Provincial Clinical Knowledge Topic
Antipsychotics and Metabolic Monitoring
Adult – Inpatient
Version 1.0

Revision History

Version	Date of Revision	Description of Revision	Revised By
1.0		Topic Completed	See Acknowledgements

Important Information Before you Begin

The recommendations contained in this knowledge topic have been provincially adjudicated and are based on best practice and available evidence. Clinicians applying these recommendations should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care. This knowledge topic will be reviewed periodically and updated as best practice evidence and clinical practice change.

The information in this topic strives to adhere to Institute for Safe Medication Practices (ISMP) safety standards and align with Quality and Safety initiatives and accreditation requirements such as the Required Organizational Practices. Some examples of these initiatives or groups include Health Quality Council Alberta (HQCA), Choosing Wisely campaign, Safer Healthcare Now campaign etc.

Guidelines

This topic is based on the following guidelines:

- Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders. Collaborative update of CANMAT guidelines for the management of patients with bipolar disorder. Update 2013
- Canadian Network for Mood & Anxiety Disorders (CANMAT). Clinical Guidelines for the Management of Adults with Major Depressive Disorder. *Can J of Psychiatry*. 2016
- NICE Clinical Guideline No. 185 – Bipolar Disorder – Assessment and Management
- NICE Clinical Guideline No. 178 – Psychosis and Schizophrenia in Adults Prevention and Management
- Canadian Psychiatric Association Clinical Practice Guidelines Treatment of Schizophrenia 2016

Keywords

- Antipsychotics
- Metabolic
- Monitoring
- Clozapine
- Adverse Events
- Second Generation

Rationale

It is important that there is a clinically appropriate indication for the use of antipsychotics when making a decision regarding the prescription of an antipsychotic. In addition to a baseline psychiatric and physical assessment regular monitoring should occur as part of the ongoing medication review process.

Clinical indications for the use of antipsychotics include:

- A confirmed diagnosis of:
  - Schizophrenia spectrum disorders,
  - Bipolar disorder,
  - Major depressive disorder (MDD),
  - Substance Induced Psychosis
- Other conditions such as Tourette's Disorder and irritability associated with Autism Spectrum Disorder
- Severe dementia of the Alzheimer type – symptomatic management of aggression and psychotic symptoms

There has been increasing concern about metabolic side effects of second generation antipsychotics including weight gain and elevation of glucose, cholesterol and triglycerides. Patients with serious mental illness have markedly elevated rates of metabolic disturbance and may have limited access to primary health care. Assessment of risk factors for metabolic disease and cardiovascular disease is vital and should be carried out regularly.[1]
A significant number of patients with psychosis, and bipolar disorder also struggle with substance use which can further contribute to a requirement for regular monitoring.

Evidence from national audit programs in secondary care show that routine monitoring of these risk factors has been inadequate. The UNITE global survey of 1300 patients reported that monitoring of safety parameters does not occur in the majority of patients. Less than 30% underwent weight and blood pressure measurements, and less than 3% received a physical examination or blood tests during interactions with their primary health care provider[2].

Goals of Management

- Appropriate clinical indication, as well as expected benefits and risks for the use of antipsychotics are documented (refer to Rationale section for clinical indications)
- Clinicians and patients should work together to find the most appropriate antipsychotic medication and lowest effective dose
- Patients are informed of different antipsychotics available, potential side effects of antipsychotic medication, management of side effects and the expected time frame for a change in symptoms
- Appropriate monitoring protocols for effectiveness and side effects of antipsychotic medication are carried out
- Monitoring of patients should include screening for:
    - Metabolic side effects including weight gain, endocrine side effects, dyslipidemia, hypertension
    - Increased risk of coronary heart disease particularly for patients diagnosed with schizophrenia
    - Increased susceptibility to metabolic disorder due to genetic and lifestyle factors
    - Identification of individuals at high risk for metabolic disorder (metabolic syndrome, pre-diabetes, severe obesity)
    - Evaluation of the association between prescribed antipsychotic medication and the development of metabolic disorder by systematic collection of data
- A review of antipsychotic treatment should be conducted ideally within the first month following initiation of treatment to assess the antipsychotic treatment for efficacy, side effects, and improved quality of life if the patient potentially has been discharged
- Based on the antipsychotic ordered additional specific monitoring may be required (e.g. regular monitoring of complete blood count (CBC) for patients prescribed clozapine)

References

- From provincial AMH Clozapine Initiation and Maintenance policy currently in development.

Alerts

Trigger: Atypical antipsychotic has been prescribed by the physician

1. **Trigger**: The following laboratory indicators have not been ordered upon initiation of an atypical antipsychotic medication or within the last 28 days
   - Hematology – Complete Blood Count (CBC) with differential
   - Chemistry – Hemoglobin A1C
     – Lipid Profile
     – Glucose Fasting or Glucose Random
2. **Trigger**: The atypical antipsychotic medication clozapine has been prescribed by the physician
   Immediate attention to clinically important data for those initiated on the clozapine protocol:
   - **Trigger**: Hematology – Complete Blood Count (CBC) with differential weekly for 26 weeks must be ordered (if on clozapine for longer than 26 weeks CBC with differential is required every 2 weeks).
   - **Trigger**: WBC results fall within the **yellow** zone – A single fall or sum of falls in WBC greater than or equal to 3.0 X 10^9/L is measured in the last 4 weeks reaching a value of less than 4.0 X 10^9/L **and/or** WBC is between 2.0 X 10^9/L and 3.5 X 10^9/L
   - **Trigger**: ANC results fall within the **yellow** zone – A single fall or sum of falls in ANC of greater than or equal to 1.5 X 10^9/L is measured in the last 4 weeks reaching a value of less than 2.5 X 10^9/L **and/or** ANC between 1.5 X 10^9/L and 2.0 X10^9/L
   - **Trigger**: Physical Symptoms fall within the **yellow** zone – Flu-like complaints, fever or other symptoms which might suggest infection.
   - **Trigger**: Hematology results fall within the **red** zone – WBC less than 2.0 X10^9/L **and/or** WBC less than 1.0 X 10^9/L (protective isolation is recommend)
   - **Trigger**: ANC results fall within the **red** zone – ANC less than 1.5 X10^9/L **and/or** ANC less than 0.5 X 10^9/L (protective isolation is recommend)

