Approach to Bipolar Disorder

Family Medicine Forum

November 14 – 17, 2018

Toronto, Ontario

Jon Davine, MD, CCFP, FRCP(C)
Associate Professor, McMaster University

Faculty/Presenter Disclosure

Faculty: Dr. Jon Davine

Department of Psychiatry

St. Joseph's Healthcare, Hamilton, Ontario

Relationship with Financial sponsors:

- **Grants/Research Support:** None
- **Speakers Bureau/Honoriaria:** Michael Garron Hospital, Toronto East Health Network, Ontario Medical Association, Ontario College of Family Physicians, Touchstone Institute (IMG), McMaster University Department of Psychiatry, Nurse Practitioners of Ontario, Medical Psychotherapy Association, Sioux Lookout Medical Group.
- **Consulting Fees:** None
- **Patents:** None
- **Other:** None

Disclosure of Financial Support

- **This program has not received financial support**
- **This program has not received in-kind support**

- **<u>Potential for conflict(s) of interest</u>:**
  - Jon Davine has not received any funding for this program

Mitigating Potential Bias

- Dr. Jon Davine

- I have received no funding from anyone for this presentation.
- Any meds I discuss are based on reviews of the literature
- My honoraria have been received from academic institutions, medical societies, and family medicine groups

Objectives

- Learn how to make the diagnosis of bipolar in a time efficient manner
- Learn how to use psychopharmacology to treat Bipolar Disorder, using current guidelines
- Learn about issues of psychopharmacology and pregnancy

Bipolar Disorder

- **MANIC**
  - 7 days or more, unless hospitalized
  - Interferes with life greatly
  - Increased mood
  - Increased energy
  - Decreased sleep
- **HYPOMANIC**
  - 4 days or more
  - Somewhat interferes with life, seen by others as uncharacteristic
  - Same features as manic, no marked impairment in functioning
- **IMPORTANT:** Separate Bipolar II from Axis II, cluster B mood lability
  - Remember time line, days vs. hours or a day
  - Out of the blue vs. response to stressors

Bipolar I vs. Bipolar II

- **Bipolar I**
  - Manic phase(s) +/- depression phase(s)
  - 1% lifetime prevalence

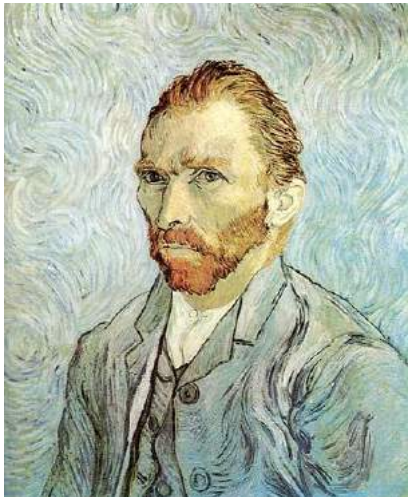
- **Bipolar II**
  - Hypomanic phase(s) + depression phase(s)
  - 1.1% lifetime prevalence

Cyclothymic

- 2 years, numerous episodes
- Does not meet criteria for hypomanic or depression
- Present at least half the time
- Impairs functioning

Bipolar Disorder

- Mean age of onset - early to mid 20's
  - Peak age is 15-19
- Usually 3-10 year lag between onset and treatment
- Initially
  - Depression in women
  - Mania in men
- Twin studies and first degree relative studies support the fact of heritability



Bipolar Terms

- **Bipolar**
  - Manic phase
  - Hypomanic phase
  - Depressed
  - Mixed phase - depression and mania essentially coexist, switching over hours, or every 1 - 2 days. Also has been called ultra rapid cycling. Must last at least one week. Causes marked impairment in functioning.
- **Rapid Cycling**
  - 4 or more episodes/year
  - Going from manic to depressed - counts as two episodes

THINGS TO DO:

- Assess for **organicity**
- **Harm to others** (e.g., driving)
- **EtOH/Substance abuse**
  - High co-morbidity rate
  - Can worsen
- **Suicidality**
  - 17-19% lifetime prevalence of completed suicide
  - More often in depressed state
- **Educate**
  - Inadequately treated patient may have 10 or more episodes
  - Intervals between episodes narrows as person ages
  - Sleep deprivation can provoke hypomanic/mania

Levels of Evidence

- **Level 1**
  - Meta-analysis or replicated RCT with placebo
- **Level 2**
  - At least one RCT with placebo or active comparison condition
- **Level 3**
  - Uncontrolled trial with 10 or more subjects
- **Level 4**
  - Anecdotal reports or expert opinion

Treatment Recommendations

- **1st line (A)**
  - Level 1 or 2 evidence plus clinical support for efficacy and safety
- **2nd line (B)**
  - Level 3 evidence or higher plus clinical support for efficacy and safety
- **3rd line (C)**
  - Level 4 evidence or higher plus clinical support for efficacy and safety
- **Not Recommended**
  - Level 1 or 2 evidence for lack of efficacy

