



# Low Dose Gabapentin for Behavioral Symptoms in Dementia with Lewy Bodies. Case Series, Brief Review of Pharmacology and a Hypothesis

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**keywords:** Gabapentin; Dementia with Lewy Bodies; Behavioral rating scale; Brain neurotransmitter balance.

**Abbreviations:** A fib: Atrial fibrillation; CGI-CL: Clinical Global Impression of Change; CHF: Congestive Heart Failure; CMAI: Cohen-Mansfeld Agitation Inventory; CMC: Co-Morbid Conditions; DD: Daily Dose; DM: Diabetes Mellitus; Ep: Epilepsy; F: Female; Gen: Gender; HT: Hypothyroidism; HTN: Hypertension; HL: Hyperlipidemia; M: Male; OH: Orthostatic Hypotension; Tx: Treatment,

## Abstract

**Aim:** To evaluate low dose gabapentin in treatment of disruptive behavioral symptoms in patients with moderate-severe dementia with Lewy bodies.

**Findings:** Improvement in symptoms seen by clinician and caregivers supported by changes on respective scales.

**Message:** Preliminary positive evidence suggesting that low dose gabapentin can be used for treatment of patients with dementia with Lewy bodies.

**Purpose:** To evaluate low dose Gabapentin (GBP) for treatment of disruptive behavioral symptoms in patients with moderate - severe dementia with Lewy bodies.

**Methods:** A case series in a community setting. Eleven (10 females) community dwelling elderly patients (79-97 years; 85.2 SD 6.4) with moderate (5 patients) and severe (6 patients) probable Dementia with Lewy Bodies (DLB) treated with low daily dose of GBP (200-600 mg; 341 SD 153) for vocal disruption, aggression, psychomotor hyperactivity and disturbed sleep. Symptoms rated by the clinician on Cohen-Mansfeld Agitation Inventory (CMAI) and on de novo designed VAPS (acronym of symptoms) scale. Caregivers rated treatment on Clinical Global Impression of Change (CGI-C) scale. GBP was used for 12 and more weeks as monotherapy (7 patients) and with other pharmaceuticals (4 patients) and was well tolerated.

**Results:** Improvement in behavioral symptoms. The scores declined on CMAI scale from 49.2 (SD 26.5) to 26.4 (SD 14.7) or by 22.8 (CI =14.2 - 31.5) and on VAPS scale from 8.2 (SD 1.3) to 1.7 (SD 0.8) or by 6.45 (CI=4 - 8). Caregivers rated improvement as moderate in 3 patients (score of 2) and substantial in 8 patients (score of 1), mean CGI-C score of 1.3 (SD 0.5).



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**Conclusions:** This uncontrolled open label study provides preliminary evidence suggesting that low dose GBP can be used for treatment of disruptive symptoms in patients with DLB. The authors hypothesize that change in glutamate/gamma aminobutyric acid balance is linked to the effect of GBP on disruptive behaviors and favor low vs high dose of GBP in patients with dementia.

## Introduction

Dementia with Lewy Bodies (DLB) [1] is a common and devastating geriatric illness with challenging behavioral symptoms. Antipsychotics are poorly tolerated [2] and alternative pharmacological approaches need to be explored. GBP, an anticonvulsant and analgesic [3] is generally safe and well tolerated. GBP has been used for treatment of patients with various dementias and in various dosages. This series presents a homogenous group of patients with DLB treated with low dose of GBP.

## Aim

To evaluate low dose GBP in treatment of disruptive behavioral symptoms in patients with DLB.

## Study design

An open label case series in a community setting. The study was approved by the Institutional Review Board of our hospital, consent for participation in the study and publication of the study results was obtained from patients and their proxies/caregivers.

