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# An evaluation of the variation and underuse of clozapine in the United Kingdom

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## Abstract

**Background:** Clozapine is the only licensed treatment for treatment refractory schizophrenia. Despite this, it remains grossly underused relative to the prevalence of refractory schizophrenia. The extent of underuse and the degree of regional variation in prescribing in the United Kingdom is unknown. It is also unclear, how the UK compares with other European countries in rates of clozapine prescribing.

**Methods:** We obtained data relating to all clozapine prescribing in the UK from the relevant clozapine registries. We examined regional variation in clozapine use across England, corrected for the known prevalence of severe mental illness (SMI). We also compared the UK rate of clozapine use per 100,000 population to that described in other European countries.

**Findings:** There is substantial variation in clozapine prescribing across different regions of England and only about a third of potentially eligible patients were prescribed the drug in the UK. Clozapine prescribing rate in the UK was lower than in several European countries.

**Interpretation:** There is clear regional inequity in access to the most effective treatment in refractory schizophrenia in England. Strategies to increase clozapine use, by overcoming both real and perceived barriers, are urgently necessary to reduce treatment inequity for patients with refractory schizophrenia.

## KEY WORDS

clozapine, schizophrenia, United Kingdom, drug utilization, geography

## 1 | INTRODUCTION

Despite its unique effectiveness in treating refractory schizophrenia, substantial evidence indicates gross underuse of clozapine.<sup>1,2</sup> Aligned with the underuse is a demonstrable international variation in use of the drug.<sup>3</sup> Widespread geographical variation in usage has been reported in the United States,<sup>4</sup> Canada,<sup>5</sup> Middle East,<sup>6</sup> Europe<sup>7</sup> and the United

Kingdom.<sup>8</sup> The factors responsible for the underuse of clozapine are numerous, varied and often interconnected; these can be separated into four key domains relating to the drug itself, the prescribers, the patients and associated infrastructure and regulatory processes.

Clozapine causes neutropenia in about (3%)<sup>9</sup> of patients and the more severe agranulocytosis in (0.4%)<sup>10</sup> in treated patients. Haematological monitoring is therefore

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a necessity for treatment. One of the major barriers to clozapine use is the requirement for haematological monitoring.<sup>11-13</sup> Haematological monitoring has been described as a double-edged sword. On the one hand reducing the risk of clozapine-associated haematological toxicity, but on the other hand, it precludes its use among patients who experience transient neutropenia that is probably unrelated to the drug.<sup>14</sup> Other prominent hurdles include small but significant risks of myocarditis,<sup>15</sup> cardiomyopathy,<sup>16</sup> gastrointestinal obstruction,<sup>17</sup> obesity and metabolic syndrome,<sup>18,19</sup> epileptic seizures<sup>20</sup> and hypersalivation, occasionally leading to potentially fatal aspiration pneumonia.<sup>21</sup> Nevertheless, it has beneficial effects in reversing the severe neurological adverse effect, Tardive Dyskinesia (TD) caused by other antipsychotics.<sup>22</sup> Also, the significant interindividual differences in clozapine kinetics and challenges in use during pregnancy are additional difficulties.<sup>23</sup> Patients of African ancestry are especially disadvantaged with respect to clozapine utilisation, being less likely to be initiated on, and more likely to discontinue, treatment. This can be explained at least in part by Benign Ethnic Neutropenia (BEN),<sup>24,25</sup> the presence of low baseline white cell count, which can preclude initiation.

Prescribers' knowledge, views, attitudes and experience constitute a major factor in the variation and underuse of clozapine.<sup>11,12,26</sup> Surveys of prescribers have consistently demonstrated a lack of confidence or expertise in clozapine prescribing, negative perceptions, insufficient knowledge about its adverse effects and their management, as key limiting factors in limiting prescribing, and consequently, increased preference for less evidence-based prescribing of other antipsychotics in high dose and combinations.<sup>26,27</sup> Prescribers also express concerns about patient compliance with clozapine treatment and monitoring,<sup>28</sup> the presence of co-morbid medical conditions<sup>12</sup> and a reluctance about initiating clozapine in the community.<sup>29</sup> Where clozapine is more widely prescribed, there is often increase in experience and the development of expertise that serve to drive up prescribing standards.<sup>30,31</sup> For example, the National Psychosis Service under the South London & Maudsley NHS Foundation Trust is a tertiary referral service in the United Kingdom, specializing in the treatment of refractory schizophrenia. Data from the unit demonstrate improved outcomes in complex, refractory patients referred to the service.<sup>32-34</sup> A key aspect of the service is an extensive experience of the use of clozapine; and even in the very complex patients referred here, clozapine treatment rates are high and hospital bed utilisation post-discharge from the unit was significantly reduced compared with the period pre-admission.<sup>35</sup>

