BIPOLAR DISORDER

DIAGNOSIS AND TREATMENT INITIATION IN PRIMARY CARE

OBJECTIVES

- -Accurately recognize BP disorders in a diverse set of patients
- -Initiate a safe evidence-based treatment in a variety of common primary care populations
- -Help your patients achieve rapid and sustained symptom remission

HIGHLY RECOMMENDED RESOURCES

- Neuroscience Education Institute
  - App for smart phone
  - Master of Psychopharmacology Certificate
  - Extraordinary website with rich learner friendly content
- The florida best practices guideline
  - https://floridabhcenter.org/wp-content/uploads/2021/02/Bipolar-Disorders_Adult-Guidelines-2019-2020.pdf
- The south shore harvard algorithms
  - https://psychopharm.mobi/algo_live/#

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- "Bipolar disorder (BD) is a severe, lifelong group of disorders with an estimated prevalence of approximately 2%. ***Approximately three-quarters of individuals with BD exhibit features of the disorder prior to the age of 25*** highlighting the neurodevelopmental aspects of the disorder as well as the importance for screening and timely diagnosis, especially in younger populations presenting in clinical settings with clinically significant depressive and anxiety symptoms. Misdiagnosis representing a conflation of both false positives and false negatives continue to be one of the greatest unmet needs in BD. The consequences of missed and delayed diagnosis are protean and include the accumulation of comorbidities (e.g., obesity, substance abuse), unmitigated suicide risk, erroneous treatment selections, human suffering, and increased morbidity."

DSM 5 TR: BIPOLAR ONE AND TWO

- To be diagnosed with bipolar 1 disorder, **a person must have experienced at least one episode of mania or hypomania**. To be considered mania, the elevated, expansive, or irritable mood must last for at least one week and be present most of the day, nearly every day.
- Bipolar 2 disorder is **a type of bipolar disorder characterized by major depressive episodes and hypomanias, which are elevated moods that don't meet the threshold for manias**. While manic episodes are often severely debilitating, hypomanic episodes (sometimes called “baby” manic episodes) don’t usually impair daily living.

MANIC SYMPTOMS?

- **Mania/Hypomania**

- Three or more of the following symptoms need to be present for a diagnosis of mania.
- Inflated self-esteem and grandiosity – the patient feels they are unusually important or talented
- The patient may have a decreased need for sleep and state that they feel rested and energetic even when they have only slept for three hours.
- They are more talkative than usual and may speak in a hurried fashion. This will make their speech sound confused.
- Flight of ideas (“my thoughts are racing!”)
- Easily distracted by irrelevant external stimuli (unlike ADHD but does not occur all of the time)

MANIC SYMPTOMS?

- During manic episodes, the patient might also be engaged in activities that have high stakes or painful consequences. For instance, excessive substance use. Indiscriminate sexual activity, make risky business investments, or go on uncontrolled buying sprees.
- Mania and hypomania share the same symptoms, but mania is more extreme.
- The difference is in the length of time an individual experiences the symptoms.
- Three or more of the above symptoms need to be present for at least 7 days for it to be diagnosed as mania.
- If the symptoms last for 4 consecutive days, it is considered hypomania.
- In both mania and hypomania, the symptoms are not related to or better explained by substance use, schizoaffective disorder or do not overlap with other mood disorders, such as schizophrenia, delusional disorder, or another medical condition.

BIPOLAR II UPDATE FROM THE DSM 5-TR

Bipolar II disorder, requiring the lifetime experience of at least one major depressive episode and at

least one hypomanic episode (but no history of mania), is **no longer thought to be a less severe condition than bipolar I disorder, largely because of the burden of depression in bipolar II disorder and because the instability of mood experienced by individuals with bipolar II** disorder is often accompanied by serious impairment in work and social functioning.

WHAT IF THEY HAVE DYSREGULATED MOODS, BUT DO NOT MEET CRITERIA FOR BP I OR BP II?

The diagnosis of cyclothymic disorder is given to adults who experience at least 2 years (for children, a full year) of both hypomanic and depressive periods without ever fulfilling the criteria for an episode of mania, hypomania, or major depression."

