Stop the Roller Coaster!

Managing "Treatment-Resistant" Bipolar Disorder

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The interventions discussed in this talk not FDA-approved for these uses unless specified

Learning Objective

Incorporate at least two new strategies to address treatment resistance, resulting in fewer hospitalizations and improved patient outcomes and satisfaction.

"Treatment-resistant" bipolar disorder

1. **Rapid cycling**: Identify, evaluate, and treat rapid cycling
2. **Higher DOSE**: Lithium, divalproex, lurasidone, lamotrigine
3. **Combinations**: Gabapentin added to mood stabilizer/ SGA

   Lamotrigine added to lithium

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   Lamotrigine added to quetiapine

   Pramipexole added to mood stabilizer
4. **Clozapine** (monotherapy or adjunctive)

Rapid cycling: Identify it!

- Four or more episodes in a year
- Partial remission, full remission, OR switch to opposite polarity
- Lifetime: About one-third of patients
- Each year: About 15% of patients
- Use the specifier "**With rapid cycling**"

Carvalho et al. (2014). PMID: 25004199
Yildiz and Sachs (2004). PMID: 15023502

Address the reversible risk factors

1. Hypothyroidism
2. Substance use
3. Antidepressants

Carvalho et al. (2014). PMID: 25004199
Yildiz and Sachs (2004). PMID: 15023502

Rapid cycling: Which medications?

- Focus on cycling rather than the acute episode
- All mood stabilizers are less effective
- Anticonvulsants more effective than lithium? Unproven
- Combinations of mood stabilizers? Unproven

Fountoulakis et al. (2013). PubMed PMID: 23437958
Yatham et al. (2018). PMID: 29536616
Carvalho et al. (2014). PMID: 25004199
Calabrese et al. (2000). PMID: 11105737

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Is this serum lithium OK, low, or high?

TESTS	RESULT	FLAG	UNITS	REFERENCE INTERVAL
Thyroxine (T4) Free, Direct, S				
T4,Free(Direct)	1.37		ng/dL	0.93 - 1.60
TSH	2.200		uIU/mL	0.450 - 4.500
Lithium (Eskalith(R)), Serum	0.7		mmol/L	0.6 - 1.2
			Detection limit = 0.1	
			<0.1 indicates None Detected	
Triiodothyronine (T3), Free	2.6		pg/mL	2.3 - 5.0

Rule of thumb

- For prevention ~ 0.5 to 0.8 mEQ/L
- For treatment ~ 0.8 to 1.2 mEq/L

Higher serum level of divalproex?

- Based on clinical experience

Higher dose of lurasidone

- Linear dose-response from 20 to 120 mg/day

Chapel et al. (2016). PMID: 26730454

SA-Q#1. Which of the following is true about serum lamotrigine levels?

A. Serum lamotrigine levels above 10 mg/L are required for response
B. Serum lamotrigine levels are correlated with incidence of adverse effects
C. Serum lamotrigine levels are currently not available in commercial laboratories
D. None of the above

High dose lamotrigine?

- Is the patient on an oral contraceptive or carbamazepine?

Christesen et al. (2007). PubMed PMID: 17346247

High dose lamotrigine?

- Prescribing Information: 100 to 200 mg/day.
- "…no additional benefit was seen at 400 mg/day compared with 200 mg/day."
- BUT, stopped enrollment in 400 mg/day group, so **small numbers**.
- Also, wasn't a study of those with **inadequate response** to 200 mg/day…

Calabrese et al. (2003). PMID: 14628976

High dose lamotrigine?

- Is a trial of off-label increase above 200 mg/day justifiable?
- FDA-approved dose for epilepsy 225 – 375 mg/day
- Published case series of lamotrigine 300 mg/day

Unholzer & Haen (2015). PMID: 26252722
Turnbridge et al. (2017). PMID: 28833962
Abraham (2011). PMID: 23051124
Kagawa et al. (2014). PMID: 24819973

Serum lamotrigine level

- Check serum lamotrigine level
- Does not correlate well with efficacy but *does* correlated with side effects

Fröscher et al. (2002). PMID: 11967180
Hirsch et al. (2004). PMID: 15452293

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SA-Q#2. Which of the following medications for bipolar disorder MUST be given with food because its absorption is significantly reduced if it is given without food?