It is not clear if the underuse of clozapine prescribing is ubiquitous across the UK or if there is regional variation across the country. Earlier studies in England have used

### Significant outcomes

- Clozapine is grossly underutilized in the United Kingdom and overall, only a third of eligible patients receiving the treatment.
- The rate of clozapine per population is lower in England than other parts of the UK.
- In England, there is a three-fold variation in the rates of clozapine prescribing.

### Limitations

- This study only provides a snapshot of clozapine use in the UK in 2019 and does not provide information on the pattern of change in prescribing practice over time.
- We have used the prevalence of severe mental illness rather than the more specific prevalence of schizophrenia
- Data collection from the UK clozapine registries is not uniformly collected; thus, mapping precision is reduced.

estimated prevalence rates of severe mental illness with only partial coverage of the different regions.<sup>36,37</sup> Given that the evidence for its benefit is widely instantiated through National Institute for Health and Care Excellence (NICE) and regional guidelines,<sup>38</sup> local experience of successful use is likely to be the main predictor of use. This suggests that there will be significant regional variation across the country—with increased use around facilities with significant acquired experience. This also offers a potential solution for enhancing clozapine use—across all regions—predicated on developing a hub and spoke model<sup>39</sup> to increase local experience by leveraging regional or national expertise. The technology to enable such communication in an efficient and confidential manner has been significantly developed and tested during the recent covid-19 related lockdowns across the country.<sup>40</sup>

Here, we examine the regional variation in clozapine use across England, and contextualize that with respect to use in the United Kingdom and available data from other European countries.

## 1.1 | Aims of the study

The aim of our study was to evaluate the extent of underuse and the degree of variation in prescribing in the UK and to examine how the country compares to other European countries in the rate of clozapine prescribing.

**TABLE 1** Clozapine prescribing rate in UK in relation to UK population.

Country	Total population	Total adult population (>16 years)	No of clozapine patients	Clozapine/100,000 adult population
UK total	66,796,800	53,813,814	37,301	69.3
England	56,286,961	45,229,559	30,471	67.3
Scotland	5,463,300	4,519,061	3,600	79.6
Wales	3,152,872	2,576,816	1984	77
N. Ireland	1,893,667	1,488,378	1246	83.7

## 2 | METHOD

In October 2019, we contacted all three clozapine registries in the United Kingdom to obtain details of the current number of patients on their register. All the data were received by November 2019. The supply and monitoring of clozapine in the United Kingdom is undertaken by three registries, namely, Clozaril Patient Monitoring Service (CPMS), Zaponex Treatment Access System (ZTAS) and Denzapine Monitoring System (DMS). Any patient prescribed clozapine must be registered with one of these three services and can only be registered with only one of the three at any given time. There is no evidence that there are differences in the services provided, nor is there an effect on the number of patients enrolled on clozapine treatment. There are no specific geographic demarcations or boundaries in the areas covered by these registries. In broad outlines, ZTAS covers most of Scotland, Wales, Northern Ireland, areas in London and North West England. DMS covers most of the East of England and the West Midlands while CPMS covers many areas in the North and South of England.

We applied two different approaches to explore the rate of clozapine prescribing. To investigate the variation in clozapine prescribing in England, we used our first approach. Here, we sought to determine clozapine prescribing per prevalence of severe mental illness. To evaluate this, prevalence figures for Severe Mental Health Disorders were obtained from Public Health England based on the number of people on the Quality Outcomes Framework (QOF) register for mental health which includes people with schizophrenia, bipolar disorder or other psychoses or on lithium therapy. (The National Health Service (NHS) is a large and complex organisation and readers are referred to for an overview to <https://www.england.nhs.uk/participation/nhs/>).

