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Suicide in severe depression related to treatment

Depressive characteristics and rate of antidepressant overdose

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Abstract The objective of the present study was to assess the association between depressive characteristics and completed suicide despite adequate antidepressant therapy in severe depression and to investigate the frequency of lethal antidepressant overdoses. A record evaluation of 98 suicide victims with a primary severe depression had been performed. These had been admitted to the Department of Psychiatry, Lund University Hospital between 1956 and 1969 and followed up to 1998. Psychomotor retardation was related to completed suicide after ECT. The estimated frequency of lethal intoxication with antidepressants was low: 3 % of the suicides.

Key words depression · suicide · ECT · antidepressants

Introduction

Mood disorder is the single diagnosis with the greatest impetus on suicide (Lönnqvist 2000). Therefore, the relation between antidepressant treatment and suicide has been an urgent topic of research.

Several studies on general populations have shown that only a minority of the depressed patients had received adequate antidepressant therapy before suicide (Barracough et al. 1974; Chynoweth et al. 1980; Åsgård 1990; Isacson et al. 1994a, 1994b; Henriksson et al. 2001; Andersen et al. 2001). Patients in psychiatric care were,

however, often treated, though according to some studies adequately (Brådvik and Berglund 2000; Schou and Weeke 1988) and according to another inadequately (Isometsä et al. 1994). Still, other investigators found a high use of antidepressant medication based on toxicological analyses in elderly depressed patients (Waern et al. 1996).

It could be assumed that increased treatment of depression might reduce suicide risk. However, little attention has been paid to those patients who commit suicide despite adequate treatment, though there has been clear evidence that some patients do, be there few or many.

ECT and antidepressant pharmacotherapy do not have full effect on all patients. The response rate has been shown to be 90 % on ECT (Avery and Winokur 1978) and 70–80 % on tricyclic antidepressants (Potter et al. 1991). Thus a minority are non-responders.

Furthermore, several investigators have discussed incomplete recovery on antidepressant pharmacotherapy (Faravelli et al. 1986; Agosti et al. 1993; Fava 1999). Symptom reduction was for instance shown to be only 40.7 % for investigational drugs in one study (Khan et al. 2000).

However, to our knowledge a possible relation between individual depressive symptoms and suicide despite antidepressant therapy has not been investigated. Psychosis and psychomotor retardation are considered as severe depressive symptoms, which may motivate separate diagnostic entities (Parker 1996). The former symptom responds less well to antidepressants (Khan et al. 1991). When patients receive pharmacotherapy for their depression, the relief of psychomotor retardation before the relief of depressive symptoms has been proposed to constitute an increased risk for suicide (Benkert and Hippus 1980; Feuerstein and Jackisch 1986; Damluji and Ferguson 1988). Both psychosis and psychomotor retardation show a good response to ECT (Rasmussen 2003). However, a relapse of depression after ECT rather than insufficient response may constitute a risk factor for suicide, when continuation therapy is not given. Which of the clinical symptoms may constitute a risk is, to our knowledge, not known.

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Moreover, there is a clinical practise to take precautions in prescribing antidepressants, as they may constitute a tool for suicide. Reduced amounts are usually recommended. The number of overdoses with tricyclic antidepressants has been found to be less than around 4% of all suicides (Kelleher et al. 1992; Ohberg et al. 1996). The frequency of lethal intoxication has been shown to be 8% among depressed suicides (Isacsson et al. 1994a, 1994b; Isometsä et al. 1994). Among all deaths from overdose or poisoning 20–30% were antidepressant related in different studies (Obanunwa and Busuttill 1994a, 1994b; Neeleman and Wessely 1997; Shah et al. 2001). A majority was associated with tricyclic antidepressants (Obanunwa and Busuttill 1994a; Shah et al. 2001). Other investigators found that 14% of all patients prescribed antidepressants used those for their lethal overdose (Jick et al. 1995).