## Participants and methods

Eleven elderly patients (10 females) with probable DLB (Table 1). Five patients had moderate and six had severe dementia as determined by clinical evaluation, Mini-Mental State Examination (MMSE) score [4] and Clinical Dementia Rating (CDR) Scale.[5] Renal function was preserved in 9 and moderately impaired in 2 patients, no conduction abnormalities were found on electrocardiograms, somatic triggers of agitated behaviors were either ruled out or controlled. Two scales were used to rate behavioral symptoms before and after treatment with GBP: Cohen-Mansfeld Agitation Inventory (CMAI) [6] and de novo designed VAPS scale (Table 2). In both scales, a sum of points reflects the severity of disruptive behavior. The CMAI scores are derived from frequency of each symptom. On the VAPS scale, symptoms are grouped into 4 categories and scored day- and nighttime (Table 2). In our opinion, separate daytime and nighttime scoring better reflects the severity of the disruptive behavior. Some patients may be relatively calm during the

day but experience "Sundowning" defined as "The differential nocturnal exacerbation of disruptive behaviors and agitation" [7,8] whereas more agitated patients are disruptive both daytime and nighttime. The VAPS scale is simple and easy to apply in clinical practice, the scores can range from 0 with no disruptive behavioral symptoms to 9 with most severe symptoms.

Burden and perception of caregivers of the treatment was assessed on the CGI-C (clinical global impression of change) scale. On this scale, a score of 1-means substantial improvement, 2-moderate improvement, 3-minimal improvement, 4 -no change and scores 5-7 mean negative outcomes [9].

Treatment with GBP was initiated at a dose of 50 mg (solution) or 100 mg (capsule) given at bedtime and, if tolerated, gradually up-titrated to a dose providing reasonable control of symptoms. Data of the study were statistically processed on the R software version 3.6.3 [10].

## Results

GBP was used as the first treatment option in 2 patients and as the second option, after a failure of other pharmaceuticals (intolerance or lack of effect) in 9 patients. In 7 patients, GBP was a standalone intervention (monotherapy) and in 4 patients, GBP was used in combination with other sedating pharmaceuticals (Table 1). The daily dose was divided into two or three administrations and ranged from 200 to 600 mg (341mg, SD 153). Only in 2 out of 11 patients, the up-titration of GBP was limited by mild confusion (patient 1) and mild worsening of balance (patient 7). Patient 1 did not tolerate any other agents, patient 7 did well with addition of a low dose of lorazepam, his nocturnal symptoms improved. Overall, GBP was well tolerated.

Treatment with GBP led to clinical improvement, the impression of the treating clinician was supported by the impression of the caregivers and by changes on the 2 rating scales. The caregivers rated the results on the CGI-C scale as substantial improvement (score of 1) in 8 and as moderate improvement (score of 2) in 3 patients, the mean CGI-C score was 1.3 (SD 0.5) (Table 1). Improvement in sleep was very important to caregivers. In all 8 patients with substantial improvement, insomnia was corrected better than in the 3 patients with moderate improvement.

The decrease in the mean CMAI score from 49.2 (SD 26.5) to 26.4 (SD 14.7) or by 22.8 (CI=14.2 - 31.5) and the decrease in the mean VAPS score from 8.2 (SD 1.3) to 1.7 (SD 0.8) or by 6.45 (CI= 4 - 8) were statistically significant. Both rating scales changed in the same direction and confirmed impressions of the clinician and caregivers.

**Table 1:** Patients' characteristics, pharmaceuticals and outcomes of treatment.

	Age Gen	CMC	MMSE Score	CDR Score	GBP DD (mg)	VAPS Scores	CMAI scores	CGI - C
1 K	94 F	HTN DM OH	5	2	200 ** #	7 - 3	24-20	2
2 S	96 F	DJD HT	2	3	300 ** #	5 -1	24-16	1
3 G	80 F	Ep OH HL	7	2	300 ** #	7 - 2	36-18	1

4 M	87 F	Ep CHF A fib	10	2	600 ** ##	9 - 1	48-28	1
5 L	79 F	HTN HL HT	0	3	400 * #	9 - 2	24-14	1
6 S	82 F	HTN DM HL	5	2	600 ** #	9 - 2	63-45	1
7 T	80 M	Falls DM A fib	0	3	300 ** ##	9 - 3	112-62	2
8 M	88 f	Falls HTN A fib CHF	0	3	200 ** ##	9 - 1	66-28	1
9 R	80 f	HTN	2	3	200 ** ##	9 - 2	66-24	2
10 B	80 F	HTN DM	2	3	450 ** #	9 - 1	36-15	1
11 P	90 F	HTN CHF Falls	12	2	200 * #	8 - 1	42-20	1

\* - used as 1- st option, \*\* - used as 2 -nd option, # - used as monotherapy, ## - used in combinations with other sedating agents.