The number of patients with the diagnosis of a severe mental illness in each General Practitioner (GP) list was combined to provide a gross number at the NHS regional NHS office level. These figures were then normalized per 100,000 population to allow comparison between the different NHS regions. Details of clozapine prescriptions provided by separate registries were matched to the NHS England regional office or matched directly to these areas where granular location data was unavailable. Again, these data were also

normalized per 100,000 population using the same Clinical Commissioning Group (CCG) practice list sizes aggregated to NHS England Regional Office area. The relationship between clozapine prescription and estimated clozapine demand in each region was calculated. This was the ratio of the number of clozapine prescriptions per 100,000 population to the estimated number of people per 100,000 population with treatment refractory severe mental illness (a proxy for those eligible for clozapine). This value was expressed as the percentage of people prescribed clozapine considering the total number eligible for clozapine.

Secondly, to compare UK clozapine prescribing rates with that observed in other countries, we applied the method of Bachmann et al. (2017),<sup>3</sup> that estimates the number of clozapine patients per 100,000 population. It is based on worldwide prevalence of schizophrenia of 0.5–0.7%. Using an assumption that a third of patients with schizophrenia are treatment resistant, optimal clozapine use is estimated at 0.2%, that is, 200/100,000 of the adult population. We obtained 2018 UK population figures from the Office of National Statistics.<sup>41</sup>

## 3 | RESULTS

### 3.1 | Clozapine use in the United Kingdom

In November 2019, there were 37,301 patients prescribed clozapine in the UK. See Table 1 below. There is some variation in the clozapine use between the countries in the UK with greater use in Northern Ireland relative to England when corrected for the population.

### 3.2 | Clozapine prescribing rate in Regions of England

There is a wide variation in prescribing of clozapine between the different regions of England, the range varying from 35 to 83 clozapine prescriptions per 100,000 of the adult population (See Table 2 and Figure 1). Using a threshold of  $\geq 65$  patients/100,000 population as standard, the following regions—Greater Manchester, West Midlands, London and Lancashire and South Cumbria had higher prescription

TABLE 2 Clozapine prescribing rate in Regions of England.

NHS England Regional Office Name	Key (see map)	Clozapine prescription per 100,000 population	SMI prevalence per 100,000 population	Prescription % per prevalence
NHS England London	12	66.57	1,080.57	6.16%
NHS England North West (Cheshire and Merseyside)	5	62.40	1,039.68	6.00%
NHS England Midlands (North Midlands)	6	39.97	804.63	4.97%
NHS England Midlands (West Midlands)	8	72.60	567.16	12.80%
NHS England North West (Greater Manchester)	4	82.71	1,005.70	8.22%
NHS England North West (Lancashire and South Cumbria)	2	65.34	1,048.19	6.23%
NHS England South East (Hampshire, Isle of Wight and Thames Valley)	11	40.78	548.94	7.43%
NHS England South East (Kent, Surrey and Sussex)	13	41.38	838.70	4.93%
NHS England South West (South West North)	10	35.90	478.79	7.50%
NHS England South West (South West South)	14	43.80	898.01	4.88%
NHS England Midlands (Central Midlands)	7	43.86	816.48	5.37%
NHS England East of England (East)	9	35.26	821.72	4.29%
NHS England North East and Yorkshire (Cumbria and North East)	1	53.58	935.75	5.73%
NHS England North East and Yorkshire (Yorkshire and Humber)	3	37.56	719.60	5.22%

rates. Whereas, using a threshold of  $\leq 40$  patients/100,000 population as a proxy, East of England, South West England (North), Yorkshire and Humber and North Midlands would be in the category of lower prescribing rates.

### 3.3 | Clozapine prescription adjusted for prevalence of severe mental illness disorders

The prevalence of severe mental illness per 100,000 of population also varied across regions of England, from 479 in the South West to 1081 in London (See Table 2 and Figure 1). Adjusting the clozapine use per head of population as a proportion of the prevalence of severe mental health per head of population revealed a three-fold difference in clozapine prescribing between different regions of England (see Figure 1). The highest prescription per prevalence 12.8% was recorded in West Midlands while four regions recorded rates less than 5%—in the East of England, South West England (South), South East England and North Midlands.

