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A feasibility and tolerability study of lithium in Alzheimer's disease

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SUMMARY

Objective To assess the safety and feasibility of prescribing long term lithium to elderly people with mild to moderate Alzheimer's disease (AD).

Methods An open label treatment group with low dose lithium for up to 1 year with the Lithium Side Effects Rating Scale as the primary outcome measure. A comparison group matched for cognition and age not receiving lithium therapy.

Results Twenty-two people with AD initiated lithium. Fourteen participants discontinued therapy after a mean of 16 weeks of treatment compared to the 39 weeks for those continuing to take treatment at the end of the study. Three patients discontinued treatment due to possible side effects that abated on ceasing therapy. The reports of side effects on the primary outcome scale did not differ between those discontinuing therapy and those remaining in the study. Two patients died whilst receiving lithium—in neither case was the treatment felt to be related to cause of death. There was no difference in deaths, drop outs or change in MMSE between those receiving lithium and the comparison group.

Conclusions Lithium treatment in elderly people with AD has relatively few side effects and those that were apparently due to treatment were mild and reversible. Nonetheless discontinuation rates are high. The use of lithium as a potential disease modification therapy in AD should be explored further but is not without problems.

KEY WORDS — Alzheimer's disease; lithium; trial; GSK-3; disease modifying

INTRODUCTION

Alzheimer's disease (AD) is the commonest of the dementias that together affect over 24 million people worldwide (Ferri *et al*., 2005). Although there are currently no disease modifying therapies, advances in understanding of the molecular pathogenesis have identified two key therapeutic targets. The first of these is amyloid, the peptide that aggregates in the neuritic plaque and a variety of compounds designed to modify the generation, aggregation or clearance of amyloid are in development. An alternative potential therapeutic target in AD is the neurofibrillary tangle, formed from aggregated and phosphorylated tau protein. One approach to this therapeutic target would be to reduce the phosphorylation of tau through inhibition of the relevant kinase.

Whilst many kinases can phosphorylate tau in vitro, increasing evidence suggests that glycogen synthase kinase-3 (GSK-3) is the predominant tau-kinase in brain [reviewed in (Mudher and Lovestone, 2002; Bhat *et al*., 2004a)] and GSK-3 levels and activity are altered in people with AD (Hye *et al*., 2005) and in neurons affected by AD pathology (Pei *et al*., 1999). Moreover, over-expression of GSK-3 in mice induces neurodegeneration (Lucas *et al*., 2001; Hernandez *et al*., 2002) and over-expression of GSK-3 in Drosophila induces aggregation of tau into tangles similar to those of AD (Jackson *et al*., 2002). Inhibition of GSK-3 activity restores neuronal function in both mouse (Noble *et al*., 2005; Hooper *et al*., 2007;

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Rockenstein *et al*., 2007) and fly (Mudher *et al*., 2004) models of neurodegeneration making GSK-3 inhibition a key goal in AD therapeutic research (Huang and Klein, 2006; Mazanetz and Fischer, 2007).

Although specific and potent GSK-3 inhibitors have been developed, one drug commonly used in psychiatry, lithium, is also a GSK-3 inhibitor (Jope, 2003). The therapeutic range for lithium in man is 0–5–1.5 mM and lithium has a Ki for GSK-3 of 2 mM suggesting that partial GSK-3 inhibition is likely to be achieved during therapy. Effects of lithium on tau can be measured in a dose-response manner to levels as low as 0.1 mM (Leroy *et al*., 2000) in vitro and within the normal therapeutic range (0.6 mM) in mouse models of tau-induced neurodegeneration (Noble *et al*., 2005). Indeed lithium might prevent the progression from amyloid-related pathology to neurodegeneration as pre-treatment of both rats and rabbits with lithium prevented neurotoxicity associated with intra-cerebral amyloid injection (De Ferrari *et al*., 2003; Ghribi *et al*., 2003).

