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Editor:
Lawrence H. Price, M.D.

Highlights...

Our top story this month examines whether quetiapine is effective for acute bipolar depression. We spoke with lead author **Joseph Calabrese, M.D.,** about the importance of this new research. Be sure to read the **Letter from the Editor** on page 7 for Dr. Price's thoughts on this.

The Texas Medication Algorithm Project has just released the latest algorithm for bipolar I disorder. **Charles Bowden, M.D.,** tells us what is new and exciting about the updated version.

Inside

NEW RESEARCH ON BIPOLAR DISORDER

Quetiapine shows promise in treating acute bipolar depression

About 10% to 20% of patients with bipolar disorder commit suicide, typically while depressed. Those who live with bipolar depression "spend the majority of their symptomatic life depressed," said Joseph R. Calabrese, M.D., director of the Mood Disorders Program at the University Hospitals of Cleveland. Unfortunately, "this is the phase of the illness that we do the least well at managing," Calabrese told *The Update.*

In a recent paper, Calabrese, professor of psychiatry at Case Western Reserve University, and his colleagues noted that despite the existence of effective medications for the manic phase of bipolar I disorder, researchers know less about treating the acute depressive phase. As Calabrese and associates wrote, lithium often gives insufficient relief, and more well-controlled studies are needed to affirm the efficacy of lamotrigine (Lamictal).

précis

- Large, randomized, double-blind, 8-week study of 300 or 600 mg of quetiapine once daily for acute bipolar I or II depression
- Quetiapine surpassed placebo in relieving depression, enhancing sleep, reducing anxiety, and improving quality of life

Research suggests that the atypical antipsychotic olanzapine (Zyprexa), used alone or with the antidepressant fluoxetine (Prozac), may relieve depressive episodes in bipolar disorder. Some studies have suggested that another atypical antipsychotic, quetiapine

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TEXAS MEDICATION ALGORITHM PROJECT

New algorithm available for Bipolar I disorder — more detailed information incorporated

The Texas Medication Algorithm Project (TMAP) has updated its algorithm for bipolar I disorder to incorporate data that have become available since the previous revisions were made in 2000. With this update, the project has moved into Phase 4 and will now be known as the Texas Implementation of Medication Algorithms (TIMA). (See box, "About TMAP/TIMA," p. 5.)

In May 2004 the Consensus Conference Panel on Medication Treatment of Bipolar Disorder, made up of academic psychiatrists, clinical psychopharmacology specialists, community mental health physicians, advocates and consumers, came together in Dallas to review the newest available data. After evaluating the evidence — both published and unpublished — the panel members made their recommendations for change. This time, the panel developed two stand-alone algorithms: one for patients with hypomanic/manic/mixed episodes and another for patients presenting as primarily depressed.

précis

- New algorithm provides specific approaches to managing 3 key phases of bipolar I disorder: manic/hypomanic/mixed, depressed, and maintenance.

Charles L. Bowden, M.D., a member of the Consensus Conference Panel and professor of psychiatry at the University of Texas Health Science Center at San Antonio, says

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DRUG-DRUG INTERACTIONS

No interaction found between paroxetine and alprazolam

By Y.W. Francis Lam, Pharm.D.

It is not uncommon for depressed patients to have insomnia, anxiety, and similar symptoms for which the use of a benzodiazepine is indicated. Moreover, selective serotonin reuptake inhibitors (SSRIs), in addition to their use in depression, are often used in the management of generalized and social anxiety disorders, panic disorder, obsessive-compulsive disorder, and posttraumatic stress disorder, either alone or in combination with a benzodiazepine.[1]

The SSRIs have variable inhibitory effects on the cytochrome P-450 enzyme system and hence the elimination of a wide variety of concurrently administered drugs. The specific cytochrome P-450 enzymes that mediate the elimination of paroxetine (Paxil) and alprazolam (Xanax), two drugs frequently prescribed together, are known to be different. Therefore, the potential of an interaction between the two drugs should be minimal during concurrent use. However, until recently there had been little study of this issue in humans. Investigators from Spain recently evaluated the potential and clinical significance of this combination.[2]

CLINICAL INVESTIGATION

25 healthy subjects given different combinations of alprazolam, fluoxetine and placebo

No evidence found of an interaction between alprazolam and fluoxetine

Clinical Study

To evaluate the potential pharmacokinetic and pharmacodynamic interaction between paroxetine and alprazolam after single and multiple dosing, 25 healthy subjects (nine male and 16 female) were enrolled in a randomized, double-blind, double-dummy, placebo-controlled, 4-period crossover study. The mean age of the subjects was 26 ± 4 years and the mean height and weight were 168 ± 7 cm and 64 ± 9 kg, respectively.

