Antidepressants and Suicidal Risk

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Only 5% of suicidal patients on the average use their prescribed antidepressant to commit suicide. Underprescription of antidepressants and failure of antidepressant therapy appear to be of greater practical importance than the toxicity of individual compounds. Prescribing less toxic agents, therefore, will not be of great advantage, especially if they are less efficacious. Several antidepressants including the selective serotonin reuptake inhibitors (SSRIs) may increase suicidal behavior by energizing depressed patients to act along preexisting suicidal thoughts or by inducing akathisia with associated self-destructive impulses. For acutely suicidal patients, the use of more sedating antidepressants is recommended. Clinical trials could not confirm a superiority of SSRIs over tricyclics in reducing the number of suicide attempts. There is evidence from large international data sources and a large multicenter controlled trial that lithium prophylaxis decreases the suicide risk and overall mortality in affective disorders. A suicide-preventing effect has not been demonstrated conclusively for antidepressants or non–lithium mood stabilizers. *(J Clin Psychiatry 1999;60[suppl 2]:94–99)*

Due to the development of many new antidepressant agents in recent years the differential benefits of such compounds in the treatment of affective disorders have raised much interest—medical and commercial—and have resulted in often heated debates and controversial publications. Depression is characterized by its repetitive nature and its high excess mortality mostly due to the 50–100 times increased suicide risk. Therefore, one of the intriguing practical issues is the potential influence—positive and negative—of antidepressants and mood stabilizers on suicidality. Five essential questions to be raised in this context are the following:

1. What is the impact of self-poisoning with various antidepressants?
2. Do antidepressants increase the suicide risk?
3. Do antidepressants lower the suicide risk?
4. Do various compounds differ with respect to increasing or decreasing suicide risk?
5. Does lithium lower the suicide risk?

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The validity of the empirical data allowing us to formulate some answers to these questions differs markedly. Furthermore, a lot of idiosyncrasy and economical interests can be observed in what has been published on these issues during recent years.

WHAT IS THE IMPACT OF SELF-POISONING WITH VARIOUS ANTIDEPRESSANTS?

There has been an ongoing debate, particularly in the United Kingdom, on the alleged necessity to prescribe primarily the newer, less toxic antidepressant compounds in order to avoid possible lethal self-poisonings.[1,2] In fact, when screening cases of deaths caused by overdosing antidepressants, the older tricyclic compounds such as desipramine are overrepresented, resulting in a high fatal toxicity index.[3] Thus, an epidemiologic study from the United Kingdom showed that the number of deaths per million prescriptions of some older tricyclic antidepressants was significantly higher in relation to newer, less toxic agents.[4] It was concluded that in patients with suicidal ideas newer and less toxic antidepressants should be preferred.[2,4] In a pharmacoeconomic approach, it was postulated that the prescription of newer and less toxic drugs might save 300 to 450 lives per year in the United Kingdom.[1]

The question, however, is whether suicidal patients do often use their prescribed antidepressants to end their lives. The evidence for such assumption is rather weak and has been discussed very controversially.[5–10] We analyzed about 3000 cases with acute intoxication who had been admitted to a resuscitation center in what was formerly West Berlin.[11] In only 3% of these cases, antidepres-

Table 1. Frequency of Overdosing With Antidepressants Among Suicide Victims*

Study	Frequency (%)
San Diego[12]	4
Antidepressant monotherapy	1
Mobile, Alabama[13]	5
Finland[14]	8
United Kingdom[15] (totally or in part due to antidepressant overdosing[a])	14
Sweden[16]	6
Sweden[17]	4

*Data from references 12–17.
[a]Flupenthixol belonged to the "antidepressants" included in the study.

Table 2. Total Number of Certain and Uncertain Suicides According to the Official *Statistics Sweden

Variable	1990–1991	1992–1994	Change (%)
Suicides positive for antidepressants on toxicological screening	271	291	+7
Use of antidepressants (100,000 person-years)	1.03	1.54	+51
Risk per 100,000 person-years	263	189	–28
Number of suicides	2002	1802	–10

*Data from reference 17.

sants and/or major tranquilizers were the toxic agents; 19% of the intoxications within this group were caused by amitriptyline, and about 60% by the combination amitriptyline/chlordiazepoxide.[11] Furthermore, the clinical detoxification of these patients did not create any medical difficulties.

