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REVIEW ARTICLE

Lamotrigine therapy in elderly patients with epilepsy, bipolar disorder or dementia

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SUMMARY

Introduction In spite of circumstances that precipitate high use of anticonvulsants in geriatric populations, there is a paucity of data on the use of antiepileptic drugs in elderly patients with psychiatric and neurological disorders.
Methods Reports of lamotrigine therapy in elderly patients with epilepsy, bipolar disorder (BD), or dementia were identified by conducting an electronic search of major publication databases. Abstracts and presentations from professional meetings were searched as were the bibliographies of relevant articles.
Results Fourteen reports were identified, and included well-controlled prospective trials, retrospective analyses, and case reports of lamotrigine treatment. Controlled trials in elderly patients with epilepsy demonstrate efficacy and tolerability comparable to gabapentin. Improvement in bipolar depressive symptoms, improvement in core manic symptoms, and delay in mood relapse was reported in geriatric patients with BD. Preliminary case studies in patients with dementia note improvement in cognition and symptoms of agitation and depression.
Conclusion Review of the available literature suggests lamotrigine is effective and well tolerated in elderly patients with epilepsy and relatively well-tolerated and may be effective in delaying mood relapse, particularly in the depressive pole, in patients with BD. While very limited literature suggests that lamotrigine may be effective and relatively well-tolerated in patients with dementia, further studies are needed. Copyright © 2007 John Wiley & Sons, Ltd.

KEY WORDS — lamotrigine; anticonvulsant; bipolar disorder; dementia; epilepsy; seizures

INTRODUCTION

The number of people older than 65 years of age is increasing (CDC, 2003) and those with psychiatric disorders in the United States will increase from about 4 million in 1970 to 15 million in 2030 (Jeste *et al*., 1999). Available treatment guidelines do not provide specific recommendations for treatment of older adults with BD (Van Gerpen *et al*., 1999; Sajatovic, 2002a) and it is common for health services studies in BD to focus on younger populations (Russo *et al*., 2002). Anticonvulsant medications have supplemented the use of lithium therapy in older adults with BD (Shulman *et al*., 2003); while specifics regarding use remain to be clarified (Sajatovic, 2002b; Charney *et al*., 2003).

Dementia is most prevalent in people ≥65 year of age (Regier *et al*., 1988). Non-cognitive symptoms, such as agitation, often result in need for nursing home care where agents are used but safety concerns may limit their use. Benzodiazepines are associated with hip fractures in older populations (Wagner *et al*., 2004; Allain *et al*., 2005) and recent reports identified increased risk of fatalities associated with typical and atypical antipsychotics (FDA, 2005; Schneider *et al*., 2005; Wang *et al*., 2005).

Seizure disorder is common among the elderly with approximately 25% of new diagnoses occurring in individuals over 60 years of age (Tallis *et al*., 1991;

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Hauser, 1992; Sander and Shorvon, 1996). Older adults are prescribed more anticonvulsant medication than all other adult age groups (Cloyd *et al*., 1994; Lackner *et al*., 1998; Lackner, 2002; Garrard *et al*., 2003).

As the body ages, the balance between clinical effect and drug toxicity represents a distinct clinical challenge (Willmore, 2000). Treatment of the elderly is complicated by co-morbid medical conditions, use of multiple medications, and lack of adherence (Rollason and Vogt, 2003).

Lamotrigine is a novel anticonvulsant currently approved by the FDA to treat epilepsy and bipolar disorder. Lamotrigine is predominantly metabolized by glucuronidation. Data suggest that while the elimination of lamotrigine can be affected by increasing age, disposition is more directly impacted by concurrent antiepileptic drug therapy (Posner *et al*., 1991; Battino *et al*., 1997). Lamotrigine plasma concentration/dose ratios are significantly increased in patients receiving valproate (an enzyme inhibitor of glucuronidation) and decreased in those on glucuronidation enzyme-inducing antiepileptic drugs (carbamazepine or phenytoin), (Battino *et al*., 1997; Chan *et al*., 2001).

The aim of this analysis was to evaluate the published data on the use of lamotrigine in elderly patients with psychiatric and neurological disorders.

METHODS

The authors identified potential reports via an electronic search of PubMed, Ovid, and Searchlight up to November, 2005. Abstracts and presentations from professional meetings were searched as were the bibliographies of relevant articles. Search terms included: elderly, lamotrigine, epilepsy, antiepileptic, anticonvulsant, dementia, and bipolar disorder. The search was confined to reports in English and included patients ($\geq$55 years of age).

