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Clozapine Initiation for Schizophrenia: A Review of Clinical Effectiveness and Guidelines

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Abbreviations

AMSTAR	A Measurement Tool to Assess Systematic Reviews
CSG	Canadian Schizophrenia Guidelines
L	litre
mcg	micrograms
mg	milligrams
RANZCP	Royal Australian and New Zealand College of Psychiatrists
SR	systematic review
SIGN	Scottish Intercollegiate Guidelines Network
TRS	treatment-resistant schizophrenia

Context and Policy Issues

Clozapine is a second generation antipsychotic indicated for patients with treatment-resistant schizophrenia (TRS).[1] TRS is schizophrenia that does not respond fully to conventional schizophrenia treatments, including first-line antipsychotics.[1] According to the Canadian Schizophrenia Guidelines (CSG), treatment-resistance is indicated after failure of two antipsychotics, although definitions of TRS vary among clinical trials.[2] It has been estimated that in patients receiving conventional pharmacotherapy for schizophrenia, 50% of these patients do not respond adequately to prescribed pharmacotherapy (30% may exhibit a partial response, and 20% may exhibit no response).[3]

Clozapine is associated with a variety of side-effects, including drowsiness, dizziness, tachycardia (high resting heart rate), constipation, weight gain, lowered white blood cell count, and excess saliva production.[1] Serious side effects include myocarditis, pericarditis, neutropenia, cardiomyopathy, and death.[1] Some side effects, such as myocarditis, can occur relatively quickly (within two weeks) after initiation of the medication.[4]

Clozapine must be initiated at a low dose and titrated up to the therapeutic dose over time to avoid side effects. Therapeutic doses can range from 200 mg to 450 mg per day and are generally not exceeding 900 mg per day (although doses of more than 900 mg per day are possible).[5-7] Initiation of clozapine may start as low as 12.5 mg per day, titrating upwards until individual effectiveness is seen (for example, resolution of psychosis symptoms).[6,7]

Initiation on clozapine requires strict monitoring protocols to ensure compliance and to address the side effects associated with the medication. For example, in the United States, the Clozapine Risk Evaluation and Mitigation Strategy requires all prescribers and pharmacies to be certified in order to prescribe or dispense clozapine.[8] Part of the Clozapine Risk Evaluation and Mitigation Strategy program includes regular absolute neutrophil counts for patients on clozapine to monitor for neutropenia.[8] In Canada, after reintroduction of clozapine in 1991 (after removal from the market in 1975 because of reported infections due to low white blood cell counts), patients were required to join a patient registry program (e.g., Sandoz Clozapine Risk Management Program[1]) to monitor white blood cell counts.[9] When switching to a new brand of clozapine, patients must join the manufacturer-specific registry upon changing medications.[1]

Guidelines outlining appropriate use of clozapine are important to ensure timely, safe, and suitable prescribing of clozapine in a variety of settings. The objective of the current review is to summarize clinical effectiveness of clozapine during the initiation phase of treatment in adult patients with schizophrenia and summarize recommendations regarding monitoring of adult patients during this initiation phase.

Research Questions

1. What is the clinical effectiveness of clozapine during the initiation phase of therapy for adult patients with schizophrenia in outpatient, in-patient, and community settings?
2. What are the evidence-based guidelines for monitoring adult patients with schizophrenia initiating clozapine therapy?

Key Findings

Three systematic reviews were identified regarding the clinical effectiveness of clozapine during the initiation phase, and three evidence-based guidelines were identified regarding monitoring of patients taking clozapine during the initiation phase.

The identified systematic reviews were of limited quality and focused primarily on cardiac complications during clozapine initiation. Side effects of clozapine included myocarditis, tachycardia, hypertension, hyperglycemia, and death. The average time until side effect onset ranged from 14 days to 7 weeks after clozapine initiation, with one study reporting heart rate changes after 2 to 3 days. There were no studies identified that reported on clozapine compared with other antipsychotics during the initiation phase.

The identified guidelines indicate and recommend monitoring of patients initiating clozapine, with recommendations varying in strength of evidence from randomized controlled trials to non-analytic studies and expert opinion. Non-graded evidence suggests assessments of patient history, weight, waist circumference, fasting plasma glucose, fasting lipid profile, prolactin, full blood count, electrocardiograms, electroencephalogram, pregnancy, and ophthalmological examinations for patients who have been prescribed antipsychotics. It was not clear what the strength of evidence for these specific assessments was.

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including PubMed, the Cochrane Library, the University of York Centre for Reviews and Dissemination (CRD) databases, the websites of Canadian and major international health technology agencies, as well as a focused Internet search. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were clozapine, schizophrenia and initiation. For Q2, search filters were applied to limit retrieval to guidelines. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between Jan 1, 2014 and Dec 17, 2019.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with schizophrenia in outpatient, in-patient, and community settings
Intervention	Initiating clozapine therapy (i.e., during the initiation phase, the follow-up time from starting clozapine until reaching the therapeutic dose)
Comparator	Q1: Other pharmacotherapy (e.g., second-generation antipsychotics: aripiprazole, olanzapine, quetiapine, risperidone; first-generation antipsychotics); no treatment Q2: No comparators
Outcomes	Q1: Clinical effectiveness (symptoms of schizophrenia: delusions, hallucinations, disorganized thinking, speech, or motor behavior, hospitalization, adverse events) Q2: Recommendations regarding patient monitoring during the clozapine initiation phase
Study Designs	Health technology assessments, systematic reviews, randomized controlled trials, non-randomized studies, evidence-based guidelines

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2014. Guidelines with unclear methodology were also excluded. Articles were excluded if it was not clear that the follow-up was during the initiation phase of clozapine treatment (i.e., between initiation of the treatment and titration to the therapeutic dose). Articles were also excluded if 50% or more of the population under study were not diagnosed with schizophrenia.

Critical Appraisal of Individual Studies

The included systematic reviews (SRs) were critically appraised by one reviewer using a measurement tool to assess systematic reviews 2 (AMSTAR 2)[10] and guidelines were assessed with the AGREE II instrument.[11] Summary scores were not calculated for the included studies; rather, the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 481 citations were identified in the literature search. Following screening of titles and abstracts, 447 citations were excluded and 34 potentially relevant reports from the electronic search were retrieved for full-text review. Three potentially relevant publications were retrieved from the grey literature search for full text review. Of these potentially relevant articles, 31 publications were excluded for various reasons, and six publications met the inclusion criteria and were included in this report. These comprised three systematic reviews and three evidence-based guidelines. Appendix 1 presents the PRISMA[12] flowchart of the study selection.

Additional references of potential interest are provided in Appendix 5.

Summary of Study Characteristics

Additional details regarding the characteristics of included publications are provided inAppendix 2. One of the included SRs had slightly broader inclusion criteria than this review in that all patients with schizophrenia or schizoaffective disorder were eligible for inclusion.[13] Additionally, Yuen et al.[14] was broader in inclusion of study designs, as it

included animal studies. Studies examining patients with schizoaffective disorders and animal studies were not eligible for inclusion in this review; the study characteristics for the subset of relevant studies for this review are described below.

For the purposes of this review, "initiation phase" and "titration phase" are synonymous, referring to the time period between commencing treatment with clozapine and titration up to the therapeutic dose (generally 200 to 450 mg).[5]

Study Design

Systematic Reviews

There were three identified SRs relevant to this review, all published in 2018.[4,13,14] Clark et al. examined case studies published between 1964 and 2016,[13] Knoph et al. examined review articles and research reports published between 1988 and 2017,[4] and Yuen et al. examined case reports, animal studies, and clinical studies published between 1959 and 2016.[14]

Within Clark et al. there was one study relevant to this review,[13] within Knoph et al. there were 24 studies relevant to this review,[4] and within Yuen et al. there were five studies relevant to this review.[14]

There was no known overlap between the SRs; however, it was not clear which study in Clark et al. was the relevant study,[13] therefore, there is potential that this unknown study overlapped with one of the other included SRs.

