

MODULE 4

BIPOLAR MARKET LANDSCAPE



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MODULE 4

BIPOLAR MARKET LANDSCAPE

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BIPOLAR MARKET LANDSCAPE

- Part 1: Introduction to the Bipolar Market
- Part 2: Agents With Indications in Bipolar Disorder
- Part 3: Agents Not Indicated for Bipolar Disorder

Objectives

- Identify and describe mood stabilizers and atypical antipsychotics with indications in bipolar disorder in adults
- Highlight the main features of quetiapine fumarate and olanzapine/fluoxetine hydrochloride as they relate to the treatment of bipolar depression
- Compare and contrast key features of the bipolar marketplace and the schizophrenia marketplace

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An Introduction to the Bipolar Market

What is the size of the U.S. market?

schizophrenia



~2.0 million
patients

**Bipolar I
disorder**



~5.7 million
patients

Source: National Institute of Mental Health Website, 2017; US Census 2016.

An Introduction to the Bipolar Market

APPROVED FOR THE TREATMENT
OF BIPOLAR DISORDER

Mood stabilizers

(Some) Antipsychotics

(Some) Anticonvulsants

NOT APPROVED FOR THE
TREATMENT OF BIPOLAR
DISORDER

Antidepressants

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- Part 1: Introduction to the Bipolar Market
- **Part 2: Agents With Indications in Bipolar Disorder**
- Part 3: Agents Not Indicated for Bipolar Disorder

Commonly Used Mood Stabilizers

Anticonvulsants

LITHIUM



Generic: lithium carbonate

Some Trade Names: Eskalith®,
Lithobid®

CARBAMAZEPINE



Generic: carbamazepine

Some Trade Names: Carbatrol®,
Equetro®, Tegretol®

LAMOTRIGINE



Generic: lamotrigine



Some Trade Names:
Lamictal®, Lamictal®XR™

DIVALPROEX



Generic: divalproex sodium

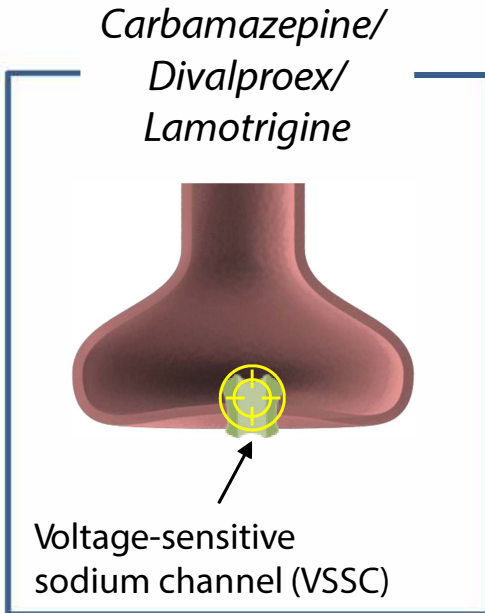
Some Trade Names: Depakote®,
Depakote ER®

 = tablet
 = capsule

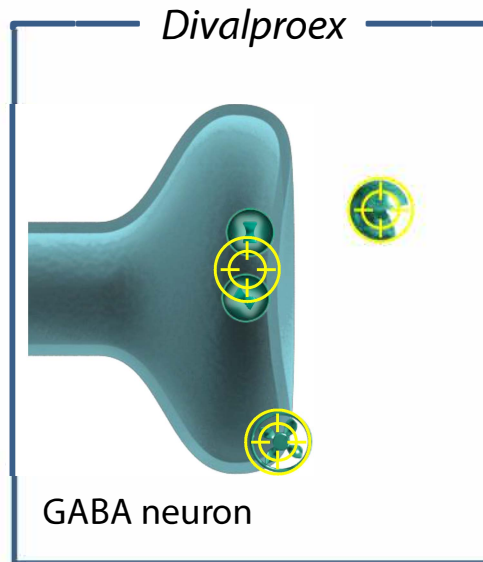
DR = delayed release
XR = extended release

NOTE: the brands listed here are
not necessarily available in all of
the formulations shown