REVIEW OF CLINICAL DATA

Epilepsy

Table 1 summarizes randomized, controlled reports of lamotrigine therapy in elderly patients with epilepsy.

Rowan *et al*. (2005) reported the results of a double-blind trial of elderly subjects with newly diagnosed seizures randomized to monotherapy with either gabapentin 1,500 mg/day, carbamazepine 600 mg/day, or lamotrigine 150 mg/day for 12 months followed by an optional 12-month treatment period. Significantly more patients receiving carbamazepine discontinued (64.5%) compared to the either the gabapentin (51%) or lamotrigine (44.2%) groups. Significantly fewer subjects receiving lamotrigine (12.1%) discontinued the study due to adverse events versus either gabapentin (21.6%) or carbamazepine (31%) groups. Significantly more patients receiving gabapentin experienced weight gain during the first 12 months than the carbamazepine or lamotrigine groups. More patients receiving lamotrigine lost weight than patients receiving gabapentin. Rash occurred significantly more frequently with carbamazepine than with lamotrigine. There were 39 deaths in the trial; however, none were considered drug-related.

In a 24-week, double-blind study, Brodie *et al*. (1999) randomized elderly patients with newly diagnosed epilepsy to treatment with either lamotrigine or carbamazepine. Significantly more patients receiving lamotrigine remained in treatment than in the carbamazepine group (71% *vs* 42%, respectively). Significantly fewer patients withdrew due to rash (3% *vs* 19% for lamotrigine *vs* carbamazepine, respectively).

Giorgi *et al*. (2001) examined pooled data from 13 clinical trials conducted in elderly patients. The incidences of drug-related adverse events were 49% (72/146) for lamotrigine, 72% (38/53) for carbamazepine, and 89% (8/9) for phenytoin. Significantly fewer lamotrigine patients withdrew from treatment due to adverse events than those who received carbamazepine (18% *vs* 34%). Withdrawal due to rash was 6% for lamotrigine and 17% for carbamazepine. There were five deaths reported in the trials; none were attributed to study drug.

A 1-year, prospective, observational trial of lamotrigine monotherapy was conducted by Mauri Llerda *et al*. (2005). At the end of 12 months, 55% of subjects remained in the trial. Eighty-nine percent of these patients remained seizure free and approximately 75% of subjects were able to be maintained on lamotrigine monotherapy. Adverse events included dizziness, rash, trembling, and gastrointestinal discomfort.

Kustra *et al*. (2002) reported a retrospective analysis of 62 elderly patients in an open-label study. Following 16 weeks of adjunctive therapy with lamotrigine, eligible patients who also took an enzyme-inducing antiepileptic drug began a 12 week monotherapy phase. Significant seizure reduction was noted. Seizure free rates were 64% and 52% in the monotherapy and adjunctive phases, respectively.

Nieto-Barrera *et al*. (2001) evaluated monotherapy with lamotrigine or carbamazepine in a sub-set of 49 patients over 65 years of age participating in a 24-week trial ($n = 417$). There were fewer withdrawals due to adverse events with lamotrigine (7/35,

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Table 1. Published randomized, controlled trials (RCTs) of lamotrigine *vs* comparator agents in elderly patients with epilepsy and healthy volunteers

Reference	Study design	Inclusion criteria	Drugs studied	No. of patients	Dose (mg/day)	Efficacy results	Safety results
Rowan *et al*., 2005	DB-RCCT	Epilepsy Pts.	LTG	200	152 ± 33*	62%	12.1% d/c due to AEs
	Parallel	≥60 years NOSz*	GPN	195	1,422 ± 288*	52%	21.6% d/c due to AEs
			CBZ	198	582 ± 218*	38%	31.0% d/c due to AEs More weight gain reported with GPN than LTG More rash reported with CBZ than LTG
Brodie *et al*. 1999	DB-RCCT	Epilepsy Pts.	LTG	102	100†	71% ,	Rash -LTG 3% *vs* CBZ 19%;
	Parallel	≥65 years NOSz	CBZ	48	400†	42%	95% CI: 7–25%
Sinclair *et al*., 2000	DB-RCCT	Healthy Volunteers	LTG	50	300‡	Not Applicable	CBZ-Significantly higher withdrawal from study and incidence of AEs.
	Cross-over	68.4 years*	CBZ		800‡		

CBZ = carbamazepine; CI = Confidence Interval; DB = double-blind; d/c = discontinued; GPN = gabapentin; LTG = lamotrigine; NOSz = New Onset seizure; RCCT = randomized controlled clinical trial.
*Mean.
†Median.
‡Target.

