Approach to Bipolar Disorder

Dr. Jon Davine, MD, FCFP, FRCP©

VANCOUVER CONVENTION CENTRE

THE COLLEGE OF FAMILY PHYSICIANS OF CANADA

LE COLLÈGE DES MÉDECINS DE FAMILLE DU CANADA

Presenter Disclosure

Presenter: Dr. Jon Davine MD, FCFP, FRCP©

Relationships with financial sponsors:

- Any direct financial relationships, including receipt of honoraria: Trillium Health Partners, William Osler Health System, Peterborough FHT, Pri-Med Canada/Humber R. Hosp., McMaster U. CE, KW Family Medicine, Ont. Coll. Of Family Phys., Touchstone Institute, CME Away by Sea Courses

- Membership on advisory boards or speakers' bureaus: No

- Patents for drugs or devices: No

- Other: CAMH, Co-Editor of book, "Psychiatry in Primary Care"

Disclosure of Financial Support

This program has not received financial support

This program has not received in-kind support

Potential for conflict(s) of interest:
Dr. Jon Davine has not received payment/funding for this program

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

Bipolar Disorder

-
- **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

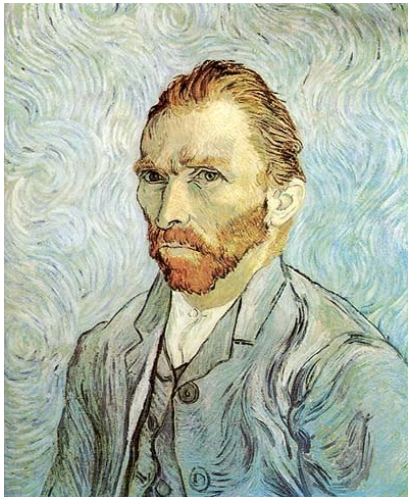
Cyclothymic

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

- Overall, 2-3% lifetime prevalence Bipolar Spectrum

Bipolar Disorder

- Mean age of onset - early to mid 20's
  - Peak age is 15-19
- 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

Acute Treatment of Mania

- Acute treatment duration = **2 to 10 weeks**

- Rule out organic
  - Cushing's
  - Thyroid
  - MS
  - Steroids
  - *antidepressants - controversy
  - Substance abuse

Psychoeducation

- **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

  - (CANMAT 2018 Bipolar Guidelines)

Lithium – Indications for 3 Phases

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

Lithium – What to do before starting:

- **Workup** – repeat every 6-12 months
  - ECG
  - CBC
  - TSH
  - Creatinine, ‘lytes, u/a
  - Ca
  - Pregnancy test if applicable

Lithium – follow up

- **Blood lithium levels**
- **12 hour trough**
  - 5-7 days after starting, and then 5-7 days after dosage changes
  - Get 2 therapeutic serum levels, then repeat q3-4 months.

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

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 - 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
- Levels
  - 350-700 µmol/L3

Lamotrigine – Indications

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

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, Bipolar 2, Depressed Phase

- **Family docs may be the first ones to make this diagnosis**
- **Always screen for hypomania when someone presents with a SIGECAPS depression**
- **Lamotrigine is approved for bipolar prophylaxis—Level 1A**
- **It is also Level 1A for bipolar depression. “ 2 birds…”**
- **It has less weight gain. People love this.**

Gabapentin, Topiramate

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

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

Atypical Neuroleptics in Bipolar Depression

- Quetiapine now approved for bipolar depression (CANMMAT)
- Level 1(A) evidence
- Also level 1(A) for mania and prophylaxis
- Recommend do metabolic screens q4monthly when on Quetiapine.
- LFT’s as hepatic metabolized

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:**
  - **Being used as mood stabilizer (Quetiapine XR)**

  - persistent psychosis (schizoaffective disorder)

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

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

Thank you!

Please fill out your session evaluation now!

#myfmf

FamilyMedicineForum

FamilyMedForum

FamilyMedForum