In the previous study of this population of severely depressed patients we found that 61% of those who were in contact with the Department within six months before their suicide had received adequate treatment with either ECT or antidepressant medication (Brådvik and Berglund 2000). Therefore some patients may be in danger of committing suicide despite adequate antidepressant therapy.

The aim of the present study was firstly to investigate a possible correlation between depressive characteristics, such as psychomotor retardation and psychosis, and completed suicide despite adequate treatment in this population of severely depressed patients. Moreover, we wanted to investigate to what extent antidepressants were used as a method of suicide in a sample of severely depressed patients.

Material and method

Sample

In the 1950s and 1960s all in-patients at the Department of Psychiatry, University Hospital, Lund were rated on a multi-axial diagnostic schedule at discharge (Essen-Möller and Wohlfahrt 1947). This database enabled the selection of patients with a severe depression/melancholia for an investigation into suicide (from 1956–1969, when this diagnosis was used).

Design

The design of the sampling procedure is presented in a flow diagram. When followed up to January 1, 1984 a total of 103 out of 1206 patients had died by their own hand (Berglund and Nilsson 1987). Another 11 had committed suicide at the second follow-up January 1, 1998 (Brådvik and Berglund 2001).

The case records were performed for a thorough blind evaluation at first follow-up (Brådvik and Berglund 1993). Secondary depressions were excluded according to Research Diagnostic Criteria (Spitzer et al. 1978). Thus we received 89 suicides, 38 men and 51 women. A retrospective diagnostics according to DSM IV (APA 1994) has been performed for the first sample with matched controls (Brådvik and Berglund 2000). It turned out that at least 91% of the patients met the criteria for major depressive disorder with melancholia or psychosis.

Likewise, two secondary depressions were excluded from the 11 more recent suicide victims (Brådvik 2002), and 6 more men and 3 more women were received. Thus there remained 98 suicide victims with a diagnosis of primary severe depression/melancholia (44 men and 54 women).

For all patients we thus had prospective data from the multi-axial schedule, including psychomotor retardation. Treatment at last contact and psychosis were independently rated by two different raters.

Half of the sample (49 patients) was in contact with the Department within six months before their suicides, as in-patients or out-patients, and thus we could evaluate treatment at suicide in relation to depressive symptoms for this group. Another 49 were not in contact at suicide (22 men and 27 women in each group). For the first group of patients we thus had data on treatment close to the time of suicide, i. e. what could be assumed to be their last depressive episode. They showed a similar age at index admission and last contact (46 versus 49 years and 49 versus 52 years, non-significant). Thus those who were in contact with the clinic were probably representative for the total sample.

Record evaluation

Two variables were studied: namely depressive characteristics and method of suicide (including antidepressant intoxication).

Two severe depressive characteristics were related to suicide despite adequate treatment:

- Psychomotor retardation. This was prospectively evaluated at index admission on the multi-axial schedule.
- Psychosis. Psychotic symptoms were evaluated in the case records, to include psychotic episodes that may occur after the period when the multi-axial schedule was used.

The following categories for adequate treatment were used:

- Antidepressant pharmacotherapy (adequate treatment): A full dose of at least 150 mg of tricyclic or tetracyclic antidepressants should be continued for at least 2 months. (One case with lower full doses –125 mg – with good effect was considered adequate.)

