

PHARMACOLOGIC TREATMENT OF BIPOLAR DISORDER

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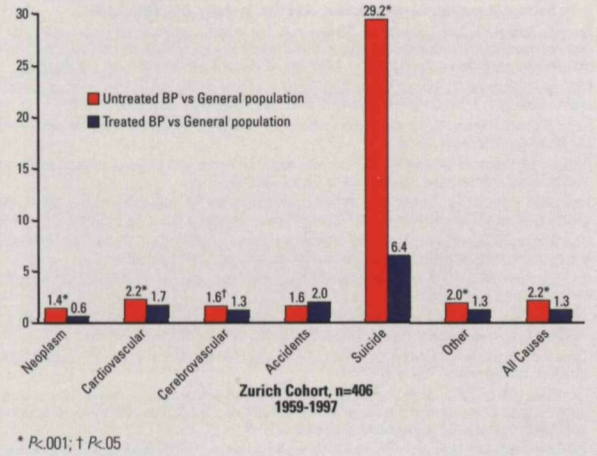
Introduction

Regarding the treatment of patients with bipolar disorder, positive findings have shown that patients engaged in treatment may live longer. Angst and Sellaro[1] studied standardized mortality ratios for patients with bipolar disorder and found a significant reduction in mortality ratio in our bipolar patients who were actively in treatment (Slide 1).[1] Data from the Collaborative Depression Study by Judd and colleagues[2] showed that bipolar patients are quite symptomatic. Judd and colleagues[2] followed bipolar patients over a 13-year period and found that these patients were symptomatic ~50% of the study period. What were these patients most likely to be symptomatic with: bipolar depression (Slide 2).[2] Thus, it is important to focus on bipolar depression and examine placebo-controlled trials that were adequately powered in its treatment.

Treatment of Bipolar Depression

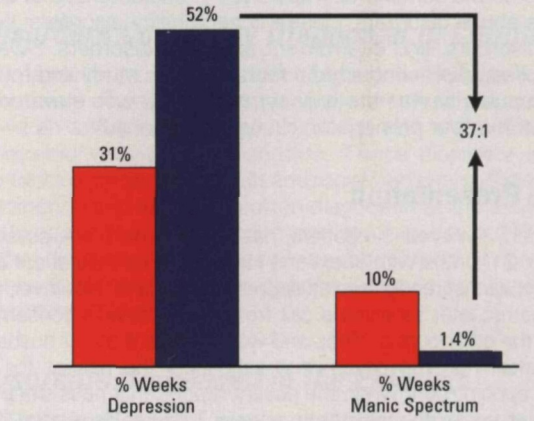
Over the last decade, there have been positive trials studying lamotrigine, quetiapine, olanzapine, and olanzapine-fluoxetine combination.[3-5] Two of these medications are United States Food and Drug Administration–approved in bipolar disorder treatment: quetiapine and olanzapine-fluoxetine. There are a number of negative trials in bipolar depression, including a number of antidepressant monotherapy trials and antidepressants in combination with mood stabilizers (Slide 3).[6-11] However, what is the most frequent pharmacotherapy treatment used for bipolar depression? It is the use of antidepressants alone[12]; antidepressant monotherapy is twice as commonly prescribed as mood stabilizers (Slide 4).[13] Thus, it is necessary for clinicians to possess knowledge of the evidence and results from both positive and negative antidepressant trials for bipolar disorder.

SLIDE 1
Standardized Mortality Ratios[1]



* $P<.001$; † $P<.05$

SLIDE 2
Depression Is the Most Common Expression of Bipolar Disorders[2]



BP-I n=135; BP-II n=71
BP-I; BP-II=Bipolar Type I and II.