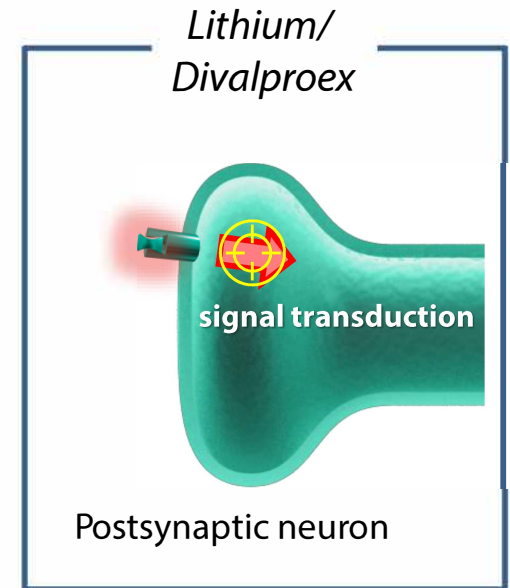
Mood Stabilizers – Hypothetical Mechanisms of Action



Reduce excessive neurotransmission



Enhance inhibitory neurotransmission (via GABA)



Change downstream signalling

Mood Stabilizers – Indications

CARBAMAZEPINE
(e.g., Equetro®)

Acute **manic and mixed episodes***
associated with bipolar I disorder

DIVALPROEX
(e.g., Depakote®)

Manic episodes of bipolar disorder

LAMOTRIGINE
(e.g., Lamictal®)

Maintenance treatment of bipolar I disorder
(depression, mania, hypomania, mixed episodes*)
in patients treated with standard therapy

LITHIUM
(e.g., Lithobid®)

Manic episodes of bipolar disorder
Maintenance treatment of bipolar disorder

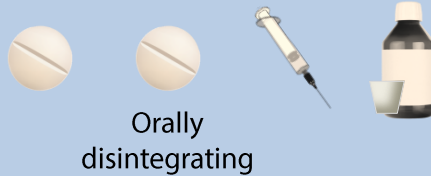
*Mixed episode as defined by the DSM-IV

Key Takeaways

- Carbamazepine, divalproex, and lithium are approved for the treatment of manic episodes, while carbamazepine is also approved for mixed episodes as defined by the DSM-IV
- Lamotrigine is indicated for maintenance treatment of bipolar I disorder (depression, mania, hypomania, mixed episodes as defined by the DSM-IV)

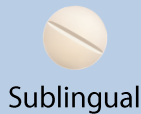
Atypical Antipsychotics *with approvals in bipolar disorder*

aripiprazole
(e.g., Abilify®,
Abilify Maintena®)



Orally
disintegrating

asenapine
(Saphris®)

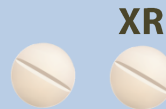


Sublingual

lurasidone HCl
(LATUDA®)



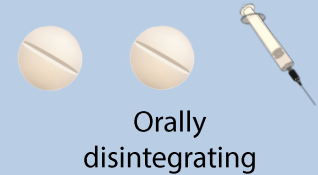
quetiapine fumarate
(e.g., Seroquel®; Seroquel XR®)



olanzapine + fluoxetine
(Symbyax®)



olanzapine
(e.g., Zyprexa®)



Orally
disintegrating

cariprazine
(Vraylar®)

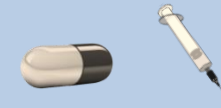


risperidone
(e.g., Risperdal®;
Risperdal Consta®)



Orally
disintegrating

ziprasidone
(e.g., Geodon®)



 = tablet



= capsule



= intramuscular (IM) injection



= oral solution

Please note that not all dosage forms are approved for the treatment of bipolar disorder.
This information is for educational purposes only, and is not meant to be a comparative.

MODULE 4 BIPOLAR MARKET LANDSCAPE

Atypical Antipsychotics – Indications Related to Bipolar Disorder

	Major depressive episodes	Manic episodes	Mixed episodes*	Maintenance treatment
aripiprazole (Abilify®)		● +	● +	
aripiprazole (Abilify Maintena®)				●
asenapine (Saphris®)		● +	● +	
cariprazine (Vraylar®)		●	●	
lurasidone HCl (Latuda®)	● +			
olanzapine (e.g., Zyprexa®)		● +	● +	●
olanzapine/fluoxetine hydrochloride (Symbyax®)	●			
quetiapine fumarate (e.g., Seroquel®)	●	● +		+
quetiapine fumarate (Seroquel XR®)	●	● +	● +	+
risperidone (e.g., Risperdal®)		● +	● +	
risperidone (Risperdal Consta®)				● +
ziprasidone (e.g., Geodon®)		●	●	+

● = monotherapy + = adjunctive therapy to lithium or valproate

*Mixed episodes as defined by the DSM-IV-TR for Vraylar®, and by the DSM-IV for all other antipsychotics.

