A NEED FOR INNOVATION IN BIPOLAR I DISORDER:

IMPROVING PATIENT ADHERENCE AND OUTCOMES

WITH LONG ACTING INJECTABLE ANTIPSYCHOTICS

This activity has been supported through an independent educational grant from Otsuka America Pharmaceutical, Inc. and Lundbeck.

DBSA

Depression and Bipolar Support Alliance

LA360

LONG-ACTING INJECTABLES

BIPOLAR360

Faculty

Craig Chepke, MD, FAPA

Adjunct Associate Professor of Psychiatry, Atrium Health

Adjunct Assistant Professor of Psychiatry, UNC School of Medicine

Medical Director, Excel Psychiatric Associates

Huntersville, North Carolina

Leslie Citrome, MD, MPH

Clinical Professor of Psychiatry and Behavioral Sciences

New York Medical College

Valhalla, New York

Faculty Disclosure

- **Dr. Chepke**: Advisory Board—AbbVie, Acadia, Alkermes, Eisai, Intracellular, Ironshore, Janssen, Jazz, Lundbeck, Karuna, Neurocrine, Noven, Otsuka, Takeda, Teva; Consultant—AbbVie, Acadia, Alkermes, Corium, Eisai, Intracellular, Janssen, Jazz, Lundbeck, Neurocrine, Noven, Otsuka; Grant/Research Support—Acadia, Axsome, Harmony, Neurocrine, Teva; Speakers Bureau—AbbVie, Acadia, Alkermes, Eisai, Genomind, Intracellular, Ironshore, Janssen, Jazz, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sunovion, Takeda, Teva.
- **Dr. Citrome**: Consultant—AbbVie, Acadia, Alkermes, Allergan, Angelini, Astellas, Avanir, Axsome, BioXcel, Cadent Therapeutics, Eisai, Impel, Intra-Cellular Therapies, Janssen, Karuna, Lundbeck, Luye, Lyndra, Medavante-ProPhase, Merck, Neurocrine, Noven, Osmotica, Otsuka, Relmada, Sage, Shire, Sunovion, Takeda, Teva, University of Arizona, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research; Speaker—AbbVie, Acadia, Alkermes, Allergan, Angelini, Eisai, Intra-Cellular Therapies, Janssen, Lundbeck, Merck, Neurocrine, Noven, Otsuka, Sage, Shire, Sunovion, Takeda, Teva, and CME activities organized by medical education companies such as Medscape, NACCME, NEI, Vindico, and Universities and Professional Organizations/Societies; Stocks (small number of shares of common stock)—Bristol-Myers Squibb, Eli Lilly, J & J, Merck, Pfizer purchased >10 years ago; Royalties—Wiley (Editor-in-Chief, *International Journal of Clinical Practice*, through end 2019), *UpToDate* (reviewer), Springer Healthcare (book), Elsevier (Topic Editor, Psychiatry, Clinical Therapeutics). In the past 5 years Dr. Citrome has engaged in collaborative research with, or received consulting or speaking fees, from: AbbVie, Acadia, Alexza, Alkermes, Allergan, Angelini, Astellas, AstraZeneca, Avanir, Axsome, BioXcel, Boehringer Ingelheim, Bristol-Myers Squibb, Cadent Therapeutics, Eisai, Eli Lilly, Forum, Genentech, Impel, Indivior, Intra-Cellular Therapies, Janssen, Jazz, Karuna, Lundbeck, Luye, Lyndra, Medavante-Prophase, Meiji, Merck, Medivation, Mylan, Neurocrine, NeuroRx, Novartis, Noven, Osmotica, Otsuka, Pfizer, Reckitt Benckiser, Relmada, Reviva, Sage, Shire, Sunovion, Takeda, Teva, University of Arizona, Valeant, Vanda, and one-off ad hoc consulting for individuals/entities conducting marketing, commercial, or scientific scoping research.

Disclosure

- The faculty have been informed of their responsibility to disclose to the audience if they will be discussing off-label or investigational use(s) of drugs, products, and/or devices (any use not approved by the US Food and Drug Administration).
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.
- This continuing medical education activity includes medicine brand names for participant clarity purposes only. No product promotion or recommendation should be inferred.

Learning Objectives

- Assess barriers to optimal management of bipolar I disorder (BD-I), including medication nonadherence
- Evaluate the potential therapeutic applications, safety, and efficacy of LAI antipsychotics in the treatment of BD-I
- Employ a timely and patient-centered treatment approach to assess the utility of LAI antipsychotics in appropriate patients

Overview of Traditional Treatment Options

Craig Chepke, MD, FAPA
Adjunct Associate Professor of Psychiatry, Atrium Health
Adjunct Assistant Professor of Psychiatry, UNC School of Medicine
Medical Director, Excel Psychiatric Associates
Huntersville, North Carolina

How Do You Solve a Problem Like Bipolar?

5-21-13: Sister called. Questions about blood work—doesn't know if he is taking meds.

3-21-16: Was off all meds for 4 months and feels much better having resumed them.

9-24-18: "Good lately. I was off all the medicine for a long time, but then I found some in the refrigerator. Now I'm back on it and doing better than I ever have."

2-5-19: "I think I'm doing great!" Denies having missed any doses.

10-3-19: Did not get labs. Animated, cognitively scattered, extremely talkative. Assessment: subclinical mania (barely subclinical).

3-17-20: He states he has been off all meds except Benadryl for *years* – at least 3. "I didn't feel it was doing me any good." He cannot explain why he continued to come to this office for medication follow-up appointments. He acknowledged he lied to me the entire time.

