Gabapentin pharmacotherapy for antipsychotic-induced akathisia: single-patient experiment and case report

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***Abstract*:** This clinical study reports upon the efficacy of gabapentin (Neurontin) for treating severe akathisia (3 on the Barnes Akathisia Rating Scale) in two patients receiving quetiapine (Seroquel), one of whom also received olanzapine (Zyprexa) for a short period. The first patient participated in an open-label experiment in which the bedtime dose of gabapentin was discontinued three times at intervals 1 week apart, resulting in severe akathisia which was quickly terminated by taking his usual 1200 mg gabapentin dose. This patient was also taking high doses of two benzodiazepines and a beta blocker, without therapeutic effect upon his akathisia; only gabapentin was efficacious. The second case is a report of a woman taking a high dose of quetiapine for anxiety who experienced severe akathisia which was relieved by taking 1200 mg of gabapentin. Possible mechanisms of action of gabapentin are discussed. Particular attention is drawn to the difference between neuroleptic-induced akathisia and the neurological condition of restless legs syndrome.

Keywords: akathisia, antipsychotics, neuroleptics, gabapentin, quetiapine, olanzapine, diazepam, clonazepam, timolol maleate, Barnes Akathisia Rating Scale, restless legs syndrome (RLS)

Gabapentin enjoys a wide spectrum of psychopharmacological and neuropharmacological indications. Curiously, we found only a single article on the efficacy of gabapentin for treating neuroleptic-induced akathisia [Pfeffer *et al.* 2005]. This is counterintuitive on theoretical and clinical grounds. Theoretically, gabapentin enhances the activity of gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter that would be predicted to suppress the abnormal involuntary movements of akathisia. Clinically, gabapentin carries US Food and Drug Administration approval for restless legs syndrome (RLS), a neurological disorder. RLS and neuroleptic-induced akathisia are not identical conditions, but they are probably related, so one wonders why the efficacy of gabapentin has not been more thoroughly investigated in the latter disorder.

The purpose of the present article is to investigate the efficacy of gabapentin for treating neuroleptic-induced akathisia in a private-practice setting. The patients' anonymity was carefully protected and the study was performed with informed consent and pursuant to all guidelines for study with human subjects as required by the institutions with which the authors are affiliated.

Methods and results

Case 1

The patient is a 64-year-old man with a lifelong history of generalized anxiety disorder (GAD), panic disorder with agoraphobia, severe insomnia, and mild bipolar disorder marked by irritability and paradoxical depression in response to tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), and monoamine oxidase inhibitors (MAOIs). He has been under the care of the first author for 7 years, consisting of weekly, 1-hour psychopharmacology/insight-orientated psychotherapy sessions.

Over the years the patient has been prescribed most classes of psychotropic drugs. It is worth noting that high doses of psychotropic drugs were required to elicit a satisfactory therapeutic

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response in the patient, although genetic testing was never performed.

The patient's medications consisted of timolol maleate 20 mg tid *per os*, clonazepam 4 mg tid, diazepam 10 mg tid and 20 mg hs, gabapentin 1200 mg tid, and quetiapine 100 mg tid and 200 mg hs. He has been taking quetiapine for 5 years and gabapentin for 7 years. The patient has been taking the other medications for 10 years or longer. Gabapentin was initially prescribed by another psychiatrist for its now-refuted mood-stabilizing effect but was continued by the first author because it exerted salutary hypnotic and anxiolytic effects which have been subsequently confirmed in the literature [Pande *et al.* 2000; Lo *et al.* 2010]. The patient's condition remained stable on this regimen.

One night the patient ran out of gabapentin and had to forgo his bedtime dose. The next day he reported that soon after getting into bed, he experienced increasingly severe restlessness in the legs, which spread to the arms and torso. He further reported that he could not lie still and that these symptoms persisted for over an hour, until he finally fell asleep. The patient is diligent about taking his medications and he was certain that he had ingested his bedtime dose of quetiapine. (His score on the Objective subscale of the Barnes Akathisia Rating Scale was 3.)

