FDA ISSUES BLACK BOX WARNING FOR ALL ANTIDEPRESSANTS

The United States Food and Drug Administration issued a public health advisory for antidepressant medications, warning of the increased risk of suicidality (ie, suicidal thinking and behavior) in children and adolescents with major depressive disorder (MDD) being treated with antidepressants. The advisory requires all labels on antidepressants to carry a "black box" warning that alerts healthcare providers to this risk and emphasizes the need for strict dose monitoring. This decision comes after more than a year of debate on the results of studies of antidepressants in children.

The public health advisory not only requires a black box warning but also modifies expanded warning statements in the package inserts and has required that manufacturers of antidepressants to include a patient medication guide to be distributed to patients, which will advise patients of any risk and precautions associated with these medications. These warnings apply to all antidepressants—currently available data are not adequate to exclude any one drug—including all selective serotonin reuptake inhibitors, such as fluoxetine, citalopram, fluvoxamine, paroxetine, and sertraline; and all atypical antidepressants, such as bupropion, mirtazapine, nefazodone, and venlafaxine.

The FDA's decision to order a black box warning stems from a meta-analysis of 24 short-term (≤4 months) placebo-controlled trials of the above antidepressants on children and adolescents with MDD, obsessive-compulsive disorder, and other psychiatric disorders. The trials included >4,400 subjects and showed a greater risk of suicidality during the first few months of treatment with an antidepressant. Of the subjects, 3.8% of children taking antidepressants became suicidal, while only 2.1% of children taking a placebo became suicidal (an increase of 80% in risk of suicide). No actual suicides occurred during the trials.

The FDA concluded that antidepressants increase the risk of suicidality in children and adolescents with MDD and other disorders, and that any physician considering the use of an antidepressant in a child should seriously weigh this risk against the clinical benefits of treatment. Patients who are started on antidepressant therapy or who have had their dosages changed should be monitored very closely for agitation, irritability, suicidality, and unusual changes in behavior. Families and caregivers should be advised to monitor the patient as well.

Although the risk of antidepressant-induced suicidal thoughts and behavior seems valid, many physicians and members of the American Psychiatric Association, have expressed concern over the black box warning, indicating that it may deter doctors from prescribing medication that may have a positive effect on the patient's health. The warning also prevents advertising of the medications' availability, although it does not necessarily prohibit the use of antidepressants in children or adolescents.

This warning took effect on October 15, 2004 and applies to all currently manufactured antidepressant medications. *–EJR*

CLOZAPINE AND OLANZAPINE MAY INCREASE THE RISK OF DIABETES FOR PATIENTS WITH SCHIZOPHRENIA

Atypical antipsychotics are considered first-line therapy for the treatment of schizophrenia. Developed in the late 1990s, atypical antipsychotics have a more favorable side-effect profile than conventional antipsychotics. However, atypical antipsychotics are thought to increase the risk of type 2 diabetes by promoting weight gain. To assess the incidence of newly diagnosed diabetes in schizophrenic patients treated with atypical antipsychotics, Douglas L. Leslie, PhD, and Robert A. Rosenheck, MD, of Yale University School of Medicine in New Haven, Connecticut, examined administrative data from the Department of Veterans Affairs health system.

"We had seen case reports of patients on atypical antipsychotics developing diabetes, and some larger studies looking at the prevalence of diabetes among patients prescribed atypical antipsychotics, but no studies looking at new-onset diabetes among patients with schizophrenia who were prescribed these drugs," Dr. Leslie said. "Our initial motivation was to examine the implications of new-onset diabetes in this population with respect to medication changes and costs. The incidence results are the first part of this research."

The patient population consisted of patients with schizophrenia who were prescribed a stable regimen of atypical antipsychotic monotherapy during any 3-month period from June 1999 through September 2000. Patients were then followed through September 2001. To determine the proportion of patients with schizophrenia who developed diabetes or were hospitalized for ketoacidosis after atypical antipsychotic treatment, Leslie and Rosenheck developed Cox proportional hazards models to identify the characteristics associated with newly diagnosed diabetes and ketoacidosis.

Of the 56,849 patients identified, 4,132 (7.3%) developed diabetes and 88 (0.2%) were hospitalized for ketoacidosis. Patients developed diabetes at an annual rate of 4.4%, much higher than the 0.6% rate in the general population. The risk of diabetes was highest for clozapine

https://doi.org/10.1017/S1092852900002212 Published online by Cambridge University Press

(hazard ratio=1.57) and olanzapine (hazard ratio=1.15); the diabetes risks for quetiapine (hazard ratio=1.20) and risperidone (hazard ratio=1.01) were not significantly different from that of conventional antipsychotics. Leslie and Rosenheck found that while clozapine and olanzapine carry a greater diabetes risk, the attributable risk of diabetes with atypical antipsychotics was small, ranging from 0.05% for risperidone to 2.03% for clozapine. However, it was unclear how much of the diabetes risk in clozapine- and olanzapine-treated patients could have been due to the underlying schizophrenia, poor overall health, or other factors.

"Doctors should be aware of the increased risk of diabetes associated with clozapine and olanzapine, and patients prescribed these medications should be monitored for excessive weight gain and signs of diabetes," Dr. Leslie said. "Doctors should also be aware that the risk of diabetes is not the same across all of the atypical antipsychotics. The diabetes risk associated with risperidone was no different than the risk associated with conventional antipsychotics."

Leslie and Rosenheck note that further research is warranted to investigate the side effects of atypical antipsychotics, with an emphasis on the metabolic syndrome.

Funding for this research was provided by the Department of Veterans Affairs, the National Institute of Mental Health Clinical Antipsychotic Trials of Intervention Effectiveness, and Bristol-Myers Squibb.
–SW (Am J Psychiatry. *2004;161:1709-1711*)

PARKINSON'S DISEASE AND EPILEPSY MAY BE LINKED TO DEPRESSION

Depression affects >19 million people annually in the United States, thus, assessing the quality of life of patients by evaluating depressive symptoms and treatment side effects as well as family, social, and employment concerns are important aspects of patient care. Two recent studies have investigated a possible link between depression and chronic brain diseases.

The first study by Irene Richard, MD, and William McDonald, MD, of the University of Rochester School of Medicine in New York, found that nearly half of all patients with Parkinson's disease also have depression. They proposed that there could be a physical link between the two conditions. Another group of researchers at Columbia University found a gene known to cause dystonia, a movement disorder that causes a form of early-onset depression, similar to Parkinson's disease. It is estimated that ~1 million people in the US have Parkinson's disease. Richard and McDonald found that other patients with serious diseases that may also become disabling (including rheumatoid arthritis) are not nearly as likely to become depressed. They suggest that doctors and patients were both unaware of the link and that patients often went untreated for depression, assuming that such symptoms were normal for Parkinson's patients. However, they point out that a patient's depression may be very treatable, and effective treatment could improve a patient's quality of life and management of Parkinson's disease.

Similar to Parkinson's disease, epilepsy is a chronic brain disease that affects >2 million people in the US. Alan Ettinger, MD, and colleagues, of the Long Island Jewish Medical Center in New Hyde Park, New York, assessed the comorbidity of depression, patient quality of life, and disability in community-based epilepsy patients. Of 775 patients, 36.5% scored positive on the Center for Epidemiology Studies-Depression Scale (CES-D) ($P<.001$), thus indicating symptoms of depression. The researchers found that 38.5% of these patients were never previously evaluated for depression. Other measures included the Short Form-36 to evaluate quality of life, the Sheehan Disability scale (SDS), the Quality of Life in Epilepsy-89 (QOLIE-89), the Social Concerns Index, Adverse Events Profile, and employment questions. The results indicated that CES-D–based depression was significantly associated with being female, being younger, having lower income, worse QOLIE-89 scores, more SDS disability, more social concerns, more adverse drug events, less past-month employment, and fewer working days.

