Reducing the Risk for Suicide in Schizophrenia and Affective Disorders

This ACADEMIC HIGHLIGHTS section of The Journal of Clinical Psychiatry *presents the highlights of the teleconference "Reducing the Risk for Suicide in Schizophrenia and Affective Disorders," held July 2, 2003.*

The teleconference was chaired by ***Herbert Y. Meltzer****, M.D., Division of Psychopharmacology, Psychiatric Hospital, Vanderbilt University Medical Center, Nashville, Tenn. The other faculty member was* ***Ross J. Baldessarini****, M.D., Department of Psychiatry and Neuroscience, Harvard Medical School, McLean Hospital, Belmont, Mass.*

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The information received is as follows: ***Dr. Baldessarini*** *is a consultant for Auritec, Biostream, Eli Lilly, IFI, SpA, Janssen, Protarga, and Vertex, and is a former research grant recipient from Biostream, Eli Lilly, and Janssen;* ***Dr. Meltzer*** *is a consultant for Novartis, Eli Lilly, Pfizer, Janssen, AstraZeneca, and Bristol-Myers Squibb, has received grant/research support from Novartis, Eli Lilly, and Janssen, has received honoraria from Novartis and Janssen, and is on the speakers/advisory board for Janssen.*

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Suicide in Schizophrenia

Herbert Y. Meltzer, M.D., began by reviewing the prevalence of suicide and suicidal behavior among patients with schizophrenia. The problem of suicide in schizophrenia is considerable. Suicide claims the lives of 9% to 13% of patients with schizophrenia, and the annual rate of suicide is around 0.2% to 0.3%, a rate that has remained constant despite the introduction of antipsychotic therapy.[1] Dr. Meltzer also reviewed results from the International Suicide Prevention Trial (InterSePT), a recent 2-year prospective study of 980 patients at risk for suicide,[2] which suggest that the atypical antipsychotic clozapine may play a role in the treatment of suicidal behavior.

Treatment With Typical Antipsychotics

Dr. Meltzer noted that few data are available specifically examining suicidality in schizophrenia with antipsychotic therapy versus without antipsychotic therapy. However, the majority of the evidence indicates that with traditional antipsychotics, although other aspects of schizophrenia are helped, the incidence of suicide does not appear to have changed. For example, in 1976, Bleuler[3] reported that the rate of suicide among patients with schizophrenia prior to the introduction of typical antipsychotics was 9% to 13%; in 1992, Axelsson and Lagerkvist-Briggs[4] reported the same rate among schizophrenic patients treated with typical antipsychotics.

Some evidence suggests that atypical antipsychotics may be somewhat more effective than typical, or conventional, antipsychotics in fighting suicide. Khan and coworkers,[5] in their analysis of short-term, phase III premarketing studies, found a lower rate of suicide attempts among patients taking atypical antipsychotics versus those taking typical agents.

Suicidality as a Separate Symptom Domain From Psychosis

Dr. Meltzer argued that suicidality in schizophrenia appears to be a symptom domain separate from other symptoms such as psychosis. Successful treatment of positive symptoms does not eliminate risk of attempted or completed suicide. In a study by Meltzer and Okayli,[6] no correlation was found between degree of psychosis or negative symptoms and degree of suicidality, although some correlation was found between mood symptoms and suicidality. In addition, patients in that study were initially categorized according to previous response to antipsychotic treatment; no statistical difference was found in the prevalence of suicidality between the treatment-responsive and treatment-resistant groups (Figure 1).

Is Clozapine Effective in Reducing Suicidality in Schizophrenia and Schizoaffective Disorder?

Dr. Meltzer related the results of the Meltzer and Okayli[6] investigation to the incidence of suicide in 88 patients during the 2 years before and then 2 years after starting clozapine treatment. These patients were a subgroup of the larger treatment-resistant group. Of those patients, 73 were diagnosed