A. Lurasidone

B. Lithium

C. Oxcarbazepine

D. Divalproex

SA-Q#3. Which of the following is true about the potential use of gabapentin in the treatment of bipolar disorder?

A. It is FDA-approved as an adjunct for maintenance treatment

B. It is efficacious as both monotherapy and combination therapy

C. It may be efficacious as combination therapy

D. It is not efficacious for the treatment of bipolar disorder

Gabapentin added to mood stabilizer/SGA

- Monotherapy?
- Adjunctive use?
- For comorbid anxiety?

Pande et al. (2003). PubMed PMID: 11249802
Vieta et al. (2006). PubMed PMID: 16649836
Perugi et al. (2002). PubMed PMID: 12454558
Yatham et al. (2018). PMID: 29536616

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Effectiveness of Adjunctive Gabapentin in Resistant Bipolar Disorder: Is It Due to Anxious-Alcohol Abuse Comorbidity?

GIULIO PERUGI, MD,*†, CRISTINA TONI, MD,†, FRANCO FRARE, MD,†‡, GIUSEPPE RUFFOLO, MD,*, LEONARDO MORETTI, MD,†, CARLO TORTI, MD,*, AND HAGOP S. AKISKAL, MD§

Lamotrigine added to lithium

- Why this particular combination?
- LamLit study: adding lamotrigine to lithium for acute bipolar depression

  Only 8 weeks, including titration

  Responders 52% versus 32% with placebo

van der Loos et al. (2009). PMID: 19200421. LamLit study

Lurasidone added to lithium/divalproex

- Lurasidone: FDA-approved as monotherapy & adjunctive for acute bipolar I depression
- Adjunctive use: Mean dose 66 mg/day
- Responders 57% versus 42% on placebo

Loebel et al. (2014). PMID: 24170221.

Lurasidone added to lithium/divalproex

- Lurasidone: **not** FDA-approved for maintenance treatment
- Data is weak for adjunctive use in maintenance
- May be better if index episode is depression & rapid cycling is absent

Calabrese et al. (2017). PMID: 28689688

Tips about lurasidone

- MUST be taken with food
- Higher doses are better

Preskorn et al. (2013). PMID: 24014143
Chapel et al. (2016). PMID: 26730454

Lamotrigine added to quetiapine

- Why this particular combination for acute bipolar depression?
- Quetiapine while lamotrigine being titrated
- If quetiapine not tolerated, lamotrigine will be in place

Geddes et al. (2016). PMID: 26687300. CEQUEL study

Lamotrigine added to quetiapine

- Quetiapine+lamotrigine > Quetiapine+placebo at 12 weeks and 52 weeks
- Addition of folic acid counteracted the benefit of lamotrigine

Geddes et al. (2016). PMID: 26687300. CEQUEL study

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SA-Q#4. In difficult-to-treat bipolar disorder, for which phase of illness could pramipexole be considered as an off-label treatment along with a mood stabilizer?

A. Mania

B. Depression

C. Maintenance treatment

D. All of the above

Pramipexole added to mood stabilizer

- Dopamine receptor agonist used for Parkinson's disease and RLS
- Adjunct to mood stabilizers
- Two studies published in 2004: 47% and 51% drug-placebo difference, which is HUGE

Goldberg et al. (2004). PMID: 14992985
Zarate et al. (2004). PMID: 15219473

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SA-Q#5. Clozapine reduces the risk of which aspects of difficult-to-treat bipolar disorder?

A. Psychotic symptoms

B. Mania

C. Depression

D. Aggressive behavior

E. All of the above

Clozapine

- Fifteen clinical trials (n= 1,044)
- Monotherapy or adjunctive
- Improved mania, depression, rapid cycling, psychotic symptoms

Li et al. (2015). PMID: 25346322

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CASE DISCUSSION

- 20 year old Latino female, dropped out of UC-I, initially seen when she was 16, when she was AP student, participating in HS water polo team.
- It started with anxiety, panic attacks and uncontrolled crying and was taking fluoxetine 20 mg prescribed by her PCP.
- When initially seen in psych, she was having periods lasting 24 hours expressing manic symptoms including: doing projects for 24 hours straight, excessive energy, not needing to fall asleep, and excessive talkativeness alternating with periods of sobbing uncontrollably and even had suicidal thoughts.

