Tolerability and Effectiveness of Lamotrigine in Complex Elderly Patients

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ABSTRACT

There is paucity of medical literature on the use of lamotrigine in elderly patients who have behavior problems and diverse psychiatric syndromes. This article is a retrospective case series summarizing the authors' experience with this medication. In a 20-patient case series from an institutional review board–approved retrospective chart review, the tolerability and efficacy of lamotrigine was evaluated for the management of agitated and aggressive behaviors in nursing home patients with a range of psychiatric and medical diagnoses. Nineteen of the elderly nursing home patients tolerated lamotrigine treatment, and 18 showed modest clinical improvement. These results support the authors' belief that controlled clinical investigations of this medication should be performed. (*J Geriatr Psychiatry Neurol* 2005; 18:8–11)

Keywords: lamotrigine; geriatrics; agitation; aggression; dementia

Psychiatric and behavioral disturbances are prevalent and difficult to treat in elderly nursing home patients. Aggression and agitation are seen in almost half of the patients with dementia at some point during disease progression.[1] These disruptive behaviors are eroding to the morale of both staff and patients; some of the threatening behaviors present potentially dangerous situations. Multiple pharmacological and nonpharmacological strategies have been used to treat these challenging patients.[2] Drug-drug interactions and adverse reactions often limit the usefulness of such drugs as benzodiazepines, antidepressants, neuroleptics, and mood-stabilizing drugs. Although research studies documenting effectiveness and tolerability of lamotrigine (LTG) for mental disorders in the elderly patient are virtually nonexistent, our clinical experience suggests that the use of LTG may be a useful and safe alternative in managing vexing clinical and behavioral presentations in the geriatric age group.

Studies have shown that LTG is effective for patients with bipolar illness[3]; other studies have revealed that LTG has demonstrable effectiveness in elderly patients with epilepsy.[4] Devarajan published an interesting case study of an elderly patient with dementia and behavioral problems. Lamotrigine was an effective treatment for the patient's verbally and physically aggressive behavior.[5]

In a VA nursing home setting, we have cared for a number of elderly patients who had severe behavioral problems. Some of these patients' behavioral problems were unresponsive to a number of treatment approaches. Because of Devarajan's case study, reporting improvement in behavioral problems after LTG had been prescribed for a patient, plus the Calabrese[3] and Giorgi[4] studies noted above, we decided to use LTG as a treatment for some of these patients whose behavioral difficulties had been unresponsive to other treatments.

The purpose of this retrospective chart review was to review our patients who had taken LTG to determine whether or not LTG was tolerated in elderly patients with behavior problems. Tolerability is an especially important issue because of the concerns about the side effects of LTG, in particular, the risk of LTG-induced rash, Stevens-Johnson syndrome, and toxic epidermal necrolysis. Although relatively rare, concern about a patient developing a rash and the above serious complications are the problems most frequently expressed by potential prescribers.[6] Headache, blurred vision, dizziness, ataxia, and gastrointestinal problems such as nausea and vomiting are of additional concern and particularly so in elderly patients

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because CNS side effects may increase the risks of falling in elderly patients.[7,8]

We also reviewed the use of LTG in our patients to ascertain whether or not it had been an effective treatment modality. This article is a summary of our current findings in a group of elderly patients residing in a VA nursing home. This retrospective chart review of consecutive nursing home cases was institutional review board–approved.

METHODS

Participants and Procedures

We did a retrospective chart review on 20 consecutive patients who received treatment with LTG. Because of the VA setting, only 2 of our 20 patients were female. All of our patients resided in a VA nursing home, which specializes in caring for patients with chronic psychiatric disorders in addition to one or more nonpsychiatric medical illnesses. The patients' ages ranged between 59 and 83 years, with a mean age of 71.95 ± 12.05 years. These patients were, on average, younger than the average age of patients entering nursing homes (80 years for men, 83 years for women).[9]

Each patient had resided in the nursing home unit for a minimum of 3 weeks prior to receiving his or her first dose of LTG.

Mini-Mental State Exam (MMSE) scores ranged from 0 to 30, with a mean of 17 and a median of 19. Twelve patients had primary Axis I and Axis II disorders including bipolar disorder, schizophrenia, schizoaffective disorder, and borderline personality disorder; 17 met *DSM-IV* criteria for dementia. Six of our patients had dementia and severe behavior disorders but had no other Axis I disorder. Each patient exhibited repeated, disruptive, aggressive, or severely agitated behaviors before LTG therapy was instituted.