Ettinger and colleagues recommend that clinicians consider treatment options that will help a patient's epilepsy in addition to improving depressive symptoms, leading to a greater overall quality of life. Further study is necessary to investigate the link between depression, epilepsy, and Parkinson's disease.
–SW (Neurology. *Richard: 2004;63:610-611; Ettinger: 2004;63:1008-1014*).

ADJUNCTIVE MODAFINIL MAY IMPROVE FATIGUE AND DEPRESSIVE SYMPTOMS IN MAJOR DEPRESSIVE DISORDER

Greater than 19 million Americans annually suffer from some form of depression, with major depressive disorder (MDD) affecting between 10% and 25% of women and 5% to 12% of men. While a variety of non-pharmacologic treatment options are available for MDD (electroconvulsive therapy, cognitive-behavioral therapy, etc.), selective serotonin reuptake inhibitors (SSRIs) are usually first-line pharmacologic treatment agents. SSRIs have a delayed onset, affecting response rate. In addition, fatigue, a fundamental

https://doi.org/10.1017/S1092852900002212 Published online by Cambridge University Press

symptom of MDD, is often poorly treated by SSRIs.

Researchers at the CNS Research Institute in Clementon, New Jersey, and Emory University School of Medicine in Atlanta, Georgia, led by Howard A. Hassman, DO, recently investigated the use of adjunctive modafinil,a psychostimulant that improves memory and wakefulness, in individuals with MDD. The researchers studied patients previously diagnosed with MDD, had a Fatigue Severity Scale (FSS) score ≥4, and had not taken antidepressant therapy for ≥4 weeks. The open-label pilot study was 6 weeks long and patients were evaluated at screening, baseline, and every week thereafter until endpoint. Twenty-nine subjects with a mean age of 36.2 years were enrolled in the trial, only 23 patients completed the study.

Treatment was begun on a combination of either fluoxetine or paroxetine 20 mg/day for 6 weeks and modafinil 100 mg/day for 3 days then increased to 200 mg/day. The FSS, Epworth Sleepiness Scale (ESS), and the Hamilton Rating Scale for Depression (HAM-D) were used for assessment purposes. FSS measures changes in fatigue, and a score of <4 post-baseline was defined as response. The ESS measures subjective sleepiness, and response was defined as a score of <10 at any post-baseline visit. HAM-D evaluations were video recorded and response and remission rates were analyzed using HAM-D_{21} total scores. Patient-rated visual analog scales were used to assess symptoms associated with depression, including fatigue, mood, and motivation.

According to the researchers, adjunctive modafinil treatment quickly reduced fatigue from a Week 1 mean FSS score of ~4.5 to a Week 6 mean score of ~3 (P<.01 change from baseline). Modafinil also reduced sleepiness from a Week 1 mean ESS score of ~7 to a Week 6 mean score of ~5 (P<.01 change from baseline). Hassman and colleagues found that adjunctive modafinil also improved depressive symptoms. The mean HAM-D_{21} scores at baseline were 20 (blinded reviewer) and ~23 (unblinded reviewer) which was lowered to a mean score of ~7 at Week 6 for both blinded and unblinded reviewers (P<.001). Reported side effects included nausea (41%; n=12) and headache (24%; n=17).

Overall, modafinil combination treatment improved response and remission rates along with subjective symptoms associated with depression. The psychostimulant could provide an increased adjunctive effect when used with an SSRI at the beginning of treatment. Furthermore, modafinil could prove efficacious in individuals who develop fatigue or other symptoms that reduce antidepressant effectiveness.

Funding for this research was provided by Cephalon, Inc. —*JRR* (*Poster 1.056, ECNP 2004*)

QUETIAPINE MAY BE EFFECTIVE IN TREATING BIPOLAR I DISORDER

Bipolar I disorder, characterized by sudden changes in mood, thought, energy, and behavior, affects >2 million Americans annually, with traditional treatment options including lithium and divalproex. However, quetiapine, an atypical antipsychotic, has shown efficacy in treating episodes of major depression in individuals suffering from bipolar I disorder.

In an effort to confirm previous findings in a large, double-blind, placebo-controlled trial, Joseph Calabrese, MD, and colleagues from the University Hospitals of Cleveland in Ohio, studied 360 patients randomized to 8 weeks of double-blind treatment with quetiapine 300 mg/day (n=122) or 600 mg/day (n=120) or placebo (n=118) randomly administered. All subjects were outpatients between 18 and 65 years of age with bipolar I depression diagnosed using *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* criteria. Each subject was required to have a 17-item Hamilton Rating Scale for Depression (HAM-D) total score of ≥20, a score of ≥2 on HAM-D item 1, and a score of ≤12 on the Young Mania Rating Scale (YMRS). Patients with other Axis I disorders were excluded from participating.

The change from baseline to endpoint on the Montgomery-Asberg Depression Rating Scale (MADRS) was the primary endpoint. Other efficacy endpoints included mean change on the HAM-D and the Clinical Global Impressions–Severity scale (CGI-S). Statistical analyses included intent-to-treat efficacy analysis, last observation carried forward, and analysis of covariance.

At the first assessment (Day 8), patients administered quetiapine had a significantly greater improvement (P<.001) in mean MADRS scores compared with placebo. Other evaluations showed that effect sizes for quetiapine 600 and 300 mg/day were 0.88 and 0.73, respectively. Quetiapine treatment also resulted in a larger number of patients reaching a response after intent-to-treat and last observation carried foward analyses at Week 8 (600 mg/day: 64%, 300 mg/day: 62.1%). Those on placebo only a showed a 33% response rate (P<.001). Remission rates were likewise significant compared with placebo. At Week 8, 58.8% of patients taking quetiapine 600 mg/day and 57.8% of patients taking quetiapine 300 mg/day achieved remission, compared with 26.8% of placebo

NEWS FROM THE 17TH CONGRESS OF
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patients. CGI-S scores showed that quetiapine at either dose was superior to placebo from Week 1 (600 mg/day: 66.7%, 300 mg/day: 60%; placebo: 33%) to Week 8 (600 mg/day: 77.2%, 300 mg/day: 85.3%; placebo: 55.4%). The researchers found quality of life and sleep were also improved by study endpoint.

Calabrese and colleagues noted minimal changes in mean YMRS total scores from baseline to endpoint. (Week 1: 600 mg/day: –0.4 [$P<.05$], 300 mg/day: –0.7 [$P<.01$]; placebo: +0.5; Week 8: –1.1 [$P<.01$], 300 mg/day: –0.9 [$P<.05$]; placebo: +0.6). Treatment-emergent mania presented in 0.9% of those on 600 mg/day, 5.2% of those on 300 mg/day, and 6.3 of those on placebo. The side effects most common reported were dry mouth, somnolence, and sedation. No deaths were reported.

Calabrese and colleagues noted that these findings suggest that quetiapine at 300 or 600 mg/day is significantly better than placebo in a population of patients with bipolar I disorder. They also noted that the onset of efficacy occurred within 1 week and continued improving throughout the duration of the study, warranting further studies with this agent.

Funding for this research was provided by AstraZeneca. *–JRR (Poster 2.153, ECNP 2004)*

SPANISH CROSS-SECTIONAL STUDY EXAMINES PREVALENCE OF COMORBIDITIES IN PATIENTS WITH SCHIZOPHRENIA

The Abordaje Clínico de la esquizofrenia en España (ACE) survey is a descriptive, non-interventional, cross-sectional, multicenter national survey conducted in the outpatient setting which was designed to document and explain the clinical management of patients with schizophrenia in Spain. The main objectives of the survey are to examine the social demographic characteristics of patients with schizophrenia in addition to their clinical profile, diagnosis, and treatment patterns for this pathology in the care of psychiatrists in Spain.

