DSH PSYCHOTROPIC MEDICATION Operational Procedures

CLOZAPINE PROTOCOL: (See also Chapter 38 Appendix – Clozapine Historical Review)

I. Indications:

A. Clozapine should be considered for patients suffering from:

1. Treatment-resistant DSM schizophrenia or schizoaffective disorder;

2. Individuals with DSM schizophrenia or schizoaffective disorder characterized by persisting suicidality or chronic assaultiveness demonstrated and documented in the chart to be inadequately responsive to behavioral interventions as part of a behavioral treatment program.

3. Treatment resistant or mixed psychotic bipolar mood disorder;

4. Individuals with moderate to severe tardive dyskinesia, especially if progressive;

5. Polydipsia, especially if associated with symptomatic hyponatremia (water intoxication);

6. Mental disorders, including personality disorders, characterized by impulsive or predatory aggression or violence, including impulsive self-injurious behavior;

7. Cases in which clozapine has been recommended by the DSH Psychopharmacology Resource Network (PRN), Medication Review Committee (MRC), or Therapeutic Review Committee (TRC) consultation.

B. Note that the definitions below apply to item I.A.1. only. That is, requirements or indications listed in items I.A.2. through I.A.6. are unrelated to present or past medication trials.

For the purpose of this protocol, treatment-resistant is defined as failure to respond adequately to at least two trials of antipsychotic medications, at least one of which must have been a second-generation or third-generation antipsychotic (SGA or TGA), given at least at standard therapeutic doses, or with drug plasma levels within the recommended therapeutic range, for a minimum period of four to six weeks.

If used, a first-generation antipsychotic must have been given for at least four to six weeks at a dose of 600 to 1600 chlorpromazine equivalents (equal to 12 – 32 mg/day of haloperidol). If the first-generation antipsychotic trial is not current, then historical information should be adequate to assure that dosage and duration parameters were met for each trial, or with drug plasma levels within recommended therapeutic range. In the absence of adequate historical information, the merits of repetition of trials of prior or alternate antipsychotic medications should be carefully discussed with the treated individual and/or conservator/guardian.

Table 1. Second/Third Generation Antipsychotic Medication Standard Daily Doses

SECOND/THIRD-GENERATION ANTIPSYCHOTIC	STANDARD DAILY DOSES (mg/day)
Aripiprazole	10 – 30
Asenapine	10 – 20
Brexpiprazole	2 – 4
Cariprazine	3 – 6
Iloperidone	12 – 24
Lurasidone	40 – 160
Olanzapine	10 – 60
Paliperidone	3 – 12
Quetiapine	400 – 1200
Risperidone	2 – 10
Ziprasidone	120 – 240
Xanomeline/Trospium (New-generation antipsychotic)	100/20 – 120/30 b.i.d.

C. Patients admitted already taking clozapine and who are stable should be continued on clozapine treatment.

D. The individual must cooperate with clozapine treatment and monitoring, including repeated venipuncture or finger stick. Informed consent must be given by the treated individual or the conservator/guardian. Alternately, substituted consent can be given by the court via court order (involuntary medication order). In any event, the treated individual and/or conservator/guardian must be fully informed of the expected benefits of clozapine treatment, the risks of clozapine treatment (see the chapter of this policy entitled Appendix -- Clozapine Historical Review), alternative treatment approaches, and the risks of no treatment.

II. Contraindications

A. Clozapine is absolutely contraindicated in individuals:

1. With present severe central nervous system depression or coma;

2. Pretreatment absolute neutrophil count (ANC) <1500 cells/mm^3 or <1000 cells/mm^3 in patients exhibiting benign ethnic neutropenia (BEN) unless the characteristic baseline ANC is <1000 cells/mm^3; (see discussion of pretreatment neutropenia in section IV, paragraphs E and F below);

3. Nonadherence to required laboratory monitoring;

4. Currently uncontrolled seizure disorder;

5. Medically unstable status likely to be complicated by clozapine treatment (e.g., present acute narrow angle glaucoma, bowel obstruction, paralytic ileus, unstable hypotension, unstable tachyarrhythmias, unstable febrile illness, etc.);

6. Age <6 years; OR

7. Allergy to clozapine or any component of the preparation.

B. Precautions (documented risk/benefit analysis supports use):

1. Use of other medications that suppress bone marrow function, such as:

a. Antineoplastic drugs;

b. Antiretroviral medications;

c. Carbamazepine, OR

d. Propylthiouracil.

2. Use of type 1C antiarrhythmics e.g.:

a. Propafenone;

b. Flecainide; OR

c. Quinidine.

