BMJ Open

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

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To cite: Jakobsen MI, Storebø OJ, Austin SF, *et al*. Patients' and psychiatrists' perspectives on clozapine treatment—a scoping review protocol. *BMJ Open* 2021;**11**:e054308. doi:10.1136/bmjopen-2021-054308

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2021-054308).

Received 09 June 2021
Accepted 20 September 2021

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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, Psychinfo, 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.

Strengths and limitations of this study

- 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 insures transparency of the review process.
- The three-stepped search strategy outlined in the protocol ensures a comprehensive search of the literature.
- The search will be restricted to publications in the English language, which may preclude the identification of some relevant studies.
- Non-empirical data sources will be excluded, which may preclude the identification of some relevant insights.

INTRODUCTION

Schizophrenia is a serious mental illness with major societal, social and personal costs.[1] Early, adequate treatment is crucial in order to improve long-term outcome,[2 3] however approximately one-third of patients with schizophrenia fail to respond to regular antipsychotics[4 5] and are considered treatment resistant.[6]

The atypical antipsychotic (AP) clozapine has shown superior to other APs in terms of overall symptom reduction for acute schizophrenia and related disorders[7] and it has for decades been known as the most effective drug for the treatment of treatment resistant schizophrenia (TRS).[8 9] It is reported that more than two-thirds of TRS patients will respond to clozapine treatment in adequate doses[10 11] and several studies have concluded that treatment with clozapine dramatically reduces the number of hospital admissions and bed days among TRS patients.[12 13] Furthermore, it is shown to reduce suicidal-behaviour,[14] self-harming-behaviour[15 16] and aggressive behaviour.[17]

However, clozapine is also associated with a wide spectrum of adverse effects, including some with a potential fatal outcome,[18] and extensive haematological monitoring is mandatory.[19] 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.[4 6 19]

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.[26–28] 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 positive[31–33] 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.[19] However, clinical practices differ between countries[19] 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 complemental 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.

Table 1 Electronic search strategy, EMBASE

Search #	Search details
1	clozapine/
2	(clozapin* or denzapin* or zaponex* or clozaril* or clopin* or fazaclo* or versaclo* or leponex*).ab,ti,tn,tw.
3	1 or 2
4	attitude/
5	attitude assessment/
6	exp satisfaction/
7	(attitude* or belief* or perception* or view* or experience* or opinion* or perspective* or preference* or satisfaction or satisfied* or refus* or reason* or dislike* or content*).ab,ti,tw.
8	4 or 5 or 6 or 7
9	patient/ or mental patient/ or outpatient/
10	consumer/
11	(patient* or user* or consumer* or subject* or individual* or client*).ab,ti,tw.
12	physician/
13	psychiatrist/
14	clinician/
15	(doctor* or physician* or psychiatrist* or clinician* or prescriber* or practitioner*).ab,ti,tw.
16	9 or 10 or 11 or 12 or 13 or 14 or 15
17	patient attitude/ or patient preference/ or patient satisfaction/
18	physician attitude/ or health personnel attitude/
19	consumer attitude/
20	exp patient-reported outcome/
21	exp treatment refusal/
22	17 or 18 or 19 or 20 or 21
23	exp medication compliance/ or exp patient compliance/
24	(barrier* or compliance*).ab,ti,tw.
25	23 or 24
26	8 and 16
27	26 or 22 or 25
28	3 and 27
29	limit 28 to english language

Selection of sources of evidence

Records from the database search-strategy and from additional sources will be imported to the reference management software Endnote[42] 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[44] (see

online additional file 2), outlining the number of studies included at each phase of the process.

Data charting process

Microsoft Excel,[45] Covidence and Endnote[42] 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 discus 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,[35–39] 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,[38] and recommended by Levac *et al*,[39] 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.[31–33] Furthermore, it has been suggested that this discrepancy might represent the most significant barrier to clozapine prescribing.[31 34]

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 Kæstel, 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 consultancy 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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