The Highs and Lows of Treating Bipolar Disorder

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Objectives

- Be prepared to prescribe and manage some common mood stabilizers
- Understand the importance of lithium as the gold-standard mood stabilizer, and increase your comfort with this important medication
- Be aware of other important aspects of managing bipolar disorder such as sleep hygiene, addressing substance use and limiting caffeine intake
- Understand the risks of prescribing traditional antidepressants, stimulants, steroids and dopamine agonists to patients with bipolar disorder
Disclosures

- I have no conflicts of interest to disclose.
- Off-label use of medications may be included in this presentation and will be identified as such. When off-label uses are referenced, they are based on evidence-based treatment recommendations and other supporting data.

Importance of the Diagnosis

- Screen every depressed patient for bipolar disorder
- Failing to identify bipolar disorder will result in ineffective treatment and increased morbidity and mortality
- Please refer to this writer’s presentation on bipolar diagnosis from 2014 for information on recognizing bipolar disorder
- Differential diagnosis includes: agitated depression, borderline personality disorder, post-traumatic stress disorder, attention deficit disorder, and stimulant intoxication
A sampling of mood stabilizers...

- We do not have time to review the complete list of mood stabilizers
- I have selected a few mood stabilizers based on their importance and utility in the PCP setting

- 3 categories of mood stabilizers
  - **Lithium**
  - Some anticonvulsants: valproic acid, carbamazepine, *lamotrigine*
  - All anti-psychotics: olanzapine, *quetiapine*, risperidone, ziprasidone, *aripiprazole*, asenapine, *lurasidone*, haloperidol. Some work better than others, and for different aspects of bipolar disorder (depressed v. manic v. mixed states)

Lithium (Lithobid, Eskolith)

- The gold standard of mood stabilizers, particularly for long-term use
- FDA indications: mania and maintenance treatment
- Under-used in the United States, mainstay of treatment in Europe
- More effective for mania than bipolar depression, but still effective for both bipolar and unipolar depression
- Number needed to treat (NNT) in mania is 4 (McIntyre 2015)
- Number needed to harm (NNH) by causing sedation is 27 (McIntyre 2015)
- Compared to the anti-psychotics, slower onset of action in acute mania (Cerimele 2013)
Lithium (Lithobid, Eskolith)

- More effective for “classic” slow-cycling bipolar, with prominent “pure manic” states. Not as good for mixed states
- Tends to be more effective on the young, who have had no or few antidepressant trials
- Per APA treatment guidelines, Lithium is the most effective antidepressant augmentation strategy for MDD, useful in up to 50% of anti-depressant non-responders (APA 2004)
- It is an excellent “hedge your bets” treatment approach if you suspect bipolar disorder, and also want to augment an antidepressant

Lithium: Dosing

- Start at 300 or 450 mg qhs
- Titrating up: increase the dose every 1-2 weeks as tolerated, by increments of 300 mg daily, getting a level 4-5 days after each dose increase
- For smaller patients, the mg/10 will roughly correspond to the blood level
  - Ex. 600 mg daily = 0.6 blood level
- If the goal is a low blood level (0.5-0.7), you can usually get away with qhs only dosing using extended release (CR), typically 450-900 mg qhs
- If side effects occur, consider BID dosing. Lithium has a long half-life. Increased tolerability is the rational for divided dosing
- If doses of greater than 1200 mg/day are not resulting in good levels, strongly suspect non-compliance. Think twice before increasing above 1200 mg/day
Lithium: Benefits

- Selling points for Lithium:
  - Less likely to cause weight gain than most other mood stabilizers, particularly at lower doses
  - Strong anti-suicide effects: 80% reduction in attempted and completed suicides (Maudsley 2015)
  - Most likely to promote long-term stability, fewer and less severe episodes
  - Promotes new neuron growth, protective of the brain. Lithium appears to reduce the risk of dementia (Kessing 2008)

