OFFERING PATIENTS THERAPEUTIC INFORMATION ON CLOZAPINE (OPTIC) ©

Patients suffering from schizophrenia often have an inadequate clinical response and less favourable functional outcome. It is important for physicians to use the most effective treatment possible. Although clozapine has proven its benefits for treatment resistant schizophrenia (TRS), it is still only prescribed in 20-50% of eligible patients.[1] The purpose of OPTIC is to provide guidance for physicians on what information to discuss with patients when offering clozapine as a treatment option. **Clozapine should be offered systematically to people with TRS as soon as they become eligible. This tool can facilitate a positive offer and increase acceptance of clozapine by your patient.**

CLINICAL RECOMMENDATIONS ON THE USE OF CLOZAPINE

Clozapine is a second-generation antipsychotic medication that has proven to be more effective than other antipsychotics for patients with TRS. Clozapine has been shown to improve remission rates, and reduce psychotic symptoms, risk of relapse, length of hospitalization, suicidal risk, and mortality. Despite its effectiveness, it remains underused in Canada, and is often prescribed as a last resort.[1] Physicians and patients often have negative perceptions towards the medication due to the side effects and specific laboratory monitoring requirements. However, according to Canadian guidelines, clozapine should be offered as a 3rd line therapy, i.e., after two unsuccessful trials of adequate dose and duration using other antipsychotic medications.[2] This is also referred to as TRS. It is important to discuss clozapine's effectiveness in treating TRS with patients to allow them to make an informed decision about their treatment. Clozapine should be offered to both in-patients and outpatients who have poor treatment response or lingering symptoms due to partial response with their current treatment. Patients who are highly suicidal, who have substance use disorders and who present with polydipsia may also benefit from clozapine.

RECOMMENDED APPROACH TO DISCUSSING CLOZAPINE

WHO

- People with treatment resistant schizophrenia (TRS) - i.e., unsatisfactory response to 2 adequate trials with other antipsychotic medication
- People with schizophrenia that have a high risk of suicidality
- People with schizophrenia and a co-morbid substance abuse disorder (possibly)
- People with schizophrenia who present polydipsia (possibly)[3]
- ***Contraindications: pre-existing myeloproliferative disorder, neutropenia, known hypersensitivity to clozapine.***[4]

WHEN

The response rate to an initial antipsychotic treatment is usually very high (roughly 70-80%). However, after the first trial, response rates significantly diminish. It is proven that repeated antipsychotic trials, other than clozapine, progressively decrease the likelihood of response. Therefore, it is important to examine the benefit of substituting antipsychotics.[5] Furthermore, resistance to treatment increases with successive relapses.[1] Given that clozapine is the only antipsychotic that demonstrates effectiveness after 2 unsuccessful trials with other antipsychotics, and that it reduces the risk of relapse, clozapine should be considered as the preferred 3rd line treatment of schizophrenia and should be considered as soon as the patient is diagnosed with TRS.[6]

TRS represents roughly one third of patients with schizophrenia. Patients with TRS often have more obvious abnormalities in brain imaging and they experience a higher individual and societal burden.[3] Therefore, it is important to initiate an effective treatment as soon as possible. A Canadian study of 244 patients showed that TRS can be identified as early as 12 weeks after treatment initiation. In that same study, patients classified as TRS showed a 75% response rate to clozapine.[2] The National Institute for Health and Care Excellence (NICE) in the United Kingdom also recommends initiating clozapine as soon as TRS is diagnosed.[1] It was shown that successful interventions have the greatest impact during the patient's critical period, i.e. within 5 years after the first symptoms.[2] Therefore, early initiation of clozapine for patients with TRS may increase its effectiveness and thus the likelihood that the patient enters a phase of personal and functional recovery.[2] It is suggested that delayed use of clozapine reduces the overall response rate to around 50-65%, as compared to 75% when it is initiated immediately after two unsuccessful trials with other antipsychotics.[2,7]

Despite all the evidence surrounding its effectiveness, clozapine is still generally perceived as a last resort and thus it is only given at a later stage of the disease. Often, it is attempted after at least 5 trials of other antipsychotic medication and when patients have been ill for 5 or more years.[1] Referring to TRS as "clozapine eligible schizophrenia" may reduce the belief that clozapine should be used as a last resort.

