CCHCS / DHCS Care Guide: Clozapine

SUMMARY | **DECISION SUPPORT** | **PATIENT EDUCATION / SELF MANAGEMENT**

GOALS

- No interruption clozapine therapy unless absolutely necessary
- Very close monitoring during clozapine initiation, titration, and dose reduction
- Appropriate clozapine titration
- Adequate therapeutic trial of clozapine
- Clear identification of primary and secondary clozapine prescribers
- Adherence with required statewide monitoring (using CCHCS/DHCS clozapine patient registry*) for all patients

ALERTS

- Fall in Absolute Neutrophil Count (ANC)
- Fever
- Constipation / abdominal pain
- Dizziness / fainting
- Chest pain / dyspnea / fatigue
- Significant tachycardia or arrhythmia
- New or increased seizures
- Eosinophilia

DIAGNOSTIC CRITERIA / EVALUATION

CLOZAPINE INDICATIONS

- Patients who meet DSM-IV TR or DSM V criteria for diagnosis of schizophrenia.
- Patients with refractory schizophrenia or schizoaffective disorder, especially with suicidality or intermittent suicidality.
- Treatment-resistant bipolar disorder which has failed at least 2-3 combinations of antipsychotics, mood stabilizers and other neuroleptics (e.g., lithium, valproic acid, carbamazepine, oxcarbazepine).
- Any significant tardive dyskinesia (pronounced, often permanent, extrapyramidal symptoms).
- Psychosis in those with Parkinson's disorder for whom quetiapine is not effective or causes too many side effects.

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PRETREATMENT CONSIDERATIONS

Patients considered for clozapine therapy shall be admitted to a designated CDCR clozapine *initiation* facility for evaluation, acceptance, and initiation of clozapine treatment. (Currently these institutions are SAC, CMF, SQ, CIW, and CCWF).

Prescriber shall:

- Ensure no contraindications to clozapine.
- Verify baseline ANC ≥1500/µl for general population or ≥1000/µl for patients with Benign Ethnic Neutropenia (BEN)
- Obtain medication informed consent (unless the patient is under PC-2602 [involuntary MH treatment court order]).
- Obtain required baseline monitoring data (see Monitoring page 3).
- Ensure reporting of initial and ongoing ANC to Clozapine Risk Evaluation and Mitigation Strategy (REMS) program.
- Consider prophylactic bowel regimen to prevent potentially serious or life-threatening constipation (see pages 10-12).
- Consider prophylactic anticonvulsant medication in patients with history of seizures who are not currently on anticonvulsant medication. (Carbamazepine should be avoided due to neutropenia risk).
- Place a Medical Hold, as required, for patients on clozapine.

CLOZAPINE RISK EVALUATION AND MITIGATION STRATEGY (REMS) PROGRAM

- The Clozapine REMS program is an FDA-mandated program implemented by the manufacturers of clozapine to provide a centralized point of access for pharmacists and prescribers to minimize the risk of clozapine-associated neutropenia.
- Starting October 12, 2015 prescribers, pharmacies, and patients must be enrolled with this new program for the prescribing, dispensing, and use of clozapine. The Clozapine REMS Program can be accessed at: www.clozapinerems.com or by calling 1-844-267-8678.
- Prior to dispensing clozapine, pharmacies must verify ANC is current and acceptable for each patient or verify the prescriber has authorized continuation of clozapine therapy by providing the treatment rationale for patients with ANC <1000/µL.
- ANC is used exclusively for patient monitoring. WBC counts are no longer accepted by the REMS program, although a prescriber may wish to consider additional monitoring.
- Patients with Benign Ethnic Neutropenia can now be treated with clozapine and have a separate monitoring algorithm.
- Prescribers can continue clozapine treatment for patients with ANC <1000/µL if prescribers believes the benefits of clozapine therapy outweigh the risk of severe neutropenia.
- Patients may be rechallenged with clozapine if the prescriber determines the risk of psychiatric illness is greater than the risk of severe neutropenia.

*CCHCS/DHCS MENTAL HEALTH PATIENT REGISTRY

Go to Lifeline → Health Care Operations → Quality Management → External Links: QM Portal → Patient Registries Header → Mental Health Registry (also named Psychotropic Medication Monitoring Registry) → Clozapine patients identified under CLOZ header.

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TREATMENT

CLOZAPINE INITIATION AND MAINTENANCE

Cautious titration and a divided dosage schedule are required to minimize the risks of hypotension, seizures, and sedation.

Initial dose	12.5 mg once daily (half of a 25 mg tablet) Clozapine therapy should be initiated on a weekday morning. Consider alternate starting dose 6.25 mg at hs with prior history of orthostatic hypotension from clozapine.
Dosing in first 2 weeks after initiation	Increase total daily dose by 12.5-25 mg every 3 days to achieve a target dose of 300-450 mg/day. Slow titration is better. A 12.5 mg dose increase every 3 days will ultimately reach therapeutic dose, although 25 mg increase every 1-3 days is often recommended. May advance more rapidly if tolerated well by patient.
Dosing after first 2 weeks of therapy	Subsequent dosage increments should not exceed 25 mg/day, and should be made once or twice per week. It should be noted that 12.5-25 mg/day is a reasonable dose increase for most patients.
Clozapine maintenance dose	Recommended maintenance dose schedule: Give clozapine twice daily, give 1/3 total daily dose in AM, 2/3 total daily dose in PM. Larger evening dose may help reduce morning sedation.

PATIENT HOUSING AND MENTAL HEALTH LEVEL OF CARE

- Patients on clozapine shall remain in the CTC/MHCB until stable for transfer.
- When stable, the patient will be discharged to a CDCR facility approved by DHCS for clozapine maintenance and remain at the EOP level of care for at least 6 months thereafter. Clozapine maintenance institutions are: **CCWF, CIW, CMF, COR, SAC, MCSP, NKSP, SQ, VSP**.

