**Abstract**

**Background:** Treatment-Resistant Schizophrenia (TRS) represents a significant challenge in mental health provision. Although underused in clinical practice, clozapine remains the treatment of first choice for TRS. This review aims at reviewing clozapine and other treatment options for TRS as recommended in the most recent schizophrenia Clinical Practice Guidelines (CPGs).

**Methods:** A literature search for CPGs was undertaken in four electronic databases, using the terms: ‘schizophrenia’, ‘clozapine’ and ‘guidelines’.

**Results:** Seven schizophrenia CPGs published by national or professional institutions were identified from the period of 2010-2020. The CPGs varied in the scope of the information provided about clozapine’s role in the management of schizophrenia. However, they provided strong supporting evidence on its efficacy in the management of TRS. Main differences in recommendations provided in the schizophrenia CPGs were in relation to the definition of TRS, on the management of patients with TRS who do not respond to clozapine treatment, and on the breadth of information in relation to clozapine’s safety profile and monitoring recommendations.

**Conclusions and Recommendations:** Future iteration of schizophrenia CPGs should address these important gaps in information, including strategies to support the safe use of clozapine to decrease treatment delays and reluctance in the use of this effective medication.

**Keywords:** Clozapine; Schizophrenia; Treatment resistance; Pharmacotherapy, Clinical Practice Guidelines

---

**Introduction**

Treatment-Resistant Schizophrenia (TRS) is estimated to occur in approximately 30% of individuals diagnosed with schizophrenia [1]. A variety of definitions for TRS has been described, with some consistency in defining non-response as: “less than 20% reduction in symptoms after the use of an adequate dose and duration of at least two trials of different antipsychotic medications” [2,3]. However, discrepancies in the clinical approaches surrounding this definition have been reported [1,3,4]. Management of TRS constitutes a significant mental health care challenge because patients often require extensive periods of hospitalization, experience significant social dysfunction, and report an overall poor quality of life [5]. Although a variety of antipsychotics and combination therapies have been explored for the management of TRS, research evidence supports the use of clozapine as the first-line agent [2,6-8]. However, studies suggest that clozapine is not only considerably underused in the management of TRS, but on a steady decline, leading to a delay in starting evidence-based treatments in this population [9-13]. As such, this scoping review of the available schizophrenia CPGs aims to give clinicians an overview of clozapine and other available pharmacological treatment options for TRS. In addition, relevant recommendations for optimizing the use of clozapine in the management of TRS will be provided.

**Methods**

**A literature search for CPGs was undertaken using the following search terms**

‘Schizophrenia’, ‘clozapine’ and ‘guidelines’, using PubMed. Inclusion criteria were as follows: (i) Written by national psychiatric or professional institutions; (ii) Published in between January 2010 and December 2020; (iii) Described the level of evidence for their recommendations; (iv) Written in English. In addition, Google Scholar was searched for any clozapine or schizophrenia guidelines published since December 2020 using the “sort by date” search strategy. The National Guideline Clearinghouse (a public repository for evidence-based clinical practice guidelines run by the Agency for Healthcare Research and Quality) and international psychiatric association websites were also searched manually. Figure 1 illustrates the literature search strategy used. Clozapine information was extracted from the included CPGs by one researcher (MN) and then reviewed by the other members of the research team (MZ, YE and OA).

Information on the following main topics was extracted and organized into tables:
The role of clozapine in the overall treatment of schizophrenia: Indications, effectiveness, and dosing recommendations.

The role of clozapine specifically in the management of Treatment Resistant Schizophrenia (TRS).

The safety profile of clozapine and monitoring recommendations.

Results

Seven CPGs met the inclusion criteria for analysis: American Psychiatric Association (APA) [14], British Association for Psychopharmacology (BAP) [15], Canadian Psychiatric Association (CPA) [16], Royal Australian and New Zealand College of Psychiatrists (RANZCP) [17], National Institute for Health and Care Excellence (NICE) [18], Scottish Intercollegiate Guidelines Network (SIGN) [19], and the World Federation of Societies of Biological Psychiatry (WFSBP) [20-22]. Table 1 provides a summary of the CPGs included, when they were published, and the description of the levels of evidence and strength of recommendations that were used in each. Table 2, 3 and 4 provide summaries of the data extracted from the various CPGs. More specifically, Table 2 provides information in regards to the overall role of clozapine in the treatment of schizophrenia; Table 3 provides information on the safety profile of clozapine, side effect management, and monitoring recommendations. Table 4 summarizes the management strategies for TRS as provided by the CPGs reviewed.

Discussion

 Relevant findings of this review of seven CPGs reveal that clozapine has strong evidence for important efficacy outcomes in schizophrenia, such as:

Reduction of mortality: No large, long-term, Randomized Controlled Trials (RCTs) have studied the effects of clozapine or of other antipsychotic medications on mortality. However, the results of two large pharmaco-epidemiological cohort studies have consistently shown that treatment with clozapine is associated with a reduction in all-cause mortality in patients with schizophrenia [23,24]. In one of these studies, the mortality rate also increased one year after clozapine discontinuation [24]. These findings are consistent with results of a recent meta-analysis where the mortality rate was reported to be significantly lower in patients who are continuously treated with clozapine as compared to those treated with other antipsychotics [25].