 **Latuda**
(lurasidone HCl) tablets
20mg | 40mg | 80mg

This information is for educational purposes only and is not meant to be comparative.

Product Profile:

quetiapine fumarate (Seroquel[®], Seroquel XR[®])

- Product of AstraZeneca PLC
- Initial U.S. approval: 1997
 - Seroquel[®] 1997 (bipolar indication 2004)
 - Seroquel XR[®] 2007 (bipolar indication 2008)
- Dosage forms and strengths

Seroquel[®] tablets



25 mg
50 mg
100 mg
200 mg
300 mg
400 mg

Seroquel XR[®] extended-release tablets



50 mg
150 mg
200 mg
300 mg
400 mg

Seroquel[®]

- Can be taken *with* or *without* food

Seroquel XR[®]

- Should be taken *without* food **or** with a light meal (approx. 300 calories)
- Should be administered once daily, preferably in the evening

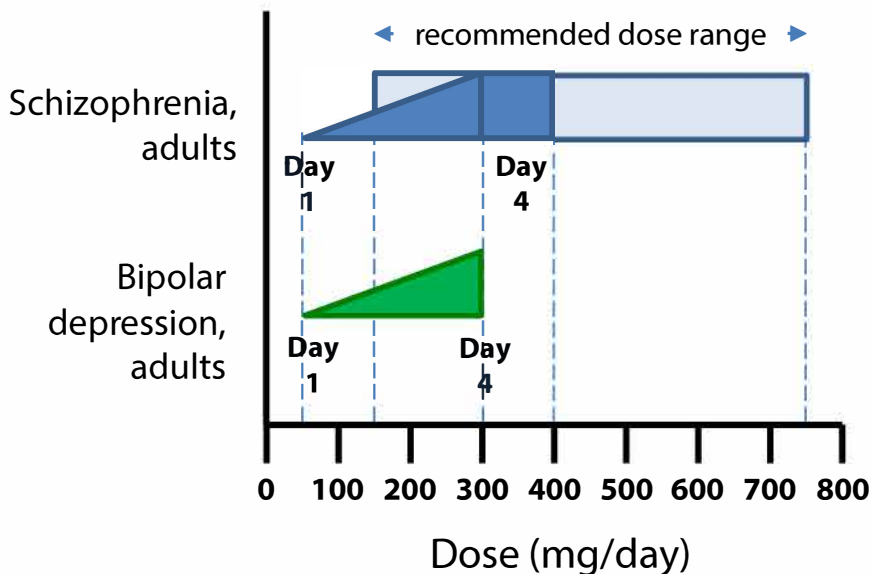


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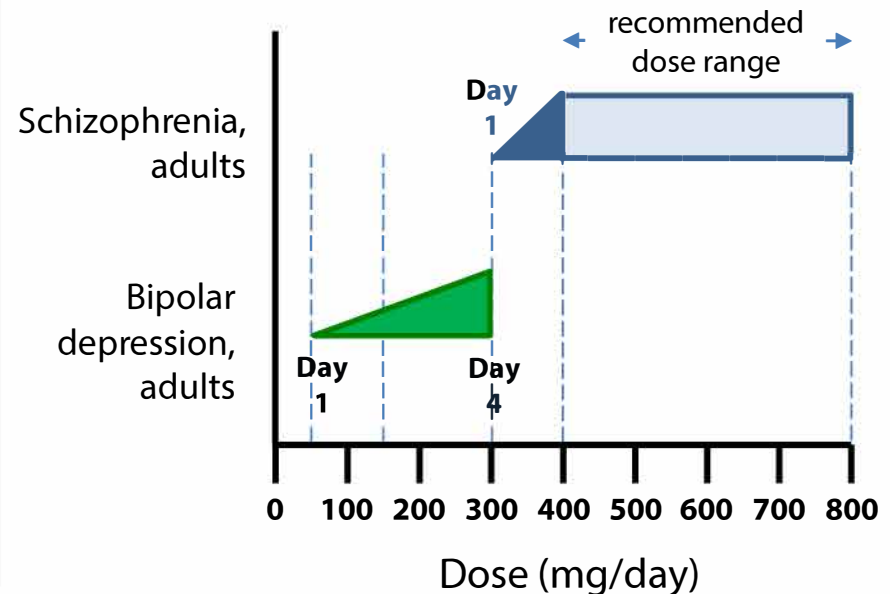
BIPOLAR MARKET LANDSCAPE

