

Competence and confidence of health care professionals in using clozapine: a qualitative systematic review and thematic synthesis

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Abstract

Background: Clozapine is the only licensed medication for treatment-resistant schizophrenia, although it is underused. Healthcare professionals (medical and non-medical professionals) play a crucial role in the management of clozapine. Consultant psychiatrists are accountable for the initiation of clozapine, whereas non-medical professionals are often responsible for the monitoring, the management of side effects and patient education. It appears that healthcare professionals' (HCPs) competence and confidence may have an effect on clozapine underutilisation.

Aim: To synthesise the most pertinent literature examining the factors influencing HCPs competence and confidence in the management of clozapine and how these factors influence variation in prescribing practice.

Methods: A review of the literature focusing on these elements was conducted. The Population, Context, Outcome (PCO) framework was adopted to support the literature search. The databases Medline, Psycinfo, Scopus, Cinahl, Pubmed, Embase, British Library, Eprints e-thesis, Google Scholar, Dart Europe e-thesis were consulted; the search was completed in January 2025. Screening, selection, data extraction and quality assessment were conducted independently by two researchers. Thematic analysis was used to investigate and compare the data emerging from the studies.

Results: Thirty-four articles were included in the review. Six themes were identified: attitude toward and knowledge about clozapine, misconceptions (regarding side effects, monitoring and co-morbidities), guidelines, education, training and experience. HCPs self-reported as competent with guidelines (local and national), yet they expressed less confidence in their ability to adhere to them and were uncertain about managing side effects. Lack of education, training and insufficient exposure to clozapine management were significant factors impacting competence and confidence, resulting in clozapine underuse and variance in prescribing practice. The review highlighted a gap in the literature, as only a few studies involving non-medical professionals were found.

Conclusions: A general lack of education and training related to clozapine use was identified amongst all professionals.

The impact of educational programmes on improving competence and enhancing confidence was considered positive, however when integrated with clinical practice.

The studies identified in this review were lacking in the involvement of non-medical professionals. Given their crucial role in managing side effects and educating patients and carers, it is evident that their inclusion in future research is imperative.

Keywords: Clozapine, Treatment-resistant schizophrenia, Competence, Confidence, Knowledge, Experience, Attitude, Training, Education

Summations

The review highlighted gaps in knowledge and experience related to the prescribing and management of clozapine among all professionals. The initiation of clozapine remains under the oversight of medical professionals, who continue to face challenges when starting the medication. However, discontinuation rates pose a significant barrier to clozapine use, with more professionals seemingly involved in this issue.

Training can enhance competence in clozapine management if it is integrated with education and experience. This training should be made available to all professionals (medical and non-medical), not just those in training.

Dedicated clozapine clinics staffed to support clozapine initiation, along with access to specialist advice services for managing the most complex cases, can bolster confidence in the use of clozapine.

Considerations

The level of competence and confidence (of all professionals) described in the studies included in the review might be overestimated, as in the majority of the cases, these were self-reported. Therefore, it is plausible to believe that more professionals might have difficulties in using clozapine.

It might be difficult to develop and implement training programmes that include teaching and experience, as different professionals might have different needs.

Although useful, special clozapine services might deskill those professionals not operating within these services. Energies and resources need to be spent to expand these services and to ensure that professionals working in mental health spend time within these services and are exposed to clozapine management.

Background

Treatment-resistant schizophrenia (TRS) is defined as a lack of response to two different antipsychotics prescribed at an adequate dose and duration of time of 6 weeks (Meltzer, 1997)(NICE, 2014). It is estimated that TRS occurs in 30% of patients with a diagnosis of schizophrenia (3). The only licensed medication available for the treatment of this condition is the antipsychotic clozapine.

Despite the proven efficacy, clozapine use has been sub-optimal since it was introduced to the market in 1960 (Naber, Haasen and Perro, 2000). The need for regular haematological blood monitoring tests (Nielsen *et al.*, 2016) and severe side effects might discourage its use (Stahl, 2021),(de Leon *et al.*, 2020). However, it appears that fear of side effects is a concern for the health care professionals (HCPs) (medical and non-medical health care professionals) more than patients who are on clozapine treatment (Hodge and Jespersen, 2008) and it might be related to a lack of expertise and knowledge (Moody and Eatman, 2019).

Bachmann *et al* (2017), estimate that an optimal treatment rate for clozapine should be 0.2% of the general population, however, its use varies between countries, regions and areas of the same country, hence it is not standardised (Bachmann *et al.*, 2017) (Bogers *et al.*, 2016) (Stroup *et al.*, 2014). Previous studies have suggested that prescribing variation and underutilisation might be due to cultural factors in managing clozapine rather than diverse incidences of TRS (Tungaraza and Farooq, 2015).

The underutilisation of clozapine and barriers to its use have been described and discussed in previous studies. Farooq *et al.* (Farooq *et al.*, 2019) have summarised these barriers in three points: those related to patients, those related to the professionals and those related to the healthcare system. These barriers are, in part, a consequence of the inadequate support patients face because of the lack of availability of skilled staff able to manage clozapine. Education, structured dedicated clinics and the use of the Point of Care (POC), capillary testing machines instead of venepuncture blood testing seem to be the most effective facilitators according to a systematic review by Baig *et al* (2021). A literature review by Thien and O'Donoghue (Thien and O'Donoghue, 2019) has reinforced the long delay before clozapine initiation. It appears that this issue is consistent across different countries and is partly caused by apprehension and diffidence of HCP towards the use of this medication. The authors advocate for the implementation of education plans as well as for the establishment of a dedicated service to help these patients. However, a dedicated service needs to be run by

“experts”. This can be achieved only by upskilling professionals, developing their competence and improving their confidence.

Examining these characteristics, competence is defined as an attribute that individuals should have to be able to do their job (Health Education England, 2020). At the same time, confidence is acknowledged as an important component of the way professionals perform. It is linked to self-esteem, trust and the ability to deal with challenges when these arise, although it is not a synonym for competence (Owens and Keller, 2018). Indeed, sometimes, professionals who rate themselves well educated, informed, and hence competent, struggle with the confidence to apply what they know in “real-world situations”. Conversely, an excess of confidence can lead to a false self-perception of being competent even when this is not the case. As a result, professionals might become unconsciously incompetent, missing out on opportunities to acquire the requisite knowledge.

The research investigating competence and confidence in the use of clozapine is limited. It would be important to explore the factors that influence these components and their contribution to variations in clozapine prescribing and management in clinical practice (Bachmann *et al.*, 2017), (Whiskey *et al.*, 2021), (Downs and Zinkler, 2007).

Aim

To synthesise the most pertinent literature examining the factors influencing HCPs’ competence and confidence in the management of clozapine and how these factors influence variation in prescribing practice.

Review question

What factors influence professionals’ competence and confidence in the management of clozapine and how might these factors influence variation in prescribing practice?

Methods

This systematic review (SR) was conducted using the guidelines outlined in the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (Page *et al.*, 2021). A protocol for this SR was generated and registered with PROSPERO with the number CRD42022346000.