Lithium: Benefits

- Selling points for Lithium:
  - Relatively inexpensive, no prior authorizations needed
  - “All natural,” it’s an elemental salt
  - Tolerability is often good when used at the lower end of the dosing range (APA 2004)
  - For lithium responders, results can be dramatic and life changing, particularly if you start treatment before the bipolar cycling becomes entrenched
Lithium: Patient Education

• Start with the selling points, and present it with conviction. If you don’t believe this is beneficial, the patient won’t either
• Before initiating lithium, warn and document risk of:
  • Thyroid: may cause hypothyroidism, which is occasionally irreversible even with discontinuation of the lithium, but correctable with thyroid hormone supplementation
  • Kidney: With long-term use, lithium may decrease the kidney’s ability to concentrate urine, over time creatinine may slowly rise. This does not happen suddenly, and may be corrected with a dose reduction if it does occur

Lithium: Patient Education

• Most common side effects: diarrhea, polyuria, nausea, mild weight gain, tremor. At the lower end of the dosing range, these are usually not present or are mild.
• Avoid dehydration, or rehydrating with only water. Sweating without replacement of sodium leads to lithium retention, and increased Li+ blood levels.
• Severe diarrhea, and resulting dehydration and electrolyte imbalances, can also cause lithium toxicity
• NSAIDs – see next slide
• Signs of lithium toxicity: confusion, severe tremor, ataxia, blurred vision, vomiting
Lithium: Interactions

- NSAIDs: warn and document discussion about NSAIDs increasing lithium level. Avoid NSAIDs if possible. If not possible, keep the NSAID dose the same every day, use a lower lithium dose, and check labs more often, especially with changes in NSAID dose.
- Ace inhibitors: Avoid in combination with lithium: unpredictably increases lithium level up to four-fold.
- Thiazide diuretics: Avoid in combination with lithium: unpredictably increases lithium level up to four-fold.

Lithium: Laboratory and Testing

- Order labs:
  - TSH (risk of hypothyroidism)
  - Creatinine (may slowly increase)
  - Calcium (risk of hyperparathyroidism resulting in hypercalcemia)
  - Lithium level (the broad therapeutic range is 0.4-1.2)
- Check labs approximately 12 hours after last dose, at least 4-5 days after last dose change.
- Ideally obtain baseline labs, after each dose adjustment, about 1 month after reaching a stead dose, then every 6 months, and or if concerning side effects are emerging. Remember lithium-induced hypothyroidism is difficult to distinguish from a shift towards depression.
- EKG is recommended for patients over 40 or with cardiovascular disease.
Lithium: Pregnancy and Breastfeeding

• Lithium is category D, but is the gold standard mood stabilizer in pregnancy
• Category D because of Ebstein’s anomaly. If used during cardiac formation, it increases the total risk of birth defects from 3% of pregnancies to 3.1% or 3.05% or less (Yonkers 2004)
• Continuation of an effective mood stabilizer during pregnancy is recommended because the risk of a recurrent mood episode during pregnancy is 71%, when an effective mood stabilizer is discontinued. Risk of post-partum psychosis is very high in this population (Viguera 2007)
• Relatively high transmission of lithium into breastmilk makes breastfeeding ill-advised for woman on more than a very low dose

Lamotrigine (Lamictal)

• Indicated for maintenance, not acute treatment. Demonstrated efficiency is for bipolar depression, little to no protection from mania or mixed states
• It is both a “do less harm,” and a “do less good” option. In treatment for acute depression
• NNT=12, NNH (sedation)=42 (Srivastava 2011)
• A relatively weak and slow, but highly tolerable anti-depressant mood stabilizer
Lamotrigine (Lamictal)

- Generally start at 25 mg daily and increase the dose by 25 mg daily each week, aiming for a target dose of approximately 200 mg daily. This is lower than the typical neurology target dose of 400 mg per day. Keep this in mind when reviewing the list of side effects, which usually refer to this higher target dose.
- Requires approximately 2 months to titrate to a therapeutic dose.
- Does not require laboratory monitoring, but checking levels is sometimes helpful.