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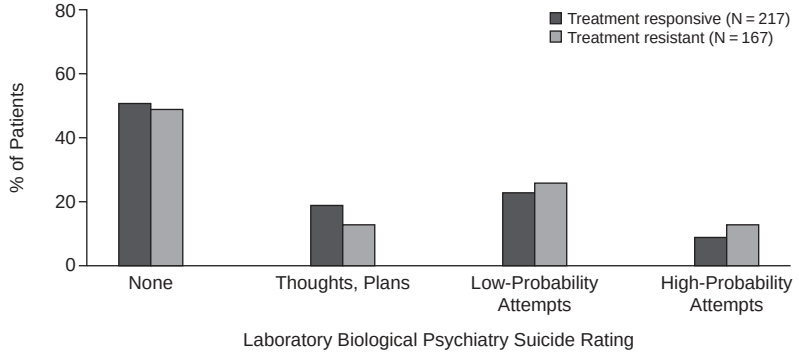
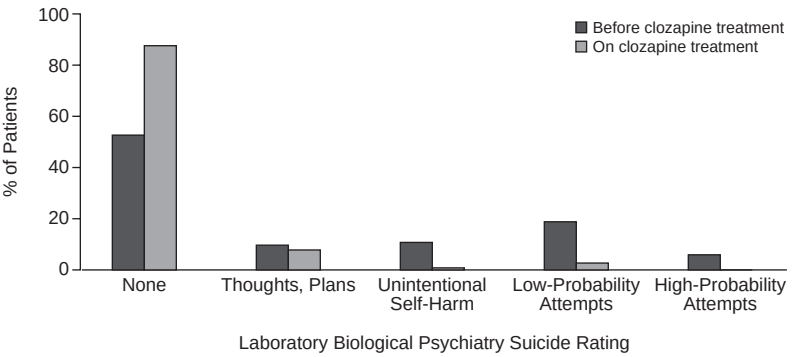
Figure 1. Lifetime Incidence of Suicidality Among Treatment-Responsive and Treatment-Resistant Schizophrenic Patients[a]



[a]Data from Meltzer and Okayli[6]; reprinted with permission from Meltzer.[1]

Figure 2. Effect of Clozapine on Suicidal Behavior[a]



[a]Data from Meltzer and Okayli[6]; adapted with permission from Meltzer.[1]

with schizophrenia and 15 with schizoaffective disorder. Retrospective and prospective information about the participants was obtained from patients and other informants as well as medical records. Patients received clozapine monotherapy along with the usual weekly monitoring and assessment. The proportion of patients with no suicidal thoughts or behaviors increased dramatically from 53% (47/88) before treatment to 87.5% (77/88) during treatment (Figure 2). Of the 22 people who had made a suicide attempt in the 2 years before starting clozapine treatment, 3 made an attempt in the subsequent 2 years. All 3 attempts occurred within the first 3 months of starting clozapine treatment and were of low lethality. Possible reasons for this decrease in suicidal behavior included a pharmacologic effect, the weekly contact for blood monitoring, poor treatment prior to study entry, an interaction between pharmacotherapy and psychosocial treatment during treatment, and a generalized reduction in suicidality within the overall study group.

Epidemiologic evidence. Dr. Meltzer also explained that epidemiologic data suggest that clozapine may reduce suicidal behavior. Walker et al.[7] cross-checked data from the Clozaril National Registry with data from the National Death Index and Social Security Administration to identify the cause of death for 67,072 current and former users of clozapine. They reported that mortality from suicide was reduced by 83% in current as opposed to past clozapine users, suggesting the risk increased after discontinuation of drug treatment.

When the registry data were examined by Reid et al.,[8] the incidence of suicide with clozapine treatment was about 0.02%. Similarly, in a 6-year retrospective study of suicide in patients in the Texas public mental health system, Reid[9] found only 1 suicide in an average of 952 patients per year treated with clozapine.

The International Suicide Prevention Trial (InterSePT). Dr. Meltzer described InterSePT[2] as an international, randomized, parallel-group study. It compared the effects of clozapine versus olanzapine on suicidal events in 980 patients with schizophrenia or schizoaffective disorder who were at high risk for suicide. Inclusion criteria were suicide attempt or hospitalization to prevent suicide within the previous 3 years, moderate-to-severe suicidal ideation and depression within 1 week of baseline, or command hallucinations within 1 week of baseline.[2] Treatment was open, but suicide monitoring was conducted by 3 blinded, independent experts (the Suicide Monitoring Board).

Critical to the integrity of this study[2] was that all patients, regardless of treatment, were seen weekly for the first 6 months and every other week thereafter. The clozapine group underwent blood monitoring as required and the olanzapine-treated patients had their blood pressure taken. At each visit, patients were questioned about suicidality.

