Migraine and Its Connections in Neurology and Psychiatry

By Jack M. Gorman, MD

At the recent meeting in Hawaii of the American Academy of Neurology, we heard many positive comments about *CNS Spectrums*. We were also urged by the attending neurologists to try and include more articles and issues devoted to neurologic disease and mechanisms.

Previously, we have had issues on epilepsy and stroke, and future issues are planned that will cover movement disorders, multiple sclerosis, child neurology, and Alzheimer's disease. We very much want and welcome both suggestions for neurological topics to which future issues may be dedicated and submission of unsolicited original research and review articles dealing with neurological topics. Our peer review process is quick and efficient. Accepted articles will be scheduled to appear as rapidly as possible.

This issue, whose articles I will discuss out of the printed order, is devoted largely to a topic of interest to neurologists and psychiatrists alike—migraine. Four papers deal with various aspects of migraine headache, a common and often plaguing disorder that still mystifies scientists and often eludes response to therapy. It is not an easy condition to diagnose; unlike many neurologic disorders, but in common with most psychiatric illness, there are no definitive objective tests that can make a positive diagnosis of migraine headache. Rather, after ruling out other causes of headache, like brain tumor, the neurologist must rely largely on history. Sometimes, the elicitation of symptoms like an aura can be nearly pathognomonic, but more often migraine is a diagnosis of exclusion by history alone. Treatment relies on palliative measures, including a variety of analgesics, some of which have abuse potential, ergotamine, β-blockers, anticonvulsants, and serotonin-enhancing drugs. Antidepressants generally are not effective in treating migraine headache; in some patients they seem to help while in others they worsen the situation.

Adding to this complexity, as Nancy C.P. Low, MD, MS, and Kathleen Ries Merikangas, PhD, of the National Institute of Mental Health, is the fact that migraine is highly comorbid with a host of other medical problems. These involve almost all organ systems and include psychiatric illness. Unfortunately, this penchant for co-occurrence with other disorders has not shed much light on the fundamental pathophysiology of migraine headache, but it does sometimes obscure the diagnosis. Their article is important as a reminder to think about migraine in patients with headache even in the face of multiple other problems.

Two articles suggest possible new treatment approaches to migraine. Keith R. Edwards, MD, from the Neurological Research Center in Bennington, Vermont, and colleages, from various other locations, combine data from two single-site, double-blind, placebo-controlled trials of the anticonvulsant topiramate for migraine prophylaxis. Seventy patients were enrolled and the results were positive: overall, topiramate produced a lower 28-day migraine frequency than placebo. About five times as many patients responded to topiramate than to placebo, although the overall response rate to the active drug was low (35.3%). Topiramate-associated adverse events included paresthesia and memory impairment. As has been observed before, topiramate also caused appetite suppression and weight loss. As I am a consultant to the manufacturer of topiramate (and therefore did not participate in the review of this article), I will refrain here from making any conclusions except to say that future studies of topiramate will be of great interest.

Nabih M. Ramadan, MD, from the Chicago Medical School argues convincingly in his paper that migraine headache may involve an abnormal activation of glutamatergic neuronal pathways and suggests that glutamate antagonists, which appear to work in animal models of migraine, might be useful therapeutically. This work provides both a mechanistic hypothesis and a suggestion for treatment approaches and deserves careful scrutiny by both investigators and clinicians.

By contrast to these positive notes about therapeutics, William B. Young, MD, and colleagues from the Thomas Jefferson University Hospital provide data from a study of 50 patients with severe headache, most of who had migraine, who were admitted to an outpatient infusion center. Seventeen of these patients also had restless legs syndrome and these individuals turned out to have a very high risk of developing akathisia following administration of intravenous dopamine receptor blocking agents. The authors suggest that increased surveillance for restless legs syndrome in headache patients might be important prior to initiating therapy with dopamine receptor antagonists.