20%) compared to carbamazepine (7/14, 50%). There was a higher percentage of rash reported in the carbamazepine group (2/14, 14%) than in the lamotrigine group (3/35, 9%).

Cooper *et al*. (2002) identified 31 patients >60 years of age who were prescribed lamotrigine. Almost all (28/31) received lamotrigine as adjunctive therapy and patients were followed for 9 to 85 months. A total of 17 patients achieved ≥50% reduction in seizure frequency compared with previous therapy; five subjects remained seizure free. Five patients discontinued therapy; one case was due to rash.

Bipolar disorder

Table 2 summarizes published reports of lamotrigine therapy in elderly patients with BD.

Sajatovic *et al*. (2005) conducted a retrospective analysis of two placebo-controlled, double-blind, 76- week phase III trials of lamotrigine therapy in 98 patients ≥55 years of age with Bipolar I Disorder. Lamotrigine, but not lithium, significantly delayed time-to-intervention for any mood episode versus placebo and significantly delayed time-to-intervention for a depressive episode versus lithium and placebo. Lithium fared significantly better than lamotrigine for time-to-intervention for mania; no significant differences for mania were noted when analyses were adjusted for index mood. Back pain was more common with lamotrigine versus lithium. More patients discontinued the study receiving lithium (29%) than lamotrigine (18%) or placebo (13%). There was no statistical difference in the incidence of rash: lamotrigine (3%) *vs* lithium (5%).

Robillard and Conn studied add-on lamotrigine therapy in five elderly women treated with lithium and valproate for at least three months previously. Four had rapid-cycling BD, and one had mixed BD. Three patients had a decrease in Hamilton Depression Rating Scale (HDRS) of 50% to 75%; one patient had a positive response (decrease in HDRS score from 34 to 30) and one patient did not respond. One patient developed a hand tremor that improved upon lamotrigine dose reduction.

Marcotte (2004) reported on a chart review of 20 elderly patients treated with adjunctive lamotrigine for a minimum of 72 weeks. The mean Clinical Global Impression Severity scale (CGI-S) score changed -2.8. Mean body weight did not change significantly. One patient reported a drug-related adverse event (headache).

Dementia

Table 3 summarizes published reports of lamotrigine therapy in patients with dementia.

Tekin *et al*. (1998) evaluated lamotrigine in 11 elderly patients with probable Alzheimer's disease.

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Table 2. Published reports on lamotrigine therapy in late-life bipolar disorder (BD)

Reference	Study design	Inclusion criteria	Drugs studied	No. of patients	Dose (mg/day)	Efficacy results	Safety results
Robillard and Conn 2002	OL Trial-LTG adjunct to Li and VPA	Age:71.5 yrs*	LTG	5	75–100†	Improvement in HDRS	Tremor - 1 patient
Sajatovic *et al*., 2005	Post hoc analysis from 2 DB-RCCT of elderly patients ≥55 years of age	Age ≥55 yrs	LTG Li PBO	33 34 31	50, 200,400† 750‡ Once a day	LTG delayed the time to intervention VS PBO	Headache, back pain, nausea, diarrhea and somnolence. No reports of serious rash
Marcotte, 2004	Retrospective Chart Review	Age: 63 yrs*	LTG	20	182*	CGI change: −2.8* LOCF.	Headache - 1 patient No change in weight
Rhodes, 2000	Case report	76 yr old female	LTG	1	100	Patient returned to a euthymic state.	Li-Renal insufficiency occurred with long-term lithium use resulting in discontinuation. LTG-Some agitation and sleep disturbance, which subsided.

DB = double-blind; CGI = Clinical Global Impression; HDRS = Hamilton Depression Rating Scale; Li = Lithium; LTG = lamotrigine; OL = open-label; PBO = Placebo; RCCT = randomized controlled clinical trial; VPA = valproate.
*Mean.
†Target.
‡Modal Total.

