Psych Congress

LONG-ACTING INJECTABLE ANTIPSYCHOTICS:

Newer Strategies for the Optimal Management of Bipolar I Disorder

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Faculty Disclosures

- **Dr. Christoph Correll:** Advisory Board—AbbVie, Acadia, Alkermes, Allergan, Angelini, Aristo, Axsome, Cardio Diagnostics, CNX Therapeutics, Compass, Damitsa, Gedeon Richter, Hikma, Holmusk, IntraCellular Therapies, Janssen/J&J, Karuna, LB Pharma, Lundbeck, MedAvante-ProPhase, MedInCell, Medscape, Merck, Mindpax, Mitsubishi Tanabe Pharma, Mylan, Neurocrine, Noven, Otsuka, Pfizer, Pharmabrain, Recordati, Relmada, Reviva, Rovi, Seqirus, Servier, SK Life Science, Sumitomo Dainippon, Sunovion, Sun Pharma, Supernus, Takeda, Teva, and Viatris; Grant/Research Support—Janssen, National Institute of Mental Health (NIMH), Patient Centered Outcomes Research Institute (PCORI), Takeda, Thrasher Foundation; Profit Shares—Cardio Diagnostics, Mindpax, LB Pharma (options).

- **Dr. Veronica Ridpath** has disclosed no relevant financial relationship with any ineligible company (commercial interest).

- **Ms. Vanessa Joy Walker** has disclosed no relevant financial relationship with any ineligible company (commercial interest).

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).
  - For this presentation we will discuss long-acting injectable medications that are pharmacologically related to medications that have FDA indication for bipolar disorder
  - First generation long acting injectable medications such as haloperidol decanoate and fluphenazine decanoate do not have indication for bipolar disorder
  - Olanzapine pamoate monohydrate not indicated for bipolar disorder and limited in use due to monitoring requirements and REMS program
- Applicable CME staff have no relationships to disclose relating to the subject matter of this activity.
- This activity has been independently reviewed for balance.

Learning Objectives

- Describe current barriers to the optimal management of bipolar disorder and the consequences of treatment nonadherence on long-term outcomes in BD-I, including reduced functioning and mood episode recurrence
- Assess safety and efficacy data regarding the use of LAI antipsychotics in the treatment of BD-I
- Implement strategies in clinical practice to identify patients who may benefit from the earlier initiation of LAI antipsychotic treatment
- Employ effective communication and patient-centered care for illness prevention and improved long-term outcomes in patients with BD-I

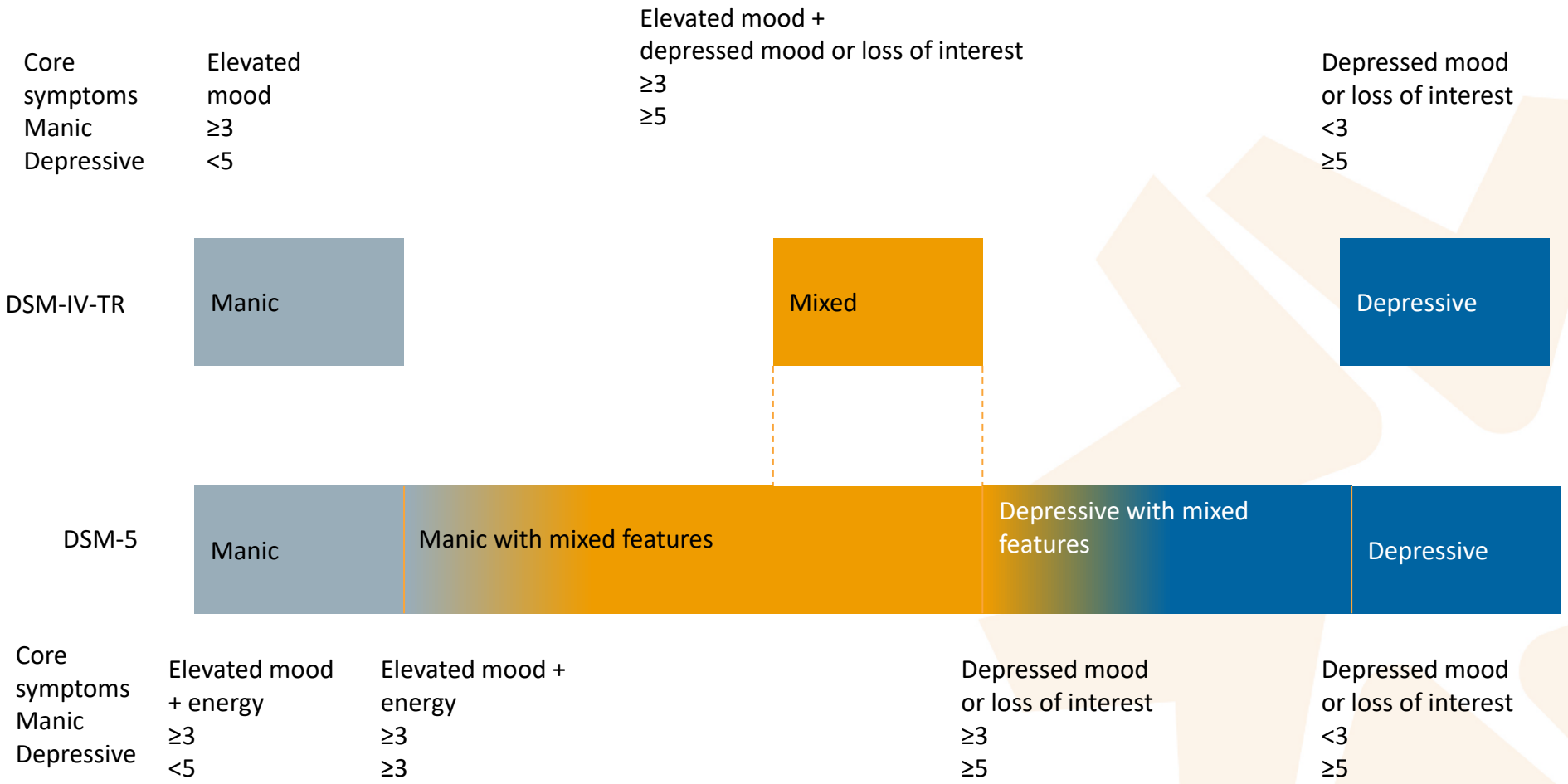
Limitations of Traditional Treatment Options in Bipolar I Disorder

Bipolar Subtyping

Specifier	Manic episode	Depressive episode	Illness course
Anxious distress	X	X	
Mixed features	X	X	
Rapid cycling			X
Melancholic features		X	
Atypical features		X	
Psychotic features	X	X	
Catatonia	X	X	
Peripartum onset	X	X	
Seasonal pattern			X
Remission	X	X	
Current episode severity	X	X	

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

The Bipolar/Unipolar Spectrum



Hu. Prim Care Companion CNS Disord. 2014;16:PCC.13r01599.

12-Month Prevalence of Untreated Mental Disorders in the US

Table 1. Prevalence of 12-Month Mental Health Service Use in Separate Service Sectors by 12-Month *DSM-IV*/WMH CIDI Disorder

