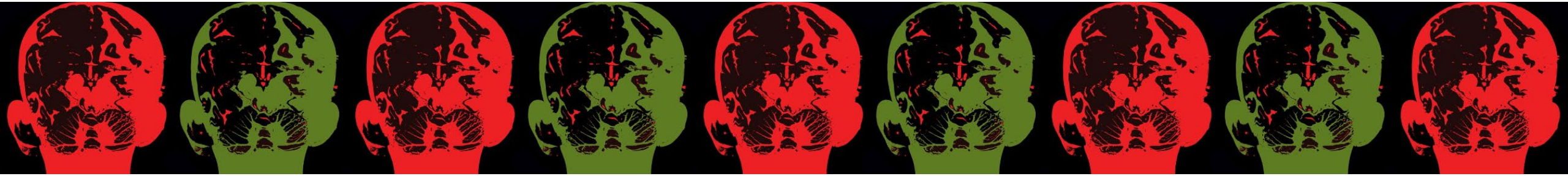


Up the Down Staircase: Addressing Adherence in Relapsing Bipolar Disorder

Sanjai Rao, MD

BRAINWEEK™

Title & Affiliation

Sanjai Rao, MD

Clinical Professor of Psychiatry

Associate Residency Training Director

UCSD Department of Psychiatry

Site Director, Residency Training

VA San Diego Healthcare System

Disclosure

- Dr. Rao has been a consultant for and/or on the speakers bureau of:
  - Janssen
  - Alkermes
  - Otsuka
  - Sunovion
  - Neurocrine

Learning Objectives

- Describe the prevalence and impact of medication non-adherence in bipolar disorder
- Discuss barriers to medication adherence
- Identify potential non-pharmacologic and pharmacologic solutions to improve medication adherence
- Evaluate the role of long acting injectable (LAI) antipsychotics in the treatment of bipolar disorder

Introduction

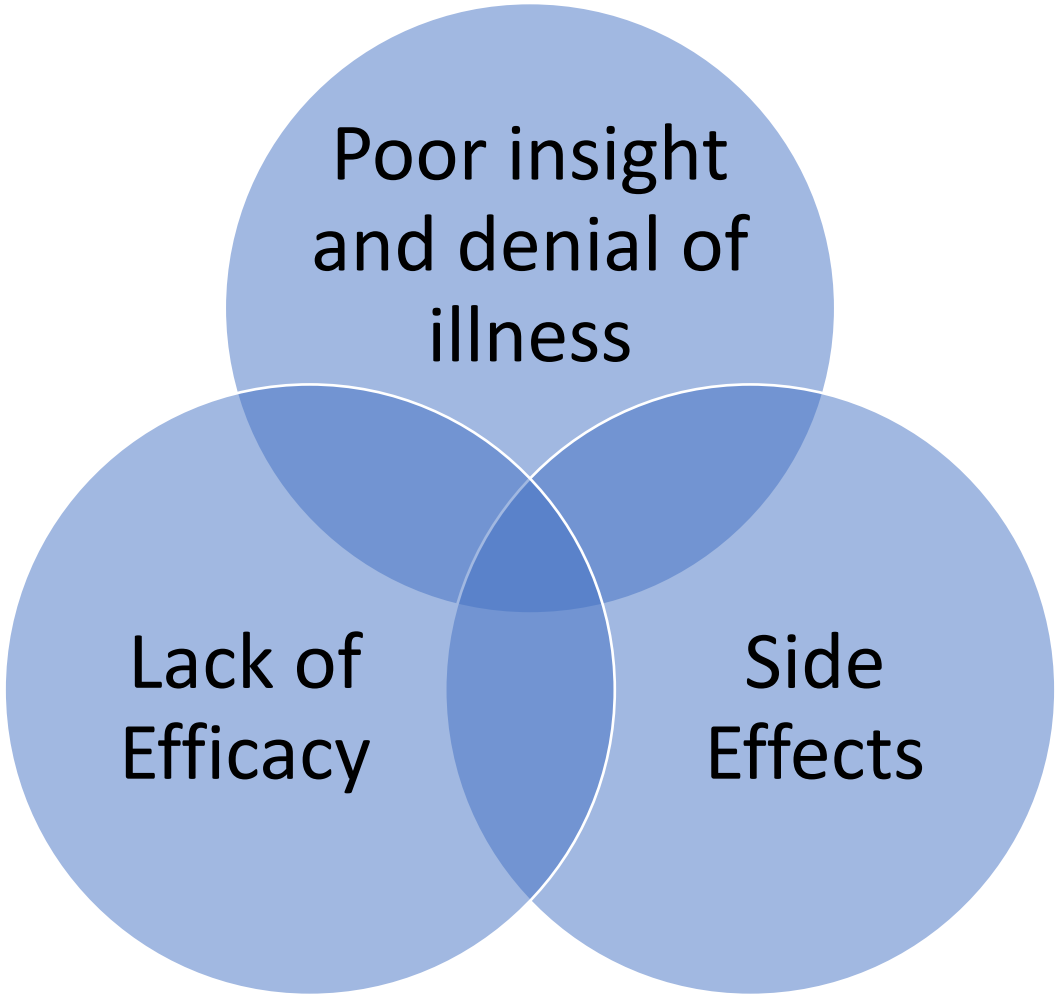
- As with other chronic illnesses, patients with bipolar disorder struggle with medication non-adherence
  - Estimated prevalence of 20%-60%
- Significantly reduces medication effectiveness
- Can lead to worsening of symptoms and more frequent relapse
- Can result in significant psychosocial and medical consequences