Traditional Treatment Options

Bupropion

Aripiprazole

Fluoxetine

Olanzapine

Citalopram

Carbamazepine

Quetiapine

Paliperidone

Vilazodone

Lamotrigine

Ziprasidone

Duloxetine

Lithium

Asenapine

Risperidone

Escitalopram

Vortioxetine

Divalproex

Brexpiprazole

Lurasidone

Lumateperone

Paroxetine

Cariprazine

Venlafaxine

Sertraline

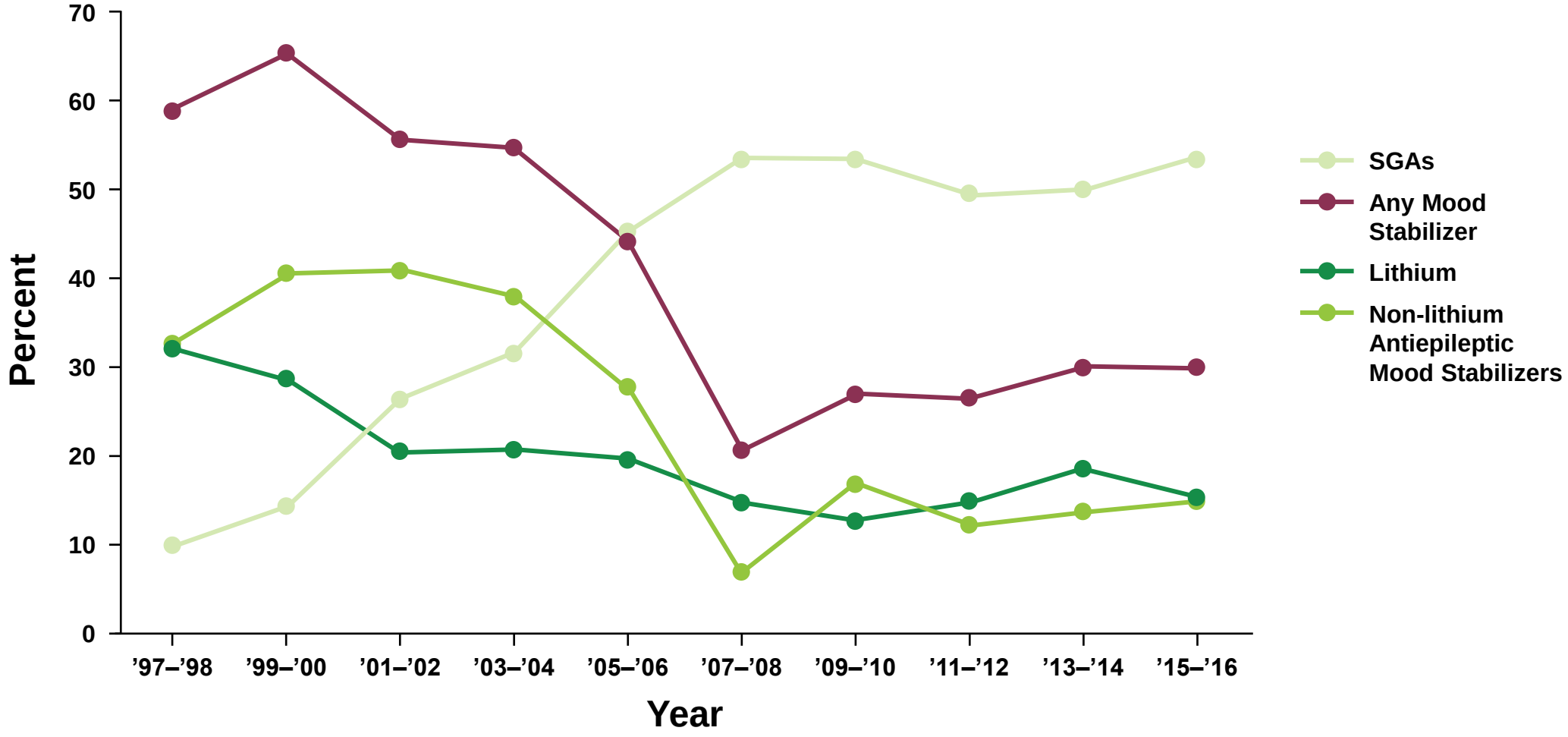
CANMAT Guidelines for Maintenance Phase

	Prevention of Any Mood Episode	Prevention of Depression	Prevention of Mania	Safety Concerns	Tolerability Concerns
First-line Treatments					
Lithium	●	●	●	++	++
Quetiapine	●	●	●	++	++
Divalproex	●	◔	◑	++	+
Lamotrigine	●	●	◔	–	–
Asenapine	◔	◔	◔	–	+
Quetiapine + Li/DVP	●	●	●	+++	++
Aripiprazole + Li/DVP	◔	n.d.	◔	++	++
Aripiprazole	◔	n.d.	◔	–	+
Aripiprazole OM	◔	n.d.	◔	–	+
Second-line Treatments					
Olanzapine	●	●	●	+++	++
Risperidone LAI	●	n.d.	●	+	++
Risperidone LAI (adj)	◔	◔	◔	+++	++
Carbamazepine	◔	◔	◔	+	++
Paliperidone (>6 mg)	◔	n.d.	◔	+	++
Lurasidone + Li/DVP	◑	◑	◔	++	++/–
Ziprasidone + Li/DVP	◔	n.d.	◔	++	+
New Options Not Yet in Guidelines					
Aripiprazole with Digital Sensor	◔	n.d.	◔	–	+
Olanzapine+Samidorphan	●	●	●	?	++

CANMAT = Canadian Network for Mood and Anxiety Treatments.

Yatham LN, et al. *Bipolar Disord*. 2018;20(2):97-170.

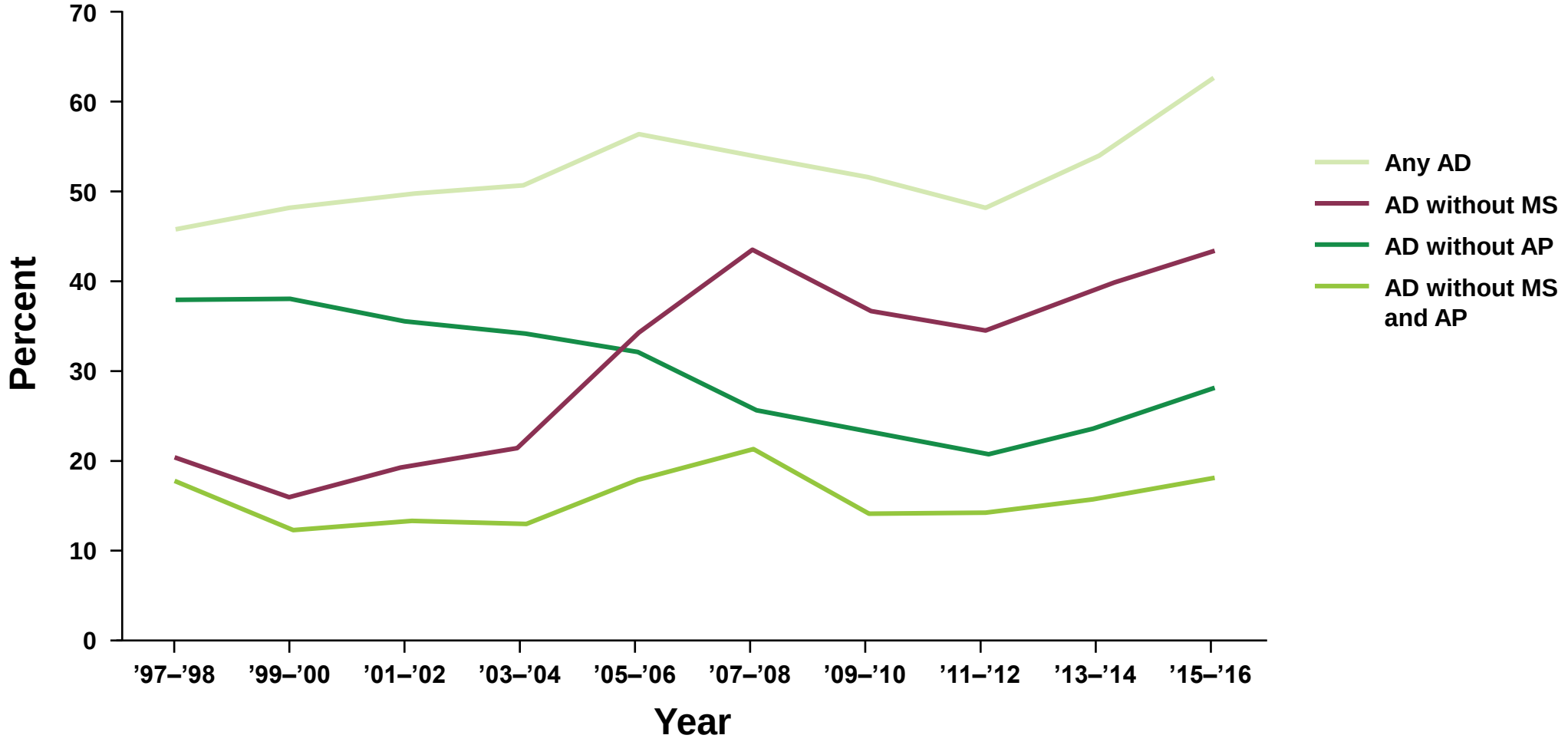
20-Year Trends in Outpatient Bipolar Disorder Treatment: *Mood Stabilizers and SGAs*



SGA = second-generation antipsychotic.

Rhee TG, et al. *Am J Psychiatry*. 2020;177(8):706-715.

20-Year Trends in Outpatient Bipolar Disorder Treatment: *Traditional Antidepressants*



AD = antidepressant; AP = antipsychotic; MS = mood stabilizer.

Rhee TG, et al. *Am J Psychiatry*. 2020;177(8):706-715.

Limitations of Mood Stabilizers

Lithium

- Narrow therapeutic index* (blood level)
- Long-term thyroid and kidney damage
- Tremor
- Weight gain
- GI issues
- Hair loss
- Rebound mania if abruptly stopped
- Stigma about use
- Benefit for mania > depression

Divalproex

- Hepatotoxicity*
- Pancreatitis*
- Very teratogenic*
- Class warning of SI
- Blood levels
- Tremor
- Weight gain
- GI issues
- Hair loss
- Sedation
- Benefit in mania

Carbamazepine

- Risk of SJS/TEN*
- Aplastic anemia, agranulocytosis*
- Class warning of SI
- Teratogenic
- Extensive drug–drug interactions
- Benefit in mania

Lamotrigine

- Risk of SJS/TEN*
- Slow titration restart if >5d missed
- Class warning of SI
- Hormonal treatment interaction
- Only prevents depression
- Found ineffective in
  - Acute mania (2/2)
  - Acute bipolar depression (3/3)
  - Rapid cycling (2/2)
  - Acute MDD (3/3)

*Boxed warning in USPI. GI = gastrointestinal; SI = suicidal ideation; MDD = major depressive disorder; SJS/TEN = Stevens-Johnson Syndrome/Toxic Epidermal Necrolysis.

