Suicide in Bipolar Disorder

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Disclosure Statement

I have no significant financial relationships to disclose . . .

presuming that you will see a few pens and fewer lunches in the early 2000s as currently insignificant.
Objectives

1. Review the epidemiology and risk factors of suicide in people with bipolar disorder.

2. Review the evidence for protective effects of drugs used in bipolar treatment against suicide in some populations.

3. Review the evidence suggesting some drugs used for the treatment of bipolar disorder may increase the risk of suicide.
Suicide Rates in Bipolar Disorder

- Lifetime risk of attempting suicide: 25-50%
- Lifetime risk of completing suicide: 6-15%
- Goodwin found a suicide rate for those with bipolar disorder that was nearly 10 times that of the general population in a large observational study of patients in Washington and California.
- The annual suicide rate in bipolar disorder was found to be 20 times higher than the general population in one study by Tondo: 0.40%/year vs. 0.017%/year

Higher Lethality of Suicide Attempts in Bipolar Disorder

In Goodwin’s observational study of >20,000 CA & WA patients, the ratio of suicide attempts to suicide completions was much lower in bipolar disorder reflecting the higher lethality of the attempts.

- general population: 10-20
- bipolar disorder: 6.4

Impulsivity

• Swann and colleagues looked at impulsivity in bipolar patients and found an association in the number of impulsive errors on a memory task and the number of prior suicide attempts.
• This correlation was independent of mood state at the time.
• Alcohol abuse was also found to have a significant correlation, but interestingly the effect disappeared when impulsiveness was controlled for.
• Impulsiveness may be an independent risk factor for both suicide and alcohol abuse.

Suicide Risk Factors Consistently Identified in Bipolar Disorder

- Some relate to phases of bipolar illness:
  - Depression
  - Hospitalization for depression
  - Mixed states
- Some are well-known for the general population:
  - A prior suicide attempt
  - Family history of suicidality
  - Alcohol and drug abuse
  - Male gender
- Others:
  - Axis I, II, or III comorbidities
  - Impulsive or aggressive traits
  - Early physical or sexual abuse
  - Early age of illness onset of illness
  - Greater duration of time spent affectively ill

Age, Recent Diagnosis, and Time in Treatment

- In Swedish study by Osby, SMRs calculated showed that these factors are also too are associated with suicide in bipolar disorder

<table>
<thead>
<tr>
<th></th>
<th>Standardized Mortality Ratios (SMRs)</th>
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<tbody>
<tr>
<td></td>
<td>Men w/ Bipolar</td>
</tr>
<tr>
<td>Overall</td>
<td>15.0</td>
</tr>
<tr>
<td>Under 30 years old</td>
<td>81.6</td>
</tr>
<tr>
<td>and in 1st year of</td>
<td></td>
</tr>
<tr>
<td>treatment</td>
<td></td>
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<tr>
<td>Over 65 years old</td>
<td>4.7</td>
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<tr>
<td>and with over 5 years of follow up treatment</td>
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Phase of Bipolar Illness as a Risk Factor

• Suicide in BP is “strongly associated” with depressive and dysphoric-agitated (mixed) states (Baldessarini & Tondo 2003)

• In STEP-BD (~75% BP1, ~25%BP2) SI according to phase:
  – depressed phase (49%)
  – mixed phase (47%)
  – manic/hypomanic phase (9%)
  – euthymic (7%) phase

Baldessarini RJ, Tondo L. Suicide Risk and Treatments for Patients with Bipolar Disorder. JAMA. 2003; 290:1517-1519.
A Broad Concept of **Mixed States**
Informs Risk of Suicide

• A study by Cassano 2004 looked at suicidal ideation in unipolar depressive and bipolar patients

• In the unipolar depression group, for each manic or hypomanic symptom endorsed the likelihood of suicidal ideation increased by 4.2%, which was statistically significant

• Growing evidence suggests that mixed states are associated with suicidality, even when they do not meet the “narrow” DSM-IV definition of a mixed episode, with requires meeting criteria for a full major depressive episode and mania criteria.)


Agitated depression: a mixed state?

**Agitated depression** = A major depressive episode with high psychomotor agitation.

- In a study by Akiskal of unipolar depression patients in 2005, 90% of the patients with agitated depression had a depressive mixed state vs. only 20% of patients with a non-agitated depression. Thus agitated depression is thought to be on the bipolar spectrum by the authors.

