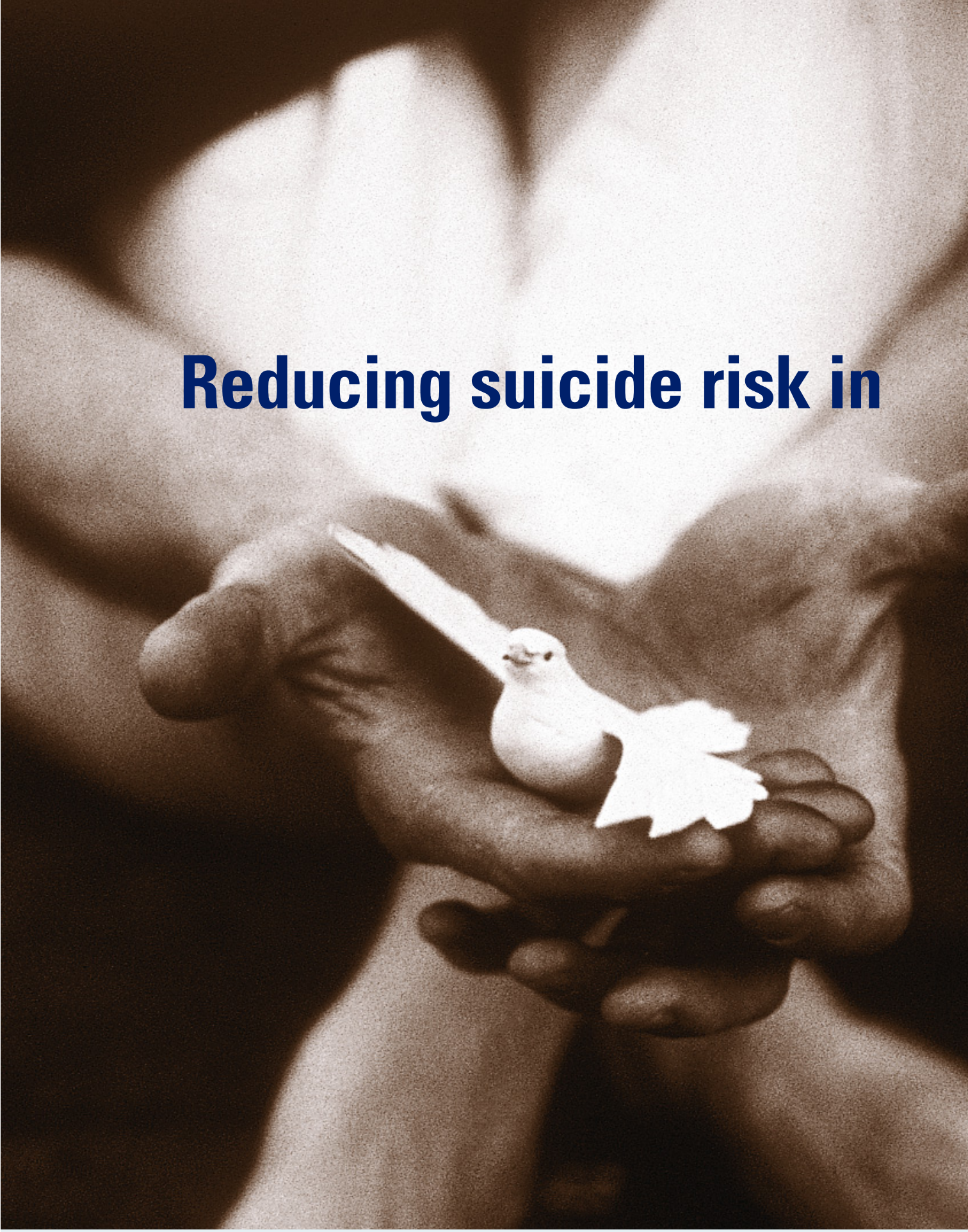
Reducing suicide risk in



Current PSYCHIATRY

psychiatric disorders

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Antidepressants show little protective effect in major depression, but more promising evidence is emerging for treating patients with bipolar or psychotic disorders.