### 3.4 | Clozapine prescribing rate in UK in comparison with other European countries

We compared the overall clozapine prescribing rate in the UK with other European countries based on the data by Bachmann et al., 2017. See Table 3 below. Given that

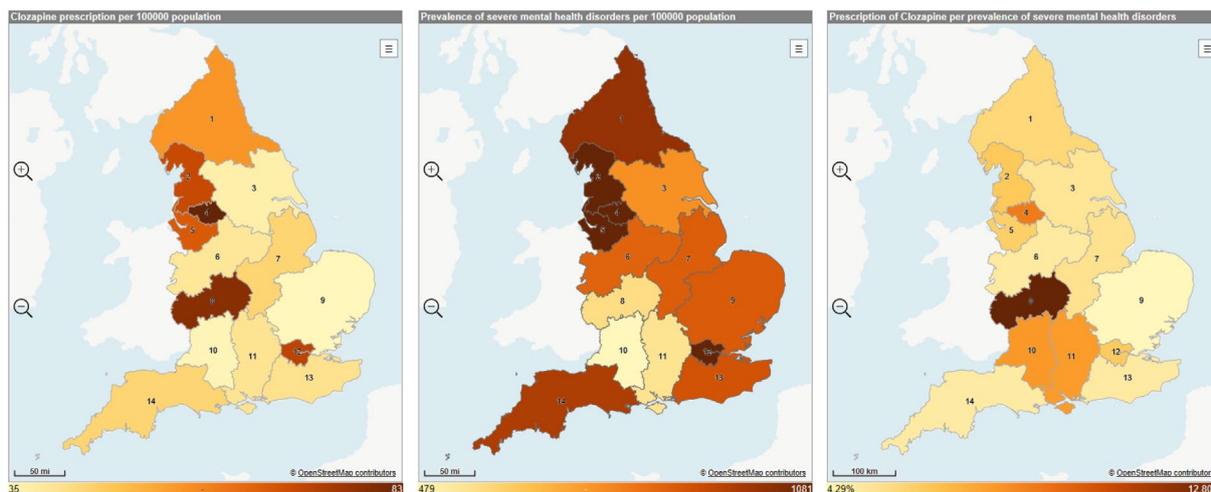
clozapine use has increased over the decade, the UK figures from 2019 is still substantially lower than countries like Finland, Netherlands and Iceland, but may be higher than countries like Italy, France and Spain.

## 4 | DISCUSSION

Clinical guidelines from NICE and other organisations have been published recommending that clozapine be offered at the earliest opportunity for patients with treatment-resistant schizophrenia.<sup>34</sup> These recommendations were intended to address well-documented underuse of clozapine despite extensive literature establishing its therapeutic superiority.<sup>42</sup> In the present study, we demonstrate that there is still under utilisation of clozapine and a marked regional variation when examining clozapine prescription rates in the United Kingdom.

Within the UK, clozapine prescribing rates vary widely with rates lower in England with significant regional variation. Using the index of rates of prescribing per 100,000 population, there is greater than a two-fold variation in England with the highest rates in Greater Manchester and the West Midlands and the lowest rates in the East of England, South West, Yorkshire and Humber.

There is naturally a variation in the incidence and prevalence of schizophrenia in the UK.<sup>43</sup> Inner city and more deprived areas are associated with a higher prevalence of psychotic disorders.<sup>44,45</sup> Furthermore, rates of schizophrenia are



A: Clozapine prescriptions/100,000 population    B: SMI prevalence/100,000 population    C: Prescription per prevalence

FIGURE 1 Variation in clozapine prescribing in the United Kingdom. [Colour figure can be viewed at wileyonlinelibrary.com]

TABLE 3 UK prevalence of clozapine use per 100,000 persons in comparison to European countries\*

Country	Clozapine prescription per 100,000 persons
Finland	189
Netherlands	103
Iceland	100
Germany	95
United Kingdom	69
Sweden	61
Denmark	58
Norway	50
Spain	49
France	43
Italy	42

\*Adapted from Bachmann et al. (2017).<sup>3</sup>

elevated in certain ethnic minority groups compared with the white British population.<sup>46,47</sup> Thus, a far more representative model is the rate of clozapine prescribing per severe mental illness (SMI) prevalence in 100,000 population. Using this model, we similarly find a three-fold variation in prescribing rates with the highest rate in the West Midlands and lowest in the East of England.