Olanzapine, rather than a typical neuroleptic, was chosen as the comparator because atypical antipsychotics are used more commonly than conventional neuroleptics in the United States and, increasingly, in other parts of the world. Olanzapine is also pharmacologically similar to clozapine. In addition, some evidence also suggests that olanzapine may reduce depression and suicidality in patients with schizophrenia.[10,11]

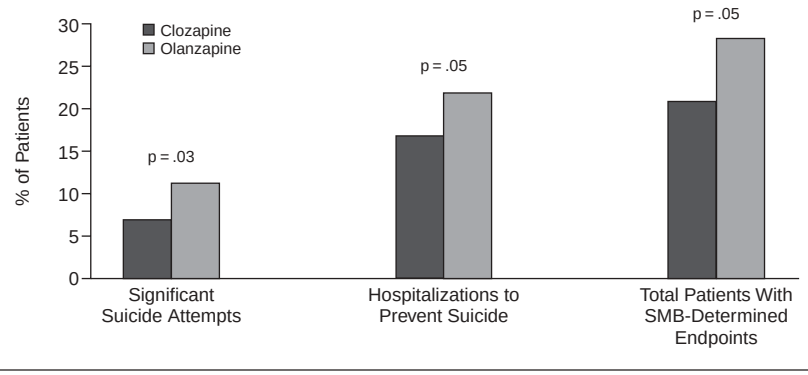
Several steps were taken to reduce the possibility of a suicide attempt or completion.[2] Treating psychiatrists

Table 1. Treatment-Related Reasons for Patient Discontinuation[a]

Reason	Clozapine (N = 490) N	Clozapine (N = 490) %	Olanzapine (N = 490) N	Olanzapine (N = 490) %	Total (N = 980) N	Total (N = 980) %
Adverse event	41	8.4	33	6.7	74	7.6
Abnormal laboratory result	2	0.4	0	0	2	0.2
Unsatisfactory effect on psychosis	5	1.0	9	1.8	14	1.4
Unsatisfactory effect for lowering suicide risk	0	0	6	1.2*	6	0.6

[a]Data from Meltzer et al.[2]
*p = .03.

Figure 3. Outcome on Suicide Monitoring Board (SMB)–Determined Endpoints[a]



[a]Data from Meltzer et al.[2]

were free to optimize doses of the study drugs to ensure patient response; clinicians were also able to use any medications they deemed necessary to reduce suicidal behavior, including additional antipsychotics, antidepressants, anxiolytics, and mood stabilizers. They could use electroconvulsive therapy, request hospitalization, or increase surveillance as needed.

The primary endpoints were reviewed by the Suicide Monitoring Board and included suicide attempts and hospitalization to prevent risk of imminent suicide. The Suicide Monitoring Board functioned independently of participating sites and the commercial supporter. Other events were assessed by blinded psychiatrists and other raters at the study sites.

Dr. Meltzer emphasized that completed suicide was not the primary endpoint of InterSePT. Multiple factors made it impossible to power a study with completed suicide as the endpoint; in fact, about 20,000 patients would have been needed. The number of patients needed to treat to show the advantage of clozapine over olanzapine in reducing the risk of suicidal behavior was 13. Suicide attempts and other suicidal behaviors represent hard endpoints that are clinically significant and, if unaddressed, are likely to lead to completed suicide.

Subjects came from 11 countries; 62% were diagnosed with schizophrenia and 38% with schizoaffective disorder.[2] Only 27% were considered to be treatment resistant. Eighty-two percent of the patients had made at least one suicide attempt, and 81%—not necessarily the same patients—had been hospitalized either to prevent an attempt or because of an attempt. Compliance as determined by pill count was high at 99%. The total dropout rate was 39%, and the reasons for discontinuation did not differ significantly between groups except for an unsatisfactory effect on suicide risk (Table 1).[2]

The number of patients who experienced a primary endpoint, confirmed by the Suicide Monitoring Board, was significantly lower in the clozapine-treated group (N = 102) compared with the olanzapine-treated group (N = 141) (Figure 3).