3. Pregnancy or breastfeeding may rarely induce neonatal dyskinesia;

4. Current serious medical illness or debilitated medical status;

5. Current partially controlled or seizure disorder without neurological consultation;

6. History of hypersensitivity to loxapine or amoxapine;

7. Personal or family history of morbid obesity, severe diabetes mellitus, or significant personal or family history of dyslipidemia;

8. Concurrent use of benzodiazepines during the first week of clozapine titration.

III. Additional Precautions:

A. Conditions which warrant particular attention during the use of clozapine include:

1. History of seizure disorder;

2. Evidence of significant hepatic, renal, or cardiopulmonary disease;

3. Prostatic enlargement or narrow angle glaucoma;

4. History of paralytic ileus, frequent constipation, or bowel obstruction;

5. Family or personal history of obesity, dyslipidemia, or diabetes mellitus; OR

6. Concurrent use of –

a. Anticholinergic medications;

b. Antihypertensive medications;

c. Highly protein-bound drugs (e.g., digoxin and warfarin);

d. Central nervous system depressants (e.g., barbiturates or benzodiazepines);

e. Valproate/divalproex;

f. Epinephrine; OR

g. CYP450 1A2 inhibitors (e.g., fluvoxamine).

IV. Initial work up includes:

1. Baseline ANC, WBC, platelets, and eosinophils

2. Electrocardiogram (ECG), if positive history of unstable cardiovascular disease;

3. Fasting blood sugar and Hgb A1c;

4. Lipid panel or total cholesterol and triglycerides;

5. For patients exhibiting BEN, at least two ANC measurements to establish the patient's baseline;

6. Physical assessment including blood pressure, BMI, abdominal girth, and AIMS.

7. Pregnancy test in premenopausal women.

8. And KUB if indicated clinically, such as history or findings of:

a. Constipation, paralytic ileus, or partial bowel obstruction;

b. Bowel or related surgery;

c. Abdominal adhesions;

d. Diverticulitis or diverticulosis;

e. Dehydration or anorexia; OR

f. Unreliability in reporting bowel movements.

B. Complete vital signs, including orthostatic blood pressure measurements recommended taken at least twice, once within 24 hours, before beginning clozapine treatment. Measurements should be separated by at least one hour.

IV. Pretreatment Neutropenia

C. Individuals with a baseline ANC < 1500 cells/mm^3 (or 1000 cells/mm^3, or below

characteristic baseline in patients exhibiting BEN): Given the clozapine's unique efficacy, patients whose initial ANC may preclude starting clozapine should undergo a work-up an evaluation to elicit potentially reversible or treatable causes for chronic neutropenia. The most common etiologies encountered in the DSH include:

1. Medication Induced Neutropenia: All antipsychotics carry a class warning regarding neutropenia, although it is rare outside of clozapine treatment. Nonetheless, this must be considered, particularly in an individual with prior evidence of normal ANC values with other antipsychotic therapies. Valproic acid (i.e., valproate or divalproex) has a reported incidence of neutropenia of up to 26%. In each case (antipsychotics or valproate), trials of alternate agents may be necessary to determine etiology, and Psychopharmacology consultation should be considered to guide this process.

2. Benign Ethnic Neutropenia (BEN): Individuals with African or eastern Mediterranean heritage commonly possess one or two polymorphisms of the Duffy Antigen Receptor for Chemokines (DARC) that results in baseline lower ANC than in other populations. The DARC gene encodes for a transmembrane glycoprotein that functions as a chemokine transporter and expresses the Duffy blood group antigens (Fy). This glycoprotein is a binding site receptor for two Plasmodium subspecies, and individuals with the null genotype (Fy -/-) are at lower risk for malarial infection. The neutropenia is a laboratory finding only, and these individuals are not at increased risk for infection, despite baseline ANC well below 1500 cells/mm^3 in many cases.

D. Management of Persistent Pretreatment Neutropenia: In individuals who are candidates for clozapine therapy but who manifest persistent neutropenia despite measures to eliminate potentially reversible etiologies, it is medically appropriate to pursue strategies to increase the ANC above the required thresholds for clozapine initiation. These are:

1. Low dose lithium therapy: The administration of lithium salts to individuals is associated with increased marrow neutrophil production due to increased production of granulocyte colony stimulating factor (G-CSF) and directly stimulating the proliferation of pluripotent stem cells. Lithium should be considered in those who are candidates for lithium therapy per DSH criteria. The impact of lithium on ANC is seen at low doses (e.g., 150 – 900 mg at bedtime) and peaks after 3 weeks, with a slight reduction at week 4. Further dose increases should be considered within the therapeutic serum range of lithium (0.6 – 0.8 mEq/L) if the ANC is not well above the required thresholds.

2. Filgrastim: Filgrastim is a recombinant form of G-CSF employed in the treatment of severe neutropenia. It has been used to raise baseline ANC in those for whom lithium is contraindicated, or insufficient to achieve the required ANC thresholds to begin clozapine therapy. A psychopharmacology consultation may be helpful in obtaining local approval for this strategy, which has been used throughout the DSH system for patients in need of clozapine therapy. Depending on the baseline ANC, the PRN consultant may recommend a starting dose of 300 mcg subcutaneously every one or two weeks for a period of 4 to 8 weeks to establish the effect of therapy. Once the minimum effective dose is established, Filgrastim may need to be continued indefinitely while the patient remains on clozapine, with dosage adjustments to avoid treatment interruptions.

V. Monitoring:

A. Absolute neutrophil counts

1. ANC are required weekly for the first 18 weeks of clozapine treatment. If a neutropenic event occurs during the first 18 weeks; weekly monitoring must continue until the patient achieves 18 consecutive weeks without a neutropenia event.