The PCO (population, context, outcome) framework, a simplified version of the PICO framework, was developed to support the literature search. The population was professionals able to prescribe clozapine; health care professionals involved in the management of clozapine and caring for patients with a diagnosis of treatment-resistant schizophrenia (TRS). The context included clozapine, clozapine clinics, and hospitals. The outcomes were knowledge, experience, confidence, and competence of the health care professionals involved in the care of patients with a diagnosis of TRS and using clozapine and variation in prescribing.

Inclusion criteria

Studies published in English, after 1989 (date when clozapine was re-introduced into the market after being discontinued); studies involving HCPs caring for patients over 18 years old with a diagnosis of TRS and on clozapine were included.

Exclusion criteria

Studies published before 1989; studies published in a language other than English; studies involving HCPs caring for patients under 18 years old; studies involving patients with a diagnosis different from TRS.

Search strategy:

This search was completed in October 2022 and updated in January 2025, using the following databases: Medline, Psychinfo, Scopus, Cinahl, Pubmed, Embase, British Library, Ethos e-thesis, Google Scholar, Dart Europe e-thesis. Additionally, references of references and the grey literature were retrieved and extensively searched. No restriction in study design was applied.

The studies discussed above, focusing on barriers to clozapine, were used to generate keywords and search terms for the SR. These words were clozapine, competence, confidence, variance, and prescribing. Synonyms and related truncation were used in combination, using the Boolean operators across all databases. Free text search and medical subject headings (MeSH) were used to identify additional terms related to the 5 keywords (Table 1).

Table 1

Search Strategies, terms and Boolean and database search

S1: "Clozapine/AD/AE/AN/AA/BL/CT/DE/EC/EI/IM/ME/PD/PK/PO/TU/UR") OR
"clozapine" OR "clozaril" OR "zaponex" OR "denzapine" OR "leponex"

S1: "competence" OR "knowledge" OR "expertise" OR "capability" OR "ability" OR "capa*" OR (MH "Education+") OR (MH "Academic Performance+") OR (MH "Professional Competence+/AM/EC/ED/EI/PF/TD/UT")

S3: (MH "Confidence/DE/CL/ED/EI/TD/PC") OR "confidence" OR "self-efficacy" OR "self-reliance" OR "self-assurance" OR (MH "Behavior and Behavior Mechanisms/DE/ED/EI/TD/PC")

S4: "variance" OR "variant" OR "dissimilar" OR "different" OR "diversity" OR (MM "Cultural Diversity/ED/EV/PF/TD/PC/OG/UT")

S5: (MM "Prescribing Patterns/AM/TD/UT/EI/ED/EC") OR (MM "Inappropriate Prescribing/EC/ED/TD/PF/ST/LJ") OR (MM "Teaching: Prescribed Activity-Exercise (Iowa NIC)") OR (MM "Teaching: Prescribed Medication (Iowa NIC)") OR (MM "Knowledge: Prescribed Activity (Iowa NOC)") OR "prescribing" OR (MH "Medication Side Effects (Saba CCC)") OR (MH "Medication Compliance") OR (MH "Medication Actions (Saba CCC)") OR (MH "Drug Substitution") OR (MH "Knowledge Deficit of Medication Regimen (Saba CCC)")

Limiters:

Date of publication: >1980

Language: English

Age: >18 years

Screening and selection

Studies retrieved from the databases listed above were entered into Rayyan®, a web application used for systematic reviews. From the initial 9835 articles uploaded, 3166 were removed as identified as duplicates by the web application, leaving 6669 titles to be screened. This includes 653 studies (after removal of duplicates) identified from an updated search conducted in January 2025.

Titles, abstracts, and full texts were screened by AS and SN independently; a blinding operation was applied to prevent the reviewers from seeing each other's decisions during the screening process. Reasons for exclusion were recorded in Rayyan®. Characteristics of excluded studies at the title and abstract screening stage included wrong medication, too generic, wrong population, and wrong outcome. For example, some of the studies referred to the management of antipsychotics other than clozapine or the general management of schizophrenia; other studies did not focus on the professionals' ability to manage clozapine, but on strategies to administer or to enforce clozapine on patients; the majority of these studies did not meet the main scope of this review as they did not focus on the competence, confidence of professionals in managing clozapine. Any disagreement was discussed between the two reviewers and included the wider team, TT and SS to achieve a shared agreement. Upon request to the corresponding author, tables (2 and 3) outlining the rationale behind the exclusion of papers at the abstract and full-text screening stages are available as supplementary material.

Data extraction

Data were extracted from the identified studies for the purpose of this study. A Cochrane tool (available as supplementary data) was redesigned to collect information about competence, confidence of professionals, and variation of clozapine prescribing. The tool was first piloted with two studies, then amended according to reviewers' comments. Competence and confidence of professionals and variation in prescribing practice were identified as key concepts and were expected to be reported in various styles; therefore, to avoid misinterpretation, two reviewers, AS and SN, extracted data independently using the tool. The data extraction was conducted using an iterative approach; reading the papers, extracting and synthesising the data in different cycles, so that codes were added when newly identified. An “inclusive” approach, as described by Thomas and Harden (Thomas and Harden, 2008), was used to extract data, meaning all eligible information outlined in the studies was

extracted, whether it was described in the results or debated in the discussion in the form of the authors' interpretation. The iterative approach used when extracting data allowed a greater familiarity with the content of the studies. The software NVIVO (Release 1.0, 2020) ® ('NVivo qualitative data analysis software', 2020), was used to aid data extraction.

Although time-consuming, this method helped to store a large amount of data that could be consulted several times.

Methods of synthesis/analysis

The multiple pieces of data extracted were synthesised using the thematic analysis described by Thomas and Harden (Thomas and Harden, 2008). Firstly, open coding (line by line) was used to include all meaningful findings and to avoid a selection of codes dictated by prejudiced ideas. This also helped to preserve consistency across the studies. This process was carried out independently by AS and SN. A framework of codes was created after the screening of the first studies. Then this was discussed, agreed and adopted for all studies. Reviewers met regularly to discuss the coding throughout the process. Moreover, additional codes were identified and generated as the analysis progressed and papers were consulted and reviewed multiple times for this purpose; in a back-and-forth process. In the second stage, correlated codes were grouped to generate descriptive themes. Papers were reviewed to guarantee adherence and fidelity of the themes to the original documents and to confirm that they were represented in the data. In the third and last stage, links between descriptive themes were identified and developed further to generate analytical themes useful to answer the research question.

Quality assessment

The quality of the studies was assessed using the Critical Appraisal Skills Programme (CASP) (CASP UK, 2018). The appropriate checklist was used for the identified studies. As CASP does not provide a scoring system, a convenient scoring system was utilised, assigning 1 point for a "yes" answer, 0.5 points for a "non-clear answer" and 0 for a "no answer". CASP was used because of its structured and clearly presented questionnaire. Moreover, CASP can be used in qualitative evidence synthesis, hence its usefulness in this review (Hannes and Macaitis, 2012).