Another main finding of the InterSePT study was that the time to a primary endpoint was significantly longer in the clozapine group. Over the 2-year study, the probability of a significant suicide attempt or hospitalization to prevent suicide was 32% in the olanzapine-treated patients and 24% in the clozapine-treated patients.

A secondary endpoint was the addition of antidepressants or change in antipsychotic treatment (switch to another antipsychotic or addition of an adjunctive antipsychotic) as a rescue intervention. Significantly fewer clozapine-treated patients received these rescue interventions compared with olanzapine-treated patients (3.1% vs. 6.7% for addition of antidepressants, p = .01; 3.1% vs. 5.9% for change in antipsychotic treatment, p = .04).

During the course of the study, 3 olanzapine-treated patients and 5 clozapine-treated patients committed suicide, but the difference was not statistically significant (p = .73). As Dr. Meltzer noted previously, completed suicide was not an outcome measure.

On the basis of this evidence, Dr. Meltzer concluded that clozapine is superior to olanzapine in reducing key measures of suicidality in patients with schizophrenia or schizoaffective disorder who are at high risk of suicide.

Risk Factors for Suicidality in Schizophrenia

Dr. Meltzer reported that, in InterSePT,[2] certain risk factors were strongly associated with the primary endpoints.

No gender or age effects were reported in the study; of 21 factors that were examined, those that were found to be significant included diagnosis of schizoaffective disorder, current or lifetime alcohol/substance abuse or smoking, hospitalization in the previous 3 years to prevent a suicide attempt, and number of lifetime suicide attempts. The degree of suicidality on the Clinical Global Impressions-Severity of

Table 2. Risk Factors for Suicide Events in Schizophrenia[a]

Previous suicide attempts
Previous hospitalizations to prevent suicide
Current or past substance abuse
Depression
Parkinsonism

[a]Data from Meltzer et al.[2]

Suicidality scale (CGI-SS), which was developed for InterSePT, predicted patients who went on to experience a suicidal event. Patients who were anxious and depressed were also more likely to have a suicide event, as were those with severe parkinsonism, compared with those without these symptoms.

A multivariate analysis was conducted to assess which risk factors were the most predictive, and 5 were distilled (Table 2). Two were related to history: number of lifetime suicide attempts and number of hospitalizations to prevent suicide within the last 3 years. Current or lifetime substance abuse, depression, and the severity of parkinsonism remained predictive of suicidality in this analysis as well. These 5 factors were the most predictive in the multivariate sense, but other factors, such as diagnosis, alcohol abuse, and CGI-SS score, may also be important predictors of risk. However, Dr. Meltzer advised that the 5 factors in Table 2 are ones that a clinician should be particularly attentive to when determining how likely suicide might be and what treatment should be pursued to prevent suicidality.

Conclusion

Dr. Meltzer concluded by emphasizing that treating suicidality in schizophrenia demands improving overall outcome, which depends on improving cognitive function, diminishing psychosis, decreasing substance abuse, decreasing depression and hopelessness, restoring work and social function, improving general health, and decreasing isolation from family and others. Treatment with atypical antipsychotics, and sometimes an antidepressant or mood stabilizer as well, should help in all these areas.

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Treatment and Suicide Risks in Affective Disorders

Ross J. Baldessarini, M.D., started his presentation by pointing out that much more is known about therapeutics and suicide in bipolar disorder than in major depression. The rate of suicidal behavior in mood disorders is considerably higher than it is in anxiety disorders or schizophrenia (Table 3).[1] The relative risk of suicide in patients with bipolar disorder compared with that in the general population is, according to a recent review,[2] at least 20 times greater. This relative risk equates to a lifetime rate of about 15% of deaths in bipolar patients being suicides, which averages to a rate of about 0.3% per year. In fact, this analysis found that bipolar disorder had a somewhat greater risk of suicide than major depression, a departure from earlier reports.[1]

Dr. Baldessarini also made the point that, since the risk of suicide among those with psychiatric disorders is so much greater than that in the general population, it may be time for psychiatry and medicine in general to view mental illness as a potentially fatal condition, much the same as heart disease and high blood pressure. Like other physical illnesses, mental disorders with a high suicide rate such as bipolar disorder and depression represent a broad public health challenge.

