

Commentary on the Low Dose Gabapentin for Behavioral Symptoms in Dementia with Lewy Bodies Case Series, Brief Review of Pharmacology and A Hypothesis

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Abstract

Over 5 million people in the United States [1] and over 35 million people worldwide [2] suffer from dementia and its prevalence is expected to increase.

Key words: Alzheimer; neurocognitive disorder; adrenergic degeneration

Introduction

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Over 5 million people in the United States [1] and over 35 million people worldwide [2] suffer from dementia and its prevalence is expected to increase. It is estimated that 80 % of patients with dementia experience behavioral and psychological symptoms of dementia (BPSD) during the course of their illness [3]. BPSD present a wide range of disruptive behaviors and neuropsychiatric symptoms [4], for instance aggression, repetitiveness, restlessness, disturbed sleep, delusions, hallucinations. BPSD are distressing for patients, burdensome for caregivers and may lead to placement in a long-term care facility [5].

In the management of BPSD, pharmacological options are added when non-pharmacological interventions fail [6]. Therapeutic decisions are difficult, being challenged by the burden of comorbidities and frailty. The recommendations and algorithms suggested for treatment of BPSD in Alzheimer's, mixed (Alzheimer's/vascular) [7] or any type of dementia [8] are not always applicable to patients affected by neurocognitive disorder with Lewy bodies / dementia with bodies (DLB). As an example, because of dopaminergic degeneration, these patients are less tolerant to antipsychotics and/or because of adrenergic degeneration, may not tolerate antiadrenergics i.e. prazosin.

The manuscript presents 11 community dwelling elderly patients affected by moderate – severe DLB treated with gabapentin (GBP)

for BPSD. Despite absence of large controlled studies with GBP in BPSD, this pharmaceutical is a part of the treatment algorithm in Canada [7]. GBP attracts clinicians with its safety and tolerability. Previous case reports and case series accumulated experience in treatment with GBP of about 90 patients with various types of dementia such as Alzheimer's, vascular, mixed and DLB. Except the 2 patients with DLB, [9] groups of patients were heterogenous and GBP was used in a wide range of dosages, from 200 to 3600 mg a day. Overall, use of GBP led to positive outcomes, except for worsening in both patients with DLB. The current series presents a homogenous group of patients treated with GBP in relatively low dosages, 200-600 mg a day. The authors advocate for a low dose range of GBP and slow, careful up-titration in patients with dementia. The authors' position is based on the analysis of pharmacokinetics, pharmacodynamics and their clinical experience.

Absorption of GBP from the GI tract and its penetration through the hemato-encephalic barrier are limited by the saturability of the LAT (large amino-acid transportation) system. Elimination of GBP is affected by the decline in renal function. Although, lack of hepatic metabolism and drug interactions is one of the attractive features of GBP, pharmacokinetic competition reviewed in the manuscript should be interesting for clinicians.

The review of pharmacodynamics led the authors to a conclusion that GBP interacts with two rather than one receptor. The first, recognized gabapentinoid receptor is the voltage gated calcium channel (VGCC) on the external membrane of multiple excitatory cells such as neurons (except cholinergic neurons!), muscles and glands. This broad range of targets explains the broad off-label use of GBP, for instance for chronic cough, restless legs syndrome etc. The magnitude of GBP effect is greater in abnormal conditions i.e., inflammation, chronic stimulation which sensitize the VGCC. “The worse, the better” rule promotes GBP from a “neuro-inhibitor” to a “neuromodulator”. GBP modulates the release of multiple neurotransmitters, notably, the principal excitatory neurotransmitter, glutamate (GLU) from glutamatergic neurons. GBP might cause dose

dependent worsening of cognition, equilibrium and other undesired effects, especially with loss of neurons/targets which further supports the authors' concept of "low dose GBP in patients with dementia."