A final paper in this issue deals with a completely separate topic, obsessive-compulsive disorder (OCD). Donatella Marazziti, MD, of the University of Pisa and an associate international editor of *CNS Spectrums* notes that about one-third of patients with OCD do not respond to serotonin reuptake inhibitor medications. Dr. Marazziti reports a positive experience with venlafaxine for such patients, a medication that blocks both serotonin and norepinephrine reuptake in a manner similar to clomipramine but with fewer adverse events. This is welcome news for clinicians and patients alike dealing with the often very hard to treat syndrome of OCD.

Finally, I want to remind our readers that *CNS Spectrums* is now accepting letters to the editor. Please send them in! CNS

Dr. Gorman is the editor of CNS Spectrums *and Leiber professor of psychiatry at Mount Sinai School of Medicine in New York City.*

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A road not *traveled before*

Unique Pharmacology Sets Abilify Apart[1]

Abilify is a partial agonist that uniquely modulates dopamine activity.[1,2]

– Functional *antagonist* activity at D_2 receptors in a *hyper*dopaminergic environment[1]

– Functional *agonist* activity at D_2 receptors in a *hypo*dopaminergic environment[1]

Serotonin *antagonist* activity at 5-HT_{2A} receptors and *partial agonist* activity at 5-HT_{1A} receptors

Abilify has moderate affinity for alpha$_1$-adrenergic and histamine (H_1) receptors

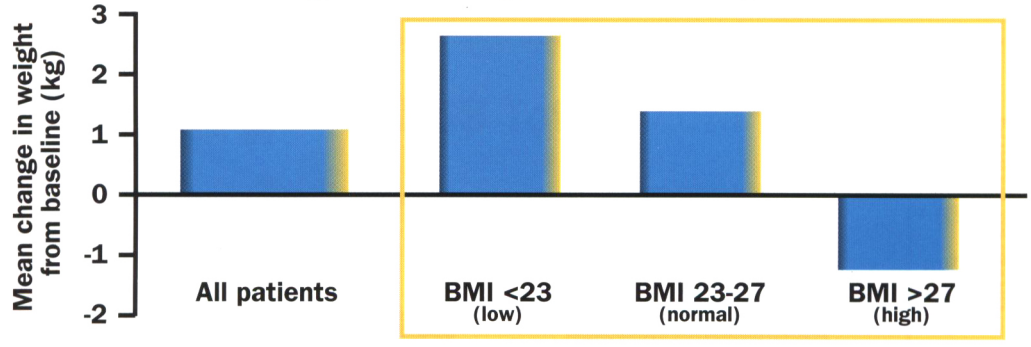
Abilify has no appreciable affinity for cholinergic muscarinic receptors

The mechanism of action of Abilify, as with other drugs having efficacy in schizophrenia, is unknown.

Abilify is indicated for the treatment of schizophrenia.

Please see Brief Summary of Prescribing Information on last page of this insert.

Effect of Abilify on weight, long term



A prospective 52-week, double-blind trial. For Abilify, BMI <23 (n=314); BMI 23 to 27 (n=265); and BMI >27 (n=260).
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.
†Last observation carried forward.

Because patients' overall health is important

Abilify is comparable to placebo on[§3]:

- **Glucose**
- **HDL**
- **LDL**
- **Triglycerides**

Data from a 6-week, placebo-controlled, clinical trial.
§As measured by routine serum chemistry analysis.

ABILIFY™
(aripiprazole)