These data have prompted the suggestion that lithium might be a potential disease modifying therapy for AD (Bhat *et al*., 2004b; Aghdam and Barger, 2007). However, if lithium modifies disease progression in AD then it might be expected that long-term lithium users would be at lower risk of AD. Three studies have examined this, with confusing results. Terao *et al*. (2006) found that psychiatric care patients who had ever taken lithium had a higher MMSE score than those who had never taken lithium. In line with this finding, Nunes *et al*. (2007) found lower rates of dementia in patients with bipolar disorder treated with lithium than in those treated with other mood-stabilisers. However, Dunn *et al*. (2005) found a slight increase in risk of dementia in those taking lithium in a large primary care database. Confounding issues constraining such analyses, and perhaps contributing to contrasting results, include the fact that depression is both a risk factor for AD and an indication for lithium therapy, and that lithium therapy is often discontinued in late life. It is difficult to see how these obstacles could be overcome in an observational study of any size.

In summary the evidence that GSK-3 phosphorylation of tau precedes and promotes tangle formation and loss of neuronal function is strong and the evidence that lithium inhibits GSK-3 function at therapeutic levels overwhelming. Together these data suggest lithium as a therapeutic strategy. Disease modification trials in AD are typically more than 12 months in duration and chronic treatment for any successful drugs inevitable. However, lithium has a narrow therapeutic window and known neurotoxic and other side effects, especially in the elderly. Furthermore, an extended period of dose-finding and stabilisation is necessary and even when stabilised, patients require regular monitoring of serum lithium levels. Interactions with many other drugs often prescribed for the elderly have been reported. All of these factors might limit the usefulness of lithium in AD, especially in the frail and elderly and in those with other co-existing illness. We therefore conducted a pilot study assessing the feasibility and tolerability of lithium carbonate at therapeutic levels in mild to moderate AD over an extended period. This pilot study was an open label, pragmatic and observational study of a series of patients treated for up to 1 year with low dose lithium. Our aims were to assess the ability of patients with mild to moderate AD to tolerate lithium therapy and to assess the frequency of adverse effects.

METHOD

Protocol

The trial was an open label pragmatic trial of up to 1 year for a maximum of 25 subjects with mild to moderate AD. Three phases of the trial were planned—screening, stabilisation and treatment. All subjects thought by Mental Health of Older Adults clinical teams in the South London and Maudsley NHS Trust to have mild to moderate dementia were eligible for screening. In total 480 subjects were screened for inclusion by examination of case notes and preliminary discussion with carers. Those included in the trial were assessed at baseline with a clinical examination together with scales to assess cognition [Mini Mental State examination; MMSE; Folstein *et al*. (1975) and Alzheimer's Disease Assessment Scale—cognitive section; ADAS-cog; Rosen *et al*. (1984)], function [Bayer Activities of Daily Living Scale; Hindmarch *et al*. (1998)], behaviour [Neuropsychiatric Inventory; NPI; Cummings *et al*. (1994)] and global deterioration [Global Deterioration Scale; GDS; Reisberg *et al*. (1982)]. In addition, all patients had an ECG and an adapted Lithium Side Effects Rating Scale (LISER; Haddad *et al*. (1999)]. The LISER is designed as a self-rating scale and in this instance the questions were addressed by the researcher to the informant.

Patients meeting inclusion criteria were commenced on low dose lithium carbonate (100 mg) and were then assessed fortnightly with lithium dose adjusted according to serum levels aiming to reach a steady

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Table 1. Plan of investigations

Assessment	Baseline	Weekly to stabilisation	Month 1	2	3	4	5	6	7	8	9	10	11	End of trial
Clinical assessment	x	x	x	x	x	x	x	x	x	x	x	x	x	x
ECG	x													
NINCDS-ADRDA diagnosis	x													
Hachinski scale	x													
MMSE	x		x					x						x
ADAS-cog	x				x						x			x
CERAD battery	x			x										x
CANTAB-PAL	x					x					x			x
NPI	x						x					x		
GDS	x				x			x			x			x
Bayer	x								x					x
Lithium Side effects scale		x	x	x	x	x	x	x	x	x	x	x	x	x
Lithium levels		x	x	x	x	x	x	x	x	x	x	x	x	x
Renal/thyroid function	x	x	x	x	x	x	x	x	x	x	x	x	x	x

state of between 0.3 and 0.8 mM. Once stabilised assessments were made monthly according to the protocol shown in Table 1. In all cases a final assessment was attempted 1 year after inclusion into the trial.