Guidelines

Three guidelines were identified.[2,6,15] They were published in 2017[2,15] and 2016.[6]

Two guidelines were sections of the CSG, developed by Canadian researchers in collaboration with the Canadian Psychiatric Association and the Schizophrenia Society of Canada.[2,15] The recommendations were adapted from previously existing guidelines using the ADAPTE process or were created *de novo* and graded using the Scottish Intercollegiate Guidelines Network (SIGN) methodology. The ADAPTE process is a systematic method to adapt existing guidelines for use in a different setting or cultural context.[2] Evidence was collected through systematic searches for both literature and existing guidelines within guideline clearinghouses, websites of guideline developers, and MEDLINE. Recommendations were finalized through consensus (80% agreement required), and the quality of the included guidelines for adaptation were assessed using AGREE II.[2,11,15]

One guideline was developed by the Royal Australian and New Zealand College of Psychiatrists (RANZCP) and was created through "informal literature reviews".[6] The specific details of the literature searches were not reported. Recommendations were drafted by a working group and included contributions from experts in the specific areas.[6] Evidence was appraised using the Australian National Health and Medical Research Council levels of evidence.

Country of Origin

The first authors of the SRs were located in Australia,[13] the US,[4] and Canada.[14]

The guidelines were published for audiences in Canada,[2,15] and for audiences jointly in Australia and New Zealand.[6]

Patient Population

The SR authored by Clark et al. examined patients with schizophrenia or schizoaffective disorder who received clozapine and who had developed clozapine toxicity, defined as either clozapine serum levels of greater than 1000 mcg/L or serum levels greater than 600 mcg/L in conjuncture with clinical symptoms associated with clozapine serum level elevation.[13] Only patients with schizophrenia were of relevance to this review (31 of 40 studies, with one study occurring during the titration phase).

The SR authored by Knoph et al.[4] examined patients exposed to clozapine who had developed cardiomyopathy or myocarditis, not including adverse events related to clozapine overdose. The SR did not specify whether only patients with schizophrenia were eligible, or if other schizophrenia spectrum disorders were included.[4] The SR by Yuen et al. examined adult patients with schizophrenia who had cardiovascular side effects and were receiving treatment with clozapine.[14]

The intended users of all included guidelines are health care professionals, extending specifically to individuals involved in the care and provision of services to patients with schizophrenia.[2,6,15] The target populations for all included guidelines are adults with schizophrenia, but the guidelines published by RANZCP and Addington et al. include all individuals in the schizophrenia spectrum as target populations (i.e., schizophrenia, schizoaffective disorder, delusional disorder, etc.), with the exception of childhood onset schizophrenia).[2,6,15]

Interventions and Comparators

The intervention examined in all included SRs was clozapine, in any dose.[4,13,14]

Comparators examined were either no treatment (i.e., before and after studies)[4,13,14] or other antipsychotic medications (e.g., haloperidol, olanzapine).[4,14]

The interventions considered within the guidelines include best practices in diagnosis and assessment of individuals within the schizophrenia spectrum,[15] pharmacotherapy in schizophrenia,[2] and both pharmacotherapy and non-pharmacological treatments for schizophrenia.[6]

Outcomes

The SR outcomes were related to adverse events occurring with clozapine treatment. These included:

fever[13]	myoclonus[13]	hypotension[14]
weakness[13]	heart rate variability[14]	cardiomyopathy[4]
tremor[13]	impact of infection[14]	sedation[13]
delirium[13]	death (mortality)[4,13,14]	speech and gait disturbance[13]
dysarthria[13]	c-reactive protein levels[13]	dizziness[13]
white blood cell count[13]	neurological symptoms[13]	hypertension[14]
myocarditis[4,13]	respiratory sinus arrhythmia[14]	tachycardia[14]

The included guidelines examined outcomes including symptom severity,[2,6,15] functional outcomes,[6] vocational outcomes,[6] and side effects.[2,6,15] As the CSG adapted existing guidelines, eligible outcomes included those from other guidelines that were relevant to the chapter that was being authored (e.g., pharmacotherapy of schizophrenia).[2,15]

Follow-up in Clinical Effectiveness Studies

Studies were included in this review if the length of follow-up reported was reasonably likely to have been during the initiation phase of treatment (e.g., data from studies with two years of follow-up were not extracted, as it is unlikely that a patient had not reached their therapeutic dose by that time). Length of follow-up was not reported for one SR, but it was reported that one included case report occurred during the titration phase of treatment.[13] In SRs that reported follow-up, the time from initiation varied from 0 days to 7 weeks in one SR,[4] and 2 days to 11 weeks in another SR.[14]

Summary of Critical Appraisal

Additional details regarding the strengths and limitations of included publications are provided in Appendix 3

Systematic Reviews

SRs were appraised using AMSTAR 2.[10]

Each SR included clear aims for the review and included a comprehensive search in multiple databases, a search through reference lists of included publications, and completion of the search within 24 months of publication.[4,13,14] The conflicts of interest (with two SRs having no conflicts[4,13]) were stated clearly.[4,13,14] Both Clark et al. and Knoph et al. did study selection and data extraction with more than two authors performing the tasks independently.[4,13] Yuen et al., however, stated that screening of studies and data extraction was performed by one author, which may limit the methodological quality of the review. It is unknown whether author biases occurred during screening, or if accidental human error potentially missed relevant studies.[14]

The SR by Clark et al. did not report some information from the included studies, such as follow-up time of the case reports (only reporting that one case was in the titration phase of treatment, and not specifying how long that was).[13] This makes interpretation of the potential side effects of clozapine difficult as it is unknown whether they occurred relatively quickly during initiation, or over a long and stable treatment interval. Knoph et al. also did not fully or consistently describe the included studies in detail, occasionally not reporting information on ages, diagnoses, and follow-up.[4] In Knoph et al, for the “clinical recommendations” extracted, it was unclear whether the reviews had systematic methodologies or were strictly narrative reviews with no systematic search. This made it unclear whether these recommendations were author opinion or evidence-based recommendations.[4] Yuen et al. thoroughly reported details in the majority of included studies, but did not report details on one study.[14] It is unclear if this was due to an error in counting of the total included studies, or due to an error in not extracting the data from this study.[14] It is unknown the impact the information in this missing study has on the evidence base.

Finally, the included SRs did not discuss bias in the primary studies that were included, did not discuss methodological quality of included studies, and did not discuss publication bias.[4,13,14]

Guidelines

Guidelines were appraised using the AGREE II tool.[11] As two guidelines were chapters of the CSG, and had the same methodology, these two chapters were appraised together.[2,15]

Overall, all three included guidelines were explicit in scope and purpose (i.e., describe scope and purpose, described the health questions covered by the guideline, and described the intended population the guideline applies to) and stakeholder involvement (i.e., included a variety of individuals, defined the target population, and sought out the populations' views and preferences).[2,6,15]

The authors of the CSG used systematic methods to search for evidence, explicitly explained how recommendations were formulated and graded, and made an explicit link between the recommendations and the evidence to support them. However, the guidelines were not clear on how the previously existing guidelines were chosen for adaptation, as there was no cut-off range for quality, nor was there an explanation on what was deemed "adaptable".[2,15]

The RANZCP guidelines were not clear in how evidence was identified for incorporation into the recommendations. There was no provided search strategy, and there was no explanation on which member of the working group authored which areas of the guideline or how this member (or members) formulated the recommendations.[6] However, as the recommendations were graded using the Australian National Health and Medical Council criteria, which specify that "recommendations made in guidelines should be informed by well-conducted systematic reviews",[16] it can be assumed that there was likely some form of search conducted for the guideline.

There is limited discussion of applicability in the identified guidelines, including discussions regarding barriers to implementation and resource implications. None of the identified guidelines provided auditing criteria.[2,6,15]

Summary of Findings

Appendix 4 presents a table of the main study findings and authors' conclusions. Appendix 4 also presents a table of guideline recommendations, alongside the level of evidence or grading for that recommendation.

Clinical Effectiveness of Initiation of Clozapine Therapy

Clark et al. did not reference the specific study that occurred during the titration phase of treatment, therefore no results from Clark et al. were available for extraction.[13]

Nine clinical studies in Knoph et al. were relevant to this Rapid Response. In patients titrating slowly (25 mg per week to a dose of 100 mg over 4 weeks), mean heart rate increased significantly, and eosinophil counts increased non-significantly. There were no significant changes in laboratory values; however, the numerical values were not reported.[4] As the numerical or statistical values were not reported, it is not possible to confirm significance or non-significance.