Enrique Baca, MD, from Clínica Puerta Hierro in Madrid, Spain, and colleagues have studied the prevalence of psychiatric and nonpsychiatric comorbidities in patients with ambulatory schizophrenia, on behalf of the ACE Group. The sample included 500 psychiatrists from public mental health centers and private offices who enrolled a total of 1,937 patients with a primary diagnosis of schizophrenia.

To obtain a representative national patient population, sample distribution was performed according to geography based on population data from different Spanish regions and setting criteria (public sector estimated to be 80%, private sector was 20%). Data collection was based on patient medical records and on the information that was collected during the patient inclusion visit. To avoid selection bias, participating investigators recruited consecutive eligible patients at psychiatrist outpatient offices.

Of the 1,937 patients, 57.8% reported one or more comorbidities. Overall, psychiatric comorbidities were more frequent than nonpsychiatric ones. Baca and colleagues found that 867 patients (44.8%) reported associate psychiatric morbidities: anxiety disorders (11.6%), depression (11.4%), sleep disorders (11.4%), phobias and obsessions (7.7%), cognitive disorders (6.6%), postpsychotic depression (6.4%), and personality disorders (5%). Women presented with psychotic depression (8% compared with 5.6%) and anxiety disorders (14.3% compared with 10.4%) more often than men. Men presented with personality disorders (5.7% compared with 3%) more often than women). A correlation between patient age and comorbidities revealed that an inverse relationship was observed between age and the presence of phobias and obsessions and personality disorders (both being less frequent in older patients). No significant differences were observed for the other morbidities.

Nonpsychiatric comorbities were observed in 491 (25.3%) patients and consisted of the following: hypercholesterolemia (8.9%), hypertriglyceridemia (5.2%), high blood pressure (3.7%), diabetes (3.1%), and obesity or overweight (1.7%). Gender was not observed as relating to nonpsychiatric comorbidities; while obesity was more frequent in women ($P=.07$), this did not reach statistical significance. However, a direct association was observed between age and high cholesterol or high triglyceride levels and with diabetes and high blood pressure.

The researchers observed that 69.7% of patients were receiving concomitant medication. Of the total patient sample, 65.6% were treated with medication (anxyolitics, antidepressants, anticholinergics, hypnotics, mood stabilizers) related to the central nervous system (CNS) and 11.56% with medication not related to the CNS (antihypertensives, hypolipidemics, antidiabetics).

The research represents part of the ACE survey which collects data on the clinical management of patients with schizophrenia in Spain. Further study results are pending. *–SW (Poster P.2.138, ECNP 2004)* CNS

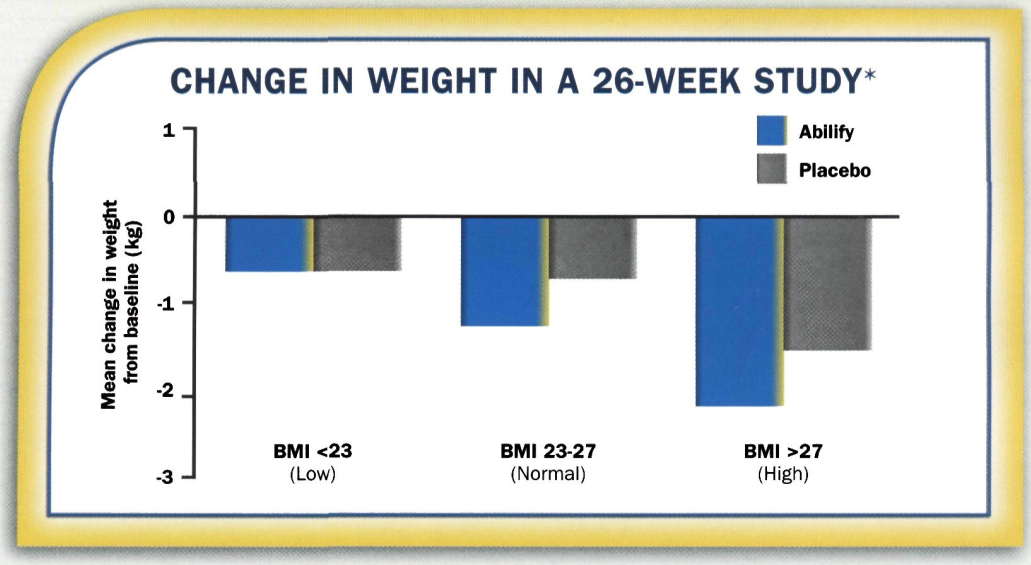
–Clinical Updates in Neuropsychiatry is compiled and written by José R. Ralat, Emil J. Ross, and Shelley Wong.

https://doi.org/10.1017/S1092852900002212 Published online by Cambridge University Press

https://doi.org/10.1017/S1092852900002212 Published online by Cambridge University Press

THERE'S MORE TO ABILIFY THAN PROVEN EFFICACY WHEN TREATING SCHIZOPHRENIA

Abilify May Also Limit the Potential for Adverse Effects on Weight[1]...



Data from a 26-week, placebo-controlled trial in patients with schizophrenia.
BMI=Body Mass Index (kg/m^2).
For Abilify 15 mg: BMI <23 (n=59); BMI 23 to 27 (n=39); and BMI >27 (n=53). For placebo: BMI <23 (n=54); BMI 23 to 27 (n=48); and BMI >27 (n=49).
*Last observation carried forward.

On average, patients on Abilify in a 26-week study lost weight, regardless of BMI[1]

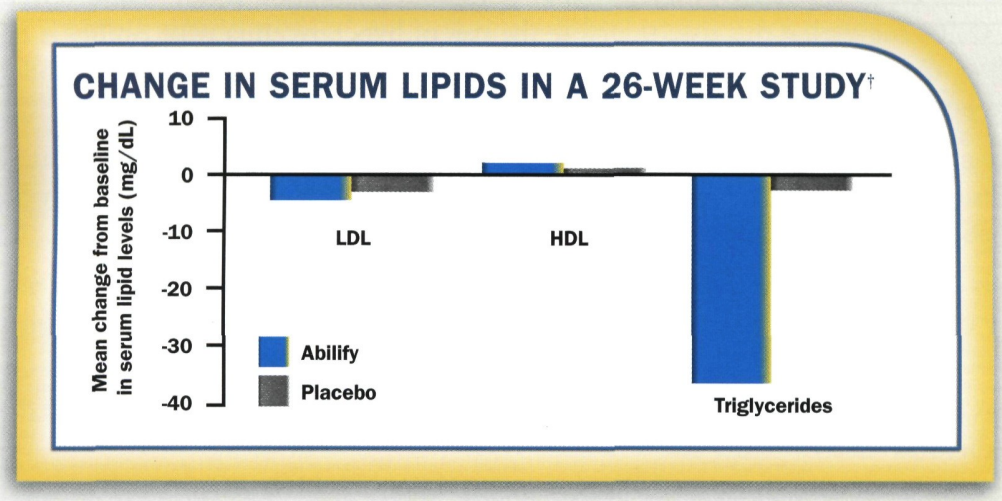
In a 26-week study, the percentage of patients on Abilify with ≥7% increase in body weight was 6.8% for those with BMI <23, 5.1% for those with BMI 23 to 27, and 5.7% for those with BMI >27. The percentage of patients on placebo with ≥7% increase in body weight was 3.7% for those with BMI <23, 4.2% for those with BMI 23 to 27, and 4.1% for those with BMI >27.

In a 52-week study, the percentage of patients with ≥7% increase in body weight was 30% for those with BMI <23, 19% for those with BMI 23 to 27, and 8% for those with BMI >27. On average, patients gained 1 kg over 52 weeks.

In short-term trials, there was a slight difference in mean weight gain between Abilify and placebo patients (+0.7 kg vs –0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight criterion of ≥7% of body weight for Abilify (8%) compared to placebo (3%).