Decreased hospitalization: The hospitalization rate among patients with schizophrenia is high, regardless of the stage of the disease [26-28]. This may be due to relapse, non-compliance, or no response to treatment. Even though clozapine is usually started while patients are in hospital, studies have consistently shown that treatment with clozapine is associated with a reduction in hospitalization and re-hospitalization rates by 20-30%, especially when it is used in patients with suicidal or aggressive behavior [29-34]. Combination of clozapine with other antipsychotics, such as aripiprazole, has shown even better reduction in hospitalization rates when compared to clozapine alone [32,34].

![Identification of new studies via databases and registers](image)

**Figure 1:** Flow chart of literature search strategy.

**Legend:** NGC: National Guideline Clearinghouse.
| CPG Publication Title (Reference) | Publication Date | Publishing Association | Levels of evidence and strength of recommendations |
|----------------------------------|-----------------|------------------------|-------------------------------------------------|
| Practice guideline for the treatment of patients with schizophrenia [14] | 2020 | American Psychiatric Association (APA) | A) High confidence that the evidence reflects the true effect. B) Moderate confidence that the evidence reflects the true effect. C) Low confidence that the evidence reflects the true effect. 1) Benefits clearly outweigh harms (recommendation). 2) Benefits are still viewed as outweighing the harms; the balance of benefits and harms is more difficult to judge (suggestion). |
| Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology [15] | 2020 | British Association for Psychopharmacology (BAP) | Ia) Evidence from MA of RCTs. Ib) Evidence from at least one RCT. Ila) Evidence from at least one controlled study without randomization. Ib) Evidence from at least one other type of quasi-experimental study. III) Evidence from non-experimental descriptive studies, such as comparative studies, correlation studies and case-control studies. IV) Evidence from expert committee reports or opinions and/or clinical experience of respected authorities. |
| Guidelines for the pharmacotherapy of schizophrenia in adults [16] | 2017 | Canadian Psychiatric Association (CPA) | Adapted from recommendations of other international CPGs. The strength or grade of the recommendations provided were extracted from the specific CPG that was used. The novo recommendations were created, and the SIGN methodology was used to grade the level of evidence and the grades of recommendation. |
| Clinical practice guidelines for the management of schizophrenia and related disorders [17] | 2016 | Royal Australian and New Zealand College of Psychiatrists (RANZCP) | I) A SR of level II studies II: A RCT. Ii-1) A pseudo-RCT (i.e. alternate allocation or some other method). II-2) A comparative study with concurrent controls (non-randomized, experimental trial). IIi-3) A comparative study without concurrent controls. IV) Case series with either post-test or pre-test/post-test outcomes. N/A: Level of evidence category does not apply. |
| Psychosis and schizophrenia in adults. Treatment and management [18] | 2014 | National Collaborating Centre for Mental Health. The National Institute for Health and Care Excellence (NICE) | Strength of recommendations: Interventions that must (or must not) be used: consequences of not following the recommendation could be extremely serious or potentially life threatening. Interventions that should (or should not) be used: a “strong” recommendation, for the majority of patients, the intervention will do more good than harm and be cost-effective. Interventions that could be used when an intervention will do more good than harm for most patients, and be cost-effective, but other options may be similarly cost-effective. |
| Management of schizophrenia [19] | 2013 | Scottish Intercollegiate Guidelines Network (SIGN) | 1++) High-quality MA; SR of RCTs, or RCTs with a very low risk of bias; 1+) Well-conducted MA, SR, or RCTs with a low risk of bias; 1: MA, SR, or RCTs with a high risk of bias 2++ High-quality SR of case control or cohort studies or high-quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal; 2+) Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal; 2) Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal 3) Nonanalytic studies (e.g, case reports, case series) 4: Expert opinion Grades of recommendation A) At least one MA, SR, or RCT rated (1++). B) A body of evidence including studies rated as (2++). C) A body of evidence including studies rated as (2+). D) Evidence level 3 or 4. Good Practice Point: Recommended best practice based on the clinical experience of the CPGs’ development group. |
Decreased relapse rate: There are a few head-to-head studies comparing different antipsychotic medications in relapse prevention. All Second-Generation Antipsychotics (SGAs) have shown superiority over First-Generation Antipsychotics (FGAs), and thus are recommended as first-line in all the schizophrenia guidelines reviewed [6,35,36]. However, CPGs do not recommend any particular SGA for relapse prevention. Clozapine and Long Acting Injectable Antipsychotics (LAIAPs) have been reported as having the highest relapse prevention rates [22]. Because LAIAPs are known to improve adherence in schizophrenia [37], some guidelines are recommending their use in combination with clozapine for relapse prevention [15,17].

Increased adherence: Non-adherence to treatment has been associated with negative patient outcomes, such as becoming aggressive, increased risk to self-harm and increased likelihood of substance misuse [38-40]. Thus, it has been suggested that the efficacy of clozapine in the management of patients with suicidal or aggressive behavior may be due to improved adherence while on clozapine treatment [33]. Both, APA and BAP guidelines provide several strategies for improving adherence in schizophrenia, such as the use of LAIAPs, regular contact with patients, or measuring the medication’s plasma concentration [14,15].

