2016; Mistry and Osborn, 2011; Warnez and Alessi-Severini, 2014), service-user compliance (Farooq et al., 2019; Swinton and Ahmed, 1999), and lack of clinician confidence with prescribing clozapine (Farooq et al., 2019; Mistry and Osborn, 2011). As clozapine is indicated in TRS, the failure to prescribe a trial of clozapine at any point during an individual's care represents a missed opportunity to improve their symptoms and their quality of life (Meltzer, 1997; Meltzer et al., 1990). This has implications spanning from reduced hospitalisation (and resulting costs associated) through to decreased mortality (Basu, 2004; Duggan et al., 2003; Hayes et al., 2015).

Some studies have reported that relatively more men receive clozapine than women (Bastiampillai et al., 2012; Cho et al., 2019; Manuel et al., 2012; Si et al., 2012; Stroup et al., 2014), while others show no differences (Bachmann et al., 2017; Beck et al., 2019; El-Badri and Mellsop, 2011; Nielsen et al., 2012; Taylor, 2004; Weinbrenner et al., 2009; Xu et al., 2019). Potential differences could have been explained by more men having TRS than women. In this regard, a recent systematic review of the literature reports mixed evidence; the majority of studies analysed observed no differences in the proportion of TRS between men and women; however, when significant differences were observed, TRS was more prevalent in men (Smart et al., 2021).

The question remains as to whether men are disproportionately more likely to be prescribed clozapine in cohorts of people with TRS. In the USA, an analysis of a TRS cohort observed no differences in prescription of clozapine by gender, after adjusting for possible confounding effects (Stroup et al., 2014). In the UK, mixed findings have been observed, Lally et al. (2016) and Beck et al. (2019), observed no differences in the prescription of clozapine in TRS samples. However, in a study regarding mortality in a cohort of service-users with TRS, Cho et al. (2019) found that men had higher rates of clozapine prescription than women.

In terms of the limitations of these studies, a key shortfall is that many studies solely evaluated clozapine use amongst service-users who were already prescribed clozapine (Bachmann et al., 2017; Bastiampillai et al., 2012; El-Badri and Mellsop, 2011; Nielsen et al., 2012; Taylor, 2004; Weinbrenner et al., 2009; Xu et al., 2019). This allows for the evaluation of patterns in the use of clozapine in the clinical population, however does not address initial prescribing of clozapine. Another recurring limitation in the literature is that some studies only collect minimal data regarding demographic information or do not address possible confounding effects (Bachmann et al., 2017; Bastiampillai et al., 2012; Taylor, 2004; Weinbrenner et al., 2009).

In the present study, our aim is to investigate the effect of gender on clozapine prescription in a large cohort of service-users with TRS, using multivariable logistic regression to reduce residual confounding. We will additionally utilise an empirically a large validated cohort of service-users with TRS, including service-users who are not prescribed clozapine. Following previous literature, our hypothesis is that women will less likely to be prescribed clozapine.

2. Methods

2.1. Setting

This retrospective cohort study used data from the South London and Maudsley NHS Foundation Trust (SLaM) Case Register. SLaM is one of the largest secondary mental health care providers in Europe, and has a near monopoly of care for the residents in its catchment; which comprises four London boroughs: Lambeth, Southwark, Lewisham and Croydon (Stewart et al., 2009), with a population of 1.23 million residents (Office for National Statistics, 2011). The Clinical Record Interactive Search (CRIS) integrates information from across SLaM records, including clinical notes from the community mental health teams, and psychiatric inpatient units, with complete coverage from 2007, when all records became electronic (Perera et al., 2016). At the time of writing, CRIS contained records of over 400,000 individuals. CRIS was approved as a de-identified data resource for secondary research the Oxford C Research Ethics Committee (18/SC/0372 – SLaM) and governance is provided for all projects through a patient-led oversight committee.

2.2. Data extraction methods

Data were extracted from electronic health records (EHR), structured and free-text fields. To retrieve information from free-text fields, Natural Language Processing (NLP) applications were developed using Generalised Architecture for Text Engineering (GATE) or TextHunter, a machine learning application (CRIS NLP Service, 2020; Jackson et al., 2017). NLP applications search the free-text fields of clinical notes for given keywords, and search the surrounding words to account for the context within which the keyword was written. NLP applications outperform keyword searches by differentiating irrelevant use of the keywords from true cases, for example if a service-user has a family member with a diagnosis rather than the service-user having it themselves. Some applications, namely the one regarding the use of cannabis, were developed using TextHunter, a machine learning application (Jackson et al., 2017; Patel et al., 2016). Information extracted via NLP applications in this study included service-user diagnosis, medications, and cannabis use (*CRIS NLP Service*, 2020; Patel et al., 2016; Perera et al., 2016).

The identification of treatment with antipsychotics was based on the use of NLP applications which analyse information in SLaM's EHR free-text fields and structured fields, such as, but not restricted to, pharmacy dispensaries (CRIS NLP Service, 2020; Perera et al., 2016). The applications identified antipsychotic prescription using the generic name and brand names. This was the case for all antipsychotics involved the TRS ascertainment. To ensure further reliability, we required mentions of all medications to be accompanied by a dose, but no minimum dose was specified.

Data were also extracted through searches of structured field inputs such as diagnosis, medication, the Health of the Nation Outcome Scale (HoNOS) and Zaponex Treatment Access System (ZTAS). SLaM has an exclusive license for Zaponex and ZTAS was the mandatory registration and monitoring system for service-users who were taking clozapine, during the study period (2007–2017). ZTAS is also used in other settings in the UK, the USA, Australia and Canada (Cho et al., 2019). ZTAS monitoring allows reporting of benign ethnic neutropenia (BEN), a condition wherein an individual of a minority ethnic group has a baseline low neutrophil count (Rajagopal, 2005). In this study, ZTAS was linked with the records of service-users who met the inclusion criteria to allow for identification of service-users with TRS and retrieve information regarding neutrophil counts. At the time of data collection, the CRIS data linkage to ZTAS enabled access to records dating back to before 2007 up until March 2016.

2.3. Inclusion criteria and treatment-resistant schizophrenia ascertainment

CRIS was searched for service-users who had all of the following: i) a recorded diagnosis of schizophrenia, schizotypal and delusional disorders (ICD-10 codes F20-F29) at any point up to 31/12/2017, ii) a mention of antipsychotic prescription between 1/1/2007 and 31/12/2017 (inclusive), were older than 18 years when first prescribed an antipsychotic after 1/1/2007, iii) were resident in the SLaM catchment area at the time of first mention of antipsychotic after 1/1/2007, or of no fixed

abode and receiving treatment in SLaM, and iv) met the algorithm-based definition of TRS.

2.4. Gold-standard TRS dataset

As part of an earlier investigation, a sample of service-users meeting criteria i) to iii) were manually coded to identify treatment-resistance. TRS was ascertained following either a failure to respond to trials of two distinct antipsychotics, each trial lasting for a minimum of six weeks, or a clozapine prescription (Kadra-Scalzo et al., unpublished manuscript). Failure to respond was assumed when a new antipsychotic was prescribed and there was no report of non-adherence or intolerable side-effects in the clinical notes. This definition of TRS followed the suggestion of the Treatment Response and Resistance in Psychosis (TRRIP) Working Group (Howes et al., 2017).