Our patients had been taking other medications for considerable periods of time (usually weeks or months) prior to starting LTG treatment. We did not discontinue these other medications before starting patients on LTG because, other than one case report, we had no published literature that supported the use of LTG in patients such as those we treat. Additionally, we were reluctant to do anything that might further destabilize our patients residing in a nursing home setting and thus risk the need that they be transferred to the acute psychiatric inpatient unit.

Our patients are medically complex in that nearly all of them have a minimum of 2 illnesses; often our patients have several nonpsychiatric medical problems in addition to one or more psychiatric disorders. Each patient placed on LTG was considered to be stable from a nonpsychiatric medical standpoint. The behavior problems reported to occur in our LTG-treated patients included frequent yelling, striking out, scratching, grabbing, pounding on windows and doors, spitting constantly, and making inappropriate sexual comments. These were extremely difficult for our nursing home staff to manage. The repetitive disruptive behaviors eroded staff morale and were very troublesome for other patients; some of the threatening behaviors presented a potentially dangerous situation. None of the patients had a known chronic pain disorder.

Table 1. Characteristics of Patients Taking Lamotrigine

Number	*Age*	*Sex*	*MMSE*	*Diagnoses*
1	78	Male	22	DNOS, SCA, SBD
2	63	Male	28	DNOS, BAD
3	81	Male	8	PDD, SBD
4	59	Male	29	DNOS, SCA, SBD
5	65	Male	29	FTD, BAD, SBD
6	72	Male	29	DNOS, BAD
7	74	Male	0	DAT, SBD
8	77	Male	26	DNOS, BAD
9	64	Male	0	DNOS, SCA, SBD
10	76	Male	5	DAT, SBD
11	79	Male	10	DNOS, SCA
12	68	Male	25	DNOS, BAD, SBD
13	67	Male	28	BAD or SCA
14	83	Female	23	DNOS, BAD
15	74	Male	0	LBD, SBD
16	83	Male	3	LBD, SBD
17	66	Male	12	DNOS, SCA
18	69	Female	30	BPD
19	66	Male	19	SCA, SBD
20	75	Male	14	VD, MDD, SD, SBD

BAD = bipolar affective disorder; BPD = borderline personality disorder; DAT = dementia of the Alzheimer's type; DNOS = dementia not otherwise specified; FTD = frontotemporal dementia; LBD = Lewy body dementia; MDD = major depressive disorder; MMSE = Mini-Mental State Exam; PDD = Parkinson's disease dementia; SD = seizure disorder; SBD = severe behavior disorder; SCA = schizoaffective disease; VD = vascular dementia.

The collected data on our patients can be seen in Table 1.

MEASURES

Clinical Global Impression. Ratings on this scale reflected the change in a patient's condition compared to his or her pre-LTG status when each patient's disruptive behaviors were severe. A 7-point scale was used: (1) very much improved, (2) much improved, (3) minimally improved, (4) no change, (5) minimally worse, (6) much worse, and (7) very much worse. A geriatric psychiatrist, a geriatrician, and a member of the nursing staff performed Clinical Global Impression (CGI) ratings. The final rating represented a consensus of the above reviewers.[10]

Although our patients were not rated with the Cohen-Mansfield Agitation Inventory (CMAI), this instrument was helpful in identifying the types of disruptive behaviors described by members of the staff in nursing notes or progress notes. The CMAI groups disruptive behaviors into 3 domains: aggressive behavior, physically nonaggressive behavior, and verbally agitated behavior.[11] The disruptive behaviors seen in our patients were very similar to those listed in CMAI. For each patient, nursing staff and other members of the treatment group recorded 1 or more of the 29 specific behaviors that are listed on the CMAI.

