American Psychiatric Nurses Association
Eighth Psychopharmacology Institute
Reston, VA; 26 June 2010

Psychopharmacology and Pharmacopolitics of Suicide Prevention

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Disclosures
--2010--

Ross J. Baldessarini, M.D.

Has recently consulted to, or collaborated in investigator-initiated research with: Alkermes, AstraZeneca, Auritec, Biotrofix, IFI, Janssen, JDS-Noven, Leupold, Lilly, Merck, NeuroHealing, Novartis, Pfizer & Solvay Corporations, but has no speakers’ panel, personal or family equity relationships with industrial organizations.
Major mental illnesses: Fatal diseases

- Mortality is increased due to accidents
- Mortality is increased due to complications of comorbid substance abuse
- Comorbid “stress-sensitive” (cardiovascular, lung, etc.) disorders increase mortality 2–3-fold, esp. in older patients (with as many excess deaths as suicide)
- The greatest relative increase in mortal risk (SMR to in BPD & severe MDD) is due to suicide, esp. early & in youth
Risk factors for suicide

- Previous suicide attempts
- Major depression or bipolar disorders
- Comorbid abuse of alcohol or drugs
- Losses, deaths, shame, poverty
- Social isolation, unmarried
- Lack of access to clinical care
- Access to firearms, toxins, medicines
The medical treatment of the propensity to suicide, whether prophylactic or therapeutic, differs not from that which is applicable in cases of ordinary insanity.

George M. Burrows, 1828
Is there a therapeutics for suicide?

- Psychotic disorders: the special case of clozapine
- Bipolar disorder: lithium
- Bipolar disorder: everything else
- Major depression: antidepressants helping or hurting?
- Does anything else work?
- Even if there are treatments of proven value, does lack of access to clinical care make them moot?
Suicide Risks in Specific Disorders

- Prior suicide attempt
- Bipolar disorder
- Severe major depression
- Mixed substance abuse
- Severe anxiety disorders
- Schizophrenia
- Alcohol abuse

[From Tondo et al. 2005]

Standardized Mortality Ratio (SMR) (with 95% CI)
Antipsychotic treatment vs. suicidal risk

- Modern antipsychotics have antimanic effects and may also have benefits in depression as well as agitation & aggression
- Clozapine (Clozaril) is the first treatment given FDA-approval for reducing suicidal risk (2003): an historic precedent
- Evidence for such an effect rests heavily on one, remarkable controlled study (InterSePT) vs. olanzapine (Zyprexa)
- There were rare deaths (clozapine > olanzapine), but greater delay to attempts or preventive interventions with clozapine
- Meta-analysis of the few clozapine studies yield ≥4x ↓ risk of attempts or preparations, but little evidence of ↓ mortality
- Other antipsychotics remain to be studied
Clozapine vs. Suicidal Risk

Meltzer & Okayli 1995
Walker et al. 1997
Reid et al. 1998
Munro et al. 1999
Sernyak et al. 2001
Meltzer et al. 2003
Modestin et al. 2006

Pooled OR
(4.64; p<0.0001)

[Hennen & Baldessarini Schizophrenia Res 2005; 73: 139–145; Baldessarini 2006]
Mortality in Antipsychotic-Treated Schizophrenia (Finland 1996–2006)

[Tiihonen et al. Lancet 2009 (67,000 cases)]

[Confounded by indication?]
Long-term Morbidity in Treated Bipolar I Patients

- Judd et al. 2002 (n=146)
- Post et al. 2003 (n=258)
- Joffe et al. 2004 (n=138)
- Paykel et al. 2006 (n=204)
- Baldessarini et al. 2009 (n=303)
- All Studies (N=1049)

[blue=mid-course, green=from onset; red=mean; D/M ratio=3.88; D-type=79.5% of total morbidity; from Baldessarini et al. 2009].