2.5. Development and validation of a TRS algorithm

In order to capture a similar definition using an automatic procedure which would allow to increase the sample size, in a previous investigation, several possible algorithms for identifying TRS using CRIS were developed and tested (Freitas et al., unpublished manuscript). These algorithms were validated against the manually coded gold-standard dataset described above. These algorithms comprised different trials of antipsychotic treatments, with or without hospitalisation, and were based on previous literature utilizing CRIS data (Cho et al., 2019; Howes et al., 2017). An antipsychotic trial was considered to have taken place if there were at least two prescriptions of the same antipsychotic at least six weeks apart. We tested 15 possible algorithms, starting with the observation of three antipsychotic trials, clozapine prescription, or ZTAS registration. The second algorithm comprised the observation of three antipsychotic trials, where the third antipsychotic was introduced during hospitalisation, clozapine prescription, or ZTAS registration; the third algorithm, comprised three antipsychotic trials, where there had been a hospitalisation at any time before the introduction of the third trial of treatment, clozapine prescription, or ZTAS registration. The further algorithms tested were similar to the ones described but included progressively more antipsychotic trials. We selected the algorithm which performed best, with a good precision (over 80%) and recall, in relation to the gold-standard dataset.

The selected algorithm required evidence of six antipsychotic trials between 2007 and 2017, or clozapine prescription, or ZTAS registration. The performance of this final algorithm achieved a precision and recall of 0.836 and 0.727 respectively. It should be noted some trials may have been ended not due to inadequate clinical response (as per the TRS definition), but also due to the side effects, non-compliance, or other concerns unrelated to the clinical effectiveness of the medication. Consequently, we identified the earliest date at which each service-user recognisably had TRS, be it from 1) the prescription date of a sixth antipsychotic, following trials of five distinct antipsychotics, each lasting for a minimum six weeks, 2) commencement on clozapine, or 3) their ZTAS registration (Freitas et al., unpublished manuscript).

2.6. Variables

Treatment with clozapine was the outcome of interest in the study. Clozapine prescription between 01/01/2007 and 31/12/2017 (inclusive) was identified either in the structured or free-text fields of the service-user's SLaM EHR, using NLP applications as described above.

Gender was the main exposure of interest, with women considered as the exposed group and men as the reference group. The confounders considered were grouped into three subgroups: sociodemographic information, clinical monitoring/service use, and clinical factors. Information on illness severity and deprivation was retrieved from the most recent record in their clinical notes, but prior to their TRS date. This was performed in order to ascertain the most accurate level of functioning near the time the service-user became eligible for prescription of clozapine. Data regarding neutrophil counts were retrieved from any available records up until the date of clozapine prescription or the end of study, whichever was first.

Sociodemographic information, at the time closest to the assigned TRS date, included service-users' age, ethnicity, the neighbourhood deprivation score of their area of residence (based on "The English Indices of Deprivation 2010," 2011), and if they had ever been homeless before the TRS date. Ethnicity was grouped into seven ethnic groups to accommodate for small group sizes.

Clinical monitoring/service use was assessed through the number of days when there was face-to-face contact with SLaM community team and the number of SLaM inpatient days in the three months before the TRS date, as well as whether the service-user had ever been under involuntary hospitalisation under the Mental Health Act 1983 (Part 2, 3, or a police detention, section 135 or 136) before TRS date ("Code of Practice: Mental Health Act 1983 - revised 2008: Department of Health - Publications," 2015).

Clinical factors were also assessed, comprising ratings in the Health of the Nation Outcome Scale (HoNOS; Wing et al., 1998), primary and comorbid psychiatric diagnoses, cannabis use and neutropenia. The HoNOS is a routinely used scale in SLaM to assess severity of illness and is composed of 12 items. These items focus on symptom severity, behaviour, and functional impairment. The ratings of HoNOS items were recoded into 'not a problem' for a score of zero, 'minor problems only' for a score of one, and 'significant problems' for scores of two-four, to increase statistical power through the use of fewer but larger groups (Hayes et al., 2015). An NLP algorithm was used to identify if the individual had ever used cannabis before being identified as TRS (CRIS NLP Service, 2020; Patel et al., 2016). A further clinical feature assessed was the presence of neutropenia, this was done either as the presence of two low neutrophil counts ($<2.2 \times 10^9$/L) at least one month apart in blood analyses recorded on SLaM or ZTAS, prior to clozapine or date of end of study, or through retrieval of information regarding benign ethnic neutropenia (BEN) from ZTAS structured fields.

2.7. Statistical analysis

Descriptive characteristics of the cohort with respect to the sociodemographic factors, clinical service use and clinical factors were presented with results from with chi-square and analyses of variance. Multivariable logistic regression models were then built to control for the influence of related potential confounders, such as the remaining sociodemographic factors and clinical factors, concluding with a 'fully adjusted' model including all considered covariates. Stata MP 15 was used for the analysis.

3. Results

3.1. Descriptive statistics

A total of 2244 service-users with TRS were identified as meeting the inclusion criteria. This cohort consisted of 803 women and 1441 men (Table 1). Of the total cohort, 82.1% were prescribed clozapine, with 84.9% of men and 77.0% of women prescribed clozapine. Overall, this was a relatively deprived cohort, with 9.6% experiencing homelessness before TRS date and 64.4% living in one of the 30% most deprived areas in the UK at TRS date ("The English Indices of Deprivation 2010," 2011).

When comparing the men and women in the cohort on sociodemographic characteristics at the time of TRS ascertainment (Table 2), there were significant differences in age, more specifically women had an older mean age (43.4, $SD = 13.4$) as compared to men (39.4, $SD = 11.9$), a higher proportion of women had schizoaffective disorder, and women had a greater number of face-to-face contact days with SLaM community services. Additionally, women were significantly more frequently detained under civil detentions and police sections of the

Table 1
Demographic and clinical characteristics of people with treatment-resistant schizophrenia.

