High Frequency of Bipolar Spectrum in Outpatients With Depression

Dear Editor:

The frequency of bipolar II disorder (BD II) is higher than the 0.5% community prevalence reported in DSM-IV-TR (1): rates are 11% in the community (2,3) and 30% to 60% in outpatients suffering from depression (4,5). Diagnostic criteria for “bipolar spectrum disorder” (6) include major depressive episode (MDE), no spontaneous mania or hypomania, family history of BD, and (or) antidepressant-induced mania or hypomania, plus some of the following: hyperthymic personality, many MDEs, short-duration MDEs, atypical and psychotic features, young and postpartum onset, short-duration antidepressant response, and no response to many antidepressants. The diagnosis of depressive mixed state (DMX), defined as MDE plus 3 or more concurrent hypomanic symptoms, has received clinical, family history, and psychometric validation (7–9) and replication (10,11). DMX is common in patients with BD II (up to 60%) and in MDE outpatients with major depressive disorder (MDD) (up to 30%). Links between MDD with DMX and BD II have been found (specifically, similar age of onset, atypical features, and bipolar family history) (7), supporting its inclusion in the bipolar spectrum (4,5). The current study aimed to determine the frequency of the bipolar spectrum in outpatients with depression, including bipolar spectrum disorder, MDD with DMX, and BD II.

Methods

Details can be found in previous reports (7–9). A sample of 433 MDE outpatients consecutively presenting in private practice (which is more representative of mood disorders treated in Italy) were interviewed with the Structured Clinical Interview for DSM-IV–Clinician Version (12), as modified by Benazzi and Akiskal (13), to focus probing for past hypomania more on overactivity (that is, increased goal-directed activity) than on mood change. Patients with the following conditions were excluded: substance-related and borderline personality disorders (rare in the setting) (14), significant general medical illnesses, and cognitive disorders. Often, family members or close friends supplemented clinical information. We investigated the BD I and II family history of first-degree relatives, using the Family History Screen (15). We defined DMX as MDE plus 3 or more concurrent hypomanic symptoms (7–9). Diagnostic criteria for bipolar spectrum disorder were followed: family history of BD, more than 3 MDEs, atypical features, and onset of first MDE before age 25 years. We used the t test to compare means (SDs) and the 2-sample test of proportion to compare proportions. We calculated 2-tailed P < 0.05.

Results

Of 433 patients, 260 (60%) suffered from BD II. Patients with BD II, compared with those having MDD, were significantly younger (mean age 41.7 years, SD 14.0 vs mean age 47.0 years, SD 15.6), had a lower age of onset (mean age 22.9 years, SD 10.8 vs mean age 32.0 years, SD 14.5), had a higher percentage of more than 3 MDEs (81.1% vs 58.9%), and had a higher percentage of atypical features (53.0% vs 25.4%), DMX (59.2% vs 29.4%) and family history of BD (54.1% vs 21.3%). In the sample with MDD, 17.9% suffered from bipolar spectrum disorder. When we added BD II and bipolar spectrum disorder, bipolar spectrum frequency was 67.2%. When we added BD II and MDD with DMX, bipolar spectrum frequency was 71.8%.

Discussion

We found high bipolar spectrum frequency according to 2 different definitions. The high frequency of BD II vs MDD was probably related to interview methods (13), which may have important treatment implications. Underdiagnosis of the bipolar spectrum can lead to underuse of mood stabilizers and to overuse of antidepressants (6). Overuse of antidepressants in treating BDs may increase mood instability.

Validated interviews, standard and systematic assessment, key informants, and an interviewer with clinical and research experience in mood disorders should have reduced the possibility of BD II overdiagnosis (BD II frequency was in the reported range; 4,5).

References

Dear Editor:

Adding anticonvulsants to antipsychotics has been reported to improve symptoms in schizophrenia (1). Dursun and others added lamotrigine to clozapine for treatment-resistant patients and obtained positive results over 24 weeks (2,3). Saba and others obtained similar results over 12 weeks (4). We further studied the effect of long-term adjunctive lamotrigine on standard antipsychotic monotherapy (specifically, haloperidol, risperidone, or clozapine) in patients with schizophrenia.