Data from various countries, e.g., the United States, the United Kingdom, Finland, and especially Sweden, indicate that very few patients—on the average only about 5%—commit suicide by overdosing their antidepressants (Table 1).[12–17] A study from Finland assessed the use of alcohol and drugs in suicides.[18] Antidepressants were used in 19% of women but only 4.8% of men. These results were confirmed by a study in Alabama. Five percent of the overdose deaths were caused by antidepressants, significantly fewer in men than in women.[13] According to Isometsä and co-workers,14 most people with major depression who commit suicide, particularly if they are men, use violent methods but not tablets. Furthermore, patients do not normally take their prescribed antidepressants for suicide attempts. Patients often take drugs they have collected from former treatment periods.[14]

The main message from Isacsson and co-workers,16,17 however, is that therapeutic failure of antidepressant drugs may be the greater problem. Prescribing less toxic compounds is no advantage if they are less efficacious. Isacsson et al. found an overrepresentation of newer compounds (fluvoxamine, citalopram, moclobemide, mianserin, and trimipramine) versus the reference drug amitriptyline among suicide victims. Jick et al.[15] reported from the large Value Added Medical Products, Ltd., (VAMP Health) data resource based in the United Kingdom that patients who were prescribed mianserin or fluoxetine had a 2-fold increased risk of committing suicide compared to amitriptyline-treated patients. On the other side, when controlling for various factors correlated with the risk of suicide, the number of deaths was similar for at least 10 different antidepressants. In the study by Isacsson et al.,[17] the highest standardized mortality ratio was found for mianserin (2.76, 95% confidence limits = 2.19 to 3.46), a typically nontoxic agent. It is the flaw of some pharmacoeconomic analyses in this context that they do not account for the possibility of lower therapeutic efficacy of some newer antidepressants.[4,9]

The available data suggest that only a small minority of people who commit suicide receive antidepressive drugs before death in spite of the high prevalence of depression in this population. Isacsson and colleagues[17] found that whereas the prescription rate of antidepressants in 1992–1994 was increased as compared to 1990–1991, the relative risk of suicide was reduced, possibly due to a more competent and widespread treatment of depression (Table 2). The observations in Gotland, Sweden, demonstrate that even short-lasting, inexpensive instruction about adequate treatment of depression given to local general practitioners can result in a markedly reduced number of suicides in the region during the following year.[19]

DO ANTIDEPRESSANTS INCREASE THE SUICIDE RISK?

For years, an intriguing question has been whether the appropriate use of antidepressants can increase the suicide risk during a depressive episode and if so—as most psychiatrists would agree—whether the available compounds differ in this respect.

General textbook wisdom—at least in Europe—recommends preference of the more sedating antidepressants in suicidal patients because of the risk of activating preexisting suicidal thoughts (e.g., references 20 and 21). Worsening of acute suicidality has been reported for many different compounds, and, according to a review of the literature, it was concluded that such paradoxical reactions may occur in patients with a history of impulsive behavioral dyscontrol and therapeutic nonresponse.[22]

Some case reports in the early 1990s suggested de novo development of serious suicidal ideation in fluoxetine-treated patients and led some authors to suspect that serotonergic drugs might intensify suicidality.[23,24] Such an effect could be explained by several characteristic features of selective serotonin reuptake inhibitors (SSRIs): They may

- energize depressed patients to act along preexisting suicidal thoughts,

- induce akathisia with associated self-destructive or aggressive impulses,
- produce severe insomnia.

The suspicion of a greater risk of inducing de novo ideation, however, could not be confirmed by several independent groups in the following years, e.g., in a study with more than 1000 outpatients in Boston[25] and within a drug surveillance program.[26]

A meta-analysis of 17 double-blind studies comparing fluoxetine, tricyclics, and placebo in major depression performed by Eli Lilly and Company did not reveal any increased risk of suicidal acts.[27] Emergence of substantial suicidal ideation occurred significantly less often with fluoxetine than with placebo. These data were confirmed by the company in a more complex analysis in the following years.[28,29] Similar findings for paroxetine partly based on data from SmithKline Beecham were published by Jenner[30] and by Montgomery et al.[31] In a pooled analysis of controlled studies of paroxetine, these authors found no significant difference between the number of suicide attempts in patients treated with either paroxetine (1.3%), placebo (1.1%), or tricyclic antidepressants (1.0%).

Nevertheless, it cannot be excluded that particularly susceptible patients may in fact experience an activation of suicidal ideas and suicidal impulses induced by the akathisia-like effects that are known to occur with SSRIs,[32] although this association may not emerge in large epidemiologic studies. It must also be considered that suicidal patients are usually not included in clinical trials, a factor that restricts the generalizability of the published pooled data analyses.