	Total N (% of total sample)	Prescribed clozapine N (% per characteristic)
Total	2244 (100)	1842 (82.1)
Gender		
Women	803 (35.8)	618 (77.0)
Men	1441 (64.2)	1224 (84.9)
Sociodemographic factors		
Age (*M* 40.9, *SD* 12.6, range 18–89 years)		
18 to <35 years	793 (35.3)	672 (84.7)
35 to <50 years	964 (43.0)	808 (83.8)
50 years and over	487 (21.7)	362 (74.3)
Ethnicity (<10 (<0.03%) missing or not stated)[a,b]		
White	869 (38.8)	756 (87.0)
African	354 (15.8)	267 (75.4)
Caribbean	391 (17.5)	303 (77.5)
Other Black background	371 (16.6)	296 (79.8)
South Asian	61 (2.7)	54 (88.5)
Other Asian	84 (3.8)	69 (82.1)
Other ethnic background	109 (4.9)	92 (84.4)
Deprivation level in area of residence at TRS diagnosis (14 (0.6%) missing)[a]		
Ever homeless before TRS date	214 (9.6)	130 (60.8)
0–10% most deprived (high deprivation)	129 (5.8)	110 (85.3)
10–20% second most deprived	670 (30.0)	559 (83.4)
20–30% third most deprived	636 (28.5)	527 (82.9)
30–100% least deprived (low deprivation)	581 (26.1)	503 (86.6)
Diagnosis		
Schizophrenia	1614 (71.9)	1353 (83.8)
Schizoaffective disorder	413 (18.4)	301 (72.9)
Other prolonged psychosis	217 (9.7)	188 (86.6)
Clinical monitoring/service use		
Number of days of face-to-face contact with SLaM services in the 3 months before TRS date (*Md* 5, *IQR* 2–9, range 0–91)		
0	296 (13.2)	269 (90.9)
1–7	1237 (55.1)	1016 (82.1)
8–14	463 (20.6)	367 (79.3)
15 and above	248 (11.1)	190 (76.6)
Number of SLaM inpatient days in the 3 months before TRS date (*Md* 0, *IQR* 0–43, range 0–91)		
0	1157 (51.6)	1008 (87.1)
1–29	401 (17.9)	289 (72.1)
30–59	216 (9.6)	166 (76.9)
60 and above	470 (20.9)	379 (80.6)
The Mental Health Act (MHA): ever involuntary hospitalised or sectioned before TRS date		
Part 2		
No	1107 (49.3)	1034 (93.4)
Yes	1137 (50.7)	808 (71.1)
Part 3		
No	2059 (91.8)	1703 (82.7)
Yes	185 (8.2)	139 (75.1)
Police sections		
No	1881 (83.8)	1616 (85.9)
Yes	363 (16.2)	226 (62.3)
The Health of the Nation Outcome Scale (HoNOS)		
Overactive, aggressive behaviour (605 (27.0%) missing)[b]		
Not a problem	749 (45.7)	612 (81.7)
Minor problems only	398 (24.3)	312 (78.4)
Significant problem	492 (30.0)	357 (72.6)
Hallucinations and delusions (609 (27.1%) missing)[b]		
Not a problem	309 (18.9)	237 (76.7)
Minor problems only	257 (15.7)	192 (74.7)
Significant problem	1069 (65.4)	850 (79.5)
Depressed mood (611 (27.2%) missing)[b]		
Not a problem	789 (48.3)	611 (77.4)
Minor problems only	482 (29.5)	380 (78.8)
Significant problem	362 (22.2)	286 (79.0)
Additional mental and physical health problems		
Non-accidental self-injury (607 (27.0%) missing)[b]		
Not a problem	1431 (87.4)	1100 (77.6)
Minor problem requiring no action	115 (7.0)	95 (82.6)
Significant problem	91 (5.6)	74 (81.3)
Problem-drinking or drug taking (618 (27.5%) missing)[b]		
Not a problem	1120 (68.9)	891 (79.6)
Minor problems only	166 (10.2)	129 (77.7)
Significant problem	340 (20.9)	254 (74.7)
Cognitive problems (609 (27.1%) missing)[b]		
Not a problem	820 (50.2)	640 (78.1)
Minor problems only	418 (25.6)	329 (78.7)
Significant problems	397 (24.3)	308 (77.6)
Physical illness or disability problems (610 (27.2%) missing)[b]		
Not a problem	966 (59.1)	770 (79.7)
Minor problems only	303 (18.5)	236 (77.9)
Significant problem	365 (22.3)	270 (74.0)
Functional status		
Activities of daily living (ADLs) (621 (27.7%) missing)[b]		
Not a problem	613 (37.8)	480 (78.3)
Minor problems only	423 (26.1)	336 (79.4)
Significant problem	587 (36.2)	456 (77.7)
Standard of living conditions (667 (29.7%) missing)[b]		
Not a problem	923 (58.5)	741 (80.3)
Minor problems only	319 (20.2)	238 (74.6)
Significant problem	335 (21.2)	260 (77.6)
Occupational and recreational activities (658 (29.3%) missing)[b]		
Not a problem	618 (39.0)	488 (79.0)
Minor problems only	406 (25.6)	312 (76.9)
Significant problem	562 (35.4)	446 (79.4)
Social relationships (617 (27.5%) missing)[b]		
Not a problem	511 (31.4)	406 (79.5)
Minor problems only	470 (28.9)	362 (77.0)
Significant problem	646 (39.7)	505 (78.2)
Comorbidities		
Personality disorder		
No	1965 (87.6)	1635 (83.2)
Yes	279 (12.4)	207 (74.2)
Obsessive-compulsive disorder		
No	2189 (97.6)	1802 (82.3)
Yes	55 (2.5)	40 (72.7)
Autism spectrum disorder		
No	2204 (98.2)	1809 (82.1)
Yes	40 (1.8)	33 (82.5)
Attention-deficit hyperactivity disorder		
No	2220 (98.9)	1827 (82.3)
Yes	24 (1.1)	15 (62.5)
Intellectual disability		
No	2177 (97.0)	1791 (82.3)
Yes	67 (3.0)	51 (76.1)
Developmental disorder		
No	2137 (95.2)	1754 (82.1)
Yes	107 (4.8)	88 (82.2)
PTSD		
No	2214 (98.7)	1820 (82.2)
Yes	30 (1.3)	22 (73.3)
Anxiety disorder		
No	2194 (97.8)	1806 (82.3)
Yes	50 (2.2)	36 (72.0)
Bipolar disorder		
No	1895 (84.4)	1616 (85.3)
Yes	349 (15.6)	226 (64.8)
Depression		
No	1904 (84.9)	1580 (83.0)
Yes	340 (15.2)	262 (77.1)
Other mood disorder		
No	2225 (99.2)	1829 (82.2)
Yes	19 (0.9)	13 (68.4)

Table 1 (*continued*)

	Total N (% of total sample)	Prescribed clozapine N (% per characteristic)
Substance use		
Any substance misuse		
No	1959 (87.3)	1644 (83.9)
Yes	285 (12.7)	198 (69.5)
Ever diagnosed with alcohol use disorder		
No	2165 (96.5)	1786 (82.5)
Yes	79 (3.5)	56 (70.9)
Ever diagnosed with opioid use disorder		
No	2217 (98.8)	1824 (82.3)
Yes	27 (1.2)	18 (66.7)
Evidence of cannabis use before TRS date		
No	849 (37.8)	754 (88.8)
Yes	1395 (62.2)	1088 (78.0)
Neutropenia/benign ethnic neutropenia (BEN) (716 (31.9%) missing)[b]		
No	1366 (89.4)	1110 (81.3)
Yes	162 (10.6)	126 (77.8)

[a] Ethnicity (UK census groups): White (British, Irish, Other White background), African (Black and White African, African), Caribbean (Black and White Caribbean, Caribbean), Other Black background, South Asian (Bangladeshi, Indian, Pakistani), Other Asian (Chinese, White and Asian, Other Asian background), Other ethnic background (Any other mixed background, Any other ethnic group).
[b] Percentage calculated from available data.

Mental Health Act, while men were significantly more frequently detained under forensic detention ("Code of Practice: Mental Health Act 1983 - revised 2008: Department of Health - Publications," 2015). Amongst the HoNOS items, women had significantly lower problems with drinking or drug-taking, more physical illness or disability problems, and increased depressed mood. In terms of comorbidities, significantly more women had bipolar disorder (23.0% vs 11.4%) and depression (21.5% vs 11.6%), however they also had lower substance misuse (9.2% vs 14.6%) and cannabis use before TRS date (48.6% vs 69.7%).

3.2. Gender and clozapine prescription

There was a stable and significant association between gender and clozapine prescribing in all models (Table 3), including the crude (OR = 0.59; 95% CI: 0.48–0.74; $p < 0.001$) and fully adjusted model (OR = 0.66; 95% CI: 0.44–0.97; $p = 0.037$), with women being less likely to be prescribed clozapine compared to men.

4. Discussion

4.1. Key findings

To the best of our knowledge, this is the first UK study where analysis adjusting for multiple confounders has been used to study

Table 2
Demographic and clinical characteristics of men and women with treatment-resistant schizophrenia.