Table 2. Maximum Tolerated and Therapeutic Dose of Lamotrigine, and Changed Clinical Global Impression Score

Number	*Age*	*Sex*	*Diagnoses*	*Dementia Diagnosis*	*Concomitant Medications*	*Daily Dose of LTG Given in Divided Doses*	*CGI of Change Score After LTG Treatment*
1	78	Male	DNOS, SCA, SBD	DNOS	Olanzapine	400 mg	2
2	63	Male	DNOS, BAD	DNOS	None	500 mg	2
3	81	Male	PDD, SBD	PDD	Quetiapine, bupropion	100 mg	1
4	59	Male	DNOS, SCA, SBD	DNOS	Quetiapine, gabapentin	100 mg	4
5	65	Male	FTD, BAD, SBD	VA	Olanzapine, bupropion	250 mg	2
6	72	Male	DNOS, BAD	DNOS	Gabapentin, carbamazepine, donepezil	150 mg	2
7	74	Male	DAT, SBD	DAT	Olanzapine	150 mg	2
8	79	Male	DNOS, BAD	DNOS	Olanzapine, donepezil, bupropion, gabapentin	300 mg	1
9	64	Male	DNOS, SCA, SBD	VD	Sertraline, olanzapine, gabapentin, donepezil, bupropion	75 mg	2
10	76	Male	DAT, SBD	DAT	Buspirone, olanzapine	250 mg	2
11	79	Male	DNOS, SCA	PDD	Olanzapine, buspirone	200 mg	1
12	68	Male	DNOS, BAD, SBD	VD	Olanzapine, gabapentin	150 mg	1
13	67	Male	BAD or SCA	NONE	Olanzapine	150 mg	1
14	83	Female	DNOS, BAD	DNOS	Bupropion	200 mg	1
15	74	Male	LBD, SBD	LBD	Buspirone, risperidone, bupropion, donepezil	100 mg	1
16	83	Male	LBD, SBD	LBD	Donepezil, gabapentin	100 mg	4
17	66	Male	DNOS, SCA	DNOS	Olanzapine, haloperidol	75 mg	2
18	69	Female	BPD	NONE	Olanzapine	100 mg	2
19	66	Male	SCA, SBD	DNOS	Olanzapine, buspirone	300 mg	2
20	75	Male	VD, MDD, SD, SBD	VD	Carbamazepine, bupropion, buspirone, donepezil	200 mg	1

LTG = lamotrigine; CGI = Clinical Global Impression; BAD = bipolar affective disorder; BPD = borderline personality disorder; DAT = dementia of the Alzheimer's type; DNOS = dementia not otherwise specified; FTD = frontotemporal dementia; LBD = Lewy body dementia; MDD = major depressive disorder; PDD = Parkinson's disease dementia; SD = seizure disorder; SBD = severe behavior disorder; SCA = schizoaffective disease; VD = vascular dementia. 1 = very much improved; 2 = much improved; 3 = minimally improved; 4 = unchanged; 5 = minimally worse; 7 = very much worse.

Clinical Evaluations

All diagnoses were made after a complete assessment by an experienced geriatric treatment team including a geropsychiatrist using *DSM-IV*.[12] Seventeen patients met criteria for dementia. Fourteen of our patients had non-dementia Axis I disorders, and 1 patient had a primary Axis II disorder. Five patients had a primary diagnosis of dementia with associated or secondary severe behavioral disorders.

During the pre-LTG treatment phase, all patients were treated with other medications for their psychiatric or behavioral disorders; frequently, patients received combination pharmacological treatment. The earlier treatments were either incompletely effective or intolerable because of side effects. Table 2 lists other medications taken by our patients when LTG treatment was initiated.

The patients received LTG for a period of time ranging from 10 months to 3 years. All patients were started on LTG 25 mg daily, and the dose was steadily titrated upward on a weekly basis by increments of 25 mg. The doses of LTG ranged from 75 to 400 mg, with a mean of 192.50 mg and a median of 150 mg.

RESULTS

One of our patients developed a rash that was felt to be most likely secondary to LTG. Nursing notes and progress notes did not record that any patients complained of side effects such as headache, blurred vision, dizziness, ataxia, and GI problems. We could not attribute any falls that occurred to LTG treatment, because for those patients who did fall, there was no increase in falls over their pre-treatment fall frequency.

As reflected by the CGI ratings, 18 of the patients receiving LTG showed what we felt were modest improvements in their behavior problems, whereas 2 patients were unchanged.

DISCUSSION

The purpose of our retrospective case review of 20 elderly patients was an attempt to demonstrate that LTG therapy was reasonably well tolerated and that it was modestly effective. This was not a controlled study, and we did not compare LTG with any other medication. Our patients represented a highly diverse cross-section of the kinds of patients seen in our VA nursing home.

