

SPECIAL ISSUE

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How should findings on antisuicidal effects of lithium be integrated into practical treatment decisions?

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Abstract Beyond its prophylactic efficacy lithium has demonstrated possibly specific antisuicidal effects. Lithium significantly reduces the high excess mortality of patients with affective disorders. Appropriate lithium prophylaxis prevents ca. 250 suicides per year in Germany although lithium salts are prescribed within the National Health Scheme at low frequency (0.06 % of the population). Rational treatment strategies most likely would demand for about 10 times higher prescription rates. Guidelines and algorithms for selecting an appropriate prophylactic strategy in affective disorders should take into consideration the suicide risk of an individual patient.

Key words lithium · affective disorders · suicide · guidelines · pharmaco-economy · antidepressants

Introduction

The marked excess mortality of affective disorders (Lundquist 1945; Kay and Petterson 1977; Tsuang and Woolson 1978; Weeke 1979) is caused primarily by their possibly 30–70fold higher suicide induced mortality (Hagnell et al. 1981) – which is 100 % higher in patients with a history of suicide attempts (Tuckman and Joungman 1963; Motto 1965). Goodwin and Jamison (1983) found in a detailed survey of studies existing until the time of their publication that 30 % of patients with affective disorders died from suicide. The meta-analysis by Guze and Robins (1970) calculated the life-time suicide risk as 15 % for affective disorders, whereas Goodwin and Jamison (1990) based on more recent literature

reported an overall risk of 19 %. The suicide related “standardized mortality rates” (= SMR; ref. Ahrens et al. 1995a) according to Harris and Barraclough (1998) is 21.24 in major depression, 11.73 in bipolar disorder, and 9.84 in schizophrenia. Some studies found higher rates in bipolar as compared to unipolar patients (Lester 1993; Angst et al. 1998; Bottlender et al. 2000).

Thus, prevention of suicide should be regarded as one of the decisive endpoints for assessing the outcome of long-term treatment in affective disorders. Strong evidence has been accumulated during the last decade that lithium prophylaxis can prevent suicidal acts and reduce the excess mortality of patients with affective disorders. It has been estimated, however, that up to 50 % of patients including even those who suffer multiple relapses and, thus, may bear an increased suicide risk do not receive prophylactic treatment (Solomon et al. 2000). The APA guidelines for the treatment of depressive disorder do not even mention lithium as a prophylactic agent (APA 2000)!

According to a reasonable estimate about 50,000 patients in Germany did receive lithium medication during the year 2001 within the National Health Scheme (Müller-Oerlinghausen and Lohse 2002). Assuming a prevalence of 1 % for bipolar disorders in the population, at least 820,000 patients in Germany would be in need of prophylactic treatment. Most likely lithium salts could be considered as first line treatment for about half of them. The question, then, must be raised whether this discrepancy does not reflect a serious deficit in the quality of psychiatric practice.

The history of studies on the suicide preventive and mortality reducing effect of lithium

Possibly Barraclough (1972) was one of the first investigators postulating a potential association between lithium long-term medication and suicide prevention. He analyzed the charts of 100 suicide victims: 64 patients had a “major depression” of which 44 were

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episodic. Barraclough concluded that about 20 % of the suicides could have been prevented by adequate lithium medication. The first systematic retrospective analysis demonstrating a highly significant reduction of suicide attempts in a sample of high-risk patients during long-term lithium treatment was published by Müller-Oerlinghausen et al. (1992b). The authors emphasized that suicides and suicide attempts occurred nearly exclusively in a group of 13 patients who had taken lithium irregularly or had stopped the medication.

Felber and Kyber (1994) analyzed suicide attempts during accumulated periods on and off lithium: 90 % of the suicide attempts occurred in the off-lithium period.

Several studies on the mortality of affective disorders during lithium long-term treatment by Coppen et al. (1991) and by the International Group for the Study of Lithium-treated Patients (IGSLI; ref. Müller-Oerlinghausen et al. 1992a; Ahrens et al. 1995b) demonstrated that the SMR of patients with affective disorders during adequate lithium medication is normalized down to the level of the general population. This reduction of mortality was observed in bipolar as well as in unipolar patients. Coppen (1994) reviewed the studies existing in the midnineties on the suicide rates in patients on versus off lithium long-term treatment (Table 1). According to Coppen adequate lithium medication reduces the suicide related mortality by 82 %.

