Patients’ and psychiatrists’ perspectives on clozapine treatment—a scoping review protocol

Michelle Iris Jakobsen 1,2, Ole Jakob Storebø 3,4, Stephen Fitzgerald Austin 2,4, Jimmi Nielsen 1,5, Erik Simonsen 1,4

ABSTRACT

Introduction The atypical antipsychotic clozapine has shown superior efficacy compared with other antipsychotics and is the gold standard for treating otherwise treatment-resistant schizophrenia. However, multiple studies have found that clozapine is underutilised in most parts of the world. A few reviews of literature addressing barriers to clozapine prescribing have been conducted. While there is some variation in the literature included in these reviews, a common feature of the studies included is that they primarily focus on clinical staff’s attitudes and perceived barriers for prescribing. Studies of patient perspectives are only sparsely included. A preliminary literature search revealed though, that additional literature on the subject exists, including literature on patient perspectives. It is therefore difficult to conclude if the formerly synthesised literature is representative of current evidence or if the topic has been adequately investigated to inform clinical practice. A scoping review is warranted in order to map and synthesise primary literature on patients’ and psychiatrists’ perspectives on clozapine treatment, and to identify gaps for future research.

Methods and analysis The electronic databases Cochrane Library, CINAHL, Web of Science, PsycINFO, MEDLINE and EMBASE will be searched for relevant publications, supplied with searches of Google scholar, The Networked Digital Library of Theses and Dissertations and OpenGrey. Citation tracking of selected studies will furthermore be undertaken. Two researchers will independently screen and extract data. Data will be collated to provide a descriptive summary of the literature, along with a qualitative content analysis of key findings. Identified gaps in research will be accompanied by recommendations for future investigations.

Ethics and dissemination Findings will be disseminated through a peer-reviewed journal and conference presentations. The scoping review does not require ethics approval.

INTRODUCTION

Schizophrenia is a serious mental illness with major societal, social and personal costs. Early, adequate treatment is crucial in order to improve long-term outcome, however approximately one-third of patients with schizophrenia fail to respond to regular antipsychotics and are considered treatment resistant.

The atypical antipsychotic (AP) clozapine has shown superior to other APs in terms of overall symptom reduction for acute schizophrenia and related disorders and it has for decades been known as the most effective drug for the treatment of treatment resistant schizophrenia (TRS). It is reported that more than two-thirds of TRS patients will respond to clozapine treatment in adequate doses and several studies have concluded that treatment with clozapine dramatically reduces the number of hospital admissions and bed days among TRS patients. Furthermore, it is shown to reduce suicidal-behaviour, self-harming-behaviour and aggressive behaviour.

However, clozapine is also associated with a wide spectrum of adverse effects, including some with a potential fatal outcome, and extensive haematological monitoring is mandatory. As a result, most treatment guidelines recommend that clozapine should be offered as a third line option, for example, to patients who continue to experience clinically significant symptoms after two adequate trials of other antipsychotics.
Despite the recommendations and advantages of clozapine treatment, clozapine continues to be underutilised in most parts of the world.20–25

The clozapine underutilisation represents a major mental health concern and a few reviews, with slightly different scopes, have aimed to identify the barriers for clozapine prescribing.26–29 While included literature varies between these reviews, a common feature is that they primarily focus on clinical staff’s attitudes and perceived barriers for prescribing. Only a few studies examining patient perspectives have been included for review. These are restricted to one study of patients in established clozapine treatment, and one study with patients in non-clozapine treatment.29,30

A preliminary literature search on Google scholar and PubMed revealed though, that additional studies on both clinicians’ and patients’ perspectives on clozapine treatment have been published, without being included in either of the existing reviews.

Some researchers argue that there is a discrepancy in that clinicians generally perceive patients’ attitudes towards clozapine as negative, whereas the patients’ actual attitudes seem to be positive31–33 and that this discrepancy might be the most significant barrier to clozapine treatment.31,34 However, to this day, no published reviews have mapped or synthesised literature addressing patients’ attitudes towards clozapine treatment. The scope and shortcomings of research on psychiatrists’ attitudes towards clozapine treatment is also unclear, although previously subjected to review. It is therefore difficult to conclude if the topic has been adequately elucidated to inform clinical practice and if any aspects still need to be investigated in order to optimise treatment feasibility in this area. An overview of the literature addressing patients’ and psychiatrists’ perspectives on clozapine treatment is warranted.