		Health Care†					Non–Health Care†			
		Mental Health Specialty								
Type of Disorder	No. of Respondents*	Psychiatrist	Nonpsychiatrist‡	Any	General Medical§	Any	Human Services‖	CAM¶	Any	Any Service Use†
Anxiety disorders										
Panic disorder	251	21.5 (2.5)	24.6 (2.8)	34.7 (2.6)	43.7 (3.3)	59.1 (3.3)	10.8 (1.9)	8.0 (2.0)	17.3 (2.3)	65.4 (3.3)
Agoraphobia without panic	79	NA	NA	NA	NA	45.8 (7.0)	NA	NA	NA	52.6 (7.4)
Specific phobia	812	12.1 (1.6)	13.6 (1.4)	19.0 (1.8)	21.2 (1.5)	32.4 (2.0)	8.6 (0.9)	7.0 (0.8)	13.5 (1.0)	38.2 (1.9)
Social phobia	632	15.2 (1.5)	18.8 (1.5)	24.7 (1.5)	25.3 (1.7)	40.1 (1.9)	7.7 (1.1)	7.7 (1.0)	13.4 (1.1)	45.6 (1.9)
Generalized anxiety disorder	247	14.2 (2.4)	17.0 (2.5)	25.5 (2.9)	31.7 (2.6)	43.2 (3.0)	14.0 (3.5)	10.1 (1.8)	21.7 (3.5)	52.3 (2.9)
Obsessive-compulsive disorder	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Separation anxiety disorder	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Posttraumatic stress disorder	203	22.6 (2.4)	26.1 (2.3)	34.4 (2.9)	31.3 (2.5)	49.9 (3.3)	10.7 (2.4)	12.6 (2.0)	19.7 (2.4)	57.4 (3.3)
Any anxiety disorder	1036	13.0 (1.0)	16.0 (1.0)	21.7 (1.2)	24.3 (1.0)	36.9 (1.4)	8.2 (0.9)	7.3 (0.6)	13.5 (0.7)	42.2 (1.3)
Mood disorders										
Major depressive disorder	623	20.6 (1.8)	23.2 (1.9)	32.9 (1.6)	32.5 (2.3)	51.7 (2.2)	10.7 (1.2)	9.0 (1.3)	16.8 (1.7)	56.8 (2.2)
Dysthymia	135	27.7 (3.7)	23.3 (3.2)	36.8 (4.1)	39.6 (5.1)	61.7 (4.5)	13.3 (3.2)	7.1 (2.3)	17.5 (3.9)	67.5 (4.1)
Bipolar I and II disorders	244	22.5 (2.2)	27.1 (2.2)	33.8 (2.3)	33.1 (3.0)	48.8 (2.7)	11.7 (2.2)	12.2 (2.7)	21.6 (3.2)	55.5 (3.0)
Any mood disorder	884	21.0 (1.3)	24.1 (1.5)	32.9 (1.3)	32.8 (1.8)	50.9 (1.8)	11.0 (1.2)	9.8 (1.3)	18.1 (1.6)	56.4 (1.8)
Impulse control disorders										
Intermittent explosive disorder	243	7.1 (1.7)	9.2 (1.7)	13.9 (2.3)	12.6 (2.4)	22.8 (2.6)	7.6 (2.3)	3.7 (1.2)	10.9 (2.6)	29.6 (2.9)
Substance disorders										
Alcohol abuse	176	12.8 (1.7)	20.2 (2.7)	25.6 (2.3)	16.4 (2.1)	33.4 (2.5)	7.0 (1.8)	7.4 (1.9)	12.8 (2.2)	37.2 (2.6)
Alcohol dependence	76	19.6 (2.9)	28.0 (5.8)	35.1 (4.4)	19.3 (3.7)	43.6 (4.9)	8.2 (2.8)	14.5 (3.3)	19.6 (3.9)	48.4 (5.4)
Drug abuse	79	15.5 (3.7)	26.3 (4.8)	32.8 (4.9)	21.8 (4.1)	40.5 (4.9)	7.1 (3.9)	7.7 (2.7)	14.2 (5.5)	43.1 (4.8)
Drug dependence	24	30.4 (10.5)	29.4 (8.1)	42.9 (10.0)	23.9 (7.3)	49.8 (9.8)	0	6.0 (3.6)	6.0 (3.6)	51.5 (9.9)
Any substance disorder	219	13.2 (1.5)	21.0 (2.9)	26.2 (2.5)	18.1 (1.7)	34.5 (2.6)	7.8 (2.1)	7.2 (1.7)	13.7 (2.6)	38.1 (2.7)
Composite										
Any disorder	1443	12.3 (0.7)	16.0 (0.9)	21.7 (0.9)	22.8 (0.9)	36.0 (1.1)	8.1 (0.8)	6.8 (0.6)	13.2 (0.7)	41.1 (1.0)
No disorder	4249	1.9 (0.2)	3.0 (0.3)	4.4 (0.4)	4.7 (0.3)	8.3 (0.5)	1.8 (0.2)	1.4 (0.2)	3.0 (0.3)	10.1 (0.6)
Total sample	5692	4.5 (0.3)	6.3 (0.4)	8.8 (0.5)	9.3 (0.4)	15.3 (0.6)	3.4 (0.3)	2.8 (0.2)	5.6 (0.4)	17.9 (0.7)

Wang PS, et al. Arch Gen Psychiatry. 2005 Jun;62(6):629-40.

Longer DUI: Outcomes in BP

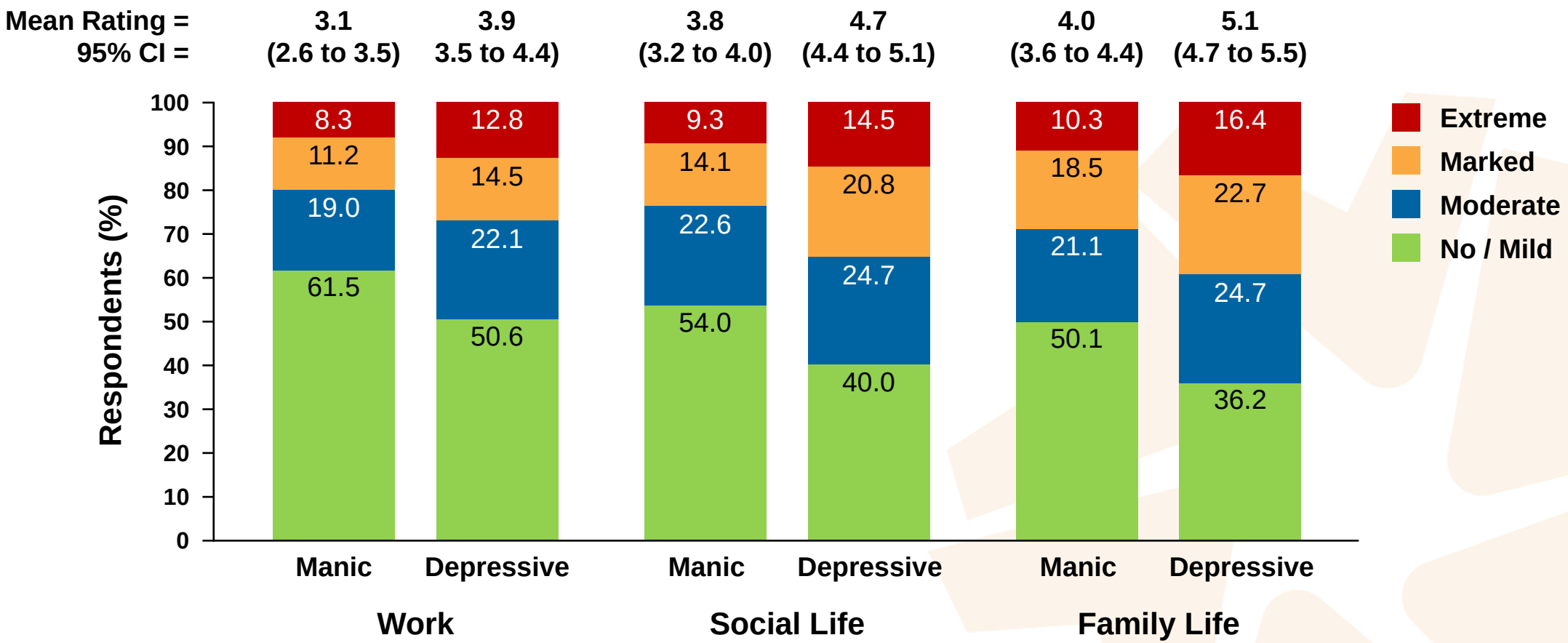
Table 3 Findings and methodological characteristics of studies that evaluated the concept of DUB

	This study	McCraw[12]	Drancourt[10]	Altamura[8]
Country	Brazil	Australia	France	Italy
Sample size	n=152	n=173	n=501	n=320
Age, years	39.8±10.8	38.1±11.4	42.3±13.9	46.0±12.8
Male	33.6	38.2	41.7	43.8
Female	66.4	61.8	58.3	56.2
BD subtype I	88.2	14.5	83.4	40.0
BD subtype II	11.8	85.5	16.6	60.0
DUB, years	10.4±9.8	18.0±11.7	9.6±9.7	8.7±7.7
Main clinical outcomes associated with longer DUB	More rapid cycling Less current remission More anxiety disorder	More employment difficulties More social costs due to mood episodes	More suicidal behaviour Early onset of BD More mood episodes	More suicidal behavior
Recruitment	Bipolar outpatient clinic	Depression clinic	General psychiatric outpatient clinic	Mood disorders outpatient clinic

Data expressed as mean ± standard deviation or percentages, unless otherwise stated.
BD = bipolar disorder; DUB = duration of untreated bipolar disorder.