Two studies retrospectively examining patient charts found myocarditis in 5 patients and 8 patients respectively. The average onset of the myocarditis was 19.4 days and 14.4 days post clozapine initiation. In a national data base assessment, myocarditis occurred in 15 out of 8000 patients, with a mean onset of 15 days post clozapine initiation.[4]

These results mirror results from a retrospective review of patients with myocarditis, in which 36 of 38 patients had a time of onset between 14 to 22 days, and in another retrospective review where 83% of myocarditis cases occurred within 21 days. Cardiac complications occurred in seven of 143 patients receiving clozapine within seven weeks of

starting treatment in another retrospective study, with the seven patients needing to stop treatment with clozapine. There were two case reports in which myocarditis occurred, in which titration rates were faster than the recommended 12.5 mg to 25 mg per day increase.[4]

Yuen et al. included five studies of relevance to this review.[14] One clinical trial included two patients who were prescribed clozapine (out of 30 patients in the intervention group, which included other antipsychotic therapies), and followed up after 2 to 3 days. Mean heart rate of the intervention group (combined group of patients taking varying antipsychotics) was significantly higher than in the control group who did not receive antipsychotics. There was no specific information regarding clozapine.[14]

Four case reports were included. Patient side effects ranged by patient – the side effects included tachycardia, hypertension, hypotension, hyperglycemia, and death.[14]

Guidelines Regarding Monitoring of Patients After Initiation of Clozapine Therapy

In addition to the identified guidelines, Knoph et al. provided some "clinical recommendations" regarding patient monitoring, from a variety of literature sources. These are detailed in Appendix 4. However, the SR was not clear on the quality of or specific sources of these "recommendations", so they should be interpreted with caution.[4] The authors noted that the studies advised for and stressed the need for monitoring of patients prescribed clozapine, but did not generally provide sufficient data for specific monitoring strategies.[4]

Canadian Schizophrenia Guidelines

The CSG addresses assessment and diagnosis of patient with schizophrenia spectrum disorders and pharmacotherapy for patients with schizophrenia.[2,15]

Assessment

A *de novo* recommendation from the CSG states that following a change in treatment, reassessment of positive symptoms (e.g., hallucinations, delusions, disorganized thinking) should be done – noting that assessment of positive symptoms and treatment response is important in patients receiving clozapine.[15]

Pharmacotherapy

Similarly, following a change in medication or an increase in the dose of medication (specifically following acute exacerbations of the disorder), CSG recommends that the medication should be reviewed at four weeks, and reassessed at eight weeks if a partial response is seen at 4 weeks (modified recommendation from SIGN, Grade D).[2] In the first episode of psychosis, when medication is initiated, it should be continued for two weeks and assessed for dose and response during the early phases of prescribing (SIGN Grade D).[2]

Royal Australian and New Zealand College of Psychiatrists Clinical Practice Guidelines

Clozapine-specific recommendations

Evidence-based recommendations for clozapine monitoring include a recommendation that monitoring protocols should be followed rigorously (level of evidence: III-1), suggesting that mandated blood monitoring should be followed, and that regular echocardiograms do not

have a strong evidence base, but should be done if clinically indicated.[6] Metabolic monitoring is also recommended (level of evidence: II).[6]

General antipsychotic recommendations

In general, it is recommended to provide adequate length of treatment and monitor the treatment and adverse effects in first episode psychosis (level of evidence II).[6] In acute behavioural disturbances, if antipsychotic medication is used "as required", it should be monitored closely to avoid overdosing (level of evidence III-1), and extrapyramidal side effects should be closely monitored (level of evidence III-2).[6]

Combination therapy (which may include clozapine), requires careful monitoring (level of evidence II).[6] A consensus based recommendation states that validated instruments should be used to record and monitor the treatment effects.[6]

There are several additional discussed monitoring strategies that were not assigned strength of evidence levels, and therefore are not considered official recommendations in this report.[6] Generally, the guideline suggests systematic and regular monitoring of antipsychotics, including monitoring of cardiac complications, weight gain, adherence, extrapyramidal side effects, and metabolic side effects. Suggested monitoring times (adapted from a table in the RANZCP guidelines, no level of evidence assigned) include monitoring at baseline (prior to initiation), four weeks, eight weeks, and 12 weeks.[6] The suggested assessments are patient history, weight, waist circumference, fasting plasma glucose, fasting lipid profile, prolactin, full blood count, electrocardiograms, electroencephalograms, pregnancy, and ophthalmological examinations for patients taking antipsychotics.[6]

Limitations

Limitations of the current evidence include a lack of high-quality, randomized controlled trials or meta-analyses exploring the clinical effectiveness of clozapine in the initiation phase of treatment. The included systematic reviews identified mostly retrospective studies or case reports that reported on outcomes during this period. The inclusion of these study designs can be useful, but there are limitations to the interpretation of the results. Case reports do not provide a comparison group, and therefore there is no information regarding comparisons between individuals on clozapine who did not develop side effects with individuals who did, and no comparisons between clozapine and other antipsychotics. Case reports also have a small sample size. The retrospective design of the other included primary studies makes it difficult to assess temporal relationships between the medication and the outcomes (i.e., it is difficult to determine if clozapine specifically caused the side effect, or if another factor was involved). Additionally, the recommendations from the guidelines included in this review did not specify the monitoring protocols needed during the initiation phase of treatment. The guideline with the most in-depth information regarding monitoring is intended for use in New Zealand and Australia and may not be transferable to the Canadian context.

Conclusions and Implications for Decision or Policy Making

Three systematic reviews and three evidence-based guidelines were identified regarding the clinical effectiveness and monitoring of clozapine during the initiation phase in patients with schizophrenia.

The identified systematic reviews focused most frequently on cardiac complications of clozapine, including myocarditis and tachycardia. Other side effects reported included hypo- and hypertension, hyperglycemia, and death. The average time of onset ranged from 14 days to 7 weeks, with one study reporting heart rate changes after 2 to 3 days.

There was no information on clinical effectiveness with regards to symptoms of schizophrenia (positive and negative symptoms), quality of life, or hospitalizations in the initiation phase of treatment.

The identified guidelines highlighted the need to monitor patients initiating clozapine, when switching from another medication, and when increasing the dose of medication. These recommendations were graded as being based on evidence ranging from randomized controlled trials to non-analytic studies and expert opinion.

Commonly cited assessment times (with no strength of evidence levels) include baseline (prior to initiation), four weeks, eight weeks, and 12 weeks, and suggested assessments are patient history, weight, waist circumference, fasting plasma glucose, fasting lipid profile, prolactin, full blood count, electrocardiograms, electroencephalogram, pregnancy, and ophthalmological examinations for patients taking antipsychotics. However, these specific monitoring timelines and assessments were included as part of the evidence summaries, and not the official recommendations, and therefore did not have level of evidence gradings.

The identified guidelines align with previously published guidelines such as the World Federation of Societies of Biological Psychiatry guidelines, published in 2012, which recommends monitoring of metabolic side effects and special monitoring for clozapine.[17] The recommendations also align with the 2014 National Institute for Clinical Excellence's guidelines regarding psychosis and schizophrenia in adults (included and adapted in the CSG) – these guidelines state that patients should be monitored for response to treatment, side effects, weight and waist circumference, blood pressure, blood glucose, adherence, and overall physical health.[18]

Previous CADTH work on this topic includes a 2010 Rapid Response Report regarding clozapine treatment in hospitalized patients.[19] The Rapid Response concluded that the most serious risks for patients initiating clozapine in the hospital setting were lowered white blood cell count, heart attack, myocarditis, weight gain, and increased risk of death,[19] which was similar to the side-effects noted in this report.

Further research on the risks and effectiveness of clozapine in the initiation phase would aid in reducing uncertainty surrounding this treatment option. Additionally, clear and graded recommendations from evidence-based monitoring guidelines would assist in providing reliable guidance on prescribing clozapine for patients with schizophrenia.

