UW PACC
Psychiatry and Addictions Case Conference
UW Medicine | Psychiatry and Behavioral Sciences

LITHIUM FOR BIPOLAR MANIA IN THE PRIMARY CARE SETTING

MADISON KORENKIEWICZ, DNP, ARNP, PMHNP-BC

SARAH KIM, DNP, ARNP, PMHNP-BC, CNL

UW ADVANCED PRACTICE PSYCHIATRIC PROVIDER FELLOWS

UW Medicine
UW SCHOOL OF MEDICINE

Integrated Care Training Program
UW Psychiatry & Behavioral Sciences

project ECHO

SPEAKER DISCLOSURES

- ✓ Any conflicts of interest?
  - None

PLANNER DISCLOSURES

The following series planners have no relevant conflicts of interest to disclose; other disclosures have been mitigated.

Mark Duncan MD
Rick Ries MD
Kari Stephens PhD
Barb McCann PhD
Anna Ratzliff MD PhD
Betsy Payn MA PMP
Esther Solano
Cara Towle MSN RN

UW PACC

OBJECTIVES

1. Review DSM-5TR criteria of mania.
2. Describe dosing strategies of lithium in bipolar mania and maintenance.
3. Describe monitoring of lithium for initiation and maintenance.
4. Discuss management of side effects of lithium.

UW PACC

CASE STUDY

- Patient is a 23-year-old female, presenting to her PCP for a follow-up about mental health
- **Mood/Anxiety:** “emotional roller coaster” for the past 3 months. Also reports insomnia, difficulty with concentration, restlessness, and anxiety. Has been feeling short-tempered and arguing with her parents more lately. Also reports chronic low self-esteem and excessive worries.
  - Denies SI; no history of suicidal thoughts/attempts
- **Psychosis**: Denies AVH. However, does endorse vague feelings that someone might be after her.
- **Substance Use**: Denies
- **Recent stressors**: Graduated from college, started grad school but was struggling and decided to leave the program. Recently moved back with her parents and started working at a school district.
- **Psychiatric History**: one voluntary hospitalization for 5 days at age 18 d/t similar symptoms after returning from a trip to Korea; diagnosed with anxiety and was not started on any medications.
- **No known family history of psychiatric or substance use issues**
- **No previous medications trials**

WHAT DO YOU THINK IS GOING ON?
ANYTHING YOU'D LIKE TO KNOW MORE ABOUT?

CASE STUDY- CONTINUED

Mom was also present during the visit

- Described patient's hospitalization at age 18 as a "psychotic break" with irrational behavior, though got better and graduated college
- Current symptoms are similar to previous episode, particularly with insomnia, restlessness, poor concentration, emotional lability, and irritability

PCP suspects possible new diagnosis bipolar and started 2mg of aripiprazole

Referrals

- Psychiatry for diagnostic clarification
- Counseling with the BHIP care manager for anxiety and depression

UW PACC

CASE STUDY- CONTINUED

Appointment with Psychiatry

- Patient did not tolerate aripiprazole and parents opted to stop it.
  - Helpful for anxiety, but caused worsening mood, sedation, and flat affect.
- She presented with **anxiety** (GAD-7: 12), **irritability** (frequent arguments with parents), feelings of **low self-worth**, **poor concentration**, **fatigue** (sleeps 6 hours/night), frequent **rumination** about an ex-boyfriend, and increased **impulsivity** (sneaking out during the night, having a one-night stand, and reaching out to old friends more)
- No grandiosity or abnormally elevated mood; no AVH; no suicidality
- Psychiatry started her on sertraline 25mg daily for GAD and adjustment disorder

Follow-up appt 2 weeks later: mood, irritability, fatigue, sleep, and anxiety have improved!

Sertraline was increased to 50mg daily

UW PACC

CASE STUDY- CONTINUED

One week later

- Patient contacted her BHIP care manager and reported new suicidal ideation, depression, and poor sleep. Provider recommended stopping sertraline.

1-2 weeks after stopping sertraline

- Patient presented to her care manager appearing disheveled and reporting that she is constantly fighting with her parents. Also lashed out and aggressively cursed at a friend. Quit her job at the school district.
- Reports difficulty sleeping
- Increased forgetfulness and racing thoughts
- Spending a lot of money and misplacing the things she bought
- Appears tangential, rapid pressured speech, irritable, easily distracted, and deflective of her symptoms.
- Increased impulsivity- tried to exit a moving car 3x due to feeling angry at her parents.

