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Highlights...

We bring you the results of the first-ever study of aripiprazole for borderline personality disorder. Results showed significant improvements without weight gain in patients with this typically difficult to treat disorder.

Also, data from the much-heralded STEP-BD study have been released, and we talk with lead author Andrew A. Nierenberg, M.D., about the the results.

Inside

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NEW RESEARCH

Aripiprazole for treating borderline personality disorder

Patients with borderline personality disorder (BPD) may find that treatment with aripiprazole (Abilify) might help to reduce their aggression, anxiety and depression without the side effect of excessive weight gain. In a first-ever study investigating aripiprazole for treating BPD, researchers found that subjects in the active-treatment group showed significant improvement in BPD symptoms compared with placebo.

The estimated prevalence of BPD is 2% of the adult population, mostly affecting young women. The disorder is characterized by short, intense episodes of depression, anxiety, impulsivity, hostility and anger, including self-injury. The American Psychiatric Association (APA) treatment guidelines for BPD recommend psychotherapy (e.g., dialectical behavior therapy or psychoanalytic/psychodynamic therapy) and/or pharmacological treatment based on specific target symptoms (e.g., selective serotonin reuptake inhibitors and other related anti-

précis

- First-ever investigation of aripiprazole (Abilify) in treatment of borderline personality disorder (BPD)
- 8-week, double-blind, placebo-controlled study of 46 subjects diagnosed with BPD
- Significant improvements in the aripiprazole group included decreased depression, anxiety and anger, with no weight gain observed

ARIPIPRAZOLE, *continued on page 5*

STEP-BD RESULTS

First effectiveness study tests treatments for refractory bipolar depression

Fundamental holes in the clinical research hinder the treatment of bipolar depression, according to Andrew A. Nierenberg, M.D., Medical Director of the Bipolar Clinic and Research Program and Associate Director of the Depression Clinical and Research Program at Massachusetts General Hospital. Fortunately, answers are coming from the Systematic Treatment Enhancement Program for Bipolar Disorder, or STEP-BD, a nationwide longitudinal look at the effects of treatment on the course of bipolar disorder.

As part of STEP-BD, Nierenberg and colleagues performed what he called "the first effectiveness study for difficult-to-treat bipolar depression that's ever been conducted." Unlike efficacy trials, which often exclude people with substantial comorbidity, Nieren-

précis

- Study of 66 patients with bipolar disorder and a current major depressive episode that had not responded to mood stabilizers plus at least one antidepressant
- Patients were randomized to receive lamotrigine, risperidone, or inositol as adjunctive therapy in strata defined by which treatments they would accept
- The primary outcome, recovery rate within strata, showed no differences between treatment groups, but secondary analyses suggested benefits for lamotrigine and, to a lesser extent, inositol; risperidone helped few patients

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• FREE PATIENT HANDOUT: ARIPIPRAZOLE (GENERIC) – ABILIFY (BRAND) •

episode was based on DSM-IV criteria, having a ≥15 HAM-D score, and independent confirmation by a geriatric psychiatrist. Within a 2-year period, there was a recurrence of major depression in 35% of patients receiving paroxetine plus psychotherapy, in 37% of patients receiving paroxetine with clinical management sessions, in 58% of patients receiving placebo and clinical management sessions, and in 68% of patients receiving placebo plus psychotherapy (p=0.02).

According to tests of hypothesized pairwise contrasts, paroxetine combined with psychotherapy was superior in preventing recurrence of depression to placebo plus psychotherapy (p=0.03) and superior to placebo plus clinical management (p=0.05). Paroxetine plus clinical management was also significantly more effective in preventing recurrence than placebo plus psychotherapy (p=0.03). Among the patients who had fewer and less severe coexisting medical conditions, the benefits were greater among those who had received paroxetine (p=0.03).

In contrast with short-term efficacy trials, "our study supports the efficacy of maintenance therapy with SSRIs in preventing a recurrence of depression among people with first episodes in later life who have apparently benefited from initial SSRI treatment and interpersonal psychotherapy," write Reynolds and colleagues. ■

* Paroxetine tablets provided by Glaxo- SmithKline.

Reynolds CF, Dew MA, Pollock BG, et al.: Maintenance treatment of major depression in old age. *N Engl J Med* 2006; 354(11):1130-1138. E-mail: reynoldscf@upmc.edu.

ARIPIPRAZOLE

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depressants such as venlafaxine; monoamine oxidase inhibitors; mood stabilizers; benzodiazepines; and neuroleptics).