Each volunteer received each of the four treatment sequences, consisting of paroxetine 20 mg and placebo alprazolam; alprazolam 1 mg and placebo paroxetine; paroxetine 20 mg and alprazolam 1 mg; and placebo alprazolam and placebo paroxetine. All study medications were administered daily in the morning for 15 days, with a one-week washout period between each of the four treatment phases.

For each treatment sequence, pre-dose blood samples were obtained on the mornings of days 13 to 15 for determination of plasma concentrations of both paroxetine and alprazolam and assessment of steady-state conditions for both drugs. In addition, multiple blood samples were obtained on day 15 for 12 hours after administration of the morning dose, for determination of paroxetine and alprazolam pharmacokinetic parameters. For evaluation of the pharmacodynamic consequences of the interaction in each treatment sequence, investigators performed consecutively in the same order six different psychomotor performance tests to determine the presence of synergistic central depressant effects and five visual analog scales to assess different mood variables.

Based on comparisons of pre-dose paroxetine and alprazolam concentrations, all 22 subjects who completed the study achieved steady-state dosing conditions for both drugs in all treatment sequences. Comparisons of maximal plasma concentrations and area under the curve (AUC) (a measure of systemic drug exposure) indicated that the steady-state pharmacokinetics of paroxetine and alprazolam were not significantly different when administered alone or in combination.

Analysis of pharmacodynamic measurements indicated that there were no differences in baseline score across treatment sequences for any of the psychomotor performance tests or visual analog scales. In addition, there were no differences in

changes from baseline score after steady-state dosing in any treatment sequence.

Bottom line

Based on the pharmacokinetic parameters of alprazolam and paroxetine derived from the four treatment sequences, there was no evidence of an interaction between the two drugs. In addition, there were no differences in the extent of psychomotor performance impairment and sedation induced by alprazolam alone or in combination with paroxetine, suggesting a lack of pharmacodynamic interaction as well. The incidence of side effects was consistent with the pharmacodynamic data, with no differences between combined treatments and monotherapy.

REFERENCES

1. Greger KJ, Way K, Young CH, et al.: Concomitant us of selective serotonin reuptake inhibitors with other cytochrome P450 2D6 or 3A4 metabolized medications: how often does it really happen? *J Affect Disord* 1997; 46:59-67.

2. Calvo G, Garcia-Gea C, Luque A, et al.: Lack of pharmacologic interaction between paroxetine and alprazolam at steady-state in healthy volunteers. *J Clin Psychopharmacol* 2004; 24;268-276.

WHAT'S NEW IN RESEARCH

Ziprasidone for acute bipolar I mania

précis

- Three-week double-blind, placebo-controlled replication trial confirms Ziprasidone is efficacious for symptoms of bipolar mania
- Mania Rating Scale improvement (-11.1) significant in active treatment group vs. placebo (-5.6)
- Treatment-related AEs include somnolence, headache, and EPS and lead to 5.8% subject withdrawal

In a double-blind, placebo-controlled replication trial, researchers confirmed the favorable results of a similarly designed trial of ziprasidone (Geodon) in acute bipolar manic or mixed states (Keck et al., 2003), suggesting that this atypical antipsychotic is well-tolerated, rapidly efficacious, and superior to placebo in symptom reduction.

The 21-day study randomized 206 male and female inpatients to receive either ziprasidone (N=140) or placebo (N=66). Subjects were 18 years or older (mean 39±11.6) and had a DSM-IV primary diagnosis of bipolar I disorder, most recent episode manic or mixed, as confirmed by the Structured Clinical Interview for Axis I Disorders I (SCID). Eligible subjects' most recent episode began ≤3 months prior to screening.

In a flexible-dose design, ziprasidone dosing was initiated at 80 mg/day, with a maximum adjustment of 40 mg/day by study day 2 and a final dose within a range of 80-160 mg/day (40-80 mg BID) for the duration. The mean daily dose was 112 mg/day.

The primary efficacy measure was the Mania Rating Scale (MRS), derived from the Schedule for Affective Disorders and Schizophrenia—Change Bipolar Scale (SADS-CB). Enrolled subjects had an MRS score ≥14 at both screening and baseline; mean baseline MRS scores were 26.2 (±7.19) for the ziprasidone group and 26.4 (±7.54) for the placebo group.

While both groups saw improvement in mean MRS scores from baseline to endpoint (Day 21), improvement in the ziprasidone group was superior to that with placebo: -11.1 vs. -5.6 ($p < 0.01$). This advantage was apparent as early as Day 2 and maintained from Day 7 to study end (no statistically significant difference from placebo was seen at Day 4). The ziprasidone group also saw a higher endpoint responder rate than the placebo group, 46% versus 29%, respectively ($p<0.05$).