Percent of Weeks Ill

- M-Type
- D-Type
- All

9.62% 36.9% 46.4%
Clozapine vs. Suicidal Risk

Pooled OR
(4.64; p<0.0001)

[Hennen & Baldessarini Schizophrenia Res 2005; 73: 139–145; Baldessarini 2006]
Causes of Excess Mortality: Bipolar Disorder Patients

- All Violence
- All Medical
- Cardiovascular
- Suicide
- Pulmonary
- Accidents+Other Violence
- Endocrine

Proportion of Excess Deaths (%)

[From Osby et al. Arch Gen Psychiatry 2001; 58: 844–850]
Suicide Attempt Risk: 5329 BP-I vs. BP-II Patients

Pooled RR [CI]: 1.09 [0.93–1.28]  
(I: 32.4%; II: 27.4%)  

[Adapted from Novick et al. Bipolar Disord 2010; 12:1–9]
Meta-Analysis:
Lithium vs. Suicides & Attempts

[Baldessarini et al. 2006
n=31 comparisons]
Meta-analyses: Lithium treatment vs. suicidal risk

<table>
<thead>
<tr>
<th>Conditions</th>
<th>Studies (N)</th>
<th>Risk Ratio (RR)</th>
<th>[95% CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All studies</td>
<td>34</td>
<td>4.91</td>
<td>[3.86–6.23]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Suicides</td>
<td>25</td>
<td>4.89</td>
<td>[3.46–6.91]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Attempts</td>
<td>20</td>
<td>4.86</td>
<td>[3.58–6.59]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>BPD</td>
<td>15</td>
<td>5.53</td>
<td>[3.72–8.20]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>MADs</td>
<td>19</td>
<td>4.58</td>
<td>[3.38–6.21]</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>RCTs</td>
<td>8</td>
<td>4.29</td>
<td>[1.46–12.6]</td>
<td>0.008</td>
</tr>
<tr>
<td>Open trials</td>
<td>26</td>
<td>5.00</td>
<td>[3.83–6.53]</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Analyses based on conservative, random-effects modeling, with stratification. From Baldessarini et al. *Bipolar Disord* 2006, in press.
### Li vs. Lethality: Attempt/Suicide Ratio

<table>
<thead>
<tr>
<th>Measure</th>
<th>Attempts (A)</th>
<th>Suicides (S)</th>
<th>A/S Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Without lithium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportions</td>
<td>491/4262/3.04</td>
<td>199/4550/3.34</td>
<td></td>
</tr>
<tr>
<td>Rate (%/year)</td>
<td>3.78</td>
<td>1.31</td>
<td>2.89</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[3.46–4.11]</td>
<td>[1.13–1.49]</td>
<td></td>
</tr>
<tr>
<td><strong>With lithium</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportions</td>
<td>274/17,631/1.44</td>
<td>114/29,000/2.35</td>
<td></td>
</tr>
<tr>
<td>Rate (%/year)</td>
<td>1.08</td>
<td>0.167</td>
<td>6.45</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[0.95–1.20]</td>
<td>[0.14–0.20]</td>
<td></td>
</tr>
<tr>
<td><strong>Relative Risk</strong></td>
<td>3.50</td>
<td>7.84</td>
<td>2.23</td>
</tr>
</tbody>
</table>

“Proportions” are acts/subjects/mean exposure times weighted by subject numbers. A/S ratio is 2.23-times higher with lithium, suggesting decreased lethality of suicidal acts. From Baldessarini et al. *Bipolar Disord* 2006 in press.
Lithium vs. Suicidal Risk in Mood Disorders

Rate (Acts/100 person-years)

Suicides

Attempts

[From Baldessarini et al.: Ann NY Acad Sci 2001; 932: 24–38]
Suicidal Risk vs. Lithium Treatment: BP I+II Patients

# Lethality: Overdoses of common psychotropic drugs

<table>
<thead>
<tr>
<th>Agents</th>
<th>Fatalities</th>
<th>Rate (%)</th>
<th>RR vs. TCAs</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TCAs</td>
<td>89/12,522</td>
<td>0.711</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Barbiturates</td>
<td>16/3274</td>
<td>0.489</td>
<td>0.689</td>
<td>[0.405–1.17]</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>22/4704</td>
<td>0.468</td>
<td>0.660</td>
<td>[0.414–1.05]</td>
</tr>
<tr>
<td>Phenothiazines</td>
<td>22/4704</td>
<td>0.468</td>
<td>0.660</td>
<td></td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>180/60,014</td>
<td>0.300</td>
<td>0.424</td>
<td>[0.329–0.546]</td>
</tr>
<tr>
<td>Lithium</td>
<td>13/5296</td>
<td>0.245</td>
<td>0.347</td>
<td>[0.194–0.620]</td>
</tr>
<tr>
<td>Atypical APDs</td>
<td>72/32,422</td>
<td>0.222</td>
<td>0.314</td>
<td>[0.230–0.428]</td>
</tr>
<tr>
<td>Valproate</td>
<td>21/9619</td>
<td>0.218</td>
<td>0.309</td>
<td>[0.192–0.496]</td>
</tr>
<tr>
<td>SRI</td>
<td>106/55,977</td>
<td>0.189</td>
<td>0.268</td>
<td>[0.202–0.355]</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>9/5144</td>
<td>0.175</td>
<td>0.247</td>
<td>[0.125–0.491]</td>
</tr>
</tbody>
</table>