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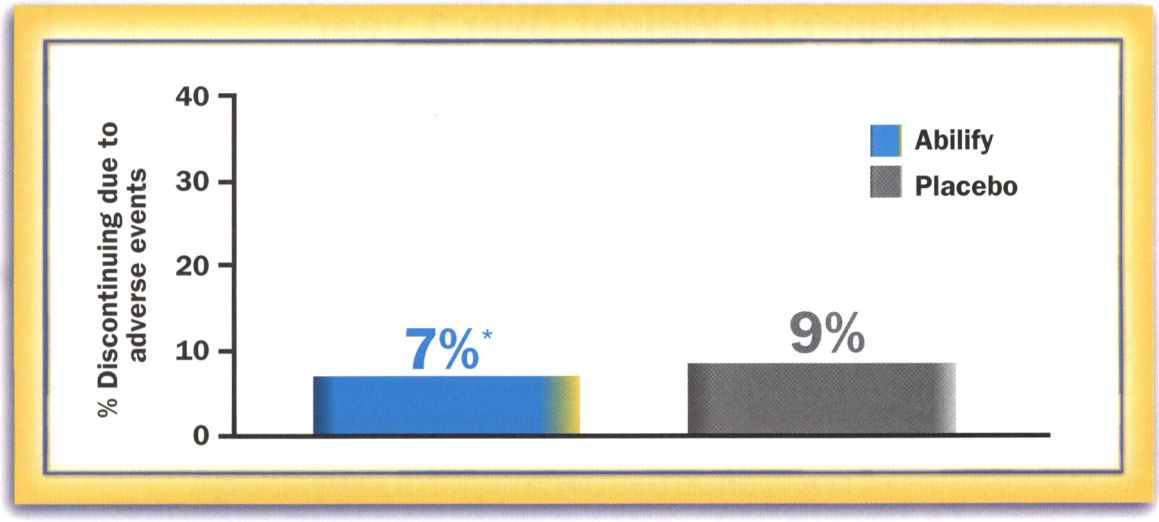
A clear path for the journey ahead

Few patients discontinue due to adverse events with Abilify



Pooled data from five 4- to 6-week, placebo-controlled clinical trials.
*There is no statistical difference in the incidence of discontinuation due to adverse events, and the types of adverse events that led to discontinuation were similar between placebo-treated patients and patients treated with Abilify.

Treatment-emergent adverse events reported at an incidence ≥10% and greater than placebo include headache, anxiety, insomnia, nausea, vomiting, lightheadedness, somnolence, akathisia, and constipation.

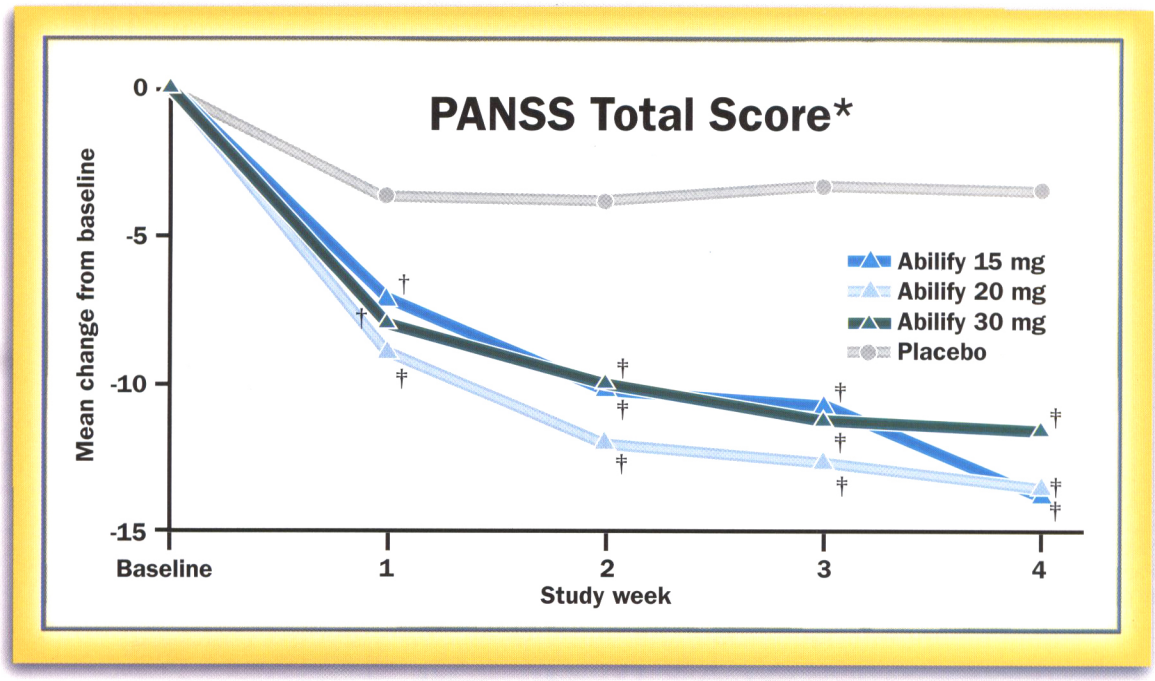
As with all antipsychotic medications, a rare condition referred to as neuroleptic malignant syndrome (NMS) has been reported. As with all antipsychotic medications, prescribing should be consistent with the need to minimize the risk of tardive dyskinesia (TD).