2. If weekly ANC are >1500 cells/mm^3, or >1000 cells/mm^3 or greater than characteristic baseline in BEN, for 18 consecutive weeks of treatment and there have been no breaks in clozapine treatment >30 days, then ANC measurements may be increased to monthly intervals.

3. If 2 years has elapsed without neutropenia, then routine ANC monitoring can be increased to annual monitoring.

4. ANC must be monitored weekly for four weeks after clozapine is discontinued or until ANC is >1500 cells/mm^3, or >1000 cells/mm^3 or greater than characteristic baseline in patients exhibiting BEN.

5. If a patient has been taking clozapine for more than 18 weeks without neutropenia and a less than one month break in treatment occurs, then ANC monitoring can resume at a monthly frequency. If a break of more than 30 days occurs, then resume monitoring as if the individual were a new clozapine patient.

6. **Even if the frequency of routine mandatory ANC monitoring is reduced, obtain an ANC immediately in the event of possible symptoms of infection such as fever, chills, sore throat, mouth/throat ulcers, etc.**

7. If neutropenia occurs, please see “VIII. Clinical Management of Neutropenia” regarding their management.

B. Fasting blood sugar should be measured monthly for the first three months. Thereafter, an Hgb A1c and a fasting lipid panel or total cholesterol and triglycerides should be measured every three months. A finding of a fasting blood sugar above 100mg/dL and/or elevated Hgb A1c (≥ 6.5%) will prompt a repeat fasting glucose and medical consultation. Dyslipidemia should prompt medical and dietary consultation, as well as consideration of treatment with lipid-lowering medications (e.g., statins).

C. Daily vital signs with orthostatic measurements are obtained during the first two weeks of clozapine treatment, with more frequent measurements as clinically indicated (e.g., during active titration or at higher doses) followed by weekly vital signs until week 8. Daily measurements should be continued beyond two weeks if measurements are abnormal.

D. A quarterly KUB should be considered if the individual has risk factors that might predispose her or him to decreased bowel functioning (e.g., use of anticholinergic medications, history of paralytic ileus, poor hydration, known or suspected constipation, or unreliability in reporting bowel movements). If radiographic evidence of fecal impaction is found, then appropriate dietary, medication, and bowel hygiene steps should be immediately initiated. Further X-ray and clinical studies should then be pursued as clinically indicated by medical consultation.

E. Electrocardiograms (ECG) are required at least annually, or every six months if the individual is taking other medications that may prolong QTc interval, as indicated by a boxed warning in the package insert. [Please see sections VII.A. and VII.B. regarding risks of myocarditis and ECG changes with clozapine treatment.]

F. An AIMS examination should be completed every twelve months. Onset of abnormal involuntary movements or a substantial change in existing movements should prompt neurological consultation, as well as MRC or TRC consultation. A positive AIMS should result in subsequent quarterly monitoring of AIMS rating until the AIMS is negative twice.

G. An Electroencephalogram should be considered if persisting myoclonic jerks are observed, as myoclonic jerks may result from myoclonic seizures or may presage tonic-clonic seizures.

H. BMI should be measured monthly. An increase of BMI from normal to overweight (>25) or from overweight to obese (>29.9) should prompt dietary consultation. Similarly, an increase in weight of 5% during the first month of treatment or 7.5% during the first three months, or 10% in six months should prompt dietary consultation, as well as consideration of treatment with GLP-1/GIP medications. In any case, the aim would be to decrease calorie intake and to increase physical activity as permitted by the individual's physical condition.

I. Although clozapine rarely causes persisting elevation of prolactin, measurement of prolactin annually should be obtained. Persisting elevation of prolactin above 100 ng/mL should prompt medical consultation, breast examination, and consideration of brain imaging to examine the pituitary/sella turcica.

Because most women treated with clozapine have a history of exposure to neuroleptics which commonly induce prolactin elevation and may induce pituitary microadenomas, annual breast examination should be retained as a monitoring tool during clozapine treatment.

Medical consultation also should be pursued if prolactin-related adverse effects (e.g., galactorrhea,

amenorrhea, hirsutism, gynecomastia, etc.) persist despite such interventions as changing to a partial dopamine agonist medication or prescribing a dopamine agonist. Prolactin-related adverse effects become increasingly likely at serum concentrations exceeding 50 ng/mL. [Please see the appendix chapter of this policy regarding hyperprolactinemia.]

J. Clozapine may rarely cause myocarditis and even more rarely may cause interstitial nephritis. Case reports and retrospective surveys indicate that risk is limited to the first eight weeks of clozapine treatment. Thus, in patients known to be at elevated risk of inflammatory responses (e.g., those with known inflammatory diseases or with positive family histories of inflammatory diseases), it is recommended, but not required, that weekly measurements of troponin-I, C-reactive protein (CRP), and serum creatinine be obtained during the first eight weeks of clozapine treatment. Monitoring of BUN, creatinine, and eGFR also is recommended, but not required, in all patients taking lithium during the first eight weeks of clozapine treatment due to lithium's narrow therapeutic index and the capacity of interstitial nephritis to dramatically reduce lithium clearance.

