Letter to the Editor

Psychiatric Uses of Newer Anticonvulsants

Sir: Over the past several years, the number of new anticonvulsants has increased considerably. As the number of new agents increases, so too does the reporting of off-label uses in psychiatric disorders. Interestingly enough, of all the anticonvulsants available in the United States, only valproate is U.S. Food and Drug Administration (FDA) approved for use in acute mania. There are about 15 controlled studies demonstrating clinical utility of carbamazepine in the treatment of acute mania; however, it is not FDA approved for that use.[1] The following discussion will look at the off-label uses of the newer anticonvulsants in psychiatric disorders.

Felbamate, introduced in the United States in 1993, was approved for treatment in Lennox-Gastaut syndrome and refractory partial-onset seizures.[2] In a recent MEDLINE search, there were no articles found describing the use of felbamate in psychiatric disorders. This is probably due to the possibility of aplastic anemia and hepatotoxicity associated with its use.[2] Also limiting felbamate's use may be that neuropsychiatric side effects have been associated with felbamate.[3]

Gabapentin is an anticonvulsant approved by the FDA for use as an add-on agent in patients with partial seizures resistant to conventional therapies.[4] It is an attractive agent due to flexibility in changing doses, a high therapeutic index, and lack of need to monitor serum levels.[5] As such, gabapentin has been the focus of much attention in the treatment of bipolar disorder. Gabapentin was initially reported to be effective in treating behavioral dyscontrol in an adolescent with intermittent explosive disorder and attention deficit disorder with hyperactivity in 1995.[6] In 1997, Stanton and colleagues[7] first reported the successful use of gabapentin as monotherapy in acute mania. Schaffer and Schaffer[8] also published in 1997 the results of an open trial of gabapentin in 28 patients with a wide range of bipolar disorder, all having failed more conventional therapies. The majority (64%) experienced positive results.[8] Several other studies, both open and retrospective, report good responses with gabapentin in the treatment of bipolar disorder.[9–13] However, despite the positive responses in the 2 controlled studies that have been published, neither showed gabapentin to be efficacious in the treatment of bipolar disorder.[14]

Apart from its use in bipolar disorder, gabapentin has been used in patients with anxiety, panic disorder, social phobia, aggressive behavior, and posttraumatic stress disorder (PTSD).[15–21] Gabapentin has also been used in treating obsessive-compulsive disorder.[15,22,23] Other areas of clinical use have been in the treatment of substance abuse disorders[24–27] and in the treatment of agitation and disruptive behavior in Alzheimer's disease.[24–30]

Lamotrigine is an anticonvulsant approved by the FDA for adjunctive therapy in adults with partial seizures. It is also approved as adjunct therapy in the generalized seizures of Lennox-Gastaut syndrome in adults and pediatric patients. Lamotrigine is reported to have a favorable pharmacokinetic profile.[31] It is approximately 55% protein-bound metabolized in the liver, and serum monitoring is not required.[4] Clinical concerns associated with lamotrigine include the development of a rash (occurring in approximately 5% of patients) and Stevens-Johnson syndrome, a potentially fatal dermatologic condition occurring in 0.1% of adults exposed to lamotrigine.[4,32] Combining lamotrigine with valproic acid may increase the risk of Stevens-Johnson syndrome; slow titration upward may lessen the risk.[32] To date, 3 double-blinded controlled studies have looked at lamotrigine in the treatment of acute manic episodes.[33–35] More positive results were yielded in a double-blind study of lamotrigine as a mood stabilizer in patients with bipolar depression and in rapid-cycling bipolar disorder.[36,37] There are 3 open-label studies utilizing lamotrigine as adjunct or monotherapy in patients with treatment-refractory bipolar disorder.[38–40] A case study reported the use of lamotrigine as a monotherapeutic agent in treatment-resistant schizoaffective disorder.[41] One retrospective review looked at lamotrigine in treatment-resistant bipolar disorder in adults, with favorable results in patients presenting with mixed or depressed states.[42]

Oxcarbazepine, a very recent arrival to the U.S. market, was approved for the treatment of partial seizures with or without secondary generalization in adults and as adjunctive therapy in the treatment of children aged 4 to 16 years with partial seizures. Oxcarbazepine was looked at in an open-label trial in 1984 randomly assigning patients to either haloperidol or oxcarbazepine, with both groups showing a decrease in their manic symptoms.[43] In a double-blind, crossover study, 6 of 7 patients treated with oxcarbazepine showed improvement and had an almost 86% decrease in Inpatient Multidimensional Psychiatric Scale score.[44] Oxcarbazepine was also studied as an add-on medication in 10 patients with either manic symptoms or schizoaffective disorder; the overall results were favorable, especially in treatment of manic symptoms and hostility.[45] Another open clinical trial studied 13 patients with bipolar disorder, mostly nonresponders to lithium, who were given either carbamazepine or oxcarbazepine. A reduction in symptoms was noted with both agents; however, there was no decrease in the frequency of the manic episodes.[46]

Tiagabine is FDA approved as an adjunct anticonvulsant for treatment of partial seizures. A review of the literature included an open-label trial of 8 patients in acute manic episodes treated with tiagabine.[47] The authors felt that tiagabine did not appear to be efficacious in acute mania. In a case series using tiagabine as an adjunctive treatment, 2 patients with bipolar disorder and 1 patient with schizoaffective disorder were noted to improve when tiagabine was added in low doses.[48] A second case report also noted improvement when tiagabine was added in a patient with bipolar I disorder with rapid cycling and in a second patient with bipolar I disorder.[49]

Topiramate is an anticonvulsant approved as an adjunct agent for adults and for children aged 2 to 16 years with partial-onset seizures or primary generalized tonic-clonic seizures.[50] To date, there are no published controlled studies in the treatment of acute bipolar mania with topiramate.[14] However, an open

study looking at the effectiveness of topiramate in 56 outpatients with bipolar disorder found that adjunctive topiramate may have positive effects in acute and long-term treatment.[51] Other open-label studies have shown at least 50% of patients to experience moderate or marked response.[5] In a retrospective review of 58 patients diagnosed with bipolar disorder (44 of those with rapid cycling and refractory to more conventional mood stabilizers), about 50% showed moderate or marked improvement when topiramate was added as adjunctive therapy.[52] There is 1 open-label study using topiramate in PTSD[53]; in 24 patients treated, there was a 92% reduction in nightmares and intrusive thoughts. An important clinical consideration regarding topiramate is that patients do (or seem to gain weight secondary to its use.[5]

The arrival of new anticonvulsants has seen more and more utility in a wide variety of psychiatric disorders. The clinical off-label use of these new agents is not surprising given the history of carbamazepine and valproic acid, both approved as anticonvulsants, but certainly used as mood stabilizers. Carbamazepine was reported as far back as 1971 as a mood stabilizer and has also been used in the treatment of alcohol dependence.[31,54] Valproic acid, as far back as 1960, was reported to have mood-stabilizing properties, and it has also been used in a wide range of psychiatric disorders.[31,55] Of all the anticonvulsants, by far the most data exist for gabapentin, and across the widest spectrum of psychiatric disorders. However, other agents such as lamotrigine and topiramate appear promising as well. The newer agents may eventually prove to be valuable additions to the psychotropic armamentarium, but will need to be studied further in a more controlled fashion.

Conclusions and opinions expressed are those of the author and do not necessarily reflect the position or policy of the U.S. Government, Department of Defense, Department of the Army, or the U.S. Army Medical Command.

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