



Clozapine Management Program Description Magellan of Arizona Pharmacy Program

Background:

Magellan Health Services of Arizona recognizes the importance of a clozapine program. Clozapine received increased attention in the NIMH studies endorsing clozapine.¹ The NIMH sponsored CATIE trial's results showed when the study's participants had discontinued their atypical antipsychotic medication and switched to clozapine, that clozapine was significantly more effective than the other atypical antipsychotics used in the study. Additionally, participants on clozapine were less likely to discontinue treatment for any reason, including inadequate response. These results suggest clozapine is a vital part of the pharmacy program.

Clozapine also has a serious side effect profile, including agranulocytosis, that warrants safety monitoring and protocols addressing these monitoring issues. Recipient safety is fundamental and the clozapine program is designed to promote safety. Due to the adverse effect profile of clozapine, the administration of this medication must be closely monitored and managed.

Magellan Health Services of Arizona delivers a clozapine management program that is designed to provide this medication to appropriate individuals in a safe and effective manner that reduces the possibility of side effects and monitors the well-being of the recipient.

Program Description:

The clozapine management program is consistent with ADHS Covered Services, II.C.1 Medication Services and includes the following components:

1. Clozapine must be prescribed by a licensed physician, nurse practitioner or physician assistant to prevent, stabilize or ameliorate symptoms arising from a psychotic disorder.
2. The prescribing clinician will register with the clozapine registry.
3. The prescribing clinician will conduct an evaluation of the recipient prior to prescribing any medication and will re-evaluate the recipient on a regular basis (e.g. monthly or every 3 months).
4. Prescriptions for clozapine will be filled by an authorized, licensed network pharmacy that has been identified and agrees to follow program description. This may include network pharmacies that may be more convenient or preferential to the recipient. Network pharmacies that are authorized to fill clozapine prescriptions agree to update the clozapine registry or work with the Magellan clozapine team to keep the registry up-to-date. If the pharmacy is unwilling to participate in the Clozapine Management Program, Magellan will recommend a coordinating pharmacy that has agreed to administer and coordinate clozapine services. The Magellan Clozapine Coordinator can assist in coordination with the coordinating pharmacy.
5. Clozapine may only be administered to recipients whose white blood count is within current normal limits. This lab count is defined as WBC greater than or equal to $3,500/\text{mm}^3$ and ANC greater than or equal to $2,000/\text{mm}^3$ and no older than the manufacturer and FDA's latest recommended dispense date. Labs are drawn on a regular basis and are analyzed by Magellan's contracted lab vendor, or another

laboratory provider if the recipient's primary payor is exclusive with another vendor. Lab draws usually occur consistent with recommended guidelines in Table 1.

6. Clozapine will not be administered when a lab is considered abnormal by FDA clozapine parameters as described below in Table 1. In this situation, the physician will prescribe appropriate follow-up care to ensure that the recipient's physical and mental well-being will be maintained.
7. The prescribing clinician, clinic staff, and others involved with the individual's care will monitor the recipient's mental status according to the treatment plan. Staff members must have sufficient training to be able to recognize the symptoms of the psychotic disorder, side effects from medications used to treat the disorder and changes in the recipients functioning.
8. The prescribing clinician will monitor body mass index (BMI), waste circumference, heart rate, blood pressure, EPS including akathisia and abnormal involuntary movements (AIMS) upon initiation of therapy and every six months thereafter or more frequently as clinically indicated. Additionally, lipid levels and fasting blood glucose levels will be monitored upon initiation of therapy and every year thereafter or more frequently as clinically indicated (See Provider Manual Section [3.15 Psychotropic Medication: Prescribing and Monitoring](#) for more information).
9. Written documentation is maintained for all aspects of the clozapine management program. Documentation must include, but is not limited to, patient demographic information, treatment/care plan, copies of the prescriptions, copies of laboratory results of white blood cell counts (including date of blood draws and who performed the blood draws) and signed and dated notes related to the management of clozapine services.
10. New prescriptions and all necessary information must be faxed to the authorized, licensed network pharmacy that is most convenient for clinic and/or recipient. Refills can be requested and must include the most recent blood results. **All orders MUST have a copy of the most recent lab work within the period required by the manufacturer and FDA.**

The pharmacy, Magellan pharmacy department and/or the manufacturer's registry will alert the prescriber when abnormal lab values are entered into the registry (abnormal lab values are: Single drop of WBC $\geq 3000/\text{mm}^3$ or ANC $\geq 1500/\text{mm}^3$).