Medeiros GC, et al. Rev Bras Psiquiatr. 2016 Mar;38(1):6-10

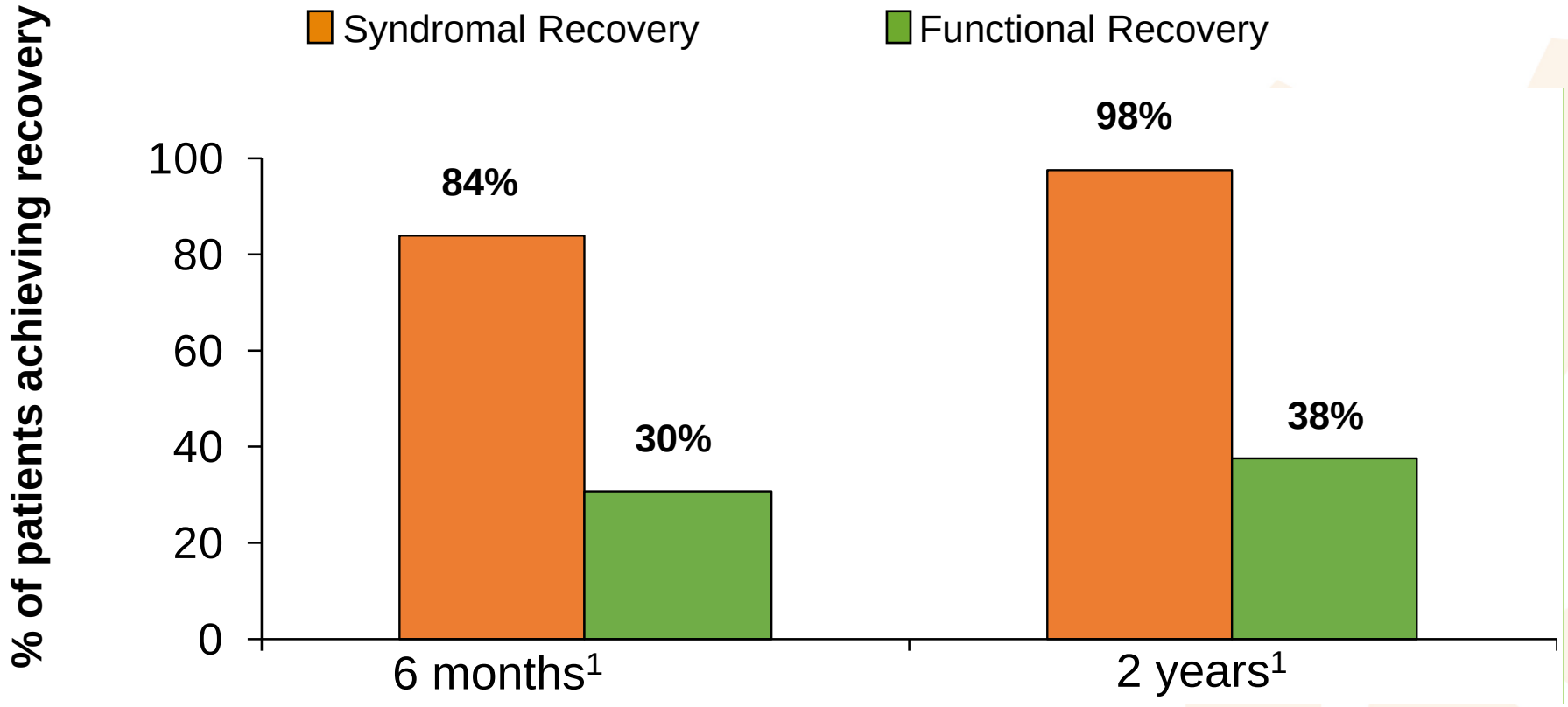
Disability: Depressed Vs Manic States



Phase II of MDQ Study: 3,191 of 4,810 questionnaires returned (66%); 593 surveys of MDQ-positive respondents with a physician diagnosis of BP selected (mean age: 37 years, 51% female, 89% White) Sheehan Disability Scores greater in depressive vs manic symptoms in each domain ($p<.0001$)

Calabrese et al. J Clin Psychiatry 2004;65:1499-1504

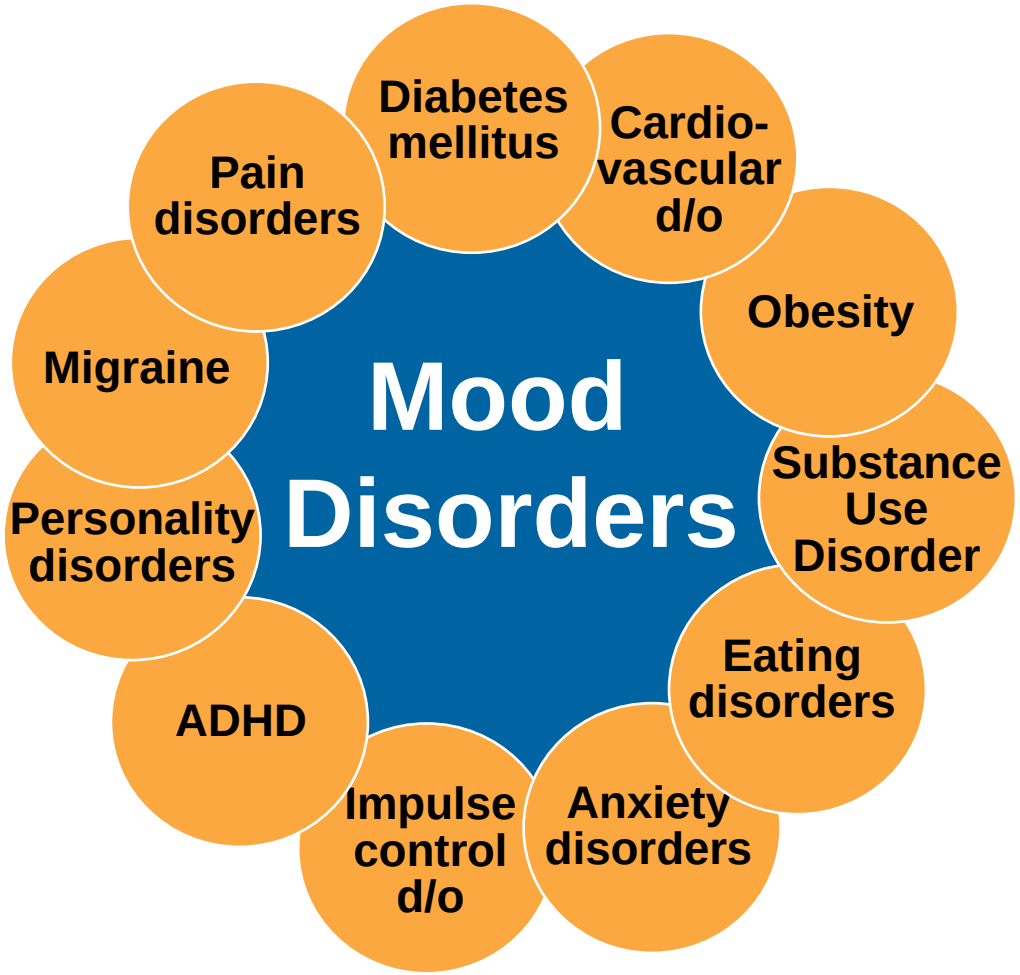
Functional Impairment Remains a Challenge in Bipolar Disorder



Syndromal recovery defined as no longer meeting criteria for an ongoing DSM-IV illness episode as described by Frank et al[2]
Functional recovery (yes/no), defined by comparing ratings on the Modified Vocational Status Index (vocational status) and Modified Location Code Index (living situation) at entry versus 6- and 24-month follow-up, required return to at least baseline levels of both measures

Tohen et al. *Am J Psychiatry* 2000;157:220–228; [2]Frank E et al *Arch Gen Psychiatry* 1991;48:851–855

Bipolar Disorder is Associated with Many Comorbid Conditions



- The prevalence and epidemiology of psychiatric and medical comorbidities in mood disorders is high
- Stress sensitive medical disorders are prevalent
- Cardiometabolic disorders most common specific cause of premature mortality.