Reminders

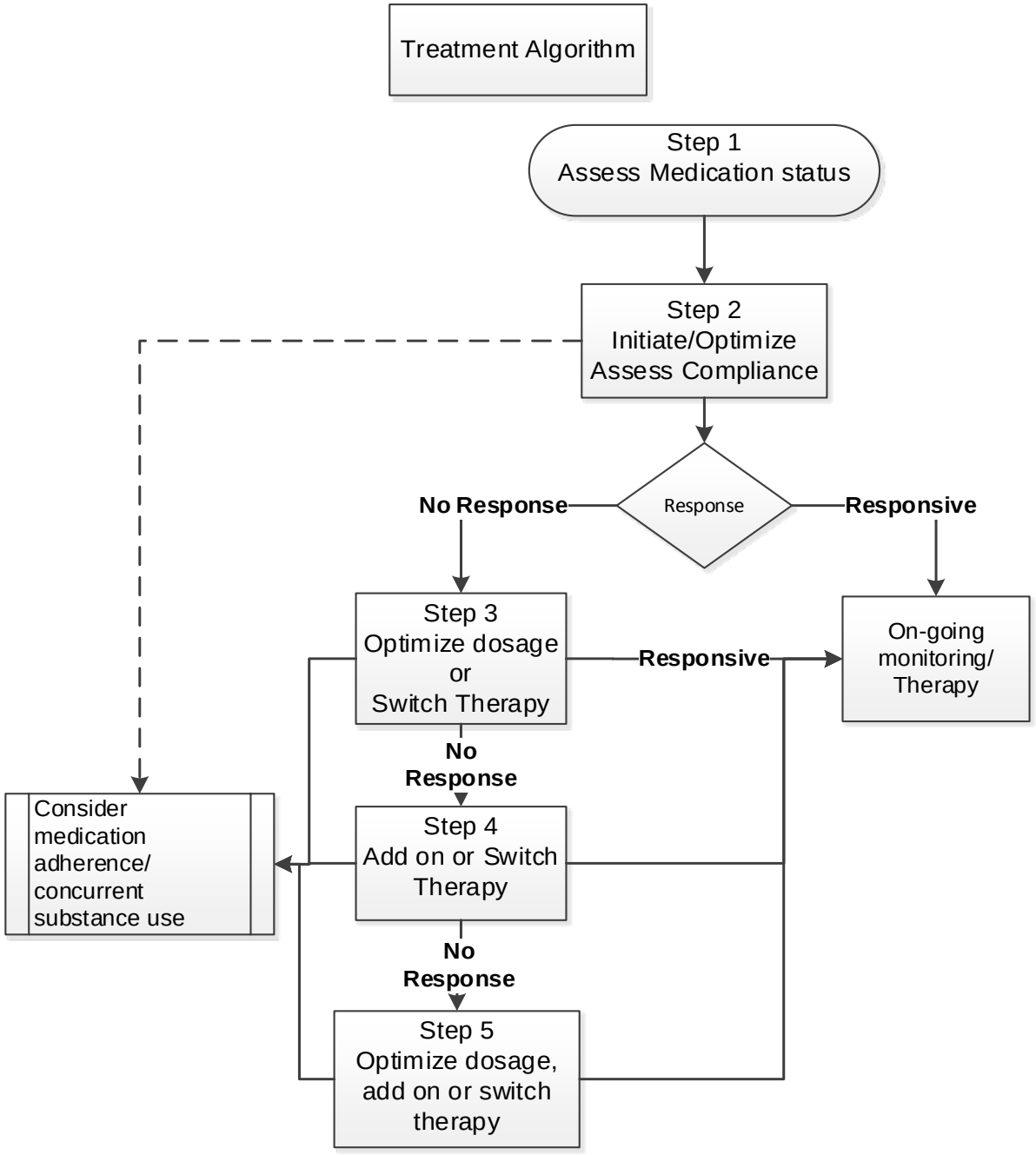
The following physical measurement metrics have not been documented in the last 30 days

- Height (if not documented on the patient record)
- Weight
- Waist circumference
- BMI calculation
- Blood Pressure

Assists

- BMI calculation upon entering of patient height and weight

Figure 1 **Treatment Algorithm**[4]



Recommendations for the appropriate use of Antipsychotics

Health Canada has approved the use of selective antipsychotics for the following conditions:

1. Schizophrenia spectrum disorders
2. Major Depressive Disorder
3. Bipolar Disorders
4. Other conditions including Tourette's disorder, Autism Spectrum disorder, substance use induced psychosis
5. Severe dementia of the Alzheimer type

Use of antipsychotics outside official Health Canada indications requires a detailed discussion with the patient as well as ongoing assessment of risks and benefits. Pharmacotherapy resource is available at: https://www.e-therapeutics.ca/search

1. Schizophrenia Spectrum Disorders

Antipsychotic medications are the first line of treatment for schizophrenia along with non-pharmacological interventions

Choosing Wisely Canada Recommendation[5]

Do not routinely prescribe high-dose or combination antipsychotic treatment strategies in the treatment of schizophrenia.

High-dose and combination strategies involving atypical antipsychotics (AAPs) are used in clinical practice for patients with schizophrenia who are inadequately controlled with one or more AAPs used at standard doses. A recent meta-analysis found no clinically significant improvements in patients with schizophrenia who were inadequately controlled on standard-dose antipsychotics when treated with combination or high-dose AAPs. In terms of safety, no clinically significant differences were evident between combination and high-dose therapy in comparison with standard-dose monotherapy.

2. Major Depressive Disorder

The most consistent evidence supporting the use of antipsychotics for patients with major depressive episodes exists in the treatment of patients with treatment resistant depression and patients with psychotic features. It is recommended to use antipsychotics as adjunctive therapy along with an antidepressant after pharmacotherapy trials with antidepressants alone. Consideration should be given to potential drug interactions when considering adjunctive therapy with antipsychotics.

For recommendations for pharmaceutical treatment for Major Depressive Disorder refer to the Canadian Network for Mood and Anxiety Disorders (CANMAT). 2016 Clinical Guidelines for the Management of Adults with Major Depressive Disorder Section 3. Pharmacological Treatments. http://journals.sagepub.com/doi/full/10.1177/0706743716659061

3. Bipolar Disorder

Antipsychotic medications are now indicated for treatment of acute mania, bipolar depression as well as maintenance treatment of bipolar disorder.

For recommendations for pharmaceutical treatment for Bipolar disorder refer to the Canadian Network for Mood and Anxiety Disorders (CANMAT) and International Society for Bipolar Disorders (ISBD) 2013 Collaborative update of CANMAT guidelines for the management of patients with bipolar disorder
https://www.ncbi.nlm.nih.gov/pubmed/29536616

4. Other Approved Uses for Antipsychotics

Some antipsychotics are also approved for select conditions including Tourette's disorder, Autism Spectrum disorder and symptomatic management of aggression and psychotic symptoms in severe dementia of the Alzheimer type, and substance use – induced psychosis. Pharmacotherapy resource is available at: https://www.e-therapeutics.ca/search

Use of Antipsychotics in the Senior Population

Clinical indications for the use of antipsychotics in the senior population should include:

- A confirmed diagnosis (as above):
  - Schizophrenia spectrum disorders
  - Bipolar disorder
  - Major depressive episode as adjunctive therapy for patients with an inadequate response to prior antidepressant medication
- Symptomatic management of aggression and psychotic symptoms in severe dementia of the Alzheimer type

Health Canada Warning re Use of Antipsychotics for Seniors with Dementia[6]

Increased Mortality in Elderly Patients with Dementia:

Elderly patients with dementia treated with atypical antipsychotic drugs are at an increased risk of death compared to placebo. Analyses of thirteen placebo controlled trials with various atypical antipsychotics (modal duration of 10 weeks) in these patients showed a mean 1.6 fold increase in the death rate in the drug treated patients. Although the causes of death were varied, most of the deaths appeared to be either cardiovascular (e.g., heart failure, sudden death) or infectious (e.g., pneumonia) in nature

Choosing Wisely Canada Recommendation[5]

Don't routinely use antipsychotics to treat **primary insomnia** in any age group.

