AMERICAN ASSOCIATION OF COMMUNITY PSYCHIATRISTS

CLINICAL TIPS SERIES

The Clinical Tips Series provides practical guides for common clinical challenges, specifically adapted to the needs and concerns of community psychiatrists.

CLOZAPINE UTILIZATION

AACP Recommendation: Clozapine is the one antipsychotic specifically determined to be effective for psychotic illnesses in which complete trials of 2 antipsychotic medications (at least one of which is second generation) has failed to adequately control symptoms. Clozapine is significantly underutilized across the United States, which means many individuals who would benefit from this medication are not receiving it. AACP recommends that ALL community psychiatrists implement systematic approaches to increase clozapine utilization, so that more such individuals can progress in their recovery.

> HOW TO:

STEP ONE: INCREASE CONSIDERATION OF CLOZAPINE.

- **All individuals who have suboptimal response to conventional antipsychotic medications should be considered candidates for clozapine.** This includes people who range from those who are severely ill and disorganized in the community, to those who may have significant benefit from conventional medications, but still have symptoms and/or disabilities that lead to suboptimal quality of life.
- **Individuals who are stable with suboptimal progress should be considered to have the right to be offered the best possible medication for their condition, as we would want for ourselves**
- **Those who are very disorganized in the community might be considered candidates for initiation of clozapine in a controlled environment, which might lead to more stability.**
- **Clozapine is also known to have a direct effect on helping individuals with psychotic disorders reduce co-occurring substance use, so those with persistent psychosis plus active SUD might also be candidates.**[1]

[1] Zimmet SV, Strous RD, et. al.. Effects of clozapine on substance use in patients with schizophrenia and schizoaffective disorders. J. Clin. Psychopharm 2000: 20:94-98.

STEP TWO: ENGAGE IN SHARED DECISION MAKING WITH THE INDIVIDUAL AND THE FAMILY

- **Shared decision making: In the context of recovery-oriented service,** our job is to present the objective consideration of an opportunity to have a significant (even miraculous) improvement, vs. the difficulties of blood draws, the risks of adverse effects, and the chance that it won't work. We should approach this with the attitude that every patient and family deserves a chance to consider this, and to reconsider at a future date if they say no.
- **Working with families:** Because of both the potential gains and risks of clozapine use, it is important to involve family members and friends as integral part of a person's treatment team when considering clozapine if possible. It is important to educate people about both the benefits and risks of clozapine.

STEP THREE: ESTABLISH A "SYSTEM" FOR CLOZAPINE MANAGEMENT IN YOUR PRACTICE AND AGENCY

- **Develop an organized process so that if a patient chooses clozapine, we can initiate the process smoothly for both them and for us.**
- **In outpatient settings, designating a specific clozapine blood draw day and a specific clozapine prescription renewal day can help both patients and clinicians better manage their time which can help with adherence to the clozapine requirements**
- **If possible it is always best to provide blood draws on site**
- **The Clozapine Risk Evaluation and Mitigation Strategy (REMS) is now a required national registration for all people who are taking clozapine. This replaced the previous clozapine registries.**
    - **All clinicians prescribing clozapine must be certified through the REMS, including those who are covering for prescribers**
    - **All pharmacies dispensing clozapine must be certified through REMS**
    - **All people on clozapine must have their white blood cell counts, absolute neutrophil count (ANC) submitted through the REMS**

STEP FOUR: INITIATION OF CLOZAPINE

Required Laboratory Testing Prior to Initiation and During Therapy

- Prior to initiating treatment with clozapine, a baseline ANC must be obtained, which must be at least 1500/µL for the general population, and at least 1000/µL for patients with documented Benign Ethnic Neutropenia (BEN). To continue treatment, ANC must be monitored regularly.
- Once a baseline ANC is established (see additional information on BEN below), ANC must be checked regularly as follows:
    - Weekly for 6 months
    - Every 2 weeks for the next 6 months if the ANC stays stable
    - Every 4 weeks after the first year if the ANC stay stable

Benign Ethnic Neutropenia (BEN)

BEN is a condition observed in certain ethnic groups whose average ANCs are lower than "standard" laboratory ranges for neutrophils. Because of this condition, patients who have been diagnosed with BEN have a separate ANC monitoring algorithm when treated with clozapine.