Lithium – Indications

- **Anti-manic**
  - 78% response rate
  - Level I evidence
- **Anti-depressant**
  - 79% response rate
  - Level I evidence
- **Prophylaxis**
  - 6 fold decrease in subsequent episodes
  - Level I evidence

Lithium – Pharmacology

- Half-life = 14-30 hours
- Not metabolized
  - Cleared by kidney (mind renal function)
  - Not protein bound

Lithium – Side Effects

- Polyuria, polydipsia (Diabetes Insipidus)
  - Treat with diuretics if necessary
- * Increase weight
- Cognitive problems
- * Tremor
  - Treat with Beta-Blockers
- Sedation
- * GI distress
- Increase WBC
- ECG changes
  - Usually benign
  - Rarely conduction abnormality

Lithium – Other Effects

- Hypothyroid (5-35%)
  - More females after 6-18 month treatment
  - Generally reversible
  - Can replace with thyroxine
- Nephrotoxicity
  - Controversy, but appears to be

Lithium – Levels and Side Effects

- **0.4-0.6** mmol/L
  - Decreased side effects
  - Increased risk of episodes
- **0.6-0.8** mmol/L
  - Most often chosen
  - Not well studied
- **0.8-1.1** mmol/L
  - Deceased risk of episodes
  - Increased side effects

- Balance must be chosen between efficacy and side effects

Lithium – Overdose

- **>1.5** mmol/L = **Toxic**
  - coarse tremor
  - Vomiting
  - Blurred vision
  - Vertigo
  - Confusion
  - Increased DTR
- **> 2.5** mmol/L = **Life threatening**

- Treatment: hemodialysis

Lithium – What to do before starting:

- **Workup** – repeat every 6-12 months
  - ECG
  - CBC
  - TSH
  - Creatinine, ‘lytes, u/a
  - Ca
  - Pregnancy test if applicable
- **Blood lithium levels**
  - 5 days after starting, and then 5-7 days after dosage changes
  - Get 2 therapeutic serum levels, then repeat q3months.

Lithium - Dosage

- Start at 300 mg PO BID
- Increase by 300 mg/day depending on levels
- Usual dosage 900-1500 mg/day
- Geriatric: Start at 150 mg. po od, and increase by 150 mg. increments

- Measure "trough" levels
  - Patient to have blood test 12 hours post last dose

Valproic Acid – Indications

- **Manic** – 56% response rate (near Lithium effectiveness)
  - Level I evidence (A for mania and mixed states)
- **Bipolar Depression** – Few studies for bipolar depression
  - Level III evidence (B)
- **Prophylaxis**
  - Level II evidence (A)

Valproic acid - Pharmacology

- 2 forms
  - Valproate and Divalproex sodium
  - Divalproex sodium (Epival) has less GI side effects, and is therefore preferred
- Half-life = 6-16 hours
- Metabolized by liver
- Protein bound

Valproic Acid – Side Effects

- * GI distress (use divalproex sodium)
- Sedation
- * Benign increased ALT, increased AST
- Tremor
- Hepatotoxicity
- Decreased platelets, WBC
- *Increased appetite, weight
- Agranulocytosis
- Polycystic ovarian disease – contraindicated

Valproic Acid – When you start:

- **Workup** before starting
  - History And Physical
  - LFT'S
  - CBC with platelets
  - Do initially, then at 4 weeks, repeat q 3-6 months
- Starting Dose 250 mg BID.
  - Increase by 250 mg Increments weekly
  - Geriatric: Start at 125 mg. po od, and increase by 125 mg. increments
  - + teratogenic
- Levels
  - 350-700 µmol/L3

Lamotrigine

- Especially helpful from down-up
  - More effective in preventing depression
- Less weight gain
- Watch for any **rash (about 5%)**
- **Severe rash 3/1000**
- Stevens-Johnson syndrome a possibility, (1/1000), thus D/C.
- Start at 12.5-25 mg PO OD
- Increase by 12.5-25 mg PO q1-2weekly
- Levels – Usually 50-200 mg/day
  - No blood level monitoring necessary

Lamotrigine – Indications

- **Mania**
  - Level III evidence (D)
- **Depression**
  - Level I evidence (A)
- **Prophylaxis**
  - Level I evidence (A)

Gabapentin, Topiramate

- For **mania**, **depression**, and **prophylaxis**:
  - Level III (D)
- Not recommended or prescribed

Acute Treatment of Mania

- Acute treatment duration = **2 to 10 weeks**
- Rule out organic
  - Cushing's
  - Thyroid
  - MS
  - Steroids
  - *antidepressants - controversy
  - Substance abuse