Abilify is indicated for the treatment of schizophrenia.

and Limit the Potential for Adverse Effects on Lipids[1]



Fasting serum lipid levels derived from a 26-week, placebo-controlled trial.
LDL: Abilify (n=74), placebo (n=82).
HDL: Abilify (n=80), placebo (n=83).
Triglycerides: Abilify (n=93), placebo (n=91).
†Last observation carried forward.

- In a 26-week study, comparable effects on lipids were seen with Abilify and placebo

Please see Brief Summary of full Prescribing Information on concluding pages.

Please see Important Safety Information on next page.

ABILIFY®
(aripiprazole)

https://doi.org/10.1017/S1092852900002212 Published online by Cambridge University Press

IMPORTANT SAFETY INFORMATION

As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia (TD).

Hyperglycemia, including some serious cases ranging from ketoacidosis to death, has been reported in patients treated with atypical antipsychotics. Abilify was not included in epidemiologic studies suggesting this risk; therefore the risk of hyperglycemia with Abilify is not known. However, there have been few reports of hyperglycemia in patients treated with Abilify. Patients should be appropriately monitored.

Abilify may be associated with orthostatic hypotension and should be used with caution in patients with known cardiovascular disease, cerebrovascular disease, or conditions which would predispose them to hypotension.

As with other antipsychotic drugs, Abilify should be used with caution in patients with a history of seizures or with conditions that lower the seizure threshold. Seizures occurred in 0.1% of patients treated with Abilify in placebo-controlled trials.

Patients should not drive or operate heavy machinery until they are certain Abilify does not affect them adversely.

Treatment-emergent adverse events reported with Abilify at an incidence ≥10% and greater than placebo, respectively, include headache (32% vs 25%), anxiety (25% vs 24%), insomnia (24% vs 19%), nausea (14% vs 10%), vomiting (12% vs 7%), somnolence (11% vs 8%), lightheadedness (11% vs 7%), akathisia (10% vs 7%), and constipation (10% vs 8%).

The adverse events reported in a 26-week, double-blind trial comparing Abilify and placebo were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor: 9% (13/153) for Abilify vs 1% (2/153) for placebo. In this study the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days), and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of Abilify. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for Abilify was 4% (34/859).

Visit www.abilify.com for more information.

Reference:
1. Pigott TA, Carson WH, Saha AR, Torbeyns AF, Stock EG, Ingenito GG. Aripiprazole for the prevention of relapse in stabilized patients with chronic schizophrenia: a placebo-controlled 26-week study. *J Clin Psychiatry*. 2003;64:1048-1056.

Please see Brief Summary of full Prescribing Information.

Marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA and Bristol-Myers Squibb Co., Princeton, NJ 08543 USA.
Manufactured and distributed by Bristol-Myers Squibb Co., Princeton, NJ 08543.
U.S. Patent Nos. 4,734,416 and 5,006,528.

Bristol-Myers Squibb Company Otsuka America Pharmaceutical, Inc.

D6-K0076 AP4648/06-04 July 2004

ABILIFY® (aripiprazole)

ABILIFY®

Rx only

(aripiprazole) Tablets

Brief Summary of Prescribing Information. For complete prescribing information please consult official package circular.

INDICATIONS AND USAGE

Schizophrenia

ABILIFY is indicated for the treatment of schizophrenia. The efficacy of ABILIFY in the treatment of schizophrenia was established in short-term (4- and 6-week) controlled trials of schizophrenic inpatients (see **CLINICAL PHARMACOLOGY: Clinical Studies** in Full Prescribing Information). The efficacy of ABILIFY in maintaining stability in patients with schizophrenia who had been symptomatically stable on other antipsychotic medications for periods of 3 months or longer, were discontinued from those other medications, and were then administered ABILIFY 15 mg/day and observed for relapse during a period of up to 26 weeks was demonstrated in a placebo-controlled trial (see **CLINICAL PHARMACOLOGY: Clinical Studies**). The physician who elects to use ABILIFY for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION** in Full Prescribing Information).

Bipolar Mania

ABILIFY is indicated for the treatment of acute manic and mixed episodes associated with Bipolar Disorder. The efficacy of ABILIFY was established in two placebo-controlled trials (3-week) of inpatients with DSM-IV criteria for Bipolar I Disorder who were experiencing an acute manic or mixed episode with or without psychotic features (see **CLINICAL PHARMACOLOGY**). However, the effectiveness of ABILIFY for longer-term use, that is, for more than 3 weeks of treatment of an acute episode, and for prophylactic use in mania, has not been established in controlled clinical trials. Therefore, physicians who elect to use ABILIFY for extended periods should periodically re-evaluate the long-term risks and benefits of the drug for the individual patient (see **DOSAGE AND ADMINISTRATION**).

CONTRAINDICATIONS

ABILIFY is contraindicated in patients with a known hypersensitivity to the product.

WARNINGS

Neuroleptic Malignant Syndrome (NMS)

A potentially fatal symptom complex sometimes referred to as Neuroleptic Malignant Syndrome (NMS) has been reported in association with administration of antipsychotic drugs, including aripiprazole. Two possible cases of NMS occurred during aripiprazole treatment in the premarketing worldwide clinical database. Clinical manifestations of NMS are hyperpyrexia, muscle rigidity, altered mental status, and evidence of autonomic instability (irregular pulse or blood pressure, tachycardia, diaphoresis, and cardiac dysrhythmia). Additional signs may include elevated creatine phosphokinase, myoglobinuria (rhabdomyolysis), and acute renal failure. The diagnostic evaluation of patients with this syndrome is complicated. In arriving at a diagnosis, it is important to exclude cases where the clinical presentation includes both serious medical illness (e.g., pneumonia, systemic infection, etc.) and untreated or inadequately treated extrapyramidal signs and symptoms (EPS). Other important considerations in the differential diagnosis include central anticholinergic toxicity, heat stroke, drug fever, and primary central nervous system pathology. The management of NMS should include: 1) immediate discontinuation of antipsychotic drugs and other drugs not essential to concurrent therapy; 2) intensive symptomatic treatment and medical monitoring; and 3) treatment of any concomitant serious medical problems for which specific treatments are available. There is no general agreement about specific pharmacological treatment regimens for uncomplicated NMS. If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be carefully considered. The patient should be carefully monitored, since recurrences of NMS have been reported.

Tardive Dyskinesia

A syndrome of potentially irreversible, involuntary, dyskinetic movements may develop in patients treated with antipsychotic drugs. Although the prevalence of the syndrome appears to be highest among the elderly, especially elderly women, it is impossible to rely upon prevalence estimates to predict, at the inception of antipsychotic treatment, which patients are likely to develop the syndrome. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown. The risk of developing tardive dyskinesia and the likelihood that it will become irreversible are believed to increase as the duration of treatment and the total cumulative dose of antipsychotic drugs administered to the patient increase. However, the syndrome can develop, although much less commonly, after relatively brief treatment periods at low doses. There is no known treatment for established cases of tardive dyskinesia, although the syndrome may remit, partially or completely, if antipsychotic treatment is withdrawn. Antipsychotic treatment, itself, however, may suppress (or partially suppress) the signs and symptoms of the syndrome and, thereby, may possibly mask the underlying process. The effect that symptomatic suppression has upon the long-term course of the syndrome is unknown. Given these considerations, ABILIFY should be prescribed in a manner that is most likely to minimize the occurrence of tardive dyskinesia. Chronic antipsychotic treatment should generally be reserved for patients who suffer from a chronic illness that (1) is known to respond to antipsychotic drugs, and (2) for whom alternative, equally effective, but potentially less harmful treatments are not available or appropriate. In patients who do require chronic treatment, the smallest dose and the shortest duration of treatment producing a satisfactory clinical response should be sought. The need for continued treatment should be reassessed periodically. If signs and symptoms of tardive dyskinesia appear in a patient on ABILIFY, drug discontinuation should be considered. However, some patients may require treatment with ABILIFY despite the presence of the syndrome.