The primary outcome measure was the Lithium Side Effects Scale and any other reported adverse events or drop-out from the trial. Secondary outcomes included change in cognition (MMSE) or function (Bayer).

Subjects

We recruited patients with a diagnosis of probable or possible NINCDS-ADRDA AD, of mild to moderate severity (MMSE range 12–24) from a large mental health NHS Trust and a memory clinic in a local acute general hospital. Exclusion criteria were age less than 60 years, evidence of another neurodegenerative disorder or physical illness that would explain the cognitive impairment, contraindications to lithium therapy (e.g. significant renal impairment or thyroid disease), recent stroke and lack of frequent carer contact. Those treated with anti-dementia medication were not excluded, nor were residents in care homes. Patients with capacity gave consent following a discussion of the trial after which they were given an information sheet and a period of reflection. Capacity was considered to be present if the potential participant could understand the nature of the trial, use this information to consider whether they wished to participate, retain the information for a period and then discuss with the assessor the nature of the trial, including the pros and cons of participating. In those subjects where capacity was considered to be impaired, and also in those who were able to consent, assent was also sought from their closest relative.

Ethical approval was granted by the Joint South London and Maudsley and the Institute of Psychiatry NHS Research Ethics Committee. The procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration of 1975, as revised in 1983.

Comparison group

In order to assess the secondary, cognitive, outcome all trial participants were matched to patients with AD enrolled in an ongoing study of biomarkers at the IoP. This study, previously reported (see Hye *et al*., 2006; Ellul *et al*., 2007), includes approximately 300 people with AD, all of whom are assessed using a very similar clinical assessment process and all of whom are recruited through an identical process from the same NHS Trust. Matching was performed blind to trial outcome on a consecutive basis from the cohort register selecting comparison subjects similar to trial subjects in age (+/− 5 years) and baseline MMSE (+/−2 points). In all other respects the inclusion and exclusion criteria were the same as for the trial subjects—those treated with anti-dementia medication were not excluded, nor were residents in care homes. For each trial participant two comparison subjects were identified. Progression of MMSE after 1 year and continuation in the cohort study was recorded.

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RESULTS

Recruitment

We initially assessed the proportion of patients in a typical Old Age Psychiatry service likely to be entered into a lithium trial. During this process we screened over 450 patients with dementia referred to the trial from the service. Over 35% failed to meet the entry criteria—either because the diagnosis of AD was questionable or because the MMSE was not in the entry range. A large proportion (17%) declined to take part in such a trial, often because of the frequency of assessments and the need for regular venepuncture, especially during the stabilisation phase, and in a further 10% were considered after assessment to be unlikely to comply with the trial procedures. A significant proportion (13%) had either a concurrent illness or therapy that contraindicated treatment with lithium. We aimed to recruit 25 patients with AD for lithium therapy.

Between December 2004 and March 2006 41 patients were identified at the screening interview as meeting trial entry criteria and 22 patients were commenced on therapy. Of those not actually entering the trial nine (47%) were found to have contra-indicated therapies or concurrent illnesses between screening and trial commencement or there was evidence suggesting non-compliance (such as with prescribed medication). The CONSORT diagram is shown in Figure 1. Of the 22 patients entering the trial, eight patients either completed the full year of therapy or were still receiving therapy at the end of the study (July 2006). The characteristics of the sample at the stages of attrition are presented in Table 2.

Side effects and withdrawal

The mean time on trial for those not completing the trial was 16.7 weeks (SD 13.8 range 1day–38 weeks) and for those completing the trial 39 weeks (SD 14.3, range 21–55 weeks). Overall the average length of treatment was 25 weeks (SD 18.4) and the trial represents a total of 549 patient weeks of therapy.