Which psychotropics reduce the risk of suicide in patients with psychiatric disorders? Although no drugs eliminate the risk, new evidence is clarifying that some therapeutic choices can make a difference:

- Long-term lithium treatment apparently reduces suicide risk in patients with affective disorders; mood-altering anticonvulsants are less well studied but show less benefit than lithium.
- Effects of antidepressants remain inconclusive without adequate long-term studies.
- At least one atypical antipsychotic—clozapine—probably lowers suicide risk, although direct comparisons of antipsychotic agents are rare.
- Surprisingly little evidence is available on nondrug interventions, including rapid hospitalization, psychotherapy, and electroconvulsive therapy.[1]

Suicide is the leading cause of malpractice liability in psychiatry and of the heightened risk of death in persons with major affective and psychotic disorders (*Box, page 16*).[1-4] Here are the latest findings to help you choose medications for at-risk patients with bipolar disorder, major depression, or chronic psychoses.

continued

Box

Suicide: High risk with major psychiatric disorders

Suicide is by far the most common cause of premature death among patients with major mood and psychotic disorders.[2,3] A major affective or psychotic disorder increases risk of suicide 8- to 22-fold (*Table 1*). A history of attempted suicide increases a person's suicide risk 38-fold, so that the likelihood of dying by suicide becomes greater than one in four (28%).

Attempted suicide is less well-documented but may be 10 to 20 times more common than completed suicide in the general population. Persons with major affective and psychotic disorders complete suicide at an estimated rate of once in five attempts. This high rate suggests that their suicidal intent and methods are particularly lethal.[4]

BIPOLAR DISORDER AND MOOD STABILIZERS

Bipolar disorder is associated with the highest suicide rate among all major psychiatric illnesses, with an international incidence averaging 0.31% of patients per year.[4] This rate may slightly exceed the suicide rate of patients with major depression, which averages 0.29%/year.

Risk of suicidal behavior is similar among patients with bipolar type II (depression with hypomania) and type I disorder (depression with mania), supporting the view that type II is not a milder form of bipolar illness.[4-6] Indeed, one study of suicide attempts found a higher risk among bipolar II patients (24%) than in bipolar I patients (17%) as well as a higher risk in both bipolar types than in persons diagnosed with unipolar major depression (12%).[4]

Suicidal behavior in bipolar disorder is associated almost entirely with ongoing depression or dysphoria and is especially likely to follow severe and highly recurrent depressive episodes.[5,6] Combinations of depressive-dysphoric and irritable, agitated, anxious features in "mixed states" may be particularly dangerous and can be hard to diagnose with confidence. Moreover, DSM-IV criteria for mixed states are far too narrow in requiring symptoms to simultaneously fulfill criteria for both mania and major depression. More broadly defined mixed states are very common. Underdiagnosis risks underestimation of suicidal potential, and misdiagnosis as "agitated depression" encourages potentially dangerous overuse of antidepressants.[5,7]

Depression or dysphoria is the most prevalent morbidity in patients with bipolar disorder. Major and minor depressive states and mixed-dysphoric phases account for nearly one-third of time in follow-up care, exceeding time in mania or hypomania by more than 4-fold.[8] Ironically, however, bipolar depression is one of the least-studied forms of major depression. Suicidal bipolar patients are typically excluded from antidepressant studies because of the risks of inducing greater instability, agitation, or mania while treating them with an antidepressant but without a mood stabilizer.[7]

Mixed states can be hard to diagnose with confidence but may be particularly dangerous

LITHIUM'S PROTECTIVE EFFECT

Decades of research and clinical use demonstrate substantially lower risks of suicide and serious suicide attempts when patients with bipolar disorder are treated long-term with lithium salts in standard clinical doses (serum concentrations typically 0.6 to 0.8 mEq/L). Lithium is highly effective in treating all phases of bipolar disorder. A recent meta-analysis of 26 long-term trials of lithium reported between 1967 and 2001 found an average 3.2-fold sparing of morbidity or relapse risk.[9]

Benefits in types I and II. A large European sam-

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ple[10] compared percent-time-ill in bipolar patients before and after they received lithium as maintenance treatment. Unexpectedly, lithium therapy reduced percent-time-ill to a greater extent among patients with type II than type I bipolar disorder. Time in mania and time in depression were reduced 2.5-fold and 2.0-fold, respectively, in type I patients, compared with nearly 5-fold for time in hypomania and 2.5-fold for time in depression among type II patients.