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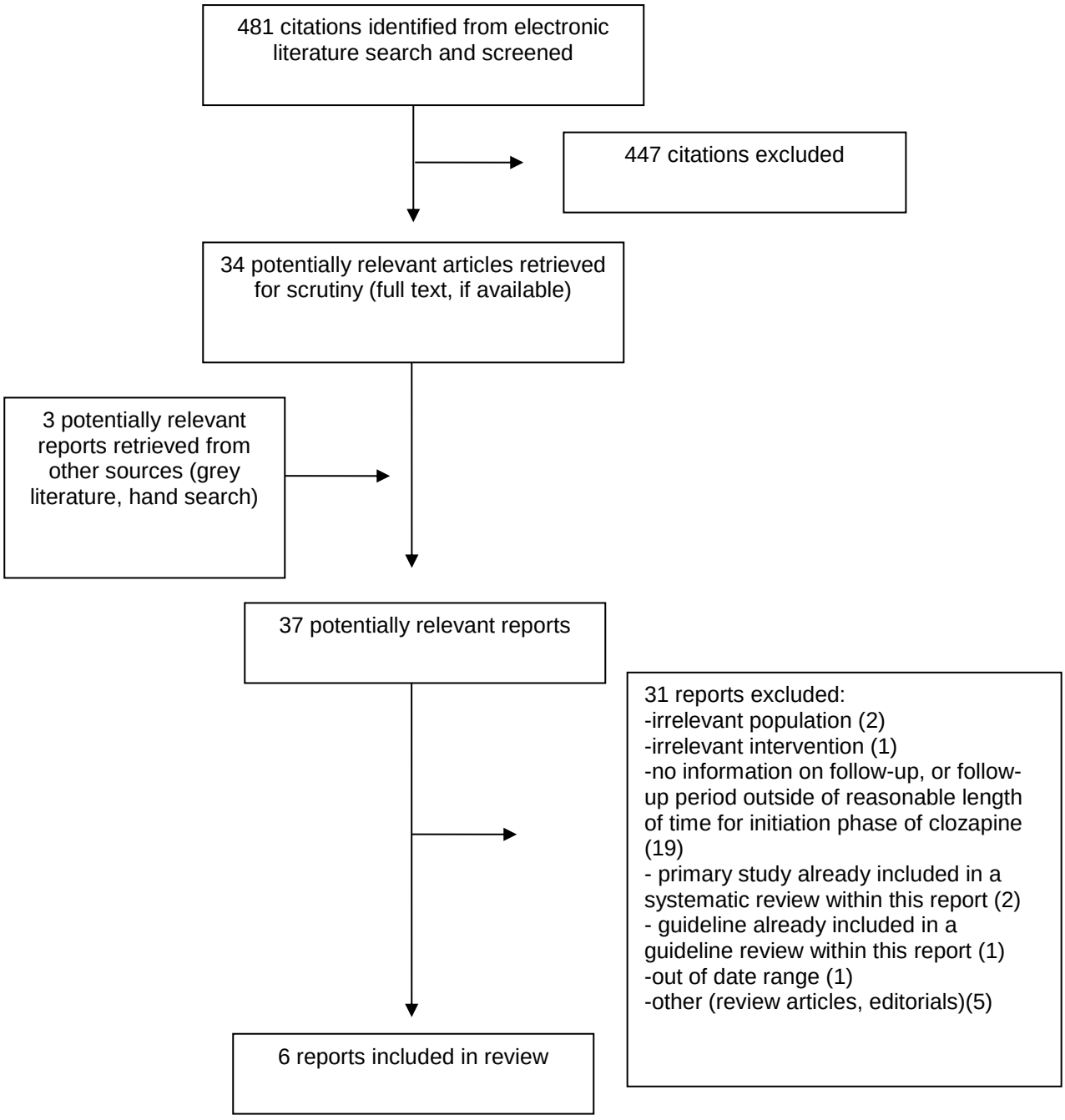
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews and Meta-Analyses

First Author, Publication Year, Country, Funding Source	Study Designs and Numbers of Primary Studies Included, Search Dates	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Clark, 2018[13] **Australia** **Investigator initiated grant from Lundbeck Institute** **Grant from NHMRC**	Case studies N = 40 One study (n = 1) reported on a patient relevant to this report (during titration phase of initiation of clozapine); however, did not specify which case study this patient referred to. Search from 1964 to April 2016 (PubMed), 1974 to April 2016 (Embase) Databases include: - PubMed - EMBASE	Patients receiving clozapine with schizophrenia or schizoaffective disorder. All patients had clozapine toxicity, measured as clozapine serum levels of > 1000 mcg/L or >600 mcg/L with clinical symptoms associated with clozapine serum level elevation (i.e., sedation, delirium, myoclonus, siallohoea (excessive saliva production), or incontinence). All cases with inflammation with no reported diagnosis of infection, or those with non-infectious causes of clozapine toxicity were excluded. n = 1 patient (1 relevant case study)	Intervention: - Clozapine (all doses) Comparator: - No treatment (before and after case study)	Adverse events, including: - fever - white blood cell count - c-reactive protein levels - dizziness - speech and gait disturbance - sedation - weakness - tremor - delirium - dysarthria - myoclonus - neurological symptoms - myocarditis - death (mortality) - impact of infection Addition of other antipsychotics or medication changes Length of follow-up NR
Knoph 2018[4] **US** **No funding source**	Review articles, “research reports” (all designs, including case reports and case series, but not including conference abstracts) N = 144	Articles and patients included within the articles were related to or had myocarditis or cardiomyopathy from exposure to clozapine.	Intervention: - Clozapine (all doses) Comparator:	Adverse events related to cardiomyopathy and myocarditis Reported follow-up in relevant clinical studies

First Author, Publication Year, Country, Funding Source	Study Designs and Numbers of Primary Studies Included, Search Dates	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
	(27 articles were review articles, 31 were original research articles, 8 were letters, and 78 were case series or case reports) Eleven (n = 11) "research reports" were of relevance to this review, eight studies were retrospective studies, one study was an open-label study. Two studies were case reports. Thirteen (n = 13) "review articles" were of relevance to this review. These included some clinical recommendations on monitoring in the early stages of initiation. Search from January 1988 through February 2017 Databases included: - Ovid MEDLINE, - Ovid EMBASE - Cochrane Database of Systematic Reviews - Web of Science - Scopus - Google Scholar	Reviews related to and studies containing patients who had clozapine overdose-related adverse events were excluded. In studies including patients that had outcomes relevant to this review, there were 8489 patients in eight clinical studies (ranging from 15 to 8000 patients). The sample size of the ninth study was not reported. The sample sizes of the two case studies was one per study (n = 2)	- Other antipsychotic medications - No treatment (before and after case studies)	ranged from 0 to 7 days to 7 weeks
Yuen 2018[14] **Canada** **Grant from NSERC Funding from BC Provincial**	Case reports, animal studies[a] and clinical studies were eligible N = 37 (3 studies were animal studies, 16 were case reports, 17 were clinical trials, 1 study design was not reported)	Only included adult patients (over 18 years of age) with schizophrenia taking clozapine and experiencing cardiovascular side effects Studies not including discussion regarding autonomic function were excluded	Intervention: - Clozapine (all doses) Comparator: - Other antipsychotic	Cardiovascular adverse events, including: - heart rate variability - hypotension - hypertension - respiratory sinus arrhythmia - tachycardia

First Author, Publication Year, Country, Funding Source	Study Designs and Numbers of Primary Studies Included, Search Dates	Population Characteristics	Intervention and Comparator(s)	Clinical Outcomes, Length of Follow-Up
Health Services Authority	5 studies were relevant to this review (4 case reports, 1 clinical trial) Search from 1959 to March 2, 2016 Databases included: - EMBASE - MEDLINE - Cochrane Database of Systematic Reviews	In studies including patients that had outcomes relevant to this review, there were 7 patients that received clozapine (5 within case reports, 60 [30 intervention/30 controls] within clinical trial [two patient received clozapine])	- medications (e.g., haloperidol, olanzapine) - No treatment (before and after case studies, placebo studies)	Reported follow-up in relevant clinical studies ranged from 2 days to 11 weeks

NHMRC = National Health and Medical Research Council [located in Australia]; NR = not reported;

[a]*Animal studies were not relevant to the current review*

Table 3: Characteristics of Included Guidelines

Funding Body	Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
Canadian Guidelines for the Assessment and Diagnosis of Patients with Schizophrenia Spectrum and Other Psychotic Disorders, 2017,[15] Chapter of the Canadian Schizophrenia Guidelines							
No financial support	*Intended Users:* Health care professionals, health policy makers, health administrators, and funding agencies (noted to potentially be of interest to	Chapter focuses on best practices in diagnosis and assessment of schizophrenia spectrum disorders	Treatment effect, e.g., schizophrenia symptoms, aggression, hostility, comorbid depression	Guidelines were developed using the ADAPTE process Evidence was collected through searches for existing guidelines (to be used for adaptation) and searches for literature	AGREE II was used to appraise the adapted guidelines SIGN methodology was used to appraise literature for *de novo* recommendations	The recommendations were adapted from existing guidelines regarding schizophrenia treatment *De novo* recommendations were	External review by *"individuals who will be affected by its uptake: practitioners, policy makers, health administrators, and patients and their families"* P.589