McIntyre RS, et al. Hum Psychopharmacol. 2004;19:369-386.

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.

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/.

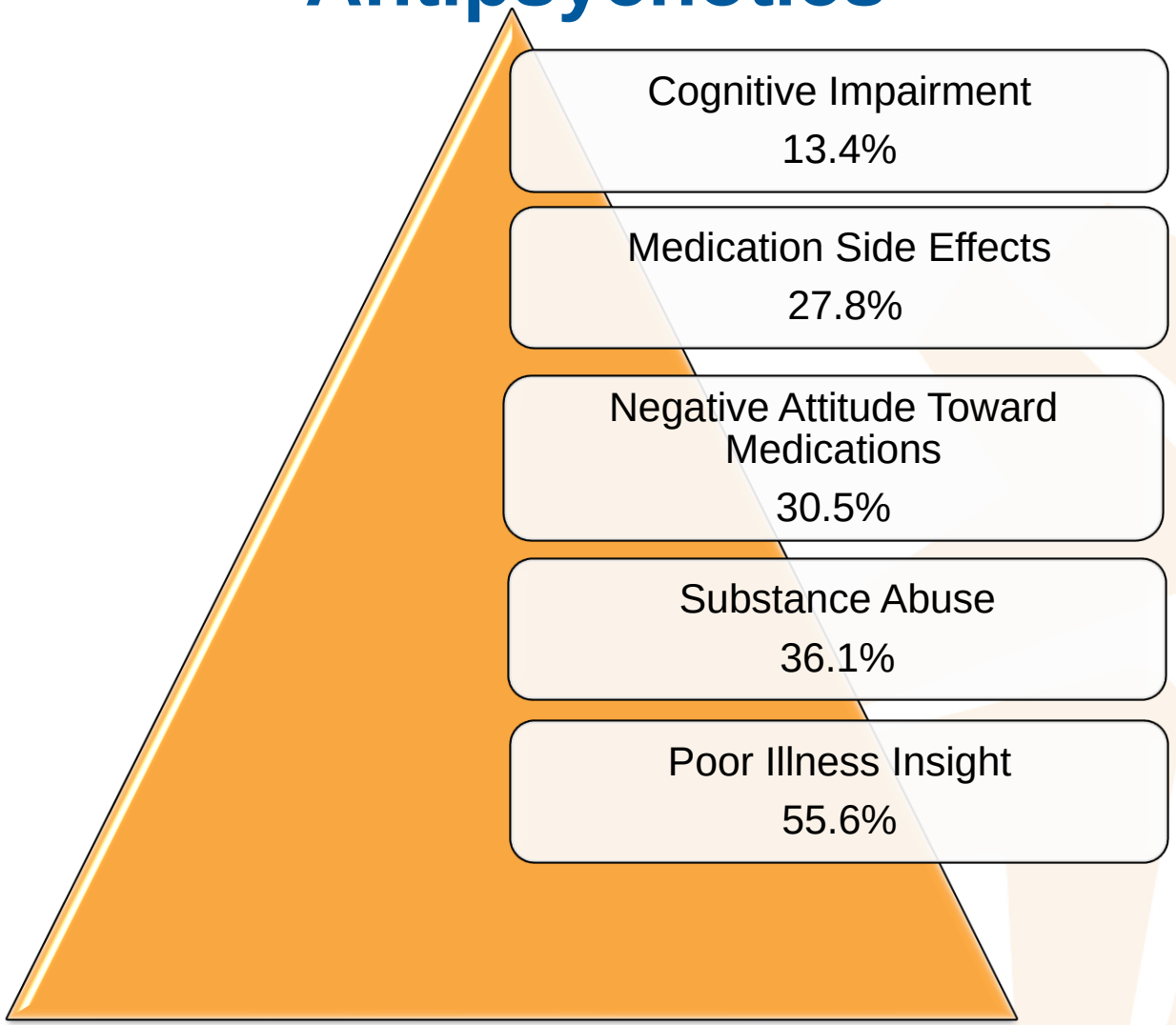
Kane JM. *J Clin Psychiatry*. 2004;65 Suppl 9:16-20. Mauri MC, et al. *Clin Pharmacokinet*. 2018;57(12):1493-1528. Colom F, et al. *Bipolar Disord*. 2005;7 Suppl 5:24-31. Correll CU, et al. *JAMA Psychiatry*. 2014;71(12):1350-1363. Gigante AD, et al. *CNS Drugs*. 2012;26(5):403-420.

Factors Predicting Non-Adherence in Patients with Bipolar Disorder

Sociodemographic characteristics
Age <40 years
Nonwhite race
Marital status (single)
Homelessness
Clinical characteristics
Greater number/severity of symptoms
Rapid cycling
Recent manic episode
Incomplete remission
Comorbid personality disorders[b]
Number of hospitalizations[b]
Substance misuse
Medication factors
Polypharmacy/complex treatment regimen
Side effects
Lack of insight about illness

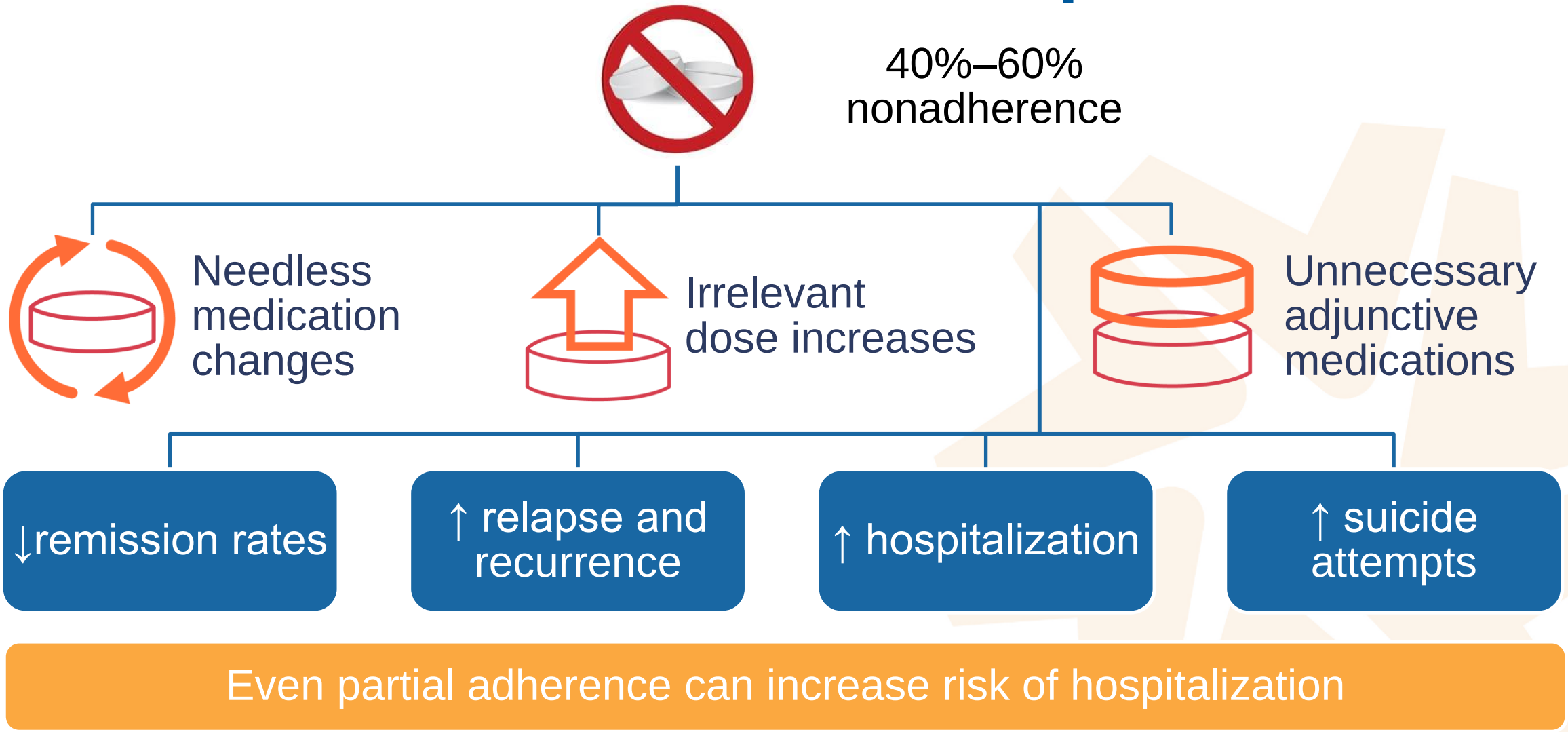
Tohen M et al. J Clin Psychiatry. 2020;81(4):OT19046AH1