Sample Clozapine Initiation and Titration Schedule (with dose increases every 3 days)

Week 1	AM Dose (mg)	PM Dose (mg)
Day 1 Initiate	0	12.5
Day 2	0	12.5
Day 3	0	12.5
Day 4	12.5	12.5
Day 5	12.5	12.5
Day 6	12.5	12.5
Day 7	12.5	25
Week 2	**AM Dose (mg)**	**PM Dose (mg)**
Day 8	12.5	25
Day 9	12.5	25
Day 10	25	25
Day 11	25	25
Day 12	25	25
Day 13	25	50
Day 14	25	50
Week 3	**AM Dose (mg)**	**PM Dose (mg)**
Day 15	25	50
Day 16	50	50
Day 17	50	50
Day 18	50	50
Day 19	50	75
Day 20	50	75
Day 21	50	75
Week 4	**AM Dose (mg)**	**PM Dose (mg)**
Day 22	50	100
Day 23	50	100
Day 24	50	100
Day 25	50	125
Day 26	50	125
Day 27	50	125
Day 28	50	150

EVALUATION OF RESPONSE TO CLOZAPINE

- Response to clozapine occurs within 6 months on average.
- Every effort should be made to achieve an adequate therapeutic trial for any patient placed on clozapine. An adequate therapeutic trial is a 6 month period during which the patient is on either 800 mg total daily dose or has a therapeutic level of clozapine (200-300 ng/ml). Clozapine plasma levels are recommended in patients with partial or no response after 3 months of treatment at a dose of at least 300 mg/day.

INTERRUPTION OF CLOZAPINE THERAPY

- If clozapine therapy is interrupted for more than 48 hours, therapy should be restarted at the initial starting dose to minimize risks of hypotension, bradycardia, and syncope.
- If clozapine therapy is interrupted, the frequency of ANC monitoring must be evaluated using the guidelines for ANC Monitoring on page 9.
- Clozapine therapy can be reinitiated (when indicated) at any CDCR institution authorized to provide maintenance clozapine therapy.

RECHALLENGE OR RETREATMENT WITH CLOZAPINE AFTER TREATMENT INTERRUPTION

- Patients may be rechallenged with clozapine if benefits of treatment outweigh the risk of neutropenia. However, generally patients with clozapine related myocarditis or cardiomyopathy should not be rechallenged with clozapine, see guidelines for ANC Monitoring, page 9.
- Patients with any neutropenia must have ANC monitored more frequently until levels reach target or baseline.

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MONITORING

(TO ENSURE PATIENT SAFETY WITH USE OF CLOZAPINE, MONITORING GUIDELINES BELOW MUST BE FOLLOWED BY CCHCS/DHCS PROVIDERS)

CLOZAPINE MONITORING (SEE ADVERSE EFFECTS & MANAGEMENT, PAGES 6 - 8)			
EVALUATION	**BASELINE OR AS INDICATED**	**3 MONTHS**	**ANNUAL OR AS INDICATED**
CONSENTS	BASELINE		ANNUAL
AIMS* (CDCR MH-7390)	BASELINE		EVERY 6 MONTHS
HEIGHT / WEIGHT / BMI	BASELINE	YES	ANNUAL
BLOOD PRESSURE VITAL SIGNS	BASELINE • **Before initiation** of clozapine, measure orthostatics twice within 24 hours, separated by at least one hour. • Then obtain **daily** orthostatic measurement for first two weeks after initiation. • **Within a day or two of each dose increase,** obtain orthostatic measurements.	SEE BASELINE COMMENT	ANNUAL
BOWEL FUNCTION ASSESSMENT	BASELINE **Weekly** during first four months of therapy		At every MH provider visit while on therapy
ECG	BASELINE		ANNUAL
PREGNANCY TEST (women < 50)	BASELINE		AS INDICATED
ANC (absolute neutrophil count)	BASELINE • Repeat weekly for first 6 months and • Every two weeks for second 6 months or as indicated based on ANC (see page 9)	SEE BASELINE COMMENT	MONTHLY AFTER ONE YEAR OF THERAPY
CMP	BASELINE	YES	ANNUAL
GLUCOSE / A1C	BASELINE	YES	ANNUAL
LIPID PANEL	BASELINE	YES	ANNUAL
TSH	BASELINE (within 5 years of initiation)		EVERY 5 YEARS
CLOZAPINE PLASMA LEVELS		After 3 Months at Therapeutic Dose in Partial or Non-responders	
COMPLETE PHYSICAL EXAM			ANNUAL

* AIMS = Abnormal Involuntary Movement Scale

MEDICATION: CLOZAPINE

MEDICATION	DOSING	ADVERSE EFFECTS*	COMMENTS
Clozapine (Clozaril®) Tablets: 25 mg, 50 mg, 100 mg, 200 mg HEAT DRUG**	Maintenance Dose: 300-900 mg/day in 2-3 divided doses Max Dose: 900 mg/day • **Titrate dose, especially slowly in the elderly, the medically fragile, patients with mental retardation or any history of seizures.** • **Other prescribed neuroleptics should be slowly tapered during clozapine initiation. Rarely, coadministration of clozapine with another neuroleptic may be indicated.**	Very significant: • Weight gain • Anticholinergic effects (especially constipation) • Orthostatic hypotension • Sedation, drowsiness • Dizziness, vertigo • Excessive salivation • Seizures • Myocarditis • Agranulocytosis • Eosinophilia • Tachycardia Less severe: • Akathisia/agitation Mild or unclear severity • EPS symptoms • Prolactinemia • Tardive dyskinesia • QTc prolongation	• Monitor serum level for daily doses >600 mg/day. • Divided dosage schedules may be necessary to minimize risks of hypotension, seizure, and sedation. Usually divided 1/3 dose AM, 2/3 dose PM to minimize daytime sedation. • TID dosing can be considered when daily doses exceed 500mg. • Pregnancy category B. Use in pregnancy only if clearly needed. • Elderly patients more sensitive to anticholinergic effects of clozapine (urinary retention/ constipation) and other adverse effects. • Do not use in elderly demented patients with psychosis. • Dose reduction may be necessary with significant renal or hepatic impairment.