Hyperglycemia and Diabetes Mellitus

Hyperglycemia, in some cases extreme and associated with ketoacidosis or hyperosmolar coma or death, has been reported in patients treated with atypical antipsychotics. There have been few reports of hyperglycemia in patients treated with ABILIFY. Although fewer patients have been treated with ABILIFY, it is not known if this more limited experience is the sole reason for the paucity of such reports. Assessment of the relationship between atypical antipsychotic use and glucose abnormalities is complicated by the possibility of an increased background risk of diabetes mellitus in patients with schizophrenia and the increasing incidence of diabetes mellitus in the general population. Given these confounders, the relationship between atypical antipsychotic use and hyperglycemia-related adverse events is not completely understood. However, epidemiological studies which did not include ABILIFY suggest an increased risk of treatment-emergent hyperglycemia-related adverse events in patients treated with the atypical antipsychotics included in these studies. Because ABILIFY was not marketed at the time these studies were performed, it is not known if ABILIFY is associated with this increased risk. Precise risk estimates for hyperglycemia-related adverse events in patients treated with atypical antipsychotics are not available. Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g., obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at the beginning of treatment and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycemia including polydipsia, polyuria, polyphagia, and weakness. Patients who develop symptoms of hyperglycemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of anti-diabetic treatment despite discontinuation of the suspect drug.

PRECAUTIONS

General

Orthostatic Hypotension

Aripiprazole may be associated with orthostatic hypotension, perhaps due to its α_1-adrenergic receptor antagonism. The incidence of orthostatic hypotension associated events from five short-term, placebo-controlled trials in schizophrenia (n=926) on ABILIFY included: orthostatic hypotension (placebo 1%, aripiprazole 1.9%), orthostatic lightheadedness (placebo 1%, aripiprazole 0.9%), and syncope (placebo 1%, aripiprazole 0.6%). The incidence of orthostatic hypotension associated events from short-term, placebo-controlled trials in bipolar mania (n=597) on ABILIFY included: orthostatic hypotension (placebo 0%, aripiprazole 0.7%), orthostatic lightheadedness (placebo 0.5%, aripiprazole 0.5%), and syncope (placebo 0.9%, aripiprazole 0.5%). The incidence of a significant orthostatic change in blood pressure (defined as a decrease of at least 30 mmHg in systolic blood pressure when changing from a supine to standing position) for aripiprazole was not statistically different from placebo (in schizophrenia: 14% among aripiprazole-treated patients and 12% among placebo-treated patients and in bipolar mania: 3% among aripiprazole-treated patients and 2% among placebo-treated patients). Aripiprazole should be used with caution in patients with known cardiovascular disease (history of myocardial infarction or ischemic heart disease, heart failure or conduction abnormalities), cerebrovascular disease, or conditions which would predispose patients to hypotension (dehydration, hypovolemia, and treatment with antihypertensive medications).

Seizure

Seizures occurred in 0.1% (1/926) of aripiprazole-treated patients with schizophrenia in short-term, placebo-controlled trials. In short-term, placebo-controlled clinical trials of patients with bipolar mania, 0.3% (2/597) of aripiprazole-treated patients and 0.2% (1/436) placebo-treated patients experienced seizures. As with other antipsychotic drugs, aripiprazole should be used cautiously in patients with a history of seizures or with conditions that lower the seizure threshold, e.g., Alzheimer's dementia. Conditions that lower the seizure threshold may be more prevalent in a population of 65 years or older.

Potential for Cognitive and Motor Impairment

In short-term, placebo-controlled trials of schizophrenia, somnolence was reported in 11% of patients on ABILIFY compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% (1/926) of patients with schizophrenia on ABILIFY in short-term, placebo-controlled trials. In short-term, placebo-controlled trials of bipolar mania, somnolence was reported in 14% of patients on ABILIFY compared to 7% of patients on placebo, but did not lead to discontinuation of any patients with bipolar mania. Despite the relatively modest increased incidence of somnolence compared to placebo, ABILIFY, like other antipsychotics, may have the potential to impair judgment, thinking, or motor skills. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that therapy with ABILIFY does not affect them adversely.

Body Temperature Regulation

Disruption of the body's ability to reduce core body temperature has been attributed to antipsychotic agents. Appropriate care is advised when prescribing aripiprazole for patients who will be experiencing conditions which may contribute to an elevation in core body temperature, e.g., exercising strenuously, exposure to extreme heat, receiving concomitant medication with anticholinergic activity, or being subject to dehydration.

Dysphagia

Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in elderly patients, in particular those with advanced Alzheimer's dementia. Aripiprazole and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia (see **PRECAUTIONS**: *Use in Patients with Concomitant Illness*).

Suicide

The possibility of a suicide attempt is inherent in psychotic illnesses and bipolar disorder, and close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY (aripiprazole) should be written for the smallest quantity of tablets consistent with good patient management in order to reduce the risk of overdose.

Use in Patients with Concomitant Illness

Safety Experience in Elderly Patients with Psychosis Associated with Alzheimer's Disease: In a flexible dose (2 to 15 mg/day), 10-week, placebo-controlled study of aripiprazole in elderly patients (mean age: 81.5 years; range: 56 to 95 years) with psychosis associated with Alzheimer's dementia, 4 of 105 patients (3.8%) who received ABILIFY died compared to no deaths among 102 patients who received placebo during or within 30 days after termination of the double-blind portion of the study. Three of the patients (age 92, 91, and 87 years) died following the discontinuation of ABILIFY in the double-blind phase of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study. The treatment-emergent adverse events that were reported at an incidence of ≥5% and having a greater incidence than placebo in this study were accidental injury, somnolence, and bronchitis. Eight percent of the ABILIFY-treated patients reported somnolence compared to one percent of placebo patients. In a small pilot, open-label, ascending-dose, cohort study (n=30) in elderly patients with dementia, ABILIFY was associated in a dose-related fashion with somnolence. The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with dementia have not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised, particularly for the emergence of difficulty swallowing or excessive somnolence, which could predispose to accidental injury or aspiration. Clinical experience with ABILIFY in patients with certain concomitant systemic illnesses (see **CLINICAL PHARMACOLOGY: Special Populations:** *Renal Impairment* and *Hepatic Impairment* in Full Prescribing Information) is limited. ABILIFY has not been evaluated or used to any appreciable extent in patients with a recent history of myocardial infarction or unstable heart disease. Patients with these diagnoses were excluded from premarketing clinical studies.

Information for Patients: Physicians are advised to consult full prescribing information to review issues to be discussed with patients for whom they prescribe ABILIFY.