Lamotrigine (Lamictal)

- Higher levels of estrogen, such as with oral contraceptive pills or during pregnancy, increase hepatic metabolism of lamotrigine, requiring dose increases, and causing some unpredictability. Blood level monitoring can assist with this, especially during pregnancy.
- Important drug-drug interactions with valproic acid and carbamazepine.
- Risk of Steven Johnson rash, approximately 1 in 5000. Warn of this and document the conversation.
- Very little risk of sedation or weight gain.
- Relatively safe in pregnancy.
Anti-psychotics

- As a class:
  - Relatively fast acting and do not require monitoring levels
  - Useful for mixed states and rapid cycling (contrast to lithium)
  - Tend to cause weight gain and sedation
  - Recommended baseline and periodic monitoring of: weight, lipids (particularly attend to triglycerides), and blood sugar. Suggested frequency of every 6-12 months
  - Also protect from and treat psychotic sx, which are a common part of bipolar disorder
  - This class is used in pregnancy and breastfeeding; haloperidol, quetiapine, risperidone and olanzapine have the most safety data available

Anti-psychotics: Patient Education

- Discuss and document risk of:
  - Metabolic side effects
  - Extrapyramidal side effects (EPS): dystonia, akathisia, parkinsonian sx, and tardive dyskinesia
  - Counsel on the need for regular exercise and a healthy diet
Quetiapine (Seroquel)

- Indicated for the treatment of: mania, bipolar depression, maintenance: a useful triple approval
- In acute mania NNT=6 NNH=9
- In acute depression NNT=6 NNH=5 (McIntyre 2015)
- Start at 25 or 50 mg qhs, and titrate up by no more than 50 mg per day. Effective mood stabilizer dose is 300 mg daily or more. Sleep is usually improved at much lower doses
- Some anti-anxiety effects (off-label use), is sometimes used in small doses as a PRN

Quetiapine (Seroquel)

- Very sedating, especially upon initiation. I suggest qhs dosing, although BID dosing is the textbook regimen
- Risk of postural hypotension is 7% (per package insert), and limits the rate of increase of the dose
- Substantial appetite stimulant, notorious for causing weight gain
- More likely to cause metabolic side effects than EPS
- Considered relatively safe in pregnancy and breastfeeding
Aripiprazole (Abilify)

- Indicated for the treatment of: acute treatment of manic and mixed states, NO indication for bipolar depression or maintenance
- Also indicated for the augmentation of antidepressants, useful to “hedge your bets” in cases of diagnostic uncertainty
- A partial dopamine agonist, approximately 70% dopamine receptor binding
  - Somewhat gentler side effect profile, “a lighter touch”
  - Somewhat less effective than some of its cousins
- In acute mania: NNT:5 NNT:9 (McIntyre 2015)

Aripiprazole (Abilify)

- Start at 2 mg daily, qam or qhs.
- 2-10 mg daily are common doses for antidepressant augmentation in MDD
- 10-30 mg daily is common for bipolar disorder
- Most common initial side effect is akathisia. Later, metabolic side effects
- Not very sedating
- Not well studied in pregnancy and breastfeeding, but does not appear teratogenic and is sometimes used with a history of a good response
Lurasidone (Latuda)

- Indicated for the treatment of: acute bipolar depression
- A relatively new member of this family, other indications may be forthcoming
- Occupies the unique position of working fairly effectively for acute bipolar depression, while not causing pronounced sedation or weight gain
- In acute bipolar depression  NNT: 5  NNH: 15  (McIntyre 2015)
  - This is a very favorable ratio

Lurasidone (Latuda)