Rates are deaths/person-overdoses regardless of intent or severity. RR = fatality risk vs. TCAs.
TCA risks: highest protriptyline (3.70%) & desipramine (1.72%), lowest nortriptyline (0.090%).
[*] p<0.001 vs. TCA risk. Note: Li ranks with other modern agents.
Suicidal Acts with Lithium vs. Anticonvulsants

Greil et al. 1997 [CBZ]
Bowden et al. 2003 [LTG]
Calabrese et al. 2003 [LTG]
Goodwin et al. 2003 [VPA>CBZ]
Yerevanian et al. 2003 [VPA>CBZ]
Collins & McFarland 2007 [VPA>CBZ]

Pooled RR
2.86 [2.29–3.57]

"Suicidality" (ideation or acts) reported to FDA with anticonvulsants or placebo

<table>
<thead>
<tr>
<th>Indication</th>
<th>Placebo (%)</th>
<th>Drug (%)</th>
<th>OR [CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects (N)</td>
<td>16,029</td>
<td>27,863</td>
<td>---</td>
</tr>
<tr>
<td>Epilepsy</td>
<td>0.10</td>
<td>0.35</td>
<td>3.53 [1.28–12.1]</td>
</tr>
<tr>
<td>Psychiatric</td>
<td>0.52</td>
<td>0.83</td>
<td>1.51 [0.95–2.45]</td>
</tr>
<tr>
<td>Other</td>
<td>0.08</td>
<td>0.20</td>
<td>1.87 [0.81–4.76]</td>
</tr>
<tr>
<td>Suicides</td>
<td>0/16029 (0.000)</td>
<td>4/27863 (0.0144)</td>
<td>&gt;200</td>
</tr>
</tbody>
</table>

Total Risk: 35/16029 (0.218) 120/27863 (0.431) 1.80 [1.24–2.66]

Adapted from FDA Websites (accessed 11/12/08):
<www.fda.gov/CDER/drug/information/HCP/antiepileptics/default.htm> [1/31/08];
<www.fda.gov/ohrms/dockets/ac/08/briefing/2008-4372b1-01-FDA.pdf>[6/12/08];

Relative Risk (RR) is ratio of reported rates for drug/placebo. Effects are considered “consistent” among 11 drugs considered (carbamazepine, divalproex, felbamate, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, tigabine, topiramate, & zonisamide), used in 62.4% of trials as a monotherapy in a total N=43,892 treated for 89 ± 85 (0–582) days. Most subjects were Caucasian (79%), female (55%), & No. American (61%).
Anticonvulsant treatment and suicide attempts in bipolar disorder patients

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Before Rx</th>
<th>During Rx</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticonvulsants</td>
<td>9.23</td>
<td>1.68</td>
<td>6.8 lower</td>
</tr>
<tr>
<td>[95% CI]</td>
<td>[2.9–15.6]</td>
<td>[0.8–2.5]</td>
<td>[1.7–11.9]</td>
</tr>
<tr>
<td>Lithium</td>
<td>9.87</td>
<td>1.75</td>
<td>5.6 lower</td>
</tr>
</tbody>
</table>

[*] Drugs are those commonly employed clinically for BPD (CBZ, oxCBZ, LTG, and VPA). Caveat: suicidality may be a confounding indication for mood-stabilizer treatment, and so inflate the pre-Rx risk. Based on analysis of PharMetrics Corp. database with 1-year exposure. Adapted from Gibbons RA et al.: Relationship between antiepileptic drugs and suicide attempts in patients with bipolar disorder. Arch Gen Psychiatry 2009; 66: 1354–1360.
Mood-stabilizers vs. suicidal risk

- Lithium has strong and consistent evidence for reducing risks of both attempts & suicides by 4–5x, consistently in >30 studies, including 8 RCTs, in bipolar or "MDI" patients.

- Lithium may also limit risk of suicides and attempts in recurrent major depression.

- Discontinuing lithium, especially rapidly, markedly increases suicidal risk temporarily.

- Acute overdoses with lithium are uncommon & their mortal risk is similar to that of modern antipsychotics or SSRIs.