WHAT WE THINK IT LOOKS LIKE

WHAT IT OFTEN LOOKS LIKE

AND THIS TOO:

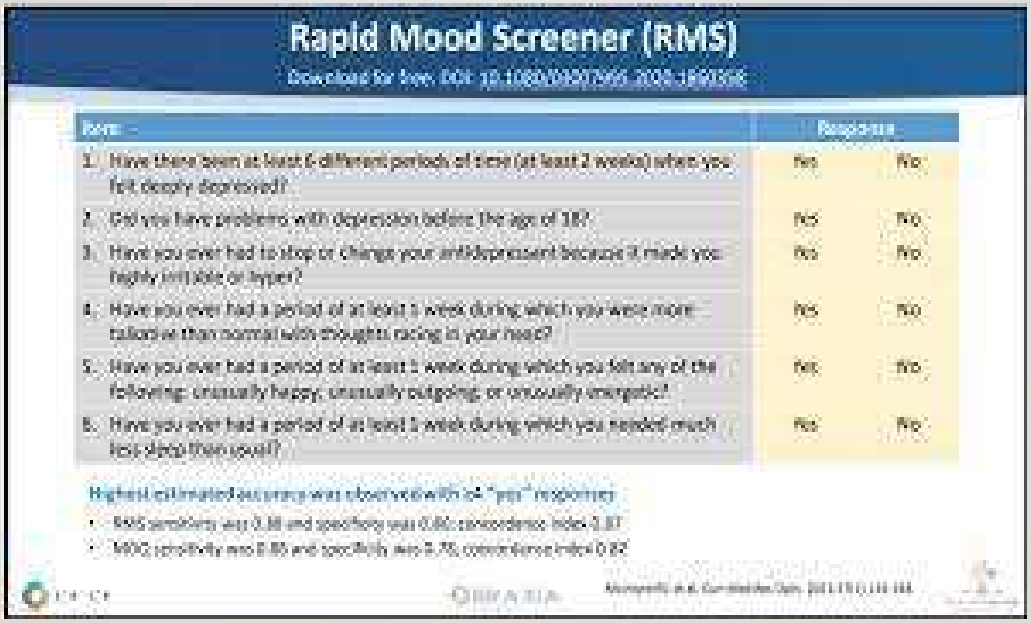
WHAT DOES BP REALLY LOOK LIKE?

- People with BP tend to be found everywhere, but particularly on the extreme ends of the social strata, they can be well educated professionals, high achievers in business and the arts, but it is also very commonly diagnosed in the homeless and incarcerated populations. 2.3 million Americans - Bipolar Disorder
- 5-10% of primary practice patients will have Bipolar Disorder diagnosis at some time American Psychiatric Association (2013)

USUALLY SEEK HELP DURING THE DEPRESSIVE PHASE OF THEIR ILLNESS

Patients with BP often present to you during the depressive phase of their illness, and it is difficult for them to remember a time when they felt better- but if they truly have BP, they usually have not responded well to the usual first line medications for depression (SSRI, SNRI), and sometimes it makes them worse.