Ziprasidone showed a significant advantage over placebo on mean improvements from baseline to endpoint on the MRS subscales Manic Syndrome and Behavior Ideation, as well as on the Clinical Global Impression-Severity Scale (CGI-S)($p\leq0.001$).

On the Hamilton Depression Rating Scale (HAM-D) and the Montgomery-Asberg Depression Rating Scale (MADRS), although ziprasidone showed an advantage over placebo at most study points, endpoint differences were not significant.

Regarding the need for concomitant benzodiazepine use (lorazepam, temazepam or diazepam), the two groups were comparable on mean daily and cumulative doses. Twenty-one (15%) of ziprasidone-treated subjects and 11 (17%) placebo-treated patients took at least one dose of lorazepam after Day 9.

The most common treatment-related adverse events (AEs) were somnolence, headache, extrapyramidal symptoms, dizziness, akathisia, tremor and nausea. Overall, 5.8% of those treated with ziprasidone discontinued due to AEs, vs. 1.5% of those taking placebo.

The incidence of clinically significant weight gain (≥7%) was comparable between the two groups. The study authors point out that this low risk for weight gain distinguishes ziprasidone from some other atypical antipsychotics, such as olanzapine and clozapine.

The study authors note that in a final event, a 41-year-old male in the active treatment group committed suicide on the day of discharge. Ziprasidone 80-120 mg/day had been discontinued at Day 9, after evidence of moderate restlessness. Topiramate was started on Day 11, followed by sertraline and quetiapine. The investigator felt the suicide was due to the disease under study.

Study limitations include a carefully selected subject group that may not represent typical patients; a failure to explore the complete ziprasidone dosage range; and a study duration that looked only at the acute treatment period. The study authors recommend trials of longer-term treatment.

*Funding provided by Pfizer, Inc.

Potkin SG, Keck PE, Segal S, et al. Ziprasidone in acute bipolar mania: a 21-day randomized, double-blind, placebo-controlled replication trial. *J Clin Psychopharmacol* 2005; 25:301-310. E-mail: sgpotkin@uci.edu.

Keck PE, Versiani M, Potkin S, et al. Ziprasidone in the treatment of acute bipolar mania: a three-week, placebo-controlled, double-blind, randomized trial. *Am J Psychiatry* 2003;160:741-748.

Divalproex for pediatric mixed mania

A new open-label study suggests that divalproex (DVPX) may be safe and potentially effective over a 6-month period in children with episodes of mixed mania in bipolar disorder. While the results of this short-term trial with DVPX look promising, the study's researchers, Manu N. Pavuluri, M.D., and colleagues at the

continued on next page

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Pediatric Mood Disorders Research Program, University of Illinois at Chicago, suggest that further studies are still needed using larger samples in placebo-controlled, randomized designs.

Mixed manic episodes are common in pediatric bipolar disorder (PBD) and often result in poor recovery and high relapse rates. The aim of the study was to examine the safety and potential for efficacy of DVPX over a 6-month period for episodes of mixed mania in PBD. Initial screening was carried out among outpatients at the Pediatric Mood Disorders Clinic. Inclusion criteria included a diagnosis of bipolar disorder I (BD type I) mixed episode using DSM-IV criteria for manic and depressed episodes at study entry; age 5-18 years; and baseline score of >20 on the Young Mania Rating Scale (YMRS). Exclusion criteria included serious medical problems; active substance abuse; history of allergy to study medications; diagnosis of another DSM-IV Axis I disorder (with the exception of attention deficit hyperactivity disorder [ADHD]) requiring psychopharmacological treatment; and a history of worsening symptoms or poor response to DVPX that required alternative treatment.

Cross-titration at study entry was not allowed. Stimulants were continued among subjects on a stable dose. The washout period involved tapering previous medications for 1 week prior to study entry. At study entry, serum concentrations had to be below 0.3mEq/L of lithium, 30 mg/L of DVPX, or 3 mg/L of carbamazepine to ensure adequate washout from previous mood stabilizers.