According to Dr. Baldessarini, the available research in this area indicates that benefits of modern treatments in reducing mortality, in general, are limited, although some benefit has been noted. In one notable study by Angst and coworkers,[3] 406 patients who were hospitalized for affective disorders were prospectively followed up for more than 20 years. Among patients with depression or bipolar disorder who received long-term medication, the suicide rate was 2.5-fold lower than in an untreated sample ($p = .04$). However, the risk with treatment was still higher than that of the general population.

Suicide in Bipolar Disorder

Dr. Baldessarini reported that suicide in bipolar illness occurs not only in bipolar I disorder, but also in bipolar II disorder at similar or possibly somewhat higher rates. Rihmer and Pestality[4] found a substantially higher risk of suicide attempts in bipolar II patients than in bipolar I patients. This finding may not be surprising because bipolar II disorder includes severe depressive illness, which is one of the main risk factors for suicide in bipolar disorder as well as unipolar depression.

Table 3. Relative Risk of Suicide in Psychiatric Disorders Compared With the General Population[a]

Disorder	SMR
Bipolar disorder	22.1
Major depression	20.4
Dysthymia	12.1
OCD	11.5
Panic disorder	10.0
Schizophrenia	8.5
Alcohol abuse	5.9

[a]Data from Harris and Barraclough,[1] except bipolar disorder data from a review by Tondo et al.[2]
Abbreviations: OCD = obsessive-compulsive disorder, SMR = standardized mortality ratio.

Table 4. Risk Factors for Suicide in Bipolar Disorder

Young age at onset
Early stage of illness (before diagnosis or treatment)
Severe prior depression
Previous suicide attempts
Current depressive or dysphoric mixed episode
Comorbid substance abuse
Rapid treatment discontinuation

Current depression and current mixed manic depressive states (especially those with severe agitation and dysphoria) are particularly potent risk factors for suicide in bipolar disorder (Table 4). Patients who have had previous severe depressions are also at high risk, and recent studies indicate that young age at onset and being in the early stage of illness are additional risk factors in bipolar patients.[2,5,6]

Indeed, according to Dr. Baldessarini, the latency between initial onset of symptoms of the illness and receiving sustained, long-term treatment is typically between 5 and 10 years in bipolar disorder,[7] and much suicidal behavior occurs within the first 2 years of the illness. People with bipolar disorder need to be diagnosed earlier and given regular maintenance therapy much earlier than happens currently. The latency to receiving treatment is longer in women and in persons with bipolar II disorder than in other subgroups. Men with bipolar I disorder tend to call attention to themselves by their manic behavior and therefore are often diagnosed and treated relatively early. For others, this problem of early recognition and timely intervention is a challenging one that is far from solved at the present time.[2,5]

Dr. Baldessarini addressed additional risk factors for suicidal behavior in bipolar patients, in addition to depression and early onset, including comorbid substance abuse and previous attempts. These are ominous predictive factors, as is rapid treatment discontinuation, which can induce a manic or depressive episode.[2,5]

The issue of depression in bipolar disorder is an important one, argued Dr. Baldessarini, since most suicides in bipolar disorder occur during a mixed or depressed phase.[2,8] One intriguing recent finding in the epidemiology literature on bipolar illness is that patients with bipolar I disorder are in depressive and dysthymic states about one third of the time,[9,10] which translates to at least 4 months of each year. Patients with bipolar II disorder, in particular, spent half their time with some degree of depressive symptoms, from subthreshold symptoms to full-blown major depressive episodes.[2,8]

Dr. Baldessarini opined that whereas the ability to control mania and hypomania with drug treatment is good, the ability to prevent and control the depressive and dysthymic symptoms of bipolar disorder is still limited. Controlling depressive symptoms continues to be a major challenge for both the patient and the treating physician, one that has direct bearing on the attempt to minimize suicidal behavior.

Pharmacotherapy of Bipolar Disorder and Its Effect on Suicide

Ironically, some of the most widely used drugs in the field, particularly anticonvulsant mood-stabilizing agents, have had the fewest long-term maintenance studies that are well-designed and well-controlled. Dr. Baldessarini explained that some of the few existing studies were very well designed, so that even though the quantity of information is limited, the quality tends to be rather good.