RAPID MOOD SCREENER

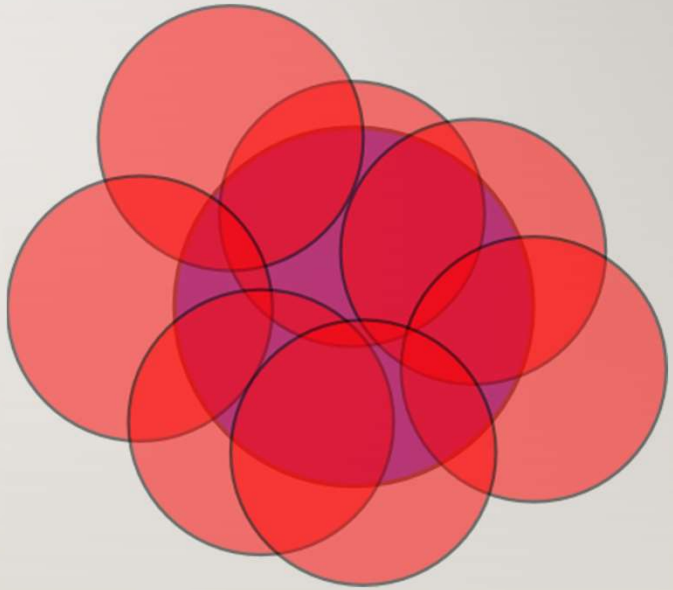


RAPID MOOD SCREENING INSTRUMENT: VALIDATED PATIENT COMPLETED 6 ITEM SCREENING TOOL

- 1. Have there been at least 6 different periods of time (at least 2 weeks) when you felt deeply depressed?
- 2. Did you have problems with depression before the age of 18?
- 3. Have you ever had to stop or change your antidepressant because it made you highly irritable or hyper?
- 4. Have you ever had a period of at least 1 week during which you were more talkative than normal with thoughts racing in your head?
- 5. Have you ever had a period of at least 1 week during which you felt any of the following: unusually happy; unusually outgoing; or unusually energetic?
- 6. Have you ever had a period of at least 1 week during which you needed much less sleep than usual?

IS IT ONLY BIPOLAR?

- Usually, patients with BP also experience other psychopathology- such as ADHD, an anxiety disorder, autism spectrum disorder, personality disorders, sleep disorders, eating/feeding disorders, and substance use disorders(60% comorbid). Indeed, many of the genetic markers, and anatomical abnormalities associated with BP are identical to those found in other common mood/cognitive disorders.



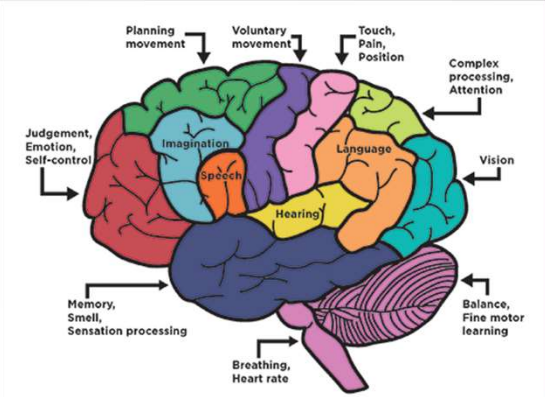
THE NEUROSCIENCE OF BIPOLAR DEPRESSION

WHAT DO WE THINK WE KNOW?

List of anatomical/physiological explanations for bipolar

- Anatomical mapping of bipolar disease, has not been particularly fruitful….however:

- Areas of the brain associated with impulsivity, emotional regulation and executive function have all been indicated.



LIST OF DRUG CLASSES SUPPORTED BY EVIDENCE (RELEVANT TO PRIMARY CARE)

- Lithium
- Antipsychotics
- Anticonvulsants

LITHIUM

- Target levels of 0.7-1.1
- Monitor levels
- Instruct patients to avoid dehydration
- Routinely monitor renal and thyroid function
- Known risks for pregnancy, but risks of relapse may justify continuing, consult with expert and document.

ANTIPSYCHOTICS

- Aripiprazole, Ziprasidone Risperidone
- Olanzapine, Haloperidol, Lurasidone, cariprazine
- USE AIMS SCEENER TO SCREEN FOR MOVEMENT DISORDERS LIKE DRUGE INDUCED PARKINSONISM AND TARDIVE DYSKINESIAS- DOCUMENT IT!

ANTICONVULSANTS

- Lamotrigine 25mg (follow titration instructions!) (low risk in pregnancy, do risk/benefit analysis, no help in acute mania, evidence strongest for prevention of recurrent depression episodes)
- Divalproex (Depakote) (no go for pregnancy, monitor LFTs, and drug levels)
- Carbamazepine (Tegretol) (no go for pregnancy, monitor LFTs, and drug levels)
- Oxcarbazepine (inadequate data for pregnancy, do risk benefit analysis)

FLORIDA MEDICAID GUIDELINES FOR TREATMENT INITIATION FOR BIPOLAR DEPRESSION (WITH APPROXIMATE RETAIL PRICING)

- Level 1 Initial treatment: Lurasidone or cariprazine monotherapy* *Note: Lurasidone and cariprazine have better metabolic profiles than quetiapine. ($1300-1400)
- Lamotrigine monotherapy ($65) (follow gradual tapering guidelines!)
- Quetiapine monotherapy for BP II ($75)
- Lithium monotherapy ($30)
- Lurasidone or lamotrigine** adjunctive to lithium or divalproex if index agent (lithium or divalproex) has been previously prescribed and optimized.
- Do not utilize conventional antidepressants (e.g., SSRIs, SNRIs, TCAs, MAOIs) as a first, 2nd or 3rd-line therapy.