Because depression is associated with the highest rates of suicidal behavior in all phases of bipolar disorders, lithium's effects in preventing depressive recurrence are especially important for reducing suicide risk.[6]

Table 1

Suicide risks in selected psychiatric disorders*

Condition	Relative risk	Incidence (%/year)	Lifetime risk (%)
Prior suicide attempt	38.4	0.549	27.5
Bipolar disorder	21.7	0.310	15.5
Major depression	20.4	0.292	14.6
Mixed drug abuse	19.2	0.275	14.7
Dysthymia	12.1	0.173	8.65
Obsessive-compulsive disorder	11.5	0.143	8.15
Panic disorder	10.0	0.160	7.15
Schizophrenia	8.45	0.121	6.05
Personality disorders	7.08	0.101	5.05
Alcohol abuse	5.86	0.084	4.20
Cancer	1.80	0.026	1.30
General population	1.00	0.014	0.72

* Estimated relative risks compared with the general population,[2] with recently updated information about bipolar disorders.[6] Annual rates are based on international general population average (14.3/100,000/year) X standardized mortality ratio; lifetime estimates are based on annual rates X 50 years as an estimate of lifetime exposure for years at major risk.

In a review of 22 studies[11]—some including patients with bipolar or recurrent unipolar major depression—risk of death by suicide was reduced at least 5-fold, based on an informal comparison of pooled rates in treated versus untreated samples. Based on quantitative meta-analysis, the pooled risk of death by suicide was reduced nearly 9-fold (or by 89%) in patients who received lithium maintenance treatment compared with those who did not. The risk for suicide attempts fell nearly 10-fold in a compilation of 33 studies (*Table 2, page 20*).[12] Available studies do not permit separate analysis of lithium's effects on suicidal behavior among patients with bipolar disorder and recurrent unipolar depression, leaving the relative benefit by diagnosis uncertain.

Dangers of stopping lithium. In our study[5] of more than 200 patients with DSM-IV bipolar I or II disorder, prophylactic lithium treatment for an average of 4 years reduced the risk of completed and attempted suicide by 6.5-fold. A subgroup of more than 100 patients discontinued lithium, usually after prolonged stability, and we excluded from analysis any cases of suspected emerging illness associated with discontinuation. Within 6 to 12 months after stopping treatment, this subgroup's rates of suicidal behavior increased markedly—by 20-fold above treated rates.[5] Thereafter, their rates returned to prelithium treatment levels.

Of particular clinical importance:

- discontinuing lithium gradually—over at

Table 2

Effect of lithium treatment on risk of completed and attempted suicide in patients with bipolar and recurrent depressive disorders*

Treatment or sample	Suicides	Attempts	All acts	A/S ratio
With lithium	0.16	0.41	0.57	2.6
Without lithium	0.88	4.02	4.90	4.6
Off/on lithium ratio	5.5	9.8	8.6	—
General population	0.014	0.21	0.22	15.3
Off lithium/general population ratio	56.4	19.1	22.3	—
On lithium/general population ratio	11.4	2.0	2.6	—

A/S ratio: Attempts versus completed suicides

* Rates (acts/year/100 persons, or %/year), based on previously reported averages derived from analyses of data from 33 studies with 55 treatment-arms,[12] from a more selected analysis of 22 studies of completed suicides,[11] and updated estimates for general population rates.[6]

least 2 weeks—was associated with a 2-fold lower suicide risk than more-abrupt discontinuation

- suicidal behavior after lithium discontinuation was almost always associated with emerging depression, which can provide an early warning of impending suicidal risk.

This is not the first time we have found evidence of a dramatic—but time-limited—increase in risk of recurrent bipolar illness when lithium treatment was discontinued.[13] Bipolar disorder patients who discontinue long-term lithium treatment abruptly are at high risk of recurrent depression and mania.[13]

Incomplete protection. Lithium's protection against suicidal risk is incomplete, as one can see by comparing lithium-treated versus untreated bipolar patients' suicide rates with those of the general population (*Table 2*).[6]

With lithium:

- suicides plus attempts declined 8.6-fold to levels 2.6 times greater than those of the general population
- suicide attempts fell 10-fold to levels that are about twice that of the general population
- risk of completed suicides declined 5.5-fold with lithium treatment but remained 11 times higher than that of the general population.

Without lithium:

- risk of suicide in bipolar patients is approximately 22 times greater than that of the general population
- ratio of attempts to suicides among bipolar disorder patients averages 4.6, suggesting that suicide attempts by patients with bipolar disorder are relatively lethal.[6]

Effect of delayed lithium therapy. Many patients with bipolar disorder do not receive sustained prophylactic treatment early in the illness.