A few important things to know about patients diagnosed with BEN:
• It is most commonly observed in individuals of African descent (approximate prevalence of 25-50%), some Middle Eastern ethnic groups, and in other non-Caucasian ethnic groups with darker skin
• BEN is more common in men
• Patients with BEN have normal hematopoietic stem-cell number and myeloid maturation, are healthy, and do not suffer from repeated or severe infections
• Patients with BEN **are not** at increased risk for developing clozapine-induced neutropenia
Additional evaluation may be needed to determine if baseline neutropenia is due to BEN. Consider a hematology consultation before starting or during clozapine treatment as necessary.

Cardiac Risk
In people who have pre-existing cardiac disease or people at risk for cardiac disease (e.g., people 60 and over) a baseline EKG or echocardiogram should be considered.

Dosage titration
• Starting Dose: 12.5 mg once daily or twice daily, depending on the comfort level and age of the person, on their sensitivity to side effects and on whether they have other co-occurring illness.
• Use cautious titration and divided dosage schedule. Rapid titration can lead to a greater risk of side effects.
• Titration: increase the total daily dosage in increments of 25 mg to 50 mg per day, if well-tolerated.
• Target dose: 300 mg to 450 mg per day, in divided doses, by the end of 2 weeks.
• Subsequent increases: increase in increments of 100 mg or less, once or twice weekly.
• Maximum daily dose: 900 mg (2.2).

Cross-Tapering
There are many factors to consider when cross tapering to clozapine from another antipsychotic. Acuity and stability of the person is the first factor.

Inpatient settings:
- May be appropriate for a person with acute or high-risk symptoms, and permits more rapid clozapine titration.

Outpatient settings:
- Go slow- changes in dose of clozapine and original antipsychotic every 4 days to 1week
- Taper the original antipsychotic as follows: 25% reduction in dose at each change point, with taper not beginning until the clozapine dosage has been titrated up to at least 100mg daily.
- Closely monitor for symptom exacerbations and side effects, and adjust rate of taper accordingly.

Augmentation
Augmentation of clozapine with risperidone has shown some improvement in positive symptoms and augmentation with aripiprazole has shown some improvement in negative symptoms and possibly with clozapine-induced/exacerbated obsessive-compulsive symptoms[2]

[2] Grillault LD, Gaillard A., Induced obsessive compulsive symptoms (OCS) in schizophrenia patients under atypical antipsychotics (AAPs): review and hypotheses. Psychiatry Res. 2016; 46:119-128.

Clozapine combined with ECT has also been shown to be effective for clozapine resistant symptoms[3]

Clozapine Plasma Level Monitoring is recommended under the following conditions:

- Any patient receiving more than 600 mg/day, given the increased risk of seizure above this dosage
- When there is a question about adherence
- Patients showing excessive side effects at normal doses who may be metabolizing clozapine less efficiently – e.g. people who are elderly or who have medical conditions affecting the liver
- When monitoring for drug-drug interaction(s) that alter clozapine metabolism
- When response is considered sub-optimal (prior to concluding a clozapine non-response)

Clozapine Blood level ranges Note: Blood levels should be drawn ~12 hours after the last dose. The ranges of blood levels indicated below assume twice daily dosing. If dosing is once daily (as some patients prefer taking the full dose at night), the corresponding effective levels would be ~ 100ng/ml higher, e.g., a medium range for single daily dosing would be 300-400ng/mL.

- Low range (50 to 150 ng/mL) is not as effective as medium or high levels
- Medium range (200 to 300 ng/mL) is a good initial target
- High range (350 to 450 ng/mL) can be tried if clinical response is insufficient, although the high range was no more effective than the medium range
- Overly high levels (i.e. >1,000 ng/mL combined clozapine and norclozapine levels) have no proven benefit and, especially over 1,300 ng/ml, likely increase seizure risk

Cautions with other medications: Clozapine level can be significantly affected by concomitant use of medications that affect metabolic pathways, as in the following:

- Concomitant use of Strong CYP1A2 Inhibitors: Reduce clozapine dose to one third when co-administered with strong CYP1A2 inhibitors (e.g. fluvoxamine, ciprofloxacin, enoxacin).
- Concomitant use of Strong CYP3A4 inducers is not recommended.
- Discontinuation of CYP1A2 or CYP3A4 Inducers: Consider reducing clozapine dose when CYP1A2 (e.g., tobacco smoke) or CYP3A4 inducers (e.g., carbamazepine) are discontinued.