- The rate of suicidal ideation in the agitated depression group was higher as well at 62% vs. 43% for the not agitated group.

Are there **Medications** for Bipolar Disorder that May Reduce the Risk of Suicide?
Has the FDA approved any drugs for suicide prevention?
Has the FDA approved any drugs for suicide prevention?

Yes! Clozapine.

- In 2003 Clozapine became the first treatment approved to prevent suicidal behavior.

- It was approved for this in the treatment of schizophrenia and schizoaffective disorder

Baldessarini RJ, Tondo L. Suicide Risk and Treatments for Patients with Bipolar Disorder. JAMA. 2003; 290:1517-1519.
Clozapine Reduces Suicide Risk in Schizophrenia.

- InterSePT was a two-year long, multicenter, randomized, single-blind prospective study of persons with schizophrenia considered to be at high risk of suicide
  - Those randomized to clozapine showed significantly less (32% less) suicidal behavior than those randomized to olanzapine.

- A 2005 metanalysis of 6 studies looking at the risk of suicide on clozapine vs. other antipsychotics in schizophrenia.
  - Found a 3-fold reduction in the risk of suicidal behaviors on clozapine as compared to other antipsychotics.

Are there Drugs that Reduce the Risk of Suicide in Bipolar Disorder?

- No FDA Approved Drugs
- **Lithium** does have well-established anti-suicidal properties however.
- Clozapine’s antisuicidal effect may extend to non-schizophrenic populations, but this has not been studied, so it is not known.
- Other drugs may increase or decrease the risk of suicide in some populations
  - Antidepressants
  - Antiepileptics
Lithium’s Protective Effect on Suicide Risk

• Tondo 1997 reviewed studies of lithium maintenance in pts with mood disorders:
  – 28 studies; 17,000 patients.
  – Risks of completed and attempted suicides were **8.6 fold higher** in pts not on lithium

• 2005 Metanalysis by Cipriani
  – 32 RCTs with 1,389 pts on lithium and 2,069 on placebo or other drug
  – Pts on lithium were **less likely** to die by suicide
    (**odds ratio 0.26, p=0.01**)


Lithium’s Protective Effect on Suicide Risk

• 2006 metanalysis by Baldessarini
  – 31 studies (open-label and RCTs) with over 85,000 person years
  – Lithium treated persons had a reduced rate of suicidal acts by a factor of 5 vs. placebo
  – Lithium treated persons also showed decreased lethality of attempts shown by a ratio of attempts to suicides that increased by a factor of 2.5

How might lithium reduce suicide risk?

- Cipriani and colleagues’ proposed mechanisms of actions for lithium’s effect on suicidality
  - Serotonin-mediated reduction in impulsivity and/or aggressive behavior
  - Benefit from enhanced monitoring required for lithium treatment
  - Reduction in risk of depressive relapse

- Ahrens and Muller-Oerlinghausen 2001 found the association of lithium and reduced rates of completed suicides to be independent of lithium’s prophylactic benefit for depressed episodes.
  - Even those that did not show a reduction in depressive episodes did show a reduced risk of suicide

- Other possibilities: reduction in mixed symptoms?


Lithium Discontinuation and Increased Risk

• Tondo’s 1997 review of lithium maintenance 28 studies in 17,000 patients with mood disorders:
  – Increased rates of suicide after lithium discontinuation:
  – Suicide rates rose by a factor of 7 after lithium discontinuation
  – 16 fold increase in the first year
  – Fatalities increased 9 fold indicating a higher lethality of attempts after lithium discontinuation.

• In a metanalysis in 2001, a sharp temporary increase in suicide risk was observed for several months following discontinuation of lithium
  • That increase was only half as large when the lithium was tapered slowly over several weeks or more before discontinuation vs. over just 1-14 days.


Baldessarini RJ, Tondo L. Suicide Risk and Treatments for Patients with Bipolar Disorder. JAMA. 2003; 290:1517-1519.
Antiepileptics and Suicide Risk

• Do antiepileptic drugs (AEDs) decrease rates of suicide in bipolar disorder too?
  – By reducing the number/severity of mood episodes?
  – By reducing impulsivity?