Product Profile: quetiapine fumarate (Seroquel®, Seroquel XR®)

Dosing Instructions, Seroquel®



Dosing Instructions, Seroquel XR®



Product Profile: quetiapine fumarate (Seroquel®)

*Efficacy Summary**

Efficacy was established in two 8-week, randomized, double-blind, placebo-controlled studies of patients with either bipolar I or II disorder, with or without rapid cycling (N=1,045)

- *Primary endpoint:* MADRS, change from baseline to Week 8
- In both studies, Seroquel® was superior to placebo on the primary endpoint

*For bipolar depression indication only

Safety Summary

Most common adverse reactions ($\geq 5\%$ and at least twice that for placebo) in 8-week, placebo-controlled clinical trials for the treatment of bipolar depression:

- Somnolence[†]: 57% (vs 15% for PBO)
- Dry mouth: 44% (vs 13% for PBO)
- Dizziness: 18% (vs 7% for PBO)
- Constipation: 10% (vs 4% for PBO)
- Lethargy: 5% (vs 2% for PBO)

[†]Somnolence combines somnolence and sedation

Product Profile: quetiapine fumarate (Seroquel XR®)

*Efficacy Summary**

Efficacy was established in one 8-week, randomized, double-blind, placebo-controlled study of patients who met DSM-IV criteria for bipolar I or II disorder, with or without rapid cycling (N=280)

- *Primary endpoint:* MADRS, change from baseline to Week 8
- Seroquel XR® was superior to placebo on the primary endpoint

*For bipolar depression indication only

Safety Summary

Most common adverse reactions ($\geq 5\%$ and at least twice that for placebo) in an 8-week, placebo-controlled clinical trial for the treatment of bipolar depression:

- Somnolence[†]: 52% (vs 13% for PBO)
- Dry mouth: 37% (vs 7% for PBO)
- Increased appetite: 12% (vs 6% for PBO)
- Weight gain: 7% (vs 1% for PBO)
- Dyspepsia: 7% (vs 1% for PBO)
- Fatigue: 6% (vs 2% for PBO)

[†]Somnolence combines somnolence and sedation

Product Profile:

Symbyax® (olanzapine and fluoxetine hydrochloride)

Symbyax® = olanzapine + fluoxetine

An atypical antipsychotic
(Zyprexa®)

An SSRI
(Prozac®)

Indicated for the acute treatment
of depressive episodes associated
with bipolar I disorder in adults.

- Product of Eli Lilly & Co.
- Initial U.S. approval: 2003

Dosage forms and strengths

Capsules:



3 mg / 25 mg
6 mg / 25 mg
6 mg / 50 mg
12 mg / 25 mg
12 mg / 50 mg
(mg equivalent olanzapine/
mg equivalent fluoxetine)

Product Profile:

Symbyax® (olanzapine and fluoxetine hydrochloride)

Efficacy Summary*

Efficacy was established in two 8-week, randomized, double-blind, controlled studies of patients who met DSM-IV criteria for bipolar I disorder (N=788)

- *Primary endpoint:* MADRS, change from baseline to Week 8
- In both studies, Symbyax® was superior to both olanzapine monotherapy and placebo on the primary endpoint

*For bipolar depression indication only

Safety Summary[†]

Most common adverse reactions (≥5% and at least twice that for placebo) were:

- Somnolence[†]: 27% (vs 11% for PBO)
- Weight increased: 25% (vs 3% for PBO)
- Increased appetite: 20% (vs 4% for PBO)
- Dry mouth: 15% (vs 6% for PBO)
- Edema: 15% (vs 2% for PBO)
- Fatigue: 12% (vs 2% for PBO)
- Tremor: 9% (vs 3% for PBO)
- Sedation: 8% (vs 4% for PBO)
- Disturbance in attention: 5% (vs 1% for PBO)
- Vision blurred: 5% (vs 2% for PBO)

[†]Includes somnolence, sedation, hypersomnia and lethargy

[‡]For all adult indications

Product Profile: aripiprazole (Abilify®, Abilify Maintena®)