Barriers to Adherence

- Sociodemographic factors
  - Age <40, unmarried, non-white
- Clinical and illness characteristics
  - Early age of onset, severity of symptoms, rapid cycling, psychotic symptoms, personality disorders, cognitive deficits
- Psychosocial variables
  - Limited insight, denial of illness severity, concern about side effects, stigma, limited social support
- External barriers
  - Socioeconomic status, complexity of treatment regimen

Levin et al.; CNS Drugs (2016) 30:819–835

Why Do Patients Choose to Stop Meds?



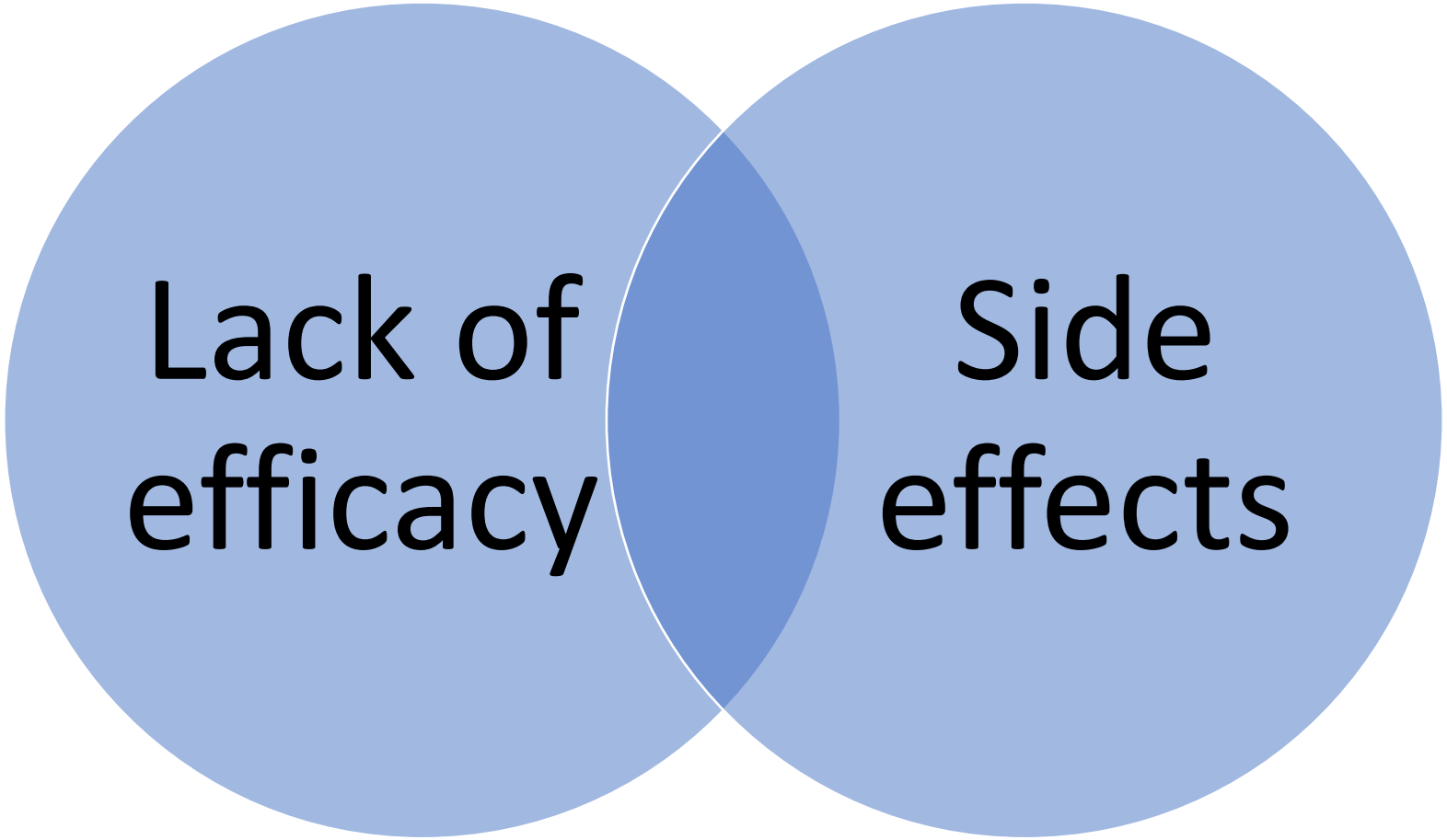
Non-Pharmacologic Interventions

Non-Pharmacologic Interventions

- Psychoeducation alone can be effective in improving adherence
- Multiple studies using motivational enhancement/ interviewing demonstrate increased adherence
- CBT, including novel approach using text messages, increased the number of patients who were adherent
- Getting $$$ to return for LAI injections → significantly improved adherence

Levin et al.; CNS Drugs (2016) 30:819–835

Pharmacologic Interventions



Menu for Mania/Mixed Episodes

- Lithium
- Valproic acid/divalproex
- Carbamazepine
- Most atypical antipsychotics
