Atypical Antipsychotic Use in the Patient with a Bipolar Manic or Mixed Episode

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Objectives:

1) Become familiar with the current Diagnostic and Statistic Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnostic criteria for Bipolar Disorder and its various sub-types.
2) Describe the current FDA-approved treatment strategies for the pharmacological management of acute Bipolar Manic and Mixed episodes.
3) Appreciate the expanding role of the Atypical Antipsychotics in the acute management of Bipolar Manic and Mixed episodes.
4) Understand the clinical consequences of the eclectic receptor binding properties of the various Atypical Antipsychotics

Case 1

The Star Spangled Banner

Case 2

The Librarian

Case 3

From a Lamb to a Lion

Bipolar Disorder

- Often unrecognized
- Often misdiagnosed
- Often untreated
- Often inadequately treated
- High incidence of suicide

How Bipolar Patients Present to Health Care Providers

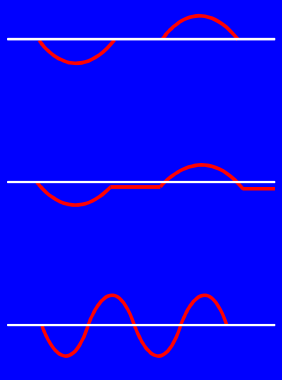
- Depressed
- Anxious
- Mood swings
- Insomnia
- Irritability
- Low energy/fatigue
- Unable to focus
- Drinking too much
- Abusing drugs
- In trouble with the law
- Relationship problems
- Impulse control problems
- No complaints
- Euphoric

Epidemiology of Bipolar Affective Illness

Lifetime prevalence	1.3% of population* 4 million (US)
Sex	Equal distribution
Onset (average)	First impairment (age 15–19) First treatment (age 20–24) First hospitalization (age 25)
Recurrence	Average 2.7–9 years
Rate of suicide without treatment	25% attempt, 15% commit

*For Bipolar I Disorder; Bipolar II Disorder prevalence may be >5%

Bipolar Disorders: Course of Illness



American Psychiatric Association. *DSM-IV*. 1994.
Tucker GJ. In: *Cecil Textbook of Medicine*. 20th ed. 1996;2:1996-2006.

Bipolar Disorder Sub-types

- Bipolar I Disorder
- Bipolar II Disorder
- Cyclothymia
- Bipolar Disorder NOS

Bipolar Disorder Sub-types

Episodes:	Manic or Mixed	Hypomanic	Major Depression
Bipolar I	Must Have	May Have	May Have
Bipolar II	NOT Have	Must Have	Must Have
Cyclothymia*	NOT Have	Must Have	NOT Have

*Symptoms must be present for > 2 years; and include mild depressive sxs

American Psychiatric Association. *DSM-IV.* 1994:317-391.

Major Depressive Episode: Symptoms

Depressed mood most of day, nearly every day, markedly decreased interest in daily activities for approximately 2 weeks and at least four of following:

- Increased or decreased appetite and/or weight
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Hopelessness and/or helplessness
- Fatigue and/or low energy
- Feelings of worthlessness or excessive guilt
- Diminished ability to concentrate/low motivation
- Recurrent ideas of suicide or thoughts of death
- Decreased interest and libido

American Psychiatric Association. *DSM-IV*. 1994:317-391.

Manic and Hypomanic Episodes:

Manic episode symptoms

- Abnormally elevated or irritable mood with at least three of the following (four or more if mood only irritable):
  - Inflated self-esteem
  - Decreased need for sleep
  - Pressured speech
  - Racing thoughts
  - Distractibility
  - Increased goal-oriented activities
  - Unrestrained involvement in pleasurable activities with high potential for painful consequences

Hypomanic episode symptoms

- Similar symptoms to manic episode, but not as severe
- Hypomanic episode lasts at least 4 days versus manic episode that lasts at least 7 days

American Psychiatric Association. *DSM-IV.* 1994:317-391.

Mixed Episode and Rapid Cycling: Definitions

Mixed episode:

- Criteria met for manic and major depressive episodes
- Mood disturbance interferes with normal functioning, necessitates hospitalization or includes psychotic features
- Symptoms not due to substance abuse or general medical condition

Rapid cycling

- At least four episodes of mood disturbance in previous 12 months

American Psychiatric Association. *DSM-IV.* 1994:317-391.