Abilify®

- Product of Bristol-Myers Squibb Company and Otsuka America Pharmaceutical, Inc.
- Initial U.S. approval: 2002 (bipolar indication 2004)
- Dosage forms and strengths

Tablets

2 mg
5 mg
10 mg
15 mg
20 mg
30 mg

Discmelt® Orally Disintegrating Tablets

10 mg
15 mg

Oral Solution

1 mg/mL

Injection for Intramuscular Use

9.75 mg/1.3 mL (7.5 mg/mL) solution
in clear, Type 1 glass vials

Abilify Maintena®

- Otsuka America Pharmaceutical, Inc.
- Initial U.S. approval: 2002 (bipolar indication 2017)
- Monthly injection

Injection for Intramuscular Use

Pre-filled Dual Chamber Syringe
available in 300-mg or 400-mg
strength syringes



Product Profile: aripiprazole (Abilify®)

Two identically-designed studies:

- 8-week
- Randomized
- Double-blind
- Placebo-controlled

Goal:

Evaluate the efficacy and safety of aripiprazole monotherapy in outpatients with bipolar I disorder experiencing a major depressive episode without psychotic features

Primary Efficacy Endpoint:

Mean change from baseline to Week 8 (LOCF) in **MADRS** total score

Key Secondary Efficacy Endpoint:

Mean change from baseline to Week 8 (LOCF) in **CGI-BP** score—depression

Results:

There were no statistically significant differences between aripiprazole and placebo at Week 8 on either the primary or the key secondary efficacy endpoints.

Reference: Thase ME et al. *J Clin Psychopharmacol* 2008;28:13-20.

Product Profile:
cariprazine (Vraylar®)

- Product of Allergan
- Initial U.S. approval: 2015
- The active ingredient is cariprazine HCl
- Given orally once daily
- Can be taken with or without food

Indicated for the acute treatment of manic or mixed episodes associated with bipolar I disorder and the treatment of schizophrenia.

Dosage forms and strengths
Capsules:



- 1.5 mg
- 3 mg
- 4.5 mg
- 6 mg

Product Profile: cariprazine (Vraylar®)

*Efficacy Summary**

Efficacy was established in three, 3-week, placebo-controlled trials in patients who met DSM-IV-TR criteria for bipolar I disorder with manic or mixed episodes with or without psychotic features (N=1,037)

- *Primary endpoint:* YMRS, decrease at the end of Week 3
- In all studies, VRAYLAR® was superior to placebo on the primary endpoint

Safety Summary

Most common adverse reactions ($\geq 5\%$ and at least twice that for placebo) were:

- Extrapyramidal symptoms 41%-45% (vs 18% for PBO)
- Parkinsonism 21%-26% (vs 10% for PBO)
- Akathisia: 20%-21% (vs 5% for PBO)
- Vomiting: 8%-10% (vs 4% for PBO)
- Dyspepsia: 7%-9% (vs 4% for PBO)
- Somnolence: 7%-8% (vs 4% for PBO)
- Restlessness: 7% (vs 2% for PBO)

*For indication of manic or mixed episodes associated with bipolar I disorder

Boxed Warnings

Seroquel[®], Seroquel XR[®], Symbyax[®], Abilify[®], and LATUDA[®], each carry 2 boxed warnings:

Suicidality and Antidepressant Drugs — Antidepressants increased the risk compared to placebo of suicidal thinking and behavior (suicidality) in children, adolescents, and young adults in short-term studies of Major Depressive Disorder (MDD) and other psychiatric disorders...

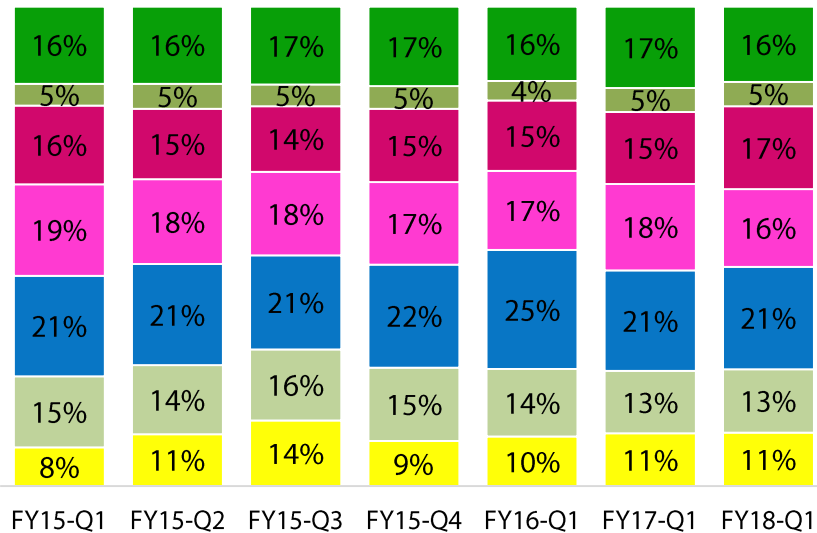
Increased Mortality in Elderly Patients with Dementia-Related Psychosis — Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death...