Cost-effectiveness: Results of the CUtLASS band 2 study, which compared clozapine with other SGA medications, clozapine showed to be more efficacious but resulted in higher treatment costs [41]. However, the NICE guideline attributes the higher costs possibly
### Table 3: Schizophrenia CPGs recommendations on the safety and monitoring requirements for clozapine therapy.

|                | CPG                  | APA | BAP | CPA | RANZ | NICE | SIGN | WFSBP |
|----------------|----------------------|-----|-----|-----|------|------|------|-------|
| **Safety profile and management** |                      |     |     |     |      |      |      |       |
| Agranulocytosis/Neutropenia | √                   | √   | √   | √   | √    | √    | √    |       |
| Reported incidence | 1.5 - 2% | NR   | NR   | NR   | NR   | NR   | NR   | NR    |
| Management | D/C | Low dose of lithium | NR | NR | NR | D/C* |       |       |
| Frequency of monitoring | Following REMS program: | Weekly from initiation to 6 months | Every 2 weeks from 6 to 12 months | Monthly after 12 months | NR | NR |       |       |
|                  | Weekly for the first 18 weeks, every 4 weeks thereafter | Routinely | NR |       |       |       |       |
|                  | Twice per month within the first 4-6 months |       |       |       |       |       |       |
| **Seizures (dose related)** | √ | √ | √ | √ | √ | √ | √ | √ |
| Reported incidence | 1 - 4.4% | NR | NR | NR | NR | NR | NR | 3% |
| Management | Neurological consultation | NR | NR | NR | NR | NR | NR |       |
| **Sialorrhea** | √ | √ | √ | √ | √ | √ | √ | √ |
| Reported incidence | Frequent | NR | NR | NR | NR | NR | NR | Frequent |
| Management | Sugarless gum | Towel on pillow | Dose reduction or sublingual anticholinergic | NR | NR | NR | NR | NR | Pirenzipine 25-50 mg/day | Dose reduction |
| **Metabolic abnormalities** |                      |     |     |     |      |      |      |       |
| **Diabetes Mellitus (DM)** | √ | √ | √ | √ | √ | √ | √ | √ |
| Reported incidence | High* | NR | NR | NR | NR | NR | NR | NR |
| Management | Follow current DM guidelines | Encourage DM self-management | Lifestyle interventions | NR | Monitor serum glucose | Diet and hypoglycemic medications | Monitor DM complications | NR | NR | Refer to a diabetologist |
| **Dyslipidemia** | √ | √ | √ | √ | √ | √ | √ | √ |
| Reported incidence | High* | NR | NR | NR | NR | NR | NR | NR |
| Management | Treat with a lipid-lowering agent | Lifestyle interventions | NR | Monitor lipid profile every 6-12 months | Lifestyle interventions | Treat with a statin | NR | NR | NR |
| **Weight gain/obesity** | √ | √ | √ | √ | √ | √ | √ | √ |
| Reported incidence | Common* | NR | NR | NR | NR | NR | High | High |
| Management | Prevention of weight gain* | Lifestyle interventions | NR | Lifestyle interventions | Consider metformin | NR | Lifestyle interventions | Consider metformin | PS | Psychosocial interventions | Add: -Amantadine -Rosaglitazone -Topiramate |
| **Myocarditis** | √ | √ | √ | √ | √ | √ | √ | √ |
| Reported incidence | 0.015 - 8.5% | NR | NR | NR | NR | NR | NR | 0.01 - 0.2% |
| Management | D/C | D/C* | NR | NR | NR | NR | NR | D/C |
| **Venous Thromboembolism** | √ | √ | √ | √ | √ | √ | √ | √ |
| Reported incidence | NR | High* | NR | NR | NR | NR | NR | NR |
| Management | NR | NR | NR | NR | NR | NR | NR | NR |
| **Sedation** | √ | √ | √ | √ | √ | √ | √ | √ |
| Reported incidence | NR | NR | NR | NR | NR | NR | NR | NR |
| Management | Lowering daily dose | Take in the evening | NR | NR | Reduce dose (if possible)* | NR | NR | NR |
| **Constipation** | √ | √ | √ | √ | √ | √ | √ | √ |
| Reported incidence | NR | NR | NR | NR | NR | NR | NR | NR |
| Management | Avoid use of other medications with anti-cholinergic effects | Increase physical activity | Laxatives | NR | NR | High-fibre dietary supplement | Increase physical activity | Laxatives | NR | NR | Dietary supplements | Increase physical activity | Laxatives | Increase fluid intake |
| **Other** | √ | √ | NR | √ | NR | NR | NR | √ |
because, at the time when the study was conducted, patients needed to be hospitalized to start clozapine therapy [18]. As clozapine treatment can nowadays be initiated in an outpatient setting in most countries, there is a need for its cost-effectiveness to be re-examined, particularly in TRS. Overall, costs of clozapine treatment differ by country and geographic region, as well as in the payment models throughout different health systems [14,15].

**Clozapine indications in people with schizophrenia**

Management of TRS: All the schizophrenia CPGs reviewed provided strong supporting evidence on clozapine’s efficacy in the management of TRS and was recommended as the agent of first choice for this indication. The main difference among the CPGs was in relation to the definition of TRS, and on recommendations about when to start clozapine in the course of the disease. It has been suggested that variations in these definitions are the result of an inconsistent criteria used to include patients with TRS in clinical trials [4]. In addition, key aspects of determining treatment resistance, such as adherence to prior antipsychotic use, is not consistently assessed [10]. Another important difference in the recommendations provided in the schizophrenia CPGs is in regards to the treatment of choice for patients experiencing Clozapine Resistance (CR). The WFSBP and the RANZCP guidelines suggest switching to another SGA as monotherapy before considering augmentation strategies, while the other guidelines recommend augmentation with antipsychotic medications as the first step. These are mostly low-grade recommendations, as evidence from RCTs for the management of CR among TRS patients is limited and mostly supported by unpowered studies [32,42]. Some CPGs recommend to consider combination with medications with a complementary receptor profile to clozapine, but with a different safety profile [14,15].