– Do antiepileptic drugs (AEDs) increase the risk of suicidal behavior in bipolar patients?
  – FDA warning regarding a possible increased risk of suicidal behavior in AEDs
FDA Warning about AEDs and Suicide

- The FDA in 2008 completed a metanalysis of 199 RCTs that suggests anticonvulsants including those used as mood stabilizers may increase rates of suicidal behavior.
  
  - They found a rate of suicidal ideation or behavior in patients taking antiepileptics was twice the rate for placebo groups: 0.43% vs. 0.22%.
  
  - This corresponds to an estimated 2.1 more patients per 1000 (95%CI: 0.7, 4.2) with suicidal ideation or behavior in the drug group than placebo.
  
  - Although the incidence is too low to draw conclusions, it is interesting to note that four patients taking anticonvulsants in these studies committed suicide, whereas none in placebo groups did.

Re-analysis of the data by Baldessarini and Tondo (2009)

- Re-analysis showed that the epileptic patients in 14 placebo-controlled RCTs on AEDs may have an increased risk of suicidal thinking or behavior with a RR=3.52 (p=0.02)

- However, the psychiatric patients in 48 placebo-controlled RCTs on anticonvulsants when considered separately were thought to probably NOT have any increased risk with a RR=1.43 (p=0.12)
VAGLAHCS Retrospective Study

• Very little evidence has accumulated to suggest a role for anticonvulsants in the prevention of suicide.

• 405 veterans charts were reviewed for pharmacotherapy and suicide completion, attempt or hospitalization. They were followed for a mean of 3 years. Two fifths were diagnosed with bipolar I and one fifth were diagnosed with each bipolar II, bipolar NOS, and SAD, bipolar type.

• **No completed suicides occurred**, so these rates reflect suicide attempts and hospitalizations for suicidal ideation. (Yerevanian, Parts 1-3, 2007)

• Rates of non-lethal suicidal behavior were similar during lithium (2.49 events per 100 patient years), divalproex (4.67) and carbamazepine (3.80) monotherapies. There were no significant differences between the three treatment groups.
  – There was a **16 fold increase in the rate of suicidal behavior after discontinuation of these mood stabilizers**, and this study showed a very high overall rate of 55 suicidal events per 100 patient years.

Metanalysis of **Lithium vs. Pooled AEDs**

- Baldessarini and Tondo in 2009 pulled all 6 of the studies published comparing bipolar patients treated with lithium vs. antiepileptics for over 6 months that reported rates of suicidal acts.
  - Depakote, carbamazepine and lamotrigine were included in the studies.
  - **Rates of suicidal acts were 2.86 times higher** \((p<0.0001)\) during treatment with anticonvulsants than with lithium.
  - No anticonvulsant emerged as superior to another, but limited conclusions can be drawn given study and metanalysis limitations.

*Baldessarini RJ, Tondo L. Suicidal Risks during Treatment of Bipolar disorder with Lithium versus Anticonvulsants. Pharmacopsychiatry 2009; 42:72-75.*
Lithium vs. Depakote

- Observational analysis of over 20,000 bipolar diagnosed patients of CA and WA in health organization computer databases:
- Does not account for potentially confounding prescribing practices or effects of other drugs prescribed like antidepressants.

<table>
<thead>
<tr>
<th></th>
<th>Divalproex vs. Lithium</th>
<th>Carbamazepine vs. Lithium</th>
<th>No mood stabilizer vs. Lithium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adjusted risk ratio of</strong></td>
<td>2.7 (p=.03)</td>
<td>1.5 <strong>Æ Not significant</strong></td>
<td>2.2 <strong>Æ Not significant</strong></td>
</tr>
<tr>
<td><strong>suicide death</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Adjusted risk ratio of</strong></td>
<td>1.7 (p=0.002)</td>
<td>2.9 (p&lt;0.001)</td>
<td>1.4 <strong>Æ Not significant</strong></td>
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<tr>
<td><strong>attempted suicide</strong></td>
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<td>(resulting in hospitalization)</td>
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Lithium vs. Carbamazepine

- Thies-Flechtener and colleagues did a 2 ½ year long prospective study of 378 pts with various affective disorders.

- They saw significantly more suicide attempts or completions with carbamazepine (9 pts) than with lithium (zero pts).

