

Sixteen-year mortality in patients with affective disorder commenced on lithium

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Background Lithium treatment is claimed to reduce mortality in patients with affective disorder, but the evidence is conflicting.

Aim To estimate mortality rates from a cohort of patients with affective disorder commenced on lithium with an observation period of two years and a follow-up after 16 years.

Method The mortality rates of patients were compared with those of the general Danish population, standardised for age, gender and calendar time with respect to death from all causes, suicide and death from cardiovascular disease.

Results Forty of the study's 133 patients died during the 16-year observation period (11 from suicide). Mortality among patients commenced on lithium was twice that of the general population. The statistically significantly elevated mortality was due largely to an excess of suicides; mortality from all other causes was similar to the background populations. Thirty-two patients died after the first two years of observation and were included in the analysis of the association between death and treatment compliance. Suicide occurred more frequently among those patients not complying with treatment.

Conclusion Mortality, especially suicide, was significantly increased in unselected patients with affective disorder commenced on lithium relative to the general population.

Declaration of interest None.

Despite the introduction of modern psychopharmacological treatments, affective disorders are still associated with an excess mortality which stems mainly from a high number of suicides (Godwin & Jamison, 1990). Lithium is the preferred drug for prophylaxis in bipolar affective disorder and is also widely used for prophylaxis in unipolar disorder (Goodwin & Jamison, 1990). Lithium treatment is expected to reduce both morbidity and mortality, especially through its alleged ability to prevent suicide (Schou, 1998). However, the degree to which lithium may reduce mortality in patients with affective disorder is still unsettled. Some investigators have found a considerable excess mortality in spite of prophylactic treatment with lithium (Norton & Whalley, 1984; Vestergaard & Aagaard, 1991; Nilsson, 1995), while others have found lithium to reduce mortality to the level of age- and gender-matched controls (Coppin *et al*, 1991; Müller-Oerlinghausen *et al*, 1992; Lenz *et al*, 1994). We have previously published mortality figures from a naturalistic study in which a cohort of patients with affective disorder commencing prophylactic lithium treatment was observed for five years (Vestergaard & Aagaard, 1991). We now report mortality figures from the same cohort after an observation period of 16 years.

METHOD

All patients from Aarhus county, Denmark, between the ages of 15 and 70 years who commenced prophylactic lithium treatment at the psychiatric hospital in Aarhus between 1 May 1981 and 31 December 1983 participated in the study. The patients were admitted to hospital as a result of manic or depressive episodes; after stabilisation on antipsychotics or antidepressants, but before discharge from hospital, prophylactic lithium treatment was started.

The hospital's criterion for starting lithium prophylaxis in both unipolar and bipolar patients was the occurrence of 2–3 affective disorder episodes in a five-year period.

During their index admission and before the start of prophylactic lithium treatment the patients were examined and interviewed, and laboratory, clinical and socio-medical variables were recorded (Maarbjerg *et al*, 1988; Aagaard *et al*, 1988). Diagnosis of the index episode was established according to the criteria of Feighner *et al* (1972). An overall classification of the disease according to polarity was established from the description of the index episode, from notes concerning past episodes and from the quality of the intervals between episodes. The overall diagnostic classification comprised three subgroups: a unipolar depressed group where at least two depressive episodes and no manic or hypomanic episodes had occurred; a bipolar group where at least one manic episode had occurred; and a group of patients described as atypical because the index episode, although affective, did not fulfil the Feighner criteria or because the course of the illness was atypical.

After a 16-year observation period, date and cause of death for each patient were obtained from the National Registration Office, and death certificates from the Danish Central Death Register were examined. Compliance with lithium treatment during the first two years of prophylactic treatment was chosen as a key predictor variable for the analysis of mortality figures. Compliance was understood as the uninterrupted intake of lithium tablets as prescribed and adherence to the lithium treatment programme.

The two-year compliance period was chosen because this is the period offered for follow-up of patients with affective disorder in the hospital lithium clinic. After two years the patients are advised to continue lithium treatment with their general practitioner.