The primary outcomes for the trial were adverse events as reported by patients and carers and as recorded by the Lithium Side Effects Scale. Two patients died whilst receiving lithium. In one, the cause of death was recorded as 'Respiratory failure, pulmonary arterial thromboemboli, chronic obstructive airways disease and pulmonary oedema' and the

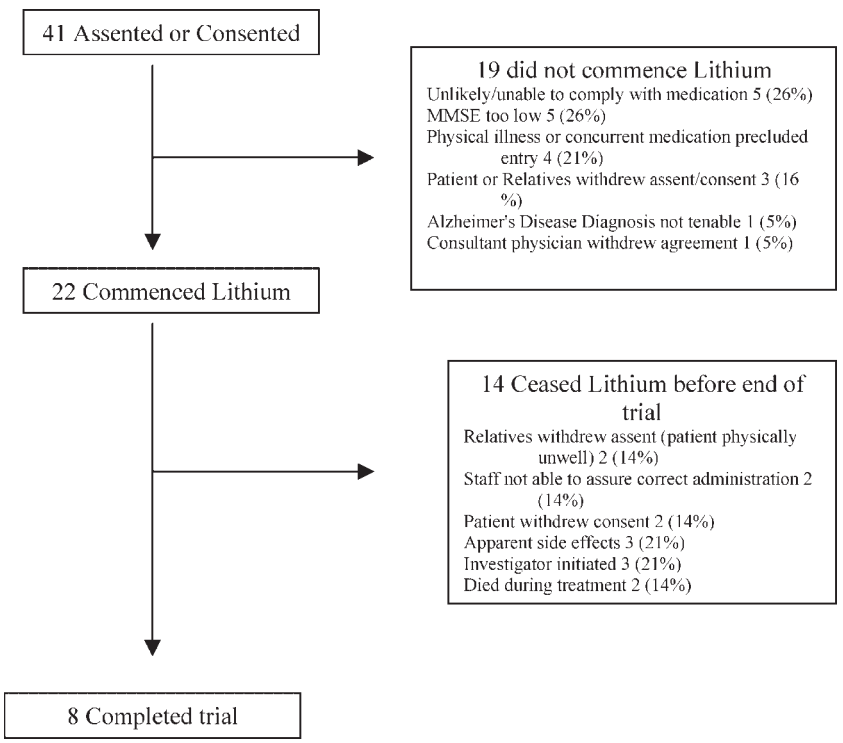

Figure 1. Consort diagram.

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Table 2. Characteristics of patients who were referred, assented/consented, commenced lithium, discontinued or completed trial

	Referred	Assented/consented	Commenced Lithium	Ceased Lithium or died during study	Still taking Lithium at 1 year or termination of trial
N	480	41	22	14	8
Mean age [SD]	81.1 [7.3]	81.0 [7.4]	80.9 [7.9]	83.4 [6.7]	76.6 [8.3]
No female (% of group)	307 (64%)	28 (69%)	13 (59%)	10 (71%)	3 (38%)
Mean years of education [SD]	—	10.7 [4.3]	11.4 [5.3]	11.8 [6.4]	10.8 [3.8]
Baseline:					
Mean Hachinski Score [SD]	—	—	1.6 [1.2]	2 [1.1]	0.8 [0.9]
Mean MMSE score [SD]	—	17.4 [5.4]	17.1 [3.5]	16.4 [2.8]	18.5 [4.3]
mean ADAS-COG score [SD]	—	—	29.5 [10.8]	33.9 [11.5]	25.1 [8.5]
Total CERAD Score [SD]	—	—	30.3 [11.6]	24.2 [11.8]	37.8 [6.1]
mean NPI score [SD]	—	—	10.2 [16.0]	11.5 [19.2]	8.3 [10.4]
mean GDS score [SD]	—	—	2.5 [1.6]	2.5 [1.8]	2.4 [1.5]
Mean Bayer ADL Score [SD]	—	—	7.3 [1.8]	8.0 [1.3]	6.2 [2.0]
Lithium Side Effects Scale (final assessment)	—	—	55.1 [7.6]	56.7 [9.3]	58.0 [9.8]
Number achieving therapeutic level (mean days from commencement [SD])	—	—	14 (35.5 [22. 0])	6 (23.7 [13.3])	8 (44.5[23.7])
Mean time on lithium (weeks) [SD; range]	—	—	25 [18.04; 0.1–55]	16.7 [13.8; 0.1–39]	39.4 [14.3; 21–55]
Mean lithium level (SD; Range)			0.40 (0.14; 0.19–0.99)	0.40 (0.18; 0.19–0.99)	0.40 (0.05; 0.37–0.49)
No with below therapeutic level at any time after initial achievement	—	—	3	1	2

other 'Cerebrovascular accident and pneumonia'. In neither case was it considered likely that lithium treatment played a part in the death.

