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Bipolar Disorder in Adults: Information for Primary Care

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Summary: Bipolar disorder is an mental health condition where people have periods of mania / hypomania and periods of depression. When there are obvious mania symptoms, it can be easier to identify. Unfortunately, it can also be challenging to recognize. Consider bipolar in patients who have had poor response to multiple antidepressant trials, and who have comorbid anxiety/depression. Primary care providers can make a significant difference by recognizing and connecting patients with appropriate resources and treatments. Psychiatrists and primary care providers alike may be involved with starting treatment for bipolar disorder as well as follow-up and monitoring of medication treatment.

Case of Hypomania: “She vacuums in the middle in the middle of the night”

B. is a 35-year-old woman who presents along with her spouse.

For the past 3-weeks, she has had increased energy, libido, and staying up the whole night, yet she appears to have tons of energy the next day. She still appears able to function at work and home, though is a bit more erratic.
What do you do?

- You wonder about hypomania based on mood symptoms, but which are not severe enough to be mania.
- As her symptoms are not severe enough to justify inpatient care, you decide to manage her as an outpatient.
- You start her on Quetiapine 50 mg at bedtime with plans to follow up in a week.
- You let the family know that if symptoms worsen, they can
    - Call the crisis line (which includes mobile crisis services),
    - Bring her to the nearest Emergency Department, and/or
    - Contact emergency medical service (EMS).

Case of Mania: “I’m scared of my husband... He's not himself..."

M is a 35-year-old man with a strong family of bipolar disorder (mother, grandfather) who you have been treating for depression.
His wife calls your office calls your office frantically to tell you that, rather abruptly, he has:

- Become very angry, is talking too fast and is not sleeping,
- Plans to spend all their money on a business that he has no experience with,
- Become threatening towards her and others, is driving at high speeds and has extreme “road rage”.

You can hear him in the background, and his wife can put you on the phone briefly with him. He denies anything is wrong but does agree that he hasn't slept in days.
What do you do?

- You wonder about a manic episode, given the very severe mood symptoms.
- Given the acute safety concerns (e.g., physical and financial), you decide to fill out a Form 1 so that the police can bring him to the emergency department to be assessed.
- You contact triage at the Emergency Department and give them a heads up.

Epidemiology

- Up to 20% of depressed patients presenting to primary care physicians have some form of bipolar disorder (CANMAT).
- Peak age of onset: Age 17-21 (CANMAT)

Screening

- Consider screening patients with risk factors such as:
    - Relatives with bipolar disorder
    - No response to 3 or more antidepressant trials
    - Comorbid anxiety/obesity
    - Patients with suspected or already diagnosed depression

Screening Tools

- Mood Disorder Questionnaire (MDQ)
    - A brief self-report instrument that takes 5 minutes.
    - Positive screens should receive a more comprehensive evaluation.
    - Sensitive for bipolar I (depression and mania); however, less sensitive for other bipolar disorders such as bipolar II (depression and hypomania) and bipolar unspecified
    - Available freely online:
      www.integration.samhsa.gov/home/ementalhealth/ementalhealth.ca/frontend/images/res/MDQ.pdf
      http://bipolar.stanford.edu/mdq.html

History / Screening Questions

- DIG FAST mnemonic, as in a person with mania who is digging very fast:
    - D)istractibility: Are more distractible than usual?
    - I)mpulsivity/irritability: Are you more impulsive than usual?
    - G)randiosity: Do you have special skills or abilities others don’t have?
    - F)light of ideas: Are your thoughts faster than usual?
    - A)ctivity increased: Are you doing more activities or find yourself busier than usual?
    - S)leep decreased: Have you had less need to sleep lately?
    - T)alkative: Have you been more talkative than usual?

Diagnosis (Dx)

- Bipolar disorder is a clinical diagnosis based on history and physical finding
- There are no diagnostic lab investigations, though they may be useful for ruling out medical conditions
- Diagnosis is often delayed because a series of depressive episodes may occur before a manic or hypomanic episode occurs
- When diagnosing depression, screen for symptoms of bipolar to ensure the patient is not actually suffering from bipolar disorder

Main Bipolar Disorders

Bipolar I	Past or present Manic episode (i.e. elevated/irritable mood lasting more than one week, along with increased energy/activity) Severe enough to cause marked impairment, such as requiring hospitalization) May also have periods of depression
Bipolar II	Past or present Hypomanic episode (i.e. elevated/irritable mood lasting at least 4 days, with increased energy/activity) Not severe enough to cause marked impairment (such as requiring hospitalization) May also have periods of depression
Cyclothymic Disorder	Subthreshold disorder with symptoms of depression and hypomania, but not sufficient to meet criteria for major depression or hypomanic disorder

DSM-5 Bipolar Disorders

More...

