

Gabapentin in the Treatment of Alzheimer's Disease and Other Dementias

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Abstract

Could gabapentin relieve some of the disabling symptoms of dementia? This open-label, nonblinded study evaluated the effectiveness of gabapentin in the symptomatic treatment of dementia, since γ -aminobutyric acid is deficient in the brains of such patients. The study demonstrated improvement in affective lability, depression, behavioral dyscontrol, cognition, and psychotic symptoms in a sample involving 37 subjects. The results were statistically valid. Gabapentin was well tolerated when titrated slowly, with the most frequent optimal dose being 900 mg/day. The drug was compatible with other pharmacologic agents and likely offered neuroprotective benefits.

Introduction

A number of open-label studies and case reports suggest that valproate may reduce behavioral agitation in some demented patients.¹⁻⁴ Verbal aggression, restlessness, and physical aggression were all ameliorated, whether dementia was of the Alzheimer's type, multi-infarct, or a combination of both. This would typically occur at serum concentrations lower than those traditionally used in controlling seizures. Deficits in γ -aminobutyric acid (GABA)⁵ and other neurotransmitters and receptors⁶⁻⁹ have been demonstrated in the brains of patients suffering from Alzheimer's dementia. Valproate stimulates GABA synthesis, potentiates postsynaptic effects of GABA, and inhibits GABA catabolism, resulting in enhanced central GABAergic neurotransmission.^{10,11} GABA, which is deficient in the brains of patients with dementia, is the major inhibitory neurotransmitter within the central nervous system. GABA agonists have anxiolytic, anticonvulsant, and aggressive-diminishing properties.¹²⁻¹⁷ These might actually reduce demented agitation by central GABAergic neurotransmission enhancement.

Behavioral agitation in demented patients usually results in the use of more costly levels of treatment from home, residential treatment settings (nursing homes), or psychiatric hospitalization.¹⁸⁻²⁰ In addition, particularly in the elderly, untreated agitation often results in head trauma, hip fractures, and physical assault, necessitating the need for one-to-one supervision, restraints, or seclusion. Agitation, which can be

defined as socially inappropriate verbal, vocal, or motor activity,²¹ can be costly and painful. Due to its GABAergic profile, its favorable side-effect profile, and its mood-stabilizing, anxiolytic action, assessing the efficacy of gabapentin in demented patients was believed to potentially be of clinical value.

Methodology

In the following open, nonblinded study, we evaluated the effectiveness of gabapentin in the symptomatic treatment of dementia. This included obtaining initial demographic information, Axis I diagnosis, 30-point Mini-Mental Status Examination (MMSE) before and after treatment, use of adjunctive medications, and the use of a subjective likert scale performed by the treating psychiatrist where 1=none and 4=severe. This scale was used to grossly measure affective lability, behavioral dyscontrol, cognitive impairment, depression, and psychotic signs and symptoms, before and after gabapentin treatment. The endpoint utilized in the study was also after a clinically stable dose of gabapentin had been established.

Results

There were 37 subjects, ranging from 49–91 years of age, where 16.2% (n=6) were African American; 2.7%

(n=1) were Asian; and 81.8% (n=30) were Caucasian. Gender distribution was 30% male and 70% female. The most frequent Axis I diagnosis was Alzheimer’s type dementia with delusions, depressed mood, and behavioral disturbance. This was followed by vascular dementia with depressed mood. Several subjects had more than one Axis I diagnosis. There were single subjects who had dementia due to Parkinson’s disease, Pick’s disease, and/or chronic substance abuse.

The duration of gabapentin treatment ranged from 2–40 months with dosage varying from 200–3,200 mg/day. The most frequent dosage was 900 mg/day (13.5%). Eight participants (21.6%) reported side effects including ataxia, somnolence, dizziness, edema, agitation, anxiety, panic, and increased blood pressure, and three discontinued gabapentin. The data of the three dropout participants were included in the statistical computation of this study, hence the overall mean scores were decreased. Thirty-five subjects (94.6%) had received other medications prior to the initiation of gabapentin or had additional medications added after the second assessment. At the initial assessment, or prior to gabapentin, 73% (n=27) were on neuroleptic medications and/or donepezil, and 51% were taking

regular vitamin supplements. Following the second assessment, two patients (5.4%) benefited from the addition of antidepressants and five (13.5%) from a second mood stabilizer.

Table 1 demonstrates a significant difference in MMSE scores before and after gabapentin treatment. These were all completed by an independent psychologist. All of the subjects demonstrated an improvement.