	Men N (%)	Women N (%)	
Sociodemographic factors			
Mean age (standard deviation)	39.4 (11.9)	43.4 (13.4)	$t(2242) = -7.31, p < 0.001$
18 to <35 years	569 (39.5)	224 (27.9)	$\chi^2(2,2244) = 36.63, p < 0.001$
35 to <50 years	601 (41.7)	363 (45.2)	
50 years and over	271 (18.8)	216 (26.9)	
Ethnicity (<10 missing or not stated)[a,b]			$\chi^2(6,2239) = 10.20, p = 0.117$
White	570 (39.6)	299 (37.3)	
African	207 (14.4)	147 (18.4)	
Caribbean	248 (17.3)	143 (17.9)	
Other Black background	252 (17.5)	119 (14.9)	
South Asian	35 (2.4)	26 (3.3)	
Other Asian	52 (3.6)	32 (4.0)	
Other ethnic background	74 (5.1)	35 (4.4)	
Deprivation level in area of residence at TRS diagnosis (14 (0.62%) missing)[b]			$\chi^2(4,2230) = 8.98, p = 0.062$
Ever homeless before TRS date	157 (11.0)	57 (7.1)	
0–10% most deprived (high deprivation)	84 (5.9)	45 (5.6)	
10–20% second most deprived	422 (29.5)	248 (31.1)	
20–30% third most deprived	405 (28.3)	231 (29.0)	
30–100% least deprived (low deprivation)	364 (25.4)	217 (27.2)	
Diagnosis			$\chi^2(2,2244) = 45.11, p < 0.001$
Schizophrenia	1101 (76.4)	513 (63.9)	
Schizoaffective disorder	210 (14.6)	203 (25.3)	
Other prolonged psychosis	130 (9.0)	87 (10.8)	
Clinical monitoring/service use			
Number of days of face-to-face contact with SLaM community services in the 3 months before TRS date			$\chi^2(3,2244) = 30.63, p < 0.001$
0	220 (15.3)	76 (9.5)	
1–7	815 (56.6)	422 (52.6)	
8–14	261 (18.1)	202 (25.2)	
15 and above	145 (10.1)	103 (12.8)	
Number of SLaM inpatient days in the 3 months before TRS date			$\chi^2(3,2244) = 4.70, p = 0.195$
0	762 (52.9)	395 (49.2)	
1–29	240 (16.7)	161 (20.1)	
30–59	138 (9.6)	78 (9.7)	
60 and above	301 (20.9)	169 (21.1)	
The Mental Health Act (MHA): ever involuntary hospitalised or sectioned under the MHA before TRS date			
Part 2	679 (47.1)	458 (57.0)	$\chi^2(1,2244) = 20.28, p < 0.001$
Part 3	163 (11.3)	22 (2.7)	$\chi^2(1,2244) = 50.09, p < 0.001$
Police sections	214 (14.9)	149 (18.6)	$\chi^2(1,2244) = 5.22, p = 0.022$
The Health of the Nation Outcome Scale (HoNOS)			

Table 2 (*continued*)

	Men N (%)	Women N (%)	
Overactive, aggressive behaviour (605 (27.0%) missing)[b]			$\chi^2(2,1639) = 4.20, p = 0.123$
Not a problem	487 (47.6)	262 (42.5)	
Minor problems only	243 (23.8)	155 (25.2)	
Significant problem	293 (28.6)	199 (32.3)	
Hallucinations and delusions (609 (27.1%) missing)[b]			$\chi^2(2,1635) = 1.07, p = 0.585$
Not a problem	199 (19.5)	110 (17.9)	
Minor problems only	164 (16.1)	93 (15.2)	
Significant problem	658 (64.5)	411 (66.9)	
Depressed mood (611 (27.2%) missing)[b]			$\chi^2(2,1633) = 7.82, p = 0.020$
Not a problem	512 (50.2)	277 (45.2)	
Minor problems only	304 (29.8)	178 (29.0)	
Significant problem	204 (20.0)	158 (25.8)	
Additional mental and physical health problems			
Non-accidental self-injury (607 (27.0%) missing)[b]			$\chi^2(2,1637) = 3.04, p = 0.218$
Not a problem	904 (88.5)	527 (85.7)	
Minor problem requiring no action	68 (6.7)	47 (7.6)	
Significant problem	50 (4.9)	41 (6.7)	
Problem-drinking or drug taking (618 (27.5%) missing)[b]			$\chi^2(2,1626) = 67.58, p < 0.001$
Not a problem	629 (61.7)	491 (80.9)	
Minor problems only	120 (11.8)	46 (7.6)	
Significant problem	270 (26.5)	70 (11.5)	
Cognitive problems (609 (27.1%) missing)[b]			$\chi^2(2,1635) = 0.93, p = 0.628$
Not a problem	521 (51.1)	299 (48.6)	
Minor problems only	256 (25.1)	162 (26.3)	
Significant problems	243 (23.8)	154 (25.0)	
Physical illness or disability problems (610 (27.2%) missing)[b]			$\chi^2(2,1634) = 26.38, p < 0.001$
Not a problem	648 (63.5)	318 (51.8)	
Minor problems only	182 (17.8)	121 (19.7)	
Significant problem	190 (18.6)	175 (28.5)	
Functional status			
Activities of daily living (ADLs) (621 (27.7%) missing)[b]			$\chi^2(2,1623) = 0.27, p = 0.874$
Not a problem	384 (37.9)	229 (37.6)	
Minor problems only	260 (25.6)	163 (26.8)	
Significant problem	370 (36.5)	217 (35.6)	
Standard of living conditions (667 (29.7%) missing)[b]			$\chi^2(2,1577) = 0.32, p = 0.851$
Not a problem	578 (58.6)	345 (58.5)	
Minor problems only	203 (20.6)	116 (19.7)	
Significant problem	206 (20.9)	129 (21.9)	
Occupational and recreational activities (658 (29.3%) missing)[b]			$\chi^2(2,1586) = 0.19, p = 0.912$
Not a problem	386 (38.9)	232 (39.1)	
Minor problems only	251 (25.3)	155 (26.1)	
Significant problem	355 (35.8)	207 (34.9)	
Social relationships (617 (27.5%) missing)[b]			$\chi^2(2,1627) = 0.89, p = 0.640$
Not a problem	323 (31.8)	188 (30.7)	
Minor problems only	298 (29.4)	172 (28.1)	
Significant problem	394 (38.8)	252 (41.2)	
Comorbidities			
Personality disorder	174 (12.1)	105 (13.1)	$\chi^2(1,2244) = 0.47, p = 0.491$
Obsessive-compulsive disorder	38 (2.6)	17 (2.1)	$\chi^2(1,2244) = 0.58, p = 0.445$
Autism spectrum disorder	30 (2.1)	10 (1.3)	$\chi^2(1,2244) = 2.06, p = 0.151$
Attention-deficit hyperactivity disorder	16 (1.1)	<10	$\chi^2(1,2244) = 0.06, p = 0.801$
Intellectual disability	43 (3.0)	24 (3.0)	$\chi^2(1,2244) = 0.00, p = 0.995$
Developmental disorder	75 (5.2)	32 (4.0)	$\chi^2(1,2244) = 1.69, p = 0.194$
PTSD	18 (1.3)	12 (1.5)	$\chi^2(1,2244) = 0.24, p = 0.628$
Anxiety disorder	29 (2.0)	21 (2.6)	$\chi^2(1,2244) = 0.86, p = 0.354$
Bipolar disorder	164 (11.4)	185 (23.0)	$\chi^2(1,2244) = 53.36, p < 0.001$
Depression	167 (11.6)	173 (21.5)	$\chi^2(1,2244) = 39.75, p < 0.001$
Other mood disorder	10 (0.7)	<10	$\chi^2(1,2244) = 1.12, p = 0.290$
Substance use			
Any substance misuse	211 (14.6)	74 (9.2)	$\chi^2(1,2244) = 13.70, p < 0.001$
Ever diagnosed with alcohol use disorder	58 (4.0)	21 (2.6)	$\chi^2(1,2244) = 3.02, p = 0.082$
Ever diagnosed with opioid use disorder	14 (1.0)	13 (1.6)	$\chi^2(1,2244) = 1.82, p = 0.178$
Evidence of cannabis use before TRS date	1005 (69.7)	390 (48.6)	$\chi^2(1,2244) = 98.31, p < 0.001$
Neutropenia/benign ethnic neutropenia (BEN) (716 (31.9%) missing)[b]			
Ever had two low neutrophil counts one month apart or BEN	112 (11.5)	50 (9.0)	$\chi^2(1,1528) = 2.28, p = 0.131$