After clinical discussion and giving informed consent, the patient omitted his bedtime dose of gabapentin 1200 mg on three subsequent occasions, spaced a week apart, but took his full bedtime dose of quetiapine. On each observational night the patient scored 3 on the Barnes Akathisia Rating Scale, as opposed to 0 when he ingested his gabapentin. On observational nights the akathisia was so intense that the patient found it intolerable for more than half an hour before he took 1200 mg gabapentin, which delivered complete relief.

During the course of this clinical investigation the patient experienced an abrupt worsening of GAD, panic, insomnia, and agitation related to a financial emergency. He was treated as an outpatient by adding olanzapine (Zyprexa) 5 mg bid to the treatment regimen, which relieved the exacerbation of his symptomatology within a few days. One night the patient, a professional scientist, exercised his initiative by discontinuing his bedtime dose of gabapentin; he reported to us that his akathisia was 'even worse' than the Barnes Akathisia Rating Scale score on previous observational nights. The patient's fiduciary crisis passed and olanzapine was discontinued after 10 days.

It is worth noting that this patient was taking two benzodiazepines and a beta blocker, but these established medications [Wilbur and Kulik, 1983; Donlon, 1973] did not relieve the patient's akathisia on nights when gabapentin was stopped.

Case 2

The patient is a 58-year-old woman with a lifelong history of GAD and bipolar depression, with infrequent hypomanic excursions. She has been under the care of the first author for 1 year. She currently takes lithium carbonate 900 mg hs, quetiapine 100 mg in the morning and 400 mg hs, and gabapentin 600 mg in the morning and 1200 mg hs. Occasionally, when she feels particularly anxious, she takes timolol maleate 10 mg bid, diazepam 10 mg prn (not to exceed two tablets daily) and clonazepam 4 mg hs prn.

Recently the patient forgot to take her bedtime dose of gabapentin. She was taking timolol, clonazepam, and diazepam at the time. Nevertheless the consequences of this lapse were severe. She scored 3 on the Observational Subscale of the Barnes Akathisia Rating Scale and experienced intense anxiety. Her symptoms were relieved when she took 1200 mg of gabapentin, which she had been cautioned not to omit, based upon our experience with the previous case.

Discussion and conclusions

This article has raised several issues that require further investigation. Gabapentin enhances the inhibitory effect of GABA throughout the central nervous system (CNS), so it would not come as a surprise if controlled trials confirmed our preliminary observations as well as [Pfeffer *et al.* 2005] that gabapentin controlled the symptoms of neuroleptic-induced akathisia. However, the mechanism of action of gabapentin remains to be elucidated, although two models have considerable heuristic value. The first [Hendrich *et al.* 2008] proposes that gabapentin binds to the calcium ion channel, thereby inhibiting the influx of calcium ions into GABA-ergic neurons. Because the calcium current is inhibitory, its blockage would promote the release of GABA at

the presynaptic terminal. A second recent model [Eroglu *et al*. 2009] maintains that gabapentin binds to the neuronal thrombospondin receptor and thereby inhibits the formation of excitatory synapses. Either theory appears to account for the reported ability of gabapentin to suppress seizures, support sleep, relieve anxiety and pain, and suppress abnormal involuntary movements such as those seen in neuroleptic-induced akathisia and RLS. Both cases make it clear that the patients experienced neuroleptic-induced akathisia per DSM IV. They evinced symptoms of greater severity than RLS. An inherent limitation of Case 2 is that case reports are constrained by the possibility of the placebo effect; this is a limitation of all case reports.

The literature contains a recent single-case report [See *et al*. 2011] describing a 76-year-old diabetic woman who presented with severe akathisia after discontinuing gabapentin abruptly. The akathisia resolved when the woman was given a dose of gabapentin. This report raises the question whether our patients might have experienced a withdrawal syndrome. However, in contrast to this cited case, our patients only withheld gabapentin for about 6 hours, not several days. Furthermore, the geriatric population is prone to abnormal involuntary movements that gabapentin might be predicted to suppress.

A noteworthy contribution of the present article is that it reports the efficacy of gabapentin when established drugs, namely benzodiazepines and a beta blocker, failed to deliver relief in treating akathisia. If this observation can be confirmed in a controlled trial, gabapentin might be a useful addition to the pharmacological armamentarium for treating akathisia.

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Conflict of interest statement

The authors have no conflicts of interest to declare.

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