Funding Body	Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
	individuals with schizophrenia and their families) *Target Population:* Adults with schizophrenia spectrum disorders		Discontinuation rates Of relevance to this review were outcomes and recommendations related to monitoring of antipsychotic use (specifically clozapine)	to create *de novo* recommendations Searches for guidelines and literature included: - guideline clearinghouses, e.g., US National Guideline Clearinghouse, Guidelines International Network. - websites of guideline developers, e.g., NICE, SIGN, the American Psychiatric Association, the American Academy of Child and Adolescent Psychiatry, and the European Psychiatric Association - MEDLINE Searches were published after 2010, the end date not specified (most recent included/adapted guideline was 2016)		created using SIGN methodology Each chapter had a separately assigned working group that developed a final set of recommendations from existing guidelines or through creation of new recommendations. These were presented to a full guideline panel (national multidisciplinary panel) and recommendations were edited through consensus facilitated by anonymous voting. 80% agreement was required for inclusion, or if 80% was not achieved, recommendations were modified for inclusion.	Peer-reviewed by the Canadian Psychiatric Association

Funding Body	Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
"Guidelines for the Pharmacotherapy of Schizophrenia in Adults", 2017[2], Chapter of the Canadian Schizophrenia Guidelines							
No financial support	*Intended Users:* Health care professionals, health policy makers, health administrators, and funding agencies (noted to potentially be of interest to individuals with schizophrenia and their families) *Target Population:* Adults with schizophrenia	Chapter focuses on pharmacotherapy-based treatment of schizophrenia, across different stages and phases of the illness	Treatment effect, e.g., schizophrenia symptoms, aggression, hostility, comorbid depression Discontinuation rates Of relevance to this review were outcomes and recommendations related to monitoring of antipsychotic use (specifically clozapine)	Guidelines were developed using the ADAPTE process Evidence was collected through searches for existing guidelines (to be used for adaptation) and searches for literature to create *de novo* recommendations Searches for guidelines and literature included: - guideline clearinghouses, e.g., US National Guideline Clearinghouse, Guidelines International Network. - websites of guideline developers, e.g., NICE, SIGN, the American Psychiatric Association, the American Academy of Child and Adolescent Psychiatry, and	AGREE II was used to appraise the adapted guidelines SIGN methodology was used to appraise literature for *de novo* recommendations	The recommendations were adapted from existing guidelines regarding schizophrenia treatment *De novo* recommendations were created using SIGN methodology Each chapter had a separately assigned working group that developed a final set of recommendations from existing guidelines or through creation of new recommendations. These were presented to a full guideline panel (national multidisciplinary panel) and recommendations were edited through consensus facilitated by anonymous voting. 80% agreement was required for inclusion, or if 80% was not achieved, recommendations were modified for inclusion.	External review by *"individuals who will be affected by its uptake: practitioners, policy makers, health administrators, and patients and their families"* P.589 Peer-reviewed by the Canadian Psychiatric Association

Funding Body	Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
				the European Psychiatric Association - MEDLINE Searches were published after 2010, the end date not specified (most recent included/adapted guideline was 2016)			
"Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders", 2016[6]							
RANZCP	*Intended users:* Health professionals in Australia and New Zealand, specifically "psychiatrists, psychiatry trainees, resident medical officers and hospital interns in psychiatry." P. 3 *Target population:* Individuals in the schizophrenia spectrum, including "schizophrenia, schizoaffective disorder,	Interventions included: - pharmacotherapy (including clozapine) - non-pharmacological treatments (including psychosocial treatments)	Clinical effectiveness Adverse events Of relevance to this review were outcomes and recommendations related to monitoring of antipsychotic use (specifically clozapine)	Created with "informal literature reviews" and with reference to existing SRs The methods for the literature reviews are unclear	Evidence appraised with the Australian National Health and Medical Research Council levels of evidence	A working group (with each section drafted by individuals with expertise in that area) analysed evidence and previous CPGs, and had experts in specific areas contribute to the recommendations	Reviewed by 11 experts in schizophrenia (both clinical and academic) from Australia and New Zealand Released for feedback and public consultation Peer review by the Australian & New Zealand Journal of Psychiatry (ANZJP)

Funding Body	Intended Users, Target Population	Intervention and Practice Considered	Major Outcomes Considered	Evidence Collection, Selection, and Synthesis	Evidence Quality Assessment	Recommendations Development and Evaluation	Guideline Validation
	schizotypal disorder, schizophreniform disorder and acute transient psychotic disorder with symptoms of schizophrenia" P. 3 This did not include childhood onset schizophrenia.						

CPG = clinical practice guideline; NICE = National Institute for Health and Care Excellence; RANZCP = Royal Australian and New Zealand College of Psychiatrists; SIGN = Scottish Intercollegiate Guidelines Network; SR = systematic reviews; US = United States.

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR 2[10]

Strengths	Limitations
Clark, 2017[13]	
- Aim of study was clear - Search was in two databases, included no language restrictions, searched reference lists of publications, search was completed within 24 months of publication of study - Both data abstraction and study selection performed independently by more than two authors - Review was registered on PROSPERO, and followed PRISMA statement guidelines - Authors reported no conflicts of interest	- Stated keywords used in search were "clozapine"," toxicity", and "infection", unknown if these were the only keywords used, and no information on MeSH terms or combinations of terms - States that data were extracted for *"…age, gender, diagnosis, clozapine dose at the time of infection, … at the time of infection, time on clozapine, … C-Reactive Protein (CRP)…" P. 51*, however some information is not reported, including duration of treatment (time on clozapine), and CRP. This made it not possible to determine which case study was in the titration phase of treatment, or which cases were patients who had increased doses recently - No list of excluded studies or rationale for exclusion - Although risk of bias assessments not relevant to case studies, no assessment or discussion of methodological quality of the case reports. The reporting of some variables by the authors of the case reports is noted as being inconsistent - No indication of grey literature searches
Knoph 2018[4]	
- Aim of study was clear - Search was in multiple databases, searched reference lists of publications, search was completed within 24 months of publication of study - Keywords with MeSH terms and search combinations reported - Article screening and article summarization performed in triplicate - Authors reported no conflicts of interest	- Search limited to English language only publications (with no justification), no indication of grey literature searches - No discussion or assessment of risk of bias of clinical studies, review articles, or case reports. Very limited discussion of quality of methodology or validity of included studies - No discussion or analysis of potential publication bias - Studies not described fully in some cases (e.g., missing ages, diagnosis, or follow-up information) - No indication of *a priori* protocol or registration of systematic review
Yuen 2018[14]	
- Aim of study was clear - Search was in multiple databases, searched reference lists of publications, search was completed within 24 months of publication of study - Keywords for search provided - Thorough reporting of 36 included studies, with clear study designs, population, interventions, comparators, and outcomes - Brief discussion of limitations of reports - Conflicts of interest stated	- One author completed both screening and data extraction of literature - Reports states 37 studies were included but provides details for 36 - Keyword combinations for search not clear - Search limited to English language only publications (with no justification), no indication of grey literature searches - No list of excluded studies or rationale for exclusion - No indication of *a priori* protocol or registration of systematic review - No discussion or analysis of potential publication bias - No discussion of risk of bias

CRP = c-reactive protein; MeSH = Medical Subject Headings; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO = International Prospective Register of Systematic Reviews.

Table 5: Strengths and Limitations of Guidelines using AGREE II[11]

Item	Guideline	
	Canadian Schizophrenia Guidelines - Canadian Guidelines for the Assessment and Diagnosis of Patients with Schizophrenia Spectrum and Other Psychotic Disorders, 2017[15] and "Guidelines for the Pharmacotherapy of Schizophrenia in Adults", 2017[2]	"Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders", 2016[6]
Domain 1: Scope and Purpose		
1. The overall objective(s) of the guideline is (are) specifically described.	Y	Y
2. The health question(s) covered by the guideline is (are) specifically described.	Y	Y
3. The population (patients, public, etc.) to whom the guideline is meant to apply is specifically described.	Y	Y
Domain 2: Stakeholder Involvement		
4. The guideline development group includes individuals from all relevant professional groups.	Y	Y
5. The views and preferences of the target population (patients, public, etc.) have been sought.	Y	Y, *there was a public stakeholder feedback period*
6. The target users of the guideline are clearly defined.	Y	Y
Domain 3: Rigour of Development		
7. Systematic methods were used to search for evidence.	Y	Unclear, *there is no reference to the specific search strategy or screening, therefore it is unclear*
8. The criteria for selecting the evidence are clearly described.	N, *there was no specific cut-offs or reasoning provided for why certain guidelines were adapted. It is unclear why some guidelines were selected for adaptation over others. There is no information on screening or data selection for de novo recommendations.*	N, *there is no reference to the specific search strategy or screening, therefore it is unclear*
9. The strengths and limitations of the body of evidence are clearly described.	Y	N, *very limited discussion of body of evidence*
10. The methods for formulating the recommendations are clearly described.	Y	N, *unclear who on the working group authored which sections*
11. The health benefits, side effects, and risks have been considered in formulating the recommendations.	Y	Y