The last treatment option for patients with TRS recommended in the CPGs reviewed is the use of Electroconvulsant Therapy (ECT) alone or as adjuvant. Although there are limited number of studies on the use of ECT in TRS, the results are generally positive in terms of safety and efficacy [43,44]. ECT has shown to reduce the rate of relapse in TRS when added to clozapine. However, this is only reported for patients who showed benefit from ECT before meeting the criteria for TRS [45]. A recent international initiative of experts in the field of schizophrenia developed consensus recommendations for the management of CR TRS patients [34]. Raising clozapine plasma levels to ≥350 ng/ml for CR patients with positive, negative, and mixed symptoms was recommended. For CR patients with mostly positive symptoms, combination with a SGA (such as amisulpride or oral aripiprazole), and augmentation with ECT or with a mood-stabilizer or with another antipsychotic medication (particularly for TRS patients with CR aggressive symptoms) were recommended. For CR patients with predominant negative symptoms, augmentation with an antidepressant or with a mood-stabilizer (particularly for TRS patients with CR suicidality) and ECT were recommended [34].

**Other indications:** Other schizophrenia-related indications for clozapine that were generally supported with relatively high levels of evidence in the CPGs was the management of aggressive behavior and of suicidal risk. Numerous studies have demonstrated the superiority of clozapine over other antipsychotic medications in reducing the rates of self-harm, suicidal attempts, and suicidal mortality [24,46-48]. The anti-hostility effect of clozapine has also

| Anticholinergic SEs | √ | NR | NR | √ | NR | NR | √ |
|---------------------|---|----|----|---|----|----|---|
| Orthostatic hypotension | √ | NR | NR | √ | NR | NR | √ |
| Lower risk of EPS | √ | NR | NR | √ | √ | √ | √ |
| Monitoring requirements | | | | | | | |
| Hematological | √ | NR | NR | √ | √ | √ | NR | √ |
| TDM | √ | √ | √ | NR | √ | √ | NR | √ |
| Emergent SEs | √ | √ | √ | NR | √ | √ | NR | √ |
| Smoking | NR | NR | √ | √ | NR | NR | NR | √ |
| ECG | NR | NR | NR | √ | NR | NR | NR | √ |
| Baseline Troponin | NR | NR | NR | √ | NR | NR | NR | NR |

Legend: CPGs: Clinical Practice Guidelines; APA: American Psychiatric Association; BAP: British Association for Psychopharmacology; NICE: National Institute for Health and Care Excellence; RANZCP: Royal Australian and New Zealand College of Psychiatrists; CPA: Canadian Psychiatric Association; SIGN: Scottish Intercollegiate Guidelines Network; WFSBP: World Federation of Societies of Biological Psychiatry; NR: None Reported; D/C: Discontinuation; NR Not Reported; BZDs: Benzodiazepines; TDM: Therapeutic Drug Monitoring; SEs: Side Effects; EPS: Extrapyramidal Symptoms; ECG: Electrocardiogram; REMS: Risk Evaluation and Mitigation Strategy.

*Cooperate with a haematologist. Prevent infections, regular monitoring of white blood cell and neutrophil counts.
*Compared to other antipsychotics, clozapine and olanzapine have the highest incidence.
*Gestational diabetes.
*Different antipsychotics have similar incidence.
*Behavioral interventions is preferred.
*Consult with cardiologist.
*Highest with clozapine, olanzapine and low-potency first generation antipsychotics. The risk is higher in younger patients.
*Avoid concomitant use of other central nervous system depressants.
*Drink small amounts of fluid frequently. Use other oral hygiene products for dry mouth.
*Advise to stand up slowly from a sitting or lying position.
*In general for all antipsychotic medications.
*Use a self-report instrument; eg: Glasgow Antipsychotic Side Effect Scale specific for clozapine (GASES-C).
*Encourage smoking cessation.
*Screening at baseline, at weeks 4, 8 and 12, and then annually.
consistently been demonstrated in several studies regardless of any symptom improvement (positive or negative) [30,33,49].

The WFSBP was the only guideline that provided supportive evidence for the use of clozapine in first episode psychosis (FEP) [20]. Recent studies have shown significant higher rates of remission and lower rates of re-hospitalization in treatment naïve patients who treated with clozapine compared to those who were given different antipsychotics [50-53]. Studies have also shown a response rate of 75-80% when clozapine was initiated early in the treatment of schizophrenia [54]. However, most CPGs do not recommend initiating clozapine for FEP primarily due to safety concerns, particularly its hematological risk profile [14,15,17,20]. In addition, concerns about a higher incidence of adverse effects in younger patients (who are likely those experiencing FEP) have been reported [55,56]. Only the WFSBP and SIGN guidelines provide general statements on the efficacy of clozapine in treating primary negative symptoms [19,20]. No studies were found on clozapine’s efficacy on primary negative symptoms compared to placebo. Although studies have shown that clozapine is effective for the treatment of negative symptoms when compared to FGA and some SGAs, in trials that lasted longer than 3 months, the efficacy of FGA on negative symptoms was not significantly different than when using SGAs [30,33,57-63]. In general, based on the recommendation provided in the CPGs reviewed, there is no pharmacological treatment for the management of primary negative symptoms. Further studies are needed to address the specific role of