Second-generation antipsychotics (SGAPs), such as OLANZapine and QUEtiapine, have sedative properties, and are often prescribed off-label for complaints of insomnia. These drugs carry significant risk of potential side-effects including weight gain and metabolic complications, even at low doses used to treat insomnia. In patients with dementia, they can also potentially cause serious side-effects of increased risk of a cerebrovascular event and increased risk of death

A complete tool kit for the Appropriate Use of Antipsychotics for Seniors is available on the AHS external web site: http://www.albertahealthservices.ca/scns/auatoolkit.aspx

Adverse Events of Antipsychotics

The side effect profile of antipsychotics differs between different antipsychotics. Major adverse events of antipsychotics may include:

- Sedation
- Weight gain
- Movement disorders
- Hyperlipidemia
- Hyperprolactinemia
- Metabolic disorders
- Prolonged QTc

People with severe mental illness (SMI) exhibit a 2-3 fold increase in mortality[30] and could lose an average of more than 25 years of potential life, relative to the general population[31]. Cardiovascular Disease (CVD) is the leading cause of death among Canadians[32] and CVD is clearly responsible for the greatest number of deaths in the SMI population as well.[33]

Diabetes, hypercholesterolemia, and a metabolic syndrome characterized by obesity, hypertension, dysglycemia, and dyslipidemia have all been implicated in risk of CVD in the general population, and all are also more prevalent in SMI samples. [34,35,36,37]

Recently, a more comprehensive evaluation of biological markers relevant to cardiovascular disease was undertaken within a multi-center investigation of patients enrolled to community health clinics in the USA. The results were consistent with the view that cardiometabolic burden is partly due to psychiatric or psychotic illness and unhealthy lifestyle prior to the onset of treatment that is accelerated over time following the initiation of antipsychotic medication.[38]

Baseline Assessment

Prior to commencing antipsychotic treatment, the authorized prescriber should ensure a baseline assessment is completed:

- Physical Assessment (if clinically indicated)
- Mental status examination
- Height, Weight (BMI calculation)
- Waist measurement (at the umbilicus)
- Baseline Vitals: to include temperature (T) , pulse (P) , respiratory rate (RR) ,and blood pressure (BP)

For patients diagnosed with a major depressive episode, treatment resistant depression, bipolar disorder, and schizophrenia the clinician should consider using evidence informed clinical scales at the baseline assessment and also periodically throughout the treatment regimen. Examples of evidence informed clinical scales include:

1. Major Depressive Disorder
   - Clinician Rated:
     - Hamilton Depression Rating Scale (Ham-D)[10]
     - Montgomery Asberg Depression Rating Scale (MADRS)[11]
     - Columbia Suicide Severity Rating Scale (CSSR)[12]
   - Patient Rated:
     - Beck Depression Inventory (BDI-II)[13]
     - Patient Health Questionnaire (PHQ – 9)[14]
2. Bipolar Disorder
   - Clinician Rated:
     - Young Mania Rating Scale (YMRS)[15]
   - Patient Rated
     - Mood Disorder Questionnaire (MDQ9)[16]
3. Schizophrenia
   - Clinician Rated:
     - Positive and Negative Syndrome Scale (PANSS)[17]
     - Brief Psychiatric Rating Scale (BPRS)[18]
4. The Glasgow Antipsychotic Side Effect Scale (GASS) [19] is a patient-rated scale to assess antipsychotic induced side-effects.
5. Cognitive Assessment
   - Folstein Mini-Mental Status Examination[20] (MMSE)
   - Screen for Cognitive Impairment in Psychiatry[21] (SCIP)

Laboratory Work Up

The following initial laboratory work up is recommended to provide a baseline assessment prior to initiating treatment with antipsychotics:

- Hematology
  - Complete Blood Count (CBC) with differential – within the last 90 days or within the last 28 days for clozapine initiation
- Chemistry
  - Hemoglobin A1C
  - Glucose (Fasting or Random)
  - Lipid Profile (HDL, LDL, Triglycerides, Cholesterol)
- Based on a physical assessment any additional lab tests should be ordered as clinically indicated such as:
  - Liver Enzymes: Alanine Aminotransferase (ALT), Alkaline Phosphatase (ALP), Aspartate Transaminase (ASP), Gamma-Glutamyl Transferase (GGT)
  - C-Reactive Protein
  - Thyroid Stimulating Hormone (TSH)
  - Prolactin

Other Investigations:

- Electrocardiogram (ECG), if clinically indicated, or family history of cardiac disease
- Electroencephalogram (EEG) within the last 12 months, if clinically indicated (such as a history of seizures)

After the initial baseline workup the following schedule is a recommendation for physical and metabolic monitoring while the patient is on antipsychotic medication. Additional monitoring may be required depending on the prescribed antipsychotic.

Table 1 **Physical Parameter**[39]

	Baseline	1 Month	3 Month	Annually
Medical History	X			
BMI Calculation				
• *Height*	X			
• *Weight*	X	X	X	X
Waist Circumference (umbilicus)	X	X	X	X
Extrapyramidal Symptoms (EPS)	X	X	X	X
Other Sexual function, menstrual changes	X			X

***Inpatient vital signs including (T, P, BP and RR) as per local protocols and clinical assessment**

Table 2 **Laboratory Parameters**[39]

	Baseline	3 Months	Annually
Lipid Profile (Total Cholesterol HDL, LDL Triglycerides)	X	X	X
Hemoglobin A1C	X	X	X
Glucose, Fasting ***or*** *Glucose, Random*	X	X	X

Additional Monitoring

Response to treatment, including changes in symptoms and behaviour, adverse events, and their impact on physical health and quality of life should be monitored. In addition, adherence to medication and treatment should also be monitored. Additional monitoring may be required for women who are pregnant.
It is also recommended to monitor patients on antipsychotics for movement disorders. In particular patients should be examined for rigidity, tremor and akathisia after initiating antipsychotic medication, after a dose change, and until the dose has been stabilized. There are several clinical scales that can be used to assist with assessing movement disorders such as the Simpson Angus EPS Scale, Abnormal Involuntary Movement Scale (AIMS) or the Barnes Akathisia Rating Scale. Ethnicity, diet, activity and substance use, including tobacco/tobacco-like product, alcohol use, also affect how patients will respond to antipsychotic medication and should be included in the monitoring of efficacy of the patient's treatment.

Antipsychotic Therapy Interruption/Switching

If a patient has been non-responsive to the initial antipsychotic medication, some adjustment to the monitoring schedule may be necessary. Any adjustment will require consideration of the duration of treatment, the patient response to the treatment, observed side effects, and any anticipated side effects associated with the revised prescription. This will assist in determination of whether the monitoring schedule should be continued at the current level, or reinstated as a new initiation. Clinical judgement will need to be utilized, patient response to therapy, laboratory results, and physical parameters will all guide whether monitoring should be increased. The antipsychotic prescribed may also have specific monitoring requirements such as clozapine.