#### 4.1 | Comparison with other studies

This is the only large-scale study to estimate rates of clozapine prescriptions in the UK. In accordance with the present

findings, earlier more selective studies have demonstrated substantial geographical variations in clozapine usage.<sup>8,32</sup> In a retrospective cohort study, a 34-fold variation in clozapine prescribing practices among 12 mental health trusts in the Greater Manchester region was shown over 2 years.<sup>32</sup> Such findings were later reaffirmed, where a reduction to 16-fold variation in prescribing was reported.<sup>48</sup> The authors attributed this reduction in geographic variation to the expiry of clozapine's patent and the publication of the national guidelines<sup>49</sup> reiterating clozapine's position in Treatment Refractory Schizophrenia (TRS). Thus, our findings provide evidence that although there have been improvements over the last decade, geographic variation in clozapine prescription rates is still persistent on a large scale in England. This has significant implications for the suffering of these undertreated patients, family, carers and the wider socio-economic milieu. These patients will often need continuing medical care in hospital and are among the most intensive users of inpatient services, the costliest option in mental health services. These costs could potentially be substantially reduced if this subgroup were identified earlier and appropriate treatment offered sooner.

One possible explanation for the variation in prescribing could be the higher prevalence of TRS in certain areas of the UK, although this is unlikely. Previous studies have found that established environmental risk factors for schizophrenia such as urban environment does not predict treatment-resistance, and in fact were negatively correlated with treatment-resistance.<sup>50</sup> While part of this variation may also have been because of medically legitimate reasons such as differences in the prevalence of comorbidities, previous studies have not highlighted this as a reason for clozapine underuse. A more plausible reason for the observed variation

is as a consequence of differences in prescribing practice between clinicians, as observed in the United States<sup>4</sup> and Denmark.<sup>7</sup>

Interestingly, our findings show lower usage of clozapine in the UK (69/100,000) relative to other European countries such as Finland (189/100,000), Iceland (100/100,000), Germany (95/100,000) and the Netherlands (103/100,000), but it is higher relative to France (43/100,000) and Italy (42/100,000).<sup>3</sup> The underlying reasons for these between-country differences are difficult to ascertain given the different health provision systems; however, the highest use is certainly in smaller countries with smaller populations where it is possible that expertise in clozapine use may consequently be more easily accessible. In addition, while the UK's relative underuse is undoubtedly a result of a multiplicity of different factors, previous studies have broadly shown prescription rates to be lower where prescribing regulations and monitoring requirements regarding clozapine are more stringent, such as the UK.<sup>51</sup> The conclusions that can be drawn are further limited because of the lack of comparative prevalence data on severe mental disorders across these countries.

## 4.2 | Clozapine underuse

It is estimated that a third of patients with schizophrenia are treatment resistant.<sup>52,53</sup> The estimated prevalence of schizophrenia across all ages in the UK is 0.7% (NICE). Based on the 2018 adult population, there are 377,000 people living with schizophrenia in the UK. From this figure, the projected number of patients with TRS is 125,000. Our results show that less than a third of potentially eligible patients currently receive clozapine in the UK. This correlates highly with our estimate based on clozapine prescriptions per 100,000 population as well as clozapine prescribing per SMI prevalence. There is therefore an urgent need to address the underuse of evidence-based, potentially life prolonging treatment in patients with schizophrenia.