The APA considers low-dose neuroleptics to have a wide range of efficacy in acute use, improving depressed mood, impulsivity, anger/hostility as well as psychotic-like symptoms. Some medications which have been previously studied in BPD trials include low-dose typical neuroleptics (e.g., haloperidol [Haldol], perphenazine [Trilafon]) and the atypical neuroleptics, such as clozapine (Clozaril), olanzapine (Zyprexa), and risperidone (Risperdal).

Marius K. Nickel, M.D., the lead investigator of the current study, told *The Update*: "The most important finding for me is that aripiprazole is worth considering as an alternative treatment for borderline patients in suitable cases, because aggression, anxiety and depressiveness can be greatly improved without weight gain. According to our observations, the health-related quality of life was greatly improved." Nickel is Chief Physician at the Clinic for Psychiatry & Psychosomatic Medicine, Inntalklinik Simbach, Simbach, Germany, and a Professor at the University Clinic for Psychiatry, Paracelsus Medizinische Privatuniversität, Salzburg, Austria.

"What fascinates me so much about aripiprazole for borderline patients is that a measurable, significant improvement occurred on the symptomatic level and that a very good efficacy could be documented with aggression." There was also no significant weight gain in the treatment group, a factor which Nickel considers to be "also of great importance in psychiatry."

Study details

Nickel and his team enrolled 52 subjects meeting DSM-IV criteria for BPD. At the time of recruitment, the subjects were involved in painful, difficult relationships, exhibiting distrustful, moody, and impulsive behavior. The sample comprised mostly women, reflecting the higher prevalence of BPD among women in the general population.

Patients taking aripiprazole or other psychotropic medications without the approval of a washout phase of at least 2 weeks were excluded, Nickel told *The Update*. Also excluded were all psychotic patients, those with suicidal ideation, patients undergoing psychotherapy, those with severe somatic illness, pregnant patients (current or planned), or those engaging in sexual activity without contraception. "For methodological research reasons, we had very strict exclusion criteria. On the one hand, it is easier to conduct a study with such a select patient group," says Nickel. "On the other hand, the results are thus not generalizable."

The primary outcome measures were changes in scores on the self-report symptom checklist (SCL-90-R), the Global Severity Index (GSI), the Hamilton Depression Rating Scale (HAM-D), the Hamilton Anxiety Rating Scale (HAM-A), and the State-Trait Anger Expression Inventory (STAXI). Assessments were carried out on a weekly basis.

Data collection was carried out using STAXI, which measures aggression on many levels, Nickel told *The Update*, such as "the perception of anger, as well as the disposition, reactions of aggression, the inward direction of aggression, virtually against oneself, and the outward expression. Even that which is so socially desirable, namely the control of aggression, is measured."

Subjects were randomized under double-blind conditions to aripiprazole (N=26; 21 women) 15 mg/day or matching placebo (N=26; 22 women). At week 8, the subjects were tested for the last time and physically examined.

Results

At baseline, there were no significant between-group differences in medical or sociodemographic data, or comorbidity. The mean age of the subjects in the aripiprazole group was 22.1 years (SD=3.4), and 21.2 years (SD=4.6) in the placebo group.

At the beginning of the study, both groups had "distinctly modified" scores on the SCL-90-R, HAM-D, HAM-A and STAXI, reflecting multiple psychopathological symptoms. Psychiatric comorbidity included depressive disorders (aripiprazole group: 80.8%; placebo: 84.6%); anxiety disorders (aripiprazole: 61.5%; placebo: 53.8%); obsessive-compulsive disorders (aripiprazole and placebo: both 11.5%); and somatoform disorders (aripiprazole: 69.2%; placebo: 73.1%).

Based on the intent-to-treat principle, there were significant changes in the aripiprazole group by week 8 on most of the SCL-90-R measures (except for somatization) compared with placebo: obsessive-compulsive (p=0.01); insecurity in social contacts, depression, anxiety, aggressiveness/hostility, phobic anxiety, paranoid thinking (all p<0.001); and psychoticism (p=0.02). There was significant improvement on the total GSI score in aripiprazole-treated subjects at week 8 compared with placebo (p<0.001).

There were significant improvements over the 8-week period on HAM-D scores

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in the aripiprazole group (p=0.002), on HAM-A scores (p=0.007), and state anger (p<0.001) compared with placebo. Although significant improvements in anxiety and depression were observed in the aripiprazole group, interestingly the initial reductions on the anxiety scale occurred gradually compared with a more rapid reduction on the depression scale.

"Aripiprazole was more effective in treating the aggression component of borderline psychopathology," write Nickel and colleagues. "Among our patients, aripiprazole appeared to influence the intensity of the subjective state of anger (state anger) as well as their readiness to react with anger (trait anger)." There was a significant decrease in the tendency for subjects in the aripiprazole group to direct anger outward and inward, which is important, say Nickel and colleagues, because "the socially desirable tendency to control anger was strengthened."