Item	Guideline	
	Canadian Schizophrenia Guidelines - Canadian Guidelines for the Assessment and Diagnosis of Patients with Schizophrenia Spectrum and Other Psychotic Disorders, 2017[15] and "Guidelines for the Pharmacotherapy of Schizophrenia in Adults", 2017[2]	"Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders", 2016[6]
12. There is an explicit link between the recommendations and the supporting evidence.	Y	Y
13. The guideline has been externally reviewed by experts prior to its publication.	Y	Y
14. A procedure for updating the guideline is provided.	Y	N
Domain 4: Clarity of Presentation		
15. The recommendations are specific and unambiguous.	Y[15] N[2]	Y
16. The different options for management of the condition or health issue are clearly presented.	N	Y
17. Key recommendations are easily identifiable.	Y	Y
Domain 5: Applicability		
18. The guideline describes facilitators and barriers to its application.	N	Y
19. The guideline provides advice and/or tools on how the recommendations can be put into practice.	N, *the guideline does provide an implementation or dissemination strategy, but it is not specific to advice or tools for practice*	Y
20. The potential resource implications of applying the recommendations have been considered.	Y	N
21. The guideline presents monitoring and/or auditing criteria.	N	N
Domain 6: Editorial Independence		
22. The views of the funding body have not influenced the content of the guideline.	N/A, *no funding body*	Unclear
23. Competing interests of guideline development group members have been recorded and addressed.	Y	Y

Appendix 4: Main Study Findings and Authors' Conclusions

Table 6: Summary of Findings Included Systematic Reviews and Meta-Analyses

Main Study Findings	Authors' Conclusion
Clark 2017[13]	
Clark et al.[13] state that one included case (of infection) occurred during the titration phase of initiated clozapine; however, they do not reference the specific study, or provide data regarding follow-up or duration of treatment, therefore the results for this patient were not available for this review.	*"The mean time on clozapine was four years. In five cases the clozapine dose had been increased within the last month and one case was in the titration phase." P. 51*
Knoph 2018[4]	
Clinical Reports **N = 9** *Curto et al.*[20] Patients received slow titration of 25 mg of clozapine per week to a dose of 100 mg at 4 weeks *The monitoring protocol performed was:* *Baseline: ECG, echocardiogram* *Week 3: CRP, troponin I, BNP* *Week 4: ECG, echocardiogram, clozapine serum level* Subclinical left ventricular impairment with no clinical manifestations was found **Significant changes:** - Mean HR increased significantly (*P* = NR) **Non-significant changes:** - Eosinophil counts increased (*P* = NR) - No significant changes in laboratory values (*P* = NR; assessed laboratory values NR) **Other findings:** - CRP increased "slightly" (*P* = NR) - Troponin I and BNP undetectable or within reference *Youssef et al.*[21] In a patient chart assessment of 129 patients receiving clozapine, 5 cases of myocarditis (mean onset of 19.4 days, range of 14 to 28 days). *Reinders et al.*[22] In another patient chart assessment, 8 cases of myocarditis were judged to be possible, probable, or highly probable in patients without prior cardiac issues (mean onset of symptoms 14.4 days, range of 11 to 18 days post-clozapine initiation). The total number of patients in the chart review was unclear. *Kilian et al.*[23] In an assessment of a national database of adverse events, 15 of 8000 patients taking clozapine had myocarditis with a median onset of 15 days (range 3 to 21 days) for myocarditis. Five patients died after 14 to 18 days post-initiation (4 with no clinically evident symptoms). *Note: The three following studies were authored by Ronaldson* et al*. The time periods in which the patients were examined overlap, and it is unclear if there are some of the same patients included in all three studies.* *Ronaldson et al. 2010*[24]	*"From this literature review, the following information can be extracted: 1) The risk of myocarditis is greatest within the first 3 weeks after clozapine initiation. 2) ESR and chest radiography may not be beneficial in routine screening for myocarditis …5) CRP and troponin monitoring is beneficial for symptomatic patients, but the utility of routine screening in asymptomatic patients is unknown." P.28* *"From this information, screening for myocarditis and cardiomyopathy in asymptomatic patients receiving clozapine could include the following:* *• Perform baseline ECG.* *• Perform echocardiography, as a part of a cardiology consultation, to establish baseline cardiac function in patients with known cardiac disease, structural abnormalities, or other cardiac risk factors.* *• Observe a low threshold for initiating CRP and troponin monitoring, especially during the initial 4 weeks of clozapine therapy if any signs or symptoms suggestive of myocarditis develop, including asymptomatic tachycardia or heart rate increases of 10 to 20 beats per minute. Positive findings warrant a cardiology consultation. Negative results with symptoms suggestive of possible myocarditis support weekly CRP and troponin monitoring during the symptomatic period. Internal medicine/cardiology consultation should be considered for persistent symptoms." P. 28*

Main Study Findings	Authors' Conclusion
- In patients with myocarditis, the onset of myocarditis occurred 14 to 22 days after clozapine initiation in 36 of 38 cases. - Clinical presentation of myocarditis varied from patient to patient. No symptoms were found in 2 patients (1 death occurred in this group) *Note: this study had 47 controls according to the title; no additional information about controls provided* *Ronaldson et al.2011a*[25] - In 75 patients with myocarditis: - 9 deaths - 83% of case occurred within 21 days of clozapine initiation - No symptoms in 6 patients - 5 mild cases continued clozapine with no cardiac injury *Note: this study had 94 controls according to the title; no additional information about controls provided* *Ronaldson et al. 2011b*[26] - In fatal cases of myocarditis (n = 10) compared with non-fatal cases, fatal cases had received clozapine for longer than nonfatal (20.8 days versus 17 days, *P* = 0.0057) *Tirupati*[27] - 7 of 143 patients stopped clozapine because of cardiac complications (all cases within first 7 weeks) *Kropp et al.*[28] - NT-proBNP increased over the first 7 days post-initiation in a group taking quetiapine, clozapine, or olanzapine (*P* = NR). It was unclear how many patients were taking clozapine. **Case Reports** N = 2 In the two case reports where myocarditis occurred, titration of clozapine was faster than 12.5 mg to 25 mg per day. No other information is provided regarding these case reports. **Recommendations** N = 7 clinical studies N = 13 reviews *Note: This SR summarized "clinical recommendations" in both research reports and "reviews". However, some recommendations are reported from systematic reviews, others are authors' conclusions from clinical studies, and others are not clear on the methodology used. It is not stated whether the recommendations are based on individual authors' opinion or generated through more rigorous guideline methodology. Recommendations reported from letters to the editor were not extracted. It is unclear the quality of these recommendations or the evidence or methodology used to formulate these recommendations, and so they should be interpreted with caution. Additionally, not all recommendations were specific to the initiation phase of clozapine. It was assumed that suggestions for monitoring within the first 3 to 4 weeks would include the initiation phase in the majority of patients.*	

Main Study Findings	Authors' Conclusion
Recommendations regarding monitoring from reviews[a]: *"persistent tachycardia requires closer monitoring for [clinical signs and symptoms] of heart failure… Frequent physical examination after initiation is needed in the first 4 years of therapy" P. 19* *"… baseline and regular ECG and evaluation of cardiovascular status" P. 19* (definition of "regular" not specified) *"At 2 and 4 weeks [post-initiation]: [perform an] ECG. At any time: [perform an] ECG, CK-MB, or troponin I with new symptoms suggestive of cardiovascular disease; [perform a] cardiology consultation with any changes" **P**.* 19 *"…suggested that weekly troponin monitoring may be beneficial" P. 19* *"[to detect subclinical myocarditis, cardiomyopathy, or pericariditis], use clinical, laboratory, and cardiac tests:* *palpitations, chest pain, dyspnea, fever, leukocytosis, eosinophilia, troponins, CK, LDH, AST, ECG, and [echocardiogram]… recommend[s]… the assessment of myocarditis in the first month of treatment and regular monitoring for cardiomyopathy* *…regardless of monitoring strategy, a high degree of awareness should be maintained if patient has cardiac symptoms" P. 19* *"After treatment initiation, maintain high degree of awareness for the following symptoms:* - *flulike symptoms;* - *chest discomfort;* - *respiratory symptoms, (including tachypnea, dyspnea, orthopnea, paroxysmal nocturnal dyspnea, and crackles on auscultation; abnormal vital signs, including hypotension, narrowed pulse pressure, and persistent resting tachycardia;* - *cardiovascular signs (including increased jugular venous pressure, presence of third or fourth heart sound, pericardial friction rub, muffled first heart sound, mitral or tricuspid regurgitation, and peripheral edema; ECG changes, including possible cardiac enlargement, pulmonary venous congestion, and pulmonary edema); and hypereosinophilia* *If any are present, recommended prompt cardiologic assessment and prompt, permanent discontinuation of clozapine" P. 19* *"Clinicians should monitor cardiac status closely in the first few months" P. 19* *"Monitoring with routine clinical assessments, cardiac tests, and laboratory monitoring" P. 19* *"Within the first 2 months monitoring of troponin and CRP and [echocardiogram] may be useful to diagnose myocarditis* *Serial NT-proBNP and [echocardiogram] ("yearly?") may be useful to detect early cardiac dysfunction" P.19* *"maintain high degree of awareness [of cardiac adverse events] during first 2 months of clozapine use" P.19* *"maintain high degree of awareness early in treatment if [clinical signs and symptoms] of cardiac toxicity are present (persistent resting tachycardia, flulike symptoms, chest pain, or dyspnea), and then repeat the ECG, check cardiac*	