A total of 35 subjects who completed baseline measures underwent standard clinical assessment consisting of a diagnostic interview with patient and family as well as child and parent/legal guardian interviews using the Washington University Kiddie Schedule for Affective Disorders and Schizophrenia (WASH-U-KSADS). Primary outcome measures were change of score on the YMRS and Child Depression Rating Scale-Revised (CDRS-R). Response was defined as ≥50% change from baseline on YMRS, and ≥40% on CDRS-R.

précis

- A prospective, 6-month, open-label trial examining divalproex (DVPX) in 34 children with mixed mania
- Results show DVPX safe and effective over a 6-month period, but further studies are needed with larger samples using placebo-controlled, randomized designs

DVPX 15-20 mg/kg/day was given, with the dose initiated at 250-500 mg on day one and increased to the full dose over 1 week. Increments in dosing were determined by tolerability, serum levels (15-120 µg/mL), and clinical progress. To avoid a high dropout rate, minimal use of rescue medications was allowed. Risperidone was allowed for a maximum of 7 consecutive days and for a total of 7 days per subject during the entire trial. Benztropine was allowed on an as-needed basis for extrapyramidal symptoms (EPS) when risperidone was used. Low doses of trazodone were given for acute sleep disturbance for a maximum of 3 consecutive doses on 2 occasions.

The final sample was 34 due to 1 dropout because of worsening symptoms in week 1. Mean length of treatment was 5.53 visits over a period of 5.05±3.36 months. The mean DVPX dose was 950±355 mg and mean serum level was 109±33 µg/mL.

Results showed that manic symptoms improved within 3 months, and depressive symptoms improved in 2 months. According to Pavuluri and colleagues, "This rapid, significant improvement in symptoms during the initial phase persisted over the entire 6 months. The response rate was 73.5% and the remission rate was 52.9% in the ITT [intent-to-treat] sample." Significant improvements from baseline were seen for mean scores on all outcome measures ($p<0.001$). DVPX was well tolerated and most adverse events were mild to moderate. The most frequently reported were weight gain (58.8%), sedation (47.1%), increased appetite (47.1%), cognitive dulling (41.2%), nausea (26.5%), stomach pain (23.5%), agitation (17.6%), and tremors (14.7%).

At the time of study design, blood testing was considered in female subjects for bioavailable androgens (free testosterone) if menstrual irregularities, obesity or hyperandrogenism were present. "During this study," the authors write, "indication did not arise to test for hyperammonemia or testosterone levels. Future studies may yield useful information by conducting these tests in asymptomatic subjects to uncover problems such as encephalopathy or polycystic ovarian syndrome."

The authors conclude "Our trial suggests that DVPX may be effective and safe over a 6-month period for mixed manic episodes in PBD. An ideal treatment for these children would be to start with a single agent, using therapeutic blood levels for an adequate period of time. This study attempted to address some of these challenges with DVPX."

*Funding from NIH, Campus Research Board Award, and Abbott Laboratories.

Pavuluri MN, Henry DB, Carbray JA, et al.: Divalproex sodium for pediatric mixed mania: a 6-month prospective trial. *Bipolar Disorders* 2005; 7(3):266-273. E-mail: mpavuluri@psych.uic.edu.

TMAP ALGORITHM

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that in addition to incorporating new data, the algorithms provide a different and more detailed treatment of depression, and "in terms of maintenance, it factors in tolerability in an almost co-equal way with efficacy."

Integrated information

At first glance, the updated algorithm looks to have changed a great deal more than that, as the previous revision, done in 2000, contained seven stages while the current update contains only four. This is a result of the authors' efforts to integrate information about tolerability and safety throughout the entire document, which resulted in some "substantial shifting of the sequence of recommended treatments," says Bowden. "Nothing was left out."

In a commentary published in the same issue of the *Journal of Clinical Psychiatry* in which the new algorithm appears, Roy H. Perlis, M.D. and Paul E. Keck, Jr. M.D. discuss notable aspects of this update:

• The recommendations are based on the assumption of an unrestricted formulary, so that the best tolerated form of a medication should always be used.

• The guidelines specify general principles of treatment, reminding us that the goals of treatment are to help people with bipolar I disorder get not just better but well.

• Structured psychotherapies are also endorsed, where clinically appropriate,

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although they are explicitly not a focus of these algorithms.

• Where the 2000 algorithm focused on mood elevation, the newer algorithm provides specific approaches to managing the three key phases of bipolar I disorder: manic/hypomanic/mixed, depressed, and maintenance.

Practitioners familiar with the previous versions of the algorithm will notice that this update is more dependent on the atypical antipsychotics than were previous versions.

"Mostly, this shows up in the section on mania," says Bowdwn. "As a class these drugs have some general acute phase benefits on mania and the guideline had to take that into account."

Bowden says the bottom line for this update is that the panel members, with no commercial input into the process at all, "tried to look at the best evidence in an algorithmic fashion addressing questions the way a clinician has to address them, so it probably comes closer to the issues that a psychiatrist or other clinician faces in his or her practice than any other set of guidelines."

As an example, he says that all guidelines — including the Expert Consensus Guidelines and the American Psychiatric Association's guideline — recommend stopping antidepressants as soon as the patient is out of a depressive episode.

