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Anticonvulsants and Psychiatric Disorders

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Dating back to the 1980s, promising clinical results with divalproex and carbamazepine sparked considerable interest in the potential value of anticonvulsants in the treatment of mood and anxiety disorders. Unfortunately, with only a few exceptions, that promise has not extended to bipolar illness, wherein newer anticonvulsants have generally produced disappointing results. The notable exceptions have been in the subgroup of patients with depression in bipolar illness and in the prevention of relapse, again primarily with respect to depression in bipolar illness.

As a consequence of the disappointing results in bipolar illness, recent controlled clinical studies of anticonvulsants have tended to focus on associated symptoms and conditions, such as craving and binge eating. More positive data from those investigations have provided a new context for clinical evaluation of anticonvulsants as potentially useful therapies for treatment of specific symptoms or comorbidities of bipolar illness. Curiously, clinical investigation of anticonvulsants in bipolar illness until recently has devoted scant attention to comorbid anxiety, which is extremely common. Encouraging results with agents such as pregabalin and gabapentin have helped renew interest in the use of anticonvulsants for treatment of anxiety symptoms and syndromes, such as panic syndrome and social anxiety disorder.

Within the clinical context described above, investigation of the anticonvulsant levetiracetam in psychiatric disorders has proceeded at a modest pace. Levetiracetam has novel mechanisms of action that center on indirect modulation of the γ-aminobutyric acid (GABA)ergic system, which has a key role in mood and anxiety disorders. To date, levetiracetam’s data cache has come primarily from preclinical studies, particularly studies related to anxiety disorders. Several good animal models exist for different types of anxiety disorders, and levetiracetam has demonstrated ability to improve symptoms in several of these model systems. Less extensive preclinical data exist for depression or manic/depression, primarily because of a lack of good model systems to evaluate candidate therapies.

The following CLINICAL UPDATE summarizes selected poster presentations from a continuing education program held in May. The studies reported by Drossner et al and by Biel et al demonstrate that patients with psychiatric disorders frequently have illnesses that are complicated by medical comorbidity or co-occurring psychiatric disorders. The studies emphasize the importance of comprehensive patient evaluation that encompasses both physical and mental health, followed by development of a clinical management strategy.

Continued on page 2

Prevalence of ADHD in Adults

Little information exists about the prevalence of attention deficit hyperactivity disorder (ADHD) in adults as compared to children. Current estimates of adult ADHD prevalence rely on longitudinal follow-up studies of children with ADHD into adulthood, community surveys using samples of convenience, and family studies of childhood ADHD. The studies have resulted in varied estimates of prevalence.

Table Prevalence of ADHD by Type of Diagnostic Criteria

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Broad, %</th>
<th>Narrow, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperactive-impulsive</td>
<td>3.7</td>
<td>1.1</td>
</tr>
<tr>
<td>Inattentive</td>
<td>5.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Combined</td>
<td>6.9</td>
<td>1.1</td>
</tr>
<tr>
<td>Total</td>
<td>16.4</td>
<td>2.9</td>
</tr>
</tbody>
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Continued on page 4

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**Clinical Update**

### Treatment of Mild or Moderate Bipolar Disorder

Patients with bipolar disorder typically require long-term, if not lifelong, treatment that often must address one or more comorbid psychiatric conditions, including anxiety disorders, drug and alcohol abuse, and attention deficit hyperactivity disorder (ADHD)/attention deficit disorder (ADD). In many instances, treatment involves multiple concomitant medications.

Anticonvulsants may have a role in the management of some patients with bipolar disorder. The novel anticonvulsant levetiracetam was evaluated in 109 outpatients with bipolar disorder. The patients were retrospectively identified from records of a large private psychiatric practice. Clinicians should note that this use is investigational and not approved by the US Food and Drug Administration.

The principal inclusion criterion was prescribed treatment with levetiracetam for mild to moderate bipolar I, bipolar II, or bipolar II subsyndromal (not otherwise specified [NOS]). Patients were excluded if they had been prescribed levetiracetam for bipolar disorder but had been treated for less than 14 days.