Ethics and informed consent

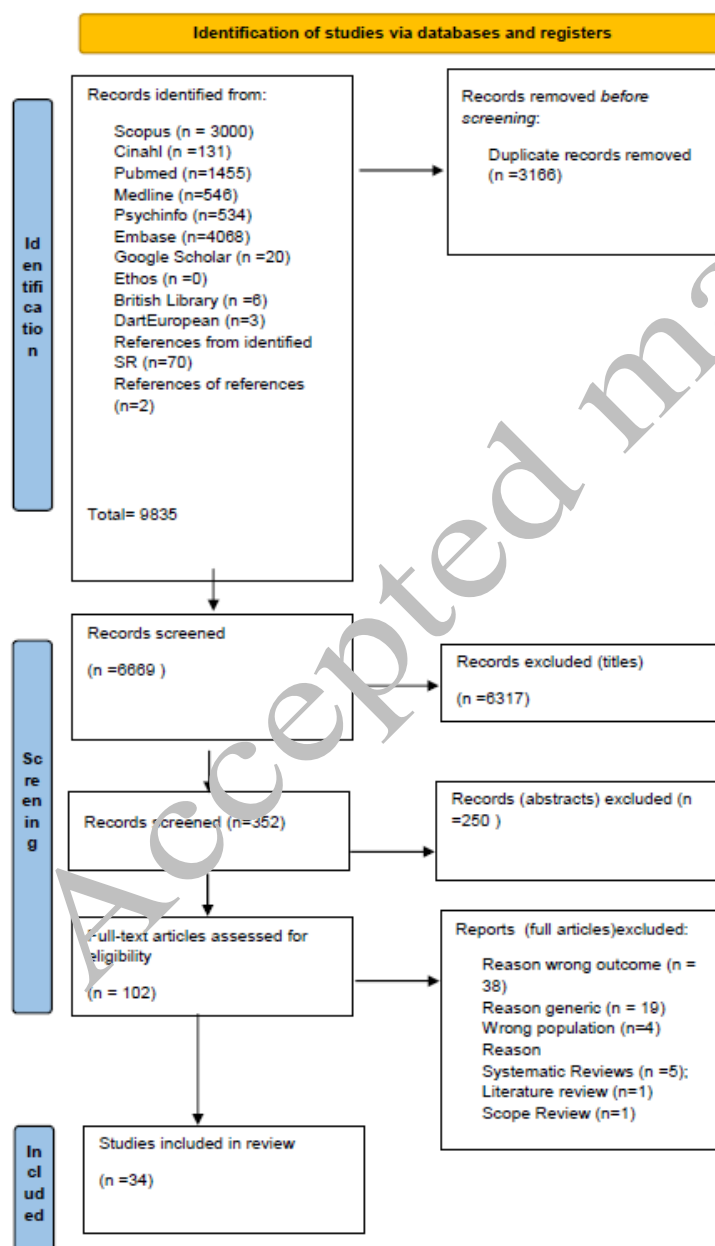
Ethics and informed consent were not required for this systematic review, as the information extracted is freely available in the public domain and informed consent was obtained by the authors of those studies at the time of original data collection.

Results

From the 9835 initial records identified, 34 met the eligibility criteria and were included in the review. Two of the studies were identified from the updated search conducted in January 2025 and included.

The Prisma diagram (Figure 1) shows the details of the screening process with reasons for the exclusion of full articles.

Figure 1 PRISMA 2020 flow diagram for new systematic reviews which included searches of databases and registers only



Selected studies were carried out in different countries, 9 in the UK (H. and S., 2000) (Whiskey *et al.*, 2003) (Paranthaman and Baldwin, 2006) (Downs and Zinkler, 2007) (Gee *et al.*, 2014) (Tungaraza and Farooq, 2015)(Whiskey *et al.*, 2021) (Oloyede, Mantell, *et al.*, 2022) (Oloyede *et al.*, 2023), 6 in the US (Mishara, Orr and Buckley, 1995) (Freudenreich *et al.*, 2013) (Singh, Hughes and Roerig, 2020) (Dvalishvili, Miller and Surya, 2021) (Cotes *et al.*, 2022) (Leung *et al.*, 2019), 6 in Asian countries (Shrivastava and Shah, 2009) (Grover *et al.*, 2015) (Si *et al.*, 2012) (Xu *et al.*, 2020) (Takeuchi *et al.*, 2016) (Xiang *et al.*, 2017), 7 in European countries (Nielsen *et al.*, 2010) (de Hert *et al.*, 2016) (Sanjeevi and Coker, 2020) (Verdoux *et al.*, 2016) (Sanz-Fuentenebro *et al.*, 2019) (Schou, Drange and Sæther, 2019) (Grant *et al.*, 2024), one in Serbia (Ignjatovic Ristic, Cohen and Ristic, 2021), one in Canada (Latimer *et al.*, 2013), one in Israel (Daod *et al.*, 2019), one in Australia (Hodge and Jespersen, 2008), one in Iran (Rezaie, Nazari and Khazaie, 2023). One was a study conducted on a large-scale using data retrieved from 17 countries (Bachmann *et al.*, 2017). The outcome of the studies varied in different aspects, for example, in the methodology, sample, settings, and purpose. Twenty-four studies used surveys or questionnaires to collect data. Two involved nurses, 2 patients, 12 consultant psychiatrists, 3 resident doctors, 4 a combination of psychiatrists, nurses, pharmacists, and other professionals, 1 included clinical staff (not specified). The rest (n=10) utilised an existing database reporting the distribution of patients using clozapine across different countries or regions. The characteristics of the studies have been summarised in Appendix 1 (available as supplementary material).

The quality appraisal for the included studies was conducted independently by AS and SN and discussed thereafter in case of disagreement. Because the value of each study's contribution became apparent only during the synthesis process, all studies were included, even those of poor quality, as long as they provided relevant information for the development of the forming theory. Appendix 2 (available as supplementary material) summarises the quality assessment of the identified studies.

Six main themes were identified and analysed: attitude to and knowledge about clozapine, misconceptions, guidance, education, training and experience.

Attitude and knowledge

Confidence in prescribing and managing clozapine is driven by the attitude of all professionals (medical, such as psychiatrists and trainee doctors, and non-medical for example, pharmacy professionals, nurses, etc) towards this medication. Rezaie et al ,(2023),

found that a lack of a positive attitude towards clozapine is influenced by the knowledge of psychiatrists who might feel not confident in using it. Moreover, the attitude of some psychiatrists in Iran, for example, is to avoid dangerous medications, preferring safer options because of possible legal and moral complications of side effects or unpredictable events if these occur (Rezaie, Nazari and Khazaie, 2023).