WHAT

Discuss clozapine with patients, emphasizing its benefits as the gold standard for TRS. It is assumed that people with whom clozapine is discussed have already failed at least two antipsychotic treatments.[8]

HOW

Suggestions for initiating the discussion:

- "We have talked about your goals and the importance of medication to manage your symptoms. We have tried different antipsychotics and have not succeeded in treating your symptoms. Now, I would like to talk to you about clozapine, which is an effective antipsychotic that is recommended for people like you who have not responded well to other medications."
- "We have already discussed your goals and why you need treatment with medication to achieve your goals. The medications we have tried so far have not allowed us to achieve your goals, I would like to discuss the option of clozapine. When compared to other antipsychotics, it has shown the best efficacy for patients with schizophrenia that do not respond to other medication."
- *If you are comfortable with this idea, you may add that you would offer this same treatment to your own family member suffering from treatment resistant schizophrenia.*
- "Now that you understand the importance of finding a medication that successfully reduces your symptoms, I would like to talk about a medication that is proven to be the most effective, clozapine. It is the gold standard for patients with treatment resistant schizophrenia like yourself.[8]"
- "Clozapine has a negative reputation among some patients because of its side effects and the requirement of regular blood tests. However, most side effects can be managed by lifestyle changes and medications. The blood tests are frequent at the beginning, but after the first year of treatment, the frequency of monitoring drops to every 4 weeks. It is also important to realize that the benefit of clozapine on your symptoms significantly outweighs its side effects and the need for blood tests."

Proceed to review the Clozapine Decision Aid and the Questionnaire with the patient. Ensure that answers are filled in before proceeding to the next question. Questions 1 and 2 below, taken directly from the *Clozapine Decision Aid*, are intended to initiate a discussion before proceeding to the *OPTIC Questionnaire*. At the end of the questionnaire, ask the patient to make a decision. Questions 4 and 5 below are intended to help guide that decision-making process.

> **Question 1**: **Why are you being offered clozapine for your symptoms?**
> *Review and help the patient understand the benefits of clozapine after two failed antipsychotic treatments (remission).*
> *Every other trial after the second antipsychotic has a response rate of roughly 10-20%, except for clozapine which has a response rate of 60-77%.*[9]

Question 2: **What are your options?**
The options are trying another antipsychotic medication, taking a combination of antipsychotics or clozapine. Review these options.

Question 3: **What do you think about the benefits and risks of clozapine?** *Use the questionnaire and decision aid.*
*Review each point of the questionnaire and have the patient respond **YES** or **NO** to the question about the importance of each benefit of clozapine. Repeat for the risks of clozapine. Make sure the patient's answers are recorded on the decision aid.*

Question 4: **Which option do you prefer?**
Have the patient indicate his or her preference.

Question 5: **What are your decision-making needs?**
Have the patient answer the four questions in this section. If the patient is still unsure about taking clozapine, ask about barriers to decision-making, answer questions, and attempt to resolve any uncertainties.

If the patient has not yet made a firm decision, review the Clozapine Decision Aid and the patient's responses to the OPTIC Questionnaire again. if the patient has not yet made a firm decision. This can be repeated as often as necessary. Once these forms have been reviewed and completed, place the originals in the individual's chart.