Patients were randomly assigned to either placebo or lamotrigine in double-blind fashion for eight weeks and then crossed-over to the other therapy following a 2-week wash-out period. Lamotrigine was administered with no titration regimen in three divided daily doses (up to 300 mg/day). For patients receiving lamotrigine (300 mg/day), there was statistically significant improvement in the Alzheimer Disease

Table 3. Published reports on lamotrigine therapy in dementia

Reference	Study design	Inclusion criteria	Drugs studied	No. of patients	Dose (mg/day)	Efficacy results	Safety results
Tekin *et al*., 1998	DB-RCCT Cross-over	Alzheimer's 66.9 yrs.*	LTG	11	150 and 300†	Significant changes in ADAS and cognitive scores.	Rash-1 patient
Berkowitz and Semenchuk, 2003	Retrospective Chart Review	Dementia 76.0 yrs*	LTG	26	191*	Positive effects on aggression and agitation	Mild Tremor-1 patient Ataxia-1 patient Sedation-1 patient
Aulakh *et al*., 2005	Retrospective Case Series	Dementia	LTG	20	192.5*	18/20 patients had improvement in CGI	Rash-1 patient.
Devarajan and Dursun, 2000	Case report	Dementia 65 yr. old female	LTG	1	100	Improvement in aggression and disinhibition.	None
De Leon, 2004	Case report	Alzheimer's 94 yr. old female	LTG	1	125	Paranoid symptoms and auditory hallucinations improved.	None

ADAS = Alzheimer Disease Assessment Scale; CGI = Clinical Global Impression; DB = double-blind; GDS = Global Deterioration Scale; LTG = lamotrigine; MMSE = Mini-Mental State Examination; RCCT = randomized controlled clinical trial.
*Mean.
†Target.

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Assessment Scale (ADAS) total and cognitive scores with mean scores of 33.18 ± 9.33 and 32.18 ± 9.33 at week 8, respectively. One patient developed a skin rash after 8 days of treatment with lamotrigine 150 mg/day, which cleared following discontinuation of therapy.

Berkowitz and Semenchuk (2003) conducted a chart review of 26 elderly patients with moderate-to-severe dementia and behavioral problems who were admitted to an acute care hospital. Add-on lamotrigine was initiated at 50 mg/day and rapidly titrated. Clinically meaningful CGI Severity of Illness response ('very much' or 'much' improved) was noted in 24 of 26 (92%) patients given lamotrigine; two patients discontinued lamotrigine due to non-response. Three patients (11.5%) experienced side effects (mild tremor, ataxia, sedation).

DISCUSSION

The ideal antiepileptic drug for older adults with neurological and psychiatric disorders should have a favorable pharmacokinetic profile, acceptable level of efficacy, be well tolerated, and not adversely affect cognition.

Lamotrigine therapy in geriatric epilepsy is well supported in the literature. A recent 'expert opinion' on the treatment of epilepsy in adults concluded that lamotrigine is a treatment of choice for elderly individuals despite similar rates of seizure control to other treatments (Karceski *et al*., 2005). As a class, antiepileptic drugs have been associated with impairment of cognitive function although to varying degrees (Ortinski and Meador, 2004). In other reports, lamotrigine either had a neutral effect or improved cognitive functioning in some patients (Martin *et al*., 1999; Gillham *et al*., 2000; Meador *et al*., 2001; Khan *et al*., 2004; Kockelmann *et al*., 2004).

Literature regarding lamotrigine treatment of geriatric patients with BD or dementia is limited by the relatively small sample size or retrospective analysis of the reports. Preliminarily, lamotrigine may be of benefit for BD, by delaying mood relapse, particularly in the depressive pole, and may be of benefit for improving cognitive function in patients with dementia.

Total daily dosing of lamotrigine in trials of older adults with epilepsy have generally ranged from ~75–500 mg/day with various titration schedules employed starting as low as 25 mg/day. In the geriatric bipolar literature, lamotrigine has been administered in daily doses ranging from 25–400 mg/day; mean dosing in older adult patients was 182–240 mg/day. Lamotrigine daily doses in patients with dementia are reported to range from 50–400 mg/day. It is prudent to initiate therapy with lamotrigine in elderly patients at a low dose given expected alterations in kidney, liver, and cardiovascular function (Lamictal Package Insert, 2005).

Among elderly patients with psychiatric and neurological conditions, the most common side effects noted with lamotrigine therapy were headache, nausea, diarrhea, somnolence, dizziness, and rash. In epilepsy and bipolar studies, elderly patients receiving lamotrigine were less likely to discontinue prematurely. Rates of adverse effects appeared to be similar to that reported for younger patients (Giorgi *et al*., 2001; Robillard and Conn, 2002; Sajatovic *et al*., 2005).

Anticonvulsant medications are widely utilized in clinical settings, although there is a relative paucity of controlled or large-scale data. Review of the available literature suggests lamotrigine is effective and well tolerated in elderly patients with epilepsy and relatively well-tolerated and may be effective in delaying mood relapse, particularly in the depressive pole, in patients with BD. Lamotrigine appears to be associated with some clinical improvement and is relatively well tolerated in patients with dementia, but further studies are needed.

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