IMPORTANT DRUG INTERACTIONS WITH CLOZAPINE*

DRUG	COMMENTS
Anticholinergics (e.g., benztropine, diphenhydramine, hydroxyzine)	Use with caution due to additive anticholinergic activity. Monitor closely for significant anticholinergic adverse effects (e.g., constipation, hypotension).
Antihypertensives (e.g., alpha-blockers, beta-blockers)	Caution is advised due to potentiation of hypotensive effects.
Bone marrow suppressants (e.g., antineoplastics, carbamazepine)	Use caution when clozapine is administered with agents having well-known potential for bone marrow suppression due to increased risk and/or severity of bone marrow suppression. Consider monitoring patients more closely. Consult with oncologist in patients receiving chemotherapy.
CNS depressants, general anesthesia (e.g., alcohol, benzodiazepines, narcotics)	Use with caution because of additive CNS depressant effects (e.g., excessive sedation, confusion, loss of coordination) from clozapine. Respiratory depression is a major concern when clozapine used concurrently with these agents.
CYP450 enzyme inducers (e.g., phenytoin, rifampin, phenobarbital, smoking)	These inducers may reduce clozapine levels, resulting in decreased efficacy of clozapine.
CYP450 enzyme inhibitors (e.g., fluvoxamine, erythromycin)	Use caution and monitor patients closely when these inhibitors are prescribed. Clozapine levels may be increased, leading to adverse reactions.
Drugs known to prolong the QT interval (e.g., quinidine, ziprasidone, methadone)	Use with caution due to additive effects on QT interval prolongation which may increase risk of life-threatening arrhythmias.
Highly protein bound drugs (e.g., warfarin, digoxin)	Clozapine may increase levels of protein bound drugs and vice versa. Adjust dose if necessary.
Medications that lower seizure threshold (e.g., bupropion)	Use extreme caution when coadministering with clozapine due to increased risk of seizures. Use low initial doses of bupropion and increase the dose gradually.

*See Clozapine prescribing information for complete description of adverse effects and drug interactions.

**Heat Drug: Clozapine may disrupt the body's ability to reduce core body temperature and could result in hyperthermia with exposure to extreme heat, strenuous exercise, etc. See Thermoregulatory Problems, page 8.

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CONTRAINDICATIONS TO CLOZAPINE USE

ABSOLUTE CONTRAINDICATIONS

- Previous hypersensitivity to clozapine or any other component of the drug.
- Baseline ANC <1500/µl in the general population or <1000/µl in the Benign Ethnic Neutropenia Population, page 9.
- Uncontrolled seizure disorder.
- Paralytic ileus.
- No prior history of antipsychotic treatment.
- Previous clozapine-induced myocarditis or cardiomyopathy.

RELATIVE CONTRAINDICATIONS

- History of clozapine-induced agranulocytosis or severe granulocytopenia.
- Noncompliance with mandatory laboratory studies.
- Severe central nervous system depression or comatose state from any cause.
- Diagnosis of a myeloproliferative disorder.
- Breastfeeding.
- Currently unstable serious medical illness that would hinder cooperation with therapy.
- Debilitated medical status.
- Concurrent use of benzodiazepines during clozapine titration.
- Use of type 1C antiarrhythmics (propafenone, flecainide, encainide).

USE PRECAUTIONS WITH CLOZAPINE

- History of seizure disorder.
- History of neuroleptic malignant syndrome.
- Evidence of significant hepatic, renal, or cardiopulmonary disease.
- Prostate enlargement.
- Narrow angle glaucoma.
- History of frequent constipation or bowel obstruction.
- Jewish background (due to increased risk of agranulocytosis).
- History of DVTs.
- History of triglyceride-induced pancreatitis.
- Use of other medications that suppress bone marrow function. Consider monitoring patients more closely than recommended in the treatment algorithms, page 9.
  - Antineoplastic drugs—consult with treating oncologist in patients receiving concomitant therapy.
  - Antiretroviral medications.
  - Carbamazepine.
  - Propylthiouracil.

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CLOZAPINE ADVERSE EFFECTS* AND SUGGESTED MANAGEMENT

Adverse Effect	Clinical Presentation	Action /Comments
ABNORMAL INVOLUNTARY MOVEMENTS	Abnormal movements caused by clozapine are very rare. When seen, they are primarily mild and orolingual	• Clozapine has been shown to improve tardive dyskinesia (TD) symptoms. • Clozapine has rarely been reported to cause TD symptoms. • Evaluate medication regimen to identify likely cause if TD symptoms develop (as clozapine is unlikely cause).

AGRANULOCY-TOSIS / LEUKOPENIA	Fever, weakness, lethargy, and/or sore throat	• Fatal agranulocytosis:
		  • Occurs in 1.3% of patients.
		  • Incidence increases with age.
		  • Incidence higher in Jewish population.
		• Monitoring and reporting CBC/ANC to clozapine registry is critical.
		• Some patients will require interruption or permanent discontinuation of clozapine. Rechallenge may be considered in some cases based on degree of ANC reduction. (Benefits must outweigh risks).
		• Results must be reviewed promptly and indicated treatment adjustments ordered. (See Clinical Management of Leukopenia / Neutropenia, page 9)
		• Leukocytosis may occur upon initiation of therapy. As WBC returns to normal, this drop may be incorrectly interpreted as impending neutropenia.