US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/. Ghaemi SN. *Clinical Psychopharmacology: Principles and Practice*. Oxford University Press; 2019. Suppes T, et al. *Arch Gen Psychiatry*. 1991;48(12):1082-1088.

Limitations of Traditional Antidepressants

- Increased suicidality <25 yo*
- None FDA-approved
- Potential for depressive relapse, increased cycling
- No possible benefit in mania
- Efficacy in acute bipolar depression not established, let alone maintenance
- Lack of efficacy may lead to mistrust of clinicians

***Boxed warning in USPI.**

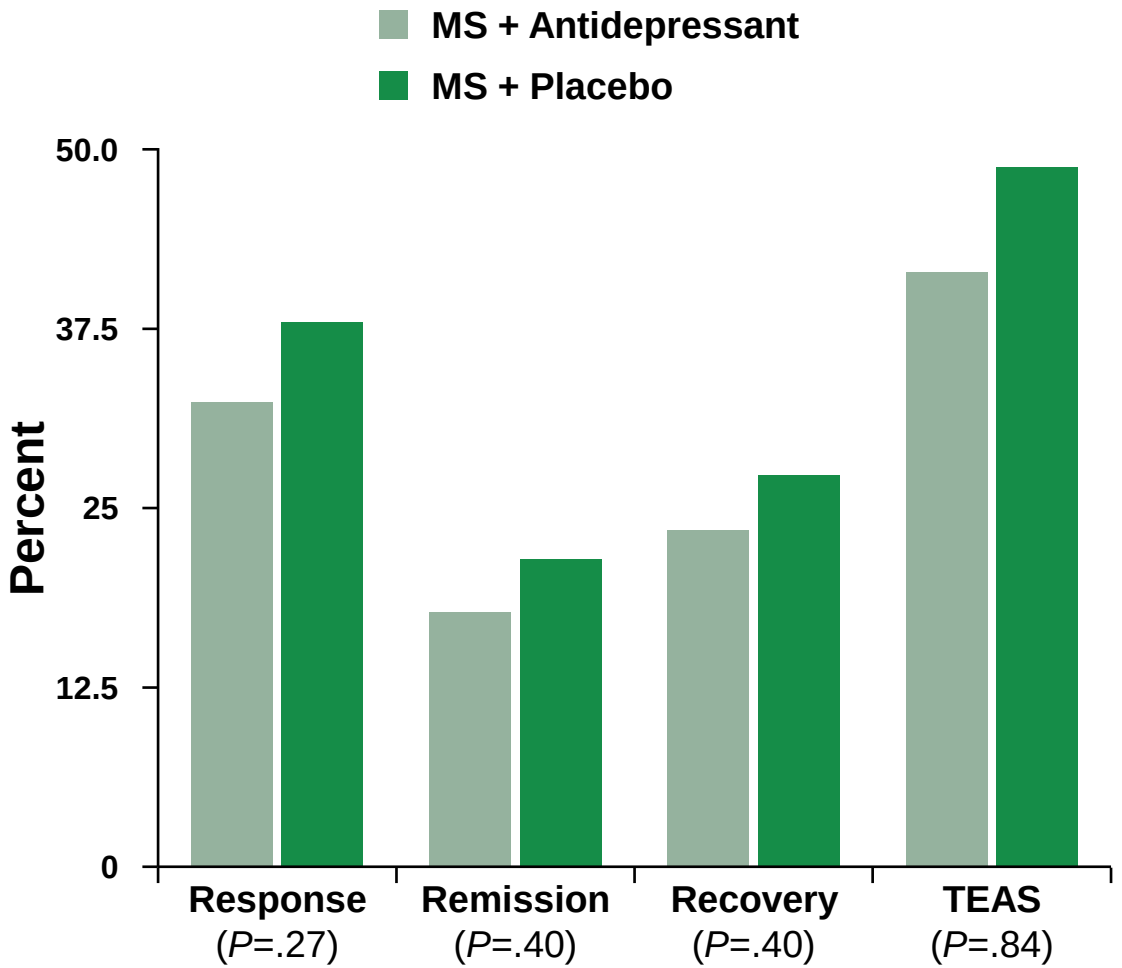
Altshuler L, et al. *Am J Psychiatry*. 2003;160(7):1252-1262. El-Mallakh RS, et al. *J Affect Disord*. 2015;184:318-321. Pacchiarotti I, et al. *Am J Psychiatry*. 2013 Nov;170(11):1249-62. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835.

Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD)

366 patients in an acute episode of bipolar depression

26 weeks of treatment with MS + placebo vs MS + antidepressant (bupropion or paroxetine)

Allowed patients with bipolar I or II, coexisting anxiety, substance use disorders, or psychotic symptoms