Key definitions

Patients

TRS is the main indication for clozapine use in all countries.18 However, clinical practices differ between countries19 and clozapine has other indications than TRS for example, tardive dyskinesia induced by other neuroleptics or high risk of suicidality in schizophrenia patients, treatment refractory schizoaffective disorder or treatment refractory psychosis related to Parkinson’s disease.19 The term ‘patients’ used forth will therefore refer to adult (age ≥18 years) patients affiliated with mental health services due to psychiatric conditions.

Psychiatrists

The term ‘psychiatrist’ will be used for all medical doctors affiliated with mental health services treating adult patients.

Objectives

In line with the original framework by Arksey and O’Malley,35 we aim to conduct a scoping review in order to (a) investigate the extend and variety of primary literature covering patients’ and psychiatrists’ perceptions of, or attitudes towards, clozapine treatment, (b) summarise key findings and (c) to identify gaps in research. The research questions are as follow:

1. What is the extent and variety of primary literature covering patients’ and psychiatrists’ perceptions of, or attitudes towards, clozapine treatment?
2. What aspects of patients’ and psychiatrists’ perceptions of, or attitudes towards, clozapine treatment have been investigated and by what measures?
3. What are the key findings of primary evidence related to patients’ and psychiatrists’ perceptions of, or attitudes towards, clozapine treatment?
4. What are the gaps in research related to patients’ and psychiatrists’ perceptions of, or attitudes towards, clozapine treatment?

METHODS AND ANALYSIS

This scoping review protocol is designed in congruence with the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)36 and guided by the corresponding Joanna Briggs Institute (JBI) guidelines ‘Guidance for conducting systematic scoping reviews’37 and the ‘Updated methodological guidance for the conduct of scoping reviews’.38 We have furthermore sought complementary guidance in the advanced framework recommendations by Levac et al.39

A completed (as applicable) checklist for reporting of scoping reviews (online additional file 1) has been submitted with the protocol manuscript.

Registration

PROSPERO does not offer registration of scoping reviews; however, the review protocol was prospectively registered with the Open Science Framework (OSF), registration DOI 10.17605/OSF.IO/5K4S3.40

Eligibility criteria

Publications will be considered eligible for inclusion if they meet the following selection criteria.

Inclusion criteria

► Published in English
► Empirical literature addressing patients’ or psychiatrists’ perceptions of, or attitudes towards, clozapine treatment (including both peer-reviewed research papers and grey literature such as conference abstracts and dissertation papers).

Exclusion criteria

► Non-empirical literature including case reports, editorials and discussion papers,
► Reviews/overviews (however, their reference lists will be included for citation tracking)

Rationale

We have chosen to limit our search to empirical data. The rationale for this is our focus on attitudes and perceptions,
which, naturally, is data of subjective and broad origin. In order to uphold scientific evidence, empirical data are considered a necessity. Both published and unpublished literature is included in order to ensure a comprehensive scope of the existing evidence on the concept.

Due to feasibility resources, the language is restricted to English. No limitation has been set for year of publication or type of study.

The inclusion criteria may need to be adjusted according to the search results. Such adjustments will be accounted for in the final review.

**Information sources**

The electronic databases Cochrane Library, CINAHL, Web of Science, Psychinfo, MEDLINE and EMBASE will be searched for relevant publications, supplemented with a limited search of Google scholar. This combination of sources have previously been reported to guarantee adequate and efficient coverage.41

Furthermore, The Networked Digital Library of Theses and Dissertations and OpenGrey will be searched for additional relevant literature, and citation tracking of selected studies will be undertaken.

**Search**

The search strategy used for this scoping review was developed by the lead investigator in collaboration with an experienced research librarian. In accordance with established scoping review methodology,37 38 it consists of three steps: first, an initial search of selected databases, in this case MEDLINE and EMBASE, will be performed. Search terms will include, but not be restricted to, doctor, psychiatrist, patient, consumer, attitude, perception, perspective, clozapine, (leponex) and (clozaril). The search will then be followed by screening the identified articles for relevant text words and index terms.