- Needs to be taken with dinner or a large snack for optimal absorption
- Dosing range: 40-120 mg daily. Higher doses (120 mg) significantly increase the risk of akathisia and restless legs, without a substantial increase in efficiency
- Will not be approved by Medicaid without trials of 2 other atypical anti-psychotics
- A new medication, so significant data available on safety in pregnancy and breastfeeding
Polypharmacy

- Unfortunately, polypharmacy is the rule rather than the exception
- Combine medications from different categories and with coverage for both depression and mania, tailor this to the patient’s predominant symptoms
- Suggested pairings:
  - Lithium and lamotrigine
  - Lithium and an antipsychotic with antidepressant efficiency
  - Lamotrigine and an antipsychotic with anti-manic efficiency
- If lithium is tolerated, even at a low dose, consider including it for long term stability and episode prevention

A Word of Caution...Antidepressants

- Use of an antidepressant without a mood stabilizer is strongly discouraged in the treatment of bipolar disorder
- Possible outcomes of an “unopposed antidepressant”:
  - Ineffective, this is the most likely outcome
  - Triggers mania
  - Triggers mood instability in the form of mixed states and rapid cycling
- Some postulate that exposure the antidepressants makes bipolar less responsive to mood stabilizers, especially lithium
- Antidepressants are wildly overused in bipolar disorder, including by psychiatrists
  (Cerimele 2013)
A Word of Caution...Antidepressants

- There is only a small minority of patients with bipolar disorder who respond effectively to antidepressants. They are hard to identify and easily confused with patients who have a fast hypomanic response to antidepressant initiation (actually a sign of mood destabilization).
- I advise only considering adding an antidepressant once the patient is well-established on a mood stabilizer, you are monitoring closely, and if you have a legitimate data-driven treatment target, such as:
  - adding an SSRI to treat comorbid anxiety
  - adding bupropion for smoking cessation
  - adding a tricyclic for pain syndromes

A Word of Caution...Other medications

- Stimulants – avoid use in bipolar unless well stabilized on mood stabilizer. If manic sx emerge, discontinue.
  - Modafinil (Provigil): the exception to the rule. As an adjunct to a mood stabilizer, it does not seem to exacerbate or destabilize bipolar disorder and improves energy (Gross 2013)
- Dopamine agonists – such as pramipexole (Mirapex) and ropinirole (Requip) used to treat RLS, can substantially destabilize bipolar disorder and trigger mania and psychotic sx. Remember anti-psychotics are dopamine antagonists
- Steroids – Can trigger mania, depression and psychosis in patients with bipolar. Use caution, minimize exposure, and coordinate with the psychiatric prescriber
Vignette #1

Mr. A is a 35 year old man who has been struggling with an irritable and depressed mood, sleeping only about 4 hours a night, has swirling rapid and distressing thoughts, and angry outbursts for the last 2 weeks. He really can’t stand this any more, especially not being able to sleep, and feeling so edgy and anxious.

Because you are a careful and astute clinician, you do not assume this is an agitated depression and do not start him on an antidepressant.

Vignette #1, part A

With additional questioning you learn that he has had several other episodes like this in the past, and they are distinctly different from his normal mood. He has been spending a lot of money lately, is very interested in sex, and feels more bold than usual. His father has bipolar disorder. He has also had episodes of low-energy depressions. He is not using stimulants, drugs, or overusing caffeine. No medical problems.

What would you call this?

What medication(s) would you consider and why?
Vignette #1, part B

- What medication(s) would you consider if he is overweight and has a strong family history of diabetes?

Vignette #2

- Mr. B is a 48 year old man who was previously diagnosed with bipolar disorder, but stopped seeing his psychiatrist several years ago and has not been on any medication recently. He is beginning to have insomnia, and wants your help in heading off this episode.

- He describes a history of severe manic episodes, psychiatric hospitalizations, resulting divorce, and extreme debt. His manias are marked by euphoria and irritability, nearly no sleep for days on end, risk taking, and tend to last 1-2 months.