The patients’ median age was 30 years, and they had an even gender distribution. Most of the patients had diagnoses of bipolar II (45%) or bipolar II NOS (37%). On average, the patients had two comorbid conditions and were on two concurrent medications. The most common comorbid conditions were drug and alcohol abuse, generalized anxiety disorder, and ADHD. Antidepressants were the most frequently prescribed concomitant medication.

In most cases, levetiracetam was the initial medication for bipolar disorder. Levetiracetam treatment duration averaged 76 days and ranged between 14 days and 1 year. The average levetiracetam dose was 1838 mg/day, ranging from 125 to 5250 mg/day. Patient response was assessed retrospectively by means of an electronic medical record (Behavior2004), and symptom severity was tracked by means of a Likert scale.

Approximately half the patients had a good response to treatment, and 20% had partial responses, resulting in significant improvement in overall symptom severity (P < 0.001). Separate analysis of selected individual symptoms demonstrated statistically significant (P = 0.01) improvement in irritability, racing thoughts, mood swings, and extra energy.

Compliance with levetiracetam was good, and the incidence of side effects was low, as 81% of patients reported no adverse effects during treatment with the anticonvulsant. The most common side effect associated with levetiracetam was sedation (9%), which was managed by dosing the affected patients at bedtime. Overall, 8% of patients discontinued treatment, 5% because of lack of efficacy.

The results of this open-label, retrospective study suggest that levetiracetam has promise as an alternative therapy for selected patients with bipolar disorder. Further study is necessary to confirm and clarify the potential role of levetiracetam in the treatment of bipolar disorder.


### Prevalence of Medical Comorbidity in Severe Psychiatric Disorders

Comorbid physical and medical problems can complicate management of patients with psychiatric diagnoses. Recognizing the frequency with which these comorbid conditions occur can help clinicians develop clinical management strategies that address patients’ physical and mental health issues. A study was undertaken to determine the prevalence of comorbid physical conditions among 77 young adults (16 to 25 years of age) receiving services through a community-based mental health organization. All the patients had severe and persistent psychiatric disorders associated with limited functionality. Primary psychiatric diagnoses included schizophrenia, schizoaffective disorder, psychosis not otherwise specified, bipolar disorder, and major depression.

The patients’ physical health status was evaluated by review of medical records and compared with data from an age-matched population without a history of severe or persistent mental health problems. The review showed that 56.5% of the patients were obese and 71.7% were overweight or obese. Additionally, 64.2% of the patients had hypercholesterolemia, 35.7% had abnormal glucose metabolism, and 12.9% were hypertensive. Rates for all of the comorbid conditions exceeded those of the control group.

The results emphasize the frequency of comorbid medical conditions in patients with primary psychiatric disorders. The patient population came predominantly from low-income and minority backgrounds, which contrasts with many clinical psychiatric practices. Nonetheless, the findings point to the need for comprehensive health evaluations for psychiatric patients and appropriate interventions to address the patients’ physical health problems as well as their mental health problems.


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Evaluation of Therapy for Aggression Disorders

Aggression disorders comprise a variety of conditions that include oppositional defiant disorder (ODD), conduct disorder (CD), and intermittent explosive disorder (IED). Characteristics of these conditions include defiant, disobedient, and hostile behavior toward authority figures, violation of basic rights of others, and serious acts of assault or destruction of property. Estimated prevalence of the conditions ranges between 5% and 10% of the population in general, and higher in adolescent males.

In the search for an effective, well-tolerated therapy for aggression disorders, the novel antiepileptic levetiracetam was evaluated in 54 outpatients, who were treated for 1 year. Safety and efficacy data were analyzed retrospectively. Patients were included in the analysis if they were prescribed levetiracetam for treatment of ODD, CD, or IED. Patients treated for less than 14 days were excluded. Clinicians should note that this usage is investigational and not approved by the US Food and Drug Administration.