Subjects included 10 outpatients with a DSM-IV diagnosis of schizophrenia (8 men and 2 women aged 22 to 49 years; mean age, 30.7 years) enrolled in the following studies: RIS-INT-35 (n = 7), a double-blind study of risperidone vs haloperidol in new-onset schizophrenia; RIS-INT-57 and RIS-INT-63, (RIS-CONSTA studies, n = 1 each); and InterSePT study (n = 1) of clozapine vs olanzapine in suicidal patients with schizophrenia (5). Lamotrigine was used as open-label adjunctive therapy. The mean daily dosage of lamotrigine was 232.5 mg (range 25 to 400 mg/daily) over a mean period of 132 weeks (range 30 to 220 weeks).

Patients were treated for up to 220 weeks with no relapses. The medication was well tolerated, with no major adverse events. We measured changes in Positive and Negative Symptoms Scale (PANSS) scores and Clinical Global Improvement (CGI) scores from initiation of lamotrigine to most recent observation. No patient worsened significantly. Six out of 10 patients showed an average improvement of 1.5 points on the CGI. The mean (SD) change in CGI for the entire group was 4.1 (0.9) to 3.2 (0.8). Two of 10 patients had a marked decrease in their total PANSS scores (–39 and –49 points). The mean (SD) change in total PANSS score for the entire group was 77.3 (35.1) to 64 (25.5).

A model of psychosis based on N-methyl-D-aspartate (NMDA) antagonists (specifically, phencyclidine or ketamine) proposes that NMDA-receptor hypofunction contributes to the pathophysiology of schizophrenia (6). Anand and others reported that lamotrigine attenuates the neuropsychiatric effects of ketamine in healthy volunteers (7). Olney and others propose that lamotrigine may compensate for the functional hypo-NMDA state by suppressing excessive glutamate release and the spread of abnormal neural activity occurring in schizophrenia (8). Abnormal glutamatergic neurotransmission in the prefrontal cortex may represent a mechanism by which stress exacerbates symptoms in this vulnerable population (9).

Our data are consistent with the report of Dursun and others (2). We conclude that the addition of lamotrigine to low-dose risperidone, haloperidol, or clozapine produces overall benefit in patients with schizophrenia, including first-episode patients. Controlled clinical trials are warranted to evaluate efficacy and to clarify which patients benefit most from adjunctive lamotrigine.

References


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Evidence for Early Intervention in First-Episode Psychosis

Dear Editor:

Early intervention (EI) in first-episode psychotic illness is now a well-recognized practice, with good face validity for its effectiveness. In Australia, it is often performed by specialized teams of clinicians with smaller case-loads than those of general adult mental health services.
health workers. They focus on engaging the client, they consider medication (usually low-dosage atypical antipsychotics), and they attempt to restore vocational or educational functioning as symptoms improve. Families or other caregivers are closely involved in monitoring the patient’s mental state and are given education and support. Studies in this area encounter methodological difficulties, particularly in sample size, purity, and retrospective designs; however, emerging evidence supports this work.

Clinicians can now identify young people exhibiting prodromal symptoms of impending psychosis with increasing accuracy (1). However, clinical and ethical concerns exist with treatment at this stage (particularly with medication). Moreover, family reactions may possibly be unhelpful, and stigma accompanies the use of psychiatric services. Using psychosocial strategies targeted to the presenting complaint and monitoring without medication, except when positive symptoms develop, should allay many concerns (2). The attractiveness of this work from clinical, epidemiologic, and resource perspectives encourages further investigation.

Where positive symptoms develop, the duration of untreated psychosis (DUP) is emerging as a predictor of future disability and illness course, particularly when it exceeds 1 year. Specifically, Loebel found that, rather than premorbid adjustment, age of onset, mode of onset, or illness severity, DUP best predicted the time to treatment response (3). The Northwick Park Study showed that DUP of less than 1 year was a stronger predictor of avoiding relapse at 2 years than was maintenance-medicine status (4). Loebel postulated that active psychosis may represent the expression of a toxic neurobiological process, with each subsequent relapse rendering the patient more susceptible to another (3). For these reasons, early detection and prevention, or early treatment of relapse, are crucial foci of services. The etiology of delayed initial treatment is complex; it includes factors related to the mode and rapidity of illness onset, patient factors related to help seeking and the social support network, and systems issues relevant to the ease of service access (6). Therefore, any attempts to reduce the DUP must come from a multilayered approach; a broad educational focus is needed to reduce treatment delay and to ensure prompt, effective treatment from EI teams once psychosis is detected.