[a] Ethnicity (UK census groups): White (British, Irish, Other White background), African (Black and White African, African), Caribbean (Black and White Caribbean, Caribbean), Other Black background, South Asian (Bangladeshi, Indian, Pakistani), Other Asian (Chinese, White and Asian, Other Asian background), Other ethnic background (Any other mixed background, Any other ethnic group).

[b] Percentage calculated from available data. Percentages may not add to 100% due to rounding.

Table 3
Multivariable logistic regression analyses of association between gender (women) and clozapine prescription in a cohort with TRS.

Prescribed clozapine in the study observation period[a]	Odds ratio (95% CI)	*p* value
Crude	0.59 (0.48–0.74)	<0.001
Adjusted for sociodemographic factors[b]	0.60 (0.48–0.76)	<0.001
Adjusted for SLaM service use[c]	0.63 (0.50–0.80)	<0.001
Adjusted for clinical factors (excluding HoNOS)[d]	0.55 (0.43–0.70)	<0.001
Adjusted for clinical HoNOS factors[e]	0.59 (0.46–0.76)	<0.001
Adjusted for social and functional HoNOS factors[f]	0.61 (0.48–0.78)	<0.001
Adjusted for presence of neutropenia[g]	0.61 (0.47–0.79)	<0.001
Fully adjusted	0.66 (0.44–0.97)	0.037

[a] Observation period ran until December 31, 2017.
[b] Age, ethnicity, level of deprivation in area of residence and homelessness.
[c] Number of face-to-face and inpatient contact days in the 3 months before data extraction date, and MHA police sections (s135 and s136), MHA Part 2 or MHA Part 3 section ever.
[d] Main schizophrenia spectrum diagnosis, comorbid diagnoses, substance use.
[e] Clinical factor level of severity from HONOS (aggression, self-injury, substance abuse, cognitive problems, physical disability, hallucinations, depressed mood).
[f] Social and functional level of severity from HONOS (relationship problems, problems with activities of daily living, problems with living conditions, occupational problems).
[g] Ever had benign ethnic neutropenia recorded on ZTAS, or two low neutrophil counts on ZTAS or in clinical notes with one month apart.

differences in clozapine prescription between genders. This study investigated a cohort of over 2000 service-users with TRS from SLaM and found that women with TRS were less likely to be prescribed clozapine than men, and this association persisted after adjustment for multiple covariates, including other sociodemographic factors, SLaM service use (for example number of inpatient days in the three months prior to assigned TRS date), clinical factors (comorbidities, drug use and severity of symptoms, assessed through HoNOS), indices of living condition and functional status (assessed through HoNOS), and the presence of neutropenia.

This study agrees with previous reports of reduced odds for women receiving clozapine (Cho et al., 2019; Si et al., 2012; Stroup et al., 2014), but it is novel in presenting results from a large cohort of service-users in the UK with TRS, with adjustment for multiple potential confounders. In some studies, although not all, TRS has been observed to be more common in men (Smart et al., 2021), which may impact upon clinicians' readiness to recognise TRS in men and proceed with treatment with clozapine. Without investigating a cohort of service-users with TRS it is difficult to disentangle higher rates due to the higher prevalence of TRS in men from potential gender inequalities in prescribing practices. In line with previous literature observed in cohorts of people with TRS (Cho et al., 2019; Si et al., 2012; Stroup et al., 2014), our study shows that men are more likely to be prescribed clozapine. Moreover, like observed in Stroup et al. (2014) and Si et al. (2012), this association persisted even after accounting for a wide range of clinical and functional factors. The gender difference suggests women are not being prescribed clozapine in line with men and may indicate gender-based discrimination in the use of this antipsychotic (Cho et al., 2019; Si et al., 2012).

4.2. Limitations

One limitation of the present study lies in the algorithm used for recognising TRS, which did not assess service-user's records for antipsychotic trials shorter than six weeks [NICE (2014) guidelines include trials which can have a shorter duration (four weeks)], and did not account for the class of antipsychotic used or dosage (NICE, 2014). The current algorithm was validated against a manually coded TRS sample, using the TRRIP working group guidelines (Howes et al., 2017) and it could be accounting to some extent for the likelihood that many antipsychotics are discontinued due to side effects, and non-compliance, at which point treatment response may not be accurately measured. This might have underestimated the number of service-users with TRS in this study.

Additionally, pregnancy, contraindications to clozapine prescription, service-user refusal of the medication due to the required blood monitoring tests, or side effects (such as weight gain), service-user non-attendance to appointments or non-compliance with pharmacological treatment, or treatment with any other medications (either of mental or physical conditions) were not included in the present study (Dayabandara et al., 2017; NICE, 2014). It was decided either that the EHR would not have a reliable record of this information due to missing, incomplete or that suitable NLP algorithms are not yet developed to process the multiple phraseologies that may surround these more nuanced concepts.

Third, there is considerable missing data for some confounders. For the HoNOS items, the increased proportion of missing data lead to reduced power in the statistical analyses, which may have resulted in the broader confidence intervals for the odd ratio observed in the models which adjusted for these variables. Also, the observation period began when service-user records transferred on to an electronic system in 2007, from which information can be retrieved via CRIS. As we extracted data from different databases, namely CRIS and ZTAS, which were digitised at different times, there is a chance that there may be increased missing data if service-users were using services around the time of the records moving online. This may present difficulty in accurately measuring exposures, and the order in which they occurred with regards to developing TRS and/or prescription of clozapine. This potential discrepancy is less important with respect to the main exposure of gender, which is generally not a variable that changes with time. One hundred and eighteen service-users were recognised as having TRS via ZTAS records prior to 2007, as the digitisation of ZTAS pre-dates that of CRIS. On inspection of the missing data in the 118 individuals who met the inclusion criteria through ZTAS before 2007, there was no evidence of significant increases in missing data compared to the rest of the cohort. This study had a large cohort of 2244 individuals, conferring increased statistical power in comparison to other studies (Beck et al., 2019; El-Badri and Mellsop, 2011; Lally et al., 2016; Manuel et al., 2012).

Fourth, this study utilised the HoNOS to assess symptom severity, which is not a specific measure of severity of illness in schizophrenia, and does not include a rating for negative symptoms, which have been reported to not only be more prevalent in service-users with TRS (Lally et al., 2016; Si et al., 2012) but also more common in men with schizophrenia compared to women (Bobes et al., 2010; Lee et al., 2011; Novick et al., 2016; Ring et al., 1991; Seeman, 2018; Wójciak et al., 2020). Although clozapine is superior to other antipsychotics in the treatment of positive symptoms and not in negative symptoms (Mizuno et al., 2020; Siskind et al., 2016), it had been observed that clozapine was more likely to be prescribed for people with TRS with higher levels of negative symptoms (Lally et al., 2016). Thus, it is possible that gender differences in negative symptoms may be related to the observed inequalities. Although HoNOS does not directly measure negative symptoms, it is plausible that their impact could be indirectly expressed amongst the items listed under 'functional status' in our analyses. There is limited evidence regarding gender differences in symptomatic profiles in cohorts of people with TRS. Future research might investigate this further using specific scales to assess symptoms in schizophrenia (e.g., the Positive and Negative Symptoms Scale), as well as the impact of symptomatic profiles on the gender differences in treatment with clozapine.