However, although elsewhere the attitude towards clozapine is positive, prescribing rates remain low. Positive attitudes towards clozapine might be influenced by self-perceived knowledge; for example, medical professionals surveyed by Grover et al (Grover *et al.*, 2015), rated themselves as knowledgeable (61.5% of those interviewed) or very knowledgeable (34.5%) about clozapine. However, they used this medication sporadically, because they believed that patients with a history of poor compliance or with medical comorbidities were not suitable. Mishara et al (Mishara, Orr and Buckley, 1995) highlighted how more knowledge and positive attitudes were observed among those members of the staff who had more contact with clozapine patients; for these professionals, the main sources of education were direct observation, seminars and courses.

Psychiatrists interviewed by Nielsen et al (Nielsen *et al.*, 2010) had a positive attitude to clozapine. However, knowledge around clozapine side effects was poor, as only 33% of the responders were knowledgeable about the duration of the risk of agranulocytosis, and only 9% knew about symptoms of myocarditis.

Verdoux et al (Verdoux *et al.*, 2016) suggested that psychiatrists' lack of knowledge in the use of antipsychotics influenced the prescribing habit as the use of clozapine was seen as a burden and as a potential danger, whereas the use of other second-generation antipsychotics was perceived as safer.

The majority (75.4%), of the psychiatrists surveyed by Tungaraza et al (Tungaraza and Farooq, 2015), reported sufficient exposure to the use of clozapine during their training. However, when questioned, it was evident that they lacked knowledge. For example, 36.2% were not able to identify suitable patients, hence not able to implement NICE guidelines (National Institute for Health and Care Excellence (NICE), 2013); 25.1% were not sure if starting clozapine in the community was safe; one-third believed that the risk of agranulocytosis persists throughout the treatment. In addition, there was a general lack of understanding and awareness of the side effects. For example, some HCPs believed that extrapyramidal effects were common with clozapine, whereas evidence suggests the opposite (Hodge and Jespersen, 2008); equally, they were not able to recognise more frequent side

effects such as hypersalivation (Hodge and Jespersen, 2008) or constipation (Ignjatovic Ristic, Cohen and Ristic, 2021) and were unsure about the management of metabolic effects and blood dyscrasias (Tungaraza and Farooq, 2015)(Grover *et al.*, 2015) (Xu *et al.*, 2020)(Shrivastava and Shah, 2009)(Daod *et al.*, 2019).

The survey by Cotes (Cotes *et al.*, 2022) showed that medical professionals practising in areas with a lower prescribing rate of clozapine were less knowledgeable about the incidence of side effects such as agranulocytosis compared to a group of community psychiatrists. Only 36% of them, compared to 87% of the community psychiatrists, answered questions correctly related to agranulocytosis incidence. Interestingly, the former group, compared to the latter, was also more likely to have received some training on clozapine during their residency (26% vs 15%).

Psychiatrists, advanced practice providers (APP) and trainees from academic medical centres surveyed by Leung *et al* (Leung *et al.*, 2019) answered questions correctly regarding neutropenia (73.9%) and myocarditis (44.1%). Whereas, questions regarding smoking tobacco were answered incorrectly by 76.8%.

The papers from Sanjeevi and Cocoman (Sanjeevi and Cocoman, 2020) and de Hert *et al* (de Hert *et al.*, 2016) investigated the level of knowledge of psychiatric nurses on clozapine and its side effects. Both concluded that although there was a general understanding of the role of clozapine in treating TRS, knowledge about potential serious side effects such as metabolic effects, seizures and myocarditis was scarce. For example, 70.5% (n=91) of the nurses surveyed by Sanjeevi and Cocoman gave incorrect answers when questioned about the risk of seizures; 65.1% (n=84) gave incorrect answers when questioned about the risk of metabolic effects and 95.3% (n=125) answered incorrectly on myocarditis risk. The earlier study by de Hert reported a lack of knowledge around agranulocytosis as 3 questions out of 4 were answered incorrectly by the majority of the participants (>50%); only 22.4% of the respondents answered correctly on risk of seizures and less than 40% answered correctly on questions related to metabolic effects. Questions related to benign ethnic neutropenia (BEN), a phenomenon where individuals of African ancestry have a baseline low white blood cell count, were answered correctly by less than one-third of the participants (de Hert *et al.*, 2016).

The authors of these studies reported that those nurses with a higher academic background and those more exposed to psychotic cases were more knowledgeable. Similarly, studies evaluating the knowledge of psychiatrists, pharmacists and other professionals (Nielsen *et al.*,

2010) (Gee *et al.*, 2014) (Grover *et al.*, 2015) (Oloyede, Mantell, *et al.*, 2022), showed that there is a general understanding of the schizophrenia guidelines, however, equally, unawareness of the incidence of side effects such as agranulocytosis or myocarditis for example (Nielsen *et al.*, 2010) (Shrivastava and Shah, 2009) (Tungaraza and Farooq, 2015) and this explained the reluctance in using clozapine.

Conversely, even though Serbian psychiatrists were unaware of general side effects such as myocarditis and constipation they seemed to prefer clozapine as nearly 60% of those questioned had 10 or more patients on it; agranulocytosis was considered an obstacle, however only 28% of those questioned considered blood tests obligatory (Ignjatovic Ristic, Cohen and Ristic, 2021).

Misconceptions

Three subthemes were identified: misconceptions around side effects, monitoring and comorbidities.

Misconceptions around side effects.

Fear of side effects and the need for monitoring was a reason for under-prescribing clozapine consistently reported by numerous papers and it was also one of the reasons for variation in prescribing practice observed in different countries or regions (Hodge and Jespersen, 2008)(Nielsen *et al.*, 2010)(Grover *et al.*, 2015).

For example, HCP (doctors, nurses and allied health workers) surveyed by Hodge & Jespersen (2008), overestimated the prevalence of the side effects by more than 10% on the majority (37 out of 51) of the items listed in the LUNSERS®, a scale used to measure antipsychotic side effects. The structured interview used by Nielsen *et al.* (2010), revealed that prescribing rates were higher in areas where clozapine was used more, where psychiatrists were more exposed to clozapine ($p=0.0048$), indicating that experience had a positive effect. The mean prescribing rate amongst 548 Indian psychiatrists surveyed by Grover *et al.* (2015) was 432.92 (SD=4415.52).

In Spain (Sanz-Fuentenebro *et al.*, 2019) prescribing rate was low, especially in small areas, such as some provinces in the Basque country (between 12.25% and 17.30% of patients with schizophrenia treated with clozapine) and in some districts in Madrid (11.91%), and it was the result of cultural factors, imputable to an excessive fear of side effects professionals had towards clozapine as well as lack of knowledge.

The overestimation of side effects and lack of knowledge on how to manage them, as well as perceived reluctance towards blood monitoring, were reported as reasons for delaying

clozapine (Tungaraza and Farooq, 2015). For this reason, the prescribing rate amongst these psychiatrists was low; despite an experience of 7 years, 42% of them had fewer than 5 patients on clozapine.

Misconceptions around monitoring

Psychiatrists interviewed by Nielsen *et al* (Nielsen *et al.*, 2010) and surveyed by Tungaraza (Tungaraza and Farooq, 2015), perceived that patients would be reluctant to undergo blood monitoring tests, even though previous studies had shown positive attitudes of patients towards clozapine monitoring (Taylor *et al.*, 2000).