Some suggested considerations for interruption/switching of antipsychotics include:

1. Identify target symptoms and side effects
2. Determine if the target symptoms are amenable to a pharmacologic intervention
3. Optimize current treatment regimen if possible
4. Evaluate appropriateness of adjunctive interventions
5. Conduct risk/benefit assessment with the patient

Refer to the Antipsychotic Safety Monitoring Recommendation Record (#18658 rev 2015-12) for documentation of all prescribed antipsychotics

Clozapine

Clozapine is indicated in the management of symptoms of treatment resistant psychiatric disorders such as treatment resistant depression. Along with the recommended monitoring above, due to the significant risk of agranulocytosis and seizure associated with the use of clozapine additional recommendations requirements for monitoring are established. (Referenced from provincial AMH Clozapine Initiation and Maintenance policy currently in development)

For patients initiated on clozapine a complete blood count and differential within the last 28 days prior to the first dose should be available and then drawn following initiation:

- Weekly for 26 weeks
- **Then** every 2 weeks for another 26 weeks
- **Then** every 4 weeks.

Prior to initiation of clozapine patients need to be enrolled in the manufacturer's monitoring service program.

Initiation of Clozapine

Pharmacy shall only dispense the clozapine once the patient registration is completed and patient-specific manufacturer's approved monitoring service number is obtained. Subsequent dispensing and administration of clozapine requires that hematological monitoring has been completed and assessed by the physician.

A color code system to indicate patients' hematologic status is outlined below.

Table 3 **Interpretation of Hematology Results**

Status	Patients Lab Results	Action Required
GREEN	WBC greater than or equal to 3.5 X 10^9/L or more ANC greater than or equal to 2.0 X 10^9/L or more	Continue clozapine treatment CBC and Differential Lab work once weekly, every 2 weeks, or every 4 weeks Pharmacy continues to dispense clozapine once weekly, every 2 weeks or every 4 weeks
YELLOW	**Low values** • WBC between 2.0 X 10^9/L and 3.5 X 10^9/L • ANC between 1.5 X 10^9/L and 2.0 X10^9/L **Falling Values** • WBC: a single fall or sum of falls greater than or equal to 3.0 X 10^9/L is measured in the last 4 weeks, reaching a value of less than 4.0 X 10^9/L • ANC: a single fall or sum of greater than or equal to 1.5 X 10^9/L is measured in the last 4 weeks reaching a value of less than 2.5 X 10^9/L • Physical Symptoms: Flu-like complaints, fever or other symptoms which might suggest infection	Continue clozapine treatment CBC and Differential lab work twice weekly Evaluate for flu like complaints, fever, signs and symptoms of infection
RED	WBC less than 2.0 X10^9/L ANC less than 1.5 X 10^9/L	Clozapine must be immediately withheld and the patient closely monitored Pharmacy consults physician Confirm results within 24 hours Results confirmed = STOP clozapine treatment Evaluation for flue like complaints, fever, signs and symptoms of infection CBC and Differential continue weekly for 4 weeks. CLOZAPINE TREATMENT MUST NOT BE RESUMED: PATIENT NON-RECHALLENGEABLE
RED	**Note:** WBC less than 1.0 X 10^9/L ANC less than 0.5 X 10^9/L	Protective isolation is recommended. If evidence of infection develops appropriate cultures and antibiotic regime should be performed

Interruption of Clozapine Therapy

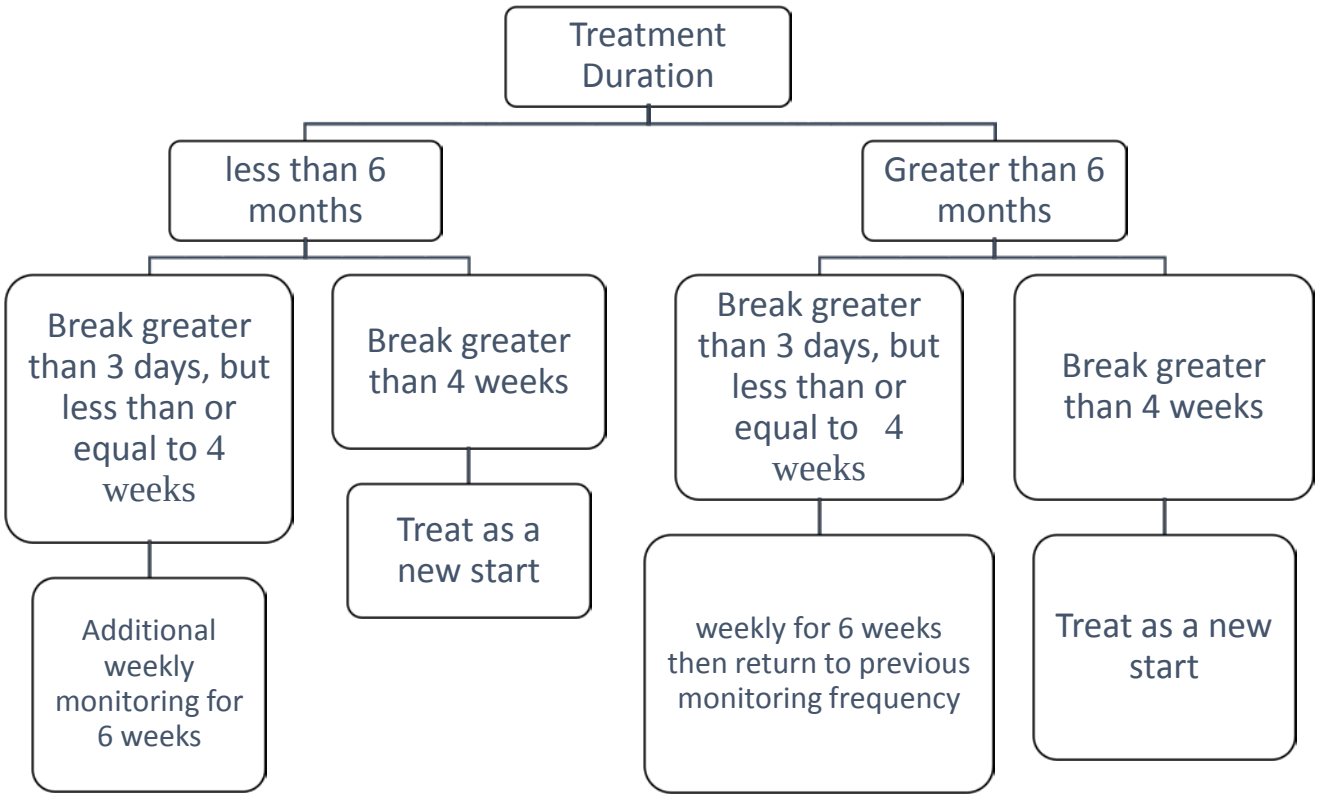
Due to clozapine's unique monitoring requirements and pharmacological profile, special consideration needs to be taken when restarting clozapine after treatment interruption.