Second, the search will be refined, incorporating the identified keywords and index terms. Search terms will be adapted to the requirements of each selected database. Table 1 outlines the refined electronic search strategy for MEDLINE via Ovid.

When refinement has been completed across all selected databases, a second search (the actual search), will be undertaken.

The third step of the search strategy consists of searching the additional sources of literature, including a hand-search of reference lists of all included studies, to ensure a comprehensive literature identification.

**Selection of sources of evidence**

Records from the database search-strategy and from additional sources will be imported to the reference management software Endnote12 and duplicates will be removed. The search results will then be exported to Covidence.43

Two reviewers will individually screen the titles and abstracts of all identified publications and identify potential eligible studies based on the previously mentioned criteria. Next, full-text review of selected papers will be conducted, again by two independent reviewers and with reference to the inclusion and exclusion criteria. In case of disagreement related to study eligibility at either stage, this will be resolved through discussion between the two reviewers and alternatively in conclusion by a third reviewer.

A narrative description of the search decision process will be accompanied by a PRISMA flowchart (see Table 1).
online additional file 2), outlining the number of studies included at each phase of the process.

**Data charting process**

Microsoft Excel, Covidence and Endnote will be used to organise data, manage the screening process, and to categorise and manage full-text versions of included references.

A preliminary data extraction form was developed (see online additional file 3) and will be piloted by two reviewers to record the information needed to answer the research questions.

The data extraction form will be used to chart data by a minimum of two independent reviewers. The extraction form may need to be refined during the conduct of the full review and the independent reviewers will continuously discuss the results and update the form if needed.

**Data items**

In the data charting phase of the review, the following information will be collected:

- Author(s)
- Title
- Year of publication
- Country of origin
- Study population and study context/relevant characteristics (mixed staff/psychiatrists only, clozapine-/non-clozapine-/mixed patients, inpatients/outpatients etc.)
- Type of study
- Relevant outcome measures and method of assessment (any assessments of attitude or perception of clozapine treatment, eg, measures of treatment satisfaction or perceived effectiveness, perception of barriers for its usage, reasons for treatment withholding or refusal, proposals for increasing treatment utility, etc.).
- Key findings related to patients’ or psychiatrists’ perceptions of, or attitudes towards, clozapine treatment

**Critical appraisal of individual sources of evidence**

Consistent with scoping review methodology, no critical appraisal will be conducted for this review.

**Synthesis of results**

Studies will be grouped and mapped according to subpopulation (eg, clozapine patients, former clozapine patients, etc.) and the map will be accompanied by a tabular presentation of charted data (eg, the number of studies on specific subpopulations, their characteristics and key findings).

As mentioned in the JBI guideline, and recommended by Levac et al., the synthesis will include a qualitative content analysis on charted key findings.

A narrative summary will provide a description of characteristics and results of the extracted literature.

In line with the objectives of the review, the conclusion will present recommendations for future investigations based on identified gaps in research.

**Patient and public involvement**

This protocol was developed without public or patient involvement.

**Study status**

As of June 2021, we are in step 2 of the search process, ready to perform the refined database search. We expect the charting of data to be completed by December 2021 and the final scoping review by the end of February 2022.

**DISCUSSION**

It has been argued that there is a discrepancy in that psychiatrists perceive major barriers to clozapine treatment to be patient-related, whereas patients’ attitudes towards clozapine treatment have shown to be positive. Furthermore, it has been suggested that this discrepancy might represent the most significant barrier to clozapine prescribing.

The existing reviews addressing psychiatrists’ opinions about clozapine treatment seem, however, to represent an inadequate search of the literature and it is hence difficult to assess, if the previously synthesised literature is representative of current evidence, and if the topic has been sufficiently investigated to inform clinical practice.

We believe that a scoping review will present a timely, and warranted, overview and synthesis of current evidence and furthermore enable us to identify potential gaps in research.