Table 5. Effect of Lithium Maintenance Treatment in Patients With Bipolar Disorder[a]

	% Time Ill (mean ± SD)		
Measure	Before Treatment	During Treatment	% Decrease
Bipolar I disorder			
Mania	23.6 ± 24.5	11.2 ± 14.7	53
Depression	19.8 ± 21.8	10.8 ± 15.8	45
Bipolar II disorder			
Hypomania	16.7 ± 17.6	3.40 ± 6.76	80
Depression	32.6 ± 21.4	13.0 ± 18.1	60

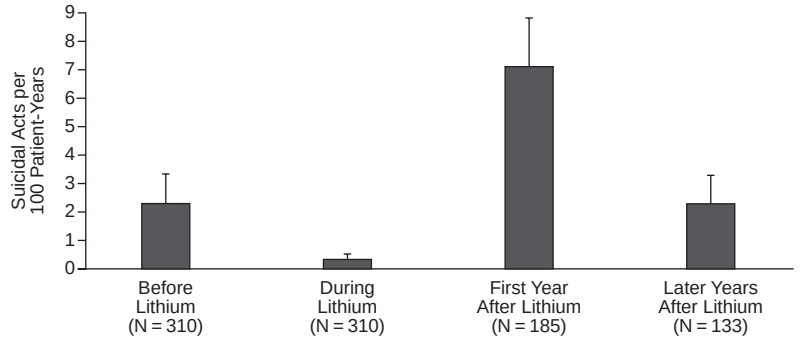
[a]Data from Baldessarini et al.[11]; 360 patients with bipolar disorder were followed for a mean of 8.8 years before lithium treatment and 4.5 years during lithium treatment.

Lithium. In contrast, a large quantity of data has been reported about lithium, which has been used in psychiatry for more than 50 years, but the quality of these studies is uneven. Nevertheless, the available information about lithium treatment indicates its importance in the prevention of suicide. It also follows that lithium has a substantial impact on the depressive phase of the illness as well as the manic and hypomanic phases.[11]

Dr. Baldessarini and his colleagues reviewed results of published reports on the efficacy of lithium, including results of a collaborative study between his group and Tondo and colleagues.[11] In a large clinical sample of bipolar I and bipolar II patients who were followed over many years, lithium had substantial beneficial effects against depression in bipolar I and particularly in bipolar II patients (Table 5). In this group of patients, the impact of lithium maintenance treatment on depression in bipolar II patients was as great if not greater than the ability to stave off recurrences of mania in bipolar I disorder. In other words, the idea that lithium is simply an antimanic agent is misleading; it has a beneficial effect on bipolar depression as well.

Dr. Baldessarini and his colleagues[12] have also analyzed published

Figure 4. Risk of Suicidal Event Before, During, and After Lithium Treatment[a]



[a]Reprinted with permission from Tondo et al.[14] A 6.5-fold decrease in suicidal behavior was found from before lithium treatment to during lithium treatment, and a 20-fold increase was found from during lithium treatment to the first year off lithium treatment.

studies that included conditions with and without lithium maintenance treatment. They pooled the data quantitatively and found an overall reduction of mortality due to suicide—not just attempts but actual fatalities—during lithium treatment. In fact, suicide was 82% less common among patients receiving lithium (0.159/100 patient years) compared with patients who were not on lithium treatment (0.875/100 patient years). The on/off lithium treatment computed risk ratio was 8.85, and this difference was highly significant ($p < .0001$; 95% CI = 4.12 to 19.1).

In another review,[13] Dr. Baldessarini and his colleagues performed a comparative analysis of the worldwide lithium research literature and what is known from the epidemiologic studies about international rates of suicides and suicide attempts. They found a dramatic overall reduction in the rate of suicides and suicide attempts from the untreated group to the treated group, a 5-fold reduction for suicides, and a 10-fold reduction for suicide attempts. Although the rate of completed suicides in bipolar patients on lithium treatment remained higher than the rate in the general population, the rate of suicide attempts was similar in lithium-treated patients to that in the general population.

Dr. Baldessarini continued the discussion of the impact of lithium on suicide in bipolar disorder by reviewing additional findings from work in collaboration with Tondo and colleagues.[14] In that work, the authors studied suicidal behaviors in the same persons for a mean of 8.8 years before they started long-term lithium maintenance therapy and then again during their treatment, which continued for an average of 4.5 years, essentially as a monotherapy. They found a dramatic reduction (more than 6-fold) in risk of overall suicidal behavior during versus before treatment (Figure 4). This benefit was sustained for periods as long as 5 to 10 years in patients who stayed in treatment that long. The benefit was not only dramatic but also sustained.