FDA-Approved Medication for treating Bipolar I Mania*

- Lithium (Eskalith, Lithobid)
- Divalproex (Depakote)
- Carbamazepine (Equetro)
- Chlorpromazine (Thorazine)
- Risperidone (Risperdal)
- Olanzapine (Zyprexa)
- Quetiapine (Seroquel)
- Ziprasidone (Geodon)
- Aripiprazole (Abilify)
- Asenapine (Saphris)

* 2012 Physicians Desk Reference

FDA-Approved Medication for treating Bipolar I Mixed*

- Divalproex (Depakote)
- Carbamazepine (Equetro)
- Risperidone (Risperdal)
- Olanzapine (Zyprexa)
- Ziprasidone (Geodon)
- Aripiprazole (Abilify)
- Asenapine (Saphris)

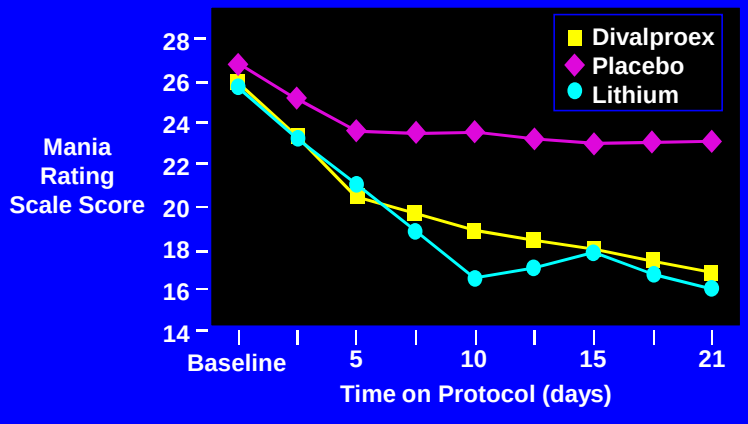
* 2012 Physicians Desk Reference

Traditional Medications for Bipolar I Disorder

- Lithium (citrate, carbonate, delayed release)
  - Therapeutic level = 0.8 – 1.5 (12 hour trough)
  - ECG, lytes, BUN, creatinine, CBC, TFTs, UA, pregnancy test
- Carbamazepine (Tegretol; Equetro = ER)
  - Therapeutic level = 6 – 12 (12 hour trough)
  - CBC/platelets, LFTs, pregnancy test
- Divalproex (Depakote DR and ER)
  - Therapeutic level = 50 – 125 (12 hour trough)
  - CBC/platelets, LFTs, pregnancy test

Mania Rating Scale Scores

Divalproex vs. Lithium vs. Placebo



Bowden CL, et al. *JAMA* 1994.

FDA-Approved dosage range for Atypical Antipsychotics in the treatment of acute Bipolar Mania

Atypical	Mg/day	Half-Life (hours)
Aripiprazole	15-30	75
Olanzapine	5-20	33
Quetiapine	100-800	6
Risperidone	1-6	24
Ziprasidone	80-160	7

* 2006 Physician's Desk Reference

Risk of Obesity, Diabetes, and Dyslipidemia Varies Among the Atypical Antipsychotics*

From the American Diabetic Association's and the American Psychiatric Association's independent Consensus Guidelines:

Drug	Weight Gain	Risk of Diabetes	Worsening Lipid Profile
Olanzapine	+++	+	+
Clozapine	+++	+	+
Quetiapine	++	D	D
Risperidone	++	D	D
Aripiprazole	+/-	-	-
Ziprasidone	+/-	-	-

* (+ Increased effect; - No effect; D Discrepant results)

Adapted from: *Diabetes Care* 2004; 27:596-601 and *J Clin Psychiatry* 2004; 65:267-272

Routine monitoring on all Atypical Antipsychotics

- Weight (Body Mass Index)
  - baseline and every visit
- Blood Pressure
  - baseline, 3 months, 6 months, yearly
- Waist Circumference
  - baseline, 3 months, 6 months, yearly
- Fasting plasma glucose (may get Hg A1c)
  - baseline, 3 months, 6 months, yearly
- Fasting lipid profile
  - baseline, 3 months, 6 months, yearly

Receptor binding affinities of atypical antipsychotics

K_i (nM)

	Ziprasidone	Risperidone	Olanzapine	Quetiapine	Clozapine
D_2	3.1	2.2	20	180	130
5-HT_{2A}	0.39	0.29	3.3	220	8.9
5-HT_{2C}	0.72	10	10	1400	17
5-HT_{1A}	2.5	210	2100	230	140
5-HT_{1D*}	2.0	170	530	>5100	1700
α_1-adrenergic	13	1.4	54	15	4.0
M_1-muscarinic	5100	2800	4.7	100	1.8
H_1-histaminergic	47	19	2.8	8.7	1.8

K_i <1 nM — very high affinity; K_i = 1-10 nM — high; K_i = 11-100 nM — moderate;
K_i =101-1000 nM — low; K_i >1000 nM — negligible.
*Bovine binding affinity; †rat synaptosomes; all other affinities human.

Zorn SH et al. *Interactive Monoaminergic Brain Disorders*. 1999;377-393.
Schmidt AW et al. *Eur J Pharmacol*. 2001;425:197-201.