KEY POINTS TO REMEMBER ABOUT CLOZAPINE

1. SIDE EFFECTS

When reviewing clozapine's side effects with patients, it is important to adequately describe them so that patients can have an honest depiction of the medication. However, it should be mentioned that even though they are "common" side effects, not all patients will experience these symptoms. Furthermore, most of them can be adequately managed with a healthy lifestyle and/or pharmaceutical treatments. As for the severe side effects, given that clozapine is an older medication, a lot of information is available about its potential side effects and their associated risks are well documented. Also, many experts have recommended strategies to reduce the incidence of severe side effects. Therefore, they are now considered well-managed risks. It is also important to point out that despite the potentially severe side effects of clozapine, the medication is associated with a lower incidence of all-cause mortality when compared to schizophrenia treated with other antipsychotics and untreated schizophrenia. This demonstrates that clozapine's benefits significantly outweigh its potential side effects, especially if they are adequately managed.

When offering clozapine to patients, side effects should be presented relative to the other antipsychotics they may take, and emphasis should be placed on clozapine's unparalleled effectiveness in TRS.

Rare but severe

Agranulocytosis is the most feared side effect with clozapine, despite its incidence being very low.[10] Since the implementation of laboratory monitoring in the early 1990s, the incidence of agranulocytosis at its highest risk period, within the first year of treatment, is approximately 1%.[11] After the first year, the incidence decreases significantly to roughly 0.04%.[1,12] Laboratory monitoring allows for safer usage, as the physician is alerted at the first sign of neutropenia, thus reducing the risk of any serious complication. Therefore, agranulocytosis and severe neutropenia are now considered well-managed risks.[3]

Pneumonia is the most life-threatening side effect of clozapine, with a 30% fatality rate. Clozapine may increase the risk of pneumonia in patients; however, the high mortality is explained by pneumonia's ability to increase clozapine's concentration, increasing its risk of toxicity.[3] Lowering the patient's clozapine dosage during the time they are ill with pneumonia could help reduce this risk.

Clozapine has been associated with myocarditis with an incidence of approximately 0.3% with the highest risk being within the first 6 months of initiation.[12] Myocarditis is possibly explained by a type 1 hypersensitivity reaction due to a fast titration of clozapine or to its anticholinergic blockade. Therefore, to reduce the risk of myocarditis, it is recommended to initiate clozapine with a slow, personalized titration. Some clinicians also consider monitoring C-reactive protein (CRP) levels before initiation and during the 8 weeks of titration.[3] Despite increased risk of myocarditis, clozapine was not shown to increase mortality from ischemic heart disease when compared with other medication. In fact, along with olanzapine, after 7 years of exposure, it had a slightly lower incidence of total mortality and cardiovascular mortality compared to other antipsychotic medications.[13] If patients develop flulike symptoms (fever, headache, sore throat, myalgia, gastrointestinal distress, or fatigue), dyspnea, chest pain, peripheral edema, hypotension, or tachycardia, it is important to consider an echocardiogram to rule out potential myocarditis.[12,14]

The risk of developing seizures on clozapine is around 10% at 3.8 years of treatment. Seizures are a dose-dependent side effect, therefore lowering the dose can reduce its risk. Seizures are not a contraindication to continuing clozapine, since they can be adequately managed by antiseizure medications.[15]

Common

Constipation due to gastrohypomotility remains the most common side effect of clozapine. To prevent its occurrence and complications therefrom, physicians should recommend a high fiber diet, or prescribe laxatives, depending on patient risk factors. It is vital to advise patients to notify a healthcare professional if constipation occurs, since it needs to be treated promptly.[16]

Tachycardia and/or palpitations can be caused by clozapine, especially during initiation or upward dose-titration. It is normally a benign side effect that subsides after a few months of

treatment. If debilitating or persistent, tachycardia can be managed by a small dose of bisoprolol or another beta blocker.[12,17]

Hypersalivation, known as sialorrhea, is a common side effect with clozapine and it is often worse at nighttime. Chewing gum may help promote swallowing, thus reducing the quantity of saliva in the patient's mouth. The use of an atropine spray or an anticholinergic medication, such as benztropine, can also help manage symptoms. If necessary, a clozapine dose reduction may help diminish hypersalivation.[15, 18]