The patients ranged from 5 to 48 years of age (median, 13), and 39 of the patients were male. A majority of the patients (62%) had a diagnosis of ODD. The patients had a variety of comorbid mental conditions, including attention deficit hyperactivity disorder (ADHD)/attention deficit disorder, bipolar disorder, depression, dysthymia, drug and alcohol abuse, obsessive-compulsive disorder, pervasive developmental disorders, and generalized anxiety.

For most patients, levetiracetam was the first medication trial for aggressive behavior. However, their medical records reflected concomitant use of a wide range of drugs that included antidepressants, ADHS therapies, anticonvulsants, and antipsychotics.

Median duration of levetiracetam therapy was 52 days and ranged between 14 days and 1 year. The levetiracetam dose averaged 1835 mg/day, and the dose range for the population was 125 to 5000 mg/day. An electronic medical record (Behavior2004) was used to assess response to treatment. Symptom severity was followed by means of a Likert scale.

Overall symptom severity improved significantly during treatment with levetiracetam (P=0.003). About 45% of the patients had a good response, and an additional 15% had partial responses. Moreover, significant improvement (P<0.05) was seen in the individual symptoms of anger, violence, opposition, and impulsivity.

The only notable adverse effect associated with levetiracetam was sedation, which occurred in 9% of patients. The side effect was used to advantage by dosing the affected patients at bedtime. Eleven percent of patients discontinued levetiracetam therapy because of lack of efficacy, and 12% stopped for various other reasons, including noncompliance.

The results of this open-label, retrospective study suggest that levetiracetam has promise as a potential alternative treatment approach for aggression disorders. Further study is required to confirm the findings.

Prevalence of Comorbid Anxiety Disorders

A substantial proportion of patients with primary diagnoses of anxiety or major depression have been reported to have comorbid anxiety disorders (J Nerv Ment Dis. 1986;174:63-72. J Affect Disord. 1990;19:287-296). To provide further estimates of comorbidity, the prevalence of comorbid anxiety disorders in a community psychiatric setting was investigated.

The study involved 706 patients who received care at a community outpatient clinic affiliated with an academic medical center. The patients had primary diagnoses of panic disorder, obsessive-compulsive disorder (OCD), social phobia, generalized anxiety disorder (GAD), or depression. Overall, less than 30% of patients met criteria for a single diagnosis (206 of 706). For each of the primary diagnoses, a majority of patients had one or more comorbid anxiety diagnoses (Table).

The results confirm previous reports of high rates of comorbidity among patients with anxiety disorders. Medical records of the patients showed that a greater number of anxiety diagnoses was associated with poorer response to treatment.

Table. Prevalence of Comorbid Anxiety or Depression

<table>
<thead>
<tr>
<th>Primary Diagnosis</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Panic</td>
<td>196/255</td>
<td>76.9</td>
</tr>
<tr>
<td>Depression</td>
<td>192/281</td>
<td>68.2</td>
</tr>
<tr>
<td>Social phobia</td>
<td>28/48</td>
<td>58.3</td>
</tr>
<tr>
<td>OCD</td>
<td>57/90</td>
<td>63.3</td>
</tr>
</tbody>
</table>

Evaluation of Therapy for Bipolar Mania

Preliminary studies have suggested that the novel N-type calcium channel blocker levetiracetam might have anxiolytic or anxiety-like properties that could be useful in the treatment of selected patients with bipolar disorder. Few data from empirical investigation exist regarding levetiracetam’s possible psychotropic properties. However, preliminary open-label studies have provided evidence of potential efficacy in the treatment of mood disorders (J Clin Psychiatry. 2003; 64:781-784). Clinicians should note that this usage is investigational and not approved by the US Food and Drug Administration.

The effects of levetiracetam in bipolar mania were evaluated in an initial series of five adult outpatients who had bipolar illness with features of hypomania that had responded poorly to standard pharmacotherapy. The objective was to estimate the potential anxiolytic and antidepressant effects of levetiracetam in patients with bipolar mania or hypomania.