Differential Diagnosis (DDx)

Medical DDx

Rule out medical causes such as the following:

- Substance/medication-induced bipolar disorder
- Recreational drugs
  - Amphetamines, cocaine, hallucinogens, opiates, alcohol
- Medications causing mania:
  - Antihypertensives – Captopril
  - Neurologic – Levodopa, D2 agonists (Pramipexole)
  - Endocrine– Estrogens, testosterone, glucocorticoids, ACTH, thyroid hormones
  - Antibiotics -- Fluoroquinolones (Ciprofloxacin)
- Neurologic conditions, e.g. Head trauma
- Thyroid problems

Psychiatric DDx

- Major depressive disorder
- Bipolar I Disorder
- Bipolar II Disorder
- Cyclothymia
- Generalized anxiety disorder, panic disorder, posttraumatic stress disorder, or other anxiety disorders
- Attention-deficit/hyperactivity disorder

- Personality disorders

Comorbidity

- High rates of comorbid conditions, such as
    - Alcohol and substance abuse
    - Anxiety disorders
    - Personality disorders

Investigations

There are no diagnostic tests for bipolar disorder, however, consider the following to rule out contributory medical conditions:

- CBC - Pernicious anemia
- Fasting glucose level, lipid profile - Diabetes mellitus, hyperlipidemia, Cushing syndrome)
- Liver function tests - hepatitis
- TSH level - thyroid disorders
- Urinalysis - infection in older patients
- Urine toxicology - substance abuse
- With new-onset psychosis, consider investigations to rule out seizure disorder, intracranial mass, and other causes of secondary psychosis such as:
    - EEG
    - MRI or CT

In the event that medications will be started, CANMAT guidelines recommend the following baseline indices (CANMAT, 2010)

- CBC – baseline for anticonvulsants
- Electrolytes
- Fasting glucose - baseline for any medication that may cause weight gain or hyperglycemia
- Fasting lipid profile (TC, VLDL, LDL, HDL, TG) - baseline for any medication that may cause weight gain or hyperglycemia
- Liver enzymes – baseline for anticonvulsants and antipsychotics
- Serum bilirubin
- Platelets, Prothrombin time and partial thromboplastin time
- Urinalysis
- Urine toxicology for substance use
- Serum creatinine
- 24-h creatinine clearance (if there is a history of renal disease)
- Thyroid-stimulating hormone (TSH) – baseline for lithium
- Electrocardiogram (ECG) (>40 years or if indicated) – baseline for medications like lithium and antipsychotics that can prolog QTc interval
- Pregnancy test in females (if positive, teratogenic medications would be avoided)
- Prolactin (baseline)

Physical exam

- Baseline monitoring (in the event medications are started for bipolar)
    - Body mass index (height, weight)
    - Blood pressure
    - Waist circumference

- Neurological evaluation
    - Monitor for medication adverse effects such as extrapyramidal effects (if on antipsychotics), tremors / cerebellar symptoms (if on lithium)

Management: When and Where to Refer

Is the patient acutely manic? Are there concerns about self-harm or inability to care for oneself? Is there a risk of financial self-harm (e.g. spending excessively)? Is there a risk of employment harm (e.g. going to work in a hypomanic/manic state)?

- If so, then consider acute hospitalization via referral to an Emergency Department
- See if there is a family member able to transport the patient otherwise contact Emergency Medical Services (e.g. 911 for an ambulance transfer)

Is the patient somewhat unwell (such as beginning signs of mania or hypomania) but not so severe enough to require hospitalization?

- Consider urgent follow-up options through mental health services
- Consider starting medication such as a sedating antipsychotic (with mood-stabilizing properties) to hopefully stabilize sleep/wake cycles until the patient can be seen soon
- Options include
    - Olanzapine (Zyprexa)
        - Start at 5-10 mg /day
        - Target 5-20 mg/day
        - Max daily dosage is 20 mg/day
    - Resperidone (Risperdal)
        - Start at 1-2 mg daily, given once or twice daily
        - Target dose 4-6 mg daily
        - Max 8 mg daily
    - Quetiapine (Seroquel)
        - Start at 100 mg daily
        - Target to 300-800 mg / daily for depression
        - Max daily dosage 600 mg daily
    - Aripiprazole (Abilify)
        - Start at 15 mg/day
        - Target to 15-30 mg daily
        - Max daily dosage = 30 mg daily

Is the patient stable, however the presentation is complex, with unclear diagnosis?

- Consider referral to outpatient mental health services for diagnostic clarification and treatment recommendations

Is the patient stable, with a known diagnosis of bipolar?