Statistical analysis

The mortality rates of patients receiving lithium were compared with those of the general Danish population, standardised for age, gender and calendar time (in four periods: 1981–85, 1986–89, 1990–93, 1994–97), with respect to death from all causes, from suicide (ICD-8 E950–E959, ICD-10 X60–X84, Y87.0) and from

Table 1 Characteristics of patients at study entry

Characteristic	Value
Median age (years)	40 (IQR=31–56)
Gender (males/females)	57/76
Patients with bipolar disorder (<i>n</i>)	61
Patients with unipolar disorder (<i>n</i>)	23
Patients with other or unclassified disorder (<i>n</i>)	49
Median duration of illness (years)	6 (IQR=3–13)
Number of previous episodes	1–3: 49%; 4–10: 41%; 11–25: 10%

IQR, interquartile range.

cardiovascular disease (ICD–8 390–458, ICD–10 100–199) (World Health Organization, 1974, 1986). The standardised mortality ratios (SMRs) were supplied with exact 95% confidence limits (Breslow & Day, 1987). On the basis of the first two years' observation, the 125 patients who survived were grouped as either compliant or non-compliant with lithium treatment and the suicide SMRs of these groups were compared as described in Breslow & Day (1987).

Comparison of the time between two-year follow-up and death from any cause between compliant and non-compliant patients was performed by using Cox regression analysis, with adjustments made for age, gender, diagnosis at the start of the study and number of previous episodes. On the basis of Kaplan–Meier plots we also made a crude comparison of time to suicide between compliant and non-compliant patients, using the non-parametric log rank test (Klein & Moeschberger, 1997).

RESULTS

Participant flow

During the study, 158 patients at the psychiatric hospital in Aarhus were put through physical and laboratory examinations before the start of prophylactic lithium treatment. Twenty-five patients were not eligible for inclusion in the study for reasons previously described (Maarbjerg *et al*, 1988). The characteristics of the patients at study entry are shown in Table 1. Forty of the 133 patients who entered the study died during the 16-year observation period (11 from suicide). Thirty-two patients died after the first 24 months of observation and were thus eligible for inclusion in the analysis of the association between death and 24-month compliance with lithium.

Suicide

An autopsy was performed in 11 of the 40 cases of death. The nature of the suicides as

they were described on the death certificate is shown in Table 2, together with the available information about the patients' pattern of lithium intake until the time of their suicides.

Conservative estimates were applied when choices were made between suicide and natural death. No cases of 'other unnatural death' on the death certificate were assigned to the suicides group; neither did the authors suspect that such cases were misclassified by the forensic authorities.

Standardised mortality ratios

Table 3 shows that the standardised mortality ratio among patients who started lithium treatment was elevated for death from all causes. This risk increase, however, was mainly confined to a statistically significantly increased risk for suicide (SMR=20.5). The mortality from all causes other than suicide was slightly increased (SMR = 1.9), and statistically significant only for female patients. The risk of death from cardiovascular disease did not differ from that in the general population.

Seventy-seven (62%) of the 125 patients who survived the first two years of observation were compliant with lithium treatment.

The intervals between two-year follow-up and death from any cause did not differ between compliant and non-compliant patients when compared by Cox regression (risk ratio 0.81, $P=0.56$). This result did not change much when adjusting for age, gender, diagnosis at study start and the number of previous episodes (risk ratio 0.88, $P=0.74$).

Table 2 Characteristics of the 11 cases of suicide among 133 patients with affective disorder commenced on lithium: 16-year follow-up

Case no.	Age (years)	Gender	Number of years until death	Number of years on lithium	Nature of suicide
1	51	F	9	6	Intoxication (ethylene)
2	30	M	7	<1	Jumping in front of train
3	70	F	8	<1	Intoxication (sedatives)
4	49	M	11	4	Intoxication (antipsychotics)
5	32	F	1 ¹	1	Jumping in front of train
6	58	F	6	2	Intoxication (tricyclic antidepressants)
7	24	F	<1 ¹	<1	Drowning
8	50	M	13 ¹	13	Intoxication (carbon monoxide from car exhaust)
9	52	M	4	3	Intoxication (sedatives)
10	70	F	2 ¹	2	Jumping from bridge
11	25	F	3	<1	Drowning

1. In cases where the follow-up period equals the number of years on lithium, the patients presumably took lithium up to the time of death.

Table 3 Causes of death among 133 patients with affective disorder commenced on lithium: 16-year follow up