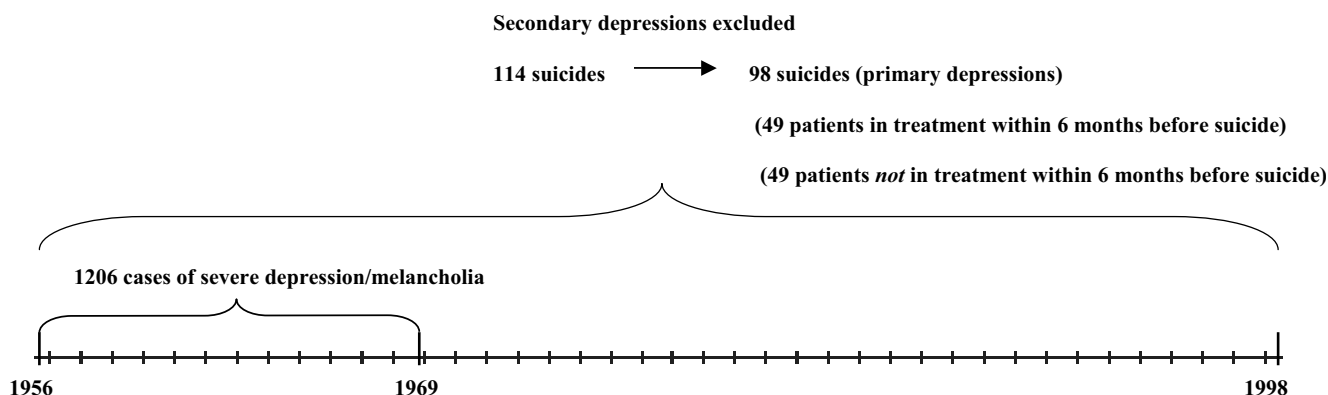


Fig. 1 Flow-diagram for the sample of patients with severe depression admitted to the Department of Psychiatry, Lund University Hospital

(A few cases of treatment with MAO-inhibitor were included.) It should be followed by continuation treatment of at least 75 mg, which should not be disrupted until 6 months after the onset of the depressive episode (Ottosson 1983).

- ECT. A series of at least 6 treatments (given three times a week) was considered adequate. (According to the tradition of the Department treatment was sometimes discontinued after 4 seizures, which was considered adequate if there was a persistent effect. Two such cases were included as adequate.)
- ECT and continuation treatment with antidepressants: Continuation treatment should be initiated within 2 weeks after the last ECT.

(Lithium treatment was rare due to a small number of bipolar I cases, the main indication for lithium therapy at the time. None of the suicides followed until within 6 months before suicide was on lithium and hence this treatment is excluded from the analysis).

A thorough description of the scoring of treatment has been made in a previous paper (Brådvik and Berglund 2000). Suicide may occur during different phases of treatment, which was taken into consideration.

Depressive symptoms in those 49 patients who were adequately treated for their last depressive episode (i.e. within 6 months before they took their life) were compared to those who were in contact with the Department but did not receive any treatment or (in five cases) were inadequately treated. Secondly, depressive symptoms related to adequate treatment at suicide were related to the total sample of patients, including those 49 who did not commit suicide, when in contact with the Department. Finally, a comparison was made between the frequency of depressive symptoms among those who committed suicide despite adequate treatment and those who received the same adequate treatment at their last contact but did not commit suicide. Some of the patients who were not followed up close to suicide might have received treatment from other doctors, but we can only compare the last contact. Those treatments were, however, prescribed about equally late in the course of depression, which justifies a comparison (Brådvik and Berglund 2000).

The method of suicide for the 114 suicides in the total sample of severely depressed patients has been presented in a previous investigation (Brådvik and Berglund 2001). However, in the present study only the 98 primarily depressed suicides were included. Data on the type of drug used for intoxication were available for all but three cases. The number of fatal antidepressant overdoses among the total number of suicides and among the patients who had been prescribed antidepressants for their last depressive episode was scored.

Statistics

Chi-square tests were used for comparisons between groups and Fisher's exact test for small samples.

Results

Depressive characteristics and completed suicide

The depressive characteristics psychomotor retardation and psychosis in relation to treatment within 6 months before suicide are presented in Table 1. The patients who completed suicide after ECT had more often shown psychomotor retardation as compared to those who had not received adequate antidepressant treatment ($p < 0.02$).