**Table 2:** The VAPS behavior rating scale.

Symptoms / Points	Daytime	Nighttime
Vocal disruption	1	1
Aggression (verbal, physical)	1	1
Physical Hyperactivity (restlessness, pacing)	1	1
Sleep duration		
< 2 hours		3
2-4 hours		2
5-6 hours		1

Examples of Vocal disruption are ceaseless vocalization, perseverative speech. Examples of Aggression are insulting speech or physical aggression such as hitting, throwing objects. Examples Physical hyperactivity are restlessness, pacing. Sleep duration is specified in Table 2.

### Discussion

The patients in the current series presented a homogenous group (DLB), GBP was used in a lower dose range 200–600 mg, the positive effect was observed for 12 and more weeks. In other case reports/series, participants had various types of dementia, GBP was used either in a similar low dose range [11-14] or in higher doses. The average daily dosages were 2100 mg in 3 patients [15], 1318 mg in 22 patients [16], 900 mg in 12 patients [17], 980 mg in 20 patients [18]. GBP was relatively well tolerated and revealed at least some efficacy. In 2 patients with DLB [19], GBP daily dosages of 900 mg and 1200 mg caused worsening of cognition. The following brief review of GBP pharmacology leads to our hypothesis on its effect and explains our preference of the low dose range.

GBP is a water-soluble compound administered orally as a capsule, tablet or solution [3]. It would be desirable to have an alternate route of administration in treatment of agitated patients however rectal use proved ineffective [20] and paren-

teral formulations including transdermal route do not exist. GBP solution (50 mg/ml) allows initiation of treatment at a lower dose and more gradual up-titration of the daily dose, important in elderly patients with dementia. Because of its structural resemblance to amino-acids L-leucine and L-isoleucine, the LAT (large amino-acids transportation) system carriers GBP through the intestinal and haemato-encephalic barriers [21,22]. The LAT system is saturable and limits the amount of GBP absorbed and reaching its receptors [21,22]. Dietary protein does not hinder interaction of GBP with the LAT system [23] but competition with L-leucine and L-isoleucine occurs at the receptor site in the brain [24,25]. Therefore, it is better to separate GBP from food proteins. Levodopa (LD), given to some patients with LBD, is also carried through the barriers by the LAT system and should also be separated from food proteins [26]. With both GBP and LD on the Rx list, “Barrier Crossing” becomes complicated and is best addressed by separating the two pharmaceuticals from each other and from a meal by 1-2 hours. There is no need for dose adjustment in patients with low levels of plasma proteins or in patients with liver disease since GBP is not protein bound and is not metabolized. However, decline in renal function affects GBP clearance [3,23].

GBP binds with high affinity to its membranous gabapentinoid receptor, the  $\alpha 2\delta$ -1 subunit of presynaptic Voltage Gated Calcium (Ca<sup>++</sup>) Channels (VGCC) in excitatory tissues: multiple types of neurons, glands and muscles [27,28]. In the brain, this receptor is abundant (neocortex, hippocampus, amygdala, thalamus, cerebellum, pigmented brainstem nuclei) [28] and favors excitatory vs inhibitory neurons [28]. Binding of GBP to the  $\alpha 2\delta$ -1 receptor decreases Ca<sup>++</sup> influx into the neuronal cells [29-31] and synaptic release of multiple neurotransmitters such as Glutamate (GLU), aspartame, norepinephrine, dopamine, substance P, calcitonin gene related peptide [32-36]. Cholinergic (releasing acetylcholine) neurons are not affected by GBP [28,37] which makes it an attractive option in patients with dementias. Notably, effect of GBP is minimal in normal but significant in abnormal conditions such as inflammation, overstimula-

tion, changes in cellular signaling. In these instances, the  $\alpha 2\delta$ -1 receptor is "Sensitized" or overexpressed [36,38-40]. GBP prevents excessive rather than normal release of neurotransmitters and is a modulator, not an inhibitor, of multiple neuronal systems [40]. Anticonvulsant, anxiolytic and analgesic effects of GBP are associated with modulation of hyperexcitable neurons releasing GLU and substance P [41].