- Aripiprazole 5 mg added first, then replaced with lamotrigine 200 mg daily (she was gaining weight and reluctant to take aripiprazole). Fluoxetine discontinued.
- Started experimenting with THC, unprotected sex, ordering sex toys online, and watching porn. Mood swings continued, divalproex 1000mg was added.
- Needed hospitalization in context of manic episode. Haldol 5 mg added to divalproex and lamotrigine.

- Mood was stable and she started at UCI, staying at the dorms but could not continue after first quarter. Now on quetiapine 100 mg every night, divalproex 1000 mg and lamotrigine 200 mg. Divalproex level range from 80-90. Breakthrough episodes time to time.

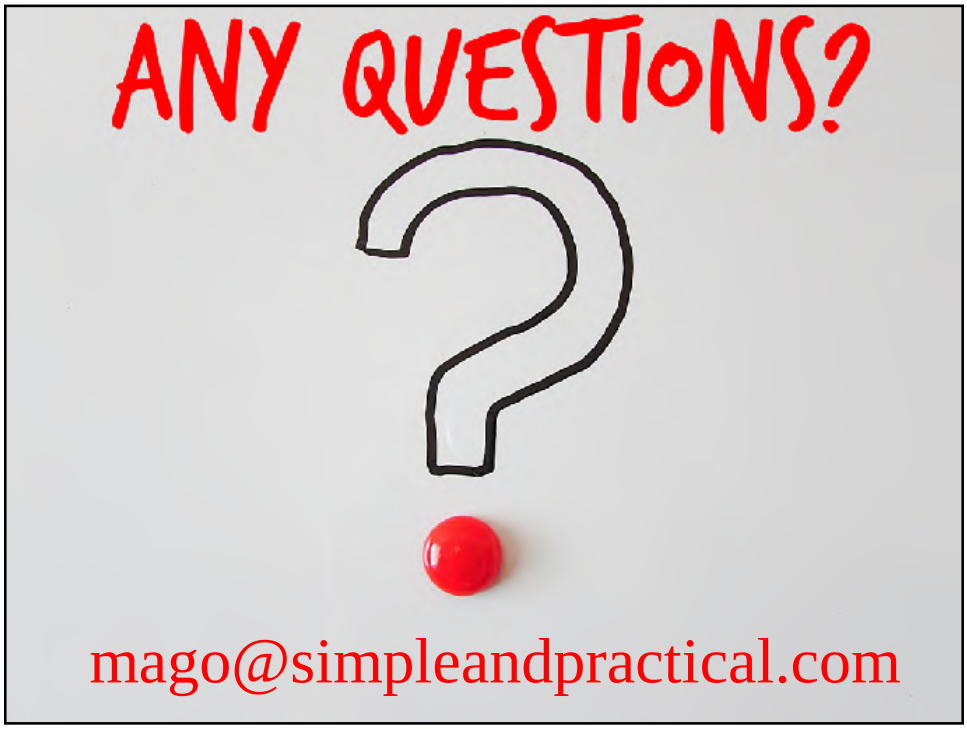
This is on the background of ...

- Her maternal grandfather's a psychotic episode several years ago; he was diagnosed with schizophrenia in Mexico
- Her mother who perhaps had mood problems and was caught sleeping with patient's swim coach, making it embarrassing for the patient at school
- Her decision to ultimately quit water polo and isolate at home for months during her senior year

TABLETOP DISCUSSION

- Issue: Ongoing mood swings, side effects of meds if the dose is increased. Missing out on education and social life.

What would you recommend for this patient now?



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Bright Light Therapy

- Two controlled studies published in 2018 show its efficacy
- Risk of switch to mania
- Consider administering in the afternoon?

Zhou et al. (2018). PMID: 29053981
Sit et al. (2018). PMID: 28969438