Methodological rigour has been secured by developing this scoping review protocol in accordance with established scoping review methodology. The registration and publication of the protocol will furthermore ensure transparency of the review process. The three-stepped search strategy involving a broad range of relevant databases, combined with additional sources of grey literature, will ensure a comprehensive search of the literature.

The limitations of this scoping review are linked to its strengths: the broad research questions and the comprehensive search strategy entails a risk of extracting an overwhelmingly large amount of literature, including commentaries and letters expressing individual opinions. As a mean to ensure a certain level of scientific evidence, the exclusion of such non-empirical data sources is deemed necessary. Due to feasibility reasons, the search will furthermore be restricted to publications in English. These pragmatic decisions may, however, preclude the identification of some relevant insights and studies.

**Acknowledgements**

Trine Kaestel, Research Librarian, Psychiatric Research Unit, Region Zealand Psychiatry, Denmark.

**Contributors**

Coauthorship is based upon the Vancouver recommendations. All authors (MIJ, OJS, SFA, JN and ES) participated in conceptualising the review. Author MIJ developed the search strategy in consultation with a research librarian (see ‘Acknowledgements’). Author MIJ wrote the first draft of the manuscript. All
authors critically revised the manuscript for methodological and intellectual errors. All authors read and approved the final manuscript.

Funding This work is part of a PhD project funded by the Psychiatric Research Unit, Region Zealand Psychiatry, Denmark and the Psychiatry East, Region Zealand Psychiatry, Denmark. Grant number not applicable. Region Zealand Psychiatry received, from a former patient, a bequeathed donation favouring patient-oriented research within the region. The PhD project in question is partially funded by that donation.

Competing interests Region Zealand Psychiatry received, from a former patient, a bequeathed donation favouring patient-oriented research within the region. This work was partially funded by that donation.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

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# Additional file 1

## Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist

| SECTION          | ITEM | PRISMA-ScR CHECKLIST ITEM                                                                 | REPORTED ON PAGE # |
|------------------|------|-------------------------------------------------------------------------------------------|--------------------|
| **TITLE**        | Title| Identify the report as a scoping review.                                                   | 1                  |
| **ABSTRACT**     | Structured summary 2| Provide a structured summary that includes (as applicable): background, objectives, eligibility criteria, sources of evidence, charting methods, results, and conclusions that relate to the review questions and objectives. | 1                  |
| **INTRODUCTION** | Rationale 3| Describe the rationale for the review in the context of what is already known. Explain why the review questions/objectives lend themselves to a scoping review approach. | 2-3                |
|                  | Objectives 4| Provide an explicit statement of the questions and objectives being addressed with reference to their key elements (e.g., population or participants, concepts, and context) or other relevant key elements used to conceptualize the review questions and/or objectives. | 3                  |
| **METHODS**      | Protocol and registration 5| Indicate whether a review protocol exists; state if and where it can be accessed (e.g., a Web address), and if available, provide registration information, including the registration number. | 4                  |
|                  | Eligibility criteria 6| Specify characteristics of the sources of evidence used as eligibility criteria (e.g., years considered, language, and publication status), and provide a rationale. | 4                  |
|                  | Information sources* 7| Describe all information sources in the search (e.g., databases with dates of coverage and contact with authors to identify additional sources), as well as the date the most recent search was executed. | 4                  |
|                  | Search 8| Present the full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated. | 5                  |
|                  | Selection of sources of evidence† 9| State the process for selecting sources of evidence (i.e., screening and eligibility) included in the scoping review. | 6                  |
|                  | Data charting process‡ 10| Describe the methods of charting data from the included sources of evidence (e.g., calibrated forms or forms that have been tested by the team before their use, and whether data charting was done independently or in duplicate) and any processes for obtaining and confirming data from investigators. | 7                  |
|                  | Data items 11| List and define all variables for which data were sought and any assumptions and simplifications made. | 7                  |
|                  | Critical appraisal of individual sources of evidence§ 12| If done, provide a rationale for conducting a critical appraisal of included sources of evidence; describe | Not applicable (NA) |