- Typical antipsychotics are not FDA indicated but can be effective for acute mania/mixed episodes*

*OFF LABEL

Mania/Mixed Episode Treatment

- Can use almost anything, so choice will depend on prior response, side effect profile, etc
- Resolving acute mania often requires aggressive dosing
- Whenever possible, consider long term tolerability of your initial treatment choice
  - ie, do you really want to start your 21-year-old first episode patient on olanzapine/divalproex combination?
- Lithium/divalproex + antipsychotic = faster response but also more side effects

Yatham LN et al.; Bipolar Disord. 2018 Mar; 20(2): 97–170

Bipolar Depression Treatment

- Far fewer options with evidence than in mania/mixed
  - Quetiapine, olanzapine/fluoxetine, lurasidone, cariprazine
  - Lithium not indicated but has extensive evidence
  - Lamotrigine not indicated, has evidence, may be better for relapse prevention in bipolar depression than acute treatment
- Some agents that are commonly used in clinical practice actually have negative studies
  - Divalproex
  - Carbamazepine
  - Aripiprazole

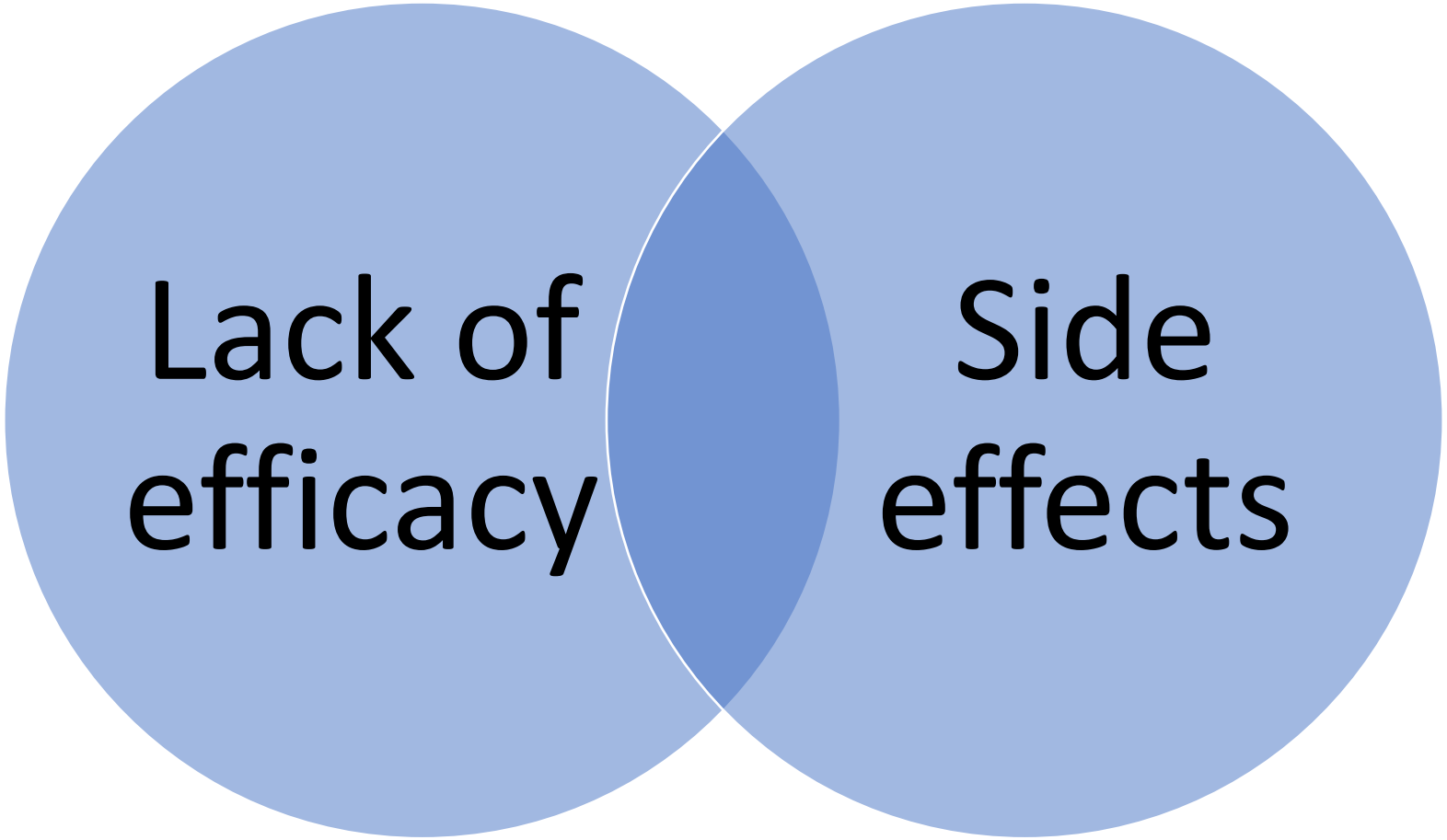
Yatham LN et al.; Bipolar Disord. 2018 Mar; 20(2): 97–170