Main Study Findings	Authors' Conclusion
enzyme levels, and consider [echocardiogram] and cardiology consultation" P.19 *"Suggested weekly (for first 4 weeks) evaluation of peripheral eosinophils, CRP, CK-MB, troponin, and/or WBCs along with possible troponin monitoring; if laboratory results show elevations, ECG and echocardiogram are indicated" P.19*	
Yuen 2018[14]	
N = 5 **Clinical reports:** N = 60 (30 intervention group, 30 controls, 2 in intervention groups receiving clozapine), follow-up of 2 to 3 days post-initiation - heart rate was significantly higher in groups receiving antipsychotic therapy (*P* = NR) **Case reports**: *Tachycardia* N = 4 (n = 5 patients) - Male, 35 years old, titrated to 150 mg of clozapine over 3 weeks (unclear titration schedule) had tachycardia (up to 150 BPM), hallucinations, and fever - Male, 19 years old, taking 175 mg/day over 7 days (unclear titration schedule), had tachycardia (up to 130 BPM) - Male, 62 years old, 100 mg per day, < 6 days on treatment - Male, 43 years old, 175 mg per day, 14 days of treatment, had fever, neuroleptic malignant syndrome, muscle rigidity - Male, 37 years old, every 3 days titrated up 25 mg/day over 11 weeks, ventricular tachycardia *Hypertension* N = 1 - Male, 19 years old, taking 175 mg/day over 7 days (unclear titration schedule), SBP rose to 140 to 170 mmHg and DBP rose to 90 to 115 mmHg from 130/90 mmHg *Hypotension* N = 1 - Male, 37 years old, every 3 days titrated up 25 mg/day over 11 weeks, hypotension (SBP 70 mmHg) *Hyperglycemia* N = 1 - Male, 37 years old, every 3 days titrated up 25 mg/day over 11 weeks, severe hyperglycemia *Death* N = 1 - Male, 37 years old, every 3 days titrated up 25 mg/day over 11 weeks, became comatose, experienced repeated cardiac arrest, and died	*"Reduced HRV, elevated catecholamines, tachycardia and hypotension are known effects of CLZ treatment. Yet there is a lack of controlled trials to confirm that these autonomic abnormalities are caused specifically by CLZ." P. 10*

AST = aspartate aminotransferase; BNP = brain natriuretic peptide; BPM = beats per minute; CK = creatine kinase; CK-MB = creatine kinase-MB; CRP = c-reactive protein; DBP = diastolic blood pressure; ECG = electrocardiogram; ESR = erythrocyte sedimentation rate; HR = heart rate; LDH = low-density lipoprotein; mg = milligram; mmHg = millimetres of mercury; NT-proBNT = N-terminal pro-brain natriuretic peptide; NR = not reported; SBP = systolic blood pressure; ULN = upper limit of normal; WBC = white blood cell count.

Table 7: Summary of Recommendations in Included Guidelines

Guidelines Used for Adaptation	Recommendations	Strength of Evidence and Recommendations
Canadian Guidelines for the Assessment and Diagnosis of Patients with Schizophrenia Spectrum and Other Psychotic Disorders, 2017,[15] Chapter of the Canadian Schizophrenia Guidelines		
Recommendations were adapted from: *NICE:* - NICE National Clinical Guideline Number 178. Psychosis and Schizophrenia in Adults. Treatment and Management[a] 2014[18] *SIGN:* - SIGN 131. Management of Schizophrenia, 2013[29] *American Psychiatric Association:* - American Psychiatric Association Practice Guidelines for Psychiatric Evaluation of Adults, 2016[30]	*de novo* recommendation from the GDG of the Canadian Schizophrenia Guidelines: **"Following** a change in treatment**,** reassess the severity of key positive symptoms for the amount of change at regular intervals**. An assessment of the level of positive symptoms and treatment responses is** especially important for **selecting and** monitoring patients for the second-line antipsychotic clozapine.**" P. 599**	Good Practice Point – i.e., based on clinical experience of GDG
"Guidelines for the Pharmacotherapy of Schizophrenia in Adults", 2017,[2] Chapter of the Canadian Schizophrenia Guidelines		
Recommendations were adapted from: *NICE:* - NICE National Clinical Guideline Number 178. Psychosis and Schizophrenia in Adults. Treatment and Management[a], 2014**[18]** - NICE National Clinical Guideline Number 155. Psychosis and Schizophrenia in Children and Young People. Recognition and Management, 2013**[31]** - NICE National Clinical Guideline Number 120. Psychosis with Coexisting Substance Misuse. Assessment and Management in Adults and Young People[a], 2011**[32]** *SIGN:* - SIGN 131. Management of Schizophrenia, 2013[29] *European Psychiatric Association:* - European Psychiatric Association Guidance on the Early Intervention in Clinical High Risk States of Psychoses, 2015**[33]**	*"Following initiation **of an antipsychotic medication for patients in the first episode of psychosis,** the medication should be continued for at least 2 weeks unless there are significant tolerability issues**.** Assessment of dose and response should be monitored during the early phase of prescribing. **Where there is poor response to medication, there should be assessment of medication adherence and substance use before lack of response can definitely be established…." P. 608***	SIGN Grade D[b]

Guidelines Used for Adaptation	Recommendations	Strength of Evidence and Recommendations
American Psychiatric Association: - American Psychiatric Association Practice Guidelines for Psychiatric Assessment of Adults[a], 2016[30]	***"Following** an increase or change of antipsychotic medication **in response to acute exacerbation of schizophrenia, the medication should be continued for at least 4 weeks unless there are significant tolerability issues. Where a partial response is seen after review at 4 weeks, the** medication should be reassessed after 8 weeks **unless there are significant adverse effects." P. 609***	Modified recommendation from SIGN, Grade D[b]
"Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders", 2016[6]		
Clozapine-Specific Recommendations		
N/A	**"**Clozapine monitoring protocols should be followed rigorously**." P. 37** ***Explanation:*** **"**Mandated blood monitoring (weekly for the first 18 weeks, every 4 weeks thereafter) **means that blood dyscrasia is likely to be detected, but cardiomyopathy and myocarditis are also potentially dangerous side effects. There is little evidence that the cardiac adverse events can be predicted, but baseline echocardiogram and troponin are advisable.** Regular echocardiograms do not have a strong evidence base and it has been suggested that they be undertaken only if clinically indicated**…** Metabolic monitoring **and advice about diet and exercise** are essential**." P.38** ***Note: mandatory blood monitoring weekly for the first 18 weeks, every 4 weeks thereafter is a requirement of prescription of clozapine in Australia[34] Blood work is also a mandatory requirement of clozapine prescription in Canada.[1]***	Type of recommendation: EBR Level of Evidence: III-1[c]
	"Metabolic monitoring and interventions to manage the metabolic side effects of clozapine are essential**." P. 37**	Type of recommendation: EBR Level of Evidence: II[c]
General Antipsychotic Recommendations		
N/A	***Regarding medication in first-episode psychosis:*** **"Provide an adequate duration of treatment.** Monitor treatment and adverse effects appropriately**." P. 31**	Type of recommendation: EBR Level of Evidence: II[c]
	Regarding acute behavioural disturbances:	Type of recommendation: EBR