*supplemental material*
| SECTION              | ITEM | PRISMA-ScR CHECKLIST ITEM                                                                 | REPORTED ON PAGE # |
|----------------------|------|-------------------------------------------------------------------------------------------|--------------------|
| Synthesis of results | 13   | the methods used and how this information was used in any data synthesis (if appropriate). | 7                  |
| RESULTS              |      |                                                                                           |                    |
| Selection of sources of evidence | 14 | Give numbers of sources of evidence screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally using a flow diagram. | NA                 |
| Characteristics of sources of evidence | 15 | For each source of evidence, present characteristics for which data were charted and provide the citations. | NA                 |
| Critical appraisal within sources of evidence | 16 | If done, present data on critical appraisal of included sources of evidence (see item 12). | NA                 |
| Results of individual sources of evidence | 17 | For each included source of evidence, present the relevant data that were charted that relate to the review questions and objectives. | NA                 |
| Synthesis of results | 18   | Summarize and/or present the charting results as they relate to the review questions and objectives. | NA                 |
| DISCUSSION           |      |                                                                                           |                    |
| Summary of evidence  | 19   | Summarize the main results (including an overview of concepts, themes, and types of evidence available), link to the review questions and objectives, and consider the relevance to key groups. | NA                 |
| Limitations          | 20   | Discuss the limitations of the scoping review process.                                     | 8                  |
| Conclusions          | 21   | Provide a general interpretation of the results with respect to the review questions and objectives, as well as potential implications and/or next steps. | NA                 |
| FUNDING              |      |                                                                                           |                    |
| Funding              | 22   | Describe sources of funding for the included sources of evidence, as well as sources of funding for the scoping review. Describe the role of the funders of the scoping review. | 9                  |

JBI = Joanna Briggs Institute; PRISMA-ScR = Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews.
* Where sources of evidence (see second footnote) are compiled from, such as bibliographic databases, social media platforms, and Web sites.
† A more inclusive/heterogeneous term used to account for the different types of evidence or data sources (e.g., quantitative and/or qualitative research, expert opinion, and policy documents) that may be eligible in a scoping review as opposed to only studies. This is not to be confused with information sources (see first footnote).
‡ The frameworks by Arksey and O’Malley (6) and Levac and colleagues (7) and the JBI guidance (4, 5) refer to the process of data extraction in a scoping review as data charting.
§ The process of systematically examining research evidence to assess its validity, results, and relevance before using it to inform a decision. This term is used for items 12 and 19 instead of “risk of bias” (which is more applicable to systematic reviews of interventions) to include and acknowledge the various sources of evidence that may be used in a scoping review (e.g., quantitative and/or qualitative research, expert opinion, and policy document).

From: Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): Checklist and Explanation. Ann Intern Med. 2018;169:467–473. doi: 10.7326/M18-0850.
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Additional file 2

PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources

Identification of studies via databases and registers

Records identified from*: Databases (n = )
Registers (n = )

Records removed before screening:
Duplicate records removed (n = )
Records marked as ineligible by automation tools (n = )
Records removed for other reasons (n = )

Records screened (n = )

Records excluded** (n = )

Reports sought for retrieval (n = )

Reports not retrieved (n = )

Reports assessed for eligibility (n = )

Reports excluded:
Reason 1 (n = )
Reason 2 (n = )
Reason 3 (n = )
etc.

Studies included in review (n = )
Reports of included studies (n = )

Identification of studies via other methods

Records identified from:
Websites (n = )
Organisations (n = )
Citation searching (n = )
etc.

Reports sought for retrieval (n = )

Reports not retrieved (n = )

Reports assessed for eligibility (n = )

Reports excluded:
Reason 1 (n = )
Reason 2 (n = )
Reason 3 (n = )
etc.

*Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).

**If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/
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**Additional file 3, Data charting template**

| Author | Title | Year | Country of origin | Study population and context | Type of study | Relevant outcome measures and method of assessment | Key findings (relevant to review objectives) |
|--------|-------|------|-------------------|------------------------------|---------------|-----------------------------------------------|---------------------------------------------|
|        |       |      |                   |                              |               |                                               |                                             |
|        |       |      |                   |                              |               |                                               |                                             |
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doi: 10.1136/bmjopen-2021-054308