As Figure 4 shows, 185 patients discontinued lithium treatment. Most of these patients elected to stop treatment because their symptoms had stabilized or they experienced uncomfortable or clinically significant side effects. Within the first 6 to 12 months off lithium treatment, the rate of suicidal acts—fatalities and attempts—increased 20-fold compared with the rate during maintenance treatment.

The rate of discontinuation of lithium seemed to make a difference in suicidal behavior. Those who discontinued gradually had about one half the risk of those who discontinued abruptly, perhaps because a gradual discontinuation may help prevent recurrences of depression. Since 73% of suicidal behavior in this study occurred during a depressed state, gradually stopping lithium treatment in such a way that prevents depression could also prevent suicide.

Other treatments. Dr. Baldessarini explained that little is known about alternatives to lithium treatment in bipolar disorder and their effect on suicide. A large collaborative, prospective study was carried out over 2½ years in Germany.[15] In the study population of 378 patients with various severe mood disorders on prophylactic treatment, 9 patients committed suicide and 5 patients attempted suicide. None of these patients were taking lithium at the time. Nine (4 suicides and 5 attempts) were taking carbamazepine, and 5 (suicides) were taking another medication, such as an antidepressant or a neuroleptic. This one study does not answer the question whether carbamazepine may have some beneficial effects, but the contrast to lithium was quite striking.

Goodwin and colleagues[16] have recently analyzed computer databases from 2 large health maintenance organizations. They compared bipolar patients who were being maintained on either lithium treatment or anticonvulsant treatment, most often valproate. The overall finding was that the rate of suicidal acts, mostly attempts, was nearly 3 times higher in patients treated with anticonvulsants versus patients treated with lithium.

One recent development is that lamotrigine, a modern anticonvulsant, has been approved as a maintenance treatment for bipolar disorder. However, the number of studies and number of patients who have been studied with this and other anticonvulsants remains limited, and Dr. Baldessarini stated that much work has yet to be done to compare the effects of modern treatments on bipolar depression.

The published research on the effects of treatments on suicide in bipolar disorder is, for the most part, not ideal—much of it is neither prospective nor randomized. However, these data deserve close attention and will hopefully stimulate the desire for better designed studies, which can test what, if any, benefits alternatives to lithium have on suicidal behavior.

Table 6. Treatment of Major Depression Before and After Attempted Suicide (N = 43)[a]

	Before		After	
Treatment Type	N	%	N	%
Antidepressant				
None	30	70	25	61
Inadequate	6	14	9	22
Adequate	7	16	7	17
Psychotherapy	7	16	9	22
ECT	0	0	0	0

[a]Data from Suominen et al.[17]
Abbreviation: ECT = electroconvulsive therapy.

Table 7. Suicide Rate in Antidepressant Trials by Patient Exposure Years[a]

		Patient Suicides		
Treatment	Patient Exposure Years	N	%	95% CI
SSRIs[b]	2864	17	0.59	0.31 to 0.87
Other antidepressants[c]	4094	31	0.76	0.49 to 1.03
Placebo	897	4	0.45	0.01 to 0.89

[a]Data from Khan et al.[18]
[b]SSRIs included sertraline, paroxetine, citalopram, or fluvoxamine. Data based on patient exposure years were not available from fluoxetine trials.
[c]Other antidepressants included nefazodone, venlafaxine (immediate and extended release), and mirtazapine; comparator drugs in the reviewed trials included maprotiline, trazodone, mianserin, dothiepin, imipramine, and amitriptyline.
Abbreviations: CI = confidence interval, SSRIs = selective serotonin reuptake inhibitors.

Suicide in Major Depression

Dr. Baldessarini moved on to address the effects of treatment of depression on suicidal behavior. A provocative report[17] on suicide attempts by depressed persons found that not only were many of them inadequately treated before the suicide attempt, but most continued to receive inadequate treatment after the attempt (Table 6).