Table 1: Frequency of Monitoring based on Stage of Therapy or Monitoring Results

Duration on Clozapine	Frequency of monitoring
<p>Initiation of therapy</p> <p>(Note: Do not initiate in patients with history of myeloproliferative disorder or clozapine induced agranulocytosis or granulocytopenia)</p>	Labs must be obtained every week for 6 months, provided labs are within normal limits (all WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³)
6 to 12 months	Labs must be obtained every 2 weeks for 6 months, provided labs are within normal limits (all WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³)
After 1 year	Labs must be obtained every 4 weeks thereafter provided labs are within normal limits (all WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³)
Discontinuation of Therapy	Monitor weekly for at least 4 weeks from day of discontinuation or until WBC \geq 3500/mm ³ and ANC \geq 2000/mm ³
<p>Substantial Drop in WBC or ANC</p> <p>Single or cumulative drop within 3 weeks of WBC \geq 3000/mm³ and ANC \geq 1500/mm³</p>	<ol style="list-style-type: none"> 1. Repeat WBC and ANC. 2. If repeat values are 3000/mm³ \leq WBC \leq 3500/mm³ and ANC $>$ 2000/mm³, then monitor twice weekly
<p>Mild Leukopenia or Granulocytopenia</p> <p>3500/mm³ $>$ WBC \geq 3000/mm³ and/or 2000/mm³ $>$ ANC $>$ 1500/mm³</p>	Twice-weekly until WBC $>$ 3500/mm ³ and ANC $>$ 2000/mm ³ then return to previous monitoring frequency
<p>Moderate Leukopenia or Granulocytopenia</p> <p>3000/mm³ $>$ WBC \geq 2000/mm³ and/or 1500/mm³ $>$ ANC $>$ 1000/mm³</p>	<ol style="list-style-type: none"> 1. Interrupt therapy 2. Daily until WBC $>$ 3000/mm³ and ANC $>$ 1500/mm³ 3. Twice-weekly until WBC $>$ 3500/mm³ and ANC $>$ 2000/mm³ 4. May rechallenge when WBC $>$ 3500/mm³ and ANC $>$ 2000/mm³ 5. If rechallenged, monitor weekly for 1 year before returning to the usual monitoring schedule of every 2 weeks for 6 months and then every 4 weeks
<p>Severe Leukopenia or Granulocytopenia</p> <p>WBC $<$ 2000/mm³ and/or ANC $<$ 1000/mm³</p>	<ol style="list-style-type: none"> 1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: <ul style="list-style-type: none"> • Daily until WBC $>$ 3000/mm³ and ANC $>$ 1500/mm³ • Twice weekly until WBC $>$ 3500/mm³ and ANC $>$ 2000/mm³ • Weekly after WBC $>$ 3500/mm³
<p>Agranulocytosis</p> <p>ANC \leq 500/mm³</p>	<ol style="list-style-type: none"> 1. Discontinue treatment and do not rechallenge patient 2. Monitor until normal and for at least 4 weeks from day of discontinuation as follows: <ul style="list-style-type: none"> • Daily until WBC $>$ 3000/mm³ and ANC $>$ 1500/mm³ • Twice weekly until WBC $>$ 3500/mm³ and ANC $>$ 2000/mm³ • Weekly after WBC $>$ 3500/mm³

Administration and Dosage

Initially, dosing should be started at 12.5mg once or twice daily with daily dose increases of 25 to 50 mg/day, if well tolerated, to achieve a target dose of 300 to 450 mg/day. Subsequent dosage increases should be made no more than once to twice weekly, in an amount not to exceed 100mg. Cautious titration should occur to minimize the risk of hypotension, sedation and seizure. Examples of Clozapine Titration schedules including a 14 day, 16 day, 3 week, 4 week, 5 week and 6 week schedules are included in Attachment D.