Drug-Drug Interactions: Given the primary CNS effects of aripiprazole, caution should be used when ABILIFY is taken in combination with other centrally acting drugs and alcohol. Due to its α_1-adrenergic receptor antagonism, aripiprazole has the potential to enhance the effect of certain antihypertensive agents. *Potential for Other Drugs to Affect ABILIFY:* Aripiprazole is not a substrate of CYP1A1, CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, or CYP2E1 enzymes. Aripiprazole also does not undergo direct glucuronidation. This suggests that an interaction of aripiprazole with inhibitors or inducers of these enzymes, or other factors, like smoking, is unlikely. Both CYP3A4 and CYP2D6 are responsible for aripiprazole metabolism. Agents that induce CYP3A4 (e.g., carbamazepine) could cause an increase in aripiprazole clearance and lower blood levels. Inhibitors of CYP3A4 (e.g., ketoconazole) or CYP2D6 (e.g., quinidine, fluoxetine, or paroxetine) can inhibit aripiprazole elimination and cause increased blood levels. *Ketoconazole:* Coadministration of ketoconazole (200 mg/day for 14 days) with a 15-mg single dose of aripiprazole increased the AUC of aripiprazole and its active metabolite by 63% and 77%, respectively. The effect of a higher ketoconazole dose (400 mg/day) has not been studied. When concomitant administration of ketoconazole with aripiprazole occurs, aripiprazole dose should be reduced to one-half of its normal dose. Other strong inhibitors of CYP3A4 (itraconazole) would be expected to have similar effects and need similar dose reductions; weaker inhibitors (erythromycin, grapefruit juice) have not been studied. When the CYP3A4 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased. *Quinidine:* Coadministration of a 10-mg single dose of aripiprazole with quinidine (166 mg/day for 13 days), a potent inhibitor of CYP2D6, increased the AUC of aripiprazole by 112% but decreased the AUC of its active metabolite, dehydro-aripiprazole, by 35%. Aripiprazole dose should be reduced to one-half of its normal dose when concomitant administration of quinidine with aripiprazole occurs. Other significant inhibitors of CYP2D6, such as fluoxetine or paroxetine, would be expected to have similar effects and, therefore, should be accompanied by similar dose reductions. When the CYP2D6 inhibitor is withdrawn from the combination therapy, aripiprazole dose should then be increased. *Carbamazepine:* Coadministration of carbamazepine (200 mg BID), a potent CYP3A4 inducer, with aripiprazole (30 mg QD) resulted in an approximate 70% decrease in C_{max} and AUC values of both aripiprazole and its active metabolite, dehydro-aripiprazole. When carbamazepine is added to aripiprazole therapy, aripiprazole dose should be doubled. Additional dose increases should be based on clinical evaluation. When carbamazepine is withdrawn from the combination therapy, aripiprazole dose should then be reduced. No clinically significant effect of famotidine, valproate, or lithium was seen on the pharmacokinetics of aripiprazole (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions** in Full Prescribing Information). *Potential for ABILIFY to Affect Other Drugs:* Aripiprazole is unlikely to cause clinically important pharmacokinetic interactions with drugs metabolized by cytochrome P450 enzymes. In *in vivo* studies, 10- to 30-mg/day doses of aripiprazole had no significant effect on metabolism by CYP2D6 (dextromethorphan), CYP2C9 (warfarin), CYP2C19 (omeprazole, warfarin), and CYP3A4 (dextromethorphan) substrates. Additionally, aripiprazole and dehydro-aripiprazole did not show potential for altering CYP1A2-mediated metabolism *in vitro* (see **CLINICAL PHARMACOLOGY: Drug-Drug Interactions**). *Alcohol:* There was no significant difference between aripiprazole coadministered with ethanol and placebo coadministered with ethanol on performance of gross motor skills or stimulus response in healthy subjects. As with most psychoactive medications, patients should be advised to avoid alcohol while taking ABILIFY.

Carcinogenesis, Mutagenesis, Impairment of Fertility: (Please See Full Prescribing Information).

Pregnancy

Pregnancy Category C

In animal studies, aripiprazole demonstrated developmental toxicity, including possible teratogenic effects in rats and rabbits. Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the maximum recommended human dose [MRHD] on a mg/m^2 basis) of aripiprazole during the period of organogenesis. Gestation was slightly prolonged at 30 mg/kg. Treatment caused a slight delay in fetal development, as evidenced by decreased fetal weight (30 mg/kg), undescended testes (30 mg/kg), and delayed skeletal ossification (10 and 30 mg/kg). There were no adverse effects on embryofetal or pup survival. Delivered offspring had decreased bodyweights (10 and 30 mg/kg), and increased incidences of hepatodiaphragmatic nodules and diaphragmatic hernia at 30 mg/kg (the other dose groups were not examined for these findings). (A low incidence of diaphragmatic hernia was also seen in the fetuses exposed to 30 mg/kg.) Postnatally, delayed vaginal opening was seen at 10 and 30 mg/kg and impaired reproductive performance (decreased fertility rate, corpora lutea, implants, and live fetuses, and increased post-implantation loss, likely mediated through effects on female offspring) was seen at 30 mg/kg. Some maternal toxicity was seen at 30 mg/kg, however, there was no evidence to suggest that these developmental effects were secondary to maternal toxicity. Pregnant rabbits were treated with oral doses of 10, 30, and 100 mg/kg/day (2, 3, and 11 times human exposure at MRHD based on AUC and 6, 19, and 65 times the MRHD based on mg/m^2) of aripiprazole during the period of organogenesis. Decreased maternal food consumption and increased abortions were seen at 100 mg/kg. Treatment caused increased fetal mortality (100 mg/kg), decreased fetal weight (30 and 100 mg/kg), increased incidence of skeletal abnormality (fused sternebrae at 30 and 100 mg/kg) and minor skeletal variations (100 mg/kg). In a study in which rats were treated with oral doses of 3, 10, and 30 mg/kg/day (1, 3, and 10 times the MRHD on a mg/m^2 basis) of aripiprazole perinatally and postnatally (from day 17 of gestation through day 21 postpartum), slight maternal toxicity and slightly prolonged gestation were seen at 30 mg/kg. An increase in stillbirths, and decreases in pup weight (persisting into adulthood) and survival, were seen at this dose. There are no adequate and well-controlled studies in pregnant women. It is not known whether aripiprazole can cause fetal harm when administered to a pregnant woman or can affect reproductive capacity. Aripiprazole should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Labor and Delivery

The effect of aripiprazole on labor and delivery in humans is unknown.

Nursing Mothers

Aripiprazole was excreted in milk of rats during lactation. It is not known whether aripiprazole or its metabolites are excreted in human milk. It is recommended that women receiving aripiprazole should not breast-feed.

Pediatric Use

Safety and effectiveness in pediatric and adolescent patients have not been established.

Geriatric Use

Of the 7951 patients treated with aripiprazole in premarketing clinical trials, 991 (12%) were ≥65 years old and 789 (10%) were ≥75 years old. The majority (88%) of the 991 patients were diagnosed with dementia of the Alzheimer's type. Placebo-controlled studies of aripiprazole in schizophrenia or bipolar mania did not include sufficient numbers of subjects aged 65 and over to determine whether they respond differently from younger subjects. There was no effect of age on the pharmacokinetics of a single 15-mg dose of aripiprazole. Aripiprazole clearance was decreased by 20% in elderly subjects (≥65 years) compared to younger adult subjects (18 to 64 years), but there was no detectable effect of age in the population pharmacokinetic analysis in schizophrenia patients. Studies of elderly patients with psychosis associated with Alzheimer's disease have suggested that there may be a different tolerability profile in this population compared to younger patients with schizophrenia (see **PRECAUTIONS:** *Use in Patients with Concomitant Illness*). The safety and efficacy of ABILIFY in the treatment of patients with psychosis associated with Alzheimer's disease has not been established. If the prescriber elects to treat such patients with ABILIFY, vigilance should be exercised.

ADVERSE REACTIONS

Aripiprazole has been evaluated for safety in 7951 patients who participated in multiple-dose, premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 5235 patient-years of exposure. A total of 2280 aripiprazole-treated patients were treated for at least 180 days and 1558 aripiprazole-treated patients had at least 1 year of exposure. The conditions and duration of treatment with aripiprazole included (in overlapping categories) double-blind, comparative and noncomparative open-label studies, inpatient and outpatient studies, fixed- and flexible-dose studies, and short- and longer-term exposure. Adverse events during exposure were obtained by collecting volunteered adverse events, as well as results of physical examinations, vital signs, weights, laboratory analyses, and ECG. Adverse experiences were recorded by clinical investigators using terminology of their own choosing. In the tables and tabulations that follow, modified COSTART dictionary terminology has been used initially to classify reported adverse events into a smaller number of standardized event categories, in order to provide a meaningful estimate of the proportion of individuals experiencing adverse events. The stated frequencies of adverse events represent the proportion of individuals who experienced at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation. There was no attempt to use investigator causality assessments; i.e., all reported events are included. The prescriber should be aware that the figures in the tables and tabulations cannot be used to predict the incidence of side effects in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatment, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and nondrug factors to the adverse event incidence in the population studied.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Schizophrenia

The following findings are based on a pool of five placebo-controlled trials (four 4-week and one 6-week) in which aripiprazole was administered in doses ranging from 2 to 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (7%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Adverse Findings Observed in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

The following findings are based on a pool of 3-week, placebo-controlled bipolar mania trials in which aripiprazole was administered at doses of 15 or 30 mg/day.