As reported by some papers (Nielsen *et al.*, 2010) (Rezaie, Nazari and Khazaie, 2023) (Grover *et al.*, 2015), medical professionals felt that the process of initiating and continuing clozapine (registration of the patient and monitoring) was too onerous and because of the lack of support they received (especially in the community settings) they preferred to opt for less complicated treatments (alternative antipsychotic). Psychiatrists felt they did not have enough support from other medical and non-medical colleagues, especially in the community, and this was a reason for delaying clozapine initiation. Indeed, according to Verdoux *et al* (Verdoux *et al.*, 2018), a higher rate of clozapine use was registered in areas where psychiatrists could delegate the monitoring of the side effects to GPs or other professionals.

Beliefs around clozapine monitoring requirements had an impact on the diverse prescribing habits of HCPs. For example, in France, the use of clozapine amongst other antipsychotics ranged between 0% and 8.8% (Verdoux *et al.*, 2016). Areas with hospitals linked with academic institutions, with a higher number of private psychiatrists, with a higher number of general practitioners (GPs) and specialist doctors registered a higher rate of clozapine use. The availability of other professionals from other disciplines had a positive impact on the prescribing rates as psychiatrists could rely on other more expert colleagues for the monitoring of clozapine.

Similarly, in Canada, clozapine prescribing and management seemed regulated by the personal preference of the medical professionals. In the region of Quebec, the clozapine prescription rate varied from 3.9% to 10.8% among patients with a diagnosis of schizophrenia (Latimer *et al.*, 2013). Higher rates were seen in larger hospitals where access to specialist services such as cardiologists and haematologists was easier and cultural factors seemed to influence the prescribing pattern. The authors suggested education, audit and feedback to motivate the use of clozapine. In Iran, psychiatrists believed that the lack of

hospital beds was a reason for not initiating clozapine, implying that hospitalisation was needed to be able to monitor the patients closely (Rezaie, Nazari and Khazaie, 2023).

Misconceptions around co-morbidities

Even though medical professionals acknowledged the role of clozapine in treating patients with TRS, they were reluctant to use it in patients with co-morbidities (Daod *et al.*, 2019). This was particularly evident in psychiatrists working in elderly care as 79.3 % of those surveyed (n=135) by Paranthaman and Baldwin (2006) considered co-morbidities as a major barrier to clozapine.

The majority of psychiatrists (51.3%) interviewed by Grover *et al* (Grover *et al.*, 2015) considered co-morbidities as one of the common reasons for not using clozapine.

Similarly, HCPs interviewed by Gee *et al* (2014), perceived medical factors and medical complications as somewhat frequent (36%) or fairly frequent (23%) causes for delaying and initiating clozapine.

Guidance

Israeli psychiatrists surveyed by Daod *et al* (Daod *et al.*, 2019), claimed to have a good knowledge of clozapine national guidelines, however, only half admitted to adhering to these and described beliefs around fear of side effects, blood test requirements, comorbid health disease as prominent causes for not following the guidelines, and for not prescribing.

Despite the self-reported awareness of national or local guidelines, professionals were reluctant to use clozapine. As a consequence, an inconsistent prescribing practice across different areas and in different countries was observed. Even when prescribed, in some countries, the management of clozapine did not seem to not follow a standardised regulation. In countries such as India, despite self-rating themselves as knowledgeable, professionals adopted an arbitrary dose initiation schedule and a diverse blood monitoring frequency rather than following local guidelines, possibly because of the absence of a centralised blood monitoring system (Grover *et al.*, 2015) (Shrivastava and Shah, 2009).

In Norway, the arbitrary use of the guidelines seemed manipulated by cultural prescribing habits. Prescribing rates were higher in rural, small areas, whereas in large cities such Oslo, only 40 prescriptions per 100,000 inhabitants were registered (Schou, Drange and Sæther, 2019). These differences were not related to the diverse distribution of the patients with a diagnosis of treatment-resistant schizophrenia. Schou *et al* (Schou, Drange and Sæther, 2019)

attributed this variability to the difficulties in planning clozapine management in urban areas where there were fewer opportunities to follow the guidelines, for example, by offering an adequate monitoring regime to the patients. Conversely, in Iran, professionals felt that the lack of laboratory centres in small cities or villages was a reason for not using clozapine even when patients were eligible for it under guidelines (Rezaie, Nazari and Khazaie, 2023). Interestingly, the majority of the Irish consultant psychiatrists (95% of those surveyed) were familiar with the guidelines and 92% had 10 or more patients on clozapine; 81% would use clozapine after failure to 2 antipsychotics (Grant *et al.*, 2024). However, nearly half (48%) of them would find it challenging to treat the most complex cases without sufficient experience and 64% of them would need advice from special services for this purpose.

On the contrary, in other countries, strict adherence to the guidelines was a barrier to clozapine. For example, Bachmann and colleagues (Bachmann *et al.*, 2017) found that in Japan only 0.6 clozapine use prevalence per 100,000 of the population was recorded at the time of the study. This is because of the rigid guidelines, which require hospitalisation and the availability of specialists such as cardiologists and hematologists to initiate clozapine treatment is mandatory.

Eighty-one percent of professionals surveyed by Gee *et al.* (Gee *et al.*, 2014) (doctors, pharmacists, nurses, psychologists etc) perceived themselves familiar with the UK NICE guidelines and 48% of the respondents were familiar with clozapine initiation guidelines. However, the authors acknowledged that claimed familiarity with guidelines did not reflect the number of clozapine prescriptions. Possible reasons were as described above, misconceptions around side effects, monitoring including blood tests and co-morbidities.

In the UK, Parcell and Lewis (H. and S., 2000) reported data from all NHS mental health units in a county and observed a 34-fold variation in prescribing rates. This was related to the diverse use of evidence-based practice. Those trusts not using clozapine were instead using polypharmacy (more than one antipsychotic) despite the lack of evidence for this. Since then, the development and publication of the NICE guidelines on schizophrenia have reduced the variation in prescribing practice. Hayhurst *et al.* in 2003 (Hayhurst, Brown and Lewis, 2002) reported a reduced variation of 16-fold after publication of the guidelines. Later, a study involving 75 NHS mental health trusts in England registered a further reduction of variation in prescribing rates to 5-fold (Downs and Zinkler, 2007), showing that the increased

knowledge of and confidence in the guidelines helped to standardise the use of clozapine and reduced the prescribing differences in the country.

Although implementation of the guidelines has resulted in a reduced variation in prescribing practice, the use of clozapine has been (and still is) below the expected rates and a study by Downs and Zinkler (Downs and Zinkler, 2007) has found that only 30% of eligible patients are offered clozapine. Although the overall prescribing rate in the UK is greater than in other countries in Europe and has improved in the last few years, it is still below the expected figures and it still registers some variation amongst the regions. Whiskey et al (Whiskey et al., 2021) estimated that the number of patients with a diagnosis of TRS was 125,000 in 2019, however, only 37301 patients were prescribed clozapine at the time of the study. Variation in clozapine use is still observed, especially amongst the English counties and it is not related to the diverse distribution of schizophrenia prevalence or incidence, yet possibly due to the experience and ability of professionals using evidence-based practice and working according to guidelines.