Weight gain may occur in patients taking clozapine and it is most significant within the first year of treatment. Patients with schizophrenia often have weight problems because of a sedentary lifestyle and unhealthy diets. Therefore, the addition of an antipsychotic that increases the risk of weight gain is a concern. Although clozapine is one of the antipsychotics associated with weight gain (2.10-4.45kg), stabilized patients can adopt a healthy lifestyle which allows them to maintain a normal body mass index (BMI). Furthermore, some medications can be given with clozapine to stimulate weight loss such as aripiprazole, topiramate, or metformin.[19,20] In addition to weight gain, hyperglycemia and hyperlipidemia can also increase the overall cardiometabolic risk. However, the decreased overall mortality rate, including mortality caused by ischemic heart disease, suggests that the positive effects of clozapine outweigh its cardiometabolic risk.[3,12] The lack of increased cardiovascular risk, despite the adverse effects mentioned, could be explained by the clinical improvement of psychiatric symptoms.

Schizophrenia is often associated with a sedentary lifestyle, obesity and smoking. However, a better management of symptoms allows the patient to maintain a healthier lifestyle, as well as consult health services for their other illnesses.[21] Clozapine may also help patients reduce their cigarette use, which plays an important role in decreasing their cardiovascular risk.[22] To evaluate the patient's metabolic risk, it is recommended to measure their waist circumference, their weight, their blood pressure, their blood glucose level and their lipid profile regularly.[12]

Sedation is common at the initiation of clozapine, but it often dissipates after a 6-12 weeks of treatment.[12,23] If sedation persists, the addition of a small dose of aripiprazole or a psychostimulant such as methylphenidate can be considered.[24]

Enuresis, although infrequent, is also a possible side effect of clozapine. Since it is often related to excessive fluid intake, patients experiencing this adverse effect should restrict fluid intake several hours before bed and fully empty their bladder before going to sleep. If necessary, a clozapine dose reduction can be considered.[12]

Fear of poor adherence to blood monitoring is often a concern of physicians and the requirement of regular blood tests is a drawback for patients considering clozapine. However, after the first year of treatment, people taking clozapine are often stabilized on their dosage and blood monitoring is performed less frequently (every 4 weeks).[25] For patients that are reluctant to undergo regular venous blood draws, an innovative point of care device using

capillary blood testing (*fingerprick*) may be an option. This device, CSAN® PRONTO™, provides a simple alternative for patients who are uncomfortable with blood tests, thereby increasing their adherence to the regular monitoring of leukocytes. Before recommending its use, you will need to verify if this is an option for patients in your area as the availability of such devices varies across the country.

2. BENEFITS

Clozapine was shown to be more effective than other antipsychotics in many studies. In fact, one particular study showed that after 3 months of treatment with clozapine, patients showed significant improvement in symptoms, improved quality of life and greater improvement in their overall mental health compared to other antipsychotics.[26]

Improved adherence: Clozapine is reported to have the best compliance and the lowest discontinuation rate, when compared to other antipsychotics.[12]

Low incidence of extrapyramidal effects, tardive dyskinesia: Clozapine, as well as quetiapine, are associated with a lower incidence of extrapyramidal side effects when compared to other antipsychotics. Furthermore, clozapine, like other second-generation antipsychotics, has a lower risk of tardive dyskinesia. Therefore, clozapine is a safe option for people with movement disorders.[1,27]

Reduced risk of mortality: Clozapine was associated with the lowest risk of all-cause mortality compared to all other antipsychotic medication. This reduced mortality can be partly explained by its intensive monitoring and its high effectiveness.[1,12]

Reduced risk of suicide: Suicide is very common in schizophrenia patients, where the lifetime risk of completed suicide is 9-13%.[27] Clozapine has a substantially lower suicidal rate compared to other antipsychotics.[12] In the InterSePT study, when compared to olanzapine, clozapine showed a significantly lower incidence of suicide attempts or hospitalizations to prevent suicide in schizophrenia patients with a high suicidal risk.[13] Furthermore, Dal Pian and Agarwalla[28] showed a reduction of suicidal behavior from 28% to 3% when treated with clozapine, and at discontinuation, the risk of suicidal behavior increased to 18%. To date, clozapine is the only antipsychotic agent with an FDA indication for reducing risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.[29]