| Table 4: Definition and recommendations for the management of TRS in the schizophrenia CPGs. |
|---------------------------------|---------------------------------|---------------------------------|
| CPG | Definition of TRS (when to start clozapine) | Management Algorithm |
|---------------------------------|---------------------------------|---------------------------------|
| APA [14] | Persistence of Sx despite adequate Rx Tx: Total duration of Sx of at least 12 weeks, of at least moderate severity, and associated with at least moderate functional impairment as determined by validated rating scales. or If a prospective medication trial of 2 APs at least six weeks at adequate dose has not led to Sx reduction of more than 20%, and if the likelihood of substantial Sx improvement (e.g., >50%) is small. | Clozapine with careful monitoring to minimize the risk of harm*(1B) ↓ Augmentation of clozapine with another AP/AD/MS, or Augment clozapine/other AP with ECT |
| BAP [15] | Failure to respond to 2 trials of AP medication, of adequate dose and duration. | Clozapine is first-line Tx*(A) ↓ Augmentation strategies with clozapine*(B), or Combined non-clozapine AP medications*(B), or Augmentation strategies with other classes of medications*(B), High-dose AP medication*(B) |
| CPA [16] | Two clearly identified adequate but failed AP trials or Persistence of 2 or more positive Sx (less than 20% reduction) of at least a moderate level of severity, or a single positive Sx with severe or greater severity, following 2 or more adequate trials with different AP medications. | Clozapine should be offered as first-line treatment*(B) |
| RANZCP [17] | Continued positive Sx after trials of at least 2 different APs at moderate doses (usually at least 300 mg of chlorpromazine equivalents per day) for a reasonable period (usually at least 6 weeks). Tx-resistant disease should be recognized within 6-12 months of starting potentially effective AP Tx and confirmed as soon as possible. | Clozapine is first-line Tx*(I) ↓ If no response and/or side effects are severe, a switch is suggested ↓ When clozapine monotherapy is ineffective, augmentation with other medicines or ECT*(III-1) |
| NICE [18] | Lack of satisfactory clinical improvement despite the use of adequate doses of at least 2 different AP medications, including an atypical AP, prescribed for adequate duration (at least 4 weeks each) or ‘Incomplete recovery’ defined as the presence of lasting disability in functional and psychosocial aspects despite psychological/psychosocial and Rx interventions, while also recognizing the potential for improvement. | Clozapine is first-line Tx |
| SIGN [19] | Lack of satisfactory clinical improvement despite the use of adequate doses of at least 2 different AP medications, including an atypical AP, prescribed for adequate duration (at least 4 weeks each) or ‘Incomplete recovery’ defined as the presence of lasting disability in functional and psychosocial aspects despite psychological/psychosocial and Rx interventions, while also recognizing the potential for improvement. | Clozapine is first-line Tx |
| WFSBP [20] | A situation in which a significant improvement of psychopathology and/or other target symptoms has not been demonstrated despite Tx with 2 different AP medications from at least 2 different chemical classes (at least one should be an atypical AP), at the recommended AP dosages for a Tx period of at least 2-8 weeks per drug trial. | Clozapine is first-line Tx*(I) |

Legend: CPGs: Clinical Practice Guidelines; APA: American Psychiatric Association; BAP: British Association for Psychopharmacology; NICE: National Institute for Health and Care Excellence; RANZCP: Royal Australian and New Zealand College of Psychiatrists; CPA: Canadian Psychiatric Association; SIGN: Scottish Intercollegiate Guidelines Network; WFSBP: World Federation of Societies of Biological Psychiatry; Sx: Symptoms; Rx: Pharmacological; Tx: Treatment; AP: Antipsychotic; AD: Antidepressant; MS: Mood Stabilizer; ECT: Electroconvulsant Therapy; SGA: Second Generation Antipsychotics.

*Level of evidence or grade of recommendation, as per the specific clinical practice guideline (described in Table 1). †This level of evidence is only reported in combination with lamotrigine. ‡Depending on the drug, the level of evidence is varied from B to F.
Clozapine's safety profile

Our review identified that overall CPGs provided limited information about certain aspects of clozapine’s safety profile and monitoring recommendations. Agranulocytosis is the most serious, but rare, side effect of clozapine, but its incidence has significantly been reduced from 1-2% (when first reported) to 0.9% [64]. This was mostly achieved because of the mandatory hematological monitoring that is required for all patients during the first year of clozapine treatment [65,66]. Although all the CPGs promote adherence to the monitoring requirements in order to ensure positive efficacy and safety outcomes in patients with TRS, there are discrepancies in regards to the required hematological monitoring among all the CPGs. Some guidelines are very prescriptive, for example, the APA requires that clozapine prescribers register under the Food and Drug Administration (FDA) Risk Evaluation and Mitigation Strategy (REMS) program, which requires weekly hematological monitoring from initiation to 6 months, followed by every 2 weeks from 6 to 12 months [14], while the NICE guideline only recommends routine monitoring without being too prescriptive [18]. Considering that this particular safety aspect of clozapine is associated to clinicians preferring the use of less effective treatment options [67], it is important that consensus among the different CPGs is established in regards to the optimal (and safest) frequency of hematological monitoring. Another aspect of limited information on all the CPGs is in relation to clozapine’s interactions with smoking. Only APA, NICE, and RANZCP guidelines describe the effect of smoking on clozapine metabolism and how to manage schizophrenia treatment among smokers [14,17,18]. Smoking induces the main enzyme system responsible for the metabolism of clozapine (particularly CYP 1A2), leading to a potential reduction of clozapine plasma levels by up to 50% [68-70]. Therefore, higher doses of clozapine are required to achieve the therapeutic plasma levels in smokers. However, the majority of the schizophrenia CPGs do not sufficiently address this interaction in the smoker population. Recommendations, such as offering patient smoking cessation therapies, dose adjustments and monitoring of clozapine plasma levels, to minimize the potential decreased efficacy of clozapine among smokers, need to be consistently provided in CPGs.