Adverse Events Associated with Discontinuation of Treatment in Short-Term, Placebo-Controlled Trials

Overall, in patients with bipolar mania, there was no difference in the incidence of discontinuation due to adverse events between aripiprazole-treated (11%) and placebo-treated (9%) patients. The types of adverse events that led to discontinuation were similar between the aripiprazole and placebo-treated patients.

Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials of Patients with Bipolar Mania

Commonly observed adverse events associated with the use of aripiprazole in patients with bipolar mania (incidence of 5% or greater and aripiprazole incidence at least twice that for placebo) are shown in Table 1. There were no adverse events in the short-term trials of schizophrenia that met these criteria.

Table 1: Commonly Observed Adverse Events in Short-Term, Placebo-Controlled Trials in Patients with Bipolar Mania

	Percentage of Patients Reporting Event	
Adverse Event	Aripiprazole (n=597)	Placebo (n=436)
Accidental Injury	6	3
Constipation	13	6
Akathisia	15	4

Adverse Events Occurring at an Incidence of 2% or More Among Aripiprazole-Treated Patients and Greater than Placebo in Short-Term, Placebo-Controlled Trials

Treatment-emergent adverse events that occurred during acute therapy (up to 6 weeks in schizophrenia and up to 3 weeks in bipolar mania), including only those events that occurred in 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence in patients treated with aripiprazole was greater than the incidence in patients treated with placebo in the combined dataset were: *Body as a Whole*—headache, asthenia, accidental injury, peripheral edema; *Cardiovascular System*—hypertension; *Digestive System*—nausea, dyspepsia, vomiting, constipation; *Musculoskeletal System*—myalgia; *Nervous System*—agitation, anxiety, insomnia, somnolence, akathisia, lightheadedness, extrapyramidal syndrome, tremor, increased salivation; *Respiratory System*—pharyngitis, rhinitis, coughing; *Special Senses*—blurred vision. An examination of population subgroups did not reveal any clear evidence of differential adverse event incidence on the basis of age, gender, or race.

Dose-Related Adverse Events

Schizophrenia

Dose response relationships for the incidence of treatment-emergent adverse events were evaluated from four trials in patients with schizophrenia comparing various fixed doses (2, 10, 15, 20, and 30 mg/day) of aripiprazole to placebo. This analysis, stratified by study, indicated that the only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; 30 mg, 15.3%).

Extrapyramidal Symptoms

In the short-term, placebo-controlled trials of schizophrenia, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of reported EPS-related events excluding events related to akathisia for aripiprazole-treated patients was 17% vs. 12% for placebo. In the short-term, placebo-controlled trials in bipolar mania, the incidence of akathisia-related events for aripiprazole-treated patients was 15% vs. 4% for placebo. Objectively collected data from those trials was collected on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia) and the Assessments of Involuntary Movement Scales (for dyskinesias). In the schizophrenia trials, the objectively collected data did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). In the bipolar mania trials, the Simpson Angus Rating Scale and the Barnes Akathisia Scale showed a significant difference between aripiprazole and placebo (aripiprazole, 0.61; placebo, 0.03 and aripiprazole, 0.25; placebo, -0.06). Changes in the Assessments of Involuntary Movement Scales were similar for the aripiprazole and placebo groups. Similarly, in a long-term (26-week), placebo-controlled trial of schizophrenia, objectively collected data on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) did not show a difference between aripiprazole and placebo.

Laboratory Test Abnormalities

A between group comparison for 3- to 6-week, placebo-controlled trials revealed no medically important differences between the aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no aripiprazole/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. In a long-term (26-week), placebo-controlled trial there were no medically important differences between the aripiprazole and placebo patients in the mean change from baseline in prolactin, fasting glucose, triglyceride, HDL, LDL, and total cholesterol measurements.

Weight Gain

In 4- to 6-week trials in schizophrenia, there was a slight difference in mean weight gain between aripiprazole and placebo patients (+0.7 kg vs. -0.05 kg, respectively), and also a difference in the proportion of patients meeting a weight gain criterion of ≥7% of body weight [aripiprazole (8%) compared to placebo (3%)]. In 3-week trials in mania, the mean weight gain for aripiprazole and placebo patients was 0.0 kg vs. -0.2 kg, respectively. The proportion of patients meeting a weight gain criterion of ≥7% of body weight was aripiprazole (3%) compared to placebo (2%). Table 2 provides the weight change results from a long-term (26-week), placebo-controlled study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 2: Weight Change Results Categorized by BMI at Baseline: Placebo-Controlled Study in Schizophrenia, Safety Sample

	BMI <23		BMI 23-27		BMI >27	
	Placebo	Aripiprazole	Placebo	Aripiprazole	Placebo	Aripiprazole
Mean change from baseline (kg)	-0.5	-0.5	-0.6	-1.3	-1.5	-2.1
% with ≥7% increase BW	3.7%	6.8%	4.2%	5.1%	4.1%	5.7%

Table 3 provides the weight change results from a long-term (52-week) study of aripiprazole, both mean change from baseline and proportions of patients meeting a weight gain criterion of ≥7% of body weight relative to baseline, categorized by BMI at baseline:

Table 3: Weight Change Results Categorized by BMI at Baseline: Active-Controlled Study in Schizophrenia, Safety Sample

	BMI <23	BMI 23-27	BMI >27
Mean change from baseline (kg)	2.6	1.4	-1.2
% with ≥7% increase BW	30%	19%	8%

ECG Changes

Between group comparisons for pooled, placebo-controlled trials in patients with schizophrenia, revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters; in fact, within the dose range of 10 to 30 mg/day, aripiprazole tended to slightly shorten the QT_c interval. Aripiprazole was associated with a median increase in heart rate of 4 beats per minute compared to a 1 beat per minute increase among placebo patients.

Additional Findings Observed in Clinical Trials

Adverse Events in a Long-Term, Double-Blind, Placebo-Controlled Trial

The adverse events reported in a 26-week, double-blind trial comparing ABILIFY (aripiprazole) and placebo were generally consistent with those reported in the short-term, placebo-controlled trials, except for a higher incidence of tremor [9% (13/153) for ABILIFY vs. 1% (2/153) for placebo]. In this study, the majority of the cases of tremor were of mild intensity (9/13 mild and 4/13 moderate), occurred early in therapy (9/13 ≤49 days), and were of limited duration (9/13 ≤10 days). Tremor infrequently led to discontinuation (<1%) of ABILIFY. In addition, in a long-term (52-week), active-controlled study, the incidence of tremor for ABILIFY was 4% (34/859).