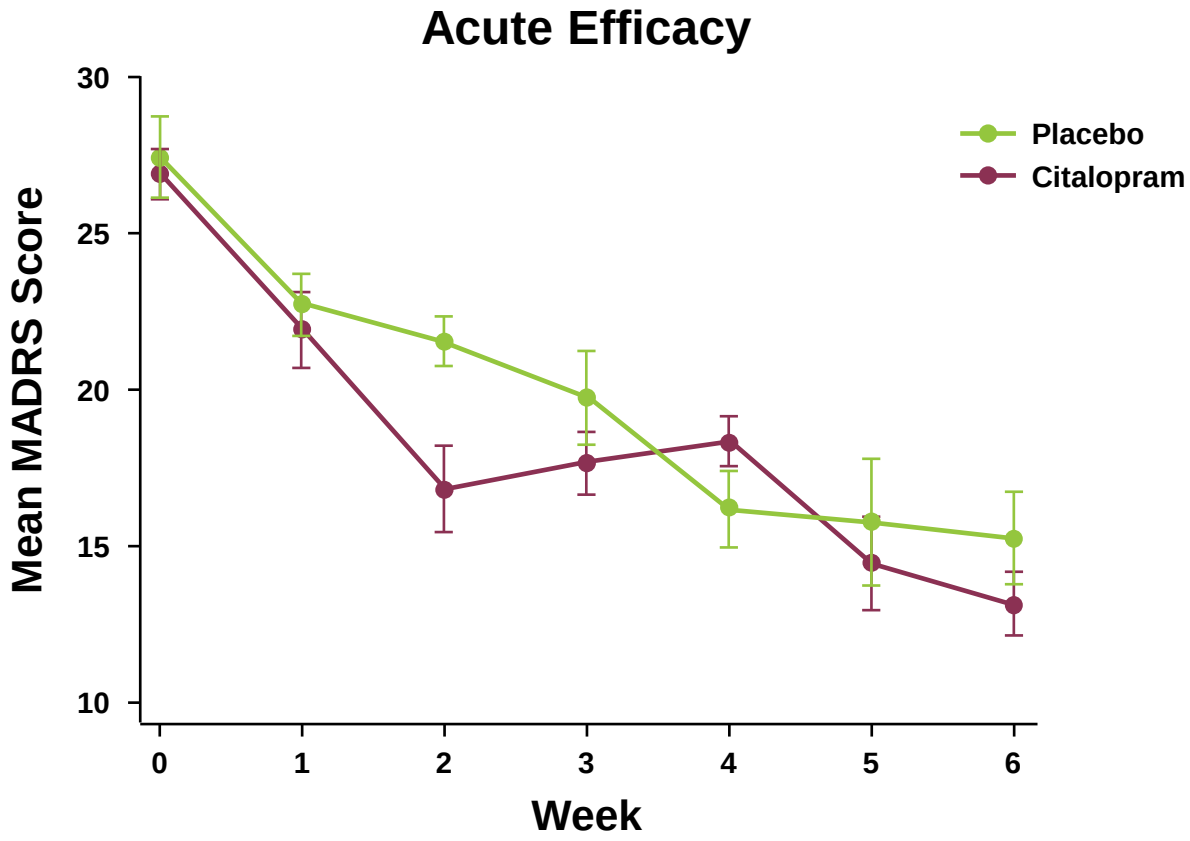


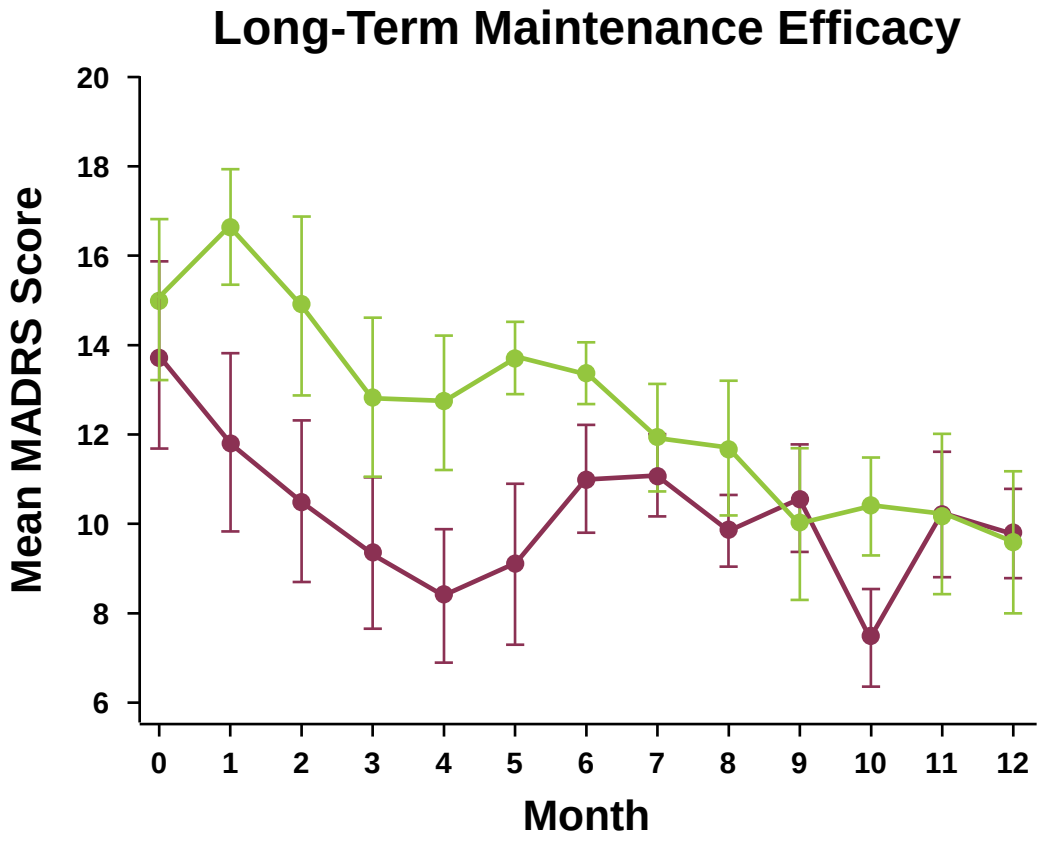
TEAS = treatment emergent affective switch.

Sachs GS, et al. *N Engl J Med*. 2007;356(17):1711-1722.

Citalopram for Acute and Preventive Efficacy in Bipolar Depression (CAPE-BD)

First placebo-controlled RCT (N=119) of any SRI in 1-year maintenance prevention of depressive episodes in bipolar disorder.





MADRS = Montgomery–Åsberg Depression Rating Scale; RCT = randomized controlled trial; SRI = serotonin reuptake inhibitor.

Ghaemi SN, et al. *J Clin Psychiatry*. 2021;82(1):19m13136.

Limitations of Other Treatments

Oral Antipsychotics

- Increased suicidality <25 yo*
- Drug-induced movement disorders
  - Akathisia, dystonia, DIP, TD
- Sedation
- Weight gain
- Metabolic disorders
- Prolactin elevation
- FGAs may induce depression

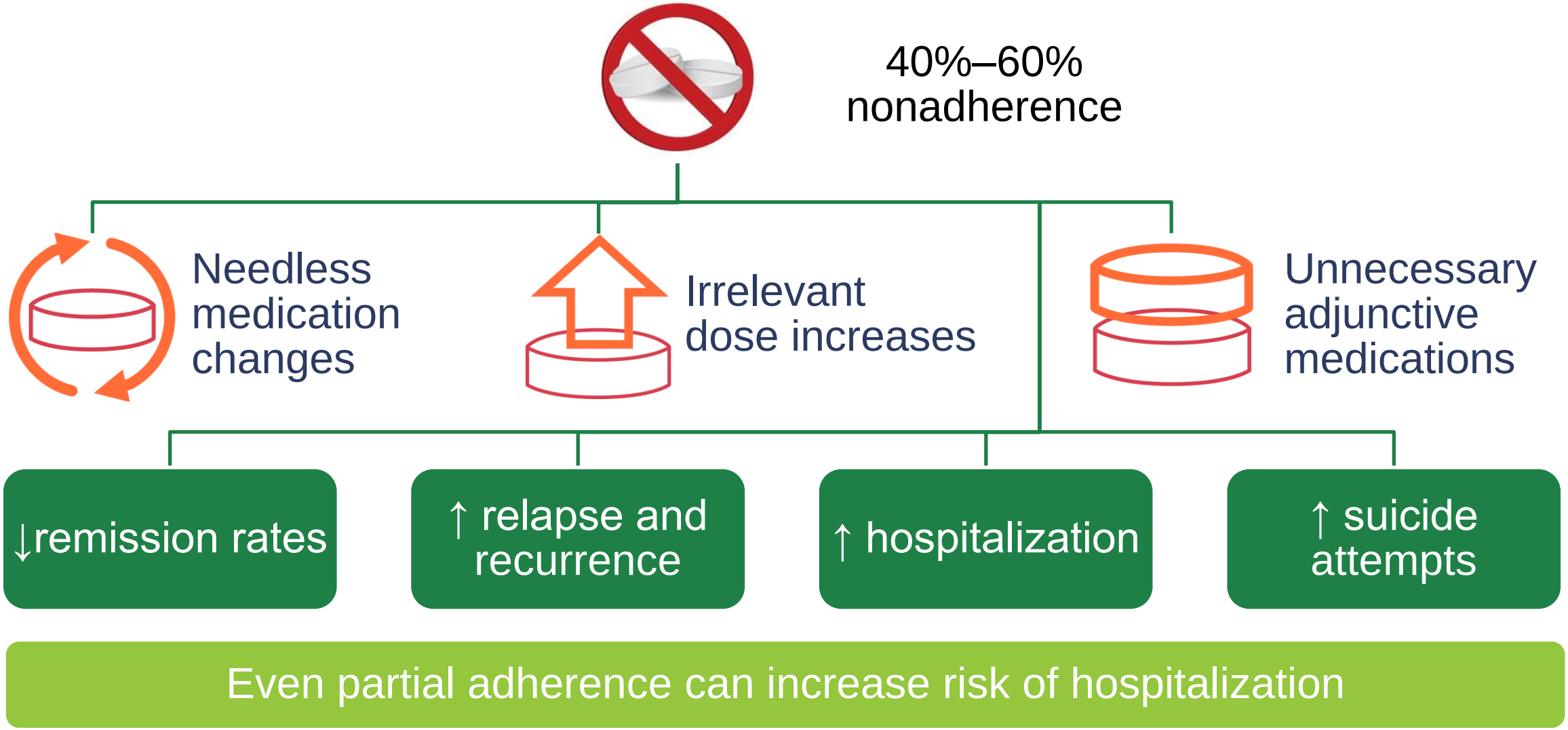
Oral Medications

- Large peak–trough ratios
- Blood levels may decline very quickly if just a few doses missed
- Subject to first pass metabolism
- May have food–drink restrictions
- Unknown if actually taken

***Boxed warning in USPI. DIP = drug-induced parkinsonism; FGA = first-generation antipsychotic; TD = tardive dyskinesia.**