MODULE 4 BIPOLAR MARKET LANDSCAPE

Proportion of Bipolar Depression Patients Prescribed Each Class of Medication Over Time

Current Use of Drug Classes to Treat Bipolar Depression
All respondents

- Mood stabilizers only
- Antidepressants only
- Atypical antipsychotics only
- Antidepressants and Mood stabilizers
- Atypical antipsychotics and Mood stabilizers
- Antidepressants and Atypical antipsychotics
- Antidepressants, Atypical antipsychotics and Mood stabilizers



	FY15 Q1 (N=304)	FY15 Q2 (N=302)	FY15 Q3 (N=296)	FY15 Q4 (N=300)	FY16 Q1 (N=253)	FY17 Q1 (N=251)	FY18 Q1 (N=251)
Monotherapy	37%	36%	36%	29%	34%	37%	39%
Doublet therapy	68%	53%	54%	60%	68%	52%	50%
Triplet therapy	8%	11%	10%	11%	10%	11%	11%
Mood stabilizers	64%	66%	66%	68%	67%	67%	67%
Antidepressants	47%	48%	48%	48%	45%	47%	45%
Atypical antipsychotics	60%	61%	60%	66%	64%	60%	63%

Source: Blueprint Research Group LATUDA HCP ATU FY18-Q1. Information is current as of November 2018.

Latuda
(lurasidone HCl) tablets
20mg | 40mg | 80mg

Key Takeaways

- Of the 8 atypicals covered in this module (aripiprazole, asenapine, cariprazine, lurasidone HCl, quetiapine fumarate, olanzapine, risperidone, ziprasidone), all are approved as monotherapy for the treatment of bipolar mania in adults except lurasidone HCl
- Quetiapine fumarate has an indication for the treatment of depressive episodes associated with bipolar disorder

Key Takeaways (cont'd)

- LATUDA® is the only agent with an indication for the treatment of depressive episodes associated with bipolar I disorder as both a monotherapy and as adjunctive therapy
- Symbyax® is a combination of olanzapine and the SSRI fluoxetine that is approved for the treatment of depressive episodes associated with bipolar I disorder in adults

Key Takeaways (cont'd)

- Abilify® is approved for the treatment of MDD, as an adjunct to antidepressants; Abilify® is not approved for the treatment of bipolar depression
- Vraylar® is approved for multiple indications, including the acute treatment of manic or mixed episodes associated with bipolar I disorder; however, it is not approved for the treatment of depressive episodes

MODULE 4

BIPOLAR MARKET LANDSCAPE

- Part 1: Introduction to the Bipolar Market
- Part 2: Agents With Indications in Bipolar Disorder
- **Part 3: Agents Not Indicated for Bipolar Disorder**

Antidepressants – Some examples

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Examples:*
- citalopram (e.g., Celexa®)
 - escitalopram (e.g., Lexapro®)
 - fluoxetine (e.g., Prozac®)
 - paroxetine (e.g., Paxil®)
 - sertraline (e.g., Zoloft®)

Serotonin–Norepinephrine Reuptake Inhibitors (SNRIs)

- Examples:*
- venlafaxine (e.g., Effexor XR®)
 - desvenlafaxine (e.g., Pristiq®)
 - duloxetine (e.g., Cymbalta®)

Norepinephrine–Dopamine Reuptake Inhibitor (NDRI)

- Example:* bupropion (e.g., Wellbutrin SR®)

All are indicated for the treatment of **MDD**.

Why are antidepressants not recommended for the treatment of bipolar depression?