- Antisuicidal effects of other mood-stabilizers is limited to rare studies of carbamazepine and divalproex, against which lithium proved to be ca. 3x more effective.
Lithium Treatment: Reduced Suicidal Risk in Unipolar Major Depression

[From Guzzetta et al. 2006]

- Bech et al. 1976
- Lepifker et al. 1985
- Müller-Oerlinghausen et al. 1992
- Greil et al. 1996
- Bocchetta et al. 1998
- Coppen & Farmer 1998
- Bauer et al. 2000
- Tondo et al. 2006

Pooled RR
2.01 (1.81–2.22)
Antidepressant treatment: Suicidal risk

- Modern antidepressants: much safer on overdose but other methods replace lethal overdoses
- Suicide rates have fallen since 1990 in some countries as use of modern antidepressants increased: effect vs coincidence?
- US & UK regulators reported in 2004–06 that SRIs may be associated with increased “suicidality” in juveniles
- SRIs: minimally effective in juvenile depression, & strongly associated with manic-switching before age 16
- Many adult & juvenile antidepressant trials provide data on suicide & attempt risks with drugs vs. placebo
- If antidepressants are effective (& depression the strongest risk factor), should they not prevent suicide?
US Suicide Rate vs. Modern Antidepressant Use

rs = –0.953
p = 0.0004

### Ecological studies: Suicide rates vs. antidepressant prescriptions

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Rate</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inverse correlation</td>
<td>5/25</td>
<td>20.0%</td>
</tr>
<tr>
<td>Inconclusive</td>
<td>14/25</td>
<td>56.0%</td>
</tr>
<tr>
<td>No association found</td>
<td>6/25</td>
<td>24.0%</td>
</tr>
</tbody>
</table>

From Baldessarini et al. 2006 (submitted), for regions or years. Most positive findings were from overlapping Nordic & US studies.
International Suicide Rate Trends: 2003 vs. 1990
(WHO Data; Tondo & Baldessarini 2006)

N=78 nations
54% show decreases
46% show increases
The graph illustrates the suicide rate (%) of 1978 in Sweden and the USA from 1975 to 2000. The data shows a notable decrease in the suicide rate in Sweden during the era of modern antidepressants, marked by a green shaded area on the graph. The x-axis represents the years from 1975 to 2000, while the y-axis represents the suicide rate (% of 1978). The graphs for Sweden and the USA are distinguished by different symbols and colors: Sweden is represented by red circles, and the USA by blue squares.
Factors associated with US state suicide rates (2001)

<table>
<thead>
<tr>
<th>Factors</th>
<th>Corr. (r)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Population density</td>
<td>-0.735</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male sex</td>
<td>+0.576</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Annual income/capita</td>
<td>-0.550</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Psychiatrists/100,000</td>
<td>-0.544</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Native-American (%)</td>
<td>+0.543</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Physicians/100,000</td>
<td>-0.528</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Federal MH aid</td>
<td>-0.443</td>
<td>0.001</td>
</tr>
<tr>
<td>African-American (%)</td>
<td>-0.430</td>
<td>0.002</td>
</tr>
<tr>
<td>Uninsured residents (%)</td>
<td>+0.391</td>
<td>0.005</td>
</tr>
</tbody>
</table>

Antidepressants

Meta-analysis of suicides+attempts in adults
[Baldessarini et al. 2006]

SRIs vs. Others
RR=1.06 [0.74–1.52]
### Meta-analyses: Suicidal acts in antidepressant trials

<table>
<thead>
<tr>
<th>Comparison</th>
<th>Trials</th>
<th>RR</th>
<th>[95%CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All agents vs. controls</td>
<td>20</td>
<td>1.06</td>
<td>[0.74–1.52]</td>
<td>0.77</td>
</tr>
<tr>
<td>Very large studies omitted</td>
<td>16</td>
<td>1.03</td>
<td>[0.60–1.76]</td>
<td>0.91</td>
</tr>
<tr>
<td>SRIs vs. controls</td>
<td>15</td>
<td>1.27</td>
<td>[0.58–2.01]</td>
<td>0.65</td>
</tr>
<tr>
<td>SRIs vs. all other agents</td>
<td>11</td>
<td>1.27</td>
<td>[0.58–2.01]</td>
<td>0.32</td>
</tr>
<tr>
<td>SRIs vs. TCAs</td>
<td>9</td>
<td>1.30</td>
<td>[0.85–1.99]</td>
<td>0.23</td>
</tr>
</tbody>
</table>

RR = Risk-Ratio with confidence-interval (rates of suicides or attempts with placebo or other control vs. with antidepressant treatment).