"I've been guilty of that since I've been a part of these other guidelines, and it made a certain degree of sense to recommend this because the antidepressants are associated with mood destabilization," he says. "That turns out to probably be bad advice, because there is some evidence that some patients do better now if an antidepressant is continued, so if you look at the evidence you've got to part company with what's in the expert consensus guideline or what's in the 2002 revised APA guideline."

The authors point out that practitioners can view these materials as a codification of available evidence and expert opinion intended to guide clinician decision-making, but not as rigid or choice-limiting dictates.

Phase IV

"This is the fourth version of a Texas guideline for the treatment of bipolar disorder, and each version incorporates significant changes in response to increased treatment options, clinical research findings and clinical experience," the authors write. "The remarkable changes in the Texas Medication Algorithms for bipolar I disorder over the last 7 years are a reflection of the rate at which the field is advancing. The opportunity to update medication treatment algorithms in response to new developments is central to the strengths and limitations of medication algorithms. As the scientific findings in both acute and maintenance treatment of bipolar disorder continue to advance, these materials will be revised to reflect changes in our knowledge."

Bowden concludes, "A clinician could go to this and find direct, non-verbiage-filled answers, either in the text or in the figures, to… a good portion of the kinds of questions that he has problems in answering." He adds, "In other words, don't just put this on the shelf, it has a practical recommendation to it."

About TMAP/TIMA

The Texas Medication Algorithm Project (TMAP) was started in 1996 as a public and academic collaborative effort to develop, implement and evaluate a set of medication algorithms for major adult psychiatric disorders treated in the Texas public mental health sector. A major result of this project has been the development of TMAP, now the Texas Implementation Medication Algorithns (TIMA), for schizophrenia, major depressive disorder and bipolar disorder. The project consists of four phases:

Phase 1 involved the creation of the algorithms through consensus conferences. The guidelines that were developed (in Phase 1) were based on scientific evidence and expert clinical consensus. The products that were created at the end of the conferences were specific stepwise graphical sequences (algorithms). These algorithms illustrated the order (strategies) and method (tactics) to use various psychotropic medications for each of the above mentioned conditions.

Phase 2 was a feasibility trial to evaluate the suitability and applicability of the algorithms. This portion of the project was done to see if the algorithms could be adequately implemented by physicians and clients and to estimate the outcomes that were achieved. An additional aspect of Phase 2 included the evaluation of resources needed to implement the algorithms. Thus, TMAP Phase 2 provided a preliminary estimate of the algorithm's effectiveness.

Phase 3 was a prospective comparison of the clinical outcomes and economic costs of using the algorithms with "treatment as usual" within the Texas Mental Health and Mental Retardation system (TXMHMR). Impact on systems outside of mental health, i.e., general medical, service utilization, criminal justice, etc., was also studied.

Phase 4 — described in the accompanying article — is the actual roll-out, or implementation, of these algorithms in the "real world" of the clinics and hospitals of the TXMHMR. This portion of the project began as the Texas Implementation of Medication Algorithms (TIMA). It is based on the findings and experiences of the previous phases.

One of the goals of the TMAP/TIMA project is to develop and continuously update treatment algorithms and to train systems to use them in order to reduce the immediate and long-term emotional, physical and financial burdens of mental disorders for clients, their families, and their health care systems.

Collaboration for this project has included TXMHMR, The University of Texas at Austin College of Pharmacy, The University of Texas Southwestern Medical Center at Dallas, The University of Texas Health Science Center at San Antonio, parent and family representatives, and representatives from various mental health advocacy groups, i.e., NAMI-Texas, DMDA, Texas MH Consumers, and the Mental Health Association of Texas.

Graphic representations of the previous algorithms and other support materials for the project are available at www.dshs.state.us/hprograms. Graphics for the phase 4 update are not yet posted on the site but can be seen in the *Journal of Clinical Psychiatry* article.

SOURCE:

Suppes T, Dennehy EB, Hirshfeld MA, et al.:The Texas Implementation of Medication Algorithms: Update to the Algorithms for Treatment of Bipolar I Disorder. *J Clin Psychiatry,* 2005; 66(7): 870-886. Correspondence to: Trisha Suppes, M.D., Ph.D., Associate Professor of Psychiatry, University of Texas, Southwestern Medical Center at Dallas, 5323 Harry Hines Boulevard, Dallas, TX 75390-9121; e-mail: trisha.suppes@utsouthwestern.edu

Perlis RH, Keck PE Jr.: The Texas Implementation of Medication Algorithms Update for Treatment of Bipolar I Disorder. *J Clin Psychiatry,* 2005; 66(7): 818-820. Correspondence to: Roy H. Perlis, M.D., Bipolar Clinical and Research Program, 15 Parkman St., WACC 812, Boston, MA 02114; e-mail: rperlis@partners.org.