Education

Education, training and experience influence the way professionals perform in their roles (Health Education England, 2020), (*NHS National Graduate Management Training Scheme*, 2017). Education is the core element of how and how much an individual is taught and learns in an educational environment, although it is not limited to this. Education was a theme found in 7 studies (Nielsen et al., 2010) (Sanjeevi and Cocoman, 2020) (de Hert et al., 2016) (Sanz-Fuentenebro et al., 2019) (Verdoux et al., 2016) (Oloyede et al., 2023) (Grant et al., 2024). In the study from Sanjeevi and Cocoman (Sanjeevi and Cocoman, 2020), registered psychiatric mental health nurses were asked if they received satisfactory information about clozapine during their undergraduate studies and nearly half (41%) denied they did. In the study from de Hert et al (de Hert et al., 2016), only 19 psychiatry nurses (23.5%) consulted declared they received sufficient education around clozapine. Verdoux et al (Verdoux et al., 2016) reported that higher use of clozapine was observed in the presence of academic institutions, although the findings were not statistically significant ($p=0.10$). Similarly, Whiskey et al (Whiskey et al., 2003) reported that those patients under the care of a mental health institution in the UK, linked to academia, were more likely to continue clozapine treatment and HCPs had a high level of awareness of evidence-based practice. However, Nielsen et al (Nielsen et al., 2010) showed no correlation between knowledge obtained by linkage with a university and the prescribing rate of clozapine, whereas higher prescribing rates were

observed in areas where the use of clozapine was high, indicating that exposure to clozapine use was decisive in improving knowledge. Education is not limited to professionals. Sanz-Fuentenebro et al (Sanz-Fuentenebro *et al.*, 2019) and Oloyede et al (Oloyede *et al.*, 2023) for example, highlighted the importance of developing educational programs for patients and carers, using testimonials. Grant et al. (2024) reinforced the need to increase patients' education and to improve their understanding of the beneficial effects of clozapine; dedicated staff, specialist services and educational programmes for professionals can also be used to improve clozapine use in most complex cases. Nielsen et al (Nielsen *et al.*, 2010) supported the idea of increasing the educational exposure to young doctors who become psychiatrists so that in the future, they can support patients to access specialist treatments such as clozapine. This is important because professionals need to promote shared decision-making, hence, they need to involve patients in their treatment by providing adequate information. Patients should be empowered, should be educated about the risks, benefits and possible side effects of the medications prescribed (Ní Dhubhlaing, Young and Sahm, 2017).

Training

Training is needed to ensure that professionals acquire the ability and skills to perform in everyday practice. A recent survey by Oloyede et al (2022), highlighted the lack of training received by professionals working in the early intervention psychosis services (EIPs) in England. This was particularly noticeable amongst the non-prescribers, as just 30% of them received training on clozapine management compared to 60% of the prescribers. Medical professionals in the Tungaraza and Farooq study (Tungaraza and Farooq, 2015) felt they had received adequate training as trainees, however, they showed gaps in knowledge when asked specific questions regarding side effects, as mentioned earlier. Previous studies have shown how training (online and/or face-to-face) can improve competence in clozapine management (Freudenreich *et al.*, 2013), (Cotes *et al.*, 2022), (Oloyede *et al.*, 2023), reducing the time of initiation and early identification of patients with TRS. If equally offered to a large cohort of professionals, a multicomponent training programme can also contribute to reducing variance in clozapine prescribing practice (Carruthers *et al.*, 2016). However, as Oloyede et al (Oloyede *et al.*, 2023) report, currently, there is no clear and consistent procedure to train HCPs, hence, they suggest educational interventions such as e-learning as a possible solution. They also advocate for more efficient instructions on how to monitor side effects. Previously, Freudenreich et al (Freudenreich *et al.*, 2013) described an innovative training package called the Freudenreich Clozapine Training Programme, which was embedded into a community

rotation. This robust programme consisted of a combination of face-to-face workshops where residents could learn from the literature the pharmacology of clozapine and where they could discuss clinical cases; this was integrated with weekly participation in a community clozapine clinic where a more practical experience was acquired. The programme was tested on a small cohort of trainees (n=15) who showed a significant improvement in general knowledge about clozapine ($p<0.001$) after 6 weeks.

Experience

Experience is a process of earning knowledge and skills and it is acquired by shadowing others and practising in any work activity. Experience in managing clozapine is certainly acquired when professionals are exposed to situations where this medication is used or can be used. Indeed, de Hert et al (de Hert *et al.*, 2016), showed that all those nurses working in psychosis wards (n=57) had experience in managing clozapine compared to only a third of those working in general mental health units (de Hert *et al.*, 2016). Exposure to clozapine management has certainly increased the knowledge and “comfort” in prescribing clozapine amongst the post-graduate resident psychiatrists at Augusta University Medical Centre, where an intense training experience is offered in in-patient units with a high turnover of complex psychiatric cases (Dvalishvili, Miller and Surya, 2021). Among these residents, 48% had prescribed clozapine for 11-20 patients, 11% to 21-30 patients and 19% to >30 patients at the time of the survey.

Similarly, the majority of the residents (83%) surveyed by Singh et al (Singh, Hughes and Roerig, 2020) found the knowledge, resources and experience provided in the clinics would make them more comfortable in prescribing clozapine.

HCPs with experience are more likely to use clozapine and patients under their care are more likely to continue the treatment (Whiskey *et al.*, 2003).

HCPs with more experience have stronger positive views of clozapine efficacy, safety and patient satisfaction compared to their “less expert” colleagues and this can contribute to a wider use of clozapine. For example among the HCPs interviewed by Takeuchi et al (Takeuchi *et al.*, 2016), those more experienced in managing clozapine (having treated a mean of 7.5+/- 17 patients on clozapine), compared to those less experienced (having treated zero patients on clozapine), had stronger views on efficacy (22.8% vs 14.9%) and on safety (3.5/35.1% vs 0/21.3%) even though both had worked in mental health settings for 9.8+/-7.8 years. This shows that on its own, mental health experience does not increase awareness and knowledge of clozapine management. The psychiatrists surveyed by Grover et al (Grover *et*

al., 2015) were reluctant to prescribe clozapine despite 12.59 years (mean) of experience in clinical practice. Tungaraza *et al* found that 16.7% of the consultant psychiatrists surveyed had no patients on clozapine despite an experience of 7 years in clinical practice (Tungaraza and Farooq, 2015). Nielsen *et al* (Nielsen *et al.*, 2010) found similar results and concluded that the only correlation is that psychiatrists not exposed to clozapine use are less likely to prescribe clozapine or do not use effective doses when needed. Paranthaman *et al* (Paranthaman and Baldwin, 2006) also found that limited exposure to clozapine use was the reason for not prescribing amongst the consultants working with old age patients.