- Monitor any signs that might indicate a need for hospitalization.
- Monitor medications and case management.
- If the patient would benefit from counselling/psychotherapy, then consider referral for counselling/psychotherapy.

Office Counseling for bipolar

- Lifestyle Changes
    - Stop any stimulants (e.g. caffeine, nicotine), alcohol, nicotine, and recreational drugs
    - Regular exercise

    - Go to bed regularly at the same time on weekdays and weekends (as opposed to staying up later on weekends)
    - Have a well-balanced diet
        - Omega 3 fatty acids may possibly be helpful in addition to medications, but are not a replacement for medication (Balanza-Martinez, 2011.)
- Coping and action plans
    - Help the patient develop an action which includes
    - What are the signs that I am well?
    - What are the signs I am having a relapse?
    - What are my triggers?
    - What can I do about it? What are healthy ways I can cope with stress in general?
- Positive mental health strategies
    - Help the patient live a meaningful life with meaningful activities and relationships (Frankl, 1946; Fredrickson, 2013)
    - For example:
        - Altruism: Helping others and making a contribution to the lives of others (as opposed to focusing on just oneself)
        - Nature: Spending time outside in nature (as opposed to spending time indoors, in artificial urban environments)
        - Practicing gratitude: Making a conscious effort to be grateful for what one has (as opposed to obsessing over what one doesn't have)
- Self-monitoring using Mood Charts
    - Ask patients to chart their moods to assist with diagnosis and monitoring
    - Patients assess their mood morning and night
    - Mood charts are available freely online such as:
        - http://www.blackdoginstitute.org.au/docs/12.MoodChartforBipolarDisorder.pdf
        - http://www.cqaimh.org/pdf/tool_edu_moodchart.pdf

Types of Counseling / Therapy

Mental health professionals may provide different treatments, such as:

- Psychoeducation
- Cognitive behaviour therapy (CBT)
- Interpersonal psychotherapy (IPT)
- Interpersonal and social rhythm therapy (IPSRT)
- Family focused therapy

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Medications for Bipolar I Disorder

Medications for acute management are often started by psychiatry when patients are acutely ill, but family physicians may also be starting bipolar medications as well.

Classic options were lithium and Divalproex, but nowadays, atypical antipsychotics can easily be started if necessary and without the need to monitor serum levels

Family physicians continue to be involved with ongoing monitoring when patients are stable on their bipolar medications

Acute Management of Manic Episode: First Line

Lithium	Start at 900 mg daily Check serum level after 3-4 days and adjust Target dose to 900-2400 mg daily Max 3600 mg daily
Divalproex (Valproate)	Start at 500-1000 mg daily, given twice daily or at night Increase by 500 mg/day every 1-2 weeks Target 750-2000 mg daily Max 60 mg /daily
Resperidone (Risperdal)	Start at 1-2 mg daily, given once or twice daily Target dose 4-6 mg daily Max 8 mg daily
Olanzapine (Zyprexa)	Start at 5-10 mg /day Target 5-20 mg/day Max daily dosage is 20 mg/day
Quetiapine (Seroquel)	Start at 100 mg daily Target to 300-800 mg / daily for depression Max daily dosage 800 mg daily
Aripiprazole (Abilify)	Start at 15 mg/day Target to 15-30 mg daily Max daily dosage = 30/day

* Note that doses for medications in manic phases may be higher than in maintenance therapy

For additional medication information, please see CANMAT Guidelines; Texas Medication Algorithm for Bipolar Disorder (TMABD); Lexi-Comp.

Maintenance therapy for Bipolar I Disorder

First Line

Lithium	Start and titrate up to 300 mg twice daily Target dosage: Titrate every 1 to 5 days up to 900-1800 mg daily Target serum level: 0.8-1.2 mmol/L
Lamotrigine (Lamictal)	Start 25 mg daily Target dose: Slowly increase over 6 weeks to 200 mg daily
Divalproex (Valproate)	Start 500-750 mg daily Target to 1000-3000 mg daily (administered twice daily); Target serum level: 400-700 mmol/L
Olanzapine (Zyprexa)	Start 10-15 mg daily Target dose 10-30 mg daily
Quetiapine (Seroquel)	Start 100-200 mg daily Target dose 400-800 mg at bedtime
Risperidone (Risperdal)	Start 1-2 mg daily Target dose 4-8 mg daily (usually given morning and bedtime)
Aripiprazole (Abilify)	Start 10-30 mg once daily Target dose 15-30 mg once daily