Acute Treatment of Mania, Mixed State, Rapid Cycling

- **History** and **physical**
- **Labwork**
  - CBC with diff
  - Lytes, creatinine
  - LFT's
  - TSH
  - EKG (if >40)
  - U/A
  - Ca
  - Pregnancy test if relevant

CANMAT 2018: 1st Line Mania

- Lithium
- Quetiapine
- Divalproex
- Asenapine
- Aripiprazole
- Paliperidone (>6 mg.)
- Risperidone
- Cariprazine

All Level 1

CANMAT (2018)
First line combination, Acute Mania

Quetiapine + Li/DVP	Level 1
Aripiprazole + Li/DVP	Level 2
Risperidone + Li/DVP	Level 1
Asenapine + Li/DVP	Level 2

Atypical Neuroleptics

- Risperidone, Olanzapine, and Quetiapine are all approved for use as anti manic agents
- Risperidone--1-4 mg/day
- Olanzapine 5-20 mg/day
- Quetiapine 200-800 mg/day
- Aripiprazole 10 -15 mg/day
- Ziprasidone 20-80 mg BID
- Anti-manic, anti-psychotic

Bipolar Depression

- 20% of Bipolar Depressive Episodes run a chronic course
- Mild depressive symptomatology may be successfully treated with CBT or IPT
- **Lithium**
  - Response rates from 64% to 100%. Level I (A) evidence
- **Antidepressants**
  - Level I (B) evidence.
  - Watch for flips (more common with tricyclics)
  - Use with concomitant mood stabilizer to avoid flips

Lamotrigine in Bipolar Depression

- Lamotrigine
- Level 1(A)
  - Sometimes added to lithium as mood stabilizer
  - It works better from the “bottom up”
  - Lithium and Epival work better from the “top down”

1st Line for Depression (2018 CANMAT)

- Quetiapine — Level 1
- Lurasidone + Li/DVP — Level 1
- Lithium — Level 2
- Lamotrigine — Level 2
- Lamotrigine (adj) — Level 2

2nd line Depression (CANMAT 2018)

- Divalproex Level 2
- SSRI's/Buproprion (adj) Level 1
- ECT Level 3
- Cariprazine Level 1
- Olanzapine-Fluoxetine Level 2

Continuation Phase of Treatment

- Continue with psychoeducation/counseling
  - Develop relationship
  - Helps compliance with meds—Very Important
  - Stay off Alcohol and drugs—Very Important
  - Deal with stressors—Stress Diathesis model applies

Drugs in Continuation Phase

- If Benzos were used, try to wean off
  - No evidence for them as prophylactic agents

- If Atypical Neuroleptics were used, gradually wean and discontinue after 2-3 months of stability, **unless:**
  - (1) persistent psychosis, or (2) adjunctive prophylaxis

CANMAT (2018)1st line, Propylaxis

- Lithium — Level 1
- Quetiapine — Level 1
- DVP — Level 1
- Lamotrigine — Level 1
- Asenapine — Level 2
- Quetiapine + Li/DVP — Level 1
- Aripiprazole +Li/DVP — Level 2
- Aripiprazole — Level 2
- Aripiprazole (OM) — Level 2

Therapy in Pregnancy

- **All** mood stabilizers are teratogenic
  - Risk vs. benefit
- Lithium lower risk (Ebstein's anomaly, 0.1%)
  - Tricuspid valve displacement
- If illness not that severe, consider planned pregnancy without meds
  - 4 week medication-free period pre-conception
- ECT, SSRI, Neuroleptics all lower risk in 1st trimester

Epival in Pregnancy

- Epival (sodium valproate) much more problematic
  - Neural tube defects may increase to 5%
  - Try to avoid in women of child bearing age, especially weeks 1-10.
- Can use folic acid 5 mg. PO OD
- Can do serial ultrasounds examining the neural tube

Lamotrigine in Pregnancy

- Cleft lip and palate
- Possible less teratogenic

Dosage in Pregnancy

- Post partum has >50% risk of an episode
  - Recommend re-start therapy after delivery

- **All** secreted through breast milk
  - Data suggests no immediate risk
  - No data regarding later behavioural effects
  - Speak to Motherisk or Womens Health Concerns about concerns surrounding breastfeeding

Disability Issues

- Stable bipolar is not disabling
  - Most people should hit their normal “life arc”, including working
  - Let patients know this!
- A minority of treatment resistant cases may require disability

MDQ: Mood Disorders Questionnaire

- Self report for bipolar
- 5 questions
  - 13 items on question 1

Please fill out your session evaluation now!

Complete a session evaluation one of two ways:

- FMF app
- Fmf.cfpc.c

Session #: S92

Session Name: Approach to Bipolar Disorder in Primary Care

YOUR FEEDBACK IS IMPORTANT TO US!