Despite the mentioned limitations, the present study capitalised on the cross-linkage of EHR from across services within SLaM to allow for the inclusion of varied aspects of the secondary mental health services, including community face-to-face appointments and inpatient days, as well as the inclusion of ZTAS records to assess neutrophil counts. The inclusion of a wide variety of covariates from across the EHR in the analysis acted to reduce residual confounding, taking into account clinical factors, service use and neutropenia to name a few. The cohort has the advantage conferred by the near-monopoly coverage of the South London and Maudsley NHS Trust upon the healthcare of its local population in hospital and community care, and the Clinical Record Interactive Search (CRIS) system which integrates clinical notes from across

the trust to give a large amount of data for each service-user. This makes the sample highly representative of the local population, and increases service-user participation in the database due to an opt-out mechanism, while reducing the number of cases lost to follow-up through maintaining a longitudinal record of service-user care.

4.3. Implications for policy and practice

This study identifies a disparity in the treatment of men and women with TRS, with women having poorer treatment, which, in turn, can lead to increased hospitalisation, mortality, and worsened quality of life when compared to men (Duggan et al., 2003; Hayes et al., 2015; Meltzer, 1997; Meltzer et al., 1990). This may be targeted through programs for recognising TRS in women and reducing implicit biases across healthcare (Hamberg, 2008; Sukhera and Watling, 2018) and to specifically correct gender-biased medical practice using evidence-based examples (Verdonk et al., 2009). The aims of these interventions are in accordance with one of the recommendations of the WHO's Women and Gender Equity Knowledge Network, namely, to improve awareness in order to tackle gender inequity in healthcare (Sen and Östlin, 2008). Integration of such courses into the national medical curriculum under the guidance of specialists in the field would be a crucial step in striving for gender equity in healthcare.

4.4. Further research

The explanations which may underlie the difference in clozapine prescription between men and women lie beyond the scope of this paper. Some potential confounders not measured in this study (e.g., pregnancy, comorbidities as diabetes or cardiovascular disease, or even gender differences in symptomatic profile) could be related to the observed inequities and future research should address this. Moreover, it is possible that the expectations, attitudes and unconscious biases of clinicians may each impact upon recognition of TRS and subsequent clozapine prescription (or lack thereof). This area warrants further investigation to explore the underlying causes of clozapine under-prescription in women with TRS.

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Declaration of competing interest

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Data availability

The data from the clinical electronic records is owned by the South London and Maudsley NHS Trust and can be accessed via the Clinical Records Interactive Search. Access to the CRIS dataset is permitted to authorized individuals. For applications to access CRIS please contact cris.administrator@slam.nhs.uk.

References

Bachmann, C.J., Aagaard, L., Bernardo, M., Brandt, L., Cartabia, M., Clavenna, A., Coma Fusté, A., Furu, K., Garuolienė, K., Hoffmann, F., Hollingworth, S., Huybrechts, K.F., Kalverdijk, L.J., Kawakami, K., Kieler, H., Kinoshita, T., López, S.C., Machado-Alba, J.E., Machado-Duque, M.E., Mahesri, M., Nishtala, P.S., Piovani, D., Reutfors, J., Saastamoinen, L.K., Sato, I., Schuiling-Veninga, C.C.M., Shyu, Y.C., Siskind, D., Skurtveit, S., Verdoux, H., Wang, L.J., Zara Yahni, C., Zoëga, H., Taylor, D., 2017. International trends in clozapine use: a study in 17 countries. Acta Psychiatr. Scand. 136, 37–51. https://doi.org/10.1111/acps.12742.

Bastiampillai, T., Avina, P., Malalagama, G., Bidargaddi, N., Chan, S.K.W., Dhillon, R., Schrader, G., 2012. Gender differences in clozapine prescription in Australia. Curr. Psychopharmacol. 1, 111–116. https://doi.org/10.2174/2211556011201020111.

Basu, A., 2004. Cost-effectiveness analysis of pharmacological treatments in schizophrenia: critical review of results and methodological issues. Schizophr. Res. 71, 445–462. https://doi.org/10.1016/j.schres.2004.02.012.

Beck, K., McCutcheon, R., Stephenson, L., Schilderman, M., Patel, N., Ramsay, R., Howes, O.D., 2019. Prevalence of treatment-resistant psychoses in the community: a naturalistic study. J. Psychopharmacol. 33, 1248–1253. https://doi.org/10.1177/0269881119855995.

Bobes, J., Arango, C., Garcia-Garcia, M., Rejas, J., 2010. Prevalence of negative symptoms in outpatients with schizophrenia spectrum disorders treated with antipsychotics in routine clinical practice: findings from the CLAMORS study. J. Clin. Psychiatry 71, 280–286. https://doi.org/10.4088/JCP.08m04250yel.

Bryant, T., Leaver, C., Dunn, J., 2009. Unmet healthcare need, gender, and health inequalities in Canada. Health Policy (New York) 91, 24–32. https://doi.org/10.1016/j.healthpol.2008.11.002.

Cho, J., Hayes, R.D., Jewell, A., Kadra, G., Shetty, H., MacCabe, J.H., Downs, J., 2019. Clozapine and all-cause mortality in treatment-resistant schizophrenia: a historical cohort study. Acta Psychiatr. Scand. 139, 237–247. https://doi.org/10.1111/acps.12989.

Code of Practice: Mental Health Act 1983 - revised 2008: Department of Health - Publications [WWW Document], 2015. . URL. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/435512/MHA_Code_of_Practice.PDF (accessed 2.4.21).

Conley, R.R., Kelly, D.L., 2001. Management of treatment resistance in schizophrenia. Biol. Psychiatry 50, 898–911. https://doi.org/10.1016/S0006-3223(01)01271-9.

CRIS NLP Service: Library of production-ready applications v1.2 [WWW Document], 2020. . URL. https://maudsleybrc.nihr.ac.uk/media/313767/nlp-applications-library-v12.pdf (accessed 2.4.21).

Dayabandara, M., Hanwella, R., Ratnatunga, S., Seneviratne, S., Suraweera, C., de Silva, V.A., 2017. Antipsychotic-associated weight gain: management strategies and impact on treatment adherence. Neuropsychiatr. Dis. Treat. 13, 2231–2241. https://doi.org/10.2147/NDT.S113099.

Dovidio, J.F., Fiske, S.T., 2012. Under the radar: how unexamined biases in decision-making processes in clinical interactions can contribute to health care disparities. Am. J. Public Health 102, 945–952. https://doi.org/10.2105/AJPH.2011.300601.

Duggan, A., Warner, J., Knapp, M., Kerwin, R., 2003. Modelling the impact of clozapine on suicide in patients with treatment-resistant schizophrenia in the UK. Br. J. Psychiatry 182, 505–508. https://doi.org/10.1192/bjp.182.6.505.

El-Badri, S., Mellsop, G., 2011. Clozapine use and outcomes among patients with treatment resistant schizophrenia. Australas. Psychiatry 19, 410–414. https://doi.org/10.3109/10398562.2011.602078.