For more information about the updated algorithm and support materials, visit the TIMA Web site at www.dshs.state.us/mhprograms.

QUETIAPINE

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(Seroquel), may also exert antidepressant properties. Quetiapine alleviates acute bipolar mania.

Against this backdrop, Calabrese and others in the BOLDER (BipOLar DEpRession) Study Group decided to test quetiapine's usefulness for treating acute bipolar depression. Describing their study, they wrote, "To our knowledge, this is the first randomized, parallel-group, placebo-controlled trial to evaluate the efficacy of quetiapine in bipolar depression."

Most studies of acute bipolar depression have looked at patients with bipolar I disorder, Calabrese said. In contrast, the BOLDER trial also enrolled patients with bipolar II disorder, in which the high periods present as hypomania rather than full-fledged mania. The study also recruited patients with rapid cycling, despite what Calabrese calls the "conventional wisdom" that "rapid cycling is a predictor of non-response to treatment."

Results promising

Quetiapine improved MADRS scores significantly better than placebo at week 1 and at all subsequent assessments. Effect size calculations showed that the 300 mg dose produced a moderate effect and the 600 mg dose a large one. Analyses using the Hamilton Depression Scale obtained parallel results.

A drop in MADRS scores by half or more relative to baseline comprised a protocol-defined positive clinical response. After two months, about 58% of patients in each quetiapine group, versus 36% of the placebo group, met this criterion. Differences from placebo emerged by week 1 for the higher dose and by week 2 for the lower dose. By the final assessment, 53% of those in both quetiapine groups, versus 28% in the control group, met the study criterion for remission by scoring 12 or less on the MADRS. Patients on quetiapine 300 and 600 mg reached remission in an average of 29 and 27 days, respectively; those on placebo took 65 days.

Patients prescribed the 300 mg dose improved more on 8 of 10 MADRS items than the placebo group; those taking 600 mg improved on 9 items. Both doses curbed suicidal thinking, but only the higher dose did so by week 1. As Calabrese noted, "Seroquel was twice as effective as placebo in reducing suicidal thoughts." Although other drugs, including lithium, curtail suicidal tendencies long-term, Calabrese said this study is the first to find a medication to make "suicidal thoughts go away right away."

In looking at subgroups of patients, the study found large effects for each dose of quetiapine on MADRS scores in bipolar I patients. For bipolar II patients, although the drug was superior to placebo at most assessments, it yielded only small effects and failed to help these patients in the long run. Rapid-cycling patients, despite their typically poor prognosis, improved after 8 weeks on quetiapine.

Quetiapine enhanced patients' sleep and quality of life, and diminished their anxiety. It is this anxiolytic effect that makes the drug Calabrese's first choice for treating agitated or anxious patients with bipolar depression.

The CGI scales confirmed the drug's edge over placebo. At the final assessment, significantly more quetiapine than placebo patients were rated as "normal, not at all ill" or "borderline ill." Patients taking quetiapine were also more likely to receive ratings of "much" or "very much" improved.

Study Details

The 8-week, double-blind trial enrolled 542 outpatients, 18 to 65 years old, with bipolar I or II disorder who were experiencing an episode of major depression. It randomly assigned 360 people with bipolar I disorder and 182 with bipolar II disorder to one of three treatment groups in a design stratified by bipolar type. Depending on their group assignment, patients took a once daily bedtime dose of either quetiapine 300 or 600 mg, or placebo.

The study evaluated the effects of quetiapine on participants' depression, anxiety, sleep, and quality of life. Each assessment included the Montgomery-Åsberg Depression Rating Scale (MADRS), the Hamilton Depression Rating Scale, and the Hamilton Anxiety Rating Scale, as well as the Clinical Global Impressions (CGI) severity of illness and improvement scales. They tracked treatment-emergent mania using the Young Mania Rating Scale.

Adverse events

Over a fourth (26%) of the patients taking quetiapine 600 mg left the study due to adverse events, compared to 16% of those on 300 mg and 9% of those on placebo. However, the two quetiapine groups experienced similar rates of serious adverse events and treatment-emergent mania as the placebo group.

Patients on quetiapine most commonly reported dry mouth, sedation, somnolence, and dizziness. Most patients who quit the study did so during the first week, usually because of sedation or somnolence. Calabrese said that over half of the quetiapine patients experienced sedation or somnolence, yet those taking the drug experienced less lassitude than controls. The tranquilizing effects of quetiapine did not appear to be responsible for its overall efficacy, since "even in those who did not have sedation or somnolence, there was still this robust antidepressant effect," Calabrese explained.