CONSTIPATION	Abdominal discomfort, distension, cramping, slow or absent bowel movements or intestinal obstruction and paralytic ileus which may be fatal	• Prophylactic bowel regimen often indicated. • Avoid use of other constipating agents. • See Prevention and Management of Bowel Dysfunction, pages 11-13. • Prompt treatment of symptoms as clinically indicated.
ECG CHANGES	QT prolongation, syncope, presyncope, dizziness, palpitations, arrhythmias, cardiac arrest	• QT prolongation and life-threatening arrhythmias may occur. • Discontinue if QTc > 500 msec. • Risk is increased with other QT prolonging agents, electrolyte abnormalities, significant arrhythmia, recent MI, uncompensated CHF. • Monitor for other signs of myocarditis or ischemia closely, especially if ECG changes are occurring within the first month of therapy. • ECG changes typically normalize when drug discontinued.
EOSINOPHILIA	Eosinophil count > 700/µl	• Eosinophilia develops in about 1% of patient. If eosinophilia occurs, evaluate patient for signs of rash or other allergic symptoms. • Eosinophilia from clozapine without organ involvement can resolve without intervention and clozapine may be continued with careful monitoring. • If clinically indicated, obtain ECG and look for sign/symptoms of myocarditis or other organ specific disease (pancreatitis, hepatitis, colitis, nephritis). Fatal organ injury may occur. • Treat underlying cause of eosinophilia unrelated to clozapine (e.g., asthma, allergies, parasites, specific neoplasms).
HYPERTHERMIA (BENIGN)	Transient clozapine-related fever may occur (up to 100.4˚F)	• Reduce speed of dose titration and decrease dose of clozapine if any hyperthermia develops. • Peak incidence of transient benign fever occurs in first 3 weeks of treatment. • Benign hyperthermia resolves over time and responds to antipyretics. • Discontinue clozapine if temperature exceeds 101˚F. • Gradually restart when hyperthermia subsides. • Fever may be associated with increase or decrease in WBC. • Infection and agranulocytosis should be ruled out. Also consider possibility of myocarditis or neuroleptic malignant syndrome.

*See prescribing information for complete description of adverse effects and drug interactions.

CLOZAPINE ADVERSE EFFECTS* AND SUGGESTED MANAGEMENT

Adverse Effect	Clinical Presentation	Action /Comments
HYPOTENSION, ORTHOSTATIC	Dizziness, orthostatic hypotension and/or bradycardia	• Risk highest during initial titration period, initial dose should not exceed 12.5 mg once or twice daily. • Monitor orthostatics closely upon initiation and with dose increases (see Monitoring, page 3). • Use cautious titration and divided dosage schedule to minimize risk of serious cardiovascular reactions. • Use with caution in patients with ASCVD, cerebrovascular disease, and those receiving antihypertensive agents.
METABOLIC CHANGES	Signs of insulin resistance: · Hyperglycemia · Dyslipidemia · Weight gain	• Monitor weight/BMI: clozapine can cause significant weight gain (average of 30 lbs in a 10 year cohort study). Most weight gain occurs in first 6-12 months of therapy. • DM developed in 34% of 96 patients followed up to 10 years. • Monitor BP, lipids (see Monitoring, page 3). • Increased risk of cardiovascular and cerebrovascular events from obesity, DM, dyslipidemia, hypertension.
MYOCARDITIS	Unexplained fatigue, dyspnea, tachypnea, fever, chest pain, palpitations, other signs/ symptoms of heart failure, ECG abnormalities or arrhythmias, markedly elevated eosinophils	• Immediately discontinue clozapine and refer to TTA. • Monitor closely, especially during first 4 weeks of therapy. Myocarditis is associated with elevated eosinophils, CRP, ESR, CPK, troponin, and brain natriuretic peptide (BNP). • Clozapine-induced myocarditis is an absolute contraindication to clozapine therapy. • Evidence suggests myocarditis is a Type I IgE mediated acute hypersensitivity reaction.

NEUROLEPTIC MALIGNANT SYNDROME (NMS)	Hyperpyrexia, muscle rigidity, altered mental status, autonomic instability	• Although clozapine has only a weak affinity for dopamine receptors, NMS, which is potentially fatal, can develop during clozapine monotherapy or when used concomitantly with other CNS active agents.
		• Management includes:
		  • Immediate discontinuation of antipsychotic drugs and other nonessential medications.
		  • Intensive symptomatic treatment and medical monitoring, and/or
		  • Treatment of comorbid conditions.

PULMONARY EMBOLISM	Dyspnea, pleuritic pain, orthopnea, cough, calf or thigh pain with or without swelling, hemoptysis, wheezing,	• There have been cases of deep vein thrombosis and pulmonary embolism associated with the use of clozapine, in some cases fatal.
		• Clozapine should be withdrawn promptly under the supervision of a psychiatrist in the case of venous thromboembolic events, and alternative antipsychotic therapy should be commenced to avoid recurrence of target symptoms.
		• In order to minimize risk of DVT or PE:
		  • Minimize weight gain.
		  • Avoid sedentary lifestyle (encourage frequent movement/exercise).

SALIVATION	Excessive salivation, drooling	• May be treatment limiting as excessive drooling is stigmatizing and may interfere with sleep. • May respond to dose reduction. • Symptoms often resolve after two to three months of clozapine treatment. • May respond to the anticholinergic agent glycopyrrolate (Robinul®) 2-4 mg at bedtime. This therapy will add to peripheral anticholinergic effects but this drug does not cross the blood brain barrier.

*See prescribing information for complete description of adverse effects and drug interactions.

SUMMARY	DECISION SUPPORT	PATIENT EDUCATION / SELF MANAGEMENT

CLOZAPINE ADVERSE EFFECTS* AND SUGGESTED MANAGEMENT

Adverse Effect	Clinical Presentation	Action / Comments
SEIZURE	Seizures	• Prophylactic therapy should be considered in patients previously treated for seizures who are currently not on anticonvulsants. • Obtain an EEG if patient seizes during clozapine treatment as an underlying seizure focus may be unmasked. • Seizure risk is dose related. Initiate treatment at low dose, titrate slowly, use divided dosing. Patients on doses ≥ 600 mg/day have four times more seizures than those on ≤ 300 mg/day. • Seizure risk increases in relation to the rapidity of dose titration (faster than 25mg/day), or in relation to the total daily dose.
TACHYCARDIA, SUSTAINED	HR increase ≥10-15 bpm	• Monitor for other signs of myocarditis closely, especially if resting tachycardia persists during the first two months of therapy. • Tachycardia is a common side effect of clozapine, occurs in about 25% of users, especially during initiation and dose titration.
THERMO-REGULATORY PROBLEMS	High body temperature or low body temperature	Appropriate care is advised in patients who will be experiencing: • conditions which may contribute to an elevation in core body temperature (e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration). • conditions which may lower core body temperature. Antipsychotics, including clozapine, may disrupt the body's ability to reduce core body temperature and could result in hyperthermia with exposure to extreme heat, strenuous exercise, etc. Antipsychotics, particularly risperidone, can also make it difficult for patients to adjust to cold temperatures, and therefore can precipitate hypothermia, particularly when the temperature is cold or if patients are not well covered.