If clozapine treatment is interrupted for **greater than 48 hours but less than 72 hours**, it is recommended that the patient's clozapine dose return to the initial starting dose and be retitrated. The CBC monitoring frequency may remain the same.

If clozapine treatment is interrupted for **more than 72 hours but less than or equal to 4 weeks**, it is recommended that the patient's dose return to the starting dose and be retitrated. Additionally it is recommended that CBC's are done weekly for 6 weeks, then may return to their regular frequency. The manufacturer's approved monitoring service should be notified of the interruption.

If clozapine treatment is interrupted for **more than 4 weeks**, then the patient should be treated as a new start. The manufacturer's approved monitoring service should be notified of the interruption.

Figure 2
Summary of CBC Monitoring Frequency Changes Following Treatment Interruption



Antipsychotics and Metabolic Monitoring Adult Inpatient Order Set

Order Set Keywords: antipsychotic, metabolic, monitoring

Metabolic Monitoring is required when patients are on medications listed in this order set for chronic or long term use.

Monitoring

- ☐ Vital Signs: Vital signs to include: temperature (T), pulse rate (P), respiratory rate (RR), blood pressure (BP):
  - ☐ Every _____ minutes
  - ☐ Every _____ hour(s)
  - ☐ Daily

If no baseline documented

- ☐ Height

- ☑ Weight (*calculate BMI*)
  - On initiation of antipsychotic treatment. Start Date _____
  - On week 4 of treatment (1 Month). Start Date _____
  - On week 12 of treatment (3 Months). Start Date _____
  - On month 13 of treatment (annually). Start Date_____
- ☑ Waist circumference
  - On initiation of antipsychotic treatment. Start Date _____
  - On week 4 of treatment (1 month). Start Date _____
  - On week 12 of treatment (3 months). Start Date _____
  - On month 13 of treatment (annually). Start Date_____
- ☐ Monitor for extrapyramidal symptoms (EPS) for movement disorders on initiation for baseline, at 1 month, 3 months (at minimum)

Laboratory Investigations

Prior to Initiation of Antipsychotic Medication

If no result within the last 90 days

Hematology

- ☐ Complete Blood Count (CBC) with differential

Chemistry

- ☐ Hemoglobin A1C
- ☐ Lipid Profile
- ☐ Glucose, Fasting
- ☐ Glucose, Random

Weeks 12, 24, 36 (3, 6, 9 Months and annually thereafter) Date _____

Chemistry

- ☐ Hemoglobin A1C
- ☐ Lipid Profile
- ☐ Glucose, Fasting
- ☐ Glucose, Random

Other Investigations

If clinically indicated or family history of cardiac disease

- ☐ Electrocardiograph (ECG)

If clinically indicated and not done within the last 12 months

- ☐ Electroencephalograph (EEG)

Medications

Refer to the following resources for drug information and appropriate drug dosage as doses varies based on conditions:

- *Refer to AHS Internal website to access the Provincial Drug Formulary for formulary status and Health Canada product monographs for appropriate dosage recommendations based on clinical assessment*
- *Refer to AHS Internal website to access the Parenteral Drug Manual*
- *Lexicomp*
- *Micromedex*
- *Clinical Handbook of Psychotropic Drugs Online*

When ordering antipsychotics consideration should be given to payment coverage. For more information see - Alberta Drug Benefit List (ADBL).

The following medications are currently covered by Alberta Health and Assured Income for the Severely Handicapped (AISH).

Typical Antipsychotic

Short Acting Typical Antipsychotics

- ☐ chlorproMAZine _____ mg PO every _____ hours
- ☐ flupentixol _____ mg PO every _____ hours

For haloperidol, use lower starting doses in elderly

- ☐ haloperidol ____ mg PO every _____ hours
- ☐ haloperidol ____mg IM every ___hours PRN

- ☐ loxapine _____ mg PO every _____ hours
- ☐ loxapine _____ mg IM every _____ hours PRN
- ☐ methotrimeprazine _____ mg PO every _____ hours
- ☐ methotrimeprazine _____ mg IM every _____ hours PRN
- ☐ periciazine _____ mg PO every _____ hours
- ☐ perphenazine _____ mg PO every _____ hours
- ☐ pimozide _____ mg PO every _____ hours
- ☐ trifluoperazine ____ mg PO every _____ hours
- ☐ zuclopenthixol ____ mg PO every _____ hours

Long Acting Injectable Typical Antipsychotics

Prior to initiation of Long Acting Injectable Typical Antipsychotics, efficacy and tolerance of oral formulation should be established.

- ☐ flupentixol decanonate _____ mg IM every _____ days
- ☐ haloperidol decanonate ____ mg IM every _____ days
- ☐ zuclopenthixol acetate ____ mg IM every _____ days PRN

☐ zuclopenthixol decanonate ____ mg IM every _____ days

Atypical Antipsychotics

Short acting Atypical Antipsychotics

For lurasidone, dosage requires adjustment in renal or hepatic impairment

☐ lurasidone _____ mg PO daily. Administer with food of at least 350 calories

For olanzapine, use lower starting doses in the elderly

☐ OLANzapine _____ mg PO daily at bedtime

☐ OLANzapine disintegrating tablet _____ mg PO daily at bedtime

Maximun recommended dose is 20mg/24hour (all routes). Do not exceed three injections in a 24 hour period

☐ OLANzapine _____ mg IM NOW and then OLANzapine _____ mg IM PRN. Do not exceed three injections in a 24 hour period. Avoid giving within 2 hours of IV/IM benzodiazepine.

For quetiapine, use lower starting doses in the elderly

☐ QUEtiapine _____ mg PO every _____ hours

☐ risperidone _____ mg PO every _____ hours

☐ risperidone liquid _____ mg PO every _____ hours.

☐ ziprasidone _____ mg PO every ___ hours. Administer with food.

The following drugs are AHS formulary restricted medications. RESTRICTIONS apply to the use of these drugs - please refer to the AHS Internal website to access the AHS Provincial Drug Formulary

☐ ARIPiprazole _____ mg PO daily

The following medications are currently restricted or require special authorization (particularly for renewal. Coverage restricted to acute treatment of manic or mixed episodes associated with bipolar I disorder as co-therapy with lithium and divalproex sodium, and as monotherapy after a trial of lithium, or divalproex sodium has failed or presence of contraindication to lithium or divalproex sodium.

☐ asenapine _____ mg SL every _____ hours. Avoid eating or drinking 10 minutes after administration.

Coverage restricted to patients stabilized/maintained on paliperidone, or to patients who exhibit abuse/abuse potential or adverse events to QUEtiapine immediate release.

☐ paliperidone ER _____ mg PO daily

Coverage restricted to patients stabilized prior to admission, patients who exhibit abuse/abuse potential, adverse events, or poor compliance to paliperidone immediate release)

☐ QUEtiapine XR _____ mg PO daily at bedtime

Long Acting Injectable Atypical Antipsychotics

The following medications currently all require special authorization for Alberta Health and Assured Income for the Severely Handicapped (AISH) clients.