Conclusions and Recommendations

A total of seven schizophrenia CPGs were identified in this systematic review of the literature, and vary in the scope of information presented. Numerous recommendations were consistently provided across all the CPGs reviewed, which would assist in clinical decision making when treating patients experiencing TRS, including:

- Clozapine remains the first treatment option with the strongest supportive evidence.
- Clozapine monotherapy is preferred. There is lack of evidence in support of antipsychotic polypharmacy.
- The evidence for augmentation of medications for clozapine refractory (CR) patients is limited, and mostly supported by unpowered studies.

This study also helped to identify some gaps in our knowledge about TRS treatment. Main differences in the recommendations provided were in relation to the definition of TRS, on the management of TRS patients who do not respond to clozapine treatment, on the breath of information in relation to clozapine’s safety profile, and on the frequency of hematological monitoring, that is required during clozapine treatment.

Future iterations of CPGs should seek consensus on certain aspects of TRS, particularly in regards to a clear definition of TRS and standardized measurements of response to treatment. As the safety profile of clozapine appears to be the main limiting factor for starting clozapine, CPGs should also provide support and advice on strategies to address them, such as implementation of clozapine clinics, multidisciplinary team involvement, and smoking cessation programs.

Declaration

Acknowledgements: We extend our thanks to the students in the Doctor in Pharmacy program at College of Pharmacy, Qatar University, who through their clinical rotations in mental health practice contributed to the literature review.

Author contributions: MZ contributed to the conception, design, and research protocol, in addition to being involved in all aspects of data analysis and manuscript revisions for intellectual content MN contributed to data collection, data analysis, and preparation of the manuscript. YE and OA contributed to the data collection process and critically revising the manuscript.

References

1. Kane JM. Addressing nonresponse in schizophrenia. J Clin Psychiatry. 2012; 73: e07.
2. Kane J, Honigfeld G, Singer J, Meltzer H. Clozapine for the treatment-resistant schizophrenic: a double-blind comparison with chlorpromazine. Arch Gen Psychiatry. 1988; 45: 789-796.
3. Suzuki T, Remington G, Mulsant BH, Uchida H, Rajji TK, Graf-Guerrero A, et al. Defining treatment-resistant schizophrenia and response to antipsychotics: a review and recommendation. Psychiatry Res. 2012; 197: 1-6.
4. Howes OD, McCutcheon R, Agid O, De Bartolomeis A, Van Beveren NJ, Birnbaum ML, et al. Treatment-resistant schizophrenia: Treatment Response and Resistance in Psychosis (TRRIP) working group consensus guidelines on diagnosis and terminology. Am J Psychiatry. 2017; 174: 216-229.
5. Miyamoto S, Jarskog LF, Fleischhacker WW. New therapeutic approaches for treatment-resistant schizophrenia: a look to the future. J Psychiatr Res. 2014; 58: 1-6.
6. Chakos M, Lieberman J, Hoffman E, Bradford D, Sheitman B. Effectiveness of second-generation antipsychotics in patients with treatment-resistant schizophrenia: a review and meta-analysis of randomized trials. Am J Psychiatry. 2001; 158: 518-526.
7. Lewis SW, Barnes TR, Davies L, Murray RM, Dunn G, Hayhurst KP, et al. Randomized controlled trial of effect of prescription of clozapine versus other second-generation antipsychotic drugs in resistant schizophrenia. Schizophr Bull. 2006; 32: 715-723.
8. McEvoy JP, Lieberman JA, Stroup TS, Davis SM, Meltzer HY, Rosenheck RA, et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. Am J Psychiatry. 2006; 163: 600-610.
9. Faye K, Flowers C, Signorelli D, Simpson G. Psychopharmacology: underuse of evidence-based treatments in psychiatry. Psychiatr Serv. 2003; 54: 1453-1454, 1456.
10. Howes OD, Vergunst F, Gee S, McGuire P, Kapur S, Taylor D. Adherence to...
treatment guidelines in clinical practice: study of antipsychotic treatment prior to clozapine initiation. Br J Psychiatry. 2012; 201: 481-485.

11. Ismail D, Tounsi K, Zolezzi M, Eltorky Y. A qualitative exploration of clozapine prescribing and monitoring practices in the Arabian Gulf countries. Asian J Psychiatr. 2019; 39: 93-97.

12. Kelly D, Kreyenbuhl J, Buchanan R, Malhotra A. Why not clozapine? Clinical Schizophrenia & Related Psychoses. 2007; 1: 92-96.

13. Wamze S, Alessi-Severini S. Clozapine: a review of clinical practice guidelines and prescribing trends. BMC Psychiatry. 2014; 14: 102.

14. American Psychiatric Association. The American psychiatric association practice guideline for the treatment of patients with schizophrenia. American Psychiatric Pub. 2020.