*See prescribing information for complete description of adverse effects and drug interactions.

CLOZAPINE TREATMENT RECOMMENDATIONS BASED ON ABSOLUTE NEUTROPHIL COUNT (ANC) MONITORING

ANC LEVEL	TREATMENT RECOMMENDATION	ANC MONITORING
GENERAL POPULATION		

NORMAL (≥ 1500/µl)	• Initiate treatment.
	• If treatment interrupted:
	  • < 30 days, continue monitoring as before.
	  • ≥ 30 days, monitor as if new patient.
		• Weekly from initiation to 6 months.
		• Every 2 weeks from 6 to 12 months.
		• Monthly after 12 months.

MILD NEUTROPENIA (1000-1499/µl)*	• Continue treatment.	• Three times weekly until ANC ≥ 1500/µl. • Once ANC ≥ 1500/µl, return to patient's last "Normal Range" ANC monitoring interval.**
MODERATE NEUTROPENIA (500-999/µl)*	• Recommend hematology consultation. • Interrupt treatment for suspected clozapine induced neutropenia. • Resume treatment once ANC normalizes to ≥ 1000/µl.	• Daily until ANC ≥ 1000/µl then, • Three times weekly until ANC ≥ 1500/µl. • Once ANC ≥ 1500/µl, check ANC weekly for 4 weeks, then return to patient's last "Normal Range" ANC monitoring interval.**
SEVERE NEUTROPENIA (< 500/µl)*	• Recommend hematology consultation. • Interrupt treatment for suspected clozapine induced neutropenia. • Do not rechallenge unless prescriber determines benefits outweigh risks.	• Daily until ANC ≥ 1000/µl then, • Three times weekly until ANC ≥ 1500/µl. • If patient is rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1500/µl.
BENIGN ETHNIC NEUTROPENIA (BEN) POPULATION • BEN is a condition observed in certain ethnic groups whose average ANC levels are lower than "standard" ranges for neutrophils. • Most commonly observed in individuals of African descent (approx. prevalence 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 numbers and myeloid maturation, are healthy, do not suffer from repeated or severe infections, and are not at increased risk of developing clozapine-induced neutropenia. • Consider hematology consultation before initiating or during clozapine treatment as necessary.		

NORMAL BEN RANGE (≥ 1000/µl)	• Obtain at least 2 baseline ANC levels before initiating treatment.
	• If treatment interrupted:
	  • < 30 days, continue monitoring as before.
	  • ≥ 30 days, monitor as if new patient.
		• Weekly from initiation to 6 months.
		• Every 2 weeks from 6 to 12 months.
		• Monthly after 12 months.

BEN NEUTROPENIA (500—999/µl)*	• Recommend hematology consultation. • Continue treatment.	• Three times weekly until ANC ≥ 1000/µl or ≥ patient's known baseline. • Once ANC ≥ 1000/µl or at patient's known baseline, check ANC weekly for 4 weeks, then return to patient's last "Normal BEN Range" ANC monitoring interval.**
BEN SEVERE NEUTROPENIA (< 500/µl)*	• Recommend hematology consultation. • Interrupt treatment for suspected clozapine induced neutropenia. • Do not rechallenge unless prescriber determines benefits outweigh risks.	• Daily until ANC ≥ 500/µl then, • Three times weekly until ANC ≥ patient's established baseline. • If patient is rechallenged, resume treatment as a new patient under "Normal Range" monitoring once ANC ≥ 1000/µl or at patient's baseline.

*Confirm all initial reports of ANC less than 1500/µl (ANC < 1000/µl for BEN patients) with a repeat ANC measurement within 24 hours. See prescribing information for complete description of adverse effects and drug interactions.

** If clinically appropriate.

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PREVENTION AND MANAGEMENT OF CONSTIPATION / BOWEL OBSTRUCTION

DIAGNOSIS / EVALUATION

CLOZAPINE HAS BEEN ASSOCIATED WITH FATAL BOWEL OBSTRUCTION

Screen clozapine patients at least weekly during the first 4 months of clozapine therapy.

- Significant risk factors for clozapine induced gastrointestinal hypomotility:
  - High dose of Clozapine.
  - High clozapine serum levels.
  - Coadministration with other anticholinergic medications.
  - Concomitant administration of CYP450 inhibitors which may increase clozapine levels (see table below).

BOWEL FUNCTION EVALUATION

- Document baseline bowel function, stool frequency, and consistency.
- Document comorbid medical conditions affecting bowel function.
- Review entire medication regimen including OTC medications that are potentially constipating.
- Elicit history of:
  - Changes in stool frequency and consistency.
  - Straining, pain, or bloating.
  - The sensation of incomplete evacuation.
  - Use of manual efforts for successful defecation.
- Assess abdominal tone, bowel sounds, tenderness or masses.
- Inspect the perineum.
- Perform digital rectal exam.
- Obtain laboratory tests to exclude a treatable cause of constipation (e.g., hypothyroidism).
- Order imaging studies as indicated.
- Consider further evaluation and/or consultation for alarm symptoms of colon cancer or other GI pathologies.