What About Antidepressants?

- Typically don’t improve depressive symptoms over mood stabilization alone
  - Possible exception: bipolar 2 disorder, predominantly depressed
- You still get the side effects
- May lead to increased mood lability
  - Increased risk of mania/hypomania with SNRIs, even when adequately mood stabilized
- Reduced adherence to entire regimen due to lack of efficacy and increased side effects

Yatham LN et al.; Bipolar Disord. 2018 Mar; 20(2): 97–170

Pharmacologic Interventions



Side Effects Leading to Discontinuation

- Weight gain/metabolic
- Sedation
- Sexual side effects
- Tremors
- Perceived cognitive impairment
  - [Resolution of mania/hypomania]

Mago et al.; Harvard Review of Psychiatry: November/December 2014 - Volume 22 - Issue 6 - p 363-366

Weight Gain/Metabolic

- Typically associated with atypical antipsychotics; varies with drug
- Cause not fully understood but likely combination of H_1 and $5HT_{2c}$ antagonism
  - High: olanzapine
  - Moderate: quetiapine > risperidone
  - Low: aripiprazole, cariprazine > lurasidone/ziprasidone
- Lithium and traditional mood stabilizers cause modest weight gain, no significant changes in glucose/lipids
  - Divalproex + antipsychotic (especially olanzapine) = increased weight gain vs antipsychotic alone

Marteene W, et al. Expert Opin Drug Saf. 2019;18(12):1149-1160.