Receptor binding affinities and putative clinical effects with clozapine (Clozaril)

Receptor	Ki (nM)	Putative Clinical Effect
Antihistaminergic	1.8	Sedation/weight gain
Anticholinergic	1.8	Cognitive impairment, dry mouth, constipation, blurred vision
Alpha-adrenergic	4.0	Orthostatsis/sedation
Serotonin 5-HT 2A	8.9	Decreases EPS/Improves negative Sxs
Serotonin 5-HT 2C	17	Improves cognition/affect
Dopamine D-2	130	Antipsychotic/Antimanic
Serotonin 5-HT 1A	140	Improves cognition/anxiety/depression
Serotonin 5-HT 1D	1700	Antidepressant/antianxiety

Receptor binding affinities and putative clinical effects with olanzapine (Zyprexa)

Receptor	Ki (nM)	Putative Clinical Effect
Antihistaminergic	2.8	Sedation/weight gain
Serotonin 5-HT 2A	3.3	Decreases EPS/Improves negative Sxs
Anticholinergic	4.7	Cognitive impairment, dry mouth, constipation, blurred vision
Serotonin 5-HT 2C	10	Improves cognition/affect
Dopamine D-2	20	Antipsychotic/Antimanic
Alpha-adrenergic	54	Orthostatsis/sedation
Serotonin 5-HT 1D	530	Antidepressant/antianxiety
Serotonin 5-HT 1A	2100	Improves cognition/anxiety/depression

Receptor binding affinities and putative clinical effects with quetiapine (Seroquel)

Receptor	Ki (nM)	Putative Clinical Effect
Antihistaminergic	8.7	Sedation/weight gain
Alpha-adrenergic	15	Orthostatsis/sedation
Anticholinergic	100	Cognitive impairment, dry mouth, constipation, blurred vision
Dopamine D-2	180	Antipsychotic/Antimanic
Serotonin 5-HT 2A	220	Decreases EPS/Improves negative Sxs
Serotonin 5-HT 1A	230	Improves cognition/anxiety/depression
Serotonin 5-HT 2C	1400	Improves cognition/affect
Serotonin 5-HT 1D	>5100	Antidepressant/antianxiety

Receptor binding affinities and putative clinical effects with risperidone (Risperdal)

Receptor	Ki (nM)	Putative Clinical Effect
Serotonin 5-HT 2A	0.29	Decreases EPS/Improves negative Sxs
Alpha-adrenergic	1.4	Orthostatsis/sedation
Dopamine D-2	2.2	Antipsychotic/Antimanic
Serotonin 5-HT 2C	10	Improves cognition/affect
Antihistaminergic	19	Sedation/weight gain
Serotonin 5-HT 1D	170	Antidepressant/antianxiety
Serotonin 5-HT 1A	210	Improves cognition/anxiety/depression
Anticholinergic	2800	Cognitive impairment, dry mouth, constipation, blurred vision

Receptor binding affinities and putative clinical effects with ziprasidone (Geodon)

Receptor	Ki (nM)	Putative Clinical Effect
Serotonin 5-HT 2A	0.39	Decreases EPS/Improves negative Sxs
Serotonin 5-HT 2C	0.72	Improves cognition/affect
Serotonin 5-HT 1D	2.0	Antidepressant/antianxiety
Serotonin 5-HT 1A	2.5	Improves cognition/anxiety/depression
Dopamine D-2	3.1	Antipsychotic/Antimanic
Alpha-adrenergic	13	Orthostatsis/sedation
Antihistaminergic	47	Sedation/weight gain
Anticholinergic	5100	Cognitive impairment, dry mouth, constipation, blurred vision

Receptor binding affinities and putative clinical effects with aripiprazole (Abilify)*

Receptor	Ki (nM)	Putative Clinical Effect
Dopamine D-2	0.34	Antipsychotic/Antimanic
Serotonin 5-HT 1A	1.7	Improves cognition/anxiety/depression
Serotonin 5-HT 2A	3.4	Decreases EPS/Improves negative Sxs
Serotonin 5-HT 2C	15	Improves cognition/affect
Serotonin 5-HT 1D	?	Antidepressant/antianxiety
Alpha-adrenergic	57	Orthostatsis/sedation
Antihistaminergic	61	Sedation/weight gain
Anticholinergic	>1000	Cognitive impairment, dry mouth, constipation, blurred vision

*from FDA approved 2005 product insert

For Non-responders to initial monotherapy in Bipolar Manic/Mixed Episodes

- Is patient compliant with the medication?
- Is medication dosed adequately?
- Any prescription medications aggravating Sxs?
- Is patient recreational drug free?
- Is patient getting adequate sleep?
- Is psychosocial support adequate?
- Have medical conditions been ruled out?
- If serum levels are available, are they 12 hour troughs? Are these levels therapeutic?

For Non-responders to initial monotherapy in Bipolar Manic/Mixed Episodes

- Begin combination medication therapy:
  - Divalproex and Atypical Antipsychotic
  - Lithium and Atypical Antipsychotic
  - Lithium and divalproex
  - Divalproex and carbamazepine
  - Lithium and carbamazepine

Conclusions

- The patient with Bipolar Disorder requires a careful assessment to discern the specific sub-type.
- Patients with acute manic and mixed symptoms should be aggressively treated.
- Lithium, divalproex, carbamazepine and the Atypical Antipsychotics are the foundation of pharmacological treatment in this setting.
- The Atypical Antipsychotics are a heterogeneous group of molecules with significant receptor binding profile and side effect differences.