Of the remaining 12 patients who were withdrawn from the trial this was due to probable side effects in two patients, whose adverse symptoms abated when lithium was stopped (including one whose lithium levels were below the therapeutic range). Adverse effects included tremor and increased confusion confirmed on cognitive testing. One patient was withdrawn from therapy after being admitted to hospital with a fall. On admission she had a lithium level of 0.99 mM. Relatives requested removal of treatment in two cases, and patients in a further two, although in one case the reason was unclear and in others the reported symptoms were unlikely to be related to lithium treatment. Reasons included a possible increased confusion that was not evidenced on cognitive testing, a concern about a change in skin colour and a sensation of 'wobbly legs'. In two cases staff in the hospital or care home were unable to guarantee regular and accurate administration of lithium. In three patients the investigator withdrew the patient from the study. In one of these, the GP started a thiazide diuretic and did not wish to use an alternative, another patient became acutely ill with Clostridium difficile gastroenteritis, and in another it became impossible to obtain blood samples for lithium levels.

We analysed the results of the lithium side effects scale in three ways—by the mean for each participant across all assessment points in the study, by the score at the final assessment point and by the highest score on the scale reached by each participant at any time point. In those commencing lithium the mean lithium side effects scale score across the duration of the trial was 57.3 (SD 9.2) in those who withdrew or died and 55.8 (SD 4.3) in those who completed the trial. The mean final score on the scale was 56.7 (S.D. 9.3) in those who withdrew and 58.0 (SD 9.8) in those completed (Table 2). The mean highest score on the lithium side effect scale achieved during the trial was 58.0 (SD 9.3) in those who withdrew and 59.6 (SD 6.8) in those who completed. There was no significant difference in this scale however aggregated between those who completed and those who did not.

The secondary outcome measures were functional and cognitive measures. There was no correlation of either the MMSE or the Bayer functional scale with either mean lithium level achieved or with weeks on therapy. In order to explore further the change in cognition over the course of the study, subjects receiving lithium were compared to a comparison group (1:2 matching) identified and assessed using a

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near-identical protocol and recruited from the same source by the same research group. Comparison subjects were matched by initial MMSE (mean trial MMSE 17.1; mean comparison MMSE 17.1) and by age (mean trial 80.9 years; mean comparison 81.2 years). There were three deaths over the course of one year in the comparison group and two in the trial group. In the trial group 16 (73%) participants remained available for assessment 1 year after entry into trial. In the comparison group 37 (84%) remained available for assessment. Neither deaths nor drop outs significantly differed between trial and comparison groups. The mean change in MMSE over 1 year in the trial group was 4.8 points (SD 5.5) which was not significantly different to the mean change in the comparison group [4.0 (SD 5.0) points].

DISCUSSION

The convergence of in vitro and in vivo evidence together with some, but not all, clinical studies suggesting that lithium might have disease modification utility in AD has excited considerable interest. However, lithium is a complex molecule with many cellular effects beyond the inhibition of GSK-3 including both neurotoxic and neuroprotective properties in vitro and also in vivo. A systematic review of studies of long term treatment suggested that the data was conflicting regarding the potential toxicity of lithium although it was concluded that it is likely that there are relatively rare neurotoxic events even within the therapeutic range (Fountoulakis *et al*., 2007). A large and long term community study of people taking medication for bipolar disorder found no difference in the incidence of delirium in those receiving lithium compared to those on valproate, suggesting that concerns about neurotoxicity might be exaggerated (Shulman *et al*., 2005) and in line with this in a study of non-suicide mortality in people with bipolar disorder lithium was actually a protective factor (Tsai *et al*., 2005). The neuroprotective effects of lithium have only become apparent more recently. In cellular studies lithium has significant neuroprotective and neurotrophic effects (reviewed in (Chuang and Manji, 2007)) and in man lithium has been reported to increase grey matter and hippocampal volume (Moore *et al*., 2000; Bearden *et a*l., 2007a, 2007b).