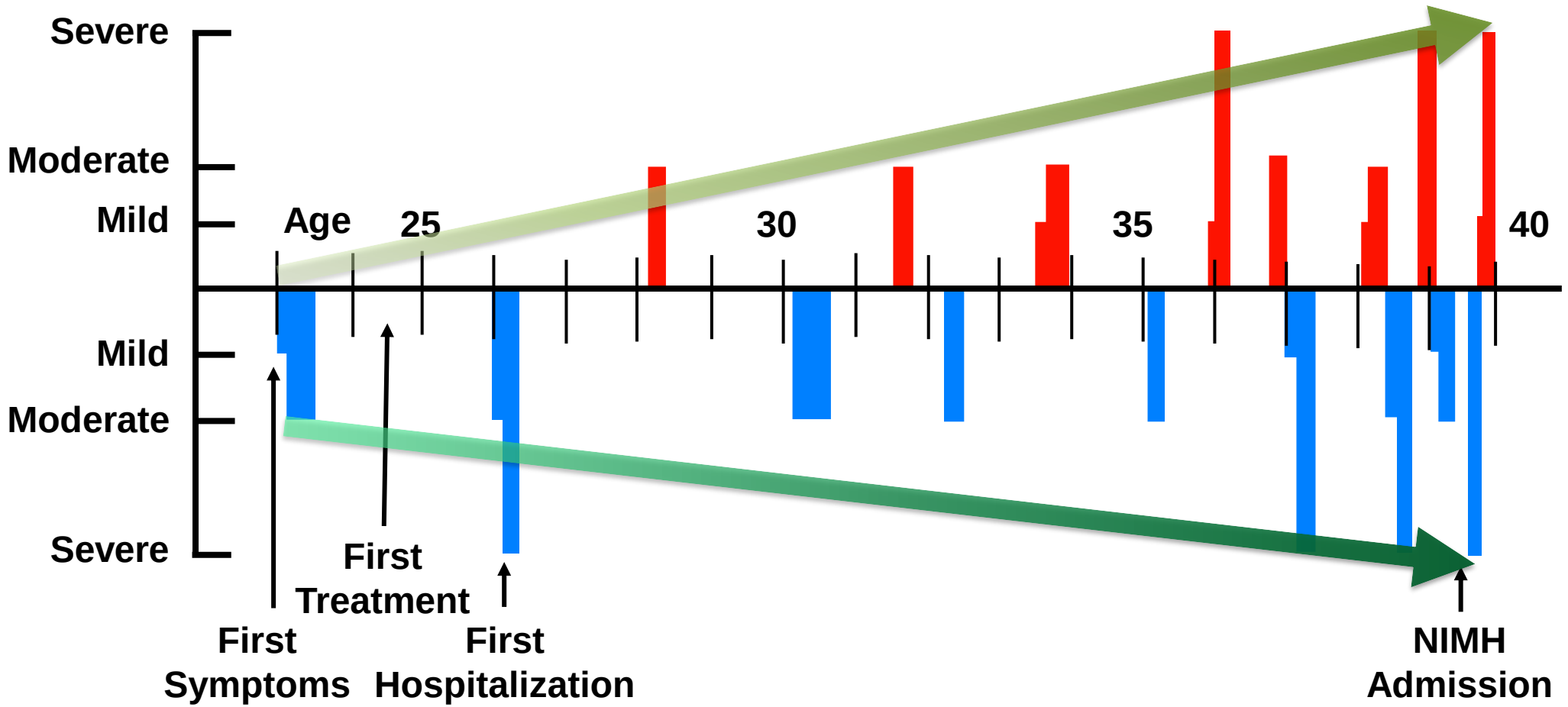
US Food and Drug Administration. Drugs@FDA: FDA Approved Drug Products. www.accessdata.fda.gov/scripts/cder/daf/. Kane JM. *J Clin Psychiatry*. 2004;65 Suppl 9:16-20. Mauri MC, et al. *Clin Pharmacokinet*. 2018;57(12):1493-1528. Colom F, et al. *Bipolar Disord*. 2005;7 Suppl 5:24-31. Correll CU, et al. *JAMA Psychiatry*. 2014;71(12):1350-1363. Gigante AD, et al. *CNS Drugs*. 2012;26(5):403-420.

Burden of Nonadherence in Bipolar Disorder



Hong J, et al. *Psychiatry Res*. 2011;190(1):110-114. Velligan DI, et al. *J Clin Psychiatry*. 2009;70 Suppl 4:1-46. Levin JB, et al. *CNS Drugs*. 2016;30(9):819-835. Scott J, et al. *Am J Psychiatry*. 2002;159(11):1927-1929. Svarstad BL, et al. *Psychiatr Serv*. 2001;52(6):805-811.

Median Course of Illness in 82 Patients with Treatment-Resistant Bipolar Disorder



Post RM, et al. *Am J Psychiatry*. 1988;145(7):844-848.

Key Learning Point

Patients with bipolar disorder are about 40% to 60% nonadherent to their medication regimens.

LAI Landscape in Bipolar I Disorder

Leslie Citrome, MD, MPH

Clinical Professor of Psychiatry and Behavioral Sciences

New York Medical College

Valhalla, New York

Overview of FDA-Approved Agents for Bipolar Disorder

Only 2 are LAIs

Acute Mania

- 1970 Lithium
- 1973 Chlorpromazine
- 1996 Divalproex, ER (2005)
- 2000 Olanzapine*, Olanzapine+Samidorphan (2021)*
- 2003 Risperidone*
- 2004 Quetiapine, XR (2008)*; Ziprasidone; Aripiprazole*; Carbamazepine ERC
- 2015 Asenapine*
- 2019 Cariprazine

Acute Depression

- 2003 Olanzapine+fluoxetine
- 2004 Quetiapine, XR (2008)
- 2013 Lurasidone*
- 2019 Cariprazine

Long-Term Maintenance

- 1974 Lithium
- 2003 Lamotrigine
- 2004 Olanzapine, Olanzapine+Samidorphan (2021)
- 2005 Aripiprazole*
- 2008 Quetiapine, XR*
- 2009 **Risperidone LAI***; Ziprasidone*
- 2017 **Aripiprazole monohydrate LAI**

***Adjunctive and monotherapy.**

Updated from: Butler M, Urosevic S, Desai P, et al. Treatment for Bipolar Disorder in Adults: A Systematic Review. Rockville (MD): Agency for Healthcare Research and Quality (US); 2018 Aug. (Comparative Effectiveness Review, No. 208.)

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.* American Psychiatric Association Publishing; 2013.

Risperidone Microspheres

In 2009, risperidone microspheres received FDA approval as a monotherapy or as adjunctive therapy to lithium or valproate for the maintenance treatment of BD-I

Author, Year	N	Design Details	Outcome
Macfadden W, et al. 2009	240	• Adjunctive study • Patients were enrolled with bipolar disorder type I or type II but there were very few enrolled patients with bipolar disorder type II and were not included in the published report. Patients in any phase of bipolar illness (manic, hypomanic, depressed, mixed or euthymic) at study entry were included • 16-week, open-label stabilization phase with risperidone microspheres 25–50 mg every 2 weeks plus “treatment as usual”, 52-week, double-blind, placebo-controlled, relapse-prevention phase	• Time to relapse was longer in patients receiving adjunctive risperidone microspheres; relative relapse risk was 2.3-fold higher with adjunctive placebo and did not differ among relapse episode types • Relapse rates for adjunctive risperidone microspheres vs placebo were 15/65 (23.1%) vs 27/59 (45.8%), for a NNT of 5 (95% CI 3–16) • AEs: tremor (24.6% vs 10.2%), insomnia (20.0% vs 18.6%), muscle rigidity (12.3% vs 5.1%), weight increased (6.2% vs 1.7%), and hypokinesia (7.7% vs 0.0%). Potential prolactin-related AEs were 6.2% vs 5.1%. Weight gain ≥7% was 28.1% vs 31.0%

AE = adverse event; NNT = number needed to treat.

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043. Macfadden W, et al. *Bipolar Disord*. 2009;11(8):827-839.

Risperidone Microspheres (cont'd)

Author, Year	N	Design Details	Outcome
Quiroz JA, et al. 2010	559	• Monotherapy study • Acute manic or mixed episode, or were stable on risperidone (oral or LAI), or on other oral antipsychotics or mood stabilizers but requiring change due to safety or tolerability concerns • 3-week open-label oral risperidone treatment phase and a 26-week open-label risperidone microspheres 25–50 mg every 2 weeks treatment phase, 24 months double-blind, placebo-controlled, relapse-prevention phase	• Time to recurrence for any mood episode was longer in patients receiving risperidone microspheres; hazard ratio .40 (95% CI .27–.59) – ie, recurrence risk was 2.5-fold higher with placebo • The difference was significant for time to recurrence of elevated-mood episode but not time to recurrence of depressive episode • Recurrence rates for risperidone microspheres vs placebo were 42/140 (30.0%) vs 76/135 (56.3%), for a NNT of 4 (95% CI 3–7) • AEs: weight increased (4.6% vs 0.7%), headache (7.1% vs 6.7%), insomnia (7.8% vs 6.0%). Potential prolactin-related AEs were 4% vs 1%. Weight gain ≥7% was 12% vs 3%

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043. Quiroz JA, et al. *Biol Psychiatry*. 2010;68(2):156-162.