MEDICATIONS ASSOCIATED WITH CONSTIPATION (SLOWING INTESTINAL TRANSIT)

MEDICATION CLASS	COMMON MEDICATIONS*
ANTICHOLINERGICS:	
• ANTIHISTAMINES	diphenhydramine, chlorpheniramine, meclizine, cetirizine, fexofenadine, loratadine
• ANTIPSYCHOTICS	clozapine, olanzapine, perphenazine, thioridazine
• ANTIPARKINSON'S DRUGS	benztropine, amantadine
• ANTIDEPRESSANTS	tricyclics antidepressants, paroxetine
• ANTICONVULSANTS	oxcarbazepine, carbamazepine
• ANTISPASMODICS	methocarbamol, cyclobenzaprine
• OVERACTIVE BLADDER AGENTS	oxybutynin, tolterodine
ANTIDIARRHEAL AGENTS	loperamide
BETA BLOCKERS	atenolol
CALCIUM CHANNEL BLOCKERS	verapamil, diltiazem, nifedipine
CATION CONTAINING AGENTS	iron, aluminum, calcium, barium
DIURETICS	furosemide, thiazides
CENTRALLY ACTING ALPHA 2 AGONIST	clonidine
5HT3 RECEPTOR ANTAGONISTS	ondansetron
NSAIDS	Ibuprofen, naproxen
OPIATES	morphine, methadone, codeine, hydrocodone, etc.

*See Laxative Medication, page 12.

PREVENTION AND MANAGEMENT OF CONSTIPATION / BOWEL OBSTRUCTION

TREATMENT

PROPHYLACTIC TREATMENT FOR CONSTIPATION*

Prophylaxis for prevention of constipation / bowel obstruction should be considered in all patients initiating clozapine therapy.

Therapy goals

- Maintain normal bowel function.
- Minimize polypharmacy in constipation management.
- Prevent acute constipation, ileus, bowel obstruction.

For all clozapine patients

- Discontinue other constipating medications (especially other anticholinergics), if possible (see page 11).
- Increase daily fluid and fiber intake (cereals, wheat bran, fruits and vegetables).
- Encourage regular exercise.

Minimal or mild symptoms of bowel slowing or constipation

- Change to an antipsychotic with less anticholinergic effects, if possible.
- Reduce antipsychotic dose, if possible.
- **Docusate** (softener/surfactant) 100 mg orally daily or twice daily, may have very minimal efficacy.
- **Polycarbophil** (fiber supplement/bulk forming agent) 2 tabs orally one to four times daily.
  - Dose must be increased slowly, effect will not be seen for several weeks.
  - Does not significantly increase stool transit time.

Moderate to severe symptoms of constipation
(or when bowel cleansing or "rescue" has been required):

- Change to an antipsychotic with less anticholinergic effects, if possible.
- Reduce antipsychotic dose, if possible.
- Osmotic agents recommended (first choice).
  - **lactulose**: 15-30 ml orally once or twice daily.
    Improves stool frequency and consistency, liquid formulation.
  - **polyethylene glycol powder** (PEG) (MiraLAX®) usual dose 17 gm (1 Tbsp), range 8.5 to 34 gm (1/2 to 2 Tbsp).
    Mixed in 8 oz fluid, taken orally once daily.
    Improves stool frequency and consistency, powder formulation.
- Stimulant laxatives (alternative or adjunct therapy with osmotic agents).
  - **bisacodyl** 5 mg tablets, 1-3 tablets orally once daily.
  - **bisacodyl** 10 mg suppositories, 1 suppository per rectum once daily.
  - **senna** 8.6 mg tablets, 1-2 tablets once or twice daily, may increase up to 10 tablets per day.
- Patients who are poorly responsive or unresponsive to maximal therapy with these agents alone or in combination should be referred for further management.

ACUTE CONSTIPATION TREATMENT*— "RESCUE"

Interventions to evacuate colon and provide symptom relief include:

- ✓ Milk of Magnesia (osmotic agent), 2 tbsp orally, may repeat every 6-8 hours
- ✓ Magnesium Citrate (osmotic agent), 150-300 ml orally
- ✓ Bisacodyl (Dulcolax), 10 mg suppository
- ✓ Large volume enema
- ✓ Manual disimpaction

*See Laxative Medication, page 12.

CCHCS / DHCS Care Guide: Clozapine

LAXATIVE MEDICATION	DOSE	ACTION ONSET	COMMENTS/ ADVERSE EFFECTS
BULK-FORMING			
Polycarbophil (FiberCon®) Tablet: 625 mg (500 mg fiber/tab) $	2 tablets 1 to 4 times a day with at least 8 ounces of fluid Max: 8 tabs/24 hours Separate from other drugs by at least 2 hours	24 to 48 hours	• Increases frequency and softens consistency of stool. • Dose must be increased slowly to minimize bloating. • Effect on bowel function will not be seen for several weeks. • Contraindicated in patients with difficulty swallowing. • May cause epigastric fullness, flatulence.
SURFACTANTS (SOFTENERS)			
Docusate Sodium (Colace®) Capsule: 100 mg $	100 mg 2 times per day (Max dose 500 mg/day)	24 to 72 hours	• No laxative effect alone, use with another laxative. • Shown to be ineffective with long term use. • Not useful in patients with mushy or soft stools. • *More effective in preventing constipation in patients who should avoid straining rather than treating acute episodes.* • Rarely causes nausea, abnormal taste in mouth, cramping.
OSMOTIC AGENTS			
Lactulose (Enulose®) Oral solution: 10 g/15 ml $	10 to 20 grams (15 to 30 ml) once daily. May increase up to 2 times per day. May mix with fruit juice, water, or milk.	24 to 48 hours	• Avoid if patient is lactose intolerant (contains galactose and lactose). • Potential electrolyte imbalance when used > 6 months or in patients predisposed to electrolyte imbalance (elderly). • Caution in diabetics due to lactose/galactose content. • May cause abdominal bloating, flatulence, belching, cramping, diarrhea (excessive dose), nausea/vomiting.
Polyethylene glycol 3350 (Miralax®) Powder $	8.5 to 34 grams in 240 ml (8 ounces) liquid daily Typical dose 17g (1 heaping tablespoonful, or one measuring cap)	1 to 4 days	• Use with caution in older adults and those with renal impairment. • Requires dissolving powder in 8 ounces of liquid before administration. *May make nurse administration more complicated than lactulose.* • Nausea, bloating, cramping.
Magnesium Hydroxide (milk of magnesia) Liquid: 400mg/5ml $	2400-4800 mg (30-60 ml) with 8 ounces of liquid once daily at bedtime or in divided doses 400 mg Mg hydroxide = 166.7 mg (13.7 mEq) elemental Mg	30 min to 3 hours	• Use with caution in renal impairment (possible hypermagnesemia). • Avoid in renal failure. • Nausea, vomiting, cramping.
Magnesium citrate (Citroma®) Solution:1.75g/30ml $	150-300 ml given once or in divided doses with 8 ounces of water 300 ml magnesium citrate = 2.8 g (235 mEq) elemental Mg	0.5 to 3 hours	• Use with caution in renal impairment (possible hypermagnesemia). • Avoid in renal failure. • Nausea, vomiting.
STIMULANTS			
Chronic use of stimulant laxatives has not been shown to cause structural or functional impairment of the colon or increased risk of colon cancer or other tumors.			
Bisacodyl (Dulcolax®) Tablets: 5 mg Suppository: 10 mg $	10 to 30 mg as enteric coated tabs orally once daily Separate administration of oral tabs with antacids or milk by at least 1 hour	6 to 10 hours	Very infrequent: • Mild abdominal cramps. • Electrolyte disturbances (acidosis, alkalosis, or hypocalcemia). • Nausea or vomiting. • Vertigo.
	10 mg suppository per rectum once daily	15 to 60 min	• Infrequent cause of rectal irritation (burning).
Senna (Senokot®) Tablets: 8.6 mg sennosides $	For constipation: 2 to 4 tabs as a single daily dose or divided dose twice daily (Max dose: 70-100 mg sennosides/day divided Q 12 hours) For bowel evacuation: up to 130 mg sennosides the day prior to procedure	6 to 12 hours	• Abdominal cramps, diarrhea, nausea, or vomiting. Contraindications: • Intestinal obstruction, nausea/vomiting, abdominal pain of unknown origin, appendicitis, Crohn's disease, sudden change in BM lasting more than 2 weeks.