Essali, A., Al-Haj Haasan, N., Li, C., Rathbone, J., 2009. Clozapine versus typical neuroleptic medication for schizophrenia. Cochrane Database Syst. Rev. https://doi.org/10.1002/14651858.CD000059.pub2.

Farooq, S., Choudry, A., Cohen, D., Naeem, F., Ayub, M., 2019. Barriers to using clozapine in treatment-resistant schizophrenia: systematic review. BJ Psych. Bull. 43, 8–16. https://doi.org/10.1192/bjb.2018.67.

Foust, K.D., Kaspar, B.K., 2012. The role of unconscious bias in surgical safety and outcomes. Surg. Clin. North Am. 92, 137–151. https://doi.org/10.1002/bmb.20244.DNA.

Freitas, D.F., Patel, I., Kadra-Scalzo, G., Pritchard, M., Shetty, H., Broadbent, M., Patel, R., Downs, J., Segev, A., Khondoker, M., MacCabe, J.H., Bhui, K., Hayes, R.D., unpublished manuscript. Ethnic inequalities in clozapine utilisation among people with treatment-resistant schizophrenia: a retrospective cohort study using electronic clinical records.

Govender, V., Penn-Kekana, L., 2008. Gender biases and discrimination: a review of health care interpersonal interactions. Glob. Public Health 3, 90–103. https://doi.org/10.1080/17441690801892208.

Hamberg, K., 2008. Gender bias in medicine. Women Health 4, 237–243. https://doi.org/10.2217/17455057.4.3.237.

Hayes, R.D., Downs, J., Chang, C.K., Jackson, R.G., Shetty, H., Broadbent, M., Hotopf, M., Stewart, R., 2015. The effect of clozapine on premature mortality: an assessment of