Lithium vs. Lamotrigine

• Bowden 2003 found a **2.35 times increased risk** of suicidal acts in bipolar patients treated with lamotrigine as opposed to lithium.

• Calabrese 2003 found a **2.14 times increased risk** of suicidal acts in bipolar patients treated with lamotrigine vs. lithium.

• Using data from the Bowden and Calabrese 2003 RCTs, Baldessarini and Tondo 2009 metanalysis found the pooled rate of suicidal acts was not significantly lower (p=0.73) with lamotrigine (0.55% per year) than with placebo (0.33% per year.)


Discontinuation Risks

• Suicidal risk increased sharply in the months following discontinuation of Lithium, Divalproex and Carbamazepine.

  – Lithium discontinuation → 24 fold increased risk
  – Divalproex discontinuation → 11 fold increased risk
  – Lithium, Divalproex, and
    Carbamazepine d/c pooled → 16 fold increased risk

Antidepressants and Suicide

• Do antidepressants decrease rates of suicide in bipolar disorder?
  – By reducing depression?

• Do antidepressants increase rates of suicide in bipolar disorder?
  – FDA black box warning regarding a increased risk of suicidal behavior in with antidepressant use.
Antidepressant **Black Box Warning**

- Antidepressants increased the risk of suicidal thinking and behavior in children, adolescents, and young adults in short-term studies with major depressive disorder (MDD) and other psychiatric disorders.

- Short term studies did not show an increase in the risk of suicidality with antidepressants compared to placebo in adults beyond age 24, and there was a reduction in risk with antidepressants compared to placebo in adults aged 65 and older.

- This risk must be balanced with the clinical need. Monitor patients closely for clinical worsening, suicidality, or unusual changes in behavior. Families and caregivers should be advised of the need for close observation and communication with the prescriber.
Controversy about antidepressants risks and benefits in terms of suicide risk

• Epidemiological studies and general population trends have shown suicide rates decline in adults, geriatrics and even in adolescents as antidepressant use increases, which some have suggested argue for anti-suicide properties of these drugs (at least in unipolar depression.)

• But other studies and a growing number of analyses show no reduction in suicidality from antidepressants.

• Simon and Savarino (2007) looked at suicide rates among persons seeking treatment for depression: over 70,000 getting antidepressant prescriptions from PCP, over 7,000 getting script from psychiatrist, and over 54,000 entering psychotherapy.
  • Highest number of suicide attempts occur in the month prior to treatment in all groups
  • No difference in rates of suicide related behaviors for those getting antidepressants vs. psychotherapy


Is there any evidence that antidepressants increase suicidality in patients with bipolar disorder?

• Goldberg (1999) looked at correlates of suicidal ideation in 100 pts with bipolar mania with mixed features (= 2 depressive symptoms except SI)
  • SI was present in 59% of mixed manic patients
    – SI was 4 times as common in those who took antidepressants in the week prior to admission, which was statistically significant

• Akiskal 2003 compared antidepressant-associated hypomanias (bipolar III in Akiskal’s nosology) vs. spontaneous hypomania (bipolar II)
  – 80% of the antidepressant-associated hypomanias were admitted for suicidality vs. only 43% for spontaneous hypomania (significant with p=0.002)

Is there any evidence that antidepressants increase suicidality in patients with bipolar disorder?

• Kessing 2005 looked at all lithium prescriptions and suicides in Denmark over 4 years.
  – They found that purchasing antidepressant meds was associated with an 6-fold increase in the risk of suicide.
  – This risk was not altered by lithium prescription.

• Goldberg 2005 looked at medications and SI in a 1000 patients in the STEP-BD trial.
  – SI was present in 25% of patients taking an antidepressant and only 14% of those who were not.

Is there any evidence that antidepressants increase suicidality in patients with bipolar disorder?

Shi 2004 compared the suicide attempt risk of patients with recognized bipolar disorder vs. unrecognized bipolar disorder in over 24,000 adults in the CA Medicaid program with a new antidepressant therapy episode.