Exposure to clozapine use is therefore the essential principle to gain experience and this was evident in those studies reporting prescribing variation. For example, in Japan, the use of clozapine was one of the lowest among the countries mentioned in the Bachmann *et al* study (Bachmann *et al.*, 2017). Whereas, in China, despite stringent guidelines (Chinese Medical Association, 2003), and the need for mandatory blood tests, HCPs seemed to prefer clozapine over other antipsychotics. Indeed, in China, clozapine has been utilised continuously since 1976, even when discontinued in other countries. Therefore, HCPs have gained extensive experience in its utilisation (Xiang *et al.*, 2017). On the contrary, in Japan, clozapine has been made available since 2009 only, and prescribers might have missed learning opportunities and direct experience. According to a study by Si *et al* (Si *et al.*, 2012), in 2006 in China, clozapine was used in 31.9% of the population with schizophrenia, nevertheless, even here, prescribing patterns varied significantly amongst different regions with 39.3% in Sichuan and 17.3% in Beijing; the socioeconomic and clinical presentation of the patients were identified as possible explanations for this variation.

However, although the prescribing rate of clozapine in China was reported to be higher compared to the European countries and the US, the average dose used was lower and polypharmacy seemed a common practice, with 25.1% of patients being prescribed clozapine and another antipsychotic (Si *et al.*, 2012). A more recent study examining the prescribing patterns of clozapine in Asian countries found similar results (Xu *et al.*, 2020).

Discussion

The findings of this SR provide significant insights into the factors affecting competence and confidence in the use of clozapine.

Interestingly, numerous studies have demonstrated that self-perceived competence does not correspond to an adequate prescribing pattern.

Although self-rating themselves as knowledgeable and familiar with guidelines, the professionals seemed less confident in following them (Gee *et al.*, 2014); (Daod *et al.*, 2019) and for this reason, were reluctant to use clozapine in a timely manner. Given that clozapine was typically underused, the self-reporting nature of the questionnaires utilised in these studies may help to explain why professionals' professed awareness of guidelines and knowledge of clozapine did not translate into actual prescriptions in clinical practice. Professionals also appeared less informed than they claimed to be when questioned. More specifically, they appeared to be struggling with certain aspects of managing co-morbidities and adverse effects associated with clozapine.

Unquestionably, there was a general uncertainty in the management of side effects and often an overestimation of adverse effects that impacted the prescribing rate across different countries or regions. Places where mental health experts could consult general practitioners (GPs) or specialists like cardiologists, haematologists, or neurologists showed greater rates of clozapine use (Verdoux *et al.*, 2018).

Misconceptions around the use of clozapine were recurrent themes and derived from a “fear” of side effects, co-morbidities and need for monitoring. Recently, Agid *et al.* (Agid *et al.*, 2024) outlined some myths and misconceptions regarding the use of clozapine and gave some guidance on how these could be addressed. For example, misconceptions around co-morbidities and side effects could be addressed by implementing learning programmes delivered by experts, by using patients’ testimonials or by using other interventions such as e-learning. According to Oloyede *et al.* (Oloyede *et al.*, 2023), this can increase knowledge and confidence in clozapine management. The management of the side effects requires a level of familiarity or knowledge of managing physical co-morbidities, which sometimes, as implied in the studies aforementioned, appear outside the competence of the professionals working in mental health settings.

For any HCP working in the medical sector, education is essential both early in their career (undergraduate) and later (post-graduate). Education, available in different delivery formats, should cover learning in several areas of practice, such as physical and mental health. However, it is necessary but not sufficient to change practice. Experience is essential to improving confidence, reducing apprehension of making mistakes, to learning about difficulties and incidents occurring in clinical practice (Porter *et al.*, 2013).

Experience in prescribing and handling a medication is achieved when HCPs are exposed to that medication. Certainly, years of practice are not translated into experience, it depends on the environment in which the professional has been practising. It appears that in those

institutions where the use of clozapine is widespread, HCPs become more confident not only in initiating the treatment but also in encouraging patients to continue it, particularly at early stages when side effects are more distressing and discontinuation rates can be high (Whiskey *et al.*, 2003). The more the professionals are in contact with patients on clozapine, the more they become knowledgeable and the more they become satisfied with its use (Mishara, Orr and Buckley, 1995).

Clozapine prescribing rates rise and discontinuation rates fall in organisations where practitioners have access to learning opportunities, are more aware of evidence-based practice, and where training programmes are mandatory (Whiskey *et al.*, 2003). However, training programmes should be offered not only to trainee psychiatrists, they should be extended to all those professionals who are involved in the care of patients with psychiatric disorders. This includes the general practitioners (Cotes *et al.*, 2022).

The introduction of national guidelines in 2002 appears to have improved the use of clozapine across different regions in the UK (Downs and Zinder, 2007). The guidelines have also standardised and reduced the variability across different nations and regions. However, previous studies have demonstrated that current guidelines (national and local) do not provide exhaustive indications on how to manage specific side effects such as myocarditis, tachycardia, seizures or constipation (Smesaert *et al.*, 2024); guidelines are not standardised and differ on the recommendations regarding the duration of haematological monitoring, the management of BEN and are deficient in providing indications on how to re-challenge clozapine following an episode of neutropenia (Oloyede, Blackman, *et al.*, 2022). For this reason, professionals might find it difficult to follow and adhere to them.

Moreover, although the guidelines have helped to reduce the dissimilarities of prescription rates and have improved the use of clozapine, the way they are used and implemented might have generated a barrier, as Nielsen *et al.* (2016) suggest. Indeed, guidelines do not allow deviations when needed, for example, when treating complex cases (patients with comorbidities), or when adjustments are needed to enable a patient to initiate or continue the treatment. Deviations from the guidelines might be necessary in complicated situations, for example, when re-challenging a patient who had a confirmed episode of neutropenia (two consecutive low neutrophil counts) or has co-morbidities. Evidence suggests that less stringent regulations have not resulted in more incidents of severe side effects such as agranulocytosis and have not altered the outcome of the therapeutic effect of clozapine (Shrivastava and Shah, 2009). We could hypothesise that only those professionals with a high

level of knowledge, expertise, competence and confidence would feel able to deviate from the guidelines, safely prescribe clozapine and adopt a more flexible approach when needed.

Some studies have indicated the utility of “special clinics” to treat patients with a diagnosis of TRS (Gee *et al.*, 2014); (Latimer *et al.*, 2013), (Bachmann *et al.*, 2017), (Nielsen *et al.*, 2010). However, there is a risk that those professionals working outside these units become deskilled as they are not exposed to clozapine management. It would be more useful if these special clinics became a point of referral and were seen as special services rather than separate units and if professionals initiating their career in mental health were requested to spend time with those working in that service. Existing clozapine clinics could become a point of referral. However, as Leung *et al.* explain (Leung *et al.*, 2019), currently, the level of service provided in these clinics varies from simple monitoring of the blood tests supervised by the pharmacy team to more complex management where more professionals are involved. An earlier study by Kelly *et al.* (Kelly and Love, 2019) emphasises how the role of pharmacists becomes crucial as they can perform blood tests, assess side effects, identify interactions with current medications, smoking status, assess adherence and liaise with consultant psychiatrists or advanced clinical practitioners for any concerns. However, a multidisciplinary approach seems to be a more successful expedient (Williams and Purvis, 2012)(Maryan *et al.*, 2019). This approach has been proven to increase patients' and carers' satisfaction and knowledge about clozapine (Williams and Purvis, 2012);(Ní Dhubhlaing, Young and Sahm, 2017). Moreover, dedicated clozapine clinics with staff supporting clozapine initiation and access to specialist advice services for the management of the most complex cases can increase confidence in the use of clozapine (Grant *et al.*, 2024).