BOLD = Formulary

State of California — Department of Corrections and Rehabilitation

Mental Health AIMS Examination for Tardive Dyskinesia

CDCR MH-7390 (Rev. 06/12)

Antipsychotic Medication History
Current:
Past:
Tardive Dyskinesia History:

Abnormal Involuntary Movement Scale Examination

Code: 0 = None; 1 = Minimal, Extreme Normal; 2 = Mild; 3 = Moderate; 4 = Severe, Incapacitating

		Examination Date:					
Facial and Oral Movements	Muscles of facial expression: e.g., forehead eyebrow area, cheeks, frowning, blinking, smiling, grimacing.						
	Lips and peri-oral area: e.g., puckering, pouting, smacking.						
	Jaw: e.g. biting, clenching, chewing, mouth opening, lateral movement.						
	Tongue: Rate movement increases in and out of mouth, NOT inability to sustain movement, or vermicular.						
Extremity Movements	Arm: Choreiic, rapid, purposeless, irregular, spontaneous, athetoid, repetitive, serpentine, NOT tremor.						
	Leg: Lateral knee movement, foot tapping, heel dropping, foot squirming, inversion and eversion foot.						
Trunk Movement	Neck, shoulders, hips: Rocking, twisting, squirming, pelvic gyrations.						
	Total Score (Scores of five or above need validation by a second opinion and assessment by the IDTT.)						

Staff Name and Title:	Signature:	Date:
Institution:	**Inmate Bed Number:**	**Level of Care:**

1. Disability Code:
☐ TABE score ≤ 4.0
☐ DPH ☐ DPV ☐ LD
☐ DPS ☐ DNH
☐ DNS ☐ DDP
☐ NOT APPLICABLE

2. Accommodation:
☐ Additional time
☐ Equipment ☐ SLI
☐ Louder ☐ Slower
☐ Basic ☐ Transcribe
☐ Other*

3. Effective Communication:
☐ P/I asked questions
☐ P/I summed information
Please check one:
☐ Not reached* ☐ Reached
*See chrono/notes

4. Comments:

Inmate's Name (Last, First, MI), CDCR Number, DOB

Mental Health AIMS Examination for Tardive Dyskinesia, CDCR 7390-MH (Rev. 06/12) Page 1 of 1

STATE OF CALIFORNIA
Statewide Clozapine Medication Consent Form
CDCR 7455 (06/09)

DEPARTMENT OF CORRECTIONS AND REHABILITATION
DIVISION OF CORRECTIONAL HEALTH CARE SERVICES

STATEWIDE CLOZAPINE MEDICATION CONSENT FORM

My physician, _____MD, has met with me and discussed my mental problems. The physician has recommended that I take the following medications(s) and has discussed the reasons why the medication(s) may be helpful, including the likelihood of my improving or not improving with the medication(s) or without. I understand that the medication(s) is usually given by mouth dependent on the staff's assessment of my behavioral problems and my reported response to the medication(s). The physician has provided me a "best estimate" of this treatment time. As with any medication, there may be side effects. I understand that I am to inform the staff if I have side effects. Some side effects can be reduced by lowering the dose of medication, using another medication, or adding another medication. I understand that ALL possible side effects can neither be predicted nor are listed below. I acknowledge that the side effects of Clozapine was discussed with me.

INDICATION:
Clozapine is an atypical antipsychotic medication that is used for the treatment of treatment resistant schizophrenia with symptoms of psychosis that may include hearing voices, seeing things, or sensing things that are not there, mistaken beliefs, unusual suspiciousness or in individuals who have not responded to traditional antipsychotics or have had intolerable side effects to these medications. It has also been used to help with disorganized or confused thinking, anxiety, agitation or feelings of violence or losing control. In addition it has also be used to reduce the risk of recurrent suicidal behavior in schizophrenic or schizoaffective disorder.