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 Abilify-treated patients in placebo-controlled trials.

The Confidence of Proven Efficacy

Significant improvement as early as Week 1[3]



Abilify 15 mg (n=202), 20 mg (n=195), 30 mg (n=196), and placebo (n=312). Analysis included data from all fixed-dose trials.
*Last observation carried forward.
†$P<0.05$ vs placebo.
‡$P<0.01$ vs placebo.

In efficacy studies, 88% of responders *did not* experience sedation[3]

In multiple, placebo-controlled trials, somnolence was reported in 11% of patients on Abilify compared to 8% of patients on placebo; somnolence led to discontinuation in 0.1% of patients on Abilify in these clinical trials. In clinical trials, the only adverse event to have a possible dose-response relationship was somnolence (placebo, 7.7%; 15 mg, 8.7%; 20 mg, 7.5%; and 30 mg, 15.3%).

ABILIFY™
(aripiprazole)

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Tolerability and Safety for the Road Ahead

- **Weight**[3] – Mean weight change of 1 kg over 1 year
- **Sedation*** – 11% vs placebo 8%
- **EPS*** – 6% vs placebo 6%
- **Hyperprolactinemia**[†3] – 1.8% vs placebo 6.9%
- **QT_c interval** – No significant difference vs placebo

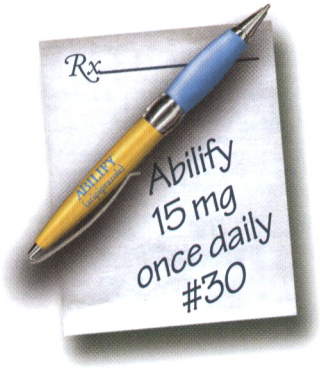
*Patient-reported adverse events in 4- and 6-week placebo-controlled trials.
†In patients with prolactin levels less than or equal to the upper limit of normal at baseline.

In a 52-week study, the percentage of patients with ≥7% increase in body weight was 30% for those with BMI (Body Mass Index [kg/m^2]) <23, 19% for those with BMI 23 to 27, and 8% for those with BMI >27.

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 gain criterion of ≥7% of body weight for Abilify (8%) compared to placebo (3%).

Abilify Makes Dosing Easy for the Patient and You

- **Convenient, once-daily dosing**
- **A range of strengths available from 10 mg to 30 mg to customize treatment**
- **Recommended starting *and* target dose of 15 mg is effective**
- **No titration required to reach an effective dose**
- **May be taken with or without food**



Abilify is on target right from the start. Prescribe *Abilify* 15 mg.

Visit www.abilify.com

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References:

1. Burris KD, Molski TF, XU C, et al. Aripiprazole, a novel antipsychotic, is a high-affinity partial agonist at human dopamine D_2 receptors. *The Journal of Pharmacology and Experimental Therapeutics.* 2002;302:381-389.
2. Kikuchi T, Tottori K, Üwahodo Y, et al. 7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butyloxy}-3,4-dihydro-2 (1H)-quinolinone (OPC-14597), a new putative antipsychotic drug with both presynaptic dopamine autoreceptor agonist activity and postsynaptic D_2 receptor antagonistic activity. *The Journal of Pharmacology and Experimental Therapeutics.* 1995;274:329-336.
3. Data on file. Otsuka America Pharmaceutical, Inc., Rockville, Md.

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ABILIFY™ (aripiprazole)

Bristol-Myers Squibb Company

Otsuka America Pharmaceutical, Inc.