The following drugs are AHS formulary restricted medications. RESTRICTIONS apply to the use of these drugs - please refer to the AHS Internal website to access the AHS Provincial Drug Formulary

For the maintenance treatment of schizophrenia in patients who demonstrate a significant non-compliance that compromises therapeutic success. Patients must meet at least one of the following criteria:

a) Experience extra-pyramidal symptoms with either an oral or depot injection first generation antipsychotic agent, or refractory to trials of at least 2 other antipsychotic therapies;
b) Patients stabilized/maintained on ARIPiprazole Prolonged Release injectable prior to admission.

Prior to the initiation of aripiprazole LAI, efficacy and tolerability should be established using oral aripiprazole; due to the half-life of oral aripiprazole it may take up to 2 weeks to fully assess tolerability. Continue oral aripiprazole (or other oral antipsychotic) for 14 days during initiation of parenteral therapy. Recommended to administer dose once monthly and no sooner than every 26 days.

☐ ARIPiprazole _____ mg IM every _____ weeks

For the management of manifestations of schizophrenia in patients who demonstrate a significant non-compliance that compromises therapeutic success. Patients must meet one of the following criteria: a) experience extra-pyramidal symptoms with either an oral or depot injection that precludes the use of a first generation antipsychotic agent or refractory to trials of at least 2 other antipsychotic therapies, b) possess clinical evidence of previous successful treatment with risperidone or paliperidone therapy.

Prior to initiation of paliperidone palmitate, efficacy and tolerance of oral paliperidone/risperidone therapy should be establised. Previous oral antipsychotic regimen can be gradually discontinued at the time of initiation of monthly IM paliperidone. D*osage requires adjustment in renal impairment*

Day 1

☐ paliperidone palmitate ____ 150 mg IM

Day 8

☐ paliperidone palmitate ____ 150 mg IM
AND then
☐ paliperidone palmitate_____ mg IM every _____ days. Administer doses in alternating deltoids
OR
☐ paliperidone palmitate_____ mg IM every _____ weeks. Administer doses in alternating deltoids.

For the management of manifestations of schizophrenia in patients who demonstrate a significant non-compliance that compromises therapeutic success. Patients must meet one of the following criteria:

1. *Patient either previously stabalized on risperidone long acting injection*
   OR
2. *a) experience extra-pyramidal symptoms with either an oral or depot injection of a first generation antipsychotic agent or refractory to at least two other antipsychotic therapies, b) possess clinical evidence of successful treatment with risperidone therapy.*

☐ risperidone _____ mg IM every ____ weeks

Transitions and Referrals

- ☐ Consult Hematology
- ☐ Consult Endocrinology
- ☐ Consult _____

Discharge Planning

Discharge Instructions

- ☐ Provide recommendations for physical and laboratory monitoring, medication dosage
- ☐ Patient to follow up with Primary Care Physician
- ☐ Patient to follow up in _____ clinic (Bipolar or Schizophrenia)

Alberta Health Services

Clozapine and Metabolic Monitoring, Adult – Inpatient Order Set

Order Set Keywords: cloZAPine, antipsychotic, metabolic, monitoring
Order Set Requirements: Date of initiation of cloZAPine medication to be entered upon initiation of the order set.

Patient Care

Monitoring

- ☐ Vital Signs: Vital signs to include: temperature (T), pulse rate (P), respiratory rate (RR), and orthostatic blood pressure (BP):
  - **Day One to Day Two**
    - Prior to administration – Baseline measurement
    - Repeat two and six hours post administration
  - **Day Three** (until maintenance dose achieved)
    - Prior to first administration
    - Repeat six to eight hours post administration
  - **Maintenance Dose** (once achieved)
    - Daily
- ☑ Weight (*calculate BMI*)
  - On initiation of cloZAPine treatment. Start Date _____
  - On week 4 of treatment (1 month). Start Date _____
  - On week 12 of treatment (3 month). Start Date _____
  - On month 13 of treatment (annually). Start Date _____
- ☑ Waist circumference
  - On initiation of cloZAPine treatment. Start Date _____
  - On week 4 of treatment (1 month) . Start Date _____
  - On week 12 of treatment (3 month) . Start Date _____
  - On month 13 of treatment (annually). Start Date _____
- ☐ Monitor for extrapyramidal symptoms (EPS movement disorders) upon initiation, at 1 month, and 3 months (at minimum)

Laboratory Investigations

Prior to Initiation of Antipsychotic (within 28 days):

Hematology

- ☐ Complete Blood Count with differential (CBC) repeat weekly X 26 weeks

Chemistry

- ☐ Hemoglobin A1C
- ☐ Lipid Panel
- ☐ Glucose, Fasting
- ☐ Glucose, Random

Week 12 (3 months from initiation) Date _____

Chemistry

- ☐ Hemoglobin A1C
- ☐ Lipid Panel
- ☐ Glucose, Fasting
- ☐ Glucose, Random

Other Investigations

If clinically indicated or family history of cardiac disease

☐ Electrocardiograph (ECG)

Medications

Refer to the following resources for drug information and appropriate drug dosage as doses varies based on conditions:

- *Refer to AHS Internal website to access the Provincial Drug Formulary for formulary status and Health Canada product monographs for appropriate dosage recommendations based on clinical assessment*
- *Refer to AHS Internal website to access the Parenteral Drug Manual*
- *Lexicomp*
- *Micromedex*
- *Clinical Handbook of Psychotropic Drugs Online*

Formulary RESTRICTIONS for clozapine - please refer to AHS Internal website to access the Provincial Drug Formulary

Titrating dose

Recommended starting dose 12.5 mg

☐ cloZAPine _____ mg PO ONCE X 1 dose. Start Date _____

☐ clozapine _____ mg PO daily at _____ *(am or at bedtime)*. Start Date _____ Stop After _____ times

☐ clozapine _____ mg PO daily at _____ *(am or at bedtime)*. Start Date _____ Stop After _____ times

☐ clozapine _____ mg PO daily at _____ *(am or at bedtime)*. Start Date _____ Stop After _____ times

☐ clozapine _____ mg PO daily at _____ *(am or at bedtime)*. Start Date _____ Stop After _____ times

Maintenance dose

☐ clozapine _____ mg PO daily at _____ *(am or at bedtime)*

Transitions and Referrals

☐ Consult Hematology (Recommended if the patient has moderate neutropenia)
☐ MD Consult Endocrinology
☐ MD Consult Cardiology
☐ MD Consult Pharmacy
☐ Consult _____

Discharge Planning

Discharge Instructions

☐ Provide recommendations for physical and laboratory monitoring, medication dosage
☐ Patient to follow up with Primary Care Physician
☐ Patient to follow up in _____ clinic (Bipolar or Schizophrenia)
☐ Provide Community Pharmacy name and contact information
☐ Clozapine: Community Physician and Pharmacist: Complete manufacturers registration form for modification of patient's registration

Disposition Planning

1. Considerations for Discharge/Transfer
    - Availability of medication/coverage for patient on the prescribed antipsychotic.
    - Patient stabilized on current medication regimen