Patient Reported Factors for Non-Adherence to Atypical Antipsychotics



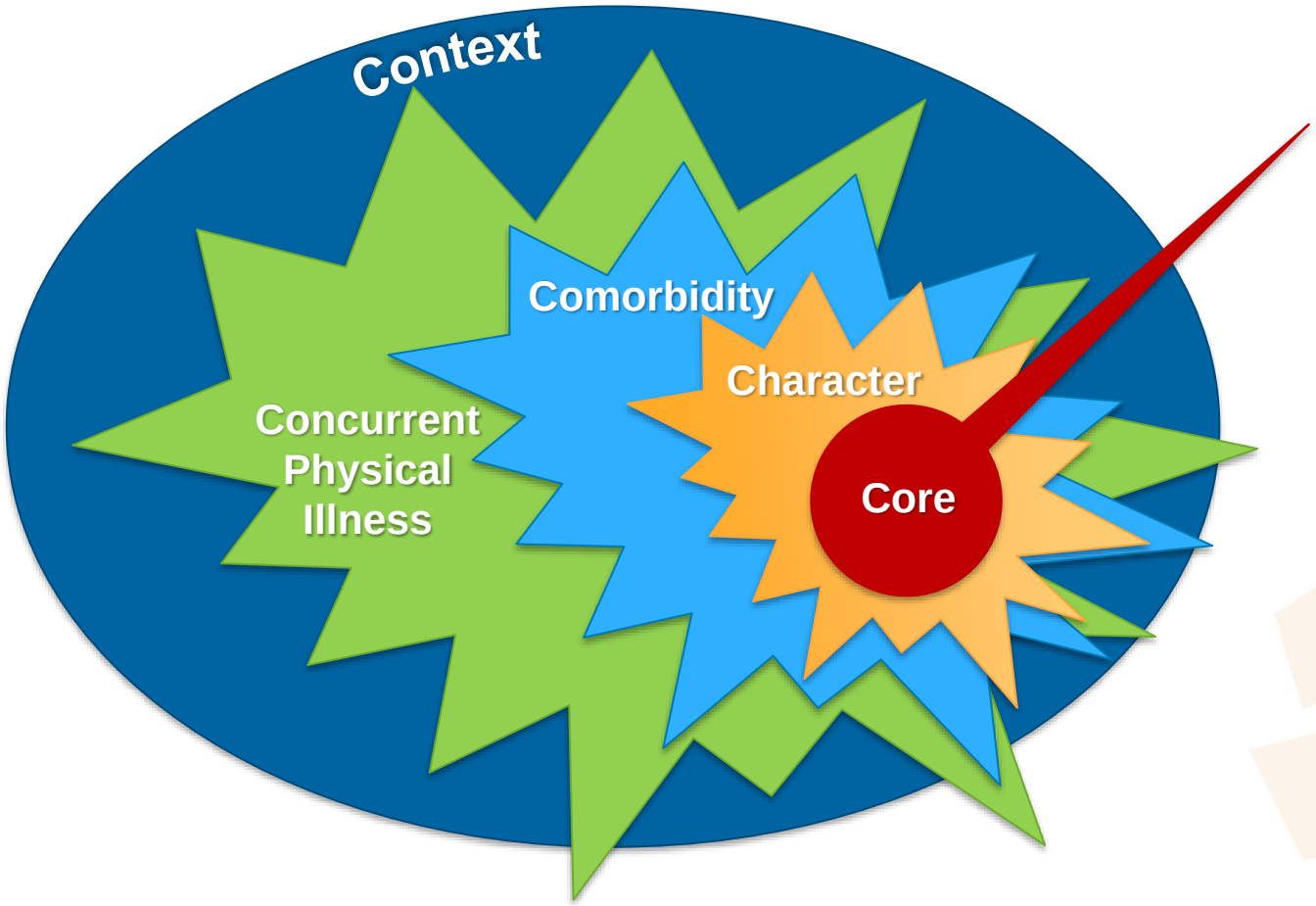
Velligan DI, Sajatovic M, Hatch A, Kramata P, Docherty JP.. *Patient Prefer Adherence*. 2017;11:449-468. Published 2017 Mar 3.

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.

Managing the Complexities in Bipolar Disorder



Core
Extreme and/or severe changes in mood, energy, and biorhythms

Character
Cyclothymia; personality traits / disorder

Comorbidity
Anxiety and substance abuse (especially alcohol)

Concurrent Physical Illness
Physical illness and medications

Context
Age and pregnancy

Malhi GS *et* al. Bipolar Disorders 2012: 14 (Suppl. 2): 66-89.

Meet Vanessa

Consequences and Burden of Medication Non-Adherence

The LAI Antipsychotic Treatment Landscape in Bipolar I Disorder

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
- 2021 Lumateperone* (bipolar I and II)

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**
- 2021 Lumateperone*(bipolar I and II)

***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

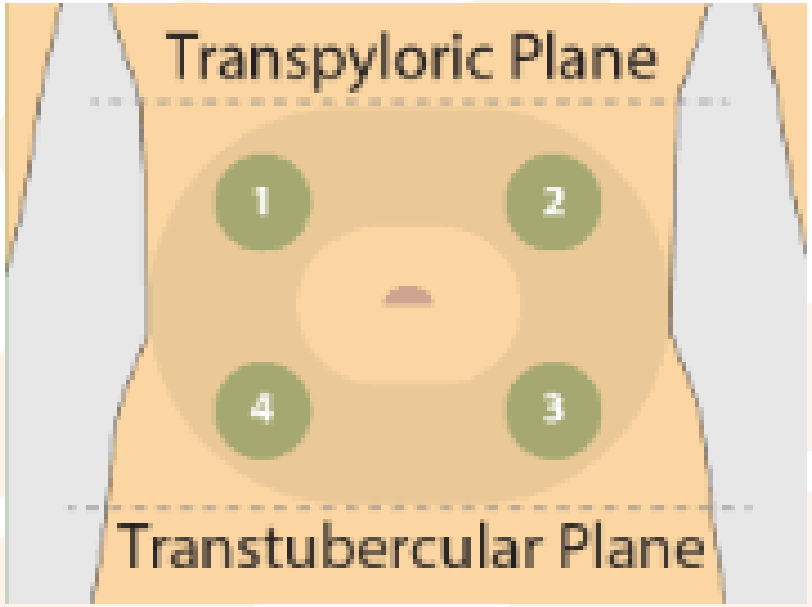
- Use as adjunctive treatment not explicitly approved

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

Long Acting Injectable Antipsychotics: Off label use for Bipolar Disorder

Risperidone (subcutaneous injectable)