Reference: CANMAT, 2010

Acute Management of Bipolar I depression

First-line monotherapy options

Lamotrigine	Without concomitant valproate • Start weeks 1 and 2: 25 mg once daily; Weeks 3 and 4: 50 mg once daily; Week 5: 100 mg once daily; Week 6: 200 mg once daily • Target: 200 mg daily • With concomitant valproate • Start: Weeks 1 and 2: 25 mg every other day; Weeks 3 and 4: 25 mg once daily; Week 5: 50 mg once daily; Week 6: 100 mg once daily • Target: 100 mg daily With concomitant carbamazepine, phenytoin, phenobarbital, primidone, rifampin, or lopinavir/ritonavir, and without valproic acid: • Start: Weeks 1 and 2: 50 mg once daily; Weeks 3 and 4: 100 mg daily in divided doses; Week 5: 200 mg daily in divided doses; Week 6: 300 mg daily in divided doses • Target: 400 mg daily in divided doses
Quetiapine	Start 50 mg once daily at bedtime on day 1; increase to 100 mg once daily on day 2; further increase by 100 mg daily each day until 300 mg once daily is reached by day 4. Target dose: 300 mg once daily Maximum dose: 300 mg once daily.
Quetiapine XR	Start 50 mg once daily on day 1; increase to 100 mg once daily on day 2, further increase by 100 mg once daily until 300 mg once daily is reached by day 4. Target dose: 300 mg once daily Maximum dose: 300 mg once daily (US labelling) or 600 mg once daily (Canadian labelling).
Lithium	Start 300 mg to 300 mg po bid Check Li level (12 hours after the last dose) after 5-7 days Increase gradually in 300 mg increments, targeting a blood level of 0.8-1.2 as tolerated.
Lurasidone	Start 20 mg daily, increase up to 120 mg/daily.

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Medications for Bipolar II Disorder

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Maintenance therapy of Bipolar II Disorder: CANMAT

First line

- Lithium
- Lamotrigine
- Quetiapine

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Reference: Medication Charts

Mood stabilizers Used in Bipolar Disorder

Medication	Dosage	Monitoring

Divalproex (Valproate)	Start at 500-1000 mg/day Titrate by 500 mg/day every 1-2 weeks Target dose 750-2000 mg/daily	Baseline • Weight • CBC with differential • Liver function tests (LFTS), e.g. AST, ALT, ALK) • Coagulation tests Ongoing investigations • Every 3-months for the first year, then once yearly • Weight • CBC • LFTs • Menstrual changes • On history, monitor for any liver problems (e.g. bleeding problems, jaundice) Divalproex serum levels: • Therapeutic range 400-700 mmol/L • Obtain 3-5 days after the most recent dose titration • Establish 2 consecutive serum levels in the therapeutic range during acute phase
Lithium	Start at 300 mg po bid (with elderly, start at lower doses such as 150 mg po bid) Adjust by 300-600 mg increments Target dose usually 900 to 1,800 mg daily in divided doses.	Baseline investigations • Weight • TSH • Renal function (BUN/Cr) • Calcium Ongoing investigations • Lithium level every 3-6 months • Renal function (BUN/Cr) every 3-6 months • TSH, weight, calcium every 6-months Lithium serum levels: • Check serum level 5-7 days after the most recent dose titration (12 hours after the last dose, i.e. trough level) • Target blood level 0.6-0.8 mmol/L for maintenance; above > 1.2 mmol is potentially toxic • Establish 2 consecutive serum levels in the therapeutic range during acute phase
Carbamazepine	Start at 400 mg/day in 2 divided doses (oral) or 4 divided doses (oral suspension) May adjust by 200 mg/day increments; Maximum dose: 1600 mg/day.	Baseline • Monthly for the first 3 months • CBC • Liver function tests (LFTS), e.g. AST, ALT, ALK) • Electrolytes • Urea / Creatinine Ongoing monitoring • Once yearly • CBC • Liver function tests (LFTS), e.g. AST, ALT, ALK) • Electrolytes • Urea / Creatinine • At least 2 drug serum levels in initiation phase of treatment and then every 3 to 6 months or with dosing changes

Atypical Antipsychotics Used in Bipolar Disorder

Medication	**Dosage**
Olanzapine (Zyprexa)	Start 5-10 mg daily Target 10-20 mg daily
Risperidone (Risperdal)	Start 1-2 mg daily Target 2-3 mg daily
Quetiapine (Seroquel)	Start 50 mg bid Target 300-600 mg daily

Quetiapine XR (Seroquel XR)	Start 50 mg at supper Target 300-600 mg daily
Aripiprazole (Abilify)	Start 5-10 mg daily Target 15-30 mg daily

Monitoring

- View CAMESA Guidelines for more detailed monitoring information for antipsychotics http://camesaguideline.org/information-for-doctors

Clinical algorithms

- Texas Implementation of Medication Algorithms (TIMA) for Bipolar http://www.medscape.org/viewarticle/524957

Clinical Practice Guidelines

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