In GABA (gamma - aminobutyric acid)-ergic neurons, GBP galvanizes the enzymatic system, glutamic acid decarboxylase (GAD 65/67) + Pyridoxal - 5 - phosphate. This enzyme, loved by many specialties, converts GLU into its counterpart, GABA, the principal inhibitory neurotransmitter. The authors define this enzymatic system as the second, yet unrecognized cytoplasmic GBP receptor. The two receptors model explains the dual effect of GBP on GLU. GBP down-regulates the release of GLU (via VGCC) and promotes the conversion of GLU into GABA (via GAD). The net result of the GBP effect is the change in GLU/ GABA brain balance with less GLU and more GABA. However, large doses of GBP diminish both GLU and GABA10 (since less GLU is converted into GABA) which might lead to "paradoxical" agitation. This could have been the scenario with the 2 patients with DLB reported by P. Rossi et.al. [9] The low dose concept seems to have theoretical and clinical grounds; however, the dose range might be higher if tolerated and beneficial. Undoubtedly, the ability of GBP to change the neurotransmitter balance solidifies its reputation as a neuromodulator.

The authors hypothesize that the change in GLU/ GABA balance is the major contributor to the advantageous effect of GBP on BPSD in patients with DLB. The authors support their hypothesis by indirect evidence referring to the analgesic and anticonvulsant effects of GBP also linked to changes in GLU and GABA and to prevailing degeneration of dopaminergic and adrenergic systems [11,12] in DLB making these systems less likely mediators of GBP effect. While this hypothesis is awaiting further research testing it, GLU/GABA ratio is studied in other conditions as well [10,13,14].

In the presented patients, behavioral symptoms improved. The authors proposed to measure the burden and changes of symptoms on a de novo designed V A P S scale. V stands for verbally disruptive behaviors, A, for aggressive behaviors, P, for psychomotor behaviors and S, for sleeplessness. The V, A and P subscales are categorical scored in a binary fashion, present (1) or absent (0), separately for daytime and nighttime. The time split approach reflects the extension of symptoms from sundowning/nocturnal to daylight. The S-score reflects sleeplessness i.e., 4-6 hours of sleep score 1, 2-4 hours score 2 and less than 2 hours score 3. The VAPS score is a sum of points assigned for the presence of disruptive behaviors. The calculation is quick and convenient in clinical practice, the score ranges from 0 (no symptoms) to 9 (all symptoms present day and night, sleep duration is less than 2 hours). In the presented group, the VAPS scale better reflected the homogeneity of the group and the severity of the disease than the Cohen-Mansfeld Agitation Inventory (CMAI) scale.

Although data were not published in this report, the VAPS allows to score the response to treatment in separate symptom categories during day and night. Thus, the V score decreased from 22 to 1, the A score from 16 to 1, the P score from 20 to 5 and the S score from 32 to 12. The nocturnal P symptoms and the Sleep disturbances were most resistant to treatment.

The authors acknowledge the limitations of the uncontrolled study design and raise a series of questions for the future large and controlled studies. Since GLU has neuro-excitotoxicity, is GBP neuroprotective/disease modifying in patients with dementia? Would the co-enzyme of GAD 65/67, pyridoxal -5- phosphate have a synergistic with GBP effect? Would GLU antagonists, L-theanine or

memantine have a synergism with GBP? The note we would like make at the end. Patients with dementia and co-morbid conditions may have a busy traffic ascending from the nociceptors. Because of the chaos in networking, this traffic can spread to multiple brain areas but not be perceived or expressed as pain and masquerade as BPSD. We suggest a term "masked pain." Hence, the analgesic effect of GBP may contribute to the control of behavioral symptoms leaving the clinician to unveil their origin.

In conclusion, the manuscript addresses an issue challenging for both patients and clinicians, treatment of disruptive symptoms in DLB. This interesting pharmaceutical should be further researched in large controlled studies where the proposed hypothesis and the rating scale can also be tested.

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