Risperidone Microspheres (cont'd)

Author, Year	N	Design Details	Outcome
Vieta E, et al. 2012	560	• Monotherapy study with olanzapine as active control • Acute manic or non-acute • 12-week open-label period with risperidone microspheres, 18-month randomized, double-blind period	• Time to recurrence of any mood episode did not differ significantly between risperidone microspheres vs placebo • Recurrence rates for risperidone microspheres vs placebo were 51/131 (38.9%) vs 75/133 (56.4%), for a NNT of 6 (95% CI 4–18) • Recurrence rate for oral olanzapine was 31/130 (23.7%), for a NNT vs placebo of 4 (95% CI 3–5) and a NNT vs risperidone microspheres of 7 (95% CI 4–26) • AEs: weight increased (24.2% vs 8.9%), amenorrhea (8.3% vs 2.2%), galactorrhea (5.3% vs 0), somnolence (6.1% vs 3.0%), fatigue (3.8% vs 0). Potential prolactin-related AEs were 14% vs 3%. Weight gain >7% was 18% vs 5%

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043. Vieta E, et al. *Eur Neuropsychopharmacol*. 2012;22(11):825-835.

Risperidone Microspheres

- An obstacle to the use of risperidone microspheres is its absorption characteristics: there is a small initial release of the drug (<1% of the dose), followed by a lag time of 3 weeks, with the main release of the drug starting from 3 weeks onward, thus supplemental oral risperidone is required for 21 days after the first injection **and after any dose increase**

- Risperidone is rapidly metabolized by CYP2D6 to 9-OH-risperidone (paliperidone), which has also been commercialized as an LAI antipsychotic approved for the treatment of schizoaffective disorder but not approved for the treatment of bipolar disorder

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

Aripiprazole Monohydrate

In 2017, aripiprazole monohydrate received FDA approval for the indication of maintenance monotherapy treatment of BD-I

Author, Year	N	Design Details	Outcome
Calabrese JR, et al. 2017	632	• Monotherapy study • Acute manic • Conversion to oral aripiprazole monotherapy for 4–6 weeks, oral stabilization for 2–8 weeks, single-blind aripiprazole monohydrate stabilization for 12–28 weeks, 52-week randomized, double-blind period	• Aripiprazole monohydrate significantly delayed the time to recurrence of any mood episode compared with placebo (hazard ratio 0.45; 95% CI 0.30–0.68) • Recurrence rates of any mood episode were 35/132 (26.5%) with aripiprazole monohydrate vs 68/133 (51.1%) for placebo, resulting in a NNT vs placebo of 5 (95% CI 3–8) • The treatment effects observed were predominantly on manic episodes; there was no difference between treatments for recurrence of depressive episodes • AEs: weight increase (23.5% vs 18.0%), akathisia (21.2% vs 12.8%), insomnia (7.6% vs 7.5%), anxiety (6.8% vs 4.5%), and parkinsonism events (5.3% vs 3.8%)

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043. Calabrese JR, et al. J *Clin Psychiatry*. 2017;78(3):324-331.

Aripiprazole Monohydrate (cont'd)

Aripiprazole Monohydrate 400 mg/4 Weeks for Maintenance of BD-I: Recurrence by Type of Mood Episode and NNT

	Placebo (N=133)		Aripiprazole Monohydrate (N=132)		
Type of Recurrence	**n**	**%**	**n**	**%**	**NNT (95% CI)**
Any Mood Episode	68	51.1	35	26.5	5 (3–8)
Mania	40	30.1	12	9.1	5 (4–9)
Depression	19	14.3	20	15.2	-116 (ns)[a]
Mixed	9	6.8	2	1.5	19 (10–200)

NNT values calculated by the author.
[a]A negative value for NNT results when the favorable outcome was observed more frequently with placebo.
ns = not significant (95% CI for the NNT includes infinity).
Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043. Calabrese JR, et al. J *Clin Psychiatry*. 2017;78(3):324-331.

Aripiprazole Monohydrate

- Supplemental oral antipsychotic is required for 14 days after the first injection

- Use as adjunctive treatment not explicitly approved

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

Amenities of Care

How often are the injections administered?
What is the needle gauge?
What is the injection volume?
Is there a choice of injection site?
Does this product require reconstitution?
Is oral supplementation required?
Does storage of this product require refrigeration?
Are there any special requirements for post-injection observation?
Are there any important drug–drug interactions, and can they be remedied?
Missed doses: What is the “grace period?”
Is reimbursement an issue if used “off-label”?
In case of reimbursement obstacles, can I easily access a patient assistance program?

Citrome L. *CNS Spectr*. 2021;26(2):118-129.

Summary of Characteristics

	Risperidone Microspheres	Aripiprazole Monohydrate
Brand Name (US)	Risperdal Consta®	Abilify Maintena®
Year Commercialized	2003	2013
Active Moiety	Risperidone and 9-OH-risperidone	Aripiprazole and dehydro-aripiprazole
Approved Indications	Schizophrenia; BD-I maintenance treatment (monotherapy or adjunctive to lithium or valproate)	Schizophrenia; BD-I maintenance treatment (monotherapy)
Contraindications	Known hypersensitivity	Known hypersensitivity
Dosage Forms/Strengths	Vial kits: 12.5 mg, 25 mg, 37.5 mg, 50 mg	Vial kits and dual-chambered pre-filled syringes: 300 mg, 400 mg
Requires Adding Diluent	Yes	Yes
Approved Injection Sites	Deltoid or gluteal muscle	Deltoid or gluteal muscle
Needle Gauge	20 G or 21 G	21, 22, or 23 G
Injection Volume	Approximately 2 mL	200 mg/mL; range 0.8 mL (160 mg) to 2 mL (400 mg)
Injection Interval (weeks)	2	4
Starting Dose	25 mg	400 mg
Maintenance Dose	25 mg, maximum 50 mg/2 weeks	300 or 400 mg/4 weeks
Half-life	3–6 days	29.9 days (300 mg), 46.5 days (400 mg)
Oral Supplementation?	21 days after the initial injection and after any change in dose	14 days after the initial injection
Missed Dose Grace Period*	No data	Up to 2 weeks
Early Dosing Permitted?	No data	26 days after last injection
Refrigeration?	Yes	No

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

Drug Interactions and Adverse Reactions per PI

Medication	Drug Interactions	Adverse Reactions
Risperidone Microspheres	Due to CNS effects, use caution when administering with other centrally-acting drugs; avoid alcohol. Due to hypotensive effects, hypotensive effects of other drugs with this potential may be enhanced. Effects of levodopa and dopamine agonists may be antagonized. Cimetidine and ranitidine increase the bioavailability of risperidone. Clozapine may decrease clearance of risperidone. Fluoxetine and paroxetine increase plasma concentrations of risperidone. Carbamazepine and other enzyme inducers decrease plasma concentrations of risperidone.	The most common adverse reactions in clinical trials in patients with schizophrenia (≥5%) were headache, parkinsonism, dizziness, akathisia, fatigue, constipation, dyspepsia, sedation, weight increased, pain in extremity, and dry mouth. The most common adverse reactions in clinical trials in patients with bipolar disorder were weight increased (5% in monotherapy trial) and tremor and parkinsonism (≥10% in adjunctive therapy trial). The most common adverse reactions that were associated with discontinuation from clinical trials in patients with schizophrenia were agitation, depression, anxiety, and akathisia. Adverse reactions that were associated with discontinuation from bipolar disorder trials were hyperglycemia (one subject monotherapy trial) and hypokinesia and tardive dyskinesia (one subject each in adjunctive therapy trial).
Aripiprazole Monohydrate	Dose adjustments for patients who are taking CYP2D6 and/or CYP3A4 inhibitors for greater than 14 days; avoid use in patients taking CYP3A4 inducers for greater than 14 days.	Most commonly observed adverse reactions with aripiprazole monohydrate (incidence ≥5% and at least twice that for placebo) were increased weight, akathisia, injection site pain, and sedation.