Upon discontinuation of therapy, a gradual reduction in dose is recommended over a 1 to 2 week period. If abrupt discontinuation is required (e.g. leukopenia), monitoring for the recurrence of psychosis or cholinergic rebound (headache, nausea, vomiting, diarrhea) should occur.

If the behavioral health recipient misses clozapine for up to 24 hours, dosing may be resumed at the current dosage level. If doses are missed for 24-48 hours, the previous dosing may be continued unless the BHR previously experienced respiratory or cardiac arrest during titration. In those cases, dosage titration should occur with low doses (12.5 mg once or twice daily) with close observation for adverse events. For missed doses beyond 48 hours, the medication should be titrated as with initial therapy, restarting with a dose of 12.5 mg once or twice a day. If the initial dose is well tolerated, titration may occur more quickly than is recommended with initial treatment.

BHRs discontinued for WBC counts below 2000/mm³ or an ANC below 1000/mm³ must not be restarted on clozapine.

Treatment of Children:

The treatment of children in the clozapine management program is consistent with the Arizona DHS practice protocol, "Psychotropic Medication Use in Children, Adolescents, and Young Adults".

Behavioral Health clinicians must promote effective care that is individualized and comprehensive -- medication management is just one component of the overall treatment. Psychiatric evaluations should be conducted prior to prescribing any psychiatric medication and at regular intervals thereafter. Children/youth and their families and care givers must be provided with complete and accurate information about this medication and the management program so that informed consent for treatment can be given.

Non-Clinic Processes:

Contracted providers who prescribe clozapine and clozapine management must provide all components of the program as described above in the "Program Description". Providers will have assistance with coordinating these services, consistent with clinic processes.

The provider may draw the labs or ensure the labs are drawn by a contracted laboratory or a Magellan phlebotomist. Results must be obtained in a timely fashion. The provider will ensure that the recipient receives the medications as scheduled and that clozapine will not be administered when a lab result is abnormal.

Clinic Processes:

All recipients on clozapine will be monitored and assessed by nursing staff. The frequency of this monitoring will correlate with how long the recipient has been on clozapine and how often lab draws are required. The nursing assessment will include monitoring adherence, monitoring the effectiveness of the medication, assessing for side effects and providing education to the recipient as needed.

Each clinic will have a system in place to ensure that there is a current list of all recipients on clozapine. This list will be an ongoing list and will be updated daily as needed.

The nursing staff/phlebotomists will draw the CBC levels in the clinic or at the recipient's residential program and ensure that the appropriate lab vendor picks up and processes the labs for testing. The nursing staff will track the receipt of the CBC results and route to the ordering BHMP for review and reorder of the clozapine. Records of lab work will be maintained at the clinic.

Clozapine should be ordered so that delivery will be the day prior to the recipient coming in. Changes in doses, new starts, and hospital discharge patients will follow the standard delivery schedule.

Lab Processes:

Lab draws: Specific days are designated clozapine clinic days at clinics with high volume of clozapine recipients. During the Clozapine Clinic Days the Magellan phlebotomists or clinic nurses will draw labs. The designated laboratory vendor will pick up lab specimens from the clinics. Recipients unable to attend a clozapine clinic day may either (a) have their labs drawn by a nurse at the clinic or (b) visit one of the designated laboratory draw stations. Recipients do not need an appointment to visit a draw station.

Lab specimen pickups: The designated laboratory vendor will have scheduled specimen pickups at least once a day. The clinic can request additional pickups by calling the lab vendor. The appropriate clinic staff will complete the lab requisition form to order lab draw. When results are received the Clozapine Coordinator will enter the results into the clozapine registry or audit the pharmacy registry and the clinic will ensure the results are in the recipient's medical record. If the recipient's primary third party payor has an exclusive contract with another laboratory vendor, the clinic will request a special pickup by calling that vendor.

No-Shows for Regularly Scheduled lab Draws: If a recipient is a no-show for a scheduled clozapine clinic appointment, Nursing will work collaboratively with the case management staff to locate the recipient and have their CBC drawn and medication delivered. If the recipient is not able to obtain their CBC and medication within 48 hours, the ordering BHMP will be notified for future orders.