FLORIDA MEDICAID GUIDELINES FOR TREATMENT INITIATION FOR BIPOLAR DEPRESSION

- **2nd line treatment:**
- Divalproex + lurasidone
- Olanzapine + fluoxetine (bipolar I disorder) *Note: Tolerability limitations include weight gain and metabolic concerns.
- Two (2) drug combination of Level 1 medications but NOT TWO antipsychotic medications. *Note: Efficacy limitations, relatively few positive randomized controlled trials.
- **Third Line Treatment:**
- Electroconvulsive therapy (ECT) *Note: Consideration is merited due to clinical need, (catatonia, psychosis, suicidality) despite even greater efficacy/tolerability limitations than Level 1 and 2 treatments.

CASE # ONE MR. MONEY

- Busy entrepreneur, several active businesses, treated for depression with Cymbalta for 20 years, but never really felt he was able to achieve remission, save for little windows of clarity that would happen just for a few weeks each year. We tried a dose increase to 40mg then didn't need to sleep, family worried, purchased several new businesses, which seem risky to them. It is not in his character to be acting like this.
- Depression not well managed until now, now he feels great and he didn't want to stop feeling this way.
- What would you do to help this guy? What happened….

CASE # 2 HOT MESS HANNA

- Family hx of disruptive mood, trauma and severe substance abuse
- Recovering Meth-addict
- Several incarcerations, getting into trouble, dropped out of school at a young age
- Multiple sexual partners and unprotected sex, being treated now for STI.
- Getting married… really wants this one to work
- What would you do to help this gal?
- Moods are much better now, able to organize her life, and had a successful wedding
- Now she wonders if she still needs medication…… and her family, who are all bipolar are uncomfortable with her "normal" life and want her to stop taking medications.

PSYCHOSOCIAL SUPPORT

- Normalize experiencing regular moods
- Identify and treat co-morbidities
- Encourage patient to set and keep personal goals
- As they progress in life help them adjust to new more constructive social group and every day stressors of employment and interpersonal drama
- Frequently affirm their efforts and contrast their current troubles with the more severe and dangerous troubles they endured while unmedicated.

GENERAL ADVICE FOR LIVING WELL WITH MANIC/HYPOMANIC SYMPTOMS

- Learning about the link between Bipolar Disorder and impulsive choices:
  - Drugs, Alcohol, sex, spending money, arguing, fighting, school/work refusal
- Practicing slow down techniques (e.g., mindfulness; stop, think, and act).
- Working on relaxation and problem solving skills.
- Identification of hypomanic thoughts that lead to impulsivity
- Avoid financial decisions, drugs and alcohol, relationship decisions, confrontation, and credit card usage.
- Rule of “2” – checking with 2 family members/friends before engaging in these activities.

LOOK OUT!

- First manifested in late adolescence or early adulthood generally
- Some manifested in childhood:
- Poor prognosis
- More likely to rapid cycle with conduct problems and substance abuse
- Treatment important to preserve nuerological functioning-
- Suicide – up to 5-10% of those with Bipolar Disorders

- www.nimh.gov

ACUTE SEVERE BIPOLAR MANIA (USUALLY ER PRESENTATION)

- Lithium* or divalproex* + aripiprazole, asenapine, quetiapine, or risperidone
- Electroconvulsive therapy (ECT) is recommended if medical emergency/patient welfare at risk and pharmacotherapy is insufficient. Per Florida Best Practice Guidelines
- Commonly used agents
- Haloperidol Immediate release 5-10mg IM
- Lorazepam (acute adjunctive only) 1-2mg IM
- Ziprasidone 10-20mg IM
- Olanzapine 10mg IM
- Aripiprazole 9.75mg IM

ACUTE MODERATE BIPOLAR MANIA (MAY PRESENT IN PRIMARY CARE)

• Lithium	600-1200mg/day*
• Valproate	1200-3000mg/day*
• Aripiprazole	15-30mg/day
• Quetiapine	400-800mg/day
• Risperidone	2-6mg/day
• Ziprasidone	80-160mg/day
• Haloperidol	5-20mg/day
• Lorazepam	10mg/day

BIPOLAR DISORDER- MAINTENANCE CONSIDERATIONS

- Patient concerns: side effects, treatment dependence, maintaining independence and medication costs
- **Pregnancy:**
- Assess risks of taper verses continuation of therapy
- Avoid Valproate, Carbamazepine, and when possible Lithium
- **Older patients:**
- Re-evaluate treatment plan based on risk factors for new co-morbidities- and document justification to continue standard therapy, closely monitor

Table 1. Current first-line and second-line options for the treatment of acute mania.