The patients who had received ECT before their suicide were also more often retarded as compared to the total sample of depressed suicides (12/12 versus 36/86, chi-square = 14.24, $p < 0.001$). Further, they were more often retarded than those who received ECT equally late in course but did not commit suicide (12/12 vs. 6/16, chi-

Table 1 Depressive characteristics and suicide despite adequate treatment

	In contact within 6 months before suicide		
	ECT n = 12	Antidepressants n = 18	No treatment with antidepressants or ECT** n = 19
Psychomotor retardation	12*	7	10
Psychosis	7	10	9

* $p < 0.025$; ** including 5 patients with inadequate treatment, of whom one received ECT (Note that one patient could have both or none of the depressive characteristics. Thus the rows and columns could not be summed up.)

square = 11.67, $p < 0.001$). However, some patients may receive continuation pharmacotherapy after ECT. Such was not given at the time of suicide (Brådvik and Berglund 2000) but to some of the patients who were not followed until their last depressive episode. Correcting for this confounding factor the significance remained (12/12 versus 3/10, Fisher's exact test $p < 0.008$). Patients receiving ECT were somewhat older, but age was not related to psychomotor retardation in this sample.

Thus the correlation between completed suicide after ECT and psychomotor retardation appears as a robust finding.

There was no correlation between psychomotor retardation and suicide among those who received antidepressant pharmacotherapy.

Psychosis was not correlated with suicide despite adequate antidepressant therapy, neither ECT nor antidepressant pharmacotherapy.

Method of suicide

The method of suicide is presented in Table 2. Intoxication was *not* the most common method of suicide among these severely depressed patients 21/98 (21%). In four cases of intoxication the drug used was unknown and in three cases antidepressants caused or contributed to death (in one case alone, in one case as the probable

Table 2 Method of suicide in primary severe depression

Overdose	
antidepressants	3
other	14
unknown	4
CO poisoning	4
Drowning	19
Hanging	43
Cutting	1
Shooting	5
Jumping	1
Other	4
Total	98

drug and in one case in combination with alcohol and metaqualone). Thus 3% (3/94) of all suicide cases and 18% (3/17) of all intoxications (where the drug was known) were completely or partly due to antidepressant overdose.

Thus lethal intoxication by antidepressants was rare among these severely depressed patients, and the patients most often used other drugs or violent methods for suicide. To our knowledge, none of the 18 patients who had been prescribed antidepressants at last contact used this medication for suicide.

■ Phase of treatment

As mentioned, there were 18 (out of 49) depressed patients who had received antidepressants within six months before suicide. Out of those there were only three who committed suicide within 4 weeks after the initiation of antidepressant pharmacotherapy at the clinic, when it possibly had not yet received its effect. Another three were on maintenance treatment. Thus 3/15 patients on medication during active treatment for a depressive episode (lasting 6 months) took their own life during the first month versus an expected frequency of 2.5/15 (non-significant). Thus no obvious increased frequency of suicide early in the course could be demonstrated, though numbers are too small to be conclusive.

None of the three patients who committed suicide early in the course (before 4 weeks) took an overdose of antidepressants. Two of them hung themselves and one took an overdose of analgesics, dextropropoxyphene, in combination with alcohol. Thus none of the patients could be shown to have died from an overdose of the antidepressants prescribed, before it could be expected to have attained its effect!

No patient committed suicide during the course of ECT.

Discussion

■ The sample

The present study deals with a sample of severely depressed suicide. The multi-axial ratings included a diagnosis that was prospectively made. The agreement with DSM IV appears to be high with a minimum of 91% of the patients fulfilling the criteria for major depressive disorder with melancholia or psychoses. The exclusion of secondary depressions enhanced the homogeneity of the sample.

Psychomotor retardation, which was positively related to suicide despite ECT, had been prospectively rated at index admission. Thus we are not certain that the patients were retarded when they received ECT. However, this was a prospective rating, unbiased by knowledge of the suicidal outcome. Ratings of a note in the case-record at last contact would have been more

uncertain. It has further been assumed that psychomotor disturbances constitute a special syndrome and thus may be consistent over time (Parker and Hadzi-Pavlovic 1996).