Hospital Discharges:

Hospital staff will collaborate with the Clozapine Coordinator prior to discharge to arrange services with the nursing and case management staff. The Clozapine Coordinator will ensure that any recipients started on clozapine in the hospital will maintain their scheduled clozapine dosages and CBC lab draws in the outpatient clinics. The Clozapine Coordinator will supply the hospital discharge staff with a Clozapine Discharge packet (attachment D). Hospital staff will provide a prescription for clozapine and a copy of the last CBC to both the Clozapine Coordinator, the outpatient clinical team and the pharmacy. Clinical staff should contact the recipient with information on "Clozapine Clinic Days" and set up appointments for them to pick up the medication. In urgent cases the clinical staff should contact the Clozapine Coordinator to locate the most convenient clozapine registered pharmacy.

Clozapine Coordination

Magellan Health Services employees a Clozapine Coordinator who is responsible for the following:

- Monitors the clozapine recipient list for recipients in the Magellan Provider Network Clinics and other Magellan facilities.

- Coordinates with the clinics by requesting and receiving information to monitor or “track” clozapine recipient status.
- Is the “contact person” for clozapine issues, this includes but is not limited to lab draw schedules, courier service organization and medication questions of all types, i.e. billing, early fills, overrides and prior authorizations.
- Monitors and updates the designated manufacturer’s Clozapine National Registry and audits the dispensing pharmacies’ registry to ensure it is current for all Magellan clozapine recipients.
- Ensure the Magellan phlebotomists follow the schedule created for CBC lab draws on “Clozapine Clinic Days.” Non Magellan direct care clinics recipients on clozapine will go directly to the designated laboratory vendor for routine CBC draws.

The clozapine program includes access to a Clozapine Coordinator (602) 572-5957 who will assist trouble-shooting clozapine-related issues. Some examples of issues may include those related to obtaining medications, reporting lab results to the National Registry. The Clozapine Coordinator is available 8:00 am to 5:00 pm, Monday through Friday by calling the number listed above.

Federal Reporting:

The pharmacy preferred by the clinic and/or recipient that dispenses clozapine ensures that all members are registered in the National Clozapine Registry and will report laboratory results in accordance with federal monitoring guidelines.

References:

1. McEvoy JP, Lieberman JA, Stroup JS et al. Effectiveness of clozapine versus olanzapine, quetiapine, and risperidone in patients with chronic schizophrenia who did not respond to prior atypical antipsychotic treatment. *Am J Psychiatry* 2006; 163:600–610.
2. <http://www.clozaril.com/pdfs/ConversionFormTable.pdf> accessed 10/14/13
3. <https://www.clozapineregistry.com/AboutClozapine/Bioequiv.aspx> accessed
4. <http://www.clozapineregistry.com/Table1.pdf.ashx> accessed 10/14/13

Substantial Drop in CBC Labs Alert

Attention: NURSING/Medical STAFF _____ Fax # _____

Prescriber: _____ Clinic: _____

A drop in WBC or ANC received lab report met the criteria for a substantial drop as defined in the Clozapine package insert; you are being notified for the following recipient:

Consumer Name: _____
Last First

Date of CBC: _____ WBC: _____ ANC: _____

Situation	Criteria
Substantial drop in WBC or ANC	Single drop of WBC $\geq 3000/\text{mm}^3$ or ANC $\geq 1500/\text{mm}^3$

**** PLEASE REVIEW LAST CBC RESULTS AS SOON AS POSSIBLE ****

Magellan Health Services Pharmacy Department
Phone # 602-572-5957 Fax # 800-424-4278



Clozapine Flow sheet

DATE	DOSE	WBC	ANC	PROVIDER

Recipient Name: _____

Recipient ID# _____

**Magellan Health Services
Clozapine Recipient Discharge Form
Fax complete form to 1-800-424-4278**

Discharge Information

_____	_____ am/pm	
Discharge Facility	Date/Time	
_____	_____	_____
Discharge Physician	DEA#	Contact phone #
_____	_____	
Discharge Nurse	Contact phone #	

Recipient Information

_____	_____	_____
Recipient Last Name	Recipient First Name	MI
_____	_____	_____
CIS #	Social Security # (required)	Date of Birth
Gender: Female Male (circle one)		
Discharge Information:		