A recent collaborative effort (R. J. Baldessarini, J. Hennen, K. W. Kwock, et al., unpublished manuscript, 2003) attempted to systematically pull together data from well-designed controlled trials, but this analysis came up with some confusing results, according to Dr. Baldessarini. The resulting database included more than 50,000 patients with major depressive disorders by modern diagnoses. The general finding was that when any antidepressant was compared with placebo, the difference in the computed risk ratio based on random effects meta-analytic modeling was close to 1.0. In other words, no evidence of reduction of risk of suicide attempts or suicides was found among antidepressant-treated patients compared with placebo-treated patients. The comparison of subtypes of antidepressants—for example, selective serotonin reuptake inhibitors (SSRIs) with other types of antidepressants—also found minor differences slightly disfavoring the SSRIs, particularly in comparison with older drugs such as the tricyclic antidepressants. However, none of these findings was statistically significant. Curiously, despite screening for suicidality and designating suicidal behavior as an exclusion criterion, the rate of suicidal behavior in many placebo-controlled antidepressant trials was similar to that of general clinical populations of depressed patients—that is, 0.1% to 0.3% per year on an annualized basis.

Moreover, a paradoxical finding is that not only was there little difference between drug and placebo effectiveness, but the overall rate of suicidal behavior was lower among many placebo-treated patients than patients receiving active drug treatment (R. J. Baldessarini, J. Hennen, K. W. Kwock, et al., unpublished manuscript, 2003). A recent review[18] of clinical trial data submitted to the U.S. Food and Drug Administration supports these conclusions. In that study, Khan and collaborators calculated the risk of suicide in patients assigned to an SSRI, other antidepressant, or placebo. Placebo was associated with the *lowest* risk of suicide (Table 7), although no significant differences were found among the 3 groups.

Dr. Baldessarini was careful to point out that he does not believe that these findings constitute evidence that antidepressants increase risk of suicide. Instead, he explained that both clinicians and patients, knowing that any patient has a 33% to 50% risk of being assigned to placebo in these trials, may observe the patient's symptoms vigilantly. If suicidal symptoms begin to appear clinically, that patient may be quickly removed from the study and started on an active treatment. Removing a placebo-treated patient from a study before symptoms become serious may then lead to a certain amount of bias in the results, making suicidal behavior in the placebo group look less likely. Dr. Baldessarini supported this hypothesis by noting that the duration of participation in placebo arms of placebo-controlled antidepressant trials is substantially shorter on average than it is during the active treatment (R. J. Baldessarini, J. Hennen, K. W. Kwock, et al., unpublished manuscript, 2003). Therefore, even the best designed studies can lead to confusing and ambiguous results. However, this ambiguity is no reason for a clinician to abandon hope that treating depression will be effective in reducing suicide risk. The available evidence is simply inadequate.

More discussion and thought are needed about how to design trials of antisuicide treatments in major depression. Long-term studies may be needed to show this kind of benefit, and short-term trials that are typical in antidepressant research may simply be inadequate to demonstrate the ultimate strengths or weaknesses of antidepressants as treatments for suicidal behavior.

Conclusion

According to Dr. Baldessarini, mortality in major affective disorders is greater than that in the general population for several reasons, including suicide, accidents, substance abuse, and medical illness. Although predicting suicide is an imperfect science at best, several risk factors are associated with suicide attempts and completions (e.g., see Table 4). In addition, suicide risk is similar in bipolar disorders and major depression; many people with these disorders may attempt suicide early in

the course of illness, even before treatment is established or, at times, before the diagnosis is made. More studies are urgently needed that address the lethality of these disorders.

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Drug names: *amitriptyline (Elavil, Endep, and others), carbamazepine (Epitol, Tegretol, and others), citalopram (Celexa), clozapine (Clozaril and others), fluoxetine (Prozac and others), imipramine (Tofranil and others), lamotrigine (Lamictal), maprotiline (Ludiomil and others), mirtazapine (Remeron and others), nefazodone (Serzone), olanzapine (Zyprexa), paroxetine (Paxil), sertraline (Zoloft), trazodone (Desyrel and others), venlafaxine (Effexor).*

Disclosure of off-label usage: *The chair has determined that, to the best of his knowledge, no investigational information about pharmaceutical agents has been presented in this section that is outside U.S. Food and Drug Administration–approved labeling.*

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