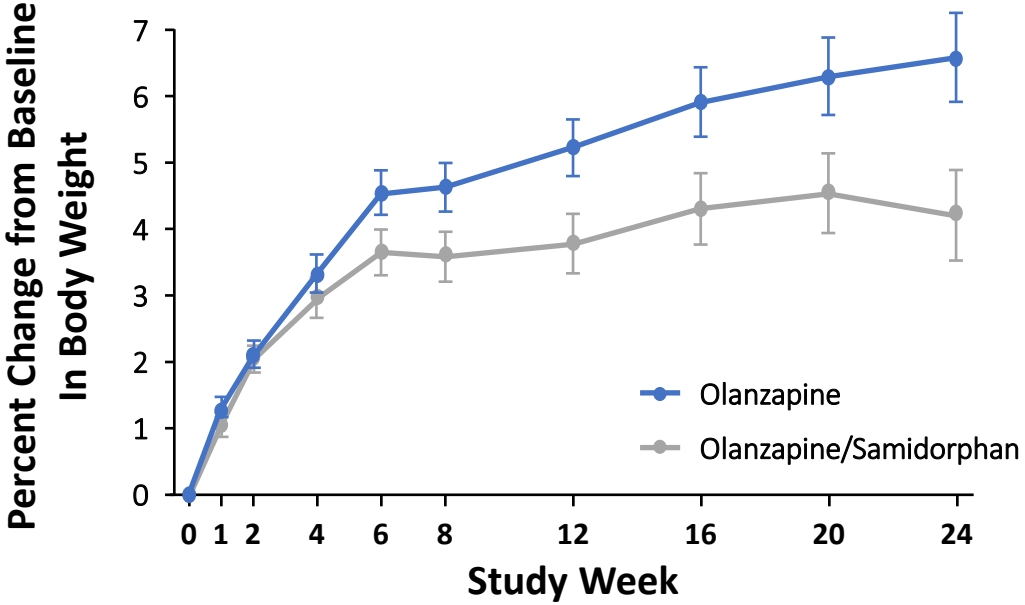
Weight Gain/Metabolic Treatment

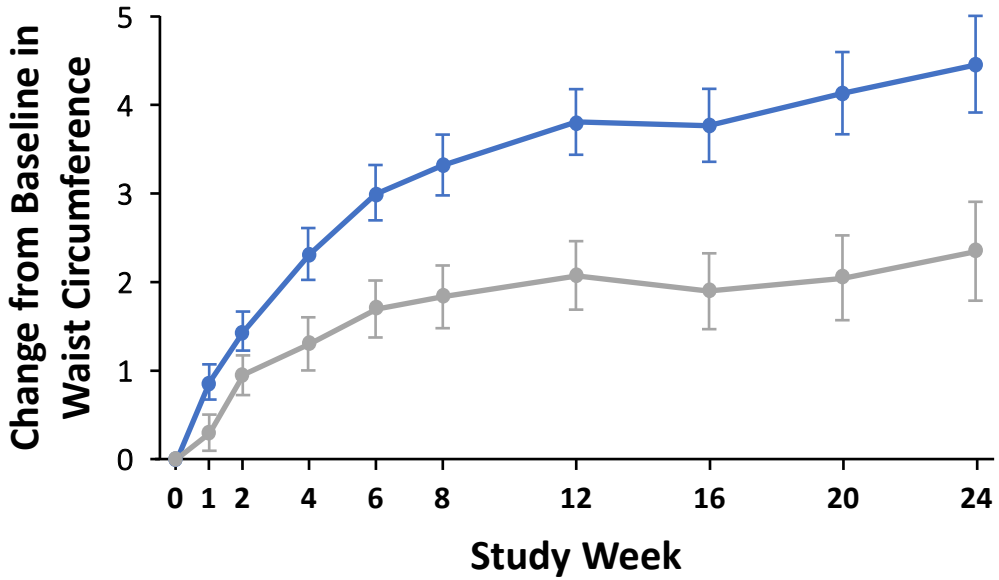
- Conventional options
  - Lifestyle → Can work, but many can't follow it
  - Switch drug → Can work, but no guarantee of efficacy with 2nd drug
- What about dose reduction?
  - Within FDA dose range, metabolic effects of atypical antipsychotics are mostly dose independent
- Adjunctive treatment* (OFF LABEL)
  - Metformin
  - Topiramate

Marteene W, et al. Expert Opin Drug Saf. 2019;18(12):1149-1160.

Olanzapine/Samidorphan for Weight Gain

- Samidorphan = μ-opioid antagonist
  - May reduce perceived reward from food intake
  - Similar (but lower magnitude) effect also observed with naltrexone





Correll CU, et al. *Am J Psychiatry*. 2020;177(12):1168-1178.

Sedation

- Primarily due to H_1 antagonism, modest contribution from $Alpha_1$ antagonism
  - High: olanzapine, quetiapine
  - Moderate: risperidone
  - Low: aripiprazole, cariprazine, lurasidone, ziprasidone
- Lithium, divalproex not intrinsically sedating but can sometimes increase sleep just through antimanic effects
- Bedtime dosing is best for more sedating medications

Mago et al.; Harvard Review of Psychiatry: November/December 2014 - Volume 22 - Issue 6 - p 363-366

Sexual Side Effects

- Likely due to prolactin elevation
- Tuberoinfundibular pathway regulates prolactin
  - (Hypothalamus → pituitary)
  - Inhibited by endogenous dopamine
- D_2 antagonism increases prolactin output
  - High: risperidone, haloperidol
  - Moderate: olanzapine, lurasidone, ziprasidone
  - Low: aripiprazole (and other partial agonists)
- Gynecomastia, galactorrhea, amenorrhea, decreased libido

Labad J, et al. Data Brief. 2020;31:105904.