From Baldessarini et al. 2006
Suicide Attempts: Juvenile SRI Trials
[From Hammad TA: FDA, 2004]

- Citalopram (MDD)
- Citalopram (MDD)
- Venlafaxine (GAD)
- Venlafaxine (MDD)
- Paroxetine (MDD)
- Paroxetine (MDD)
- Paroxetine (MDD)
- Fluoxetine (MDD)
- Fluoxetine (MDD)
- Fluoxetine (MDD)
- Fluoxetine (OCD)
- Sertraline (MDD)
- Sertraline (MDD)

**Overall RR**
1.90 [CI: 1.00–3.63]
Antidepressant Trials in Juvenile Depression

[Tsapakis et al. 2007]
## Meta-analyses: Pooled efficacy measures (RR) from AD-trials in juvenile depression

<table>
<thead>
<tr>
<th>Subgroups</th>
<th>Trials</th>
<th>RR</th>
<th>[95%CI]</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>All agents</td>
<td>30</td>
<td>1.22</td>
<td>[1.15–1.31]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TCAs</td>
<td>14</td>
<td>1.15</td>
<td>[0.98–1.34]</td>
<td>0.09</td>
</tr>
<tr>
<td>SRIs</td>
<td>12</td>
<td>1.23</td>
<td>[1.14–1.33]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Other agents</td>
<td>4</td>
<td>1.27</td>
<td>[1.06–1.52]</td>
<td>0.008</td>
</tr>
<tr>
<td><strong>Ages</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adolescents</td>
<td>16</td>
<td>1.27</td>
<td>[1.15–1.40]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Mixed ages</td>
<td>10</td>
<td>1.19</td>
<td>[1.09–1.30]</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Children</td>
<td>4</td>
<td>1.11</td>
<td>[0.75–1.66]</td>
<td>0.59</td>
</tr>
</tbody>
</table>


Note: age-efficacy correlation, rarity of child trials, lack of SRI vs. TCA difference (statistics reflect larger Ns with SRIs).
Outcomes of serious suicide attempts: Patients with major depression

<table>
<thead>
<tr>
<th>Measures</th>
<th>All Deaths</th>
<th>Completed Suicides</th>
<th>Repeat Attempts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cases (n)</td>
<td>237</td>
<td>109</td>
<td>564</td>
</tr>
<tr>
<td>Rates (%/year)</td>
<td>3.10</td>
<td>1.43</td>
<td>7.38</td>
</tr>
<tr>
<td>Genl Pop risk (%/yr)</td>
<td>1.00</td>
<td>0.015</td>
<td>0.300</td>
</tr>
<tr>
<td>RR vs. general pop.</td>
<td>3</td>
<td>95</td>
<td>25</td>
</tr>
<tr>
<td>Male/Female (HR)</td>
<td>2.04</td>
<td>1.92</td>
<td>0.93</td>
</tr>
<tr>
<td>AD-use (HR)</td>
<td>0.74</td>
<td>1.06</td>
<td>1.80</td>
</tr>
<tr>
<td>[95%CI]</td>
<td>[0.56–0.97]</td>
<td>[0.71–1.58]</td>
<td>[1.52–2.14]</td>
</tr>
</tbody>
</table>

N=1820 Finnish national sample followed 4.2 years for total exposure of 7640 person-years. Antidepressant (AD) treatment may reduce overall mortality, but with little effect on repeat attempts or suicides, which remained far above risks in the general population of Finland. Adapted from Suominen K et al.: Outcome of patients with major depressive disorder after serious suicide attempt. J Clin Psychiatry 2009; 70: 1372–1378.
Juvenile depression: Possible contributors to poor antidepressant responses

- Developmental changes in MDD syndrome
- Developmental pharmacodynamic changes
- Limited illness-severity, nonmelancholic cases
- Developmental decline in drug metabolism
- Measurement (rating scale) problems
Effects of Modern Antidepressants: "Suicidality" versus Age-Groups

- FDA Website Nov 2008; 396 RCTs, modern agents, 113,000 Ss
- Barbui et al. CMAJ 2009; 180:291–297; 8 cohort studies (on/off SRIs, 200,000 Ss)

Age Groups (years): <18, 18–24, 25–64, >65, All Ages

Odds Ratio ± 95% CI

[Adapted from R Valuck, 12/06]
Antidepressants (ADs) vs. suicidal risk

- No. Amer. & No. Europe had slightly falling suicide rates with massively increased use of modern ADs in 1990–2000, largely anticipated in 1970–1990; whereas half the world experienced stable or rising rates, strongly associated with other indices of access-to-care.