The common methodological problem in studies investigating potential effects of a therapeutic intervention on suicide rates is to estimate how many cases of deaths had to be expected in a matched non-treated patient sample. Since it is not possible by ethical reasons to study a control group of patients with affective disorders receiving placebo for many years a reference group of the general population has been used in various studies. Thus, one can calculate the SMR either for any causes of

death or for specific causes such as cardiovascular disease, accident, suicide, etc.

In the IGSLI main study detailed and well-documented data on the course of illness of 827 patients from lithium clinics in Austria, Canada, Denmark, and Germany who had been treated with lithium for at least six months were evaluated (Müller-Oerlinghausen et al. 1992a; Ahrens et al. 1995a). 55 % of the patients were bipolar, 25 % unipolar, 2 % unipolar-manic, 16 % schizoaffective, and 2 % had other diagnoses. At the onset of the lithium prophylaxis patients were 41 years old on average. The mean duration of lithium treatment was 81 months (6–21 years), equalling 5,600 patient years.

The ratio of 44 observed and 38 expected cases of deaths (= SMR) is not statistically different from 1.0, which is the mortality of the general population. Thus, the expected 2–3fold excess mortality in patients with affective disorders does not exist any more in this lithium-treated patient sample (Table 2). Although the specific suicide-related SMR is still higher than in the general population it can be clearly shown that it is definitely lower in all diagnostic groups compared to what could be expected in untreated patient samples (Ahrens et al. 1995).

It could be argued that possibly patients accepting a lithium prophylaxis might generally benefit from a better prognosis in terms of death by suicide. In this case the specific patient selection would have been primarily responsible for the normalization of the SMR. (On the other hand, it can be assumed that patients having an indication for a lithium prophylaxis would suffer from a higher suicide risk due to the higher morbidity.) To study this issue, in a further analysis of 270 German and Danish patients from the original IGSLI sample the initial SMR was compared to the SMR after treatment of more than one year (Müller-Oerlinghausen et al. 1994). During the first year the overall mortality was increased

Table 1 Selection of studies on the course of affective disorders and on suicide rates in patients with lithium long-term treatment (mod. acc. to Coppen 1994)

Authors	Length of studies (years)	Patient-Years	Suicides per 1000 patient years
After discharge from hospital			
Goldacre et al. (1993)	1	6050	10.4
No long-term medication			
Lee and Murray (1988)	16	1296 ^a	6.9
Kiloh et al. (1988)	15	1785 ^a	5.1
Lehmann et al. (1988)	11	948 ^a	11.6
Coppen et al. (1994)	16	330	9.1
Lithium long-term medication			
Coppen (1994)	16	1519	0.7
Nilsson (1995)	20	3911	1.5
Müller-Oerlinghausen et al. (1992a)	7	5603	1.3
Summary of lithium studies			
all patients with lithium long-term medication	7–16	11033	1.3
all patients without lithium long-term medication	11–16	4359	7.3

^a recalculated acc. to the figures of the authors

Table 2 Overall mortality and cause specific mortalities (SMR) of the major diagnostic subgroups

	Unipolar (n = 182) patient years = 1252.40	Bipolar (n = 440) patient years = 3167.88	Schizoaffective (n = 171) patient years = 1030.02	Total (n = 793) patient years = 5450.30
No. of all observed deaths	7	29	8	44
No. of all expected deaths	9.24	23.49	5.13	37.86
Ratio (observed/expected)*	0.76	1.23	1.56	1.16
95% confidence limits	0.25–1.77	0.80–1.82	0.51–3.64	0.75–1.71
No. of observed suicides	0	4	3	7
No. of expected suicides	0.31	0.76	0.23	1.30
Ratio (observed/expected)	–	5.26	13.04	5.38
95% confidence limits	–	1.43–13.48	2.69–38.11	1.75–12.57
No. of observed CVS deaths	2	11	1	14
No. of expected CVS deaths	3.43	9.49	1.93	14.85
Ratio (observed/expected)	0.58	1.16	0.52	0.94
95% confidence limits	0.07–2.11	0.56–2.13	0.01–2.89	0.45–1.73
No. of other observed deaths	5	14	4	23
No. of other expected deaths	5.50	13.24	2.97	21.71
Ratio (observed/expected)	0.91	1.06	1.35	1.06
95% confidence limits	0.30–2.12	0.51–1.94	0.37–3.45	0.65–1.64

CVS cardiovascular system

* = SMR

2fold, and the suicide related mortality 17fold as compared to the general population. The SMR normalized after the first year of treatment indicating that patients with an indication for lithium prophylaxis are in fact patients with a high risk of suicide.

Further studies supported the findings of IGSLI or at least were compatible with them.