Prolactin Elevation — Treatment

- No reason to check random prolactin in asymptomatic patients!
- Classic strategy: lower D_2 antagonism
  - Dose reduction
  - Switch to drug with lower D_2 potency
  - Bromocriptine* (D_2 agonist) has also been used, but risk of increased psychosis/mania
- New strategy: add low dose aripiprazole*
  - Multiple RCTs show reduction in prolactin
  - Typically only need 5 mg/day (range 2.5-10 mg)
  - Mechanism: aripiprazole binds D_2 receptor with much higher affinity than any $1^{st}/2^{nd}$ generation D_2 antagonist

Labad J, et al. Data Brief. 2020;31:105904.

Tremors

- Lithium → fine hand tremor, dose dependent, intention
  - 10% or more of patients, possibly 5x discontinuation rate
  - Much more common earlier in treatment, often resolves later
  - Fully reversible with lithium discontinuation
- Divalproex → fine tremor of head, mouth, tongue, limbs
  - Better with controlled release formulations
- Antipsychotics → 4-6Hz parkinsonian tremor
  - Largely depends on potency of D_2 antagonism

Mago et al.; Harvard Review of Psychiatry: November/December 2014 - Volume 22 - Issue 6 - p 363-366

Tremors — Treatment

- Lithium/divalproex tremors[1]
  - Dose reduction if possible
  - Propranolol/metoprolol have the best evidence
  - Case studies with benefit from cyproheptadine, primidone, diphenhydramine, benztropine, and others, but this is more variable
- Antipsychotic/parkinsonian tremors[2]
  - Dose reduction or switch to agent with less D_2 potency, if possible
  - Amantadine as effective as benztropine, with fewer side effects

1. Gitlin; Int J Bipolar Disord. 2016; 4: 27; 2. Mamo et al; Drug Saf. 1999 Mar;20(3):269-75

An Ode to Lithium

- Likely underutilized due to recent trend towards atypical antipsychotics in bipolar disorder
- Efficacy in mania/mixed and bipolar depression
- No metabolic issues or EPS
- Possible neuroprotective effects
- Suicide prevention

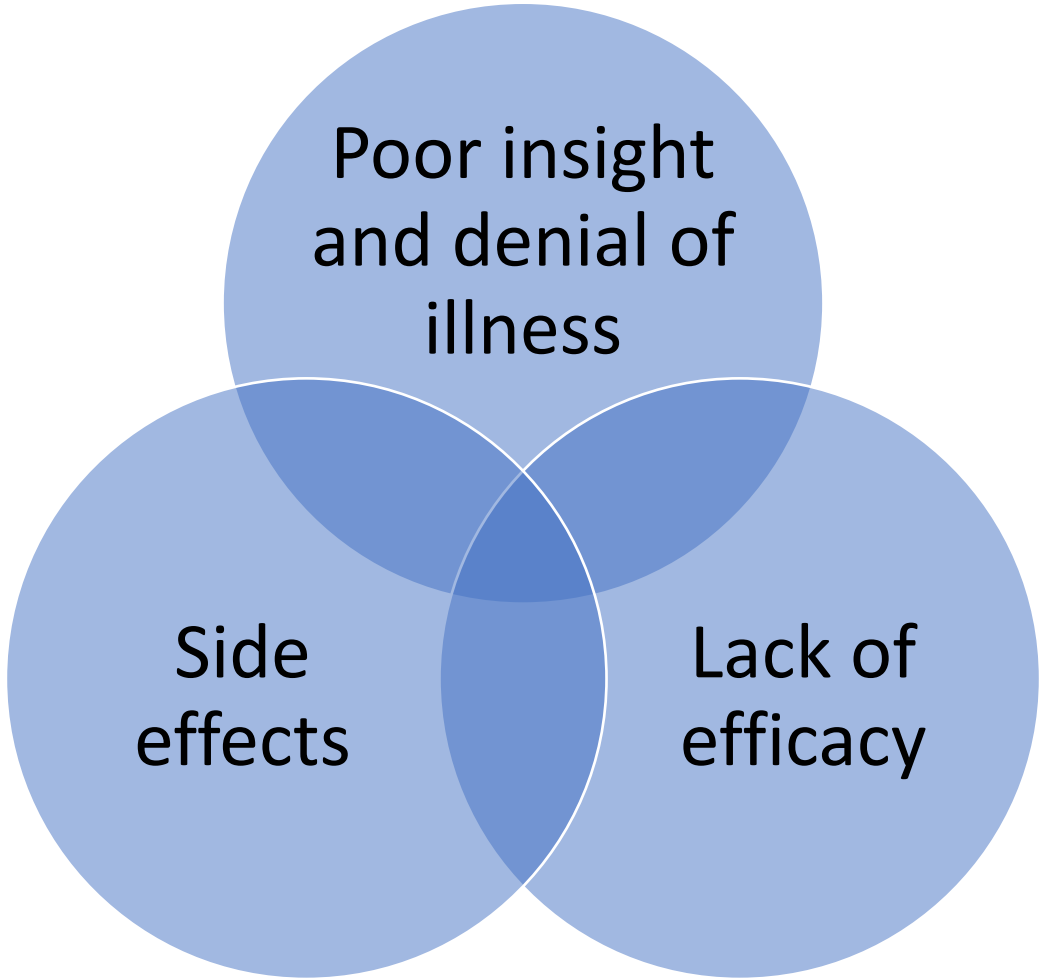
Won et al; Int J Mol Sci. 2017 Dec; 18(12): 2679.