BIPOLAR I - MANIC EPISODE (DSM-5TR)

- A distinct period of abnormally and persistently elevated, expansive, or irritable mood **AND** increased activity or energy
- Lasting ≥ 1 week, most of the day, nearly every day

- Any duration if hospitalization is necessary

UW PACC

MANIC EPISODE (DSM-5TR)

≥ 3 of the following symptoms are also present to a significant degree (≥ 4 if the mood is only irritable):

- ↑ Self-esteem or grandiosity
- ↓ Sleep
- ↑ Rapid, pressured speech
- ↑ Racing thoughts/flight of ideas
- ↑ Distractibility/poor concentration
- ↑ Increased activity or psychomotor agitation
- ↑ Impulsivity, risk-taking behaviors

- Causes severe impairment in functioning or has psychotic features
- The episode is not attributable to the physiological effects of a substance or another medical condition
  - **NOTE**: If a full manic episode emerges and persists at syndrome level beyond physiological effect of antidepressant/ECT treatment → **mania**

UW PACC

PATIENT MANIA QUESTIONNAIRE (PMQ-9)

Patient Mania Questionnaire-9 (PMQ-9)

Over the past week, how often have you …	Not at all	Several Days	More Than Half of Days	Nearly Every Day
1. Had little or no sleep, and still felt energized	0	1	2	3
2. Felt easily irritated	0	1	2	3
3. Felt overactive	0	1	2	3
4. Acted impulsively or done things without thinking about consequences	0	1	2	3
5. Felt sped up or restless	0	1	2	3
6. Been easily distracted	0	1	2	3
7. Felt pressure to keep talking or been told by someone you are more talkative	0	1	2	3
8. Felt argumentative	0	1	2	3
9. Had racing thoughts	0	1	2	3

- Used to assess and monitor manic symptom severity
- **NOT** intended for screening
- Bipolar screeners
  - CIDI
  - MDQ
  - RMS

- Scores range from 0-27
- ↑ Scores = ↑ Severity
- Remission score: < 5
- Subthreshold score: < 10

Score = ___ + ___ + ___ + ___

UW PACC

CASE STUDY:

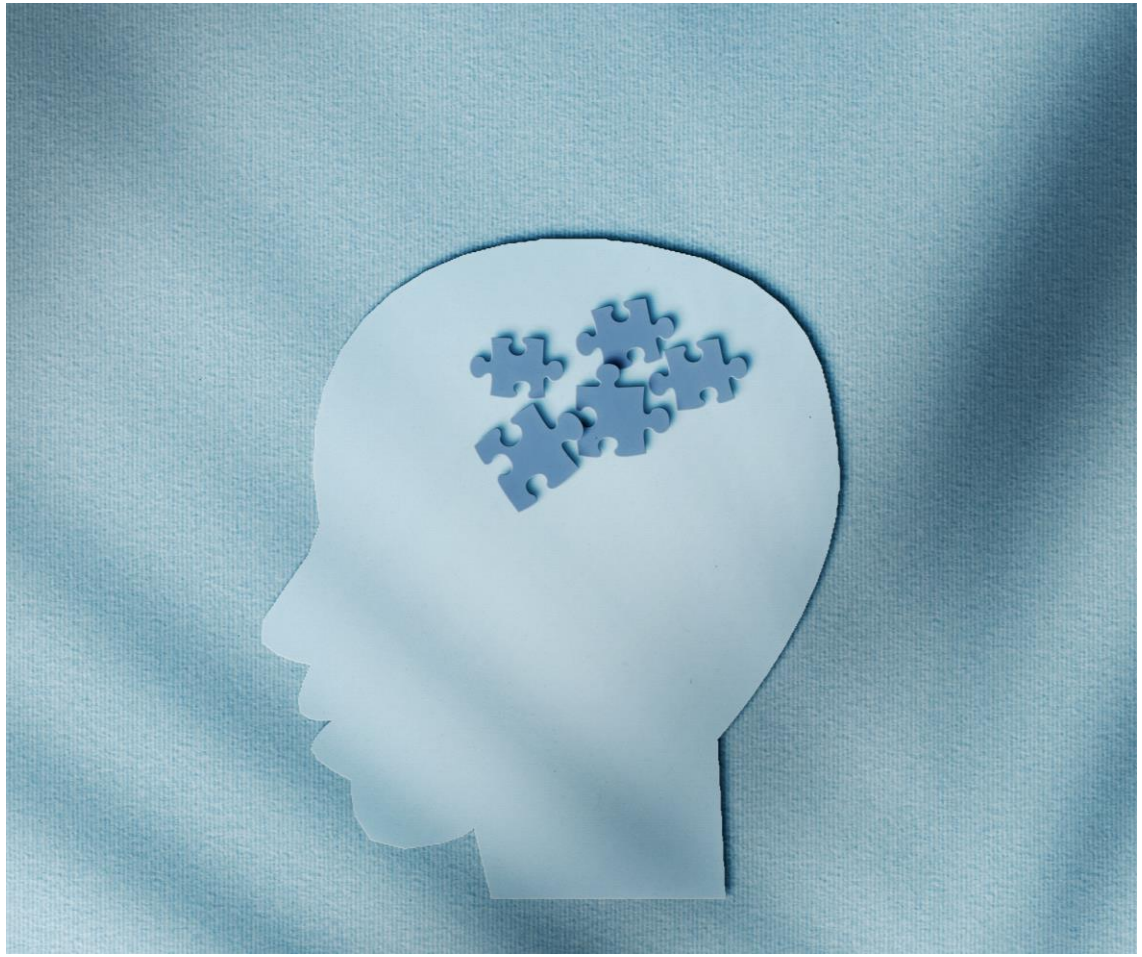
WHAT MEDICATION WOULD YOU RECOMMEND FOR THIS PATIENT?