K. MONITORING SUMMARY

Weekly	ANC X 18 weeks CRP, troponin-I, serum creatinine x 8 weeks (optional)
Monthly	ANC***** (Q-4 weeks), weight, FBS X 21 months
Quarterly	Hgb A1c, lipid panel or TG and cholesterol
Semi-annually	ECG if taking other drugs that prolong QTc
Annually	AIMS, ECG, prolactin, ANC*, physical exam and breast examination (AIMS quarterly, if possible)

*****For eligible patients.

VI. Clinical Management of ANC abnormalities:

Mild Neutropenia

A. Mild Neutropenia: If the ANC declines to <1500 cells/mm^3 (or <1000 cells/mm^3 in BEN and such declines are not known to be a stable, recurring pattern for the patient or the patient's characteristic baseline ANC is not <1000 cells/mm^3 in BEN), then:

1. Monitor vitals once or twice per day
2. Increase ANC monitoring to two times per week
3. Continue monitoring two times per week until the ANC is >1500 cells/mm^3 (or >1000 cells/mm^3 or greater than characteristic baseline in BEN). [Note that in BEN, some patients have a stable baseline ANC <1000 cells/mm^3 and this increased monitoring threshold would not apply to them.]
4. Return to standard monitoring. Infection, reflected by fever, sore throat, lethargy, and generalized weakness, is rare to absent in this situation.

Moderate Neutropenia

B. Moderate neutropenia: In this situation the patient's ANC has declined to <1000cells/mm^3 in both general and BEN patients or to below the BEN patient's characteristic ANC baseline but is ≥500 cells/mm^3. Note that some BEN patients exhibit a stable ANC <1000 cells/mm^3 and this section would not apply to them unless their ANC declines below their characteristic baseline. Infection is unlikely but may occur.

In the general patient population, clozapine treatment should be interrupted. Monitoring should include

1. Measurement of vitals once or twice per day
   a. In the general patient population, check ANC daily until it is ≥1000 cells/mm^3 and then two times per week until the ANC is ≥1500 cells/mm^3, then return to monitoring protocol.
   b. In BEN population, check ANC two times weekly until ANC ≥1000 cells/mm^3 or greater than/equal to the BEN patient's characteristic baseline ANC.
2. Aggressive workup of any signs and symptoms of infection, including chest x-ray and throat plus blood and urine cultures
3. Treatment of bacterial infections with appropriate antibiotics

Resumption of clozapine (general population) once ANC recovery has occurred (ANC levels ≥1000 cells/mm^3) or resumption/continuation (BEN population) of clozapine is at the discretion of the treating physician in both general and BEN cases.

If clozapine is discontinued, ANC should be measured weekly for four weeks or until ANC recovery has occurred. At this point, treatment with low-dose (300 – 900mg at bedtime) lithium should be considered to increase neutrophil counts. If lithium is not clinically appropriate, then use of filgrastim 300 mcg given subcutaneously may be considered to promote a higher baseline ANC.

Severe Neutropenia (Impending Agranulocytosis)

C. Severe Neutropenia (Impending Agranulocytosis): Severe neutropenia and agranulocytosis are medical emergencies. The pathophysiology involves autoimmune destruction of neutrophil progenitor cells, such that destruction continues beyond discontinuation and washout of clozapine. Although agranulocytosis literally means an ANC of 0 cells/mm^3, as well as loss of eosinophils and basophils, severe neutropenia or impending agranulocytosis is considered present when the ANC is less than 500 cells/mm^3. Although the patient may not initially exhibit signs and symptoms of infection, infection will occur once neutrophils persistently decline to less than 100 cells/mm^3. Moreover, such infections are frequently rapidly progressive and overwhelming, ending in septic shock and death.

Treatment interventions include:

1. Immediate discontinuation of clozapine (often with benztropine or diphenhydramine in a tapering dose to avert cholinergic rebound)

2. Immediate administration of filgrastim 480 mcg subcutaneously as soon as available (should not delay transfer)

3. Immediate transfer (as soon as feasible) to an acute care hospital

4. Administration of daily filgrastim (average time to response is 12 days) until ANC ≥ 1500 cells/mm^3, then stop filgrastim; an expected ANC decrease will occur. If ANC declines to ≤500 cells/mm^3 resume daily filgrastim.

5. Use of reverse isolation or other precautions (e.g., limitation of contacts with others, use of gloves, gowns, and masks, etc.) to decrease the risk of infection

6. Workup of any signs and symptoms of infection including chest x-ray plus blood, urine, and throat cultures

7. Aggressive treatment of any signs and symptoms of bacterial infection with antibiotics in conjunction with an infectious disease specialist

Throughout the episode of agranulocytosis ANCs should be monitored daily and vitals should be monitored every shift. Daily ANC monitoring should be continued until the ANC is >1000 cells/mm^3 (or, >1000 cells/mm^3 in BEN patients or the characteristic baseline in BEN patients).

ANC should be monitored two times per week until the ANC is >1500 cells/mm^3 (or, greater than the characteristic baseline ANC in BEN patients). If clozapine is discontinued permanently, weekly ANC monitoring should continue for four consecutive weeks to assure stable recovery. Clozapine should be listed as an adverse drug reaction in the patient's records.