- He is overweight and has mildly elevated blood sugar and cholesterol.

- What medication(s) are you considering and why?
Ms. C is a 21 year old college student who has been struggling with low mood for the last 4 months. Her energy is very low, she sleeps about 12 hours a day and has been gaining weight, which she feels very self-conscious about.

Your careful history reveals that about 5 months ago, she felt much better. She had a month during which she only needed about 5-6 hours of sleep a night, could concentrate on her studies for hours and hours with no difficulty, and was partying often but still got A’s. “Everything felt much easier then, I wish I could go back to that.” People told her she was talking fast then. She does not think this caused her any problems.

Vignette #3

• What do you need to rule out?
• What is your presumptive diagnosis?

• She was started on sertraline 50 mg at the college health center 2 months ago, but she doesn’t feel like it’s doing any good.
• What medications interventions are you considering? Why?
Ms. D is an 18 year old senior in high school. She has struggled with depression, anxiety, mild mood lability and insomnia periodically throughout her teen years. There is no clear trigger for these mood episodes. She has had unsuccessful trials of fluoxetine, bupropion, and venlafaxine. Her insomnia has been notably unresponsive to sleep aids. There is a family history of possible bipolar disorder. She is currently taking low dose venlafaxine.

What diagnoses are you considering?

Assuming you cannot obtain a clear history of a manic or hypomanic episode, what medications are you considering?

She presents to you 5 years late, on the medication you prescribed, at 9 weeks gestation.

What advice do you have for her?
Other Treatment Approaches

• Good sleep hygiene
  • It is a key aspect of Interpersonal and Social Rhythm Therapy (IPSRT), which is a therapy approach shown to decrease recurrences of bipolar episodes
  • Sleep disruption leads to mood episodes, and mood episodes leads to sleep disruption
  • Correcting sleep problems is relatively “low hanging fruit” in treating bipolar disorder and may lead to recovery even in the absence of a clear response to a mood stabilizer

Other Treatment Approaches

• Minimize stimulants
  • Excessive caffeine, and use of stimulants (both prescription or illicit) can be tremendously destabilizing
• Address substance abuse issues
  • High co-morbidity with bipolar disorder
  • Predictive of poor outcomes
  • Treatable
Other Treatment Approaches

- Assist the patient in identifying his/her personal “red flags”, early signs of a manic or hypomanic episode: such as sleep problems, urges to spend more money, “going out” more, etc.
  - Encourage the patient and social supports to monitor for this, and alert you immediately
  - Encourage the patient to keep a daily symptom and sleep log
  - It is much easier to treat a manic episode before it is full-blown, and can save the patient a job, a marriage, or a debt. We have many good anti-manic medications to choose from, and treatment should not be delayed

Role of the Primary Care Provider

- First, do no harm. Specifically, don’t start anti-depressants without screening for bipolar disorder first. Avoid treating bipolar with antidepressants
- Early recognition and initiation of treatment
- Consultation when unable to connect to a specialist immediately
- Referral to psychiatry. This is ideal for bipolar disorder, but may be delayed, refused, or intermittently unavailable
- Supporting and encouraging adherence to a mood stabilizer
- Triaging emergencies
- Managing comorbidities
Realistic Treatment Expectations

- This is an incredibly difficult condition to treat, even for experts
- Mood stabilizers are far from perfect; they have many side effects and inconsistent results. Nonetheless, they are the best we have
- A partial response to a medication is a success. A complete resolution of symptoms is rare. Aim for less frequent, less severe and less prolonged episodes
- This is a chronic disease. A successful treatment consists of the patient and doctor finding the most helpful medication(s), the patient accepting the need to stay on the medication(s), and the patient learning to maintain a healthy lifestyle that minimizes mood episode triggers

Questions?

Thank you for your kind attention to this important illness
References

- American Psychiatric Association: Practice Guidelines for the Treatment of Psychiatric Disorders. 2004
References