It is our initial impression that LTG treatment was reasonably well tolerated in this diverse group of elderly patients. Only 1 of our 20 patients developed a probable drug rash, and there was no recorded increase in falls in our patients. The absence of recorded patient complaints of other commonly reported side effects to LTG treatment may be useful information.

Five of our patients had a primary diagnosis of dementia, all had serious behavior problems, and none of the 5 had another Axis I disorder. Because these 5 patients had no history of having had another psychiatric disorder prior to becoming demented, it was our tentative impression that their behavioral problems were associated with

or secondary to their dementia. Four of these 5 patients improved; the fifth patient was unchanged. The improvement in behavioral problems in these 4 patients might suggest that LTG played a role in their improvement.

There are a number of possible limitations inherent in this report: only 10% of our patients were female, LTG was not compared to any other medications, 18 of our patients had dementia, and patients with dementia often forget (and don't report) periodic side effects such as those nonrash problems most commonly seen with LTG treatment. Because other medications the patients were taking were not discontinued before starting LTG treatment, we cannot know for sure whether any improvement seen was truly from LTG alone, from LTG as an adjunctive treatment, or, if we had left our patients on their prior medications for longer, that their behavioral problems might have improved. In any retrospective chart review, it is possible that the reviewers may report better results than will be seen in a controlled study. With the possible exception of the 5 patients who had dementia and associated behavior problems, no subgroup of patients was identified for which LTG treatment seemed more effective.

This case series suggests that lamotrigine may be used safely and may be modestly effective in a difficult-to-treat, diverse group of elderly patients. We feel that controlled studies need to be done with LTG as a monotherapy for elderly patients with *DSM-IV* psychiatric disorders including behavior disorders associated with dementia. As is the case in most nursing homes, we have a low staff-to-patient ratio and our staff have a relative lack of psychiatric training; a placebo-controlled study would need to be done in a more psychiatrically sophisticated setting. Also, we believe that prospective, controlled studies need to be done comparing LTG's tolerability and effectiveness with other medications more commonly used to treat psychiatric and behavioral problems. These studies would, one hopes, help us learn if LTG has a special role to play with certain subpopulations of elderly, psychiatrically ill patients.

References

1. Marx MS, Cohen-Mansfield J, Werner P. A profile of the aggressive nursing home resident. *Behav Health Aging* 1990; 1:65-73.
2. Fava M. Psychopharmacologic treatment of pathologic aggression. *Psychiatr Clin North Am* 1997; 20(2):427-451.
3. Calabrese JR, Bowden CL, Sachs GS, et al. A double-blind placebo-controlled study of lamotrigine monotherapy in outpatients with bipolar I depression: Lamictal 602 Study Group. *J Clin Psychiatry* 1999; 60(2):79-88.
4. Giorgi L, Gomez G, O'Neill F, Hammer AE, Risner M. The tolerability of lamotrigine in elderly patients with epilepsy. *Drugs Aging* 2001; 18(8):621-630.
5. Devarajan S, Dursun SM. Aggression in dementia with lamotrigine treatment [Letter]. *Am J Psychiatry* 2000; 157(7):1178.
6. Calabrese JR, Sullivan JR, Bowden CL, et al. Rash in multicenter trials of lamotrigine in mood disorders: clinical relevance and management. *J Clin Psychiatry* 2002; 63(11):1012-1019.
7. Singh MM, Malhotra HS. Falls in the elderly—clinician's approach. *J Indian Med Assoc* 2003; 101(7):420, 422, 424.
8. Sabers A, Gram L. Newer anticonvulsants: comparative review of drug interactions and adverse effects. *Drugs* 2000; 60(1):23-33.
9. King MS, Lipsky MS. Evaluation of nursing home patients. *Postgraduate Medicine Online*. 2000; 107(2). Retrieved from http://www.postgradmed.com/issues/2000/02_00/king.htm
10. National Institute of Mental Health. CGI: clinical global impressions. In: Guy W, Bonato RR, eds. *Manual for ECDEU assessment battery*. 2. Rev ed. Chevy Chase, Md: National Institute of Mental Health, 1970:12-1–12-6.
11. Cohen-Mansfield J, Marx MS, Rosenthal AS. A description of agitation in a nursing home. *J Gerontol* 1989; 44(3):M77-M84.
12. American Psychiatric Association. *Diagnostic and statistical manual of mental disorders*. 4th ed. Washington, DC: American Psychiatric Association, 1994.