Particularly noteworthy is the study by Nilsson (1995): In a different setting (open field, no specialized lithium clinics as in most of the IGSLI centres) she could not observe a full normalization of the SMR. However, as in other studies, reviewed by Schou (1998), she found a rise of the SMR up to the expected level in untreated affective disorders after discontinuation of lithium (ref. Table 3). Further support for the antisuicidal effect of lithium came by studies in a Sardinian patient sample (Tondo et al. 1996) and also by a recent Swedish study (Kallner et al. 2000). The Swedish study is particularly

interesting because it suggests that the suicide preventing effect might be more marked in patients taken care by specialized lithium clinics than in patients treated within routine medical care. A meta-analysis on about 17,000 bipolar patients demonstrated an 8.6fold higher mortality from suicide in patients treated without lithium than in patients during lithium long-term treatment (Tondo et al. 1997). Norton and Whalley (1984) as well as Vestergaard and Aagaard (1991) were not able to demonstrate a reduced mortality in cohorts of lithium-treated patients. However, in both studies the average duration of the lithium treatment was less than in the IGSLI study, and control of compliance might not have been sufficient. For example one third of the deaths having occurred in the study by Vestergaard and Aagaard took place after the patients had discontinued lithium.

Thus, the majority of existing studies suggests a suicide and mortality reducing effect of lithium prophylaxis. However, a few apparently contradictory findings also exist. One of the reasons for this discrepancy might be differences in the therapeutic setting and in duration of treatment. Another reason might be different ways of computing mortality rates. This issue has been studied by re-analysing the data of the IGSLI study using 3 different mathematical approaches (Wolf et al. 1996). It turned out that the “cumulative approach” used by most authors (SMR is calculated as the total number of observed deaths divided by the total number of expected deaths) unfortunately blurs possible effects of treatment duration on mortality. This explains the apparently contradictory findings of Norton and Whalley (1984) or Vestergaard and Aagaard (1991): the observation periods of their patient samples were too small to counteract the distorting effect of the cumulative approach used by these authors. In contrast, the “year-by-year approach” is the scientifically sounder method of calculation demonstrating clearly the normalized mortality of lithium-

Table 3 Standardized mortality ratio (SMR) during lithium treatment and after discontinuation*

Study	During lithium treatment	After discontinuation of lithium
Norton and Whalley (1984)	2.83 ^c	
Coppen et al. (1991)	0.60	
Vestergaard and Aagaard (1991)	4.35 ^a	
Müller-Oerlinghausen et al. (1992a) ^d	0.89	2.54 ^b
Ahrens et al. (1995) ^d	1.14	
Lenz et al. (1994) ^d	0.86	1.8 ^a
Nilsson (1995) ^d	1.8 ^c	3.1 ^c

*By courtesy of M. Schou (1998)

SMR significantly different from 1.0:

^ap < 0.05; ^bp < 0.01; ^cp < 0.001; ^dInternational Group for the Study of Lithium-Treated Patients (IGSLI)

treated patients during practically all treatment periods within an enlarged IGSLI sample.

A reasonable and probably more appropriate method would be survival analysis. However, this approach is hardly feasible because of ethical considerations. By this reason we have to live with some uncertainties about studies on the mortality of manic depressive patients that cannot be overcome.

How specific is the antisuicidal effect of lithium?

Although it has been claimed that the reduction of suicide rates observed recently in various European countries may have been caused by the increased use of modern antidepressive agents (Isacsson et al. 1997; Isacsson 2000), evidence that long-term antidepressant treatment in affective disorders could lower the life-time suicide risk does not exist (Müller-Oerlinghausen and Berghöfer 1999). A preliminary report by Angst et al. pointed to a potential mortality reducing effect of antidepressive treatment; however, many questions regarding details of treatment conditions remain unanswered in this paper (Angst et al. 1998).

A post hoc analysis from a controlled study comparing lithium and carbamazepine in bipolar and schizoaffective disorders over 2.5 years provides strong evidence for the antisuicidal effect of lithium as contrasted to carbamazepine: In the carbamazepine group 4 completed suicides and 5 suicidal acts occurred while in the lithium group no suicidal act was observed (Thies-Flechtner et al. 1996; Greil et al. 1997; Goodwin 1999). Not any comparable data exist for other anticonvulsants used as "mood stabilizers" or for atypical neuroleptics. The only exception is clozapine for which convincing evidence of an antisuicidal effect in schizophrenic patients has been demonstrated (Meltzer 1999).