The series consisted of four patients with a diagnosis of bipolar I and one with bipolar II. Levetiracetam was administered as mono-therapy in four cases and as add-on therapy in the remaining case. The patient who received the drug as add-on therapy was being treated concomitantly with olanzapine and divalproex. The mean dose of levetiracetam was 1700 mg/day, and follow-up continued for 6 weeks.

Four of five patients completed the study; one withdrew because of nausea and vomiting after 3 weeks. Common side effects during the study were nausea, vomiting, sedation, dizziness, and dry mouth.

Response data included the patient who discontinued levetiracetam treatment prematurely. During treatment, the mean score on the Young Mania Rating Scale declined significantly from 22 at baseline to 9 at the end of the study (P<0.043). Scores on the Clinical Global Impression of Severity decreased from a mean of 4.2 at baseline to 3.4 and demonstrated a trend toward significance (P<0.059). The mean score on the Positive and Negative Syndrome Scale decreased slightly from 55 to 44, and the average score on the Hamilton Depression Scale increased from 11.2 to 17.8, which was not significant.

Overall, levetiracetam was well tolerated and associated with improvement in hypomanic symptoms in adult patients with bipolar disorder. The drug appeared to have a neutral effect on depressive symptoms, although the small number of patients precluded definitive conclusions.

Anecdotal observations suggested that levetiracetam favorably affected symptoms associated with anxiety and attentional impairment. Larger, controlled trials are required to provide a more thorough assessment of the potential utility of levetiracetam in bipolar disorder.

Prevalence of ADHD in Adults

Continued from page 1

In widely ranging prevalence estimates of adult ADHD, the results might not be applicable to the general population.

In an attempt to address limitations of existing data on adult ADHD, a telephone survey of 1,019 randomly selected adults was undertaken to estimate the prevalence of the disorder in the community. Participants completed an 18-question survey based on DSM-IV symptoms (inattentive, hyperactive-impulsive, and combined). Respondents were asked to evaluate each symptom retrospectively (childhood experience) and currently (within the previous 6 months).

The survey data provided the basis for two approaches to ADHD diagnosis. A narrow diagnosis estimated the prevalence of ADHD in adulthood by identifying a group of adults demonstrating strong evidence of ADHD in childhood and adulthood. Patients were considered symptom positive if they reported that a symptom occurred often. A broad diagnosis estimated the screening prevalence (what would be expected by use of a more inclusive ADHD definition to identify patients for further assessment by a clinician) and was made on the basis of whether a symptom or symptoms occurred sometimes or often.

The broad screening diagnosis resulted in a higher prevalence of adult ADHD than did the narrow diagnosis. (Table on page 1). Use of broad diagnostic criteria resulted in a prevalence of ADHD across age groups ranging from a low of 14.5% for respondents 60 years of age or older to a high of 19.1% for respondents 40 to 49 years of age. By the narrow criteria, the highest prevalence was seen in the 40 to 49 age group (5.2%), and the 60-plus age group had the lowest prevalence (0.2%).

Neither type of ADHD diagnosis was influenced by ethnicity. By either definition, ADHD was more common in urban than in rural areas. Geographically, ADHD (both diagnostic criteria) was more common in the northeast and north central states than in southern or western states. By either diagnostic criterion, people with ADHD were less likely to have attended college or to have graduated from high school. Unemployment was associated with narrow ADHD but not broad ADHD.

On the basis of narrowly defined criteria, results of this telephone survey show an estimated ADHD prevalence of 2.9% among US adults. The broad diagnostic criteria resulted in a prevalence of 16.4%, meaning that one out of six adult patients in primary care would screen positive for ADHD. In psychiatric settings, screening prevalence would be even higher. Taken together, the data from this survey suggest that ADHD is one of the most common psychiatric disorders in adulthood.


Evaluation of Add-On Therapy for Bipolar Disorder Therapy

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