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A Guideline Review on Treatment-Resistant Schizophrenia: A Focus on Clozapine and other Pharmacotherapeutic Strategies

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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 breath 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:

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- 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].

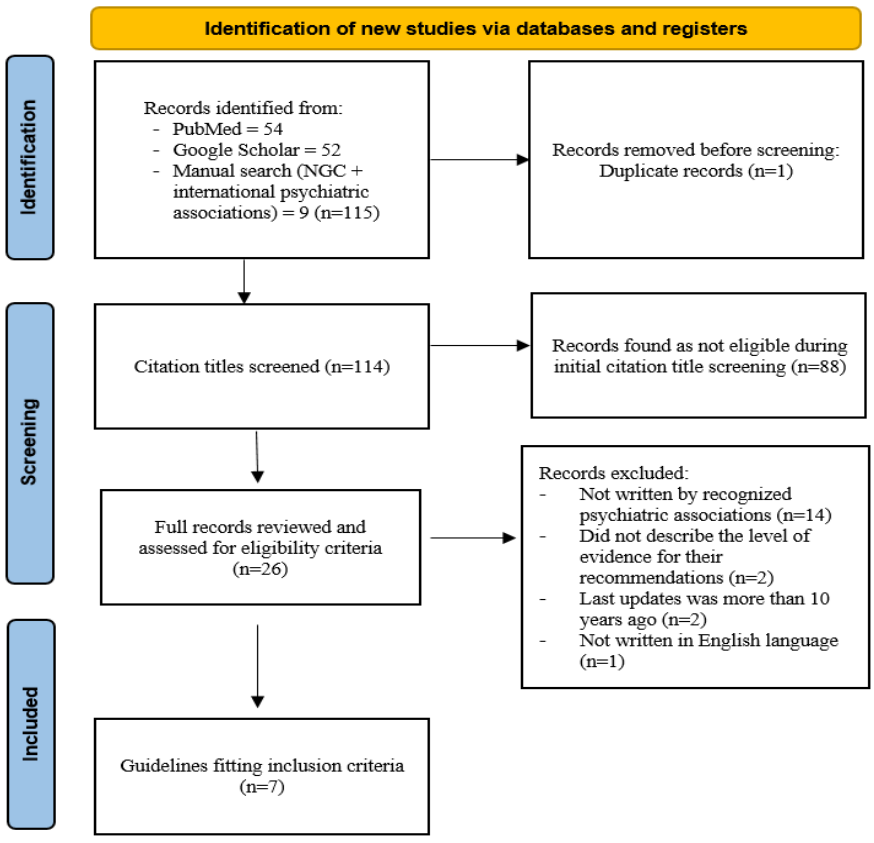

Figure 1: Flow chart of literature search strategy.
Legend: NGC: National Guideline Clearinghouse.

Table 1: Summary of schizophrenia clinical practice guidelines included in the scoping review.

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. IIa) Evidence from at least one controlled study without randomization. IIb) 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. **Strength of recommendation** A) Directly based on category I evidence. B) Directly based on category II evidence or extrapolated recommendation from category I evidence. C) Directly based on category III evidence or extrapolated recommendation from category I or II evidence. D) Directly based on category IV evidence or extrapolated recommendation from category I, II or III evidence.
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. III-1) A pseudo-RCT (i.e. alternate allocation or some other method). III-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.

Part 1) Acute treatment of schizophrenia and the management of treatment resistance [20]. Part 2) Long-term treatment of schizophrenia and management of antipsychotic-induced side effects [21]. Part 3) Management of special circumstances: Depression, suicidality, substance use disorders, and pregnancy and lactation [22].	2012 (Part 1) 2013 (Part 2) 2015 (Part 3)	World Federation of Societies of Biological Psychiatry (WFSBP)	A) Full evidence from controlled studies and one or more positive RCT. B) Limited positive evidence from controlled studies. C) Evidence from uncontrolled studies or case reports/expert opinion. D) Inconsistent results. E) Negative evidence F: Lack of evidence.

Legends: RCT: Randomized Controlled Trial; SR: Systematic Review; MA: Meta-Analysis; CPGs: Clinical Practice Guidelines.

Table 2: The role of clozapine in the treatment of schizophrenia.

CPG	APA	BAP	CPA	RANZCP	NICE	SIGN	WFSBP
Indications							
TRS	√*B1	√*A	√*A	√*I	√	√ *A	√*B
SCZ (all stages)		√					√*A[a]
Negative symptoms						√	√*B[b]
FEP		√*D					√*A
Other SCZ-related indications							
Suicide risk	√*B1			√	√		√*B
TD		√*B	√*D			√ *D	√*C
Aggression	√*C2	√*C		√*II	√		
SUD						√	√*C
MDD[c]							√
Efficacy outcomes							
Mortality rate	√*B	√					
Hospitalization rate	√*C	√d			√		√
Relapse rate		√					
Improved compliance					√		
Cost-effectiveness					√		
Dosing							
Therapeutic dose (mg/day)	300-450		400	S=12.5, M=900			400
Dosing in smokers	√		√	√	√		
Target trough levels (ng/ml)	≥350	350	350 OD 250 DD	N/A			≥350

Legends: CPG: Clinical Practice Guideline; APA: American Psychiatric Association; BAP: British Association for Psychopharmacology; NICE: National Institute for Health and Care Excellence; RANZE: 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; TRS: Treatment Resistant Schizophrenia; SCZ: Schizophrenia; TD: Tardive Dyskinesia; Red: Reduced; SUD: Substance Use Disorders; S: Starting Dose; M: Maximum Dose; OD: Once Daily Dosing; DD: Divided Dosing; FEP: First Episode Psychosis.