Although the evidence for neurotoxicity with chronic lithium treatment is not straightforward, and there is some evidence for neuroprotection, it is clear that lithium is highly toxic above a relatively narrow therapeutic window. Variance from the therapeutic window and side effects may be greater in frail elderly people because of co-morbid disease, interacting co- prescribed drugs and a higher incidence of dehydration. In the elderly in particular lithium has been reported to be associated with a wide range of adverse effects, including but not limited to diabetes insipidus (Mukhopadhyay *et al*., 2001), thyroid toxicity (Oakley *et al*., 2000), cardiac toxicity (Oudit *et al*., 2007), calcium-related and other biochemical abnormalities (Wolf *et al*., 1997) and adverse effects resulting from drug interactions. Prescribing lithium places demands on patients and services and necessitates regular venepuncture for lithium level monitoring. All of these factors are likely to be exacerbated in the elderly with dementia.

Because of these potential limitations to prescribing lithium to people with dementia we have performed a long-term feasibility and practicability study of lithium in AD. We did not perform a full randomised control trial as we, and peer reviewers, felt this was premature until further data on the acceptability and safety of lithium to this patient population was obtained. We did, however, include a comparison group, recruited using identical methods from the same base population. Future trials of lithium and other potentially disease modifying drugs will be challenging but consensus approaches to trial design in this area are emerging (Vellas *et al*., 2007)

We screened a large number of potential recruits for inclusion in the trial. This is routine for all study recruitment but rarely reported and so we cannot compare recruitment to this trial to other trials. However we note that a significant proportion (13%) of the elderly with AD in this population had contraindications to taking lithium—most frequently the prescription of thiazide diuretics. Despite this we recruited 22 people who were prescribed lithium for a mean of 25 weeks.

There were two deaths during the course of the trial neither of which were thought to be related to the study. Over the course of the year in the comparison group there were a similar number of deaths. There was, however, a high drop out from the trial—a total of 12 were withdrawn for various reasons. Of these only three were withdrawn because of probable side effects that abated after stopping lithium. It is noteworthy that one of these had a lithium level below the therapeutic range demonstrating that lithium side effects can occur at very low serum levels. There were no differences in the lithium side effects scale between those withdrawing and those continuing. Although not significant, we note that there was a trend towards older age in those not completing the trial. This is not unexpected as other events, unrelated to the trial,

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resulting in withdrawl are more likely in older people but also may indicate the particular problems of prescribing long term lithium to older and frailer people. We encountered no serious adverse events and no irreversible events. These data confirm that lithium does have adverse effects in some people within and indeed below the known therapeutic window. However, side effects appear relatively mild and side effects likely to be due to lithium were not the primary cause of withdrawing from the study in the majority of cases.

We did not set out to do an efficacy study and the data on function and on cognition is only indicative. However, we observed no effects of lithium on either when correlating with time on lithium or with mean lithium levels after achieving stability. Nor did we observe a difference in cognitive progression on the MMSE between the study participants and a comparison group.

CONCLUSIONS

In conclusion we successfully recruited to a trial of lithium in AD and treated these people with AD for a considerable period. Relatively few adverse effects clearly attributable to lithium were encountered. However, significant numbers of our base population have contraindications to lithium and discontinuation from the trial was high. These factors together with the occurrence of some adverse effects and the risk of serious toxicity may limit the potential use of lithium in AD.

CONFLICT OF INTEREST

KCL has intellectual property interests in biomarkers for use in trials relevant to this work. SL has provided consultancy to companies developing disease modifying therapies for AD.

KEY POINTS

- Evidence suggests GSK-3 inhibitors, including lithium, as potential disease modifying therapies for AD although concerns have been expressed regarding safety.
- In this study we found that many people with late onset AD have contraindications to lithium or are non-compliant with medication or drop out of treatment for some other reason.
- However, despite this we found that lithium can be safely prescribed to people with late onset AD.

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