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ASCP Corner

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How to Make an Effective Offer of Clozapine

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Estimates suggest that 1 in 3 patients with schizophrenia will meet criteria for treatment-resistant schizophrenia (TRS) at some point during their illness.[1] In fact, reports indicate that 15%–20% of patients in their first episode do not respond to standard antipsychotic treatment and meet the definition of TRS.[2] Early intervention services have been shown to have many advantages in terms of reduction in relapse and hospitalization rates and improved functional outcomes.[3] Although these services do not necessarily prevent the onset of TRS, they can facilitate earlier identification and implementation of clozapine.[2] This is important, as several studies suggest that clozapine is more likely to be effective if introduced soon after the emergence of treatment resistance.[2,4] The reality is that most patients experience TRS for many years with multiple trials of non-clozapine antipsychotics before clozapine is implemented, and many patients never receive a trial of clozapine.[4] The delay of introducing clozapine may not only reduce the chances of response if tried later on, but also result in an avoidable excessive burden of disease in these individuals.

Although clozapine is the only medication approved by the FDA for TRS[5] (also with indication for suicidality and off-label recommendation for aggression),[6] only about 5% of individuals with schizophrenia being treated with antipsychotics are receiving clozapine,[7] while the incidence of TRS alone is about 30%.[1] Given the reduction of morbidity and mortality in TRS with clozapine treatment,[1] expanding the use of clozapine in eligible individuals should be a priority for all stakeholders.

One of the barriers to the utilization of clozapine results from the challenges of offering this drug to eligible patients.[8] Here, we aim to provide basic guidance to clinicians in the process of making an effective introduction of a clozapine trial.

Identify Eligibility

Recently, a consensus group of international experts identified criteria for TRS, with the hope that researchers, practitioners, and patients would benefit from their systematic application.[9] Broadly, these include (1) meeting *DSM-5* criteria for schizophrenia, (2) at least moderate severity symptoms and functional impairment measured with a rating scale persisting > 12 weeks, (3) ≥ 2 antipsychotic trials of ≥ 6 weeks of sufficient dose and duration and with confirmation of adherence (preferably by using a long acting injectable [LAI]). However, it is very common to have insufficient information to determine whether TRS criteria are met for a given individual. For instance, trials may not have been conducted with sufficient time, dosage, and therapeutic blood level, or there may be insufficient information on consistent treatment adherence. We therefore recommend systematically categorizing patients with schizophrenia as "responsive," "resistant," or "unclear" and prioritizing treatment planning to differentiate status for "unclear" cases. Thus, it may be necessary to obtain blood levels, conduct a trial with a LAI formulation, or retry with drugs that are more easily tolerated prior to concluding the responsiveness status. Once TRS criteria are confirmed, a trial of clozapine should be offered to all individuals, excluding only those with absolute contraindications.

Make an Effective Presentation

An initial question for the provider is "Will this be a good drug for this patient, in the face of potential side effects and monitoring requirements?" This is especially true if there are complications such as treatment nonadherence or limited insight into illness. We would argue that we should make an optimal thoughtful and personalized offer to all patients regardless of our intuition about the potential success of such an offer. It should not be we who make the decision (by not offering) as to whether a therapeutic trial of clozapine is implemented or not, but the patient. Keep in mind that in these cases clozapine is the only FDA-approved medication, and use of a non-clozapine antipsychotic would be technically "off label," hence the importance of allowing the patient to make an informed decision.

When introducing clozapine, it is critical to weigh appropriately the expected benefits, risks, and alternatives. We know from the LAI literature that when talking to patients, we tend to emphasize the negative aspects of the procedure (ie, "Are you OK with needles?") rather than the potential gains.[10] In addition, some of the obstacles to clozapine use, such as the need for phlebotomy, are getting easier with the availability in some facilities of point of care

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testing for absolute neutrophil count monitoring. Overall, the appreciation of the potential consequences of not proceeding with a trial of clozapine (greater likelihood of worse functioning, danger to self/others) should instead be at the front of the discussion. It should also be considered that a patient's readiness to proceed with a clozapine trial may evolve over time, and that rather than a one-time presentation, prescribers should be ready to retake this conversation in the future if the patient is not yet ready.

Some Conversation Prompts

As an example, this is one approach to open the conversation that in our experience may be effective: "Now that we have tried at least 2 drugs with less benefit than expected, I would like to talk to you about a drug which is indicated for this type of situation, clozapine. This drug helps at least one third of individuals who failed to respond to other antipsychotics, possibly more, whereas trying other antipsychotics would help in only about 5% of individuals. In addition, for some patients the response can be really life changing. Clozapine may have side effects that require monitoring, but for most people benefits outweigh side effects. This may or may not be your case; you should judge this for yourself. To date, the only way of knowing is by having a trial of the drug, which typically is about 12 weeks. Would you be interested in hearing more?"

Obviously, the response to an initial presentation may be variable. Here are some concerns that may be expressed by patients, and what we think are appropriate responses:

Patient: I don't need treatment.
Prescriber: What are your life goals? What do you think is not letting you achieve them? This medicine may help with these problems, and if it does not, you can always stop it. It would be a pity to not know whether it would help.

Patient: I prefer treatment that does not involve bloodwork.
Prescriber: Bloodwork can be a nuisance, but over time it will be spaced out. Most people get used to it, and as symptoms improve you may determine that feeling better is worth the bloodwork. Still, if the burden of bloodwork is not worth the benefit from clozapine, you can always change to a different drug.

Patient: This drug has too many side effects.
Prescriber: Clozapine does have side effects, but we don't know if you will develop any of them, and if you do, whether they will not be worth the improvement you get from clozapine. Not trying may be a missed opportunity, and if the side effects are too bothersome you can always change to a different drug.

Conclusions

A high-quality discussion about clozapine on an ongoing basis to eligible individuals may address the underprescription of the only approved drug for TRS. Here, we provide some concrete examples to facilitate this conversation between clinicians and patients. We think that it is critical to explain that with a treatment that might work very well for some patients it is not possible to know without a clinical trial whether that would apply to an individual case. Otherwise, the decision whether clozapine is appropriate is abstract and hypothetical.

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