Mood stabilizer
+ **Antidepressant**
(N=179)

Mood stabilizer
+ **Placebo**
(N=187)

Transient remission:
1-7 consecutive weeks of
euthymia

32 (**17.9%**)

40 (**21.4%**)

P=0.40

**Durable recovery
(primary outcome):**

At least 8 consecutive
weeks of euthymia (no
more than 2 depressive or
2 manic symptoms)

42 (**23.5%**)

51 (**27.3%**)

P=0.40

Answer 1:

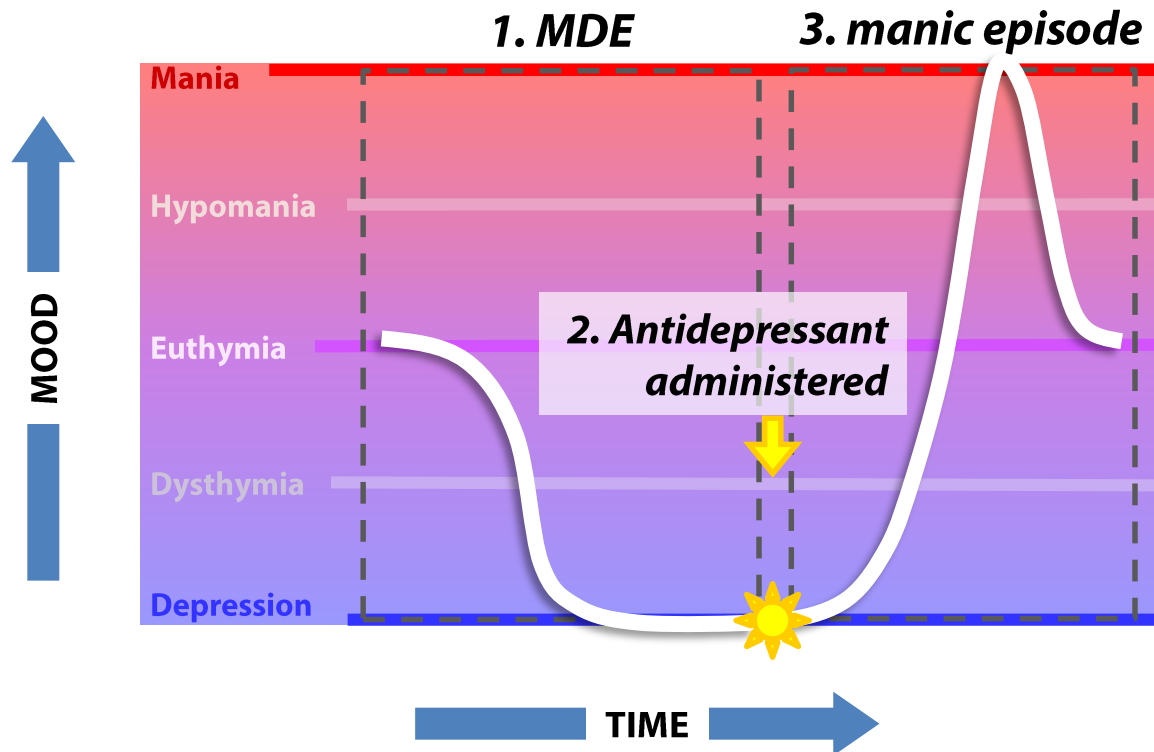
Although antidepressants are the most common initial treatment for bipolar disorder, there is limited evidence of effectiveness.

Reference:

Sachs GS, et al. *N Engl J Med* 2007;356:1711-22.