Although observations on symptomatic improvement from the subjects' families were not routinely recorded," Nickel told *The Update*, feedback from family members was very positive, particularly regarding the patients' affective stability.

Side effects

According to Nickel and his team, the most common side effects of aripiprazole are insomnia, nausea, numbness, headache, constipation and anxiety. Self-injury was observed in both groups 8 weeks prior to therapy (aripiprazole: 7/26; placebo: 5/26), and during the 8-week course of therapy (aripiprazole: 2/26; placebo: 7/26). However, there were no serious side effects or suicidal acts in either group throughout the study. Weight gain was also not observed.

Study limitations

Remarking on the small sample size of their study, Nickel told *The Update* that future studies with a greater number of patients are necessary, as well as those without such strict exclusion criteria which would broaden the findings. Another limitation was that the study focused only on 3 dimensions of borderline personality disorder (i.e., affective dysregulation, aggressive impulsivity, and cognitive perceptual impairment) and did not investigate the domain of disturbed relationships. The study was also limited by not using the Zanarini Rating Scale for Borderline Personality Disorder, which was not available in the German language when the study began.

Clinical implications

Nickel told *The Update* that although he likes using olanzapine in patients, and considers it his favorite neuroleptic agent, "one sees such a colossal weight gain with olanzapine, it appears worthwhile to look for an alternative. One could hence consider using aripiprazole. With aripiprazole, I did not observe any weight gain. What is good about aripiprazole, which we also always observe with olanzapine, is the antidepressive effect of the substance. We could furthermore observe a reduction of anxiety. That is what impressed me in this study."

Nickel says that previously he has observed affective incontinence when using aripiprazole in patients with schizophrenia, agitation, and to some extent aggressiveness. "I have not been able to document this yet in a study; these are my clinical observations."

Another observation by Nickel is that when using aripiprazole for borderline patients in whom no psychosis is present, "hardly any agitation" occurs as a side effect. "At the moment, I have no explanation for these different responses."

Nickel told *The Update* that in his daily clinical work, aripiprazole is effective and well tolerated by middle-aged and elderly patients. However, further studies with different age groups are also necessary, he concluded. ■

*Study conducted independently of any institutional influence.

Nickel MK, Muehlbacher M, Nickel C, et al.: Aripiprazole in the treatment of patients with borderline personality disorder: a double-blind, placebo-controlled study. *Am J Psychiatry* 2006; 163(5):833-838. E-mail: m.nickel@inntalklinik.de

STEP-BD

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berg said their participants could have "a full range of comorbidities," making the outcomes "more likely to be generalizable to actual practice."

The study compared three treatments that evidence suggested might help -patients with hard-to-treat bipolar depression: lamotrigine (Lamictal), a mood stabilizer; risperidone (Risperdal), an atypical antipsychotic; and inositol, a glucose isomer sold in health-food stores. The Food and Drug Administration has approved lamotrigine as maintenance monotherapy for bipolar I disorder and risperidone for acute mania.

Nierenberg said inositol "is involved in a tertiary neurotransmitter system and is part of the phosphoinositide cycle, which is really very important for signal transduction." Since lithium inhibits part of that cycle, inositol might relieve or worsen bipolar depression.

The trial enrolled 66 STEP-BD participants, age 18 and over, with bipolar I or II disorder and a current DSM-IV episode of major depression that had not responded to 12 weeks of treatment, or 2 or more trials of an antidepressant or an antidepressant plus mood stabilizer regimen. All were taking a mood stabilizer or agreed to do so and had refused electroconvulsive therapy.

The study excluded patients with hypomania, a mixed episode, or current substance abuse or dependence. Patients with a medical contraindication, or a history of nonresponse or intolerance, to at least two study medications could not participate.

Patients received up to 16 weeks of open-label treatment with risperidone, lamotrigine, or inositol to augment a mood stabilizer and antidepressant regimen. The regimens included the mood stabilizers lithium, valproate, lithium plus valproate, or carbamazepine, along with one or two antidepressants. The study allowed any other medications needed except for additional antidepressants, although it did permit up to 150 mg trazodone for sleep.

The dose of risperidone began at 0.5-1.0 mg/day, later increasing to up to 6 mg as tolerated. Lamotrigine started at 50

STEP-BD

- Broad inclusion criteria and few exclusion criteria maximize generalizability.
- Follow-up continues as patients move between naturalistic studies and randomized trials.
- In Standardized Care Pathways, clinicians receive encouragement, at key decision points, to offer treatments from "Menus of Reasonable Choices" based on published guidelines.
- In Randomized Care Pathways, such as the Refractory Depression Pathway, patients receive protocol-driven treatment.