SLIDE 3
Acute Bipolar Depression: Placebo-Controlled Therapy Trials With Adequate Sample Size[6-11]*

Positive	Negative or Failed
Lamotrigine	Imipramine
Olanzapine	Paroxetine
Quetiapine	Bifeprunox
Olanzapine + fluoxetine	Aripiprazole
	Ziprasidone
	Li+ paroxetine
	Li+ imipramine
	MS+ paroxetine
	MS+ bupropion

*Power to detect a difference > 0.8
Li=lithium; MS=mood stabilizer.

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Disclosures: Dr. Baldassano is a consultant to AstraZeneca and Pfizer. Dr. Baldassano discusses the unapproved/investigational use of clozapine, divalproex, and lamotrigine for the treatment of bipolar disorder.

https://doi.org/10.1017/S1092852910001773 Published online by Cambridge University Press

Positive Trials

Calabrese and colleagues[3] compared lamotrigine 50 mg and 200 mg to placebo. After the 6-week study period, both doses of lamotrigine outperformed placebo.[3] Lamotrigine is not FDA approved for the treatment of bipolar depression; there have been negative and failed trials of the drug following the publication of this trial. In the trial that led to its FDA approval—which was a three-arm trial including monotherapy with olanzapine—both olanzapine as well as olanzapine-fluoxetine combination performed better than placebo.[4] Quetiapine also has positive data in bipolar depression. Two identical trials compared quetiapine 300 mg to quetiapine 600 mg and placebo.[5] Results of these studies found that both doses of quetiapine outperformed placebo.[5]

Lithium, which is not FDA approved for the treatment of bipolar depression, does have some evidence in the treatment of bipolar depression.[14] Most trials with lithium were completed before 1980 and were small, placebo-controlled trials; however, the majority of these trials were positive.[14]

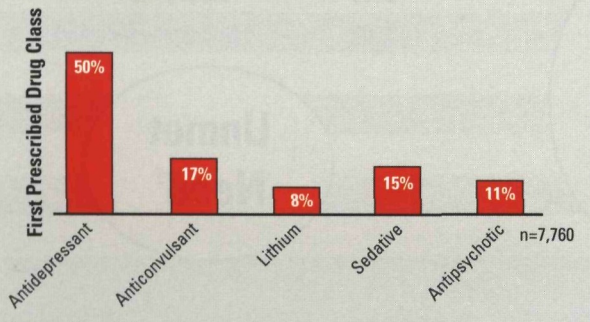
Negative Trials

Nemeroff and colleagues[6] conducted a double-blind trial studying bipolar patients who were all maintained on lithium. Patients were randomized to receive either placebo, paroxetine, or imipramine addition. This study found that there was no advantage for adding either antidepressant. A subanalysis of subjects who had low lithium levels showed that paroxetine or imipramine addition had some advantage.[6] A paroxetine monotherapy trial studied patients with bipolar Type I and Type II who had depression, and in this trial, researchers compared paroxetine 20 mg/day as monotherapy in bipolar depression with placebo.[7] At the end of the 8-week study period, no advantage for paroxetine was shown over placebo.

The largest randomized acute bipolar depression study resulted from the Standardized Treatment Enhancement Program for Bipolar Disorder (STEP-BD) and was published by Sachs and colleagues.[8] In this study, researchers studied 366 patients with bipolar disorder, all of whom were taking a mood stabilizer. Patients were then randomized to either a placebo group or an adjunctive antidepressant group. In this trial, researchers studied paroxetine and bupropion and found that there was no advantage for adding an antidepressant in these subjects. Some researchers have been critical of these studies noting that the recovery rates were very low (24% for paroxetine and 27% for bupropion). However, after examining transient remission, the authors found no advantage for the addition of antidepressants.[8]

SLIDE 4

Antidepressant Monotherapy Twice as Common as Mood Stabilizers[13]



Mood stabilizers: lithium, valproate, carbamazepine, gabapentin, lamotrigine, oxcarbazepine, topiramate, and zotepine.