Nicotine and SUD

Clozapine can cross react with various drugs and some of the side effects of clozapine can put people at increased risk of complications if they are also using illicit drugs, alcohol and nicotine.

- **Nicotine**- If clozapine is started when a person is not smoking (e.g.,: while on an inpatient unit), the clozapine blood levels may decrease if smoking resumes after discharge. Therefore periodic blood levels are recommended for people who may be increasing or decreasing their smoking.
- **Substance Use Disorders** - Clozapine use with active use of alcohol and other drugs can potentially increase risk for seizure, anticholinergic effects and cardiac complications. However, clozapine treatment of people with co-occurring substance abuse, in several case studies and retrospective studies, has shown decreased drug use and alcohol use. Therefore, substance abuse is NOT an absolute contraindication for using clozapine for individuals who may otherwise benefit, and, in fact, may be an indication that clozapine could provide added benefit.

[3] Lally J, et al., Augmentation of clozapine with electroconvulsive therapy in treatment resistant schizophrenia: a systematic review and meta-analysis. Schizophrenia Res 2016, 171:215 – 224.

Using the hospital for risky starts
Clozapine is often not considered for individuals who may benefit from it the most, because of their difficulty participating in the outpatient requirements for clozapine treatment.
AACP recommends: For people with schizophrenia who are otherwise candidates for clozapine, but who have complex needs and/or are having difficulty functioning in the outpatient setting, starting clozapine on an inpatient unit may be an essential intervention to provide best possible care.

This includes people who have

- High risk for suicide – previous suicide attempts, violent and self-injurious behavior, violent response to internal stimuli
- Pre-existing medical illness and substance use
- Difficulty following complex dosing and blood draws due to significant disorganization or limited cognitive functioning
- Social and economic needs that are not being met in the community, i.e. homelessness, limited access to blood draws or pharmacy, limited resources or family support.

Note that if these individuals respond to clozapine, the challenges that have interfered with their ability to participate in routine outpatient management often substantially disappear.

<u>STEP FIVE</u>: ONGOING MANAGEMENT OF CLOZAPINE

Moving toward a steady state. Once a stable dose of clozapine is established and people have a regular system in place for have blood draws and prescription renewals, individuals who did not respond adequately to conventional medication can do very well on clozapine. Significant improvement in psychotic symptoms can be seen in the first 6-8 weeks of treatment. Most responders show continued improvement on clozapine with longer treatment- up to 2 years or more. If a person does not show improvement in psychotic symptoms with in the first 4-6 weeks of clozapine first check for adherence to clozapine. A plasma level can be useful for checking adherence and to determine optimal dosage. If a dose is optimal (see plasma levels above) and side effects are minimal, time limited augmentation may be considered although monotherapy should always be the goal.

- These individuals can eventually move to having blood work done every 4 weeks, which then reduces the burden of clozapine
- There is future consideration by the FDA to possibly increase the time between blood draws for people who have been stably on clozapine for more than 2 years

Dealing with adverse effects along the way
Some people are very sensitive to the side effects of clozapine. Some of the more common or troublesome side effects are, in order of frequency and severity:

- **Anticholinergic effects**- constipation, sedation, dry mouth, urinary retention
- **Hypersalivation** –a relatively unique side effect of clozapine compared to other antipsychotics.
- **Cardio-metabolic risk**- Weight gain, diabetes, insulin resistance, hyperlipidemia. This is relatively higher risk than with some atypical neuroleptics, but less of an issue than with olanzapine.
- **Orthostatic hypotension** is common, especially during the initial titration phase; the rate of titration may be slowed if this is a problem.