How to Dose Lithium

- Very common side effect leading to discontinuation is polyuria
  - Lithium makes collecting duct cells less responsive to ADH (“diabetes insipidus”)
  - Degree of effect depends on time of exposure
  - Can be minimized by giving single dose of short acting lithium at night, rather than BID or extended release formulations
- But! → some patients can’t tolerate GI effect of large dose of lithium
  - Spread out their dose a little more to balance polyuria with GI effects

Won et al; Int J Mol Sci. 2017 Dec; 18(12): 2679.

Why Do Patients Choose to Stop Meds?



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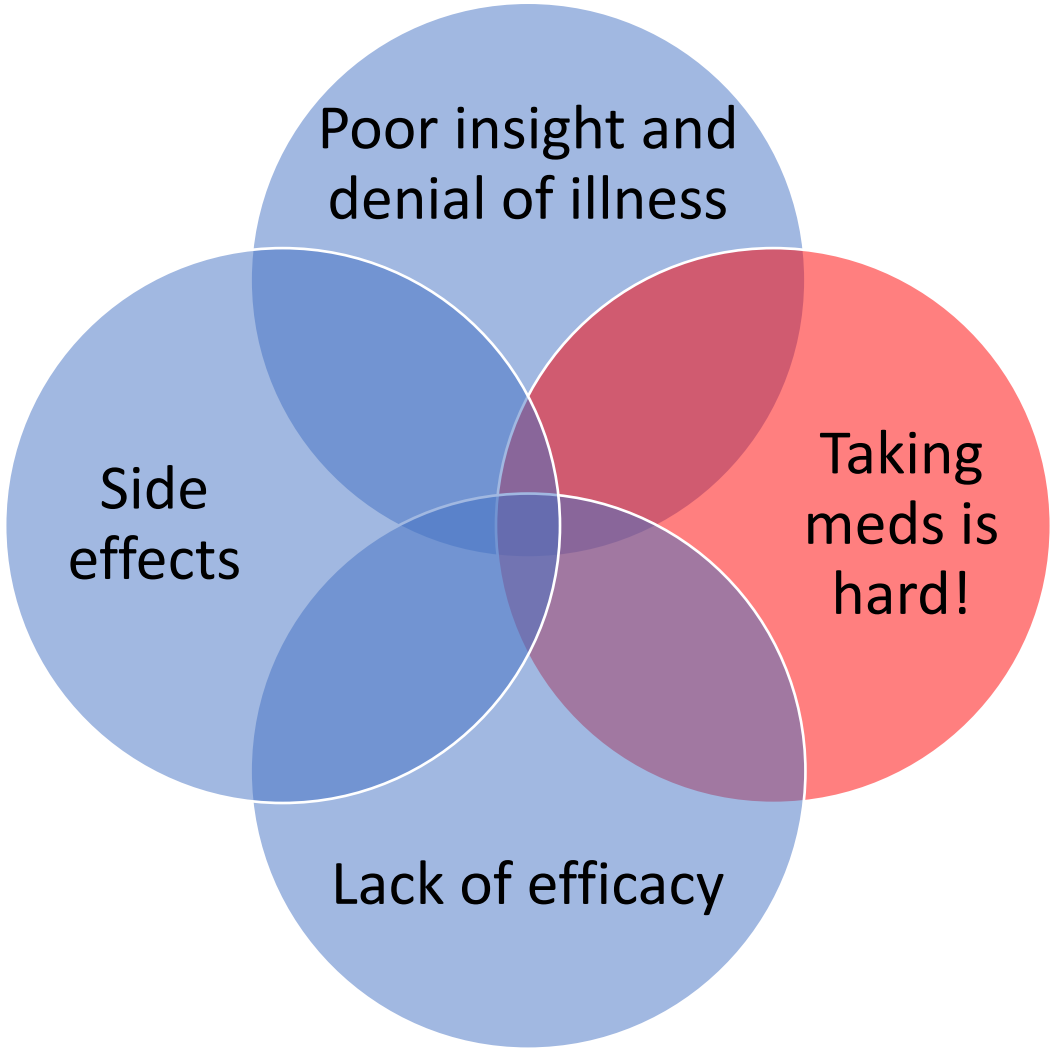

Taking Meds is Hard!