Patients on quetiapine also gained weight. In two months, 8% of the lower-dose group, 9% of the highest-dose group, and 2% of controls gained at least 7% of their baseline weight. Despite its effects on weight, quetiapine did not increase appetite.

One drug for both phases?

"Seroquel worked, and it had a large effect," Calabrese said, adding that it achieved a "very high rate of remission." In patients with bipolar depressive episodes, "It's quite reasonable to consider Seroquel," he said, particularly for those who also experience mania, an FDA-approved indication for this agent. Even so, he suggested warning patients about possible sedation or somnolence. He wishes the study revealed more about the best dosage to use; since both doses showed similar efficacy, a lower one might have sufficed.

As Calabrese said, "The BOLDER Study is the first time one drug has been shown to work in both phases of the illness." If the next BOLDER Study, now underway, replicates these findings, indications for the use of quetiapine in the management of bipolar disorder could be significantly expanded.

*Funded by AstraZeneca Pharmaceuticals

Calabrese JR, Keck PE Jr., Macfadden W, et al.: A randomized, double-blind, placebo-controlled trial of quetiapine in the treatment of bipolar I or II depression. *Am J Psychiatry* 2005; 162(7):1351-1360. E-mail: Joseph.Calabrese@uhhs.com.

Letter from the Editor: *Lawrence H. Price, M.D.*

Quetiapine for bipolar disorder

This essay has its origins in a conversation I was having with a colleague on the *Update*'s Editorial Advisory Board. Or, to be more accurate, in response to the challenge issued by my colleague as we were discussing the paper by Calabrese et al. on quetiapine [Seroquel], the subject of this month's lead story. It went something like this:

Colleague: Well, people are using atypical antipsychotics for all kinds of things. Even depression. And there are studies to back it up.

Editor: What studies?

Colleague: How about the Calabrese study in the July issue of the American Journal? Quetiapine was effective in treating acute bipolar depression.

Editor (skeptically): You believe that?

Long pause.

Colleague (tossing down gauntlet): I thought you were the one who's always talking about evidence-based medicine?

Editor: Uh…

I've been pondering this exchange. The Calabrese study is well-designed, well-powered, and clearly presented. The results are unambiguous: quetiapine at 300 mg/day and 600 mg/day was more effective than placebo in outpatients with bipolar I and II depression who were on no other mood-stabilizing or antidepressant medications. The drug was reasonably well-tolerated and there were no serious adverse effects clearly attributable to it. Benefits were clinically meaningful as well as statistically significant. Why would I have reservations?

Partly, no doubt, stemming from my innate skepticism about efforts by pharmaceutical manufacturers to extend the markets for their products. The atypical antipsychotics are particularly susceptible to such efforts, because they tend to be nonspecifically calming, fairly well-tolerated, and fairly safe (at least in the short term). Quetiapine certainly fits the profile.

At a deeper level, though, it's this: this is a study which confounds what we think we know. The conventional wisdom is that antipsychotics aren't very effective in treating depression, unipolar or bipolar. The pharmacology of quetiapine doesn't appear to be fundamentally different from that of other atypical antipsychotics. Why would it work?

A couple of points are worth noting. One is that two other atypical antipsychotics, clozapine [Clozaril] and olanzapine [Zyprexa], have also been reputed to have some antidepressant properties. Indeed, olanzapine monotherapy was more effective than placebo in a well-controlled study of bipolar I depression, although effects were modest.[1] Interestingly, clozapine, olanzapine, and quetiapine are all dibenzoxazepines, sharing a similar chemical structure.

The second point relates to neuropharmacology. Yatham et al.[2] have recently presented a detailed consideration of basic actions of quetiapine and olanzapine which could contribute to antidepressant effects. An intriguing question is the role of 5HT2A receptor antagonism and down-regulation (although other neuroleptics also have these properties). Fast dissociation from the D2 receptor may be a necessary condition for antidepressant effects in this context, although the importance of this mechanism is still controversial.[3,4]

Clearly, the clinical evidence for quetiapine as a treatment for bipolar depression has outstripped our ability to understand or explain it. In the history of psychopharmacology, that is hardly an unusual circumstance, even though one might have hoped we'd progressed to a more rational and mechanism-driven method of discovery. It would be wrong to discount the Calabrese study because its outcome doesn't conform to our expectations. While critical appraisal is indispensable in the evaluation of new ideas, so is openness. This study reminds us that it's a fine balance.

The usual caveats apply. Treatment-resistant patients were generally excluded from this study, as were inpatients, those with serious suicidality, and those with substance abuse. Response rates were robust, but still less than 60% for active drug. The study needs to be replicated. But the bottom line is that this could be an important step in the development of more effective treatments for bipolar depression.