SHOULD LITHIUM BE THE FIRST CHOICE FOR TREATING BIPOLAR DISORDER?

UW PACC

LITHIUM

- **YES!!!**
- Best started **as early as possible (after 1st mania)**
- Prevents further mood episodes
- ↓ Suicide risk
- Neuroprotective effects
  - ↓ risk of dementia
  - ↓ risk cognitive impairment



UW PACC

LITHIUM MONOTHERAPY

- Lithium monotherapy vs combined therapy for acute mania
  - How quickly do you need a response to treatment?
  - How did the patient respond to monotherapy in the past?
  - How severe are the symptoms? How many episodes have they had?
  - Are there tolerability concerns with combined therapy?
- Maintenance tx: Lithium monotherapy superior to other monotherapy options (Berk et al., 2017; Hayes et al., 2016; Kessing et al., 2018)

LITHIUM THERAPY FOR ACUTE MANIA AND BIPOLAR DISORDER EPISODES

- Can be used for acute and long-term management of bipolar disorder (and depressive episodes)
  - Labeled use: Acute mania, acute episodes with mixed features
  - Off-label use: Acute hypomania, acute bipolar major depression

DOSING FREQUENCY

- Lithium can be dosed either once daily or 2-3x daily
- ↑ dosing frequency
  - Minimizes side effects (particularly nausea)
  - Risk for adherence issues
- Once daily dosing
  - Serum concentrations are 25% higher than with divided dosing
    - Due to changes in renal excretion
  - Example: Once daily lithium level of 1.0 mEq/L is expected to drop to 0.8 mEq/L if switched to a divided dose regimen
  - Recommend once nightly to ↓ risk for kidney dysfunction

DOSAGE RECOMMENDATIONS FOR LITHIUM THERAPY

- **Initial dosage:** 600 to 900 mg/day in 2 to 3 divided doses
- **Incremental dosage adjustments:** Increase by 300 to 600 mg every 1 to 5 days based on response and tolerability
- **Usual therapeutic dose range:** 900 mg/day to 1.8 g/day in 1 to 3 divided doses

UW PACC

MONITORING: SYMPTOM IMPROVEMENT AND SERUM CONCENTRATIONS

- Monitor symptom improvement alongside serum concentrations to guide dose adjustments
- Obtain two consecutive serum concentrations in the therapeutic range during the acute phase
- Regular monitoring recommended thereafter (every 3 to 6 months)
  - Timing of serum samples:
    - Preferred: 12-hour trough level
    - Check levels approximately 5 days after a dosage adjustment

UW PACC

MONITORING: SERUM LITHIUM LEVEL

- Acute mania: **0.8 to 1.2 mEq/L**
- Maintenance: **0.6 to 1 mEq/L**
- Tailoring dosage within therapeutic ranges is critical for efficacy and safety
- Older adults may require lower target serum concentrations **(0.4-0.8 mEq/L)**
- If there are other medical comorbidities, cerebrovascular diseases, parkinsonism and dementia: **≤ 0.5 mEq/L**

UW PACC

MONITORING: OTHER LABS

Baseline:

- Renal function, electrolytes, calcium, thyroid function, serum lithium levels, weight, fluid status, ECG, CBC, pregnancy test