Studies typically show an average 5- to 10-year gap between illness onset and the start of sustained lithium maintenance treatment. This delay averages more than 3 years longer among women with bipolar II disorder than men with bipolar I disorder, evidently reflecting major clinical dissimilarities between these groups.[6,14] In contrast,

we found that nearly one-quarter of long-term risk of suicidal behavior emerges within the first year of bipolar illness.[5] Clearly, patients with recurrent major affective illness require earlier intervention and more consistent clinical care.

We have also found that delayed maintenance treatment or the number of prior episodes of bipolar illness do not seem to limit therapeutic response to lithium.[14,15] These findings support the conclusion that prophylactic lithium treatment can be worthwhile, even after years of illness and many recurrences. Moreover, our recent meta-analysis of treatment options for rapid-cycling bipolar illness indicates that—even though all treatments have yielded inferior results compared with nonrapidly-cycling patients—no alternative has outperformed lithium.[16]

For rapid-cycling patients, no alternative has outperformed long-term lithium

Anticonvulsants. Evidence regarding the effects of other mood stabilizers on suicide risk in bipolar disorder remains limited:

- In a European collaborative study, several hundred patients with bipolar or schizoaffective disorder were randomly assigned to receive lithium or carbamazepine for nearly 2 years. Rates of suicidal acts were 2.5%/year with the anticonvulsant, but there were no suicides or attempts in patients receiving lithium.[17] Direct comparisons are rare, but this difference was both striking and statistically significant.
- Computerized records of approximately 20,000 patients diagnosed with bipolar disorder at two large American HMOs were analyzed to compare suicidal behaviors associated with specific treatments. Lithium yielded 2.7-fold greater protection against suicidal behavior (mainly attempts because suicides were rare) compared with anticonvulsants (mainly divalproex).[18]

Treatment recommendation. These observations support lithium's value in long-term maintenance of patients with bipolar disorder. Lithium's apparent reduction of suicide risk is striking and may be superior to that of other mood-stabilizers. Alternate treatments and lithium's potential value for reducing suicide risk in patients with unipolar depression require further study.

It is important to emphasize that lithium can be toxic or even fatal in acute overdose. This risk is integral to the equation when you assess risks and benefits for individual patients.

MAJOR DEPRESSION AND ANTIDEPRESSANTS

Major depression and depressive components of other disorders are major risk factors for suicide.[1,2,6] Depression continues to be surprisingly underrecognized and undertreated, even though relatively safe and tolerable antidepressants are readily available.[1,6,19,20] Patients with recurrent unipolar major depression often remain inconsistently or inadequately treated, even after they attempt suicide.[19]

Recent reviews of suicide risk during research on antidepressant treatment in major depression suggest that:

- antidepressants of various kinds may tend to reduce the risk of suicidal behavior, but any such effect is small and statistically nonsignificant (Baldessarini et al, 2003, unpublished)
- tricyclic antidepressants may yield lower rates of suicidal behavior than selective serotonin reuptake inhibitors (SSRIs). Similarly, however, such trends reflect highly variable research methods and inconsistent findings and do not hold up to quantitative analysis (Baldessarini et al, 2003, unpublished).

The suicidal events encountered during research mainly involve attempts because sui-

Table 3

Preventing suicide: How effective are specific treatments?

Treatments compared	Disorder treated	Benefit/risk ratio
Mood stabilizers		
Lithium vs. none or placebo*	Bipolar disorder	
Suicides		8.8 (4.1 to 19.1)[a]
Attempts		9.9 (5.0 to 14.8)[b]
Lithium vs. carbamazepine*	Bipolar disorder	≥2.5[c]
Lithium vs. divalproex*	Bipolar disorder	2.7 (1.2 to 6.2)[d]
Antidepressants		
Antidepressants (any) vs. placebo/none	Major depressive disorder	1.1 (0.7 to 1.6)[e]
Tricyclics vs. SSRIs	Major depressive disorder	1.2 (0.7 to 2.1)[e]
Antipsychotics		
Clozapine vs. any antipsychotic*	Schizophrenia	
Suicides + attempts		3.3 (1.7 to 6.3)[f]
Attempts		2.9 (1.5 to 5.7)[f]
Clozapine vs. olanzapine*	Schizophrenia	
Suicides + attempts		1.3 (1.0 to 1.7)[g]

a. Tondo et al, 2001[11]
b. Baldessarini et al, 2003[5]
c. Thies-Flechtner et al, 1995[17]
d. Goodwin et al, 2002[18]
e. Baldessarini et al, 2003[5]
f. Baldessarini & Hennen, 2003[22]
g. Meltzer et al, 2003[24]
* First agent is statistically more effective, based on benefit/risk ratio (95% CI).