- **Mild tachycardia** is common, and may be persistent. Typically, there is no intervention for this.
- **Clozapine induced cardiomyopathy- myocarditis, left ventricular dysfunction**. This is a rare, but very serious event, and requires awareness in case of potential emergence of cardiac symptoms. **Clozapine induced myocarditis (1 in 500 risk) is an indication for stopping clozapine. This complication is more commonly seen within the first 4-6 weeks of treatment.**
  Some community mental health systems are using the following protocol to increase monitoring for myocarditis:
  - **Baseline, and weekly for six weeks: CRP, Troponin I, and vital signs including temperature. Have the person initiating clozapine report immediately – during the titration period - any signs or symptoms that include fever, cough, chest pain, palpitations, and shortness of breath. Stop clozapine if troponin is twice the upper limit of normal, or if CRP is greater than 100 mg/L. Immediately obtain an echocardiogram or cardiac MRI if signs, symptoms, or labs warrant.**
  - **Note:** This protocol is recommended only if routinely obtaining these lab studies does not pose a significant barrier to initiation of clozapine. If individuals who need clozapine will not be able to receive it because these laboratory tests are unavailable, it is better to initiate the clozapine and monitor closely for changes in vital signs and onset of symptoms.
- **Seizures** can occur, especially with high plasma levels, and are more common during initiation of therapy. Titrating slowly and monitoring steady-state blood levels help avoid seizures. A recent review also recommends considering an anticonvulsant drug when levels exceed 500 mg/l, if EEG shows clear epileptiform discharges, if seizures, myoclonic jerks or speech difficulties appear, and when there is concurrent use of epileptogenic medication. Anticonvulsants of choice for treatment and prophylaxis are valproate and lamotrigine. A pre-existing history of seizure disorder generally contraindicates the use of clozapine unless (as is not uncommon) the mental health risks outweigh seizure risk.[4]

These potential side effects should be monitored closely and treatment with clozapine may need to be stopped if side effects are severe. Specific treatments can also be started to address side effects if the benefit of clozapine outweighs the risk of the side effect.

Helpful strategies to address hypersalivation in community psychiatry practice include:
Hypersalivation usually improves over time with continued use of clozapine. This however can be a troubling side effect for some people, which can lead to medication nonadherence or discontinuation. Hypersalivation can be treated with anticholinergic medications such as benztropine or scopolamine. These medications also have potential side effects that must be taken into consideration. Some practitioners have reported success (and fewer side effects) using 1% atropine eye drops, 1-6 drops sublingually.
Non-medication approaches can include sucking on sugarless candy or chewing gum and telling people to put a towel on their pillows. Decreasing the clozapine dose or slowing titration can also help.

Helpful strategies to address constipation in community psychiatric practice include:

[4] Varma S, Bishara D, Besag FMC, Taylor D. Clozapine-related EEG changes and seizures: dose and plasma-level relationships. Ther Adv Psychopharmacol 2011, 1:47-66, 2011.

Obtain baseline information on bowel routine to enable better monitoring of potential constipation. Educate patients and families on the importance of hydration, exercise, and sufficient dietary fiber. Advise patients to avoid additional fiber/bulking agents such as Metamucil, and proactively offer stool softeners (e.g. docusate sodium) and/or osmotic laxatives (e.g. Dulcolax) to soften stool and shorten transit time through the GI tract. Stimulant laxatives can also be used if indicated.

Discontinuation and re-challenge

If neutropenia develops during treatment, clozapine needs to be either monitored more frequently, stopped temporarily, or discontinued, based on the severity of neutropenia:

- Mild neutropenia (ANC: 1000 to 1499/microL) – Continue treatment but increase monitoring frequency to three times per week.
- Moderate neutropenia (ANC: 500 to 999/microL) – Interrupt clozapine treatment, increase monitoring to daily until ANC is 1000/microL at which point clozapine can be reinstituted.
- Severe neutropenia/agranulocytosis (ANC: <500/microL) – Discontinue clozapine. Rechallenge should only occur if the benefits outweigh the risks, in consultation with hematology

USEFUL RESOURCES

Video for patients considering clozapine:
http://www.practiceinnovations.org/portals/0/Videos/considering_cloz_web_101212/course.htm?

Clozapine REMS website:
https://www.clozapinerems.com/