The patient should not be re-challenged with clozapine unless it is determined that benefits of clozapine treatment clearly outweigh the risks of severe neutropenia or agranulocytosis. Note that because an immune memory exists, re-exposure to clozapine may result in a catastrophic return of severe neutropenia or agranulocytosis, overwhelming infection, and death unless careful ANC monitoring and ongoing filgrastim supports are provided. Available data suggest that with such supports, circa 70% of patients can be successfully challenged with clozapine. Other antipsychotics can be used for treatment and are not cross-reactive, except for loxapine.

Management of Persistent Treatment Interruptions due to Neutropenia	**ANC <1500 cells/mm^3 (or <500 cells/mm^3 for BEN)**

D. Management of Persistent Treatment Interruptions Due to Neutropenia: For many patients there is no viable alternative to clozapine, and frequent treatment interruptions of clozapine therapy may result in severe psychotic symptoms, violence, or suicidal behavior. For patients who have not experienced agranulocytosis, but whose treatment is repeatedly interrupted by neutropenia, evaluation of potential causes and a plan of treatment may be proposed as outlined in section IV, paragraphs E and F. Both lithium and routine filgrastim have been employed in the DSH to maintain the ANC above relevant thresholds. Psychopharmacology consultation may be helpful if filgrastim is considered.

Summary of ANC Management

E. Tabular Summary:

General Patient Population

ANC Level	Treatment Recommendations	ANC Monitoring
Normal Range (≥1500 cells/mm^3)	• Initiate treatment • If treatment interrupted for < 30 days, continue monitoring as before • If treatment interrupted for ≥ 30 days, monitor as if new patient	• Weekly from initiation to 18 weeks • Every month from 18 weeks -2 years • Annually after 2 years
Mild Neutropenia* (1000 – 1499 cells/mm^3)	• Continue treatment (see VI.A)	• Two times weekly until ANC ≥1500cells/mm^3 • Once ANC ≥ 1500 cells/mm^3, return to patient's last "Normal Range" ANC monitoring interval**
Moderate Neutropenia* (500 – 999 cells/mm^3)	• Interrupt treatment for suspected clozapine-induced neutropenia • See management VI.B	• Daily ANC until ≥ 1000 cells/mm^3 **THEN** • Two times weekly until ANC ≥ 1500 cells/mm^3 • Once ANC ≥ 1500 cells/mm^3, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval **
Severe Neutropenia (Impending Agranulocytosis)* (< 500 cells/mm^3)	• Interrupt treatment for suspected clozapine-induced neutropenia • See VI.C • Rechallenge with caution and filgrastim supports only if benefits clearly outweigh risks.	• Daily ANC until ≥ 1000 cells/mm^3 **THEN** • Two times weekly until ANC ≥ 1500 cells/mm^3

		• If patient re-challenged, resume treatment as a new patient under “Normal Range” monitoring once ANC ≥1500 cells/mm^3

*Confirm all initial reports of ANC < 1500 cells/mm^3 with a repeat ANC measurement within 24 hours

**If clinically appropriate.

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BEN Patients

ANC Level	Treatment Recommendations	ANC Monitoring
Normal BEN Range (ANC Baseline ≥1000 cells/mm^3, or the patient's characteristic baseline)	• Obtain at least two baseline ANC levels before initiating treatment • If treatment interrupted for < 30 days, continue monitoring as before • If treatment interrupted for ≥ 30 days, monitor as if new patient	• Weekly from initiation to 18 weeks • Every month from 18 weeks to 2 years • Annually after 2 years
BEN Neutropenia***** (500 – 999 cells/mm^3)	• Continue treatment • See VI.B	• Two times weekly until ANC ≥ 1000 cells/mm^3 or ≥ patient's known baseline • Once ANC ≥ 1000 cells/mm^3, or is above the patient's known baseline, check the ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval******
BEN Severe Neutropenia (Impending Agranulocytosis)***** (< 500 cells/mm^3)	• Interrupt treatment for suspected clozapine-induced neutropenia • Recommend hematology consultation • Rechallenge with caution and filgrastim supports only if benefits clearly outweigh risks.	• Daily ANC until ≥ 500 cells/mm^3 THEN • Two times weekly until ANC ≥ patient's baseline • If patient re-challenged, resume treatment as a new patient under "Normal BEN Range" monitoring once ANC ≥1000 cells/mm^3 or at patient's baseline

*****The package insert recommends confirming all initial reports of ANC < 1500 cells/mm^3 with a repeat ANC measurement within 24 hours; however, for BEN patients whose baseline ANC is <1000 cells/mm^3 this imposes a significant burden. For those patients, the above guidelines for BEN Neutropenia are more appropriate and should be followed.

******If clinically appropriate.

VII. Clozapine Risks:

A. Myocarditis:

Clozapine has been associated with an increased risk of fatal myocarditis, especially during (but not limited to) the first eight weeks of treatment. Prevalence has been difficult to establish but is estimated up to 2% by some. Mortality rates have been estimated in verified cases up to 10%. The possibility of myocarditis should be considered in individuals who present with unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, signs or symptoms of heart failure, or ECG findings, such as S-T wave abnormalities or arrhythmias.