2. Outpatient follow-up
    - Referral as required to the appropriate Mental Health Clinic
    - Follow-up instructions provided such as follow up with Primary Care Physician and recommended monitoring for response to medication and metabolic monitoring
    - The authorized prescriber ensures appropriate delegation of tasks related to monitoring of response to prescribed antipsychotic mediation and monitoring for treatable metabolic conditions. This delegation may vary to an appropriate health care provider such as the RN in a mental health clinic or the Primary Health Care Physician. A transition plan as required is addressed and documented
    - The receiving health care provider shall arrange for scheduled follow up for assessment and on-going treatment

3. Patient and Family education/discharge instructions
    - Education provided regarding recommended monitoring of response to antipsychotic medication and any adverse events with encouragement to provide observations to the most responsible health provider
    - Education provided regarding lifestyle/healthy eating to help mitigate metabolic side effects including weight gain
    - Education provided regarding management of any adverse events such as Diabetic Ketoacidosis
    - Patient aware of follow up required for metabolic monitoring and follow up blood work
    - How to access essential and urgent services as needed, including 24 hour crisis and emergency services

Relevant Guidelines, Procedures, Protocols and Clinical Knowledge Topics

Protocols

- Provincial AMH Clozapine Initiation and Maintenance policy currently in development

Additional Guidelines

- National Institute for Health and Care Excellence. *Psychosis and Schizophrenia in Adults. Prevention and Management.* London (UK): NICE; Updated March 2014. (Clinical Guideline 178) https://www.nice.org.uk/guidance/cg178
- National Institute for Health and Care Excellence*. Bipolar Disorder – Assessment and Management*. London (UK): NICE; Updated February. 2016 (Clinical Guideline 185) https://www.nice.org.uk/guidance/cg185
- Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD). *Collaborative update of CANMAT guidelines for the management of patients with bipolar disorder*. Update 2013
- Canadian Network for Mood & Anxiety Disorders (CANMAT). Clinical Guidelines for the Management of Adults with Major Depressive Disorder. *Can J of Psychiatry*. 2016
- Australian Commission on Safety and Quality in Health Care. *National Adult Clozapine Titration Chart User Guide*, ACSQHC, 2012 Sydney Australia. NIMC-clozapine-titration-User-Guide.pdf
- Taylor David, Paton C, Kapur S. The Maudsley Prescribing Guidelines in Psychiatry 12th Edition 2015

Clinical Knowledge Topics

- Delirium, Adult – Critical Care
- Delirium, Seniors - Inpatient
- ECT, Adult - Inpatient, Ambulatory
- Transcranial Magnetic Stimulation, Adult-Inpatient, Ambulatory

Name of Measure	Appropriate indication for initiation of antipsychotic medication is identified and documented
Definition	For patients initiated on an antipsychotic medication – atypical or typical an appropriate indication is documented. The indication as well as potential side effects of the medication are discussed with the patient.
Rationale	Use of antipsychotics outside official Health Canada indications requires a detailed discussion with the patient as well as ongoing assessment of risks and benefits.
Notes for Interpretation	There is recognition that based on patient medical history and previous trials with other medications that antipsychotics may be an appropriate option. The reason for the medication and the patient response to the medication should be documented
Cited References	Health Canada. Atypical Antipsychotic Drugs and Dementia – Advisories, Warnings and Recalls for Health Professionals http://www.healthycanadians.gc.ca 2005; June. Accessed March 2017. Government of Canada Ottawa, Ontario.

Clinical Analytics – Outcome Measure No. 2

Name of Measure	Metabolic monitoring is implemented for all patients initiated on atypical antipsychotics
Definition	For patients initiated on an atypical antipsychotic medication appropriate metabolic monitoring is implemented.
Rationale	Patients prescribed atypical antipsychotic medications are at risk for metabolic side effects including weight gain and elevation of glucose, cholesterol and triglycerides. Patients with serious mental illness have markedly elevated rates of metabolic disturbance and may have limited access to primary health care. Assessment of risk factors for metabolic disease and cardiovascular disease is vital and should be carried out regularly
Notes for Interpretation	There is recognition that regular patient follow-up is an integral part of metabolic monitoring and that patient adherence to follow up may be a factor in inability to monitor metabolic parameters
Cited References	McIntyre R. Understanding needs, interactions, treatment, and expectations among individuals affected by bipolar disorder or schizophrenia: the UNITE global survey J. Clin Psychiatry 2009: 70 (Suppl. 3) 5-11

References

3. Chadda R, Ramshankar P, Deb K, Sood M, Chadda R, et al. Metabolic syndrome in schizophrenia: Differences between antipsychotic-naïve and treated patients. *J Pharmacol Pharmacother* 2013;4:176-86
4. McIntyre R. Understanding needs, interactions, treatment, and expectations among individuals affected by bipolar disorder or schizophrenia: the UNITE global survey *J. Clin Psychiatry* 2009: 70 (Suppl. 3) 5-11
5. Canadian Network for Mood and Anxiety Treatments (CANMAT) and International Society for Bipolar Disorders (ISBD). *Collaborative update of CANMAT guidelines for the management of patients with bipolar disorder*. Update 2013; 15: 1-44
4. Canadian Network for Mood & Anxiety Disorders (CANMAT). Clinical Guidelines for the Management of Adults with Major Depressive Disorder. *Can J of Psychiatry*. 2016; 61(9):561-575.
5. Choosing Wisely Canada. Canadian Psychiatric Association Recommendations http://www.choosingwiselycanada/recommendations 2015; June Accessed March 2017
6. Health Canada. Atypical Antipsychotic Drugs and Dementia – Advisories, Warnings and Recalls for Health Professionals http://www.healthycanadians.gc.ca 2005; June. Accessed March 2017. Government of Canada Ottawa, Ontario.
7. National Institute for Health and Care Excellence. *Psychosis and Schizophrenia in Adults. Prevention and Management.* London (UK): NICE; Updated March 2014. (Clinical Guideline 178)
8. National Institute for Health and Care Excellence*. Bipolar Disorder – Assessment and Management*. London (UK): NICE; Updated February. 2016 (Clinical Guideline 185)
9. Novartis Pharmaceuticals Canada. *Product Monograph Clozaril Antipsychotic Agent*. https://www.novartis.ca/sites/www.novartis.ca/files/clozaril_scrip_e.pdf Novartis Pharmaceuticals. Quebec. Canada 2015, August.
10. Hamilton, M. Rating depressive patients. *J Clin Psychiatry*. 1980; 41: 21-24
11. Montgomery S, Asberg A. A new depression scale designed to be sensitive to change*. Br. J Psychiatry*. 1979; Apr. 134 (4):382–89.
12. Centre for Suicide Risk Assessment. *Columbia Suicide Severity Rating Scale.* Columbia University Medical Centre. New York (NY)
13. Beck A, Steer R, Brown G. *Manual for the Beck Depression Inventory-II*. San Antonio (TX): 1996. Psychological Corporation
14. Kroenke, K; Spitzer, R. The PHQ-9: A New Depression Diagnostic and Severity Measure*. Psychiatric Annals.* 2002; 32: 1–7.
15. Young R, Biggs J, Ziegler V, Meyer D*.* "A rating scale for mania: reliability, validity and sensitivity". *Br J Psychiatry.* 1978; 133(5):429–435
16. Hirschfeld R. Williams J. Spitzer R. Calabrese J, et al. Development and Validation of a Screening Instrument for Bipolar Spectrum Disorder: The Mood Disorder Questionnaire*. Am J Psychiatry.* 2000: 157(11):1873–1875.
17. Kay S, Fiszbein A, Opler L. The positive and negative syndrome scale (PANSS) for schizophrenia. *Schizophr Bull.* 1987; 13(2):261–276
18. Overall J, Gorham D. The brief psychiatric rating scale. *Psychol Reports* 1962; 10:799-812
19. Waddell L, Taylor M. A new self-rating scale for detecting atypical or second-generation antipsychotic side effects. *J Psychopharmacol* 2008; 22(3): 238-243.
20. Folstein M, Folstein S, McHugh P*. 'Mini-mental status'. A practical method for grading the cognitive state of patients for the clinician". J Psych Research.* 1975; 12 (3): 189–98
21. Purdon, S. Screen for Cognitive Impairment in Psychiatry (SCIP): *Administration Manual and Norms*. 2005 Edmonton, Alberta, Canada: PNL Inc.