– In **recognized bipolar disorder** (n=3,797)
  • 47% received an antidepressant alone as initial therapy!!!!!!
  • 42% received two drugs (antidepressant plus mood stabilizer)

– In **unrecognized bipolar disorder** (n=1,582)
  • 77.5% received an antidepressant alone
  • This group was more likely to have attempted suicide (0.9%) than either the recognized bipolar patients (0.3%) or the non-bipolar patients (0.2%) all of whom were prescribed antidepressants

– The difference in the suicide risk between the recognized and unrecognized bipolar groups **increased when patients using mood stabilizers were removed** from the analysis.

Do antidepressants induce suicidality by causing **switching** of mood states?

- No RCT was published on suicidality and switching in bipolar disorder at the time of McElroy and colleagues 2006 review (and there are none I have found in literature searches on the topic done in 2011.)

Which antidepressants are more likely to cause switching?

SNRIs.

Antidepressants with serotonin & norepinephrine reuptake inhibition, like TCAs and venlafaxine, appear to be more likely to induce a switch than SSRIs or bupropion.

Which antidepressants are more likely to cause switching?

- Peet 1994 looked at antidepressant switch rates in bipolar depression and found a significant difference:
  - 11.2% with TCAs vs. only 3.7% with SSRIs

- Gijsman and Geddes 2004 did a metanalysis of 12 short-term placebo controlled RCTs with >1,000 pts with bipolar depression of which 75% were on a mood stabilizer.
  - The overall switch rate for antidepressants of 3.8% was comparable to the placebo rate of 4.7%.
  - The switch rate for TCAs, however, was 10%.

- Vieta 2002 reported similar response rates in bipolar depression with venlafaxine (48%) and paroxetine (43%), but the rates of manic switch for venlafaxine (13%) were non-significantly higher vs. paroxetine (3%)
Do antidepressants induce suicidality by causing *switching* of mood states?

- **Klein 1967** was the only placebo-controlled monotherapy trial of antidepressants in mania.
  - Imipramine titrated to 300mg/day showed non-significant worsening of mania.

- **Prien 1973** was the only placebo-controlled antidepressant monotherapy maintenance trial in bipolar disorder.
  - Over 20 months, 67% of the imipramine group had a manic episode, vs. 33% of the placebo group, and 12% of the lithium group.
  - The risk of mania increased with time on the antidepressant and was not limited to the initial period.
    - This effect has also been seen when mood stabilizers are given with the antidepressants.
  - Interestingly, depression occurred in 0% of the imipramine group, vs. 55% of the placebo group, and 12% of the lithium group.

Antidepressants given with Mood Stabilizers

– Angst and colleagues’ 30 year long study of suicides and affective disorders

– Medication treatment was associated with reduced suicide rates
  • In the unipolar group and the bipolar group
  • In each of the drug treatment subgroups

– Of the bipolar patients:
  • 62% were on a mood stabilizer
    – 45% received lithium plus antipsychotic and/or an antidepressant
    – 16% received lithium alone
  • 15% received an antidepressant alone
  • 13% received an antipsychotic and an antidepressant
  • 11% received an antipsychotic alone

– Of the unipolar patients:
  • 38% were on a mood stabilizer

Antidepressants given with Mood Stabilizers: Angst and colleagues continued

– **A very strong reduction in completed suicides** was seen in patients treated with:
  
  • Antidepressants alone!!!
  • Antidepressants plus antipsychotics
  • Lithium plus and antipsychotic and/or an antidepressant
  • But **not** for lithium alone . . . (?significance of this)
    – Confounding by indication?
    – Poor study design?

Antidepressants given with Mood Stabilizers:
Benefits may outweigh risks for some patients

• Altshuler 2003 looked at 84 pts who achieved remission from bipolar depression with the addition of an antidepressant to ongoing mood stabilizer treatment.
  
  – By 6 months 43 had stopped the antidepressant and 41 continued on it.
  – At the one year mark, 70% of the group that stopped had had a relapse of their depression, vs. 30% who had continued it.
  – Also the group that had continued did not show an association with manic relapse.

• There may be a subgroup of bipolar patients who benefit from long-term antidepressants with mood stabilizers

Key points:

• Bipolar patients are at higher risk for suicide, especially when mixed features present and after discontinuing mood stabilizers.

• Lithium and clozapine are the only drugs with good evidence supporting anti-suicide properties.

• Antidepressant monotherapy is not recommended, but used with mood stabilizers they may be an essential part of a pharmacologic regimen.