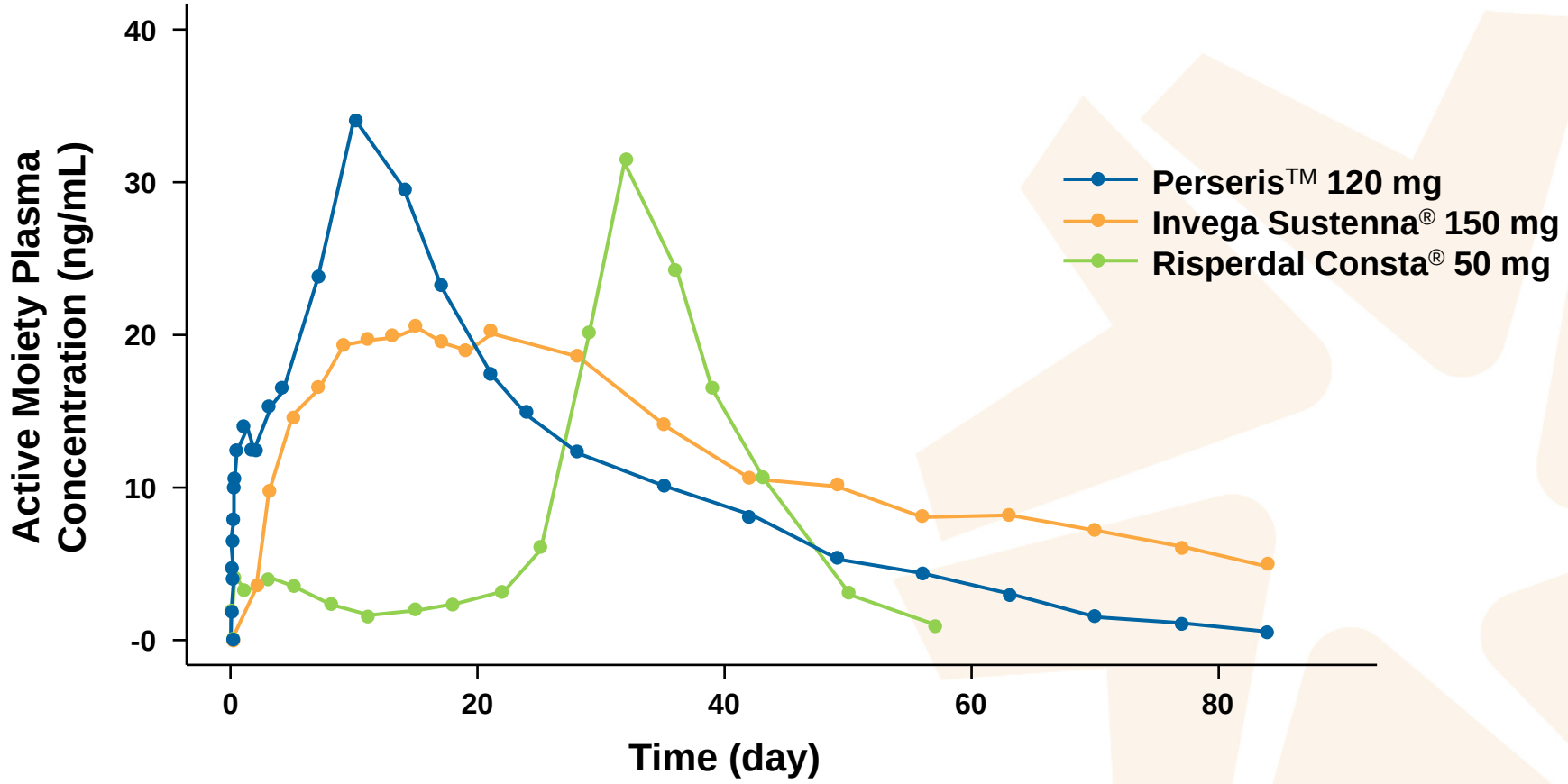
- Based on same technology (Atrigel®) as subcutaneous naltrexone injection
- Currently has indication only for schizophrenia in United States
- 4 week product with initial peak plasma levels between 4-6 hours and secondary peak 14 days later
- Needs prior demonstrated tolerance to risperidone or paliperidone
- Currently only FDA indicated for schizophrenia
- **Requires no active loading period or oral medication overlap**



Clark I, Taylor D. Newer Formulations of Risperidone: Role in the Management of Psychotic Disorders. CNS Drugs. 2020 Aug;34(8):841-852. doi: 10.1007/s40263-020-00735-3. PMID: 32462508.

Pharmacokinetic Comparison

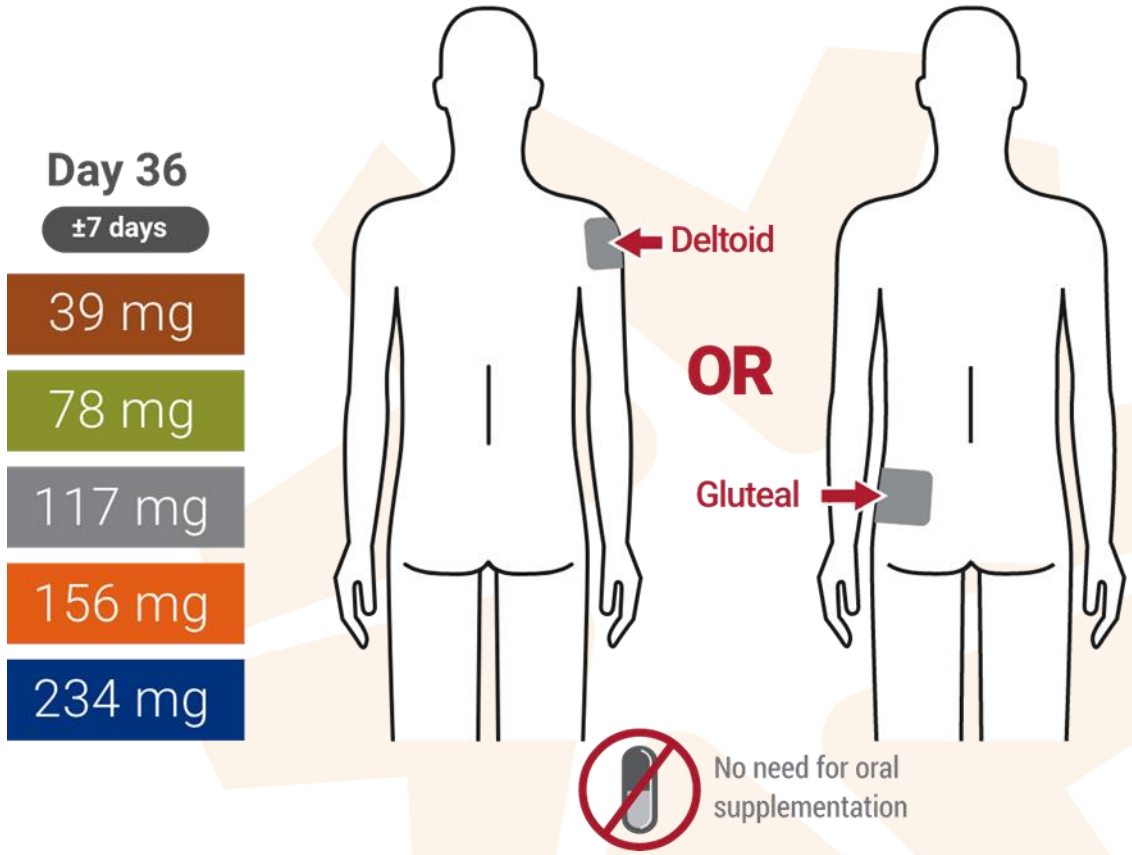
Figure 1. Typical pharmacokinetic profiles of the active moiety concentration resulting from the administration of 3 different LAI products for the treatment of schizophrenia.



Gomeni, Roberto & Bressolle-Gomeni, Françoise. (2021). Modeling Complex Pharmacokinetics of Long-Acting Injectable Products Using Convolution-Based Models With Nonparametric Input Functions. The Journal of Clinical Pharmacology. 61. 10.1002/jcph.1842.

Paliperidone Palmitate Depot Injection

- Paliperidone palmitate has not been studied for use in bipolar 1 disorder and does not have FDA indication. Some small case studies support its use
- No oral supplementation needed after initial loading phase of 234mg IM once then 156mg IM 7 days later
- Can be used in patients with poor conversion of risperidone to paliperidone via CYP2D6



Li K, et al. Case Report: Paliperidone Palmitate in the Management of Bipolar I Disorder With Non-compliance. *Front Psychiatry*. 2021 Jan 8;11:529672. doi: 10.3389/fpsyt.2020.529672. PMID: 33488408; PMCID: PMC7819884.

Paliperidone Palmitate Depot Injection

Case study 1

11 patients with history of non-adherence to medications and diagnosis of bipolar 1 with sustained treatment with paliperidone 234mg/monthly over median treatment duration of 14 months

- Significant reductions in manic and hypomanic symptoms
- 3 cases of mild-moderate depression reported
- None of the patients were hospitalized
- 54.4% discontinued treatment due lack of efficacy or adverse effects including weight gain and sedation

Case study 2:

Three patients with history of bipolar 1 disorder **with psychotic features** stabilized on paliperidone IM 234mg/monthly

- Two patients remained relapse free for one year and one patient for two years

Li K, et al. Case Report: Paliperidone Palmitate in the Management of Bipolar I Disorder With Non-compliance. *Front Psychiatry*. 2021 Jan 8;11:529672. doi: 10.3389/fpsyt.2020.529672. PMID: 33488408; PMCID: PMC7819884.