	Level of evidence and recommended dosages[a]				Safety and tolerability concerns			
	Acute mania	Recommended dose (mg/day)[b]	Maintenance after mania		Acute		Maintenance	
			Prevention of mania	Prevention of depression	Safety concerns	Tolerability concerns	Safety concerns	Tolerability concerns
First-line treatments[c]								
Lithium	●	600–1200 (serum level 0.6–1.0 mmol/l or mEq/l)	●	●	○	○	◕	◕
Divalproex[d]	●	1200–3000 (serum level 75–150 mg/l)	◖	◔	○	○	◕	○
Aripiprazole	●	15–30	◔	-	○	○	○	○
Paliperidone	●	6–12	◔	-	○	○	○	◕
Risperidone	●	2–6	▪	-	○	○	○	◕
Asenapine	●	10–20	◔	◔	○	○	○	○
Olanzapine	●	10–20	●	●	○	◕	●	◕
Quetiapine	●	400–800	●	●	○	◕	◕	◕
Cariprazine	●	3–12	-	-	○	○	○	○
Aripiprazole + Li/DVP[d]	◔	*	◔	-	○	◕	◕	◕
Risperidone + Li/DVP[d]	●	*	▪	-	○	◕	●	◕
Asenapine + Li/DVP[d]	◔	*	▪	-	○	◕	◕	○
Olanzapine + Li/DVP[d]	●	*	▪	▪	○	◕	●	◕
Quetiapine + Li/DVP[d]	●	*	●	●	○	◕	●	◕
Second-line treatments[b]								
Carbamazepine[d]	●	600–1200 (serum level 4–15 mg/l)	◔	◔	◕	○	◕	◕
Haloperidol	●	5–20	▪	▪	○	◕	●	◕
Ziprasidone	●	80–120	▪	-	◕	◕	◕	○
Lithium + DVP[d]	◖	*	◖	-	○	◕	◕	◕
ECT	◖		▪	▪	○	◕	○	◕

Abbreviations: DVP, divalproex; ECT, electroconvulsive therapy; Li, lithium.

DVP divalproex, *ECT* electroconvulsive therapy, *Li* lithium.

[a]Strength of evidence base for the efficacy of agents used to treat mania: ● level 1 evidence: meta-analysis with narrow confidence interval or replicated double-blind (DB), randomized controlled trial (RCT) placebo or active-controlled (*n* ≥ 30 in each active treatment arm); ◔ level 2 evidence: meta-analysis with wide confidence interval or one DB RCT, placebo or active-controlled (*n* ≥ 30 in each active treatment arm); ◖ level 3 evidence: at least one DB RCT placebo or active-controlled (*n* = 10–29 in each active treatment arm) or health system administrative data; ▪ level 4 evidence: uncontrolled trial, anecdotal reports or expert opinion; ● level 1 *negative* evidence; ◔ level 2 negative evidence; ◖ level 3 negative evidence; ▪ level 4 negative evidence; -: no data; ○ limited or minor impact on treatment selection; ◕ moderate impact on treatment selection; ● significant impact on treatment selection.

[b]Doses are reported as per studies.

[c]Treatments are listed by drug class: mood stabilizers, antipsychotics and combination treatments. In each subsection, the recommendations follow a hierarchical order (i.e. lithium before divalproex, aripiprazole before paliperidone, etc). Although monotherapies are listed above combination therapies in the hierarchy, polytherapy may be indicated as the best choice in patients with severe manic episodes and/or a previous history of partial response to monotherapy.

[d]Divalproex and carbamazepine should be avoided in women of childbearing age.

[e]same recommended doses as monotherapy for each individual treatment.

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