Eaton and others showed that many measures of symptomatology and psychosocial outcome taken 2 years after treatment of the initial psychotic episode are little different from those taken many years later (7). This suggests that after a “critical period” (8) early in the illness course, the sustained level of general disability does not change. This implication is double-edged: it provides further evidence against the progressive deterioration described by Kraepelin, but it also suggests that for many patients the expectations of functional or symptomatic recovery are limited after a certain period of being unwell. We propose that assertive attempts to reduce symptoms and restore social and vocational status during this period may have disproportionately beneficial long-term effects, although clear evidence for this does not yet exist.

Current research increasingly supports such clinical targets as preventing movement from the prodromal phase to acute psychosis, reducing the length of unresolved psychosis, and implementing assertive psychosocial interventions in the recovery period. Further longer-term prospective studies with data regarding illness course in treatment, as well as cost, will add to current knowledge.

References


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D2 Antagonist Augmentation in Patients With a Partial Response to Atypical Antipsychotics

Dear Editor:

Atypical antipsychotic medications have become the first-line treatment for schizophrenia (1) because of their broader efficacy and lower risk of extrapyramidal symptoms (EPS) and tardive dyskinesia (TD) (2). Clozapine is indicated in treatment-resistant schizophrenia (3); however, for patients who cannot tolerate clozapine therapy or who reveal only partial response to it (4), targeted treatment strategies tailored to the variable expression of schizophrenia in each patient are in order (5). Coprescribing typical, atypical, and depot antipsychotic agents may be considered (6).

We report 4 cases of individuals who met DSM-IV criteria for schizophrenia that only partially responded to monotherapy. For 12 weeks, a classic antipsychotic agent was added to ongoing atypical drug
therapy on an open-label basis. Results were assessed with the Clinical Global Impression (CGI) scale.

Case Report 1
A woman aged 29 years, who had been diagnosed at age 16 years with unspecified schizophrenia, had a baseline CGI score of 6. Olanzapine was initiated at 20 mg daily, and anxiety and troubling ideas of reference ameliorated (CGI score, 5). After 6 weeks, zuclopenthixol was added and titrated to 60 mg daily. The patient’s ideas of reference disappeared and anxiety diminished (CGI score, 4).

Case Report 2
A man aged 23 years, who had been diagnosed at age 17 years with severe disorganized schizophrenia (CGI score, 7), had disorganized speech and behaviour that did not respond to typical antipsychotics. Olanzapine 20 mg daily yielded only a minor improvement. Clozapine 250 mg daily was initiated, and the patient showed remarkable improvement (CGI score, 5). Three months later, clozapine 80 mg daily was added, and further progress was noted (CGI score, 4).

Case Report 3
A woman aged 40 years, with severe paranoid schizophrenia onset at age 24 years, was socially isolated following her last psychotic episode (CGI score, 7). Olanzapine 20 mg daily diminished her paranoid ideation (CGI score, 5). Three months later, her treatment regimen was augmented with haloperidol 15 mg daily. Her functioning further improved, and paranoid ideation ceased (CGI score, 4).

Case Report 4
A man aged 52 years had chronic, unremitting, paranoid schizophrenia beginning at age 24 years. He was hospitalized following severe paranoid delusions (CGI score, 7). Treatment with olanzapine 20 mg daily yielded mild improvement (CGI score, 6). Six weeks later, perphenazine was added and titrated to 16 mg daily. His paranoid delusions gradually lost their disabling nature and improvement was noted (CGI score, 5).

Discussion
Medical management of treatment-refractory psychosis patients poses a difficult challenge. Although widespread use of atypical antipsychotic agents has improved patient outcomes, some patients still do not respond to treatment. The Texas Medication Algorithm Project (7) suggested a combination of typical and atypical medications for partial responders. The rationale lies in their different mechanisms of action: dopamine and postsynaptic 5-HT2A blockade. Combined therapy has been described in case reports, but randomized trials are lacking (8–9).

In our 4 chronic schizophrenia patients, combined typical and atypical antipsychotic therapy led to marked improvement. We chose adjuvant classic antipsychotic agents according to each individual patient’s prior side effect profile.

Though remission was not achieved, the polypharmacy reduced side effects and enabled their discharge to day care. This treatment alternative provides an additional option in the ongoing struggle to treat patients with refractory schizophrenia.

References