Guidelines Used for Adaptation	Recommendations	Strength of Evidence and Recommendations
	"If 'as required' antipsychotic medication is used for acute psychosis, monitor closely to avoid overdosing**, and consider the adverse effects of polypharmacy." P. 45** **"**Extrapyramidal side effects must be closely monitored **and treated appropriately. Anticholinergic agents should not be used routinely but … ['as required']" P. 45**	Level of Evidence: III-1[c] Type of recommendation: EBR Level of Evidence: III-2[c]
	Regarding combination therapy: **"**If an adequate response is not achieved **after monotherapy treatment trials of two antipsychotic agents given separately at therapeutic doses,** antipsychotic polypharmacy may be justifiable but requires careful monitoring**." P. 39**	Type of recommendation: EBR Level of Evidence: II[c]
	"For people who do not attend a GP**, consider undertaking investigations,** monitoring **and prescribing** as needed to treat physical health problems within the mental health service**." P. 59**	Type of recommendation: CBR Level of evidence: N/A[c]
	"Use validated instruments to record clinical signs, side effects and response to treatment, where possible**." P. 84**	Type of recommendation: CBR Level of evidence: N/A[c]
	"Mental health services should routinely measure **service performance, including duration of untreated psychosis, duration to second admission,** measures of adherence to treatment, patient involvement in care and patient satisfaction with treatment**." P. 84**	Type of recommendation: CBR Level of evidence: N/A[c]
Unofficial Recommendations (extracted from evidence summaries), no strength of evidence grading		
N/A	<u>P. 42 of the guidelines detail a table regarding the monitoring of patients taking antipsychotics.</u> On baseline, it is recommended to perform: **Patient history recording, weight (BMI) measurement, waist circumference measurement, fasting plasma glucose (HbA1c) measurement, fasting lipid profile, prolactin measurement, full blood count, ECG, EEG, pregnancy test, ophthalmological examination** After 4 weeks, it is recommended to perform: **Weight (BMI) measurement** **Prolactin measurement and/or pregnancy test if clinically indicated** After 8 weeks, it is recommended to perform: **Weight (BMI) measurement** **Prolactin measurement and/or pregnancy test if clinically indicated**	No strength of evidence or recommendation reported

Guidelines Used for Adaptation	Recommendations	Strength of Evidence and Recommendations
	After 12 weeks, it is recommended to perform: **Weight (BMI) measurement, waist circumference measurement, fasting plasma glucose (HbA1c) measurement, fasting lipid profile, and prolactin measurement and/or pregnancy test if clinically indicated**	
	In the maintenance phase[d] of schizophrenia: **"Higher doses should be used cautiously, and** careful monitoring of safety and tolerability is essential**" P. 32**	No strength of evidence or recommendation reported
	Regarding stage 2 schizophrenia: **"There are high levels of non-adherence to medication among people with psychotic disorders. Adherence should be proactively and sensitively addressed.** There is a need for careful ongoing monitoring of medication in this stage of illness, combined with a willingness to decrease dosages**. This is likely to work better in the presence of a multi-dimensional psychosocial programme to assist recovery." P. 16**	No strength of evidence or recommendation reported
	"Weight gain due to side effects of medicines occurs disproportionately early in the course of illness, so monitoring and prevention at this point are obvious interventions... Monitoring needs to be systematic and regular, and monitoring protocols can assist in managing cardiometabolic health... **However, no randomised [sic] trials assessing the effectiveness of physical health monitoring in people with serious mental illness have been completed..." P. 18**	No strength of evidence or recommendation reported
	"However, some of the … [second generation antipsychotics] have serious adverse effects, especially metabolic and cardiac side effects. Metabolic changes have been detected even in the young…, so monitoring and intervention should begin early for people prescribed these medicines**." P. 30**	No strength of evidence or recommendation reported
	Regarding monitoring and treatment of side effects**:** **"**During both the acute and maintenance phases of treatment, it is essential to regularly monitor antipsychotic adverse effects, including extrapyramidal side effects, akathisia, weight gain, cardiovascular and metabolic side effects **…** and tardive dyskinesia**. Severe medication side effects, such as akathisia ([restlessness]) …, can be a risk factor for non-adherence, exacerbation of symptoms, aggression or suicide, and appropriate interventions should be undertaken promptly (see Management of antipsychotic side**	No strength of evidence or recommendation reported

Guidelines Used for Adaptation	Recommendations	Strength of Evidence and Recommendations
	effects, below). The management plan should include clear information about who is responsible for implementing physical health interventions (such as prescribing metformin, antihypertensive medication, organising [sic] dental care and/or consultation with a dietitian).**" P. 33**	
	***Regarding switching or crossover of medications*:** ***"*A slow crossover titration is preferred and** close monitoring of mental state, side effects and rebound phenomena is essential during switching**." P. 36**	No strength of evidence or recommendation reported
	Regarding smoking and clozapine: **"**Clozapine levels should be closely monitored if there is a change in smoking **behaviour, and the dose should be adjusted if necessary." P. 39**	No strength of evidence or recommendation reported

CBR = consensus-based recommendation; CG = clinical guidance; EBR = evidence-based recommendations; ECG = electrocardiogram; EEG = electroencephalogram; GDG = guideline development group; GP = general practitioner; HbA1c = hemoglobin A1C; N/A = not applicable; NICE = National Institute for Health and Care Excellence; SIGN = Scottish Intercollegiate Guidelines Network.

[a]CG178 published by NICE is reported as "treatment and management" in this review, but the correct title is *"Psychosis and schizophrenia in adults: prevention and management."* CG120 published by NICE is reported in the review as the above title, but the correct title is *"Coexisting severe mental illness (psychosis) and substance misuse: assessment and management in healthcare settings"*. For the American Psychiatric Association, the guideline title is reported as "assessment" but the correct title is *"American Psychiatric Association Practice Guidelines for Psychiatric Evaluation of Adults."* This differs from Addington et al.,[2] who reported the correct title in their chapter of the Canadian Schizophrenia Guidelines.

[b] SIGN Grade D is noted as "Evidence level 3 or 4 or extrapolated evidence from studies rated as 2+" P. 597. Evidence level 3 or 4 includes non-analytic studies and expert opinion.[2,15]

[c] Evidence levels were based on the Australian National Health and Medical Research Council (NHMRC) levels of evidence. Level II indicates evidence from RCTs. Level III-1 indicates evidence from a pseudo-randomised controlled trial. Level III-2 indicates evidence from a non-randomized comparative study with concurrent controls. Where "N/A" is indicated, the consensus-based recommendation was based "based on a combination of available evidence, clinical experience and expert consensus" P. 20.[6]

[d] Maintenance phase refers to the maintenance phase of schizophrenia, not maintenance of medication.

Appendix 5: Additional References of Potential Interest

CADTH Reports

CADTH. Health Technology Update, Issue 26. Point of care testing for clozapine monitoring. (CADTH Health Technology Update) 2019; https://www.cadth.ca/health-technology-update-issue-26. Accessed 2020 Jan 22 [in progress].

Clozapine Treatment of Hospitalized Patients: A Review of Clinical Practice Guidelines and Safety. (CADTH Rapid response report: summary with critical appraisal). Ottawa (ON): CADTH; 2010: https://cadth.ca/sites/default/files/pdf/htis/dec_2010/L0234_Clozapine_Treatment_Hospitalized_Patients.pdf

Clinical Practice Guidelines with Unclear Methodology

Guidelines for the Safe and Quality Use of Clozapine Therapy in the WA health system. East Perth (AU): Government of Western Australia, Department of Health; 2017: https://ww2.health.wa.gov.au/~/media/Files/Corporate/general%20documents/Quality/PDF/Guidelines-for-the-Safe-and-Quality-Use-of-Clozapine-in-the-WA-health-system.pdf. Accessed 2020 Jan 22.

Guidelines and Recommendations Out of Date Range

Hasan A, Falkai P, Wobrock T, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia, part 1: update 2012 on the acute treatment of schizophrenia and the management of treatment resistance. World J Biol Psychiatry. 2012;13(5):318-378. http://www.wfsbp.org/fileadmin/user_upload/Treatment_Guidelines/WFBSP_SZ_Guidelines_Part1_2012.pdf

Quality Statements:

National Institute for Health and Care Excellence. Psychosis and schizophrenia in adults. (Quality standard QS80) 2015; https://www.nice.org.uk/guidance/qs80/chapter/quality-statement-4-treatment-with-clozapine. Accessed 2020 Jan 22.