D6-K0047 A4232/05-03 June 2003 Printed in USA Printed on recycled paper.

ABILIFY™
(aripiprazole) Tablets

Rx only

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

INDICATIONS AND USAGE

ABILIFY (aripiprazole) 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**). The long-term efficacy of aripiprazole in the treatment of schizophrenia has not been established. 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.

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.

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 (aripiprazole) 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 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 (14% among aripiprazole-treated patients and 12% 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 in short-term, placebo-controlled trials. 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, 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 on ABILIFY in short-term, placebo-controlled trials. 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 close supervision of high-risk patients should accompany drug therapy. Prescriptions for ABILIFY 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*) 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 (aripiprazole).

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**). *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 Category C: 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 5592 patients treated with aripiprazole in premarketing clinical trials, 659 (12%) were ≥65 years old and 525 (9%) were ≥75 years old. The majority (91%) of the 659 patients were diagnosed with dementia of the Alzheimer's type. Placebo-controlled studies of aripiprazole in schizophrenia 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 5592 patients who participated in multiple-dose premarketing trials in schizophrenia, bipolar mania, and dementia of the Alzheimer's type, and who had approximately 3639 patient-years of exposure. *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 Events Occurring at an Incidence of >2% 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) at an incidence of 2% or more of patients treated with aripiprazole (doses ≥2 mg/day) and for which the incidence was greater than the incidence reported for placebo were: *Body as a Whole*—headache, asthenia, and fever; *Digestive System* — nausea, vomiting, and constipation; *Nervous System* — anxiety, insomnia, lightheadedness, somnolence, akathisia, and tremor; *Respiratory System* — rhinitis and coughing; *Skin and Appendages* — rash; *Special Senses* — blurred vision. *Dose-Related Adverse Events:* 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 short-term, placebo-controlled trials, the incidence of reported EPS for aripiprazole-treated patients was 6% vs. 6% for placebo. Objectively collected data from those trials on the Simpson Angus Rating Scale (for EPS), the Barnes Akathisia Scale (for akathisia), and the Assessments of Involuntary Movement Scales (for dyskinesias) also did not show a difference between aripiprazole and placebo, with the exception of the Barnes Akathisia Scale (aripiprazole, 0.08; placebo, -0.05). *Laboratory Test Abnormalities:* A between group comparison for 4- to 6-week placebo-controlled trials revealed no medically important differences between aripiprazole and placebo groups in the proportions of patients experiencing potentially clinically significant changes in routine serum chemistry, hematology, or urinalysis parameters. *Weight Gain:* In short-term trials, 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%)]. *ECG Changes:* Between group comparisons for pooled placebo-controlled trials revealed no significant differences between aripiprazole and placebo in the proportion of patients experiencing potentially important changes in ECG parameters; 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. *Other Adverse Events Observed During Clinical Trials:* Following is a list of modified COSTART terms that reflect treatment-emergent adverse events reported by patients treated with aripiprazole at multiple doses ≥2 mg/day during any phase of a trial within the database of 5592 patients. It is important to emphasize that, although the events reported occurred during treatment with aripiprazole, they were not necessarily caused by it. Frequent events