- Encourage use of pill boxes, coordinate dose with activities
- Adherence decreases as medication regimen gets more complex
  - Combination therapy may have greater efficacy
  - More medications → lower adherence
- Frequency of dosing
  - Almost no one can reliably take medications TID
  - Most of our treatments can be dosed once/day
- Leverage dosing times to improve side effects
    - ex: sedating medications given once/day at night

Levin et al.; CNS Drugs (2016) 30:819–835

Advantages of Long Acting Injections

- If the patient takes the injection, adherence is assured
- Stable plasma levels with less peak to trough fluctuation
  - Equal or increased efficacy
  - Sometimes fewer side effects than oral counterparts
- Lack of adherence can be rapidly identified and acted upon
  - No immediate drop in drug levels

Evidence for LAI Use in Bipolar Disorder

- Most data on LAI's come from schizophrenia studies

- LAI studies in bipolar disorder show:
  - Decreases in mania/mixed episodes
  - Reduced hospitalizations
  - Decreased length of hospitalization
  - Increased treatment adherence

Greene et al; Journal of Medical Economics, 2018 Vol. 21, No. 2, 127–134

LAI Options in Bipolar Disorder

- Only two LAI options are FDA approved for bipolar disorder:
  - Risperidone microspheres (Risperdal Consta)
  - Aripiprazole monohydrate (Abilify Maintenna)
- However, my OFF LABEL opinion:
  - Several oral antipsychotics with LAI versions are indicated for bipolar disorder
    - Risperidone, aripiprazole, olanzapine
  - LAI versions of these drugs deliver the same drug, with comparable plasma levels and side effect profile*

*OFF LABEL

Available LAI Medications

- Risperidone/paliperidone
  - Risperidone microspheres (Consta)
  - Risperidone subcutaneous (Perseris)*
  - Paliperidone palmitate monthly (Sustenna)*
  - Paliperidone palmitate 3-months (Trinza)*
- Aripiprazole
  - Aripiprazole monohydrate (Maintenna)
  - Aripiprazole lauroxil (Aristada)*
- Olanzapine
  - Olanzapine pamoate (Relprevv)*
- 1st generation
  - Haloperidol decanoate (Haldol Dec)*
  - Fluphenazine decanoate (Prolixin Dec)*

*OFF LABEL

Why Don’t We Use LAIs More Often?

- Historically, we have been trained that they are only for treatment resistant and non-adherent patients
- Stigma/perception that LAI = taking away patient’s rights
- Current bipolar disorder treatment guidelines have them as options, but do not necessarily encourage them

Will Patients Actually Take LAIs?

- Schizophrenia literature suggests that they will
- There are negative, neutral, and positive ways of offering an LAI
- In one study, 96% of patients were willing to try an LAI after a positive offer[1]

Negative	Neutral	Positive
• "Since you're not taking your meds, I think you should go on the shot."	• "So… do you want to take pills or get the shot?"	• "Would it be nicer for you to take your medication once a month instead of every day?"

1. Weiden et al. *J Clin Psychiatry.* 2015 Jun;76(6):684-90.

Summary

- Medication discontinuation is common in bipolar disorder, and leads to reduced medication effectiveness, worsening of symptoms, relapse, and psychosocial and medical comorbidity
- Barriers to adherence include poor insight/illness denial, lack of efficacy, and medication side effects
- Non-pharmacologic interventions such as psychoeducation, motivational interviewing, CBT, and $$$, can improve adherence
- Bipolar mania/mixed episodes can be treated by many agents/combinations; important to balance speed of response with long term tolerability

Summary

- Far fewer options for bipolar depression; in general antidepressants don’t work and add side effects
- Side effects are a common reason for discontinuation, but in many cases can be reduced with proper management
- Taking medication every day is hard, so try to simplify regimen
- LAIs have been demonstrated to improve treatment adherence and reduce manic/mixed episodes and hospitalizations
- With good education, many patients will be willing to take an LAI

THANK YOU!

QUESTIONS?