SIDE EFFECTS OF CLOZAPINE INCLUDE:

Blurred vision
Increased heart rate
Night sweats
Heavy salivation (drooling especially at night)
Dry mouth
Difficulty urinating
Dizziness
Lightheadedness
Low blood pressure
Tendency towards diabetes
Drowsiness/sedation
Nausea/vomiting
Headache
Visual disturbance
Weight gain
Sleep disturbance

RARE
Seizure
Agranulocytosis (drop in white blood cells)
Myocarditis (inflammation of the heart muscle)
Constipation
Neuroleptic Malignant Syndrome:
-High fever, muscle breakdown, kidney damage, confusion.
Sexual dysfunction
Tremors
Sun sensitivity
Increase death in elderly persons with dementia related psychosis
Fever

REPORT ALL SIDE EFFECTS TO ANY MEDIAL OR SAFETY STAFF

Medication:
Maximum Daily Dose:
Mg per day:

CAUTION: Avoid the use of alcoholic beverages while taking this medication. Weekly blood tests will be required to monitor for complications. Notify medical or safety staff of fevers, sore throat, easy bruising, or if ulcers of the mouth should appear. If female notify prescriber if you are or become pregnant.

☐ Not taking the medication as prescribed by the physician's instruction may lead to a worsening of the symptoms of your mental illness. However, some symptoms and related disorders may get better or even go away without taking medication. Also, the risk of suicide may be increased by not taking this medication.

☐ Other risk of not taking your medication may include:_____

☐ Other treatment options **MAY** include other medication with similar benefits. Other drugs may cause some of the same side effects you might experience with this medication. Other treatments may not include any medication, but may involve counseling by a psychologist or other medical professional.

☐ I have been mad aware that I am on a heat risk medication. I agree to comply with the heat management program.

☐ I have been told that this medication may produce persistent involuntary movement of the face or mouth and at times similar movements of other parts of the body. This condition is called tardive dyskinesia (TD) and in certain cases these symptoms appear to be irreversible and may even appear after the medication had been stopped. I understand that I may change my decision to accept medication at any time by telling any member of the treatment team. Should I decide to stop or decrease my psychiatric medication(s), I have been informed to do this under the guidance of staff and not to stop medication(s) suddenly. I am aware that this CONSENT original will be in my Unit Health Record. I will be given a copy of this CONSENT for my own records.

☐ **I have received a copy of the patient information sheet. I have discussed any questions I may have with my health care provider, and understand the risks and benefits of taking Clozaril.**

I AGREE TO TAKE THE ABOVE MEDICATION(S) (Inmate/Patient Signature):_____CDC #:_____DATE:_____

PHYSICIAN SIGNATURE: _____ CONSENT DATE:_____

Distribution: Original - Unit Health Record; Canary – Inmate/Patient

CLOZAPINE: WHAT YOU SHOULD KNOW

WHAT IS CLOZAPINE?

Clozapine is a highly effective medicine used to treat people with some types of mental illness who have not responded to other treatments or cannot take other treatments.

REQUIREMENTS FOR CLOZAPINE THERAPY

- ✓ Clozapine is provided through a special program in CCHCS/DCHS to ensure patient safety because of the potential risks of this therapy.
- ✓ You must agree to have all blood tests required during clozapine therapy. These include:
  - weekly blood tests for the first six months of treatment,
  - blood tests every two weeks for the second 6 months, and
  - at least monthly blood tests after one year of therapy.

WHAT ARE THE POSSIBLE RISKS AND SIDE EFFECTS OF CLOZAPINE?

- Constipation, which may be severe
- Weight gain
- Drowsiness
- Dizziness or fainting
- Heavy salivation
- Fever
- Seizures
- Rapid heart rate
- Potentially serious or life-threatening infections
- Myocarditis (inflammation of the heart
- Pulmonary Embolism (blood clot in the lungs)

CLOZAPINE: WHAT YOU SHOULD DO

Take your medications as prescribed, do not miss doses.

Tell your healthcare professional about all medications that you are taking, including anything that you take without a prescription.

Report any of the following symptoms to your treatment team right away:

- Fever
- Change in bowel pattern
- Abdominal pain
- Fatigue
- Change in heartbeat
- Shortness of breath
- Dizziness or fainting, especially when you stand
- Seizures

Be sure you also report any other new symptom that you have while you are taking clozapine to your treatment team right away.

CLOZAPINA: LO QUE DEBE SABER

¿Qué es la clozapina?

La clozapina es un medicamento muy eficaz utilizado para tratar a personas con ciertas enfermedades mentales cuando el individuo no ha respondido a otros tratamientos o no puede tomar otros tratamientos.

Los requisitos para la terapia con clozapina

- ✓ La clozapina se proporciona a través de un programa especial en la CCHCS / DCHS para garantizar la seguridad del paciente debido a los riesgos potenciales de esta terapia.
- ✓ Usted debe aceptar que se hagan todos los análisis de sangre necesarios mientras esté tomando la clozapina. Estos incluyen:
  - Un análisis de sangre cada semana durante los primeros seis meses de la terapia,
  - Un análisis de sangre cada dos semanas durante el segundo periodo de seis meses, y
  - Por lo menos un análisis de sangre cada mes después de un año de terapia con clozapina.

¿Cuáles son los riesgos y efectos secundarios posibles cuando se toma la clozapina?

- Estreñimiento (que podría ser grave)
- Aumento de peso
- Somnolencia
- Mareos o desmayos
- Aumento en la producción de saliva
- Fiebre
- Convulsiones
- Pulso rápido
- Infecciones que podrían poner en riesgo su vida
- Miocarditis (inflamación del músculo del corazón)
- Embolia pulmonar (coágulo sanguíneo en los pulmones)

CLOZAPINA: LO QUE DEBE HACER

Tome sus medicamentos según las indicaciones, no deje pasar ninguna dosis.

Informe a su médico o enfermera si Ud. está tomando otros medicamentos, incluyendo aquellos que no son recetados.

Si tiene alguno de los siguientes síntomas dígaselo inmediatamente a un miembro de su elenco tratante:

- Fiebre
- Cambio en las deposiciones
- Dolor de estomago
- Cansancio
- Cambio en el ritmo cardíaco
- Falta de aliento
- Mareos o desmayos (especialmente cuando se pone de pie)
- Convulsiones

Informe inmediatamente a un miembro de su elenco tratante si Ud. empieza a sentir cualquier otro síntoma nuevo mientras esté tomando la clozapina.