cides are rare, particularly in relatively brief treatment trials that exclude acutely suicidal subjects. Analyses are further complicated by trends toward paradoxically *lower* suicidal risks among depressed patients randomized to a placebo in controlled antidepressant trials. This paradox is paralleled by often earlier removal of patients treated with a placebo than with an active antidepressant, perhaps in association with emerging suicidality.[21]

These trends toward lower suicide risk among patients receiving a placebo are somewhat reassuring, given concern that placebo randomization for scientific purposes may endanger study subjects. However, these artifacts confound interpretation of results and make it difficult to measure the effects of antidepressant treatment.

Evidence is emerging that clozapine may reduce suicide risk in patients with psychotic disorders

Treatment recommendation. Clinical prudence requires us to treat potentially lethal major depressive illness aggressively, even though one cannot state with confidence that any antidepressant class lowers suicide risk or that one class is significantly more effective than others (*Table 3*).

SCHIZOPHRENIA AND ANTIPSYCHOTICS

For schizophrenia and other primary psychotic disorders, little research exists to indicate that atypical antipsychotics reduce suicide risk. Evidence is emerging, however, that clozapine may offer this benefit,[22] in addition to its well-sub-

stantiated clinical superiority in treatment-resistant psychotic illness.[23]

Pooled evidence from controlled trials comparing clozapine with other antipsychotics indicates a 2-fold lower risk of mortality from all causes.[23] This finding was highly suggestive but not statistically significant, and the specific contribution of suicide to this risk is unknown.[23] Our recent meta-analysis of the few available studies found that clozapine was associated with a statistically significant, 3.3-fold lower overall suicidal risk compared with other antipsychotic treatments.[22]

A well-designed, 2-year study randomly assigned 980 patients with schizophrenia or schizoaffective disorder who were at high risk for suicide to clozapine (mean 274 mg/d) or olanzapine (mean 16.6 mg/d). Clozapine showed moderately greater benefit in reducing suicide attempts and need for urgent intervention for perceived emerging suicide risk, although it did not lower suicide risk per se.[24] Another study associated olanzapine with a 2.3-fold lower risk of suicidal behavior, compared with haloperidol.[25]

Comparing two potentially effective agents may have limited the observed difference between clozapine and olanzapine.[24] Nevertheless, previous (largely uncontrolled) comparisons with other treatment options indicate substantially lower risks of both suicides and attempts with clozapine.[22] In December 2002, the FDA approved a unique indication for clozapine: to reduce the risk of recurrent suicidal behavior in patients with schizophrenia or schizoaffective disorder.

Treatment recommendation. Risks of suicide and other causes of premature death are high in patients with chronic psychotic disorders, underlining the importance of appropriate long-term care. Clozapine has shown benefit in reducing risk of suicidal behaviors. When clozapine is otherwise a plausible option, this additional potential benefit can be considered when selecting therapy for individual patients.

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continued

Bottom Line

Psychiatric disorders carry high risk of death by suicide. Long-term lithium greatly reduces suicide risk in bipolar disorder. Antidepressants' anticipated suicide-reducing effects remain unproven for recurrent unipolar major depression. Clozapine is FDA-approved for reducing suicide risk in patients with schizophrenia.

Suicide risk

Related resources

- American Psychiatric Association. Suicide-prevention practice guidelines. Washington, DC: American Psychiatric Press, 2003 (in press).
- American Foundation for Suicide Prevention. http://www.afsp.org
- American Association of Suicidology. www.suicidology.org
- National Institute of Mental Health (NIMH)/Suicide. http://www.nimh.nih.gov/publicat/depsuicidemenu.cfm

DRUG BRAND NAMES

Clozapine • Clozaril
Carbamazepine • Tegretol
Divalproex • Depakote
Haloperidol • Haldol
Lithium carbonate • Eskalith, Lithobid, others
Olanzapine • Zyprexa

DISCLOSURE

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