Table 2 demonstrates a positive difference between pre- and posttreatment scores for affective lability, behavioral dyscontrol, cognitive impairment, depression, and psychotic symptoms. These findings, though not placebo controlled, suggest that gabapentin at least temporarily improved cognitive, emotional, and behavioral functioning in patients with dementia.

Discussion

For the brain, stress constitutes an excitatory injury or an overwhelming overflow of activity. Stress is mediated in its final pathway neurochemically, whether due to psychic trauma or physical trauma, such as stroke, head trauma, dementia, or epilepsy. In all of these situations, the normal inhibitory processes are out of control and we see the release of glutamate, a neurotransmitter, which in overabundance

Table 1
Effect of Gabapentin in Dementia: Summary of Mean MMSE Scores and *t*-Test Significance for Individual Symptoms Before and After Gabapentin Treatment (N=37)

	Mean MMSE Score Before Gabapentin Treatment	Mean MMSE Score After Gabapentin Treatment	<i>t</i> Value	Degrees of Freedom	Two-Tailed Probability
Affective lability	3.3	1.3	16.75	33	.000*
Behavioral dyscontrol	2.7	1.1	12.13	33	.000*
Cognitive impairment	3.2	2.3	12.57	33	.000*
Depression	3.3	1.3	18.51	33	.000*
Psychotic symptoms	2.8	1.2	12.62	33	.000*

*Significant at $P \leq .05$.

MMSE=Mini-Mental Status Examination.

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Table 2
Effect of Gabapentin in Dementia: Summary of Scores on the MMSE Before and After Gabapentin Treatment

	Mean MMSE Score Before Gabapentin Treatment	Mean MMSE Score After Gabapentin Treatment	<i>t</i> Value	Degrees of Freedom	Two-Tailed Probability
MMSE	15.71	21.93	-12.66	31	.000*

* Significant at $P = .05$

MMSE=Mini-Mental Status Examination.

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can behave as a deadly neurotoxin (ie, excitatory neurotoxicity). In dementia, there is clearly a combination of both psychic (intense anxiety or the loss of one's psychological capacities), and physical trauma (ie, the breakdown of connections between different systems and subsystems of the brain). Since inhibition is a major brain function that allows for control of thoughts, emotions, and movement, brain injury such as that seen in dementia, can certainly lead to disinhibition. This occurs not only because the "hard wire" is damaged as a connection, but because the system can no longer modulate inhibitory processes, including the inhibitory neurochemicals, to counteract the effects of the excitatory injury.

GABA is an inhibitory neurotransmitter. It is increased more than 3-fold by gabapentin in rat hippocampal brain slices which would have the functional effect of neuronal inhibition during periods of hyperexcitability.²² These findings are consistent with studies in humans where gabapentin appears to increase brain GABA levels as measured by magnetic resonance spectroscopy.²³ Like the comparison between a standard and cellular telephone system, even when the "hard wiring" is broken, gabapentin can get the inhibitory neurotransmitters, such as GABA, to the sites where it is needed and useful. This may be part of what is reflected in the clinical observations made in this study.

Conclusion

The purpose of this study was to evaluate the effectiveness of gabapentin in relieving some of the disabling symptoms of dementia. Although this was an open, nonblinded study, gabapentin appeared to have improved affective lability, relieved depression, ameliorated behavioral dyscontrol, improved cognition, and diminished psychotic symptoms, in a small sample of patients

who suffer from dementia.

The results of the study were statistically valid. When gabapentin was slowly titrated to dosages lower than generally utilized for the treatment of chronic pain or bipolar illness, it appeared to be well tolerated with minimal transient side effects. From a pharmacokinetic perspective, gabapentin appeared to be "user-friendly" in its compatibility with other pharmacologic agents. This is particularly important for a population that typically receives multiple medications. In addition, we can speculate that the neuroprotective benefit from gabapentin would make it ideal for use immediately after psychic or physical trauma to optimize the effects in decreasing symptomatology and perhaps even minimizing damage due to release of neuroexcitatory transmitters.

Future research is warranted, including double-blind studies, to assess the effects of gabapentin on patients with dementia. Studies focusing on relief of symptoms and quality of life would also be important, as people are living longer and as families become more involved in assuming a more active role in the caregiving of relatives suffering from dementia. The findings of this study support the use of gabapentin to treat some of the behavioral and emotional sequelae of the dementia process. In addition, it appears that the drug may assist in improving, albeit transiently, cognitive functioning. ●●●

References

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