Integrating experience gained in these clinics with teaching sessions, embedding them in a rotational programme and making them compulsory for those in training could certainly improve competence in clozapine management (Freudenreich *et al.*, 2013); (Dvalishvili, Miller and Surya, 2021); (Singh, Hughes and Roerig, 2020). A mandatory training programme, as suggested by Cohen and Farooq (Cohen and Farooq, 2021), could be developed and implemented in these “special clinics” and eventually expanded to other settings, allowing professionals to attain both knowledge and experience.

The studies mentioned above have shown how training can improve competence in clozapine management (Freudenreich *et al.*, 2013),(Cotes *et al.*, 2022), reducing the time of initiation and early identification of patients with TRS. If offered to a large cohort of professionals,

training can also contribute to reducing variance in prescribing practice (Carruthers *et al.*, 2016).

However, it is interesting to notice that according to Cotes *et al* (2022), for medical professionals in more senior roles, training in residency does not impact comfort in prescribing clozapine or knowledge in managing it. For this reason, the authors advocate for an educational programme to be extended to all medical professionals post-residency and to the general practitioners who take care of patients with psychotic disorders. Educational programmes should focus on helping medical professionals to identify candidates and to become more confident in using clozapine. The multidisciplinary Clozapine Decision Support Tool developed by Ally and Stallman (2016) and the more updated checklist published by Correll *et al* (Correll *et al.*, 2022) give some recommendations on the correct initiation of clozapine, monitoring for therapeutic response, management of the side effects (such as agranulocytosis, myocarditis, gastrointestinal hypomotility, convulsions, etc) and discontinuation strategy when needed. These resources are based on international practice, yet they could be adapted and used locally to assist professionals caring for patients with treatment-resistant schizophrenia. Similar recommendations are described by Agid *et al* (Agid *et al.*, 2024) who also emphasise the need to improve education among HCPs. A guidance could be developed based on these recommendations and professionals could be educated and trained on their use.

Strengths

By our estimation and knowledge, this was the first systematic review focussing on the evaluation of competence and confidence of professionals in clozapine prescribing and management. This review was conducted following the methods outlined in the Cochrane Handbook (Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, 2022) and results were reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) (2020) (Page *et al.*, 2021). The literature search was conducted with the support of an expert librarian utilising predefined search terms and their synonyms and using multiple databases as well as the grey literature.

To reduce the risk of bias, the study selection was conducted independently (blindly) by two professionals with experience in the field of interest (mental health) and experience in conducting systematic reviews. The data extraction and the qualitative assessment were also conducted independently. Disagreements were resolved with the support of the other

researchers. The principal investigator (AS) of this study collated the data extracted as well as the qualitative analysis and completed the analysis and the report.

Limitations

The main limitation of this systematic review was the quality of the identified studies (Appendix 2, available as supplementary material). Data collection was based on surveys, questionnaires, interviews or existing reports of databases. Therefore, some bias must be considered. First, there was no randomisation or specific community-based sampling strategy of the participants and an absence of any control group in all studies. Second, some of the studies made the questionnaire available to professionals for a longer duration (Sanjeevi and Cocoman, 2020); (Gee *et al.*, 2014); (de Hert *et al.*, 2016); (Grover *et al.*, 2015), and others explored participants' knowledge by allowing self-reporting (Daod *et al.*, 2019). Therefore, it would be plausible to believe that some professionals had time to access resources or ask colleagues to answer correctly the questions testing their knowledge, and those self-reporting might have overestimated their knowledge. Thirdly, those studies utilising existing databases excluded important information. Some groups of patients were not included in those databases. For example, the study by Schou (2019), did not collect data from hospital settings, while Latimer (Latimer *et al.*, 2013) excluded data from non-hospital settings.

Fourth, although some of the studies reported numerical data, because of their heterogeneity in methodology and partly in their content, it was not possible to pool data for the purpose of a meta-analysis. However, this SR intended to extract qualitative data from the studies to better understand the thoughts, attitudes, experiences, and understandings of all professionals involved in the management of patients with TRS and in need of clozapine.

Fifth, restricting the search to studies published only in the English language may have excluded significant research that could have enriched the results. However, identifying a reliable translator for those studies would have posed a challenge, thus necessitating this limitation.

Sixth, including countries without restriction, might have introduced an additional bias as HCPs operate differently in different countries. For example, a doctor, pharmacist or nurse working in the UK might have different needs compared to their counterparts working in other European countries. However, the scope of this review was to identify those factors affecting competence and confidence in clozapine use, and addressing these professionals' needs is reserved for future work.

Furthermore, studies excluded at the title and abstract stage may have revealed additional information regarding the factors influencing professionals' competence and confidence in the use of clozapine. However, the included studies consistently emphasised the same themes. As Booth suggests (Booth, 2016), in qualitative studies such as this, the aim of the review is not to locate all possible existing studies on the same topic; rather, the aim is not to produce a statistical representation of the findings, but to identify papers relevant to the theory being developed until data reaches saturation.

Despite these limitations and potential bias, this SR highlights important gaps in the literature regarding the effects that the competence and confidence of all professionals (not only consultant psychiatrists) involved in the care of patients with TRS have in the correct prescribing and management of clozapine and the standardisation of its use across different regions.

Conclusions

The studies above have highlighted gaps in knowledge and experience in prescribing and managing clozapine.

Overall, the research in this systematic review primarily focused on psychiatrists, with only a limited number of studies incorporating insights from other professionals or evaluating their competence and confidence in using clozapine.

Given the extent of multidisciplinary involvement in the management of clozapine and in the care and education of patients with TRS and their carers, it is essential to explore the views of all professionals, particularly those working in community clinics where patients may be more vulnerable without support. Future research could beneficially focus on gathering primary data through the contributions of various professionals, as well as patients and carers, and utilise this data to develop an intervention to broaden the use of clozapine.

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Authors contribution.

AS devised the project and the main conceptual ideas. TT supervised the project. AS and SN screened the articles, extracted data and completed the quality assessment of the articles independently. TT helped AS to analyse the data. AS wrote the paper. TT, WE and SS revised the manuscript. All authors approved the final version of the manuscript.

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Supplementary material

Supplementary material is available from the corresponding author AS, on a reasonable request.

Data availability

The data that support the findings of this study are available from the corresponding author AS upon reasonable request.

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