The discussion about potential suicide-provoking risks of fluoxetine received much attention, worldwide, because findings of the neurobiology of suicidal behavior would suggest that "serotonergic" drugs should have a particularly beneficial effect on suicidality. Possibly, both concepts may possess a grain of truth.

DO ANTIDEPRESSANTS LOWER SUICIDE RISK?

Baldwin and colleagues in the United Kingdom analyzed data from controlled trials and found SSRIs to be somewhat more protective against suicidality than maprotiline, a purely noradrenergic drug.[33] In a large long-term study by Roullion et al.,[34] low-dose maprotiline was associated with an increase in suicidal acts even in relapsers despite its significant efficacy in preventing relapse of depression. In a group of 245 relapsers of 1141 long-term treated patients, 9 suicides and 5 suicide attempts occurred in the maprotiline group while no suicides and 1 suicide attempt were observed in the placebo group ($p < .05$). A general conclusion, however, that maprotiline is more prone to induce suicidal acts should not be drawn from these findings since the 2 groups were not matched as to the most important predictor variable for completed suicide, namely, the number of suicide attempts in the patient's history.[35]

There is some indirect and direct evidence that suicidal ideations will respond faster to serotonergic compounds such as zimelidine, mianserin, or fluvoxamine.[36–38] It seems also noteworthy that fewer deaths have been reported from clomipramine overdosing, although its acute toxicity is not different from that of other tricyclics.[39] Montgomery and colleagues[31] found a 2.8 times lower risk of suicidality with paroxetine compared with other active drugs. However, a superiority of SSRIs over tricyclics could not be demonstrated in successive, formalized trials. A study from Germany showed no advantage of paroxetine versus amitriptyline in a complex analysis of suicidal acts and ideations.[40] Neither did low-dose fluoxetine as compared to placebo reduce the number of suicide attempts in patients with recurrent brief depression and a history of suicide attempts.[41] Furthermore, there is no sufficient evidence from published trials that long-term antidepressant treatment can diminish the suicide risk, although some epidemiologic data, e.g., from Sweden, would support a positive association.[17,19]

Thus, we are left with the pressing question whether any available drug treatment exists for which efficacy against suicidal behavior was demonstrated.

DOES LITHIUM LOWER SUICIDE RISK?

There is convincing evidence from different data sources, that lithium, which is not only a mood stabilizer but also an effective antidepressant,[42] decreases the suicide risk when used according to the state of the art. Among the retrospective studies on large samples of reliably diagnosed and well-documented long-term lithium-treated patients, particular attention has been given to the findings of the International Group for the Study of Lithium-Treated Patients (IGSLI).[43–45] The starting point of these investigations was the observation by the lithium research group in Berlin that suicidal behavior was clearly decreased or even abolished in lithium-treated patients including those not showing a satisfactory episode-preventive effect.[46] In much larger patient samples, the IGSLI members were able to replicate and expand the original observations. From these and other studies it now can be concluded that there is a clear drop of completed suicides in patients on lithium as compared to patients off lithium (Table 3). Pre/post-comparisons also show a dramatic reduction of suicide attempts during lithium prophylaxis either in patients with suicide attempts in the past or in unselected patients (Table 4). (The study of Tondo et al.[53] could not be included here because it did not analyze numbers of patients but numbers of suicidal acts.)

Table 3. Completed Suicides On/Off Lithium (Significantly Different On/Off Lithium)*

Study	On Lithium	Off Lithium
Müller-Oerlinghausen et al[46]	1 of 55	4 of 13[a]
Felber and Kyber[48]	1 of 36	3 of 36[b]
Coppen[49]	1 of 103	13 of 103[b,c]

*By courtesy of M. Schou (reference 47).
[a]$p < .01$.
[b]$p < .001$.
[c]Nontreatment group.

Table 4. Attempted Suicides On/Off Lithium (Significantly Different On/Off Lithium)*

Patients/Study	On Lithium	Off Lithium
Patients with suicide attempts in the past		
Müller-Oerlinghausen et al[43]	4 of 55	7 of 13[b]
Felber and Kyber[48]	6 of 36	36 of 36[b]
Unselected patients		
Hanus and Zapletálek[50]	4 of 95	25 of 95
Lepkifker et al[51]	0 of 33	7 of 33[a]
Szanto et al[52]	1 of 36	15 of 36[b]

*By courtesy of M. Schou (reference 47).
[a]$p < .01$.
[b]$p < .001$.