GLU is the major excitatory neurotransmitter causing immediate excitatory and delayed metabolic effects by interaction with multiple receptors in multiple neurotransmitter networks [42]. GLU is essential in memory, learning [42] and is also the precursor of the major inhibitory neurotransmitter Gamma Amino Butyric Acid (GABA) [43]. The homeostasis of GLU is tightly controlled, excess GLU is recycled into glial cells or escorted out of the brain [42]. Failure of this regulation and GLU excess leads to excitotoxicity by overstimulation of N-methyl-D-aspartate (NMDA) glutamate receptors with exaggerated intraneuronal influx of  $Ca^{++}$  and damage/death of neurons [42,44]. On the other hand, control of GLU amount in the CNS is neuroprotective [45]. GBP not only reduces synaptic release of GLU by 30-35 % [29] but also promotes conversion of GLU into GABA [43,46,47]. As a result, there is less GLU and more GABA and its metabolites in the brain [46-48]. In our opinion, the enzymatic system in GABAergic neurons converting GLU into GABA, Glutamic acid decarboxylase (GAD 65,67) and the co-factor pyridoxal-6-phosphate has to be designated as the cytoplasmic/metabolic gabapentinoid receptor. Interaction of GBP with only membranous  $\alpha 2\delta$ -1 receptors would lead to decrease in both GLU and GABA, interaction of GBP with both membranous and cytoplasmic receptors explains synchronous decrease in GLU and rise in GABA.

Our hypothesis. In patients with DLB, dopaminergic and sympatho-adrenergic networks experience degenerative changes (as manifested by parkinsonism and orthostatic hypotension). Therefore, we hypothesize that change in GLU/GABA balance is linked to behavioral changes caused by GBP. This hypothesis is supported by the existing indirect evidence. In patients with Alzheimer's disease, lack of GABAergic activity is associated with agitation [49,50]. It is very likely that a similar relation exists in patients with DLB. GBP increases sleep efficiency and slow-wave sleep in normal adults [51], in primary insomnia [52] and in psychiatric disorders [53]. This effect resembles the effect of amino-acid L-theanine [54,55], a competitive GLU antagonist, and the effect of GABA [56]. In animal studies, inhibition of GLU conversion into GABA diminished GABA mediated effects on sleep [57]. GBP improved sleep in the current series and in patients with other dementias [15-18]. In our series, patients 1-10 did not tolerate agonists of GABA receptors, benzodiazepines but improved with GBP. All this evidence suggests that improvement in sleep and other agitated symptoms is due to the change in GLU/GABA balance.

Use of large doses of GBP has to consider the following. A. the LAT - system is saturable and limited in capacity B. ageing is associated with a decline in renal function C. excessive down-regulation of neurotransmitter systems can lead to worsening of cognitive and motor symptoms D. agitation can "Paradoxically" worsen with less release of GLU since GLU is the precursor of GABA. E. neuronal loss in ageing and dementia reduces the number of neuronal targets for intervention. F. Lower doses of GBP carry lower risk of adverse effects and might be a better match to a patient with neurodegeneration but comparison of various dose ranges is needed in large trials.

This case series provides preliminary evidence that low doses of GBP can be used in treatment of disruptive behaviors in elderly patients with moderate-severe DLB, either as monotherapy or with other pharmaceuticals. The study did not have a control group and patients were their own historical controls. A randomized control trial evaluating the effect of GBP on nocturnal symptoms is underway [58]. In future larger and controlled studies, it would be interesting to explore possible synergism of GBP with NMDA receptor antagonists such as memantine, L-theanine or with promoters of GABA synthesis such as pyridoxal-6-phosphate. Do patients with DLB and other dementias experience a neuroprotective effect of GBP like patients with amyotrophic lateral sclerosis? [59].

### Conclusions

This case series provides preliminary evidence suggesting that low doses of GBP can be used in treatment of disruptive behaviors in patients with moderate – severe DLB. In this case series, GBP was well tolerated, had a positive effect on vocal disruption, aggression, psychomotor hyperactivity and sleep disturbances. The de novo designed VAPS scale was useful in the current series and needs further validation.

### Contribution of the authors

G. Goldenberg, MD. Design, performance, analysis, preparation of the manuscript. N Aye, MD preparation of the manuscript.

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