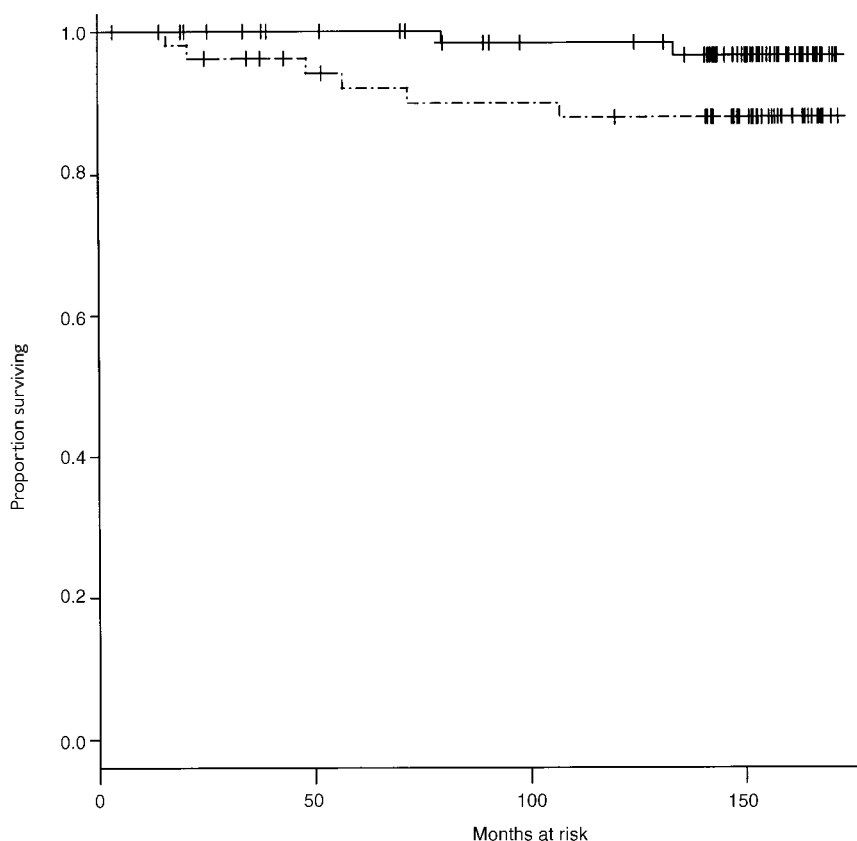
Cause of death	Men			Women			All	
	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	SMR	95% CI
All causes	16	2.42	1.38–3.93	24	2.56	1.64–3.81	2.50	1.79–3.40
Suicide	4	13.38	3.65–34.27	7	29.45	11.84–60.69	20.50	10.23–36.68
Cardiovascular disease	3	1.23	0.25–3.59	4	1.23	0.34–3.15	1.23	0.49–2.53
All causes except suicide	12	1.90	0.98–3.32	17	1.86	1.08–2.98	1.88	1.26–2.69

SMR, standardised mortality ratio.

Table 4 Causes of death among patients with compliant and non-compliant affective disorder with lithium treatment: 16-year follow up

Cause of death after 24 months of treatment	Men			Women			All	
	No. of deaths	SMR	95% CI	No. of deaths	SMR	95% CI	SMR	95% CI
All causes								
Compliant	7	2.72	1.09–5.60	13	2.29	1.22–3.91	2.42	1.48–3.74
Non-compliant	5	1.51	0.49–3.53	7	2.53	1.02–5.22	1.98	1.02–3.46
Suicide								
Compliant	2	16.57	2.01–59.84	0	0.00	0.00–29.42	8.13	0.98–29.35
Non-compliant	2	15.91	1.93–57.46	4	57.58	15.69–147.42	30.74	11.28–66.90

SMR, standardised mortality ratio.

**Fig. 1** Kaplan–Meier estimates of survival from suicide for patients with affective disorder compliant and non-compliant with lithium treatment. —, compliant; - - - - - , non-compliant.

Suicide and patient compliance

Table 4 shows that eight cases of suicide were recorded among the 125 patients who survived the two-year observation period. One of these suicides had bipolar disorder (1.8% of all bipolar disorder patients), another had unipolar disorder (4.4%), and the remaining six (13.3%) were diagnosed as having atypical affective disorders. The suicide risk was almost four times higher among those who were non-compliant with treatment. This finding was only marginally significant ($P=0.06$), presumably because of the limited sample size. However, estimates of suicide SMR were considerably greater than unity among both compliant (SMR 8.1) and non-compliant patients (SMR 30.7). Kaplan–Meier estimates of time to suicide for the compliant and non-compliant groups are shown in Fig. 1; a comparison of time to suicide using the log rank test showed a value of P of 0.06.

DISCUSSION

Mortality among patients with affective disorder commencing prophylactic lithium treatment was more than twice that of the

general population in this naturalistic follow-up study. This result was independent of whether the patients had complied with treatment during the first two years. The statistically significantly elevated mortality was mainly due to an excess of suicides, whereas mortality from all other causes, including cardiovascular disease, only differed slightly from the background population. Hence mortality from cardiovascular disease was in the expected range.

Suicide occurred more frequently among non-compliant than among compliant patients, although the difference reached only marginal statistical significance.