MODULE 4 BIPOLAR MARKET LANDSCAPE

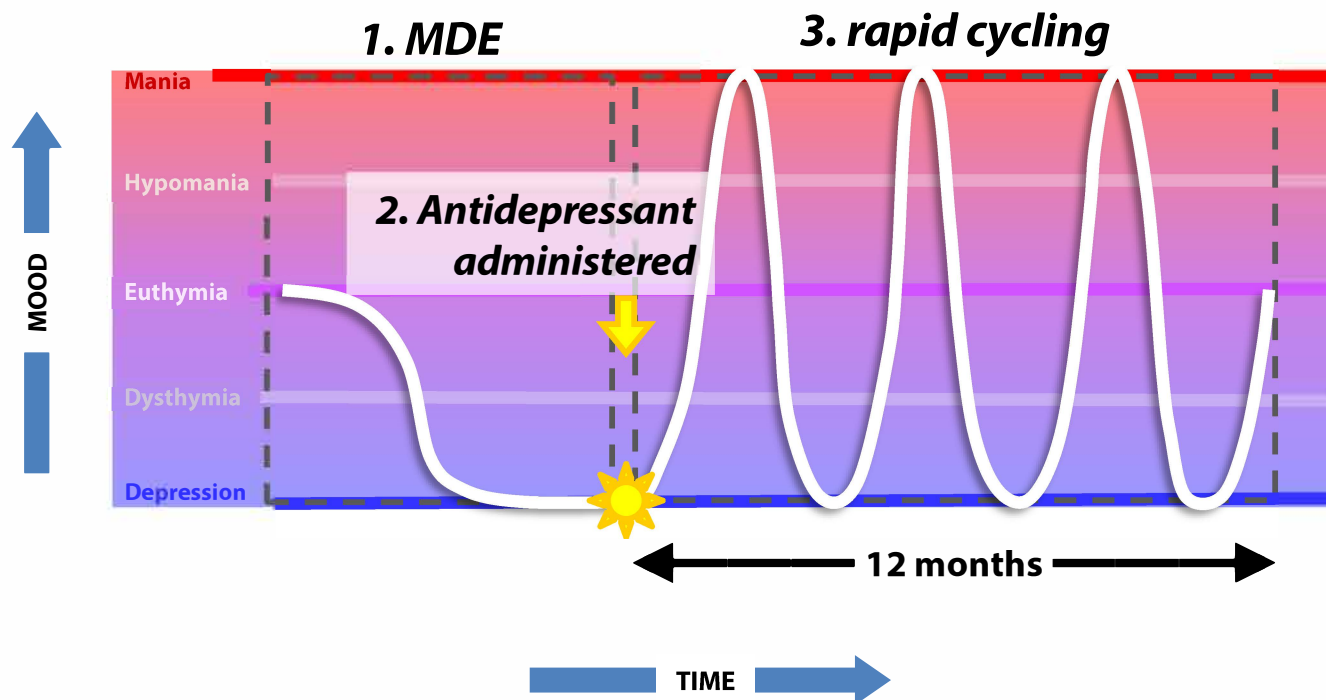
Why are antidepressants not recommended for the treatment of bipolar depression?



Answer 2:
An antidepressant administered to a bipolar patient during an MDE **may precipitate a switch to a manic episode.**

MODULE 4 BIPOLAR MARKET LANDSCAPE

Why are antidepressants not recommended for the treatment of bipolar depression?



Answer 3:
An antidepressant administered to a bipolar patient during an MDE **may also contribute to rapid cycling.**

Key Takeaways

- None of the antidepressants are indicated as monotherapy for the treatment of bipolar disorder or bipolar depression
- Antidepressant monotherapy is not recommended for the treatment of bipolar depression because:
 - Although antidepressants are the most common initial treatment for bipolar disorder, there is limited evidence of effectiveness
 - An antidepressant administered to a bipolar patient during an MDE may precipitate a switch to mania or contribute to rapid cycling

How Do Patients with Bipolar Disorder Differ From Patients with Schizophrenia?

Functional Level

- Often hold jobs
- Fewer receive Supplemental Security Income because of disability

Engagement Level

- More actively engaged in their own treatment decisions

Insight

- More aware of their condition

Expectations

- More concerned with (and less tolerant of) treatment-emergent side effects

Module 4: Bipolar Market Landscape

GLOSSARY

adjunctive therapy -	the use of a second drug in conjunction with a primary treatment to increase the efficacy of the primary
anticonvulsants -	an agent that has efficacy in the treatment of epilepsy
dyspepsia -	disturbed digestion; indigestion
edema -	an accumulation of an excessive amount of watery fluid in cells, tissues, or serious cavities
hypersomnia -	a condition in which one sleeps for an excessively long time but is normal in the waking intervals
monotherapy -	the use of a single drug to treat a particular disorder or disease
mood stabilizer -	a broad term that may encompass medication used to treat bipolar disorder in general, and bipolar mania in particular
peripheral -	related to, located, or constituting an outer boundary of periphery; of or relating to the surface or outer part of a body or organ; external
somnolence -	a state of drowsiness; sleepiness
sublingual -	situated or administered under the tongue
tremor -	an involuntary trembling movement

Module 4: Bipolar Market Landscape

REFERENCE

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