clinical monitoring and other potential confounders. Schizophr. Bull. 41, 644–655. https://doi.org/10.1093/schbul/sbu120.
Howes, O.D., McCutcheon, R., Agid, O., De Bartolomeis, A., Van Beveren, N.J.M., Birnbaum, M.L., Bloomfield, M.A.P., Bressan, R.A., Buchanan, R.W., Carpenter, W.T., Castle, D.J., Citrome, L., Daskalakis, Z.J., Davidson, M., Drake, R.J., Dursun, S., Ebdrup, B.H., Elkis, H., Falkai, P., Fleischacker, W.W., Gadelha, A., Gaughran, F., Glenthøj, B.Y., Graff-Guerrero, A., Hallak, J.E.C., Honer, W.G., Kennedy, J., Kinon, B.J., Lawrie, S.M., Lee, J., Leweke, F.M., MacCabe, J.H., McNabb, C.B., Meltzer, H., Möller, H.J., Nakajima, S., Pantelis, C., Marques, T.R., Remington, G., Rossell, S.L., Russell, B.R., Siu, C.O., Suzuki, T., Sommer, I.E., Taylor, D., Thomas, N., Üçok, A., Umbricht, D., Walters, J.T.R., Kane, J., Correll, C.U., 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. https://doi.org/10.1176/appi.ajp.2016.16050503.
The English indices of deprivation 2010 [WWW document]. URL. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/6320/1870718.pdf (accessed 2.4.21).
Jackson, R.G., Patel, R., Jayatilleke, N., Kolliakou, A., Ball, M., Gorrell, G., Roberts, A., Dobson, R.J., Stewart, R., 2017. Natural language processing to extract symptoms of severe mental illness from clinical text: the Clinical Record Interactive Search Comprehensive Data Extraction (CRIS-CODE) project. BMJ Open 7. https://doi.org/10.1136/bmjopen-2016-012012.
Kadra-Scalzo, G., Freitas, D.F., Agbedjro, D., Francis, E., Ridler, I., Pritchard, M., Shetty, H., Segev, A., Casetta, C., Smart, S., Morris, A., Downs, J., Christensen, S.H., Bak, N., Kinon, B.J., Stahl, D., Hayes, R., MacCabe, J.M., unpublished manuscript. Predicting treatment resistance in schizophrenia using clinical and demographic information: a predictor model using data from electronic health records.
Kent, J.A., Patel, V., Varela, N.A., 2012. Gender disparities in health care. Mt. Sinai J. Med. A J. Transl. Pers. Med. 79, 555–559. https://doi.org/10.1002/msj.21336.
Kirkbride, J.B., Fearon, P., Morgan, C., Dazzan, P., Morgan, K., Tarrant, J., Lloyd, T., Holloway, J., Hutchinson, G., Leff, J.P., Mallett, R.M., Harrison, G.L., Murray, R.M., Jones, P.B., 2006. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center ÆSOP study. Arch. Gen. Psychiatry 63, 250–258. https://doi.org/10.1001/archpsyc.63.3.250.
Krieger, N., 2014. In: Berkman, L.F., Kawachi, I., Glymour, M.M. (Eds.), Social Epidemiology. Oxford University Press. Oxford University Press, pp. 63–125 https://doi.org/10.1093/med/9780195377903.001.0001.
Lally, J., Ajnakina, O., Di Forti, M., Trotta, A., Demjaha, A., Kolliakou, A., Mondelli, V., Reis Marques, T., Pariante, C., Dazzan, P., Shergil, S.S., Howes, O.D., David, A.S., MacCabe, J.H., Gaughran, F., Murray, R.M., 2016. Two distinct patterns of treatment resistance: clinical predictors of treatment resistance in first-episode schizophrenia spectrum psychoses. Psychol. Med. 46, 3231–3240. https://doi.org/10.1017/S0033291716002014.
Lee, J., Jiang, J., Sim, K., Tay, J., Subramaniam, M., Chong, S.A., 2011. Gender differences in Singaporean Chinese patients with schizophrenia. Asian J. Psychiatr. 4, 60–64. https://doi.org/10.1016/j.ajp.2010.11.005.
Legge, S.E., Hamshere, M., Hayes, R.D., Downs, J., O'Donovan, M.C., Owen, M.J., Walters, J.T.R., MacCabe, J.H., 2016. Reasons for discontinuing clozapine: a cohort study of patients commencing treatment. Schizophr. Res. 174, 113–119. https://doi.org/10.1016/j.schres.2016.05.002.
Manuel, J.I., Essock, S.M., Wu, Y., Pangilinan, M., Stroup, S., 2012. Factors associated with initiation on clozapine and on other antipsychotics among medicaid enrollees. Psychiatr. Serv. 63, 1146–1149. https://doi.org/10.1176/appi.ps.201100435.
Meltzer, H.Y., 1997. Treatment-resistant schizophrenia - the role of clozapine. Curr. Med. Res. Opin. 14, 1–20. https://doi.org/10.1185/03007999709113338.
Meltzer, H.Y., Burnett, S., Bastani, B., Ramirez, L.F., 1990. Effects of six months of clozapine treatment on the quality of life of chronic schizophrenic patients. Hosp. Community Psychiatry 41, 892–897. https://doi.org/10.1176/ps.41.8.892.
Mistry, H., Osborn, D., 2011. Underuse of clozapine in treatment-resistant schizophrenia. Adv. Psychiatr. Treat. 17, 250–255. https://doi.org/10.1192/apt.bp.110.008128.
Mizuno, Y., McCutcheon, R.A., Brugger, S.P., Howes, O.D., 2020. Heterogeneity and efficacy of antipsychotic treatment for schizophrenia with or without treatment resistance: a meta-analysis. Neuropsychopharmacology 45, 622–631. https://doi.org/10.1038/s41386-019-0577-3.
NICE, 2014. Psychosis and Schizophrenia in Adults: Prevention and Management.
NICE, 2016. Psychosis and Schizophrenia [WWW Document]. NICE CKS, URL https://cks.nice.org.uk/psychosis-and-schizophrenia#!prescribingInfoSub.
Nielsen, J., Røge, R., Schjerning, O., Sørensen, H.J., Taylor, D., 2012. Geographical and temporal variations in clozapine prescription for schizophrenia. Eur. Neuropsychopharmacol. 22, 818–824. https://doi.org/10.1016/j.euroneuro.2012.03.003.
Novick, D., Montgomery, W., Treuer, T., Moneta, M.V., Haro, J.M., 2016. Sex differences in the course of schizophrenia across diverse regions of the world. Neuropsychiatr. Dis. Treat. 12, 2927–2939. https://doi.org/10.2147/NDT.S101151.
Office for National Statistics, 2011. 2011 census: population estimates for the United Kingdom. UK Census, pp. 1–12.
Patel, R., Wilson, R., Jackson, R., Ball, M., Shetty, H., Broadbent, M., Stewart, R., McGuire, P., Bhattacharyya, S., 2016. Association of cannabis use with hospital admission and antipsychotic treatment failure in first episode psychosis: an observational study. BMJ Open 6, 1–9. https://doi.org/10.1136/bmjopen-2015-009888.
Perera, G., Broadbent, M., Callard, F., Chang, C.K., Downs, J., Dutta, R., Fernandes, A., Hayes, R.D., Henderson, M., Jackson, R., Jewell, A., Kadra, G., Little, R., Pritchard, M., Shetty, H., Tulloch, A., Stewart, R., 2016. Cohort profile of the South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLaM BRC) case register: current status and recent enhancement of an electronic mental health record-derived data resource. BMJ Open 6, 1–22. https://doi.org/10.1136/bmjopen-2015-008721.
Raine, R., 2000. Does gender bias exist in the use of specialist health care? J. Heal. Serv. Res. Policy 5, 237–249. https://doi.org/10.1177/135581960000500409.
Rajagopal, S., 2005. Clozapine, agranulocytosis, and benign ethnic neutropenia. Postgrad. Med. J. 81, 545–546. https://doi.org/10.1136/pgmj.2004.031161.
Ring, N., Tantam, D., Montague, L., Newby, D., Black, D., Morris, J., 1991. Gender differences in the incidence of definite schizophrenia and atypical psychosis — focus on negative symptoms of schizophrenia. Acta Psychiatr. Scand. https://doi.org/10.1111/j.1600-0447.1991.tb03182.x.
Seeman, M.V., 2018. Clinical implications of gender differences in schizophrenia. Psychiatr. Times 35, 9–11.
Sen, G., Östlin, P., 2008. Gender inequity in health: why it exists and how we can change it. Glob. Public Health 3, 1–12. https://doi.org/10.1080/17441690801900795.
Si, T.M., Zhang, Y.S., Shu, L., Li, K.Q., Liu, X.H., Mei, Q.Y., Wang, G.H., Bai, P.S., Ji, L.P., Cheng, X.S., Ma, C., Shi, J.G., Zhang, H.Y., Ma, H., Yu, X., 2012. Use of clozapine for the treatment of schizophrenia: findings of the 2006 research on the China psychotropic prescription studies. Clin. Psychopharmacol. Neurosci. 10, 99–104. https://doi.org/10.9758/cpn.2012.10.2.99.
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. Br. J. Psychiatry 209, 385–392. https://doi.org/10.1192/bjp.bp.115.177261.
Smart, S.E., Kępińska, A.P., Murray, R.M., Maccabe, J.H., 2021. Predictors of treatment resistant schizophrenia: a systematic review of prospective observational studies. Psychol. Med. 51, 44–53. https://doi.org/10.1017/S0033291719002083.
Smith, S., 2010. Gender differences in antipsychotic prescribing. Int. Rev. Psychiatry 22, 472–484. https://doi.org/10.3109/09540261.2010.515965.
Socías, M.E., Koehoorn, M., Shoveller, J., 2016. Gender inequalities in access to health care among adults living in British Columbia, Canada. Womens Health Issues 26, 74–79. https://doi.org/10.1016/j.whi.2015.08.001.
Stewart, R., Soremekun, M., Perera, G., Broadbent, M., Callard, F., Denis, M., Hotopf, M., Thornicroft, G., Lovestone, S., 2009. The South London and Maudsley NHS Foundation Trust Biomedical Research Centre (SLAM BRC) case register: development and descriptive data. BMC Psychiatry 9. https://doi.org/10.1186/1471-244X-9-51.
Stroup, T.S., Gerhard, T., Crystal, S., Huang, C., Olfson, M., 2014. Geographic and clinical variation in clozapine use in the United States. Psychiatr. Serv. 65, 186–192. https://doi.org/10.1176/appi.ps.201300180.
Sukhera, J., Watling, C., 2018. A framework for integrating implicit bias recognition into health professions education. Acad. Med. 93, 35–40. https://doi.org/10.1097/ACM.0000000000001819.
Swinton, M., Ahmed, A.G., 1999. Reasons for non-prescription of clozapine in treatment-resistant schizophrenia. Crim. Behav. Ment. Health 9, 207–214. https://doi.org/10.1002/cbm.313.
Taylor, D.M., 2004. Prescribing of clozapine and olanzapine: dosage, polypharmacy and patient ethnicity. Psychiatr. Bull. 28, 241–243. https://doi.org/10.1192/pb.28.7.241.
Verdonk, P., Benschop, Y.W.M., De Haes, H.C.J.M., Lagro-Janssen, T.L.M., 2009. From gender bias to gender awareness in medical education. Adv. Health Sci. Educ. 14, 135–152. https://doi.org/10.1007/s10459-008-9100-z.
Warnez, S., Alessi-Severini, S., 2014. Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psychiatry 14. https://doi.org/10.1186/1471-244X-14-102.
Weinbrenner, S., Assion, H.J., Stargardt, T., Busse, R., Juckel, G., Gericke, C.A., 2009. Drug prescription patterns in schizophrenia outpatients: analysis of data from a German health insurance fund. Pharmacopsychiatry 42, 66–71. https://doi.org/10.1055/s-0028-1103293.
Wing, J.K., Beevor, A.S., Curtis, R.H., Park, S.B.G., Hadden, S., Burns, A., 1998. Health of the nation outcome scales (HoNOS): research and development. Br. J. Psychiatry 172, 11–18. https://doi.org/10.1192/bjp.172.1.11.
Wójciak, P., Domowicz, K., Andrzejewska, M., Rybakowski, J.K., 2020. Negative symptoms in schizophrenia, assessed by the brief negative symptom scale, self-evaluation of negative symptom scale, and social cognition: a gender effect. Int. J. Psychiatry Clin. Pract. 0, 1–6. https://doi.org/10.1080/13651501.2020.1810278.
Xu, S.-W., Dong, M., Zhang, Q., Yang, S.-Y., Chen, L.-Y., Sim, K., He, Y.-L., Chiu, H.F., Sartorius, N., Tan, C.-H., Chong, M.-Y., Shinfuku, N., Lin, S.-K., Ng, C.H., Ungvari, G.S., Najoan, E., Kallivayalil, R.A., Jamaluddin, R., Javed, A., Iida, H., Swe, T., Zhang, B., Xiang, Y.-T., 2019. Clozapine prescription pattern in patients with schizophrenia in Asia: the REAP survey (2016). Psychiatry Res., 1–6 https://doi.org/10.1016/j.psychres.2019.02.056.