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NEWS NOTES

Beta-blockers could treat PTSD

The journal Nature reported this week that psychiatrists believe they have discovered a breakthrough treatment for post-traumatic stress disorder (PTSD): beta-blockers, the drugs commonly used to treat high blood pressure and heart problems. Researchers explain that beta-blockers can compromise the brain's ability to store memories — good or bad — and that if timed correctly, these drugs could pinpoint traumatic recollections and effectively block them. According to the investigators, this idea is timely, given the trauma surrounding recent terrorist attacks, but could also be controversial; mental health experts fear that this radical treatment tool could be abused. [Embargoed press release, *Nature* July 25.]

Crawford named to lead FDA

The Senate has confirmed Lester Crawford as commissioner of the U.S. Food and Drug Administration. Crawford has served for the past year as acting commissioner, but his official nomination had been delayed for months due to concerns expressed by lawmakers in both parties, particularly regarding the over-the-counter sale of the emergency contraceptive pill called Plan B. Lawmakers finally voted 78-16 in favor of the nomination. [Associated Press]

Paper reports pregabalin withdrawal effects

A recent paper reported an incident of cerebral edema in an 80-year-old woman following abrupt withdrawal from pregabalin (Lyrica), an antiepileptic drug made by Pfizer with expected release this fall. The woman, suffering from severe pain associated with shingles, was taking part in a clinical trial of Lyrica. Within a week after terminating the drug, she experienced delirium and hallucinations, and an MRI revealed swelling similar to that seen in epileptic patients who abruptly stop their drugs. Her severe response has raised concern about withdrawal effects in general, but particularly in drugs such as Neurontin, another anticonvulsant that is frequently used to treat psychiatric illnesses such as bipolar disorder, anxiety and panic disorder, though not FDA-approved for these purposes. [*Annals of Neurology* early view online, August]

FDAnews creates warning letters database

The FDAnews website, a provider of news and information for executives in industries regulated by the U.S. Food and Drug Administration, has announced the creation of the FDAnews Warning Letters Database, with real-time access to every FDA warning letter created since 2000, keyword searchability and weekly email alerts. Paid subscriptions are available. [www.fdanews.com]

CASE REPORT

Neutropenia induced by sertraline and mirtazapine

Patient: Female, 44 y.o.

Medications: Mirtazapine (Remeron), sertraline (Zoloft), sultamicillin

Comment: A 44-year-old woman with no medical history was administered mirtazapine 30 mg/day to treat major depressive disorder. After three weeks, she complained of severe sore throat and loss of appetite, and had an aphthous ulcer in her oral mucosa. When blood counts revealed neutropenia (WBC count of 2200/µl) and a blood smear showed a granulocyte number of 1100/µl , mirtazapine was immediately discontinued. Sultamicillin 375 mg b.i.d. was started.

Within 2 weeks the subject's WBC and granulocyte counts had both increased, and four weeks after discontinuation of mirtazapine, sertraline 50 mg/day was administered. Six weeks later her WBC count was 6100/µl, and her depression had responded to treatment with a 50% reduction in her Hamilton Depression Rating Scale score. Six months after starting sertraline, the subject's depression had completely remitted. No adverse effects were reported.

The authors write that in the absence of concomitant medication or other apparent illness, this case suggests an association between mirtazapine and severe neutropenia, a rare side effect of antidepressant treatment. They recommend that patients taking mirtazapine be monitored closely and, if diagnosed with neutropenia, consideration be given to use of a selective serotonin reuptake inhibitor (SSRI) such as sertraline as an effective alternative treatment.

Ozcanli T, Unsalver B, Ozdemir S, et al.: Sertraline- and mirtazapine-induced severe neutropenia. *Am J Psychiatry* 2005;162:1386.

From the FDA

✓FDA expands indications for mixed salt amphetamines

The FDA has approved an expanded indication for mixed salts of a single-entity amphetamine (ADDERALL XR) as a once-daily treatment for adolescents aged 13-17 with attention deficit hyperactivity disorder (ADHD). The drug is already approved for use in children ages 6-12 and in adults 18 years and older. The approval follows favorable results in a randomized, double-blind placebo-controlled clinical trial of ADDERALL XR in adolescents. [www.fda.gov]

✓Palladone sales suspended

The FDA has issued a public health advisory and requested that Purdue Pharma L.P. withdraw Palladone (hydromorphone hydrochloride) extended release capsules from the market, citing potentially fatal adverse reactions when the potent pain medication is taken together with alcohol, even in opioid-tolerant patients. The results of a company-sponsored study reveal that alcohol can compromise the extended release mechanism, leading to dangerously rapid release of the active ingredient into the bloodstream, even at the lowest marketed dose of the drug (12 mg). [www.fda.gov]