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

Bottom Line

Effect Sizes in Maintenance Treatment Similar across the Medications and Indications

Disorder	Antipsychotic	Relapse or Recurrence		
		Rate (%)		NNT
		Placebo	Drug	(95% CI)
Schizophrenia	Paliperidone palmitate monthly, flexibly dosed, 39–156 mg/4 weeks	34.0	9.6	5 (4–7)
	Paliperidone palmitate 3-month, flexibly dosed, 273–819 mg/12 weeks	29.0	8.8	5 (4–9)
	Aripiprazole monohydrate, 400 mg/4 weeks	39.6	10.0	4 (3–5)
	Olanzapine pamoate 150 mg/2 weeks	29.2	15.7	8 (5–26)
	Olanzapine pamoate 300 mg/2 weeks	29.2	5.0	5 (4–7)
	Olanzapine pamoate 405/4 weeks	29.2	12.3	6 (4–12)
Schizoaffective Disorder	Paliperidone palmitate monthly, flexibly dosed, 78–156 mg/4 weeks	33.5	15.2	6 (4–11)
Bipolar Disorder	Risperidone microspheres, adjunctive therapy, flexibly dosed, 25–50 mg/2 weeks	45.8	23.1	5 (3–16)
	Risperidone microspheres, monotherapy, flexibly dosed, 25–50 mg/2 weeks	56.3	30.0	4 (3–7)
	Aripiprazole monohydrate, 400 mg/4 weeks	51.1	26.5	5 (3–8)

Prevention of relapse or recurrence as quantified using NNT vs placebo (vs 45 mg/4 weeks for olanzapine pamoate), data from US registration trials

Citrome L. *Expert Rev Neurother*. 2017;17(10):1029-1043.

Bottom Line

Treatment Polarity Index May Be of Interest

	NNT Mania	NNT Depression	Polarity Index
Aripiprazole-weighted mean Keck et al., 2007; Marcus et al., 2011	8.81	38.55	4.38
Aripiprazole monotherapy Keck et al., 2007	6.2	50	8.06
Aripiprazole combined with lithium / divalproex Marcus et al., 2011	10	33.3	3.33
Lamotrigine Bowden et al., 2003; Calabrese et al., 2003	50.4	20.2	0.40
Lithium Bowden et al., 2003; Calabrese et al., 2003; Weisler et al., 2008; Prien et al., 1973; Bowden et al., 2000	4.4	6.1	1.39
Olanzapine-weighted mean Tohen et al., 2004; Tohen et al., 2006; Vieta et al., accepted for publication	4.7	14	2.98
Olanzapine monotherapy Tohen et al., 2006; Vieta et al., accepted for publication	4.4	17.2	3.90
Olanzapine combined with lithium / divalproex Tohen et al., 2004	11.2	6.2	0.55
Oxcarbazepine Vieta et al., 2008b	8.2	5.1	0.62
Quetiapine-weighted mean Weisler et al., 2008; Vieta et al., 2008a; Suppes et al., 2009	3.5	4	1.14
Quetiapine combined with lithium / divalproex Vieta et al., 2008a; Suppes et al., 2009	7.1	5.9	0.83
Quetiapine monotherapy Weisler et al., 2008	2.4	3.3	1.38
Risperidone LAI Vieta et al., accepted for publication; Quiroz et al., 2010; Macfadden et al., 2009	4.4	53.2	12.09
Risperidone LAI monotherapy Vieta et al., accepted for publication; Quiroz et al., 2010	4	36.4	9.1
RLAI + treatment as usual Macfadden et al., 2009	7.9	15.8	2
Valproate Bowden et al., 2000	21.3	10.5	0.49
Ziprasidone Bowden et al., 2010	14.1	55.1	3.91

Popovic D, et al. *Eur Neuropsychopharmacol*. 2012;22(5):339-346.

Key Learning Point

There are only 2 LAI antipsychotics FDA-approved for the treatment of BD-I: aripiprazole monohydrate and risperidone microspheres.

Identifying Appropriate Patients for LAI Antipsychotics

Michele Bibby, CPS, PHR

DBSA

Depression and Bipolar Support Alliance

GAIN Approach to LAI

(Goal setting, Action planning, Initiating treatment, and Nurturing motivation)

Goal Setting	Identify patient-based reasons for using antipsychotic LATs to help patients achieve long-term goals; discuss personal life, treatment goals, and realistic goal selection with patient.
Action Planning	With the patient and family, assess and consider actions necessary to achieve goals and discuss how LAT may specifically enable patients to attain the goals.
Initiate Treatment	Begin the new treatment plan, review practical aspects of treatment and which issues could interfere with treatment, and confirm the recognition and acceptance that use of an LAT can help reduce the risk of relapse.
Nurturing Motivation	Undertake proactive discussions around the use of LATs with the patient, family, and treatment team; assess progress toward goals.

LAT = long-acting therapy.

Lasser RA, et al. *Psychiatry*. 2009;6(4):22-27.

Strategies for Effective and Timely Patient–Provider Communication

Craig Chepke, MD, FAPA
Adjunct Associate Professor of Psychiatry, Atrium Health
Adjunct Assistant Professor of Psychiatry, UNC School of Medicine
Medical Director, Excel Psychiatric Associates
Huntersville, North Carolina

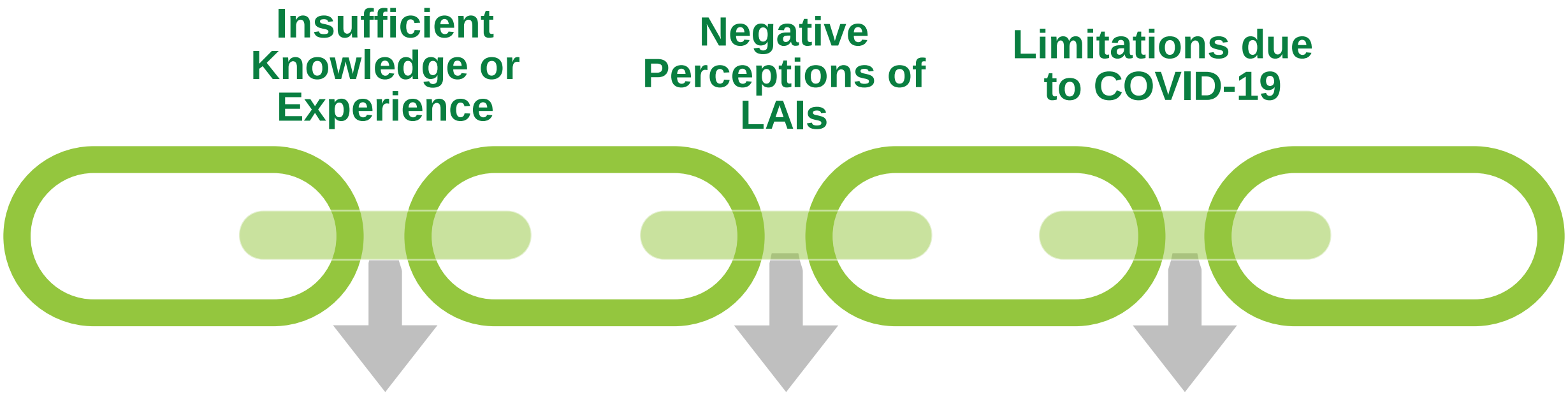
Knowledge is Power

Patient Barriers

- Lack of Awareness
- Limited Insurance Coverage
- Sense of Coerciveness
- Frequent Clinic Visits
- Fear of Injections or Needles

Getzen H, et al. *Ann Clin Psychiatry*. 2014;26(1):33-38. Lindenmayer JP, et al. *J Clin Psychopharmacol*. 2020;40(4):346-349. Potkin S, et al. *BMC Psychiatry*. 2013;13:261.

Clinician Barriers



PA = prior authorization.

Lindenmayer JP, et al. *J Clin Psychopharmacol*. 2020;40(4):346-349. Weiden PJ, et al. *J Clin Psychiatry*. 2015;76(6):684-690. Velligan DI, et al. *Patient Prefer Adherence*. 2017;11:919-928.

Addressing Barriers

- Say Anything! …and be persistent
- 91% of people with SMI want involvement in decisions about their care
- 67% of AP treatment decisions were made without patient or care partner input
- LAIs were not discussed with 50% of patients taking oral APs, but over half agreed to begin LAIs after discussing them
- Build the alliance using shared decision-making

SMI = serious mental illness.