- Suicide & attempt rates are surprisingly high in RCTs, with no evidence of lower risk, and even slightly greater apparent risks, with ADs vs placebo.

- In RCTs, spontaneously reported suicidal ideation (not a valid index of suicidal risk) may be somewhat increased with ADs vs. placebo in RCTs at ages 5–25, but suicidality items on rating scales consistently fall with ADs > placebo in adult RCTs.

- Evidence of efficacy of ADs in adolescent depression remains weak & unconvincing, poorly evaluated in children, and moderate in adults.

- FDA-required “black-box” warnings since 2004 have been associated with declining new diagnoses of major depression at all ages (mainly by non-psychiatrists), markedly declining SSRI sales, & rising suicide rates in adolescents.
FDA clinical guidelines for antidepressant therapy

- Monitor depressed patients closely early
- Intervene if depression or suicidality worsen
- Beware of emerging “activation” (anger, restlessness, insomnia, mania)
- Discontinue antidepressants slowly
- Screen for occult bipolar disorder
- Educate patient and family about risks

Interventions versus suicidal risk emerging with antidepressant use

- Decrease dose, or suspend antidepressant therapy with newly emerging agitation, insomnia, or anger.
- Introduce an atypical antipsychotic, anticonvulsant, or sedative.
- Consider lithium for cooperative patients, especially following inadequate antidepressant responses.
- Make explicit the collaborative & flexible nature of treatment.
- Emphasize availability for extra visits or calls, or in emergencies.
- Express explicit concern for growing discomfort and despair.
- Address suicidality directly and repeatedly.
- Monitor access to lethal means (hoarded drugs, toxins, firearms).
- Enlist help of family member to monitor patient and perhaps to dispense medicines.
FDA actions since associating suicidal ideation with antidepressants

- Broaden search to other classes of centrally active agents (anticonvulsants, antibiotics, dermatologic agents, etc.)

- Seek more explicit methods of assessment of suicidal risk (with added cost and consent issues unaddressed)

- Decreased suicidal risk in older adults & lack of compelling evidence of suicidal effects of anticonvulsants on non-epileptics remain unaddressed

- Risks of unintended consequences remain unaddressed (decrease in diagnosis of MDD in juveniles, avoidance of SRIs in juvenile depression)
Non-pharmacological treatments vs. Suicidal risk

- ECT: a prime option vs. acute suicidality (APA guidelines)
- No evidence that ECT reduces long-term suicidal risk
- Psychosocial interventions are very little-studied, in gross disproportion to wide humane-empirical application
- Rapid hospitalization: plausible, but unproved
- A few studies suggest efficacy of CBT vs. attempts
- At least one controlled study indicate reduced risk of suicide attempts in high schools by psychoeducational programs
- “Contracts-for-safety”: widely used but unproved and potentially risky
Treatment-access limits suicide prevention

- Variable acceptance of medical-clinical model
- Strong social biases, guilt, shame
- System-limitations (school, military, corporate)
- Limited access to care (poverty, rurality)
- Inadequate insurance for mental health
- Clinical practice patterns: brief, drug-centric
Suicide prevention: Conclusions (A)

- Suicide is a major international public health challenge.
- Federal (IOM) & international health authorities (WHO) recognize suicide as a *medical* rather than social problem.
- Empirical therapeutic research on suicide was virtually unknown a decade ago.
- Depression & bipolar disorder are major risk factors for suicide, especially with drug and alcohol abuse.
- Lithium has the strongest evidence for long-term antisuicide effectiveness, clozapine less, and antidepressants none.
- Psychosocial interventions are *appropriately* used on clinical grounds, despite very limited research support.
Suicide prevention: Conclusions (B)

- Suicide prevention by medical treatment requires early recognition and intervention.
- Suicide risk commonly arises early in mood Dxs, often well before diagnosis & treatment program are established.
- Liability-risk in psychiatry is highest for suicide.
- Successful prevention requires comprehensive assessment for suicidal & other clinical risks.
- Patient & family education & family collaboration can help.
- Recent US practice patterns for managing depressed patients have been inadequate, reflecting excessive confidence in pills & lack of economic support for time & “care.”
Where is the wisdom we have lost in knowledge? Where is the knowledge we have lost in information?

T.S. Eliot, *The Rock*, 1934