Strengths and limitations of study design

In this study all consecutively admitted patients who started lithium treatment were followed up after 16 years and analysed according to the intent-to-treat principle. The strength of this design is its ability to examine mortality in patients with affective disorder under so-called naturalistic conditions, where different doctors inside and outside hospital participate in the treatment with various degrees of patient compliance, co-medications and changes in the patients' life circumstances. The patients are truly representative of the population of affective disorder patients in a geographically well-defined catchment area with only one psychiatric hospital (to which all patients were admitted) and a fixed number of general practitioners available for their subsequent treatment.

A limitation of the design is the diagnostic heterogeneity of patients – they included both patients with unipolar and bipolar disorder and a considerable number of patients with affective disorder with atypical features (among whom the majority of recorded suicides occurred). This latter group included patients with schizo-affective disorder, bipolar II disorder, mixed episodes and rapid cycling.

Another limitation was the lack of knowledge of how many patients actually continued lithium treatment after the first-two years of observation. Only for 48 of the 93 patients who survived all 16 years of follow-up was adequate information available from case records and from personal and telephone interviews. Among these 48 patients, eight (15%) continued with lithium uninterrupted for the entire follow-up period, while approximately one half

continued with lithium for more than nine years.

For the patients who died, information about lithium treatment is scarce, but it is estimated from case notes that 20–30% were taking it at the time of death. Among the 11 cases of suicide (Table 2), four patients were assumed to be taking lithium at the time of death.

Interpretation of results

The difference in suicide figures between lithium compliant and non-compliant patients could reflect a suicide prophylactic effect of lithium treatment. The association between lithium non-compliance and suicide could, however, also reflect the disposition in a subgroup of affective disorder patients that demonstrate concomitantly non-compliance, suicidal behaviour and misuse of drugs and alcohol without any clear indication of the direction of causation. The association between misuse and non-compliance with lithium treatment has been observed in previous investigations (Vestergaard *et al*, 1998).

The mortality figures illustrate the (lack of) ability of the health care system to protect patients with affective disorder effectively from premature death once prophylactic lithium treatment has been decided upon and initiated and compliance behaviour exercised for two years. The two-year period immediately after the start of prophylactic lithium treatment is a period in which non-compliance is highly expressed. Approximately 40% of the patients discontinued prophylactic treatment in this period (Aagaard & Vestergaard, 1990). It is estimated that after this period only 5–10% of the patients discontinued their treatment each year (Vestergaard & Schou, 1988).

The results in context

Our study supports the results of previous investigations (Norton & Whalley, 1984; Nilsson, 1995) in which mortality in unselected lithium-treated patient groups under so-called naturalistic conditions was found to be significantly elevated compared with the general population. Suicide was the main reason for the elevated mortality figures and was closely associated with lithium non-compliance. Our results may also be compatible with figures from certain lithium clinics in which selected and possibly well-motivated and compliant patients were followed closely (Coppen *et al*,

1991; Müller-Oerlinghausen *et al*, 1992; Lenz *et al*, 1994). Mortality among these patients was found not to be different from that of the general population. However, our study highlights the possibility that the results from these studies may give an unduly optimistic outlook regarding the mortality-reducing effect of the lithium treatment modality in daily clinical routine. These results may merely reflect the preferential admission of patients with good prognoses to specialised facilities where less motivated, non-compliant and non-responding patients are not admitted or gradually expelled.

Implications for treatment

Mortality is increased for most or all major psychiatric disorders, including affective disorders (Hansen *et al*, 1997). This was so before the era of modern psychopharmacology and is apparently still the case in Western societies, where a considerable part of the population receives treatment with psychoactive drugs. Lithium in conjunction with other psychotropic drugs, psychotherapy and psychosocial measures may be able to reduce mortality in some patients with affective disorder. It remains to be elucidated, for patients who are not compliant with lithium treatment and non-responding affective disorder patients, to what extent more precise diagnostic subgrouping, new treatments with anticonvulsants and atypical antipsychotics and the establishment of lithium clinics or mood disorder clinics will enhance compliance and reduce mortality.

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CLINICAL IMPLICATIONS

- Under naturalistic conditions prophylactic lithium treatment may not reduce the mortality of patients with affective disorder to the level of the general population.
- Death from suicide is especially common among patients with affective disorder despite attempts to implement prophylactic lithium treatment.
- Patients not compliant with lithium treatment appear to have a higher risk of suicide than those compliant with the treatment.

LIMITATIONS

- The group of patients with affective disorders was studied under naturalistic conditions with a low degree of compliance.
- The patient group was diagnostically heterogeneous.
- For all patients, records of compliance were available only for the two initial treatment years.

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