Decreased hospitalization: An Irish study conducted in 2017 on a small group of patients demonstrated that after the initiation of clozapine, there was a significant reduction in the number of hospital admissions, as well as the length of hospitalisation when compared to the pre-clozapine period, i.e., while they were treated with other antipsychotics.[30]

Decreased likelihood of needing antipsychotic polypharmacy: Combining antipsychotics is considered when monotherapy is no longer sufficient to induce remission. This often increases

the risk of interactions and the number of adverse effects. A 20-year follow-up study comparing various combinations of antipsychotics, as well as certain monotherapies, evaluated the risk of psychiatric rehospitalization. In this study, clozapine was the only monotherapy amongst the 10 most effective treatments. Therefore, the best chance at avoiding polypharmacy in TRS patients is to attempt clozapine. Furthermore, the study demonstrated that 7 out of the 8 best therapies included clozapine as one of the medications.[31]

Possible benefit for treating co-morbid substance abuse (preliminary evidence):

Patients with schizophrenia have a higher incidence of substance use disorders, such as cannabis, alcohol, and cocaine. Clozapine might help to decrease substance abuse in this population. Buckley and al.[32] showed that 70% of patients treated with clozapine for 12 weeks were able to reduce or completely discontinue their substance use. Furthermore, a 10-year follow-up report showed that patients taking clozapine were less likely to relapse in the next year when compared to patients treated with other antipsychotics.[33,34]

Availability of Canadian support programs for physicians:

- Clozaril Support and Assistance Network (CSAN) (HLS Therapeutics) 1-800-267-2726
- AASPIRE (AA-pharma) 1-877-276-2569
- GENCan (Mylan Pharmaceuticals) 1-866-501-3338

3. HOW TO INITIATE CLOZAPINE AS AN OUTPATIENT

The suggested initial dose is 12.5 mg per day at bedtime and can be increased by 12.5 mg per week. Once the dosage has reached 150-200 mg per day, the dose adjustment can be changed by increments of 25 mg per week (optional). A very gradual taper of previous antipsychotics can be attempted once the patient is on approximately 150 mg of clozapine per day, or sooner if the patient presents side effects related to other medication or if they begin to demonstrate clinical improvement. Initiation should be individualized, taking into account factors such as slow CYP1A2 metabolizers (i.e., Asians) and drug interactions, as they may require a lower initiation dose and a slower titration.[3]

Clozapine has been shown to help with smoking cessation. However, cigarettes are a known inducer of CYP1A2. Therefore, it is important to monitor patient's smoking status and to reduce the clozapine dosage consequently if a patient stops smoking while on clozapine.

To help clinicians with clozapine initiation, please refer to clozapine initiation order set available for download at the Canadian Consortium for Early Intervention in Psychosis (CCEIP) website: https://epicanada.org/wp-content/uploads/2019/10/Clozapine-Initiation-Order-Set.pdf.

It is important to inform patients that clozapine should not be discontinued abruptly to avoid withdrawal symptoms. Sudden interruption may cause a cholinergic rebound, demonstrated by nausea, vomiting, diarrhea, diaphoresis, headache, agitation and confusion. Withdrawal may also cause worsening psychosis, abnormal movements, and possibly catatonic symptoms. Therefore, it is important for patients who wish to discontinue clozapine to consult their physician

to discuss how to properly taper the medication. It is also important to inform the patient that the remarkable improvement under clozapine may be lost and never regained after discontinuing their treatment.[3]

4. HOW TO INITIATE CLOZAPINE AS AN INPATIENT

When initiating clozapine as an inpatient, the titration schedule can be much more rapid because of the ability to more frequently monitor patients for any treatment emergent adverse effects. In general, the dose can be increased by 25-50 mg every 2-3 days so that a therapeutic dose of around 300 mg is reached by 2 weeks of treatment.

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