Weekly until stable, then every 3-6 months:

- Serum lithium levels

Months 1, 3, and 6:

- Serum lithium levels, renal function, electrolytes, calcium, thyroid function

Annually or as clinically indicated:

- Renal function, parathyroid, thyroid function, weight, fluid status, ECG, CBC

UW PACC

LITHIUM TOXICITY

- Of note, lithium toxicity can occur at any serum concentration level, especially in older adults, so it is important to monitor for signs of lithium toxicity and decrease the dose accordingly
- Signs and symptoms:
  - **>1.5 mEq/L)**: Early signs and symptoms of intoxication may include marked tremor, nausea, diarrhea, blurred vision, vertigo, confusion, and decreased deep tendon reflexes
  - **>2.5 mEq/L**: Intoxication symptoms may progress to include severe neurological complications, seizures, coma, cardiac dysrhythmia, and permanent neurological impairment
  - **>3.5 mEq/L**: Potentially lethal toxicity

MAINTENANCE TREATMENT WITH LITHIUM THERAPY

- Continue the regimen used to achieve control of the acute episode for maintenance treatment
- Consider lower doses and serum concentrations at the lower end of the therapeutic range for maintenance therapy
- Adjustment of dosage may be based on clinical response, tolerability, and serum concentration
  - Consider consolidation to a single bedtime dose after several weeks of stable therapeutic dose and serum concentrations

UW PACC

SIDE EFFECTS

- **Common**: nausea, tremor, polyuria and thirst, diarrhea
- **Less common**: weight gain, cognitive impairment
- **Other potential adverse effects**
  - **Thyroid**: hypothyroidism
  - **Parathyroid**: hyperparathyroidism
  - **Renal insufficiency**
  - **Cardiac**: may rarely cause cardiac dysrhythmias
  - **Skin/Hair**: acne, can worsen psoriasis

UW PACC

MANAGING COMMON SIDE EFFECTS

- **Polyuria / Thirst + weight gain**
  - Dose lithium once daily
  - Encourage low-calorie beverages
  - Encourage Xylitol (sugar-free) gum or Biotene rinse for dry mouth
  - Assess for arginine vasopressin resistance (nephrogenic diabetes insipidus)
- **Nausea**
  - Use extended release and divided dosing
  - Take with food; could also use ondansetron, ginger
- **Diarrhea**
  - Use immediate release (to avoid distal absorption)
  - Could use loperamide / antidiarrheal agents
- **Tremor**
  - May improve with time
  - Use extended release or divided dosing, dose reduction
  - Decrease caffeine intake
  - If persistent, could consider adding propranolol (starting 10mg TID; typically 60-120mg/day), vitamin B6/pyroxidine (typically 750mg to 1200mg/day); antiepileptics: primidone, gabapentin

UW PACC

DRUG INTERACTIONS WITH LITHIUM

- With Lithium, **No ACE** in the **H**ole
- **N**SAIDs = ↑ Lithium concentration
- **ACE** inhibitors = ↑ Lithium concentration
  - Angiotensin-II receptor antagonists (ARBs), Calcium channel blockers (CCBs)
- **H**ydrochlorothiazide (diuretics) = ↑ Lithium concentration
- **Other drugs**: metronidazole, baclofen, cotrimoxazole, acyclovir, prostaglandin-synthetase inhibitors tetracyclines, topiramate, methyldopa, carbamazepine, phenytoin
- **Low sodium diet** = ↑ Lithium concentration