Although it was postulated by Baldessarini et al. (2001) that the reduction of the suicide risk by lithium prophylaxis is primarily caused by its depression-pre-

ventive effect, other authors pointed to the serotonin-agonistic and antiaggressive effects of lithium. Thus, e.g. Ahrens and Müller-Oerlinghausen (2001) based on a recent re-analysis of data from the IGSLI study suggested that the antisuicidal property of lithium might be rather specific, i.e. it is not shared by other mood stabilizers and does not depend fully on the prevention of depressive episodes.

The intriguing issue of a potential specificity of the lithium effect is going to be clarified in an ongoing double-blind placebo controlled study on the antisuicidal effect of lithium in patients with a history of suicide attempts but without formal indication for long-term lithium prophylaxis, which is conducted within the German Network Depression supported by the Federal Ministry of Research and Technology.

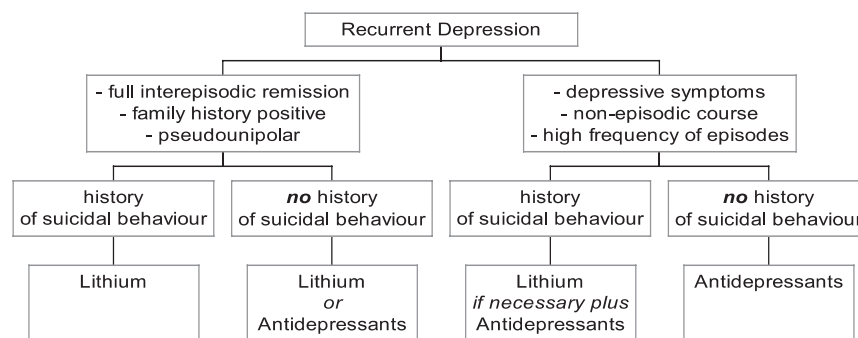
The benefit of lithium prophylaxis in economical terms

Based on data collected within the Epidemiological Catchment Area Study (ECA; Weissman et al. 1991) and the epidemiological data of Weeke (1979) as well as on the assumption that ca. 60 % of all suicides in the population are committed by patients with affective disorders a model for the calculation of deaths and suicides to be expected in the general population and in patients with affective disorders was constructed by Ahrens and Müller-Oerlinghausen (1997). Table 4 shows that for a sample of 827 subjects of the general population (matched with the patients of the IGSLI sample) 1.34 suicides had to be expected whereas in a corresponding sample of patients with affective disorders 31–37, on the average 34 suicides were predicted. In the lithium-treated IGSLI sample 7 suicides were observed, in other words 27 of predicted suicides did not occur. Based on this model we can conclude that 5 suicides/year/thousand treated patients can be prevented. This would result in ca. 250 suicides per year prevented in Germany.

Table 4 Expected and observed cases of deaths and suicides for 827 patients of the main IGSLI sample (see text)

	Expected no. of deaths among a sample of n = 827			Expected no. of suicides among a sample of n = 827		
	males	females	total	males	females	total
General population	19.69	18.74	38.43	0.80	0.54	1.34
Affective disorders (data from ECA)	42.40	25.69	68.09	23.50	7.50	31.00
Affective disorders (data from Weeke 1979)	39.85	34.35	74.20	20.96	16.16	37.12
	Observed no. of deaths among 827 patients			Observed no. of suicides among 827 patients		
	males	females	total	males	females	total
Lithium-treated affective disorders (data from IGSLI)	21	23	44	2	5	7

Fig. 1 Algorithm for prophylaxis in unipolar depressive disorders (Berghöfer et al. 2002)



The IGSLI data also show that the average age of patients having committed suicide was 44. Thus, the gain for the gross national product in Germany would be 3,060 working years before completing the age of 65.

This positive effect adds to the net gain of ca. 110 million EURO per year in Germany caused by lithium prophylaxis within the National Health Scheme, although, as outlined above, the number of lithium-treated patients in this country appears to be very low (Lehmann et al. 1997).

Integrating mortality findings into operationalized treatment decisions

In the treatment of affective disorders the devastating course of illness and the high mortality demands for an effective, long-term, safe and evidence-based strategy. Although the existing findings when applying rigid criteria of evidence-based medicine (i. e. evidence-based on several consistent RCTs) might not prove the antisuicidal effect of lithium (Burgess et al. 2001) the scientific evidence is definitely so strong and above all consistent that its practical implications should enter national and international therapeutic guidelines in the area of affective disorders (ref. Schou 1998).

Consequently, our research group has developed suitable and rational algorithms for selecting an appropriate prophylactic strategy in either unipolar or bipolar disorder (Berghöfer et al. 2002). An example is given in Fig. 1.

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