occurred in at least 1/100 patients; infrequent events occurred in 1/100 to 1/1000 patients; rare events in fewer than 1/1000 patients. *Body as a Whole: Frequent* – flu syndrome, peripheral edema, chest pain, neck pain, neck rigidity; *Infrequent* – pelvic pain, suicide attempt, face edema, malaise, photosensitivity, arm rigidity, jaw pain, chills, bloating, jaw tightness, enlarged abdomen, chest tightness; *Rare* – throat pain, back tightness, head heaviness, moniliasis, throat tightness, leg rigidity, neck tightness, Mendelson's syndrome, heat stroke. *Cardiovascular System: Frequent* – hypertension, tachycardia, hypotension, bradycardia; *Infrequent* – palpitation, hemorrhage, myocardial infarction, prolonged QT interval, cardiac arrest, atrial fibrillation, heart failure, AV block, myocardial ischemia, phlebitis, deep vein thrombosis, angina pectoris, extrasystoles; *Rare* – vasovagal reaction, cardiomegaly, atrial flutter, thrombophlebitis. *Digestive System: Frequent* – anorexia, nausea and vomiting; *Infrequent* – increased appetite, gastroenteritis, dysphagia, flatulence, gastritis, tooth caries, gingivitis, hemorrhoids, gastroesophageal reflux, gastrointestinal hemorrhage, periodontal abscess, tongue edema, fecal incontinence, colitis, rectal hemorrhage, stomatitis, mouth ulcer, cholecystitis, fecal impaction, oral moniliasis, cholelithiasis, eructation, intestinal obstruction, peptic ulcer; *Rare* – esophagitis, gum hemorrhage, glossitis, hematemesis, melena, duodenal ulcer, cheilitis, hepatitis, hepatomegaly, pancreatitis, intestinal perforation. *Endocrine System: Infrequent* – hypothyroidism; *Rare* – goiter, hyperthyroidism. *Hemic/Lymphatic System: Frequent* – ecchymosis, anemia; *Infrequent* – hypochromic anemia, leukopenia, leukocytosis, lymphadenopathy, thrombocytopenia; *Rare* – eosinophilia, thrombocythemia, macrocytic anemia. *Metabolic and Nutritional Disorders: Frequent* – weight loss, creatine phosphokinase increased; *Infrequent* – dehydration, edema, hypercholesteremia, hyperglycemia, hypokalemia, diabetes mellitus, SGPT increased, hyperlipemia, hypoglycemia, thirst, BUN increased, hyponatremia, SGOT increased, alkaline phosphatase increased, iron deficiency anemia, creatinine increased, bilirubinemia, lactic dehydrogenase increased, obesity; *Rare* – hyperkalemia, gout, hypernatremia, cyanosis, hyperuricemia, hypoglycemic reaction. *Musculoskeletal System: Frequent* – muscle cramp, *Infrequent* – arthralgia, bone pain, myasthenia, arthritis, arthrosis, muscle weakness, spasm, bursitis; *Rare* – rhabdomyolysis, tendonitis, tenosynovitis, rheumatoid arthritis, myopathy. *Nervous System: Frequent* – depression, nervousness, increased salivation, hostility, suicidal thought, manic reaction, abnormal gait, confusion, cogwheel rigidity; *Infrequent* – dystonia, twitch, impaired concentration, paresthesia, vasodilation, hypesthesia, extremity tremor, impotence, bradykinesia, decreased libido, panic attack, apathy, dyskinesia, hypersomnia, vertigo, dysarthria, tardive dyskinesia, ataxia, impaired memory, stupor, increased libido, amnesia, cerebrovascular accident, hyperactivity, depersonalization, hypokinesia, restless leg, myoclonus, dysphoria, neuropathy, increased reflexes, slowed thinking, hyperkinesia, hyperesthesia, hypotonia, oculogyric crisis; *Rare* – delirium, euphoria, buccoglossal syndrome, akinesia, blunted affect, decreased consciousness, incoordination, cerebral ischemia, decreased reflexes, obsessive thought, intracranial hemorrhage. *Respiratory System: Frequent* – dyspnea, pneumonia; *Infrequent* – asthma, epistaxis, hiccup, laryngitis; *Rare* – hemoptysis, aspiration pneumonia, increased sputum, dry nasal passages, pulmonary edema, pulmonary embolism, hypoxia, respiratory failure, apnea. *Skin and Appendages: Frequent* – dry skin, pruritus, sweating, skin ulcer; *Infrequent* – acne, vesiculobullous rash, eczema, alopecia, psoriasis, seborrhea; *Rare* – maculopapular rash, exfoliative dermatitis, urticaria. *Special Senses: Frequent* – conjunctivitis, ear pain; *Infrequent* – dry eye, eye pain, tinnitus, otitis media, cataract, altered taste, blepharitis; *Rare* – increased lacrimation, frequent blinking, otitis externa, amblyopia, deafness, diplopia, eye hemorrhage, photophobia. *Urogenital System: Frequent* – urinary incontinence