A significant change in tachycardia (increase in heart rate of 20-30 bpm above baseline) has been noted as a presenting sign in individuals with myocarditis. Patients with severe tachycardia (>120 bpm) during the first month of clozapine treatment should be monitored for myocarditis. Use of a daily flow sheet with relevant parameters during the first one to two months of clozapine treatment may be helpful in identifying cases for further evaluation.

Troponin I levels ≥ 2 times the upper limit of normal is the most sensitive and specific inflammatory marker for myocarditis. Nevertheless, very rare cases may not show prominent troponin elevation. Other inflammatory markers (e.g., sedimentation rate or CRP), are sensitive in identifying inflammation but are nonspecific for myocarditis and should not be used as the sole basis for the diagnosis of clozapine-induced myocarditis. Thus, C-reactive protein (CRP) may provide a less specific, but sensitive, confirmation of inflammation.

Echocardiogram is important to evaluate cardiac function but may not be diagnostically specific early in the course of myocarditis. Transient elevation of eosinophils occurs in circa 50% of patients early in clozapine treatment and is also not helpful in screening for myocarditis. Those individuals who develop myocarditis are at elevated risk for later cardiomyopathy.

B. Electrocardiogram Changes:

About 1% of clozapine treated individuals show nonspecific T-wave or S-T segment (repolarization) abnormalities like those seen with other antipsychotics. These typically normalize after drug discontinuation.

C. Orthostatic Hypotension:

About 9% of clozapine treated individuals experience orthostatic hypotension, especially during initial dose titration. Such hypotension may be severe and lead to respiratory arrest, especially in the presence of benzodiazepines. Avoidance of concurrent use of benzodiazepines during dose titration and a slower dose titration may decrease the risk of symptomatic orthostatic hypotension.

D. Tachycardia:

About 25% of individuals treated with clozapine evince tachycardia with an average increase of 10 – 15 beats per minute. This effect is dose-dependent but is independent of reflex tachycardia. This adverse effect often abates over the first several weeks of clozapine

treatment. Persisting resting heart rates >110 beats per minutes are a risk factor for dilated cardiomyopathy and should be treated. Treatment for this is most commonly low-dose atenolol beginning at 12.5 mg QAM with titration about once per week to effectiveness. [Note that atenolol is less lipophilic than propranolol and tends not to produce any CNS effects.]

E. Seizures

Seizure risk increases relative to the rapidity of dose titration (faster than 25 mg per day) and the total daily dose. That is, the seizure risk doubles at doses above 300 mg per day and triples the risks seen in the general population when doses exceed 600 mg per day. Valproic acid has been used to moderate seizure risk in some patients. An electroencephalogram (EEG) should be obtained on any individual who seizes during clozapine treatment, as clozapine may have unmasked an underlying seizure focus. Excessive large single doses of clozapine may cause seizures at peak plasma concentrations.

F. Sedation:

Up to 39% of individuals treated with clozapine experience excessive sedation. Tolerance to this side effect develops slowly and may be incomplete. Weighting doses toward nighttime may reduce this side effect. However, keep in mind that excessively large single doses of clozapine may induce seizures at peak plasma concentrations.

G. Hyperthermia:

Benign hyperthermia occurs in about 5% of clozapine treated individuals. This side effect usually occurs early in treatment, resolves over time, and is not a reason to terminate clozapine therapy. Fevers up to 100.4 degrees F (38 degrees C) have been encountered. This hyperthermia responds to antipyretics (e.g., aspirin or acetaminophen). As with all fevers, infectious sources should be ruled out.

H. Gastrointestinal Problems:

Constipation occurs in 14% of clozapine treated individuals and could lead to bowel obstruction and death, albeit rarely. Chronic dehydration is a risk factor for bowel obstruction. Nausea occurs in 5% of clozapine treated individuals, with another 4% developing heartburn, and 3% developing vomiting. (See chapter 35 Appendix – Treatment of Clozapine-induced and Severe Constipation.)

I. Sialorrhea:

Up to 90% of clozapine treated individuals have difficulty with excessive salivation especially at night. A towel on the pillow may be helpful. Most clinicians start with topical medications such as ipratropium nasal spray sublingually to decrease salivation without incurring systemic anticholinergic effects. The typical dose is two sprays of 0.06% solution under the tongue before bedtime. Alternatively, 2 – 3 drops of 1% atropine solution can be used. In both cases, the patient should then rinse and spit using a very small volume (i.e., a sip of circa 5mL) of water. The ipratropium spray or atropine drops can be increased to 3 sprays/drops TID if necessary.

Should these topical treatments prove unsuccessful, some clinicians have used systemic

anticholinergic medications to decrease salivation. However, such medications increase the risks of cognitive impairment, urinary retention and constipation, so bowel function must be vigilantly monitored.

Glycopyrrolate is the preferred systemic agent as it does not cross the blood-brain barrier and can be initiated at 1mg QHS, and then increased by 1mg increments. The half-life is quite short, so multiple daily dosing may be needed if the patient has daytime sialorrhea.

There is also literature supporting the use of terazosin, starting at 1mg QHS, and increased to 2mg QHS if needed. Risk of orthostasis must be considered when using terazosin.