Medication Information

Discharge Clozapine Daily Dose: _____mg			
Clozapine Dose Frequency: weekly	bi-weekly	monthly	(circle one)

Out-Patient Services

Out-patient clinic: _____

Out-patient BHMP: _____ Phone # _____

Case Manager: _____ Phone # _____
(if applicable)

Have arrangements been made w/ out-patient clinic for discharge? Yes No (circle one)

If so who is the contact? _____ Phone # _____

(if other than case mgr above)

Living arrangements: BHR home grp home assisted living shelter
other: _____ (circle only one)

14 Day Titration Schedule

Example of Clozapine Titration Schedule			
	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
Day 1	12.5	12.5 optional	12.5-25
Day 2	25	None	25
Day 3	25	25	50
Day 4	25	50	75
Day 5	50	50	100
Day 6	50	75	125
Day 7	50	100	150
Day 8	75	100	175
Day 9	100	100	200
Day 10	100	125	225
Day 11	100	150	250
Day 12	125	150	275
Day 13	150	150	300
Day 14	150	150	300

16 Day Titration Schedule

Example of Clozapine Titration Schedule			
	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
Day 1	12.5	12.5	25
Day 2	25	None	25
Day 3	25	25	50
Day 4	25	50	75
Day 5	50	50	100
Day 6	50	75	125
Day 7	50	100	150
Day 8	50	100	150
Day 9	50	100	150
Day 10	50	100	150
Day 11	100	100	200
Day 12	100	100	200
Day 13	50	200	250
Day 14	50	200	250
Day 15	75	200	275
Day 16	100	200	300

3 Week Titration Schedule

Example of Clozapine Titration Schedule			
	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
Day 1	12.5	None	12.5
Day 2	25	None	25
Day 3	25	25	50
Day 4	25	50	75
Day 5	25	50	75
Day 6	50	50	100
Day 7	50	75	125
Day 8	50	75	125
Day 9	50	100	150
Day 10	50	100	150
Day 11	50	100	150
Day 12	50	100	150
Day 13	50	100	150
Day 14	50	100	150
Day 15	100	100	200
Day 16	100	100	200
Day 17	50	200	250
Day 18	50	200	250
Day 19	50	200	250
Day 20	75	200	275
Day 21	100	200	300

4 Week Titration Schedule

Example of Clozapine Titration Schedule			
	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
Day 1	12.5	None	12.5
Day 2	25	None	25
Day 3	25	25	50
Day 4	25	25	50
Day 5	25	50	75
Day 6	25	50	75
Day 7	50	50	100
Day 8	50	50	100
Day 9	50	75	125
Day 10	50	75	125
Day 11	50	100	150
Day 12	50	100	150
Day 13	50	100	150
Day 14	50	100	150
Day 15	50	100	150
Day 16	50	100	150
Day 17	50	100	150
Day 18	50	100	150
Day 19	100	100	200
Day 20	100	100	200
Day 21	100	100	200
Day 22	100	100	200
Day 23	50	200	250
Day 24	50	200	250
Day 25	50	200	250
Day 26	50	200	250
Day 27	75	200	275
Day 28	100	200	300

5 Week Titration Schedule

Example of Clozapine Titration Schedule			
	AM Dose (mg)	PM Dose (mg)	Total Daily Dose (mg)
Day 1	12.5	None	12.5
Day 2	25	None	25
Day 3	25	25	50
Day 4	25	25	50
Day 5	25	50	75
Day 6	25	50	75
Day 7	25	50	75
Day 8	50	50	100
Day 9	50	50	100
Day 10	50	50	100
Day 11	50	75	125
Day 12	50	75	125
Day 13	50	75	125
Day 14	50	75	125
Day 15	50	100	150
Day 16	50	100	150
Day 17	50	100	150
Day 18	50	100	150
Day 19	75	100	175
Day 20	75	100	175
Day 21	75	100	175
Day 22	75	100	175
Day 23	75	100	175
Day 24	100	100	200
Day 25	100	100	200
Day 26	100	100	200
Day 27	50	200	250
Day 28	50	200	250
Day 29	50	200	250
Day 30	50	200	250
Day 31	75	200	275
Day 32	75	200	275
Day 33	75	200	275
Day 34	75	200	275
Day 35	100	200	300