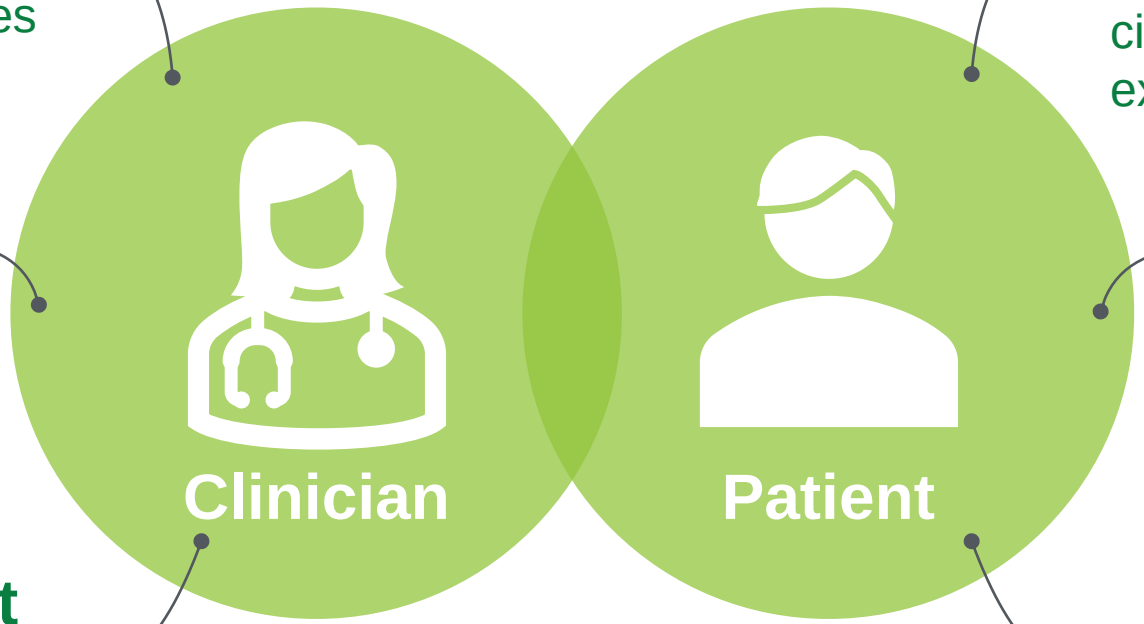
Velligan DI, et al. *Patient Prefer Adherence*. 2017;11:919-928. Potkin S, et al. *BMC Psychiatry*. 2013;13:261.

Shared Decision-Making

Provides knowledge about the condition
Including etiology, prognosis, and potential outcomes

Inquires about patient preference
Prior medication trials, lifestyle, and limitations

Shares insight about treatment options
Including risks, benefits, side effects, and alternatives



Shares experience and values
Preferences, socioeconomic circumstances, and experience of illness

Voices their concerns
Including personal risk tolerance and accessibility of treatment

Asks questions of the provider
Regarding treatment options, outcomes, anecdotal experience

Elwyn G, et al. *J Gen Intern Med*. 2012;27(10):1361-1367.

Key Learning Point

67% of treatment decisions are made without patient or caregiver/partner input.

Essential Shared Decision-Making Strategies to Optimize Treatment

Michele Bibby, CPS, PHR

DBSA

Depression and Bipolar Support Alliance

GAIN Approach to LAI

(Goal setting, Action planning, Initiating treatment, and Nurturing motivation)

Goal Setting	Identify patient-based reasons for using antipsychotic LATs to help patients achieve long-term goals; discuss personal life, treatment goals, and realistic goal selection with patient.
Action Planning	With the patient and family, assess and consider actions necessary to achieve goals and discuss how LAT may specifically enable patients to attain the goals.
Initiate Treatment	Begin the new treatment plan, review practical aspects of treatment and which issues could interfere with treatment, and confirm the recognition and acceptance that use of an LAT can help reduce the risk of relapse.
Nurturing Motivation	Undertake proactive discussions around the use of LATs with the patient, family, and treatment team; assess progress toward goals.

Lasser RA, et al. *Psychiatry*. 2009;6(4):22-27.

Roleplay Workshop

GAIN Approach to LAI

(Goal setting, Action planning, Initiating treatment, and Nurturing motivation)

Goal Setting	Action Planning	Initiate Treatment	Nurturing Motivation
Establish clinical need for improvement	Show the patient that you, as a clinician, believe that treatment with an LAT may be an overall positive step	Manage patient perceptions and experience	Engage the patient in dialogue and listen carefully
Provide sensitive feedback	Review the potential benefits and risks of LAT and explain how it works		After a few months of therapy, discuss the long-term treatment plan
Create a written goal plan with the patient	Re-link the specific goals potentially achievable with the help of an LAT		
Collaborate with the patient on a plan of action to achieve goal			

Lasser RA, et al. *Psychiatry*. 2009;6(4):22-27.

Instructions

- Please team up with 2 other people at your table.
- One person will act as a clinician, one person will act as a patient, and the third person will observe the interactions between the “clinician” and “patient.” After the end of the exercise, you will switch roles as patient and clinician.
- Please use the GAIN Approach Dr. Citrome and Dr. Chepke demonstrated to help the patient overcome their barriers.
- After the exercises are over, we will discuss them as a group.
- Have fun!

Exercise #1

The patient tells you:

"Injections hurt and I don't like pain. I don't think I want these shots you keep talking about."

Goal Setting	Identify patient-based reasons for using antipsychotic LATs to help patients achieve long-term goals; discuss personal life, treatment goals, and realistic goal selection with patient.
Action Planning	With the patient and family, assess and consider actions necessary to achieve goals and discuss how LAT may specifically enable patients to attain the goals.
Initiate Treatment	Begin the new treatment plan, review practical aspects of treatment and which issues could interfere with treatment, and confirm the recognition and acceptance that use of an LAT can help reduce the risk of relapse.
Nurturing Motivation	Undertake proactive discussions around the use of LATs with the patient, family, and treatment team; assess progress toward goals.

Please take 5 minutes to use the Gain Approach to explore your patient's concerns and to resolve them.

Exercise #2

Please switch patient – clinician roles with your partners.

The patient tells you:

“I don’t wanna drop my pants to get a shot in my butt! That’s embarrassing. I don’t want these injections.”

Goal Setting	Identify patient-based reasons for using antipsychotic LATs to help patients achieve long-term goals; discuss personal life, treatment goals, and realistic goal selection with patient.
Action Planning	With the patient and family, assess and consider actions necessary to achieve goals and discuss how LAT may specifically enable patients to attain the goals.
Initiate Treatment	Begin the new treatment plan, review practical aspects of treatment and which issues could interfere with treatment, and confirm the recognition and acceptance that use of an LAT can help reduce the risk of relapse.
Nurturing Motivation	Undertake proactive discussions around the use of LATs with the patient, family, and treatment team; assess progress toward goals.

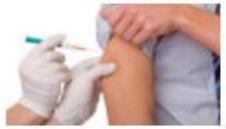
Please take 5 minutes to use the Gain Approach to explore your patient’s concerns and to resolve them.

Resource Centers

LAI 360 LONG-ACTING INJECTABLES

LAI Plus Counseling Improves Adherence, Symptoms in Patients with Bipolar Disorder
10/19/2021

Six-Month LAI for Treatment of Schizophrenia in Adults Approved by FDA
09/28/2021



LAIs Reduced Risk of Treatment Dis Schizophrenia
08/18/2021

LAIs Associated With Improved Me Benefit
06/29/2021

Barriers to LAI Use Span Prescriber, Patient, Administrative Realms
05/27/2021

Increased Use of LAIs Could Improve Schizophrenia Outcomes, Meta-Analysis Finds
04/20/2021

www.hmpgloballearningnetwork.com/site/psychbehav/meeting/lai360

BIPOLAR 360

Lumateperone Improves Major Depressive Symptoms in Patients with Bipolar Disorder
10/19/2021
Six weeks of daily lumateperone significantly improved depressive symptoms in patients with bipolar disorder experiencing a major depressive episode, study finds.

Two Years of Lurasidone Appear Safe, Effective in Adolescents with Bipolar Depression
08/18/2021
Up to 2 years of treatment with the antipsychotic lurasidone in children and adolescents with bipolar depression was generally safe, effective, and well-tolerated in an open-label extension study.

Trauma Appears to Increase Risk of Suicide Death in Patients with Bipolar Disorder
07/30/2021
Post-traumatic stress disorder (PTSD) and personality disorder diagnoses were more common among patients with bipolar disorder who died from suicide compared with those who attempted suicide but lived.

www.hmpgloballearningnetwork.com/site/psychbehav/microsite/bipolar360

Access the latest clinical updates in the treatment of schizophrenia and bipolar disorder, including videos highlighting best practices and motivational interviewing techniques.

Q&A