■ Main findings

We have focussed on patients with a severe depression – (a majority of the patients who were in contact with the Department for what could be considered as their last depressive episode) – that received adequate treatment before they committed suicide –. Literature has given support for the occurrence of suicide despite adequate treatment, be there few or many (Barraclough et al. 1974; Chynoweth et al. 1980; Åsgård 1990; Isacsson et al. 1994a, 1994b; Henriksson et al. 2001; Andersen et al. 2001; Schou and Weeke 1988; Isometsä et al. 1994; Waern et al. 1996).

However, to our knowledge, no previous study has further investigated risk factors for suicide among those who commit suicide despite adequate antidepressant therapy. It is known that only about 70–80% of all depressed patients respond to antidepressant pharmacotherapy (Potter et al. 1991) compared with 35% of all psychotic depressions (Khan et al. 1991). In both groups about 80–90% responded to ECT (Avery and Winokur 1978). The future suicides in the present sample have been shown to be improved as frequently as controls on both types of antidepressant therapy (Brådvik and Berglund 2000). Thus we could not conclude that suicides constitute a treatment-refractory group. We do not know whether recovery was incomplete (leaving depressive symptoms or an urge to commit suicide), whether the patients stopped taking the medication, or there might have been a relapse of depression despite adequate therapy. This needs further exploration. We can only conclude that prescription of pharmacotherapy and initial response does not *always* exclude suicide.

First, psychomotor retardation appeared to be correlated with completed suicide after ECT. This symptom usually responds well to ECT. However, the risk of suicide may remain, or reappear after the relapse of depression in this group of patients despite the good effect on retardation. When patients receive pharmacotherapy for their depression, the relief of psychomotor retardation before the relief of depressive symptoms has been proposed to constitute an increased risk for suicide (Benkert and Hippus 1980; Feuerstein and Jackisch 1986; Damluji and Ferguson 1988). We propose the opposite that when there is a relapse of depression after treatment it is possible that depressed mood may reoccur before psychomotor retardation and constitute a risk factor for suicide after ECT. To our knowledge, no previous study has shown a partial relapse of depression after ECT. This finding needs replication, as the clinical implication is important. ECT has been recommended both for patients with psychomotor retardation (Avery and Winokur 1978) and suicidal feelings (Rasmussen

2003), and response has been shown to be good for both. Therefore one should not be discouraged to give suicidal patients with psychomotor retardation ECT. Rather, continuation treatment with antidepressants or ECT would be recommended in these cases.

Second, there was a low frequency of suicide by intoxication with antidepressants (3%). Other studies have shown somewhat higher frequencies around 8% (Isacsson et al. 1994a, 1994b; Isometsä et al. 1994). Most suicide victims in the present sample used other drugs or violent methods. The antidepressants used for overdose were usually tricyclics. Those are known to be a higher risk due to higher toxicity (Obafunwa and Busuttill 1994a; Shah et al. 2001). Yet, the frequencies were not very high. On the other hand the present study is extended over several decades and during the first period of observation barbiturates were available. Those were not very frequently used for suicide however (6 cases). This fact taken into consideration, antidepressant overdose is still not a major cause of suicide. It is noteworthy that no patient took an antidepressant overdose early in the course of treatment. Thus we could conclude that the risk of misusing antidepressants for a fatal overdose is low in severe depression as well as for depression in general. Today, safer antidepressants are available with lower toxicity and fewer side effects. A low risk of suicide with prescription of tricyclic antidepressants probably indicates an even lower risk with newer antidepressants.

Conclusion

Patients with psychomotor retardation had a higher risk of committing suicide after ECT despite an expected good short-term effect on this symptom. The frequency of suicide by intoxication with antidepressants was low; 3%.

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