Buoli M, et al. Paliperidone Palmitate Depot in the Long-term Treatment of Psychotic Bipolar Disorder: A Case Series. *Clin Neuropharmacol*. 2015 Sep-Oct;38(5):209-11. doi: 10.1097/WNF.0000000000000103. PMID: 26366967.

Aripiprazole lauroxil

- No data for use in bipolar disorder and only FDA approved for schizophrenia
- May allow for higher dosing compared to aripiprazole monohydrate

Table 2

Aripiprazole lauroxil: Dosage and administration

Previously established oral aripiprazole dosage	Aripiprazole lauroxil		
	Dosage	Injection site	Needle gauge
10 mg/d	441 mg/month	Deltoid/Gluteal	21/20
15 mg/d	662 mg/month	Gluteal	20
≥20 mg/d	882 mg/month	Gluteal	20

Source: Reference 2

Meyer JM. Converting oral to long acting injectable antipsychotics: a guide for the perplexed. *CNS Spectrums*. 2017;22(S1):14-28.

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.

Treatment Polarity Index May Be of Interest

	NNT Mania	NNT Depression	Polarity Index (NNTd/NNTm)
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.

Class Benefits of Long Acting Injections

- Reduced risk of relapse and hospitalization, demonstrating superiority over oral medications for rapid cycling patients
- Improved clinician understanding of true adherence to medications
- Reduces much of the family conflict related to medication adherence by removing daily medication administration

Kishi T, Oya K, Iwata N.. Int J Neuropsychopharmacol. 2016 Sep 21;19(9):pyw038. doi: 10.1093/ijnp/pyw038

Shared Decision-Making and Individualized Care in Bipolar Disorder

Collaborative Care: Planning

During the planning process, several important functions are performed:

- Setting priorities and goals
- Appraising strengths
- Selecting appropriate interventions
- Determining resources

Everyone works together to:

- Clarify personal choices
- Identify environmental options
- Clarify personal values
- Identify personal interests

Key Points for Patient-Centric Discussions of Treatment Goals and Options

Assess the patient's understanding of his or her illness and beliefs and preferences about treatment (past, current, and future). Acknowledge past negative experiences and also correct any misinformation.

Inquire about the patient's goals—and if there are things bipolar illness has *kept* them from achieving. These may include:

- Occupational goals
- Social/interpersonal goals
- Living independently

Acknowledge that relapses will probably occur, but emphasize that things can be done to make them less likely. Reassure the patient that you will partner with him/her to address relapses and, if necessary, implement more assertive treatment.

Emphasize the link between consistent medication use and lower risk of relapse and better functioning.

Convey that if bothersome side effects occur,

- The patient should let you know immediately
- The patient should not stop treatment on his/her own
- You will work with the patient to adjust treatment and reduce or eliminate the side effects

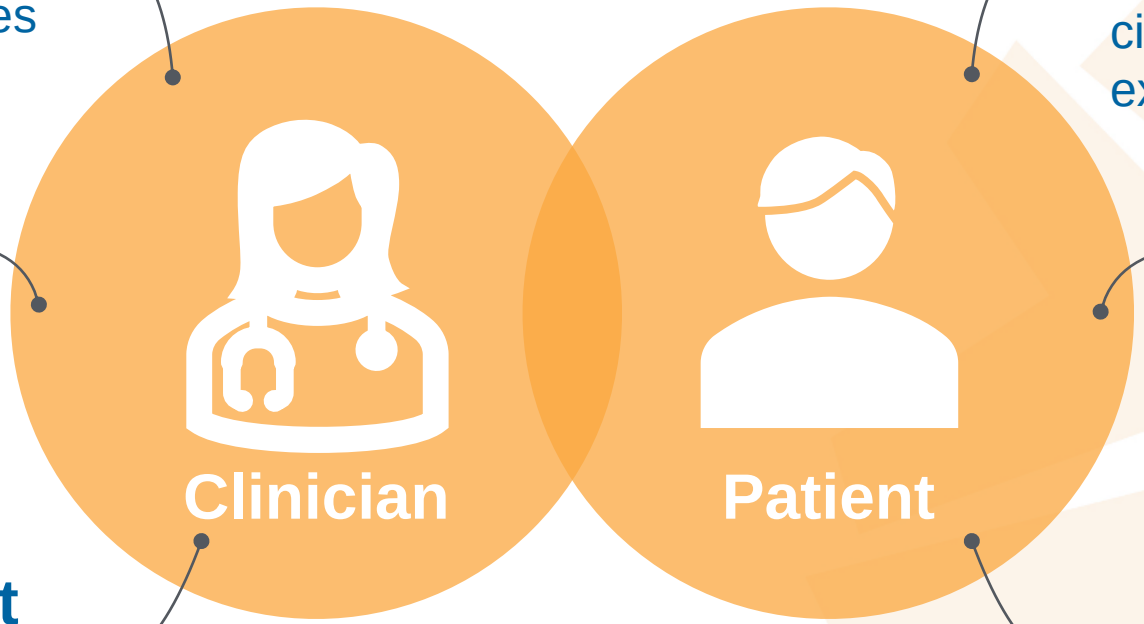
Tohen M et al. J Clin Psychiatry. 2020;81(4):OT19046AH1

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



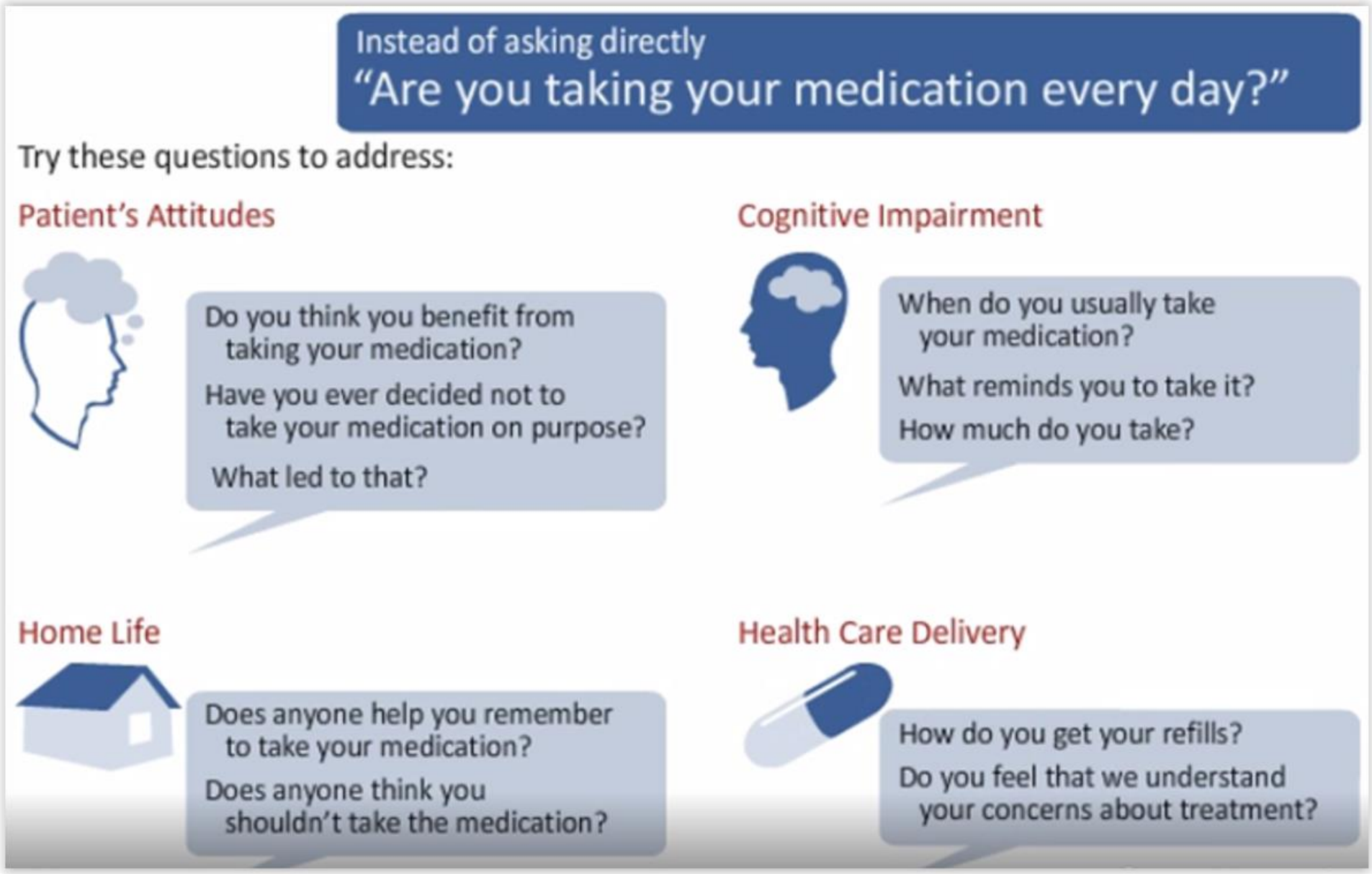
Shares experience and values
Preferences, socioeconomic circumstances, and experience of illness

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.

