

Gabapentin in the Treatment of Bipolar Disorder

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Abstract

Gabapentin, a relatively new anti-epileptic drug (AED), is emerging as a therapeutic option for treatment refractory and rapid-cycling bipolar illnesses. Pharmacotherapy for bipolar disorders traditionally involves valproate, carbamazepine, or lithium, drugs which are associated with numerous adverse effects. Conversely, gabapentin has an attractive pharmacokinetics profile and relatively few side effects. There are no large randomized controlled clinical trials to date examining gabapentin's role in mood stabilization. However, informal reports have cited encouraging results in up to 80% of patients and general tolerance to side effects. These findings make the new drug a possible choice for patients who have failed to respond to traditional agents or developed side effects which interfere with medication compliance.

METHODOLOGY

A literature search of the Medline and Silver Platter databases was performed. English language articles published between 1990–1997 were reviewed. Keywords “gabapentin,” “bipolar,” “epilepsy,” and “psychiatry” were used in various combinations. All articles which addressed the use of gabapentin in human subjects were considered. Review of citations in these articles led to further references to the clinical use of gabapentin. All citations related to the use of gabapentin in the treatment of affective disorders are included in this review. Other articles which address clinically useful pharmacological issues are also included.

CHEMISTRY

Gabapentin (Neurontin) is a cyclic gamma-amino butyric acid (GABA) analogue which may alter GABA transmission in the central nervous system (1). The molecule incorporates a lipophilic cyclohexane ring into its structure, which allows gabapentin, unlike GABA, to cross the blood-brain barrier. Pharmacokinetic and pharmacodynamic investigations have largely relied on study of animals. The drug was initially developed as a spasmolytic but demonstrated effective anticonvulsant properties, and thus entered the pharmaceutical market as an AED (2).

Early research into gabapentin's mechanism of action failed to provide strong evidence of GABAergic activity. It does not appear to significantly bind to GABA-A, GABA-B, glutamate, glycine, or benzodiazapine receptors; it does not affect voltage

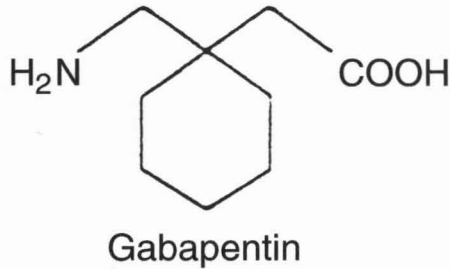


FIGURE 1. Structure of Gabapentin

gated sodium or calcium channels, and it does not elevate GABA concentration in nerve terminals (1,3). However, administration of gabapentin has been associated with increased GABA concentration in the substantia nigra, a region repeatedly indicated in the activity of GABAergic anticonvulsants (4).

Gabapentin is transported across enteric membranes and most likely through the blood-brain barrier and into neurons by an L-amino acid carrier (2,5). Its binding site has been recently identified as a subunit of a calcium channel on neuronal cell surfaces (3,6). Gabapentin increases the rate of synthesis and accumulation of GABA, decreases the release of monoamines (dopamine, norepinephrine, and serotonin), and weakly inhibits GABA-transaminase, an enzyme which degrades GABA into other amino acids (3,4).

PHARMACOKINETICS

Gabapentin is becoming popular among practitioners due to its favorable pharmacokinetics profile. It is efficiently absorbed in the gut following oral ingestion. The drug has a half-life of 5–9 hours, reaches peak plasma concentration in 2–3 hours, and achieves steady state in 1–2 days. It is water-soluble and non-protein-bound, but is distributed throughout the body (including the CNS) by means of protein transport. Gabapentin is not metabolized, is completely eliminated by the kidneys, and does not interact with hepatic enzymes. These qualities theoretically eliminate potential interactions with other medications (2,5,7).

CLINICAL USE

Controlled clinical trials of gabapentin in the treatment of psychiatric disorders have not been performed. Several anecdotal reports of use exist in the medical literature (8–12), including a growing number of documents pertaining to gabapentin's role in bipolar illness. However, most data regarding the drug's efficacy and safety appear in reports of gabapentin's use as an anticonvulsant. This information has served as a valuable guide to preliminary studies in the mental health arena.

Three large randomized controlled clinical trials have evaluated the efficacy and safety of adjunctive gabapentin therapy in treating refractory epilepsy: the UK

Gabapentin Study Group (1990), the US Gabapentin Study Group No. 5 (1993), and the International Gabapentin Study Group (1994). Drug dosages ranged from 600 mg/d to 1800 mg/d, with the most effective dosing regimen reported to be 1800 mg/d. The percentages of patients in whom seizure frequency decreased at least 50% (responders) were 25%, 26%, and 28%, respectively (19). Morris has since reported a retrospective analysis of 100 patients on gabapentin, 72 of whom experienced a greater than 50% reduction in seizure frequency. The mean drug dose in this patient population was 2107 mg/d; 37 of the 72 who responded (51%) were taking 1800 mg/d or less. The remaining patients took 1800–3600 mg/day (20).

Data regarding the role of gabapentin in the treatment of bipolar disorders is preliminary, yet encouraging. In one retrospective study of bipolar patients who had failed to respond to traditional mood stabilizers or developed intolerable side effects from these agents, 92% responded positively to gabapentin (14). All other published studies, consisting of open trials which have included gabapentin both as monotherapy and in addition to other psychotropic medications, have reported effective improvement in the majority of patients (13,15,17,18). Most patients have displayed noticeable improvement in cycling activity with 200–3600 mg/d, though doses as low as 33 mg/d and as high as 4900 mg/d have been reported (13,15). Gabapentin may also have antidepressant effects: patients on the new AED have noted improvement in mood, memory attention, energy, sleep, and libido (10,13,17). Elevation in mood which accompanied the transition from traditional AEDs to gabapentin, however, may have resulted from discontinuation of the sedating side effects of the traditional agents. Further study is needed to determine if gabapentin has inherent antidepressant effects.