Focusing on treatment-emergent affective switch, Peet[9] conducted a meta-analysis that showed that selective serotonin reuptake inhibitors (SSRIs) were no more likely to switch patients with bipolar disorder than placebo. However, more rigorous methodology used in the Stanley Foundation Bipolar Depression Study suggests slightly higher treatment emergent affective switch with antidepressants.[10,11] The study also showed that there may be differing risk factors with serotonin-norepinephrine reuptake inhibitors, most often venlafaxine, increasing the risk for treatment-emergent affective switch.[10,11]

Aripiprazole

Aripiprazole, although it is FDA approved as an adjunctive treatment in unipolar depression and for acute manic and mixed episodes associated with bipolar disorder, it fails to show positive evidence in the treatment of bipolar depression. Two 8-week, double-blind, randomized, placebo-controlled trials in aripiprazole for bipolar depression have been conducted. Aripiprazole was initiated at 10 mg, and then the dose was flexibly increased.[15] Interestingly, in both studies, aripiprazole performs better than placebo at week 1 through week 6. However, at week 8 at the end of the study, the drug fails to separate from placebo.[15]

Divalproex

Divalproex has little data in the treatment of bipolar depression, and has not been FDA approved for this indication. Only two double-blind, placebo-controlled trials have reported results with this drug. Sachs and colleagues[16] showed that divalproex did not perform better than placebo by the end of the study period (8 weeks). However, a small study (N=25) by Davis and colleagues[17] showed positive results in improving bipolar depression symptoms over placebo with use of divalproex.

Treatment-Resistant Bipolar Depression

The only treatment-resistant bipolar depression trial was a result of STEP-BD study.[18] In this trial, researchers added either lamotrigine, inositol, or risperidone to patients who were taking a mood stabilizer, had a recurrent major depressive episode, and were not responsive to a combination of adequate doses of established mood stabilizers plus at least one antidepressant. Patients were randomly assigned to open-label treatment with either lamotrigine, inositol, and risperdal. Unfortunately, enrollment in this trial was not completed and it was not adequately powered. However, results did show a trend suggesting an advantage for lamotrigine in this treatment refractory group (Slide 5).[18]

Maintenance Treatment of Bipolar Disorder

The first medication that was FDA approved for maintenance treatment of bipolar disorder was lithium in 1974. Lamotrigine was approved for this indication in 2003, with olanzapine, aripiprazole, and quetiapine approved more recently (Slide 6).[19] Reviewing bipolar maintenance studies of these drugs, if you compare mood stabilizers, lithium, lamotrigine, and antipsychotics to one another, what is found is that mood stabilizers have slightly less efficacy than the other drug types, but mood stabilizers have better tolerability than the atypical antipsychotics.[19]

In treatment-refractory patients with bipolar disorder, there is a role for clozapine, which is not FDA approved for bipolar disorder treatment. Suppes and colleagues[20] studied

https://doi.org/10.1017/S1092852900027772 Published online by Cambridge University Press

patients with bipolar disorder who were considered refractory, and patients were randomized to receive either treatment as usual or clozapine. Patients were followed over a 1-year period. Results showed that patients who were randomized to clozapine showed improvement compared to those receiving treatment as usual. This study also showed that patients who received clozapine were able to simplify their medication regimen and reduce their total number of medications. Typically, clozapine in the treatment of bipolar disorder is not considered, however, for treatment-refractory patients, it may be beneficial. Side effects of clozapine include constipation and weight gain as well as risk for reduced white blood cell count.

Suicide in Bipolar Disorder

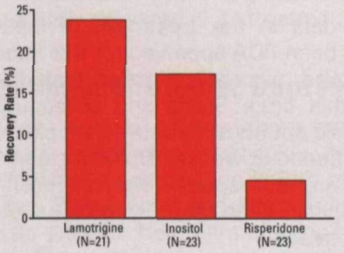
In patients with bipolar disorder, initiation of lithium treatment did show a reduction in the risk for suicide in a study by Baldessarini and colleagues.[21] In this study, it was shown that as lithium treatment was discontinued, the risk for suicide increased significantly. The risk was highest in the first few months following lithium discontinuation, then suicide risk decreased in later years.[21] Although these data are observational, given that suicide is difficult to definitively study in randomized settings, these observational data are quite relevant to clinical practice. Meta-analytic evidence also suggests that this association remains strong in different settings.[22] Thus, lithium should be considered as a mainstay treatment in patients with bipolar disorder, particularly for those who have a family history of suicide or personal history of suicide attempts.