15. Barnes TR, Drake R, Paton C, Cooper SJ, Deakin B, Ferrier IN, et al. Evidence-based guidelines for the pharmacological treatment of schizophrenia: Updated recommendations from the British Association for Psychopharmacology. J Psychopharmacol. 2020; 34: 3-78.

16. Remington G, Addington D, Honer W, Ismail Z, Raedler T, Teehan M. Guidelines for the pharmacotherapy of schizophrenia in adults. Can J Psychiatry. 2017; 62: 604-616.

17. Galletly C, Castle D, Dark F, Humberstone V, Jablensky A, Killackey E, et al. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. Aust N Z J Psychiatry. 2016; 50: 410-472.

18. National Collaborating Centre for Mental Health (UK), Psychosis and Schizophrenia in Adults: Treatment and Management: Updated Edition. London: National Institute for Health and Care Excellence (UK). 2014.

19. Scottish Intercollegiate Guidelines Network (SIGN). Management of schizophrenia. A national clinical guideline. SIGN 131.

20. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, 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: 318-378.

21. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, et al. WFSBP task force on treatment guidelines for schizophrenia. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of schizophrenia, part 2: update 2012 on the long-term treatment of schizophrenia and management of antipsychotic-induced side effects. World J Biol Psychiatry. 2013; 14: 2-44.

22. Hasan A, Falkai P, Wobrock T, Lieberman J, Glenthoj B, Gattaz WF, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Schizophrenia. Part 3: Update 2015 Management of special circumstances: Depression, Suicidality, substance use disorders and pregnancy and lactation. World J Biol Psychiatry. 2015; 16: 142-170.

23. Cho J, Hayes RD, Jewell A, Kadra G, Shetty H, MacCabe JH, et al. Clozapine and all-cause mortality in treatment-resistant schizophrenia: a longitudinal cohort study. Acta Psychiatr Scand. 2019; 139: 237-247.

24. Wimberley T, MacCabe JH, Laursen TM, Sørensen HJ, Astrup A, Horsdal HT, et al. Mortality and Self-Harm in Association With Clozapine in Treatment-Resistant Schizophrenia. Am J Psychiatry. 2017; 174: 990-998.

25. Vermeulen JM, van Roorjen G, van de Kerkhof MPJ, Alcorn SL, Correll CU, de Haan L. Clozapine and long-term mortality risk in patients with schizophrenia: a systematic review and meta-analysis of studies lasting 1.1-12.5 years. Schizophr Bull. 2019; 45: 315-329.

26. Helgason L. Twenty years’ follow-up of first psychiatric presentation for schizophrenia: what could have been prevented? Acta Psychiatr. Scand. 1990; 81: 231-235.

27. Hegarty JD, Baldessarini RJ, Tohen M, Watermuis C, Oepen G. One hundred years of schizophrenia: a meta-analysis of the outcome literature. Am J Psychiatry. 1994; 151: 1409-1416.

28. Lehman AF, Lieberman JA, Dixon LB, McGlashan TH, Miller AL, Perkins DO, et al. Practice guideline for the treatment of patients with schizophrenia, second edition. Am J Psychiatry. 2004; 161: 1-56.

29. Land R, Siskind D, McArine P, Kisely S, Winckel K, Hollingworth SA. The impact of clozapine on hospital use: a systematic review and meta-analysis. Acta Psychiatr Scand. 2017; 135: 296-309.

30. Melitz HY. Suicide in schizophrenia, clozapine, and adoption of evidence-based medicine. J Clin Psychiatry. 2005; 66: 530-533.

31. Tihhon J, Mittendorfer-Rutz E, Majak M, Mehtlal J, Hottl F, Jedenius E, et al. Real-World Effectiveness of Antipsychotic Treatments in a Nationwide Cohort of 29,823 Patients With Schizophrenia. JAMA Psychiatry. 2017; 74: 668-673.

32. Tihhon J, Taipale H, Mehtilal J, Vattulainen P, Correll CU, Tanskanen A. Association of Antipsychotic Polypharmacy vs Monotherapy With Psychiatric Rehospitalization Among Adults With Schizophrenia. JAMA Psychiatry. 2019; 76: 499-507.

33. Victoroff J, Coburn K, Reeve A, Sampson S, Shillcutt S. Pharmacological management of persistent hostility and aggression in persons with schizophrenia spectrum disorders: a systematic review. J Neuropsychiatry Clin Neurosci. 2014; 26: 283-312.

34. Wagner E, Kane JM, Correll CU, Howes O, Siskind D, Honer WG, et al. Clozapine Combination and Augmentation Strategies in Patients With Schizophrenia - Recommendations From an International Expert Survey Among the Treatment Response and Resistance in Psychosis (TRRIP) Working Group. Schizophr Bull. 2020; 46: 1459-1470.

35. Kishimoto T, Agarwal V, Kishi T, Leucht S, Kane JM, Correll CU. Relapse prevention in schizophrenia: a systematic review and meta-analysis of second-generation antipsychotics versus first-generation antipsychotics. Mol Psychiatry. 2013; 18: 53-66.

36. Leucht S, Barnes TR, Kissling W, Engel RR, Correll C, Kane JM. Relapse prevention in schizophrenia with new-generation antipsychotics: a systematic review and exploratory meta-analysis of randomized, controlled trials. Am J Psychiatry. 2003; 160: 1209-1222.

37. Salgueiro M, Segarra R. Long-acting injectable second-generation antipsychotics in first-episode psychosis: a narrative review. Int Clin Psychopharmacol. 2019; 34: 51-56.