Botulinum toxin injected into the parotid and submandibular salivary glands is likely more effective than either topical or systemic anticholinergic agents and avoids the risks of the systemic anticholinergic effects.

J. Pneumonia

Pneumonia is a common cause of medically related hospital admissions for patients on clozapine and may be among the greatest causes of mortality in clozapine-treated patients. It has an estimated cumulative incidence of 29.5%, 20 years after initiation. Aspiration pneumonia, related to sialorrhea, is most common type of pneumonia. Treatment of sialorrhea critical in prevention of aspiration pneumonia. Patients on clozapine who appear to have altered mental status or display signs of infection should receive a work-up to rule out pneumonia.

K. Weight Gain

Many individuals treated with clozapine gain substantial amounts of weight with development of morbid obesity occurring in a substantial minority of clozapine-treated individuals. One five-year retrospective study found an average weight gain of 1.4 pounds per month across the first four years of treatment (i.e., an average weight gain of 67.2 pounds). Weight gain may be mitigated in some patients by metformin early in the course of clozapine therapy, or GLP-1/GIP medications, if metformin fails to mitigate weight gain.

L. Glucose Intolerance:

The same study cited above found a 7% per year increase in the prevalence of diabetes mellitus per year of clozapine exposure, or a prevalence of 35% during the five years considered by the study cited. More recent studies have estimated a relative risk of developing diabetes during clozapine treatment as approximately 2.0, compared to haloperidol treatment. As above, metformin may reduce glucose intolerance.

M. Metabolic Syndrome:

Moreover, clozapine is associated with a substantial risk of developing metabolic syndrome, characterized by central adiposity, weight gain, hyperlipidemia, and glucose intolerance.

Henderson, et al., demonstrated in a veteran population that this syndrome is associated with a significant excess mortality due to cardiovascular disease.

N. Severe Neutropenia (Impending Agranulocytosis):

Importantly, clozapine induces a potentially fatal severe neutropenia in a small number of patients. Risk of this response begins at about week 4 of treatment and increases to a peak of circa 1.3% at about month four of treatment. Thereafter the risk declines to circa 0.38% by one year. Long-term risk has been estimated at 6 per 10,000 clozapine-treated patients.

The threshold for discontinuing clozapine treatment is set higher than for drugs that simply suppress cell mitosis (e.g., interferon, many antineoplastics, etc.) because the antibodies induced by clozapine will persist and will continue to attack neutrophil progenitor cells beyond the point where clozapine is discontinued and washes out. If the autoimmune response is permitted to continue without supporting neutrophil progenitor cell mitosis, the entire population of such cells may be destroyed.

If the patient recovers from an initial episode of severe neutropenia and is later re-challenged with clozapine, there is an immune memory that is likely to result in a fulminant decline to agranulocytosis in circa 24 hours. When infection occurs in the context of agranulocytosis, progression to sepsis and septic shock may be very rapid. Thus, development of severe neutropenia due to clozapine should be treated as a medical emergency.

VIII. Clozapine Benefits:

A. Psychosis:

After approximately three decades in the U.S. clinical arena, clozapine remains the “gold standard” in treating refractory psychotic illness, as well as refractory mixed bipolar mood states with psychotic features. Moreover, a variety of studies have demonstrated that some 30% to 60% of patients with psychosis refractory to haloperidol and chlorpromazine show a sub**s**tantial improvement in both positive and negative signs and symptoms of psychosis in response to clozapine treatment.

B. Suicide Risk:

Studies in schizophrenia and schizoaffective disordered patients have shown an approximately 5-fold decrease in suicide rates compared to psychotic individuals treated with first generation antipsychotics.

C. EPS and TD:

Because clozapine at therapeutic concentrations blocks only about 30% to 40% of D_2 dopamine receptors in the basal ganglia, rates of EPS and TD reported with clozapine treatment are much lower than those encountered with the first-generation antipsychotics and some second-generation antipsychotics. Some studies have even suggested that clozapine may actively treat tardive dyskinesia.

D. Neuroleptic Malignant Syndrome:

Because of decreased binding at D_2 dopamine receptors, clozapine is less likely than first generation antipsychotics to be associated with neuroleptic malignant syndrome, though a non-rigid variant has been reported.

E. Prolactin:

Clozapine is less provocative of prolactin secretion than are either the first-generation antipsychotics or risperidone.

IX. Dosage and Administration:

Slow titration and use of therapeutic drug monitoring are important to ensure tolerance and compliance. The patient's ancestry should be considered when determining titration schedule. While the package insert recommends initiating clozapine once or twice daily, single nightly dosing is recommended due to its 24-h half-life in average metabolizers. Split dosing may be necessary in patients who are intolerant of nightly dosing, i.e., orthostatic hypotension symptoms nightly when getting up to urinate.

Patients of US heritage who are average metabolizers give an initial dose of 12.5 mg at night. If this is tolerated, increase the dose the following day to 25 mg, followed by 25 mg increment increases nightly. Total daily dose should not exceed 100 mg by the end of the first week of treatment. Generally, the target dose for the end of the second week of treatment should be 200mg per day. If a patient has had previous orthostatic hypotension problems, dose titration should be even slower at the outset of treatment. Consider ordering a clozapine level at 100 mg to assess the patient's metabolism.