Assessing Adherence and Adherence Barriers



Kane JM and Correll CU. *J Clin Psychiatry*. 2019 Sep 17;80(5):IN18031AH1C.

What Is Motivational Interviewing?

A style of dialogue between two parties, which is intended to motivate one party into making positive changes by compassionately challenging the status quo and helping them explore alternatives

Motivational Interviewing: Basic Principles

- **Autonomy** — Patient has the right to self-direction
  Care partner affirms this, but also provides input
- **Collaboration** — Patient is their own expert
  Care partner builds partnership
- **Evocation** — Patient has the resources to change
  Care partner elicits the change

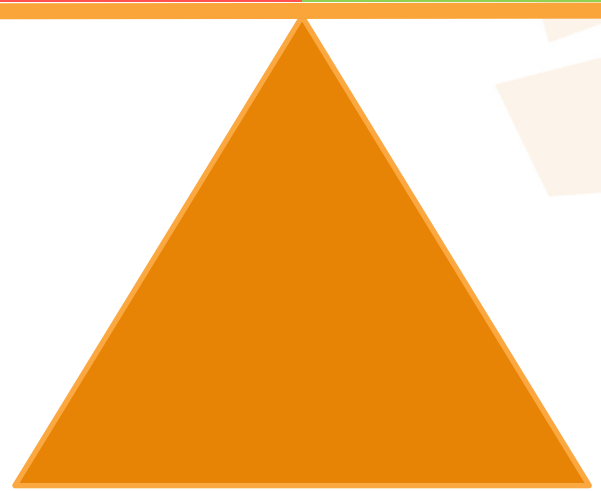
Modified based on material from: Maria Arpa, Founder of The Centre for Peaceful Solutions

Motivational Interviewing

Stages of Change	
Precontemplation	“I won’t” “I can’t”
Contemplation	Both good reasons for and against change
Preparation	Want to but…
Action	Doing it
Maintenance/Relapse	Now a habit or a risk of relapse

Long-acting Treatments (LATs): Counter-arguments for Patients/Families can each be Countered

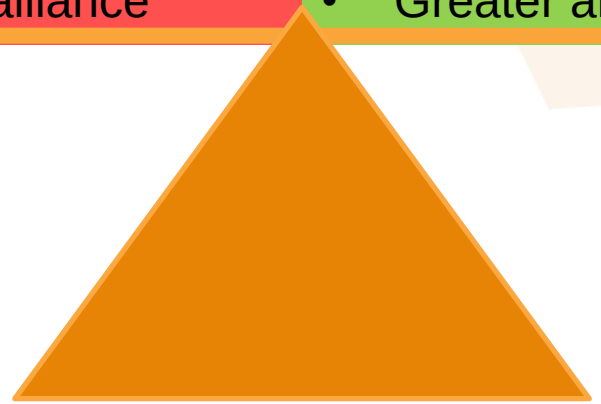
Con LAIs	Pro LAIs
• More appointments? • Perceived stigma • Conversion from oral to LAT • Fear of pain • Inflexible dosing / stopping • Lack of experience • Negative clinician appraisal • Cost/insurance coverage	• Continuous antipsychotic coverage • ↓ relapse & hospitalization • No need to remember • Less conflict over suspected non-adherence • More flexibility to travel, etc • Less hyperprolactinemia



Adapted from:
Correll CU. *J Clin Psychiatry*. 2013;74(8):e16.
Correll CU. *J Clin Psychiatry*. 2014;75(9):e25.

Long-acting Treatments: Counter-arguments for Healthcare Professionals can each be Countered

Con LAIs	Pro LAIs
• Usual care and guidelines reserve LAIs as later-line treatment • Mixed outcomes of LAIs vs Orals • Lack of training/experience • Increased time investment • Switching complicates treatment • Inflexible dosing and stopping • Absent institutional structures • Lack of appreciation of LAI benefit • Misconception about decreasing autonomy or invasiveness of treatment • Lack of conviction / enthusiasm • Feared interference with alliance	• Assured medication delivery • No guessing about reasons for inefficacy / pseudo-inefficacy • Common clinical overestimation of adherence • Uncovering covert non-adherence • Direct signal of non-adherence • Less peak-to-trough blood level variation and hyperprolactinemia • Greater patient autonomy through better illness control • Greater patient flexibility • Greater alliance with healthier patients



Adapted from:
Correll CU. *J Clin Psychiatry*. 2013;74(8):e16.
Correll CU. *J Clin Psychiatry*. 2014;75(9):e25.

GAIN Approach to LAI

(**G**oal setting, **A**ction planning, **I**nitiating treatment, and **N**urturing 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.

Practice Makes Perfect!

- Visit the Exhibit Hall on Monday from 1:45 PM – 3:15 PM and attend the **LAI and Motivational Interviewing Workshop**!
- Practice administering LAIs on prosthetics as well as interact with patients and faculty experts to learn more about best Motivational Interviewing techniques.
- Located in the back of the Exhibit Hall, at the end of the 900 aisle

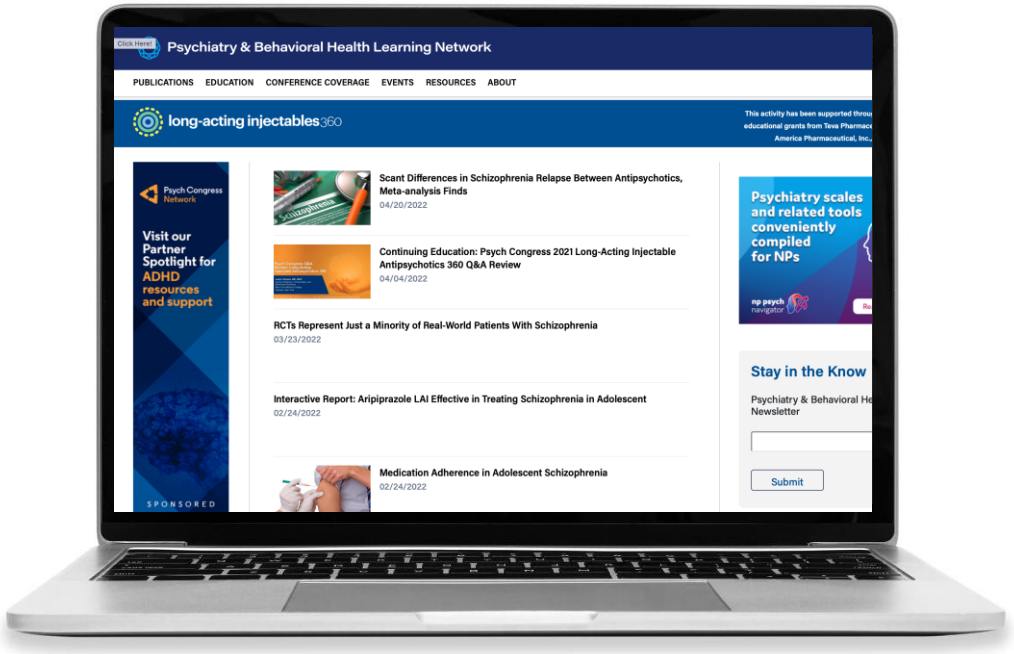
Discussion with Vanessa

Visit the Resource Centers

bipolar360

https://bit.ly/3BO2pqS

long-acting injectables360



https://bit.ly/3Uge6h7

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Questions?