38. Ascher-Svanum H, Faries DE, Zhu B, Ernst FR, Swartz MS, Swanson JW. Medication adherence and long-term functional outcomes in the treatment of schizophrenia in usual care. J Clin Psychiatry. 2006; 67: 453-460.

39. Herings RM, Erkens JA. Increased suicide attempt rate among patients interrupting use of atypical antipsychotics. Pharmacoepidemiol Drug Saf. 2003; 12: 423-424.

40. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM, Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res. 2010; 176: 109-113.

41. Davies LM, Barnes TR, Jones PB, Lewis S, Gaughran F, Hayhurst K, et al. A randomized controlled trial of the cost-utility of second-generation antipsychotics in people with psychosis and eligible for clozapine. Value Health. 2008; 11: 549-562.

42. Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 pharmaco logic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: Systematic overview and quality appraisal of the meta-analytic evidence. JAMA Psychiatry. 2017; 74: 675-684.

43. Braga RJ, Petrides G. The combined use of electroconvulsive therapy and antipsychotics in patients with psychosis and eligible for clozapine. Value Health. 2008; 11: 549-562.

44. Novick D, Haro JM, Suarez D, Perez V, Dittmann RW, Haddad PM, Predictors and clinical consequences of non-adherence with antipsychotic medication in the outpatient treatment of schizophrenia. Psychiatry Res. 2010; 176: 109-113.

45. Davies LM, Barnes TR, Jones PB, Lewis S, Gaughran F, Hayhurst K, et al. A randomized controlled trial of the cost-utility of second-generation antipsychotics in people with psychosis and eligible for clozapine. Value Health. 2008; 11: 549-562.

46. Correll CU, Rubio JM, Inczedy-Farkas G, Birnbaum ML, Kane JM, Leucht S. Efficacy of 42 pharmaco logic cotreatment strategies added to antipsychotic monotherapy in schizophrenia: Systematic overview and quality appraisal of the meta-analytic evidence. JAMA Psychiatry. 2017; 74: 675-684.

47. Braga RJ, Petrides G. The combined use of electroconvulsive therapy and antipsychotics in patients with schizophrenia. J ECT. 2005; 21: 75-83.

48. Chappattana W, Sackeim HA. Electroconvulsive therapy in treatment-resistant schizophrenia: prediction of response and the nature of symptomatic improvement. J ECT. 2010; 26: 289-298.

49. Chappattana W, Charakhaev MD, Sackeim HA, Kitaroonchai W, Kongkason R, Techakasem P, et al. Continuation ECT in treatment-resistant schizophrenia: a controlled study. J ECT. 1999; 15: 176-192.

50. Hennsen J, Baldessarini RJ. Suicidal risk during treatment with clozapine: a meta-analysis. Schizophr Res. 2005; 73: 139-145.
56. Tiihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. 2011; 168: 603-609.

57. Zhu Y, Krause M, Huhn M, Rothe P, Schneider-Thoma J, Chaimani A, et al. Antipsychotic drugs for the acute treatment of patients with a first episode of schizophrenia: a systematic review with pairwise and network meta-analyses. Acta Psychiatr Scand. 2018; 138: 281-288.

58. Tihonen J, Haukka J, Taylor M, Haddad PM, Patel MX, Korhonen P. A nationwide cohort study of oral and depot antipsychotics after first hospitalization for schizophrenia. Am J Psychiatry. 2011; 168: 603-609.

59. Henningsen H, Konig D, Tiihonen J. Antipsychotics. A Systematic Review and Meta-analysis of Cohort Studies. JAMA Psychiatry. 2016; 73: 199-210.

60. Siskind D, McCartney L, Goldschlager R, Kistry S. Clozapine vs first- and second- generation antipsychotics in treatment-refractory schizophrenia: systematic review and meta-analysis. Br J Psychiatry. 2016; 209: 385-392.

61. Myles N, Mylles H, Xia S, Large M, Kistry S, Galletly C, et al. Meta-analysis examining the epidemiology of clozapine-associated neutropenia. Acta Psychiatr Scand. 2018; 138: 101-109.

62. Alvir JM, Lieberman JA, Safferman AZ, Schwimmer JL, Schaaf JA. Clozapine-induced agranulocytosis. Incidence and risk factors in the United States. N Engl J Med. 1993; 329: 162-167.

63. Honigfeld G, Arellano F, Sethi J, Bianchi A, Schein J. Reducing clozapine-related morbidity and mortality: 5 years of experience with the Clozaril National Registry. J Clin Psychiatry. 1998; 59: 3-7.

64. Ortiz-Orendain J, Castello-de Osseso S, Colunga-Lozano LE, Hu Y, Maayan N, Adams CE. Antipsychotic combinations for schizophrenia. Cochrane Database Syst Rev. 2017; 6: CD009005.

65. Anderson GD, Chan LN. Pharmacokinetic drug interactions with tobacco, cannabinoids and smoking cessation products. Clin Pharmacokinet. 2016; 55: 1353-1366.

66. Scherf-Clavel M, Samanski L, Hommers LG, Deckert J, Menke A, Unterecker S. Analysis of smoking behavior on the pharmacokinetics of antidepressants and antipsychotics: evidence for the role of alternative pathways apart from CYP1A2. Int Clin Psychopharmacol. 2019; 34: 93-100.

67. Taylor DM, Barnes T, Young AH. The Maudsley Prescribing Guidelines in Psychiatry. John Wiley & Sons. 2018.