UW PACC

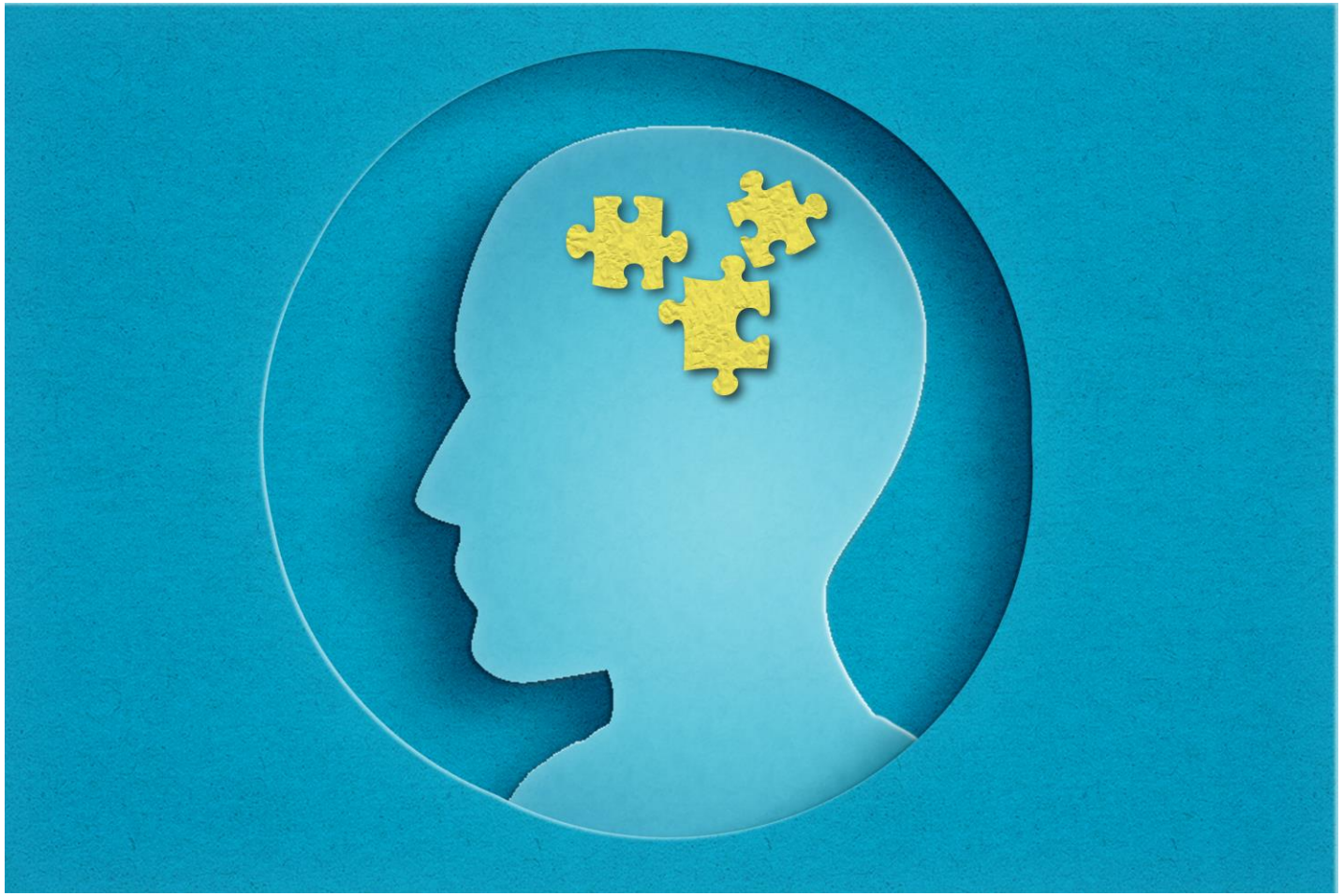
PREGNANCY / BREASTFEEDING CONSIDERATIONS

- **Consider potential benefits to mother vs risks to the fetus**
- **Prevents mood episode relapse during pregnancy and postpartum**
- **Increased risk of congenital and cardiac anomalies in the infant**
  - Ebstein's anomaly
  - ↑ risk in first trimester
  - Dosage exposure, ↓ risk < 0.64 mEq/L and dosages < 600–900 mg/day
- **Recommend close monitoring**
  - Lithium concentrations fluctuate during pregnancy

- **Lithium is present in breast milk**
  - Recommend bottle feeding; breastfeeding not recommended
  - Not an absolute contraindication; can breastfeed if closely monitoring lithium levels and thyroid function in infant
  - Can cause lithium toxicity in infants

UW PACC

CASE STUDY- CONTINUED



UW PACC

AL001, NEXT GENERATION LITHIUM DRUG

- Novel lithium-delivery system
- Combines lithium with the amino acid proline and salicylate (aspirin) to allow more of it to cross the blood brain barrier and enter the CNS
  - therapeutic brain levels with a lower serum level = ↓ physical side effects
  - 20% lower serum levels

- Currently in Phase IIA Clinical Trials
  - Alzheimer's disease, MDD, PTSD, and Bipolar

UW PACC

SUMMARY

- Lithium can be used for bipolar mania, depression, and maintenance treatment
- Best used early! Treat after the first manic episode and prevent further episodes!
- Acute mania can be treated with lithium monotherapy or in combination with an atypical antipsychotic
  - Depends on symptom severity and the need for a rapid response
- Once stable, use the lowest effective dose and once nightly dosing

UW PACC

THANK YOU!

UW PACC