Table 5. Standardized Mortality Ratio (SMR) During Lithium Treatment and After Discontinuation*†

Study	During Lithium Treatment	After Discontinuation of Lithium
Norton and Whalley[55]	2.83[c]	
Coppen et al[56]	0.60	
Vestergaard and Aagaard[57]	4.35[a]	
Müller-Oerlinghausen et al[43d]	0.89	2.54[b]
Ahrens et al[54d]	1.14	
Lenz et al[58d]	0.86	1.8[a]
Nilsson[59d]	1.8[c]	3.1[c]

*By courtesy of M. Schou (reference 47).
†SMR significantly different from 1.0:
[a]$p < .05$.
[b]$p < .01$.
[c]$p < .001$.
[d]International Group for the Study of Lithium-Treated Patients (IGSLI).

The reduction of suicide (and also cardiovascular) excess mortality consequently results in a significant reduction or even normalization of the standardized mortality ratio (SMR) in appropriately long-term treated patients (SMR 1.0).[54] The excess mortality rises again when lithium is discontinued (Table 5). An updated survey on suicide rates comprising 17,000 patients is given by Tondo et al.[60] Some authors found an unchanged SMR.[55,57] However, these differences do not contradict the concept of a suicide preventive effect of lithium but can most likely be explained by differences in treatment settings or duration.[47]

In this context it should be added that, using the conventional cumulative approach, the SMR is very high at the onset of treatment and then slowly declines toward 1.0 depending on the size of the sample and the variance of the treatment duration in the specific sample. However, applying a mathematical procedure—similar to a survival analysis—in which each treatment year is analyzed independently, it turns out that in an extended IGSLI sample the SMR is normalized from the first year onward.[61]

Another decisive piece of evidence originates from a post hoc analysis of the findings of the M.A.P.-Study (Multicenter Study of Affective Psychoses). This study, supported by the Ministry of Health and Technology of Germany, is the largest existing controlled trial comparing the prophylactic efficacy of 2 mood stabilizers and amitriptyline in 378 unipolar, bipolar, and schizoaffective patients for a treatment period of 2.5 years.[62–64] There were 9 suicides and 5 suicide attempts in the total patient sample. No suicidal act had occurred in the lithium group, but suicidal acts were mainly found in the carbamazepine group and some also occurred during antidepressive treatment, particularly when patients were not yet fully stabilized.[65] This finding is in good agreement with a follow-up of patients discharged from psychiatric hospitals in Switzerland. Among those who had committed suicide, none had received lithium shortly before death, whereas in the nonsuicidal control group, 11% had been taking lithium. There was no difference in antidepressant medication.[66]

CONCLUSIONS

In summary, the following conclusions may be drawn from the available data.

1. The acute toxicity of different antidepressants is of minor importance compared with the prevailing problem of undertreatment or inappropriate treatment.
2. Antidepressants are rarely used to commit suicide.
3. Scant evidence exists that serotonergic compounds possess a somewhat more favorable effect in acutely suicidal patients. However, antidepressants with excitatory or akathisia-like activity would most likely worsen suicidality in susceptible patients.
4. It is unknown whether long-term medication with antidepressants can lower the suicide risk and overall mortality of patients with affective disorders.
5. Convincing evidence exists that appropriate lithium long-term prophylaxis reduces the suicide risk and can possibly normalize the excess mortality of patients with affective disorders (unipolar, bipolar, schizoaffective). This antisuicidal effect may be related to the primarily presynaptic serotonergic and antiaggressive properties of lithium salts. It is possibly independent of its episode-preventing efficacy. According to some authors, the use of lithium as maintenance treatment for unipolar, bipolar, and

schizoaffective patients is not particularly widespread in the United States.[67] In the context of evidence-based medicine, it must, however, be discussed whether not giving lithium prophylaxis to patients with affective disorder and a high suicide risk can be considered as treatment according to the state of the art.

Drug names: amitriptyline (Elavil and others), carbamazepine (Tegretol and others), chlordiazepoxide (Librium and others), citalopram (Celexa), clomipramine (Anafranil), desipramine (Norpramin and others), fluoxetine (Prozac), fluvoxamine (Luvox), maprotiline (Ludiomil), paroxetine (Paxil), trimipramine (Surmontil).

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