Case Presentation

Mary is a 23-year-old single, white female who presents with her third episode of depression (Slide 7). Her first depressive episode occurred at 16 years of age, and she was not treated at that time. Mary has had a suicide attempt at 19 years of age in the setting of her second episode of depression. Her maternal grandmother committed suicide. At the time of her suicide attempt, Mary was not diagnosed with bipolar disorder. She was treated with an SSRI and found limited success. Mary reports biyearly episodes of increased energy, decreased need for sleep, racing thoughts, talkativeness, and impulsivity.

Subsequently, Mary was diagnosed with bipolar disorder, and the first question for a clinician is what would be the next step in terms of treatment? The first step is to make the appropriate diagnosis, which Mary's clinician has done. However, the correct diagnosis was missed when she pre-

SLIDE 5
Treatment-Resistant Bipolar Depression: STEP-BD[18]



- Open randomized trial
- Prior nonresponse to MS + AD
- LTG 150–250 mg/day
- INO 10–25 gms/day
- RIS up to 16 mg/day
- Up to 16 weeks
- Recovery: <2 sxs for ≥2 mos

STEP-BD=Systematic Treatment Enhancement Progr for Bipolar Disorder; MS=mood stabilizers; AD=antidepressants; LTG=lamotrigine; INO=inositol; RIS=risperidone; SXS=symptoms; MOS=months.

SLIDE 7
Case Presentation

23-year-old single, white female presents with her third episode of depression. First episode 16 years of age, not treated

Mary had a suicide attempt 19 years of age in the setting of her second episode of depression (maternal grandmother committed suicide). Treated with SSRI

Mary reports biyearly episodes of increased energy, decreased need for sleep, racing thoughts, and talkativeness

SSRI=selective serotonin reuptake inhibitors.

SLIDE 6
Approved and Unapproved Agents for Bipolar Disorder[19]

Acute Mania (Year, Drug)		Acute Depression (Year, Drug)		Maintenance (Year, Drug)	
1970	Lithium	2003	Olanzapine/fluoxetine combination	1974	Lithium
1973	Chlorpromazine	2006	Quetiapine	2003	Lamotrigine
1994	Chlorpromazine			2004	Olanzapine
2000	Olanzapine*			2005	Aripiprazole
2003	Risperidone*			2008	Quetiapine (adjunct)
2004	Quetiapine*				
2004	Ziprasidone				
2004	Aripiprazole				
2004	Carbamazepine				
2005	Divalproex ER				
2009	Asenapine				

Unmet Need†

Unmet Need†

* Adjunctive and monotherapy

† Important unmet needs: well-tolerated treatments for acute depression and maintenance.

https://doi.org/10.1017/S1092852900027772 Published online by Cambridge University Press

sented at 19 years of age, although she experienced these mood-elevated states prior to that evaluation. Regarding treatment, there is a strong case to be made for the initiation of lithium given the fact that there is some evidence of the benefit of lithium in bipolar depression. In addition, Mary has not only had a personal suicide attempt, but she also has a family history of suicide.

A clinician may consider divalproex; however, as previously discussed, there is little evidence supporting its use in bipolar depression. Although not FDA approved for bipolar depression, there is evidence that lamotrigine may be a worthwhile option. Lamotrigine is well tolerated and typically does not cause weight gain, which may be a concern for a 23-year-old woman. Lastly, an atypical antipsychotic may be considered, and there is evidence with olanzapine as well as quetiapine in bipolar depression. These may also be considered for the treatment of Mary's episode.

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