SAFETY

Gabapentin has proven itself to be a relatively safe drug. The most commonly-encountered side effects are somnolence (24%), dizziness (20%), ataxia (17%), and fatigue (14%) (19). Less frequent side effects include involuntary twitches (1.3%), rash (0.5%), leukopenia (0.2%), azotemia (0.1%), thrombocytopenia (0.1%), stuttering (1 case), and weight gain (19,21,22). There have been several reported cases of hypomania and/or increased mood cycling (14,15,17,23) and there has been one case of oculogyric crisis which was emergently reversed with a benzodiazepine (22).

A therapeutic range for gabapentin has yet to be established. Peak steady-state plasma levels of the drug average about 4 micrograms/ml (7). There has been one reported case of overdose, in which a 16-year-old ingested 163 capsules (49,900 mg) without emesis or return of pill fragments on gastric lavage. Her plasma gabapentin level was 62 micrograms/ml at 8.5 hours after ingestion. She was lethargic, but was easily aroused and able to converse normally; by 18 hours post-ingestion, she was alert and without complaints (24). This case report is consistent with animal toxicity tests, in which mice and rats experienced only ataxia and labored breathing at maximum dose of 2000 mg/kg IV and 8000 mg/kg PO. None of the animals expired (24).

Gabapentin has several properties which significantly reduce its potential for

interaction with other drugs. It is non-protein-bound, it does not affect hepatic enzyme activity, and it has no metabolites (2). Although clinical trials have not reported any cases of drug-drug interactions involving gabapentin (20), and some sources have suggested that such interactions are impossible (25,26), several reports have suggested that the drug may occasionally affect or be influenced by other medications.

In one study, a therapeutic dose of aluminum and magnesium hydroxide (Maalox), administered concomitantly with or shortly after 400 mg of gabapentin, reduced the bioavailability of the latter by 20% (27). Cimetidine has reportedly decreased the renal clearance of gabapentin by a clinically significant amount (7). There has been one case report of gabapentin interacting with phenytoin. A patient with a long history of complex partial and secondarily generalized seizures, who was on three AED's, began taking gabapentin. His plasma phenytoin concentration subsequently increased from 42 to 177 micrograms/L and returned to baseline upon removal of the new drug (28). Finally, gabapentin has been assessed as unlikely to cause contraceptive failure when taken with oral contraceptives (7).

There are few reports of pregnant women taking gabapentin. No teratogenic effects have been noted in any of the 10 reports on file (29). The drug is, however, fetotoxic in rodents, associated with delayed ossification, hydrourerter, and hydronephrosis at doses up to four times greater than relative standard human dosages (i.e. 3600 mg/d). There was also an increased incidence of pancreatic acinar cell tumors in male rats at high doses, though their life span was not affected by the neoplasms (30). Potential uses of gabapentin in the pediatric affective disorders populations have yet to be determined.

DOSING

Formal dosing guidelines are not available for the use of gabapentin in bipolar disorders. Maintenance doses for seizure control range from 900–2400 mg/d (2,6,19,26) and preliminary trials of gabapentin for mood stabilization seem to suggest a similar dose range. The drug's relatively short half-life necessitates TID administration. Gabapentin treatment for refractory seizures is generally initiated with 300 mg once on the first day, 300 mg twice on the second day and 300 mg three times on the third day, with subsequent increases in TID dose as required for symptom control (2,19).

Of some clinical significance is the fact that all studies to date examining gabapentin in the treatment of bipolar illness have included patients who responded to a dose less than 900 mg/d (13–18). In one study of 28 patients, the mean gabapentin dose was 539 mg/d (15). Hence, increasing doses by 200 mg instead of 300 mg may be more appropriate for mood stabilization.

DISCUSSION

All of the medications presently used to treat bipolar disorder have significant side effects which impact both quality of life and therapeutic compliance. Unfortu-

nately, in this patient population, dissatisfaction with treatment regimens has the potential to significantly worsen the patient's clinical course by magnifying feelings of hopelessness in a depressed patient. Gabapentin holds promise as an adjunctive form of treatment which has few inherent disadvantages and little chance of interacting with other drugs. Its favorable pharmacokinetics profile is unique among mood stabilizers. The drug has relatively few side effects, most of which are benign in nature. Its possible antidepressant effects and hypomanic side effects need further study. It has thus far demonstrated low toxicity at therapeutic doses and in overdose. Gabapentin has displayed clinical efficacy in up to 80% of bipolar patients in preliminary clinical trials, and is presently undergoing investigation as a possible agent in the treatment of migraine headaches, chronic pain, and behavioral disorders. Few reports of gabapentin's use in human pregnancy exist, and animal studies have been somewhat discouraging.

Current psychiatric use of gabapentin is restricted to patients who have failed to respond to traditional agents or developed intolerable side effects from them. The upper limit of the drug's therapeutic range must be established. Problems with medication compliance may be improved through the development of an extended-release or depot form of gabapentin. A large, multi center, randomized, controlled clinical trial has yet to be performed.

CONCLUSIONS

Gabapentin is a GABA analogue and new AED which has the unique ability to cross the blood-brain barrier. It appears to influence neuropsychological activity by acting on calcium channels in the CNS. It has a favorable pharmacokinetics profile and is proving to be relatively safe in clinical practice. The drug has displayed both mood-stabilizing and possible anti-depressant activity in preliminary trials, and is associated with a relatively benign side profile. Further study of this new AED is clearly needed.

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