22. Baron-Cohen S, Wheelwright S, Skinner R, Martin J, Clubley E. The Autism-Spectrum Quotient (AQ): Evidence from Asperger Syndrome/High-Functioning Autism, Males and Females, Scientists and Mathematicians. *J. Autism Dev. Disord* ; 2001 (31)1
23. Baron-Cohen S, Wheelwright S. The Empathy Quotient: An Investigation of Adults with Asperger Syndrome or High Functioning Autism, and Normal Sex Differences. *J. Autism Dev. Disord*, 2004; (34)2
24. Wolraich M, Lambert W, Doffing M, Bickman L, Simmons T, et al. "Psychometric Properties of the Vanderbilt ADHD Diagnostic Parent Rating Scale in a Referred Population"*. J Pediatr Psychol.* 2003; 28 (8):559–568
25. Hamilton M. The assessment of anxiety states by rating. *Br J Med Psychol* 1959; 32:50–55.
26. Spitzer, RL; Kroenke, K; Williams, JB; Löwe, B. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med.* 2006; May 166 (10): 1092–7.
27. Beck AT, Epstein N, Brown G, Steer RA (1988). An inventory for measuring clinical anxiety: Psychometric properties*. J Consulting Clinical Psych.* 56: 893–897*.*
28. Borson S, Scanlan J, Chen P, et al. The Mini-Cog as a screen for dementia: Validation in a population-based sample. *J Am Geriatr Soc* 2003; 51:1451–1454.
29. Folstein M, Folstein S, McHugh P*. '*Mini-mental status'. A practical method for grading the cognitive state of patients for the clinician". *J Psych Research.* 1975; 12 (3): 189–98
30. *Yudofsky S, Silver J, Jackson W, Endicott J, Williams, D.* The Overt Aggression Scale for the objective rating of verbal and physical aggression. *Am. J. Psychiatry. 1986* ***143*** *(1): 35–39.*
31. De Hert M, Vancampfort D, Correll C, Mercken V, et al. Guidelines for screening and monitoring of cardiometabolic risk in schizophrenia= systematic evaluation. *BJP.* 2011; 199: 99-105.
32. Colton C, Manderscheid R. Congruencies in increased mortality rates, years of potential life lost, and causes of death among public mental health clients in eight states. *Prev Chronic Dis*. 2006; Apr; 3(2): A42
33. Smith B, Smith P, Etches J, Mustard C. Overqualification and Risk of All-cause and Cardiovascular Mortality: Evidence From the Canadian Census Mortality Follow-up Study (1991-2001). *Can J Public Health*. 2012; 103(4): e297-e302.
34. Brown, S, Kim M, Mitchell, C, Inskip, H. Twenty-five year mortality of a community cohort with schizophrenia. *Br J Psychiatry*, 2010; 196(2), 116-121.
35. Newman S, Bland R. Mortality in a cohort of patients with schizophrenia: a record linkage study. *Can J Psychiatry* 1991; 36: 239–45.
36. Black D, Fisher R. Mortality in DSM-IIIR schizophrenia. *Schizophr Res* 1992; 7:109–16.
37. Brown, S. Excess mortality of schizophrenia: a meta-analysis. *Br J Psychiatry* 1997; 171, 502–508.
38. Hansen B. The metabolic syndrome X. Ann N Y *Acad Sci* 1999; 892:1–24.
39. Correll C, Robinson D, Schooler N, Brunette M, et al. Cardiometabolic risk in patients with first episode schizophrenia spectrtum disorders : Baseline results from the RAISE-ETP Study. *JAMA Psychiatry,* 2014 71(12):1350-136
40. Pringsheim T, Kelly M, Urness D, Teehan, M et al. Physical Health and Drug Safety in Individuals with Schizophrenia. *Can J of Psychiatr*. 2017; July 1-12

Acknowledgments

We would like to acknowledge the contributions of the Provincial Clinical Knowledge Working Group members as follows. Your participation and time spent is appreciated.

Appropriate Use of Antipsychotics, Adult – Inpatient Knowledge Topic Working Group Membership		
Name	**Title**	**Zone**
Knowledge Lead		
Dr. Michael Trew	Provincial Clinical Knowledge Lead – AMH	Provincial
Topic Lead		
Dr. Scot Purdon	Provincial Clinical Topic Lead	Provincial
Working Group Members		
Dr. Sudkhar Sivapalan	Psychiatrist	Edmonton
Dr. Thomas Raedler	Psychiatrist	Calgary
Dr. Lorella Ambrosano	Psychiatrist	North
Dr. Douglas Urness	Psychiatrist	Central
Dr. Rishi Singhal	Psychiatrist	South
Dr. Rohit Lodhi	Psychiatrist	Edmonton
Darren Chapman	Unit Manager	Calgary
Megan Quesseth	Outreach Worker	Central
Clinical Support Services		
Taciana Pereira	*on behalf of* Pharmacy Information Management Governance Committee (PIM-GC) - Pharmacy Services	Provincial
Dr. Bill Anderson	On behalf of Provincial Diagnostic Imaging	Provincial
Dr. James Wesenberg	On behalf of Laboratory Services – Provincial Networks	Provincial
Carlota Basualdo-Hammond & Marlis Atkins	On behalf of Provincial Nutrition and Food Services	Provincial
Strategic Clinical Network		
Addiction and Mental Health Strategic Clinical Network		
Clinical Informatics Lead		
Carla Milligan		Provincial
Leng My		Provincial
Kellie Quian		Provincial

Additional Contributors

Thank you to all provincial stakeholders who participated in the review process for this topic. Your time spent reviewing the knowledge topics and providing valuable feedback is appreciated.

For questions or feedback please contact ClinicalKnowledgeTopics@ahs.ca.