*Level of evidence or grade of recommendation, as per the specific clinical practice guideline (described in Table 1). [a]Only recommended as second-line treatment; [b]High level of evidence only for secondary negative symptoms; [c]Combined with antidepressant medications; [d]In comparison with depot antipsychotics.

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
Management	D/C	NR	NR	• Low dose of lithium	NR	NR	D/C[a]
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	3%
Management	Neurological consultation	NR	NR	NR	NR	NR	• Medical treatment with BZDs and anticonvulsant agents
Sialorrhea	√	√					√
Reported incidence	Frequent	NR	NR	NR	NR	NR	Frequent
Management	• Sugarless gum • Towel on pillow • Dose reduction or sublingual anticholinergic	NR	NR	NR	NR	NR	• Pirenzepine 25-50 mg/day • Dose reduction
Metabolic abnormalities							
Diabetes Mellitus (DM)	√	√		√		√[c]	√
Reported incidence	High[b]	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[b]	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[d]	NR	NR	NR	NR	High	High
Management	• Prevention of weight gain[e]	• Lifestyle interventions	NR	• Lifestyle interventions • Consider metformin	NR	• Lifestyle interventions • Consider metformin	• Psychosocial interventions • Add: -Amantadine -Rosaglitazone -Topiramate
Myocarditis	√	√		√			√
Reported incidence	0.015 - 8.5%	NR	NR	NR	NR	NR	0.01 - 0.2%
Management	D/C	D/C[f]	NR	NR	NR	NR	D/C[f]
Venous Thromboembolism	√	√					
Reported incidence	NR	High[g]	NR	NR	NR	NR	NR
Management	NR	NR	NR	NR	NR	NR	NR
Sedation	√	√		√		√	
Reported incidence	NR	NR	NR	NR	NR	NR	NR
Management	• Lowering daily dose • Take in the evening	NR	NR	• Reduce dose (if possible)[h]	NR	NR	NR
Constipation	√	√		√			√
Reported incidence	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							
Prolactin elevation risk	√	√	NR	√	NR	NR	√

Anticholinergic SEs	√	NR	NR	√[i]	NR	NR	√
Orthostatic hypotension	√	NR	NR	√[j]	NR	NR	√
Lower risk of EPS	√	NR	NR	NR	√	√	√
Monitoring requirements							
Hematological	√	NR	NR	√	√	NR	√
TDM	√	√	√	NR	√	√	NR
Emergent SEs	√[k,l]	√[l]		√	NR	NR	NR
Smoking	NR	NR	√[m]	√	NR	NR	NR
ECG	NR	NR	NR	√	NR	NR	√[n]
Baseline Troponin	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.

[a]Cooperate with a haematologist. Prevent infections, regular monitoring of white blood cell and neutrophil counts.

[b]Compared to other antipsychotics, clozapine and olanzapine have the highest incidence.

[c]Gestational diabetes.

[d]Different antipsychotics have similar incidence.

[e]Behavioral interventions is preferred.

[f]Consult with cardiologist.

[g]Highest with clozapine, olanzapine and low-potency first generation antipsychotics. The risk is higher in younger patients.

[h]Avoid concomitant use of other central nervous system depressants.

[i]Drink small amounts of fluid frequently. Use other oral hygiene products for dry mouth.

[j]Advise to stand up slowly from a sitting or lying position.

[k]In general for all antipsychotic medications.

[l]Use a self-report instrument; eg: Glasgow Antipsychotic Side Effect Scale specific for clozapine (GASES-C).

[m]Encourage smoking cessation.

[n]Screening at baseline, at weeks 4, 8 and 12, and then annually.

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 WFBSP 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

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), **or** 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) No consistent evidence to support the use of high doses, switching, or combining AP medications
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 ↓ If response to clozapine monotherapy is poor, augmentation strategies are considered, **or** High-dose AP medication
SIGN[19]	Failure to respond to an adequate trial of 2 different AP medications, including a SGA.	Clozapine should be offered as first-line Tx*(B) ↓ Clozapine augmentation with another AP*(C) ↓ Clozapine augmentation with other medications*(B)[a], **or** Switching to another AP, **or** High-dose AP medication*(D), **or** ECT*(C)
WFBSP[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*(B) Switch to another SGA*(B), **or** Combination of clozapine with another SGA (possibly risperidone)*(C), **or** AP combination therapy*(C), **or** Combination with other neuroactive drugs[b]: AD, anxiolytics, etc., **or** ECT*(D)

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); [a]This level of evidence is only reported in combination with lamotrigine; [b]Depending on the drug, the level of evidence is varied from B to F.

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

clozapine in this indication.

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

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