Surveys of patients prescribed clozapine show a broadly positive view of treatment. In a survey of 570 patients on clozapine treatment, the overwhelming majority (89%) would prefer to stay on clozapine and a similar percentage claim to feel better on clozapine than on previous treatments.<sup>54</sup> In another survey of patients not prescribed clozapine, only about half had heard about clozapine, but the greatest barrier to clozapine initiation appears to be the perceived necessity for hospital admission.<sup>12</sup> Yet, there remains among clinicians, inadequate knowledge about clozapine, lack of clozapine prescribing experience, fear of side effects and lack of knowledge in dealing with these.<sup>11-13,26</sup> It is apparent that strategies to overcome these barriers to clozapine prescribing are required. One obvious area of interest is an educational approach for prescribers to improve utilisation rates.

Indeed, survey evidence suggests that a lack of experience during training is a specific barrier to the more widespread use of clozapine and that clinicians often overestimate patient dissatisfaction with clozapine therapy.<sup>55</sup> Overall, these findings may be indicative of the hesitancy to initiate patients on clozapine and its status as a last-resort treatment option.

## 4.3 | Clinical implications

Variation in clozapine prescribing practice in refractory schizophrenia invariably leads to the poorly evidenced use of antipsychotics in high dose and in combination—and consequent delays in clozapine prescribing. There is now accumulating evidence that delay in clozapine initiation is associated with worse clinical outcomes.<sup>56,57</sup> Optimum benefit from clozapine treatment is achieved at the earliest clinical determination of treatment refractoriness. More importantly, various studies demonstrate reduced mortality, especially suicide risk in TRS patients prescribed clozapine,<sup>58-60</sup> with one study showing a nearly two-fold higher mortality in TRS patients not prescribed clozapine compared with individuals treated with clozapine.<sup>61</sup> This variation in prescribing illustrates the inequity in accessibility to clozapine, which for some patients is a matter of life and death.

Calls for organizational and educational efforts to promote evidence-based psychiatric treatments, including clozapine in TRS, have been made well over a decade ago.<sup>62</sup> At present, there is no established or consistent approach to the training of clozapine medicine management in TRS for clinicians in the UK. As demonstrated by preliminary data from the US, training clinicians in the use of clozapine may not only improve antipsychotic pharmacology with chronic patients and address geographical variations but lead to timely clozapine use in early-course schizophrenia.<sup>63</sup> However, further study is warranted on strategies and reasons for observed geographical variation in clozapine prescription rates.

A service option that has been successful in disseminating expertise in relatively rare disorders has been a hub and spoke model—this offers an avenue to share expertise and develop knowledge and experience in managing complex presentations with the support of a central centre of expertise.<sup>39</sup> However, further work is required to determine the impact, including cost-effectiveness of this model in the management of TRS.

## 4.4 | Limitations & future studies

While our results provide a comprehensive benchmark for clozapine prescription rates in the UK, there are study limitations to highlight. Importantly, national data

extracts do not provide information about the number of individuals with schizophrenia among the SMI prevalence. Furthermore, measuring the prevalence of mental health problems is challenging for many reasons such as variation in diagnostic practices across the country. Nevertheless, based on conservative estimates, it is reasonable to expect at least 1 in 5 patients on the SMI to be prescribed clozapine. In this paper, we have sought to explore the extent of underuse and variation of clozapine use in the UK. It is beyond our scope to thoroughly understand the reasons for this variation. Similarly, it is beyond the scope of this paper the variations in clozapine prescribing across Europe. More research is required to elucidate the factors underlying these variations.

## 5 | CONCLUSIONS

There is gross underuse of clozapine in the UK together with substantial variation in prescribing. Only a third of patients eligible for clozapine are prescribed. Overall prescribing of clozapine in England is lower than in other parts of the UK. This can be best explained by the significant variability in clozapine prescribing in England where there is a three-fold variation in prescribing rates. There is an urgent need to address the various barriers to clozapine use.

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## DECLARATION OF INTERESTS

None declared.

## AUTHOR CONTRIBUTIONS

The project was conceived, designed, implemented and written by EW and SSS. The initial draft was made by EW and EO. AB collated and mapped the data. OD reviewed the methodology and DT made substantial contribution in revising the manuscript. All authors contributed to the drafting and revision of the final manuscript.

## DATA AVAILABILITY STATEMENT

Data subject to third party restrictions: The data that support the findings of this study are available from UK clozapine registries. Restrictions apply to the availability of these data, which were used under license for this study. Data are available from the authors with the permission of the registries.

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