Other Adverse Events Observed During the Premarketing Evaluation of Aripiprazole

Following is a list of modified COSTART terms that reflect treatment-emergent adverse events as defined in the introduction to the **ADVERSE REACTIONS** section reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 7951 patients. All reported events are included except those already listed in other parts of the **ADVERSE REACTIONS** section, those considered in the **WARNINGS** or **PRECAUTIONS**, those event terms which were so general as to be uninformative, events reported with an incidence of ≤0.05% and which did not have a substantial probability of being acutely life-threatening, events that are otherwise common as background events, and events considered unlikely to be drug related. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring in at least 1/100 patients (only those not already listed in the tabulated results from placebo-controlled trials appear in this listing); infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. *Body as a Whole: Frequent* – flu syndrome, fever, chest pain, rigidity (including neck and extremity), neck pain, pelvic pain; *Infrequent* – face edema, suicide attempt, malaise, migraine, chills, photosensitivity, tightness (including abdomen, back, extremity, head, jaw, neck, and tongue), jaw pain, bloating, enlarged abdomen, chest tightness, throat pain; *Rare* – moniliasis, head heaviness, throat tightness, Mendelson's syndrome, heat stroke. *Cardiovascular System: Frequent* – tachycardia (including ventricular and supraventricular), hypotension, bradycardia; *Infrequent* – palpitation, hemorrhage, heart failure, myocardial infarction, cardiac arrest, atrial fibrillation, AV block, prolonged QT interval, extrasystoles, myocardial ischemia, deep vein thrombosis, angina pectoris, pallor, cardiopulmonary arrest, phlebitis; *Rare* – bundle branch block, atrial flutter, vasovagal reaction, cardiomegaly, thrombophlebitis, cardiopulmonary failure. *Digestive System: Frequent* – nausea and vomiting; *Infrequent* – increased appetite, dysphagia, gastroenteritis, flatulence, tooth caries, gastritis, gingivitis, gastrointestinal hemorrhage, hemorrhoids, gastroesophageal reflux, periodontal abscess, fecal incontinence, rectal hemorrhage, stomatitis, colitis, tongue edema, cholecystitis, mouth ulcer, oral moniliasis, eructation, fecal impaction, cholelithiasis; *Rare* – esophagitis, hematemesis, intestinal obstruction, gum hemorrhage, hepatitis, peptic ulcer, glossitis, melena, duodenal ulcer, cheilitis, hepatomegaly, pancreatitis. *Endocrine System: Infrequent* – hypothyroidism; *Rare* – goiter, hyperthyroidism. *Hemic/Lymphatic System: Frequent* – ecchymosis, anemia; *Infrequent* – hypochromic anemia, leukocytosis, leukopenia (including neutropenia), lymphadenopathy, eosinophilia, macrocytic anemia; *Rare* – thrombocythemia, thrombocytopenia, petechiae. *Metabolic and Nutritional Disorders: Frequent* – weight loss, creatine phosphokinase increased, dehydration; *Infrequent* – edema, hyperglycemia, hypercholesteremia, hypokalemia, diabetes mellitus, hypoglycemia, hyperlipemia, SGPT increased, thirst, BUN increased, hyponatremia, SGOT increased, creatinine increased, cyanosis, alkaline phosphatase increased, bilirubinemia, iron deficiency anemia, hyperkalemia, hyperuricemia, obesity; *Rare* – lactic dehydrogenase increased, hypernatremia, gout, hypoglycemic reaction. *Musculoskeletal System: Frequent* – muscle cramp; *Infrequent* – arthralgia, myasthenia, arthrosis, bone pain, arthritis, muscle weakness, spasm, bursitis, myopathy; *Rare* – rheumatoid arthritis, rhabdomyolysis, tendonitis, tenosynovitis. *Nervous System: Frequent* – depression, nervousness, schizophrenic reaction, hallucination, hostility, confusion, paranoid reaction, suicidal thought, abnormal gait, manic reaction, delusions, abnormal dream; *Infrequent* – emotional lability, twitch, cogwheel rigidity, impaired concentration, dystonia, vasodilation, paresthesia, impotence, extremity tremor, hypesthesia, vertigo, stupor, bradykinesia, apathy, panic attack, decreased libido, hypersomnia, dyskinesia, manic depressive reaction, ataxia, visual hallucination, cerebrovascular accident, hypokinesia, depersonalization, impaired memory, delirium, dysarthria, tardive dyskinesia, amnesia, hyperactivity, increased libido, myoclonus, restless leg, neuropathy, dysphoria, hyperkinesia, cerebral ischemia, increased reflexes, akinesia, decreased consciousness, hyperesthesia, slowed thinking; *Rare* – blunted affect, euphoria, incoordination, oculogyric crisis, obsessive thought, hypotonia, buccoglossal syndrome, decreased reflexes, derealization, intracranial hemorrhage. *Respiratory System: Frequent* – sinusitis, dyspnea, pneumonia, asthma; *Infrequent* – epistaxis, hiccup, laryngitis, aspiration pneumonia; *Rare* – pulmonary edema, increased sputum, pulmonary embolism, hypoxia, respiratory failure, apnea, dry nasal passages, hemoptysis. *Skin and Appendages: Frequent* – skin ulcer, sweating, dry skin; *Infrequent* – pruritus, vesiculobullous rash, acne, eczema, skin discoloration, alopecia, seborrhea, psoriasis; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria. *Special Senses: Frequent* – conjunctivitis; *Infrequent* – ear pain, dry eye, eye pain, tinnitus, cataract, otitis media, altered taste, blepharitis, eye hemorrhage, deafness; *Rare* – diplopia, frequent blinking, ptosis, otitis externa, amblyopia, photophobia. *Urogenital System: Frequent* – urinary incontinence; *Infrequent* – urinary frequency, leukorrhea, urinary retention, cystitis, hematuria, dysuria, amenorrhea, vaginal hemorrhage, abnormal ejaculation, kidney failure, vaginal moniliasis, urinary urgency, gynecomastia, kidney calculus, albuminuria, breast pain, urinary burning; *Rare* – nocturia, polyuria, menorrhagia, anorgasmy, glycosuria, cervicitis, uterus hemorrhage, female lactation, urolithiasis, priapism.

Other Events Observed During the Postmarketing Evaluation of Aripiprazole

Voluntary reports of adverse events in patients taking aripiprazole that have been received since market introduction and not listed above that may have no causal relationship with the drug include rare occurrences of allergic reaction (e.g., anaphylactic reaction, angioedema, laryngospasm, pruritis, or urticaria).

DRUG ABUSE AND DEPENDENCE

Controlled Substance

ABILIFY is not a controlled substance.

Abuse and Dependence

Aripiprazole has not been systematically studied in humans for its potential for abuse, tolerance, or physical dependence. In physical dependence studies in monkeys, withdrawal symptoms were observed upon abrupt cessation of dosing. While the clinical trials did not reveal any tendency for any drug-seeking behavior, these observations were not systematic and it is not possible to predict on the basis of this limited experience the extent to which a CNS-active drug will be misused, diverted, and/or abused once marketed. Consequently, patients should be evaluated carefully for a history of drug abuse, and such patients should be observed closely for signs of ABILIFY misuse or abuse (e.g., development of tolerance, increases in dose, drug-seeking behavior).

OVERDOSAGE

Management of Overdosage

No specific information is available on the treatment of overdose with aripiprazole. An electrocardiogram should be obtained in case of overdosage and, if QT_c interval prolongation is present, cardiac monitoring should be instituted. Otherwise, management of overdose should concentrate on supportive therapy, maintaining an adequate airway, oxygenation and ventilation, and management of symptoms. Close medical supervision and monitoring should continue until the patient recovers.

Charcoal: In the event of an overdose of ABILIFY, an early charcoal administration may be useful in partially preventing the absorption of aripiprazole. Administration of 50 g of activated charcoal, one hour after a single 15-mg oral dose of aripiprazole, decreased the mean AUC and C_{max} of aripiprazole by 50%.

Hemodialysis: Although there is no information on the effect of hemodialysis in treating an overdose with aripiprazole, hemodialysis is unlikely to be useful in overdose management since aripiprazole is highly bound to plasma proteins.

Storage

Store at 25° C (77° F); excursions permitted to 15-30° C (59-86° F) [see USP Controlled Room Temperature].

Marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA
and Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan

Distributed by Bristol-Myers Squibb Company, Princeton, NJ 08543 USA

U.S. Patent Nos. 4,734,416 and 5,006,528

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D6-B0001A-09-04 AP4749/10-04
1156731A8
Revised September 2004