Patients of European and western Asian ancestry (countries west of Pakistan) have lower CYP 1A2 metabolism. Give an initial dose of 12.5 mg at night. If this is tolerated, increase the dose by 12.5 mg nightly. Total daily dose should not exceed 50 mg by the end of the first week of treatment. If tolerated, 25 mg/night increase occurring no more than twice a week is recommended. Consider ordering a clozapine level at 100 mg to assess the patient's metabolism.

Patients of eastern Asian or indigenous American heritage have lower CYP 1A2 activity, hence a slower titration schedule is recommended. Give an initial dose of 6.25 mg nightly for two nights, then increase to 12.5 mg every two nights until target dose is reached. By the end of the first week the total daily dose should not exceed 25 mg. Recommend ordering a clozapine level at 25 mg to assess the patient's metabolism.

Dose titration should be especially slow in elderly, the medically fragile, individuals with intellectual disability (intellectual disability disorder), those individuals with past demonstrated sensitivity to clozapine side-effects, those on concomitant valproate/divalproex, or those with any history of seizure disorder. In patients that are vulnerable to orthostatic hypotension, it may be prudent to adopt a slow titration schedule. Once a patient reaches the target dose of 100 mg/d, obtain a 12-h trough clozapine plasma level as this will help determine the patient's metabolism of clozapine, guide titration schedule, and assist with initial target dose.

A. Although discontinuation of clozapine may be abrupt for medical reasons, clozapine should be tapered and discontinued over two to four weeks whenever possible. Several studies have shown that tapering of clozapine reduces the risk of psychotic decompensation or cholinergic rebound. Cholinergic rebound can be ameliorated by giving a taper of benztropine. The anticholinergic oral equivalents for nonsmokers: clozapine 50 mg ≈ benztropine 1 mg ≈ diphenhydramine 25 mg. The benztropine dose should approximate

the total clozapine dose, when possible. Benztropine dose should be divided and continued for two weeks after clozapine discontinuation before a slow taper of 1 mg/day/week commences, when benztropine equivalent dose is 1 mg/day, taper should decrease by 0.5 mg/day/week.

B. The effective dose range for clozapine is broad with efficacy being reported at doses as low as 50 mg daily in the elderly, while some patients require the maximum recommended dose of 900 mg per day.

Trough plasma concentrations may be helpful in guiding optimal dosing, as some studies show antipsychotic effects at a minimum plasma concentration of about 350 ng/mL. We recommend obtaining a benchmark 12-h clozapine level once a daily dose of 100 mg/day is reached. Plasma concentrations above 600 ng/mL are associated with worsening side effects with limited evidence of further benefit in most patients.

More treatment-resistant patients should be titrated to a plasma concentration of circa 1000 ng/mL while carefully monitoring for adverse effects such as excessive sedation, orthostasis, or myoclonic jerks. For average metabolizers, the minimum effective dose is likely to be at least 300 mg per day.

C. If clozapine is interrupted due to reasons other than adverse response to the medication for two days or less, then it may be resumed at the previous dose. If the period of interruption is between two days and four days, then the clozapine dose should be reduced by about one-half and then be titrated to the previous dose. If the interruption is more than four days, then clozapine should be initiated and titrated as if it were a newly introduced medication.

[Note that the wash-out period for clozapine is about five days and that adaptation of acetylcholine and alpha-adrenergic receptors is lost as the drug washes out. The principal risk of reintroduction is orthostatic hypotension. Individuals known to be prone to orthostatic hypotension should be monitored carefully during clozapine re-initiation.]

D. In an ideal world, it would be desirable to discontinue a prior antipsychotic before initiating clozapine. In the real world, however, such an approach would carry a substantial risk of producing psychotic relapse. In general, a prior antipsychotic should be gradually tapered once clozapine has reached a dose of 100 – 200 mg per day. In fragile psychiatric patients, an especially slow taper may be desirable.

X. Infection:

A. During an infection inflammatory cytokines can result in the downregulation of CYP 1A2 production resulting in elevation of clozapine plasma level. Patients who have an infection should be assessed by a physician, a WBC/ANC and clozapine level ordered. If signs of clozapine toxicity (i.e., sedation, seizures, apathy, hypotension) are present, reduce the clozapine dose by 25-50%. Recheck the clozapine plasma level 5 days after dose reduction.

XI. Length of Clozapine Trials:

A. Three patterns of response are typically seen with clozapine treatment:

1. 30% of patients respond in 4 – 6 weeks

2. A second group responds gradually over 4 – 6 months

3. A third group will have improvement in negative symptoms, cognitive function, and social function with little improvement in positive psychotic symptoms

B. For partial responders to clozapine treatment, the addition of a first, second, or third-generation antipsychotic medication for those with persisting positive psychotic symptoms may benefit these individuals.

XII. Additional Procedures:

A. Physician Responsibilities:

1. Evaluate complete blood counts and treat per section VII

2. Monitor other potential clozapine side effects and treat appropriately

3. Monitor clozapine efficacy

4. Plan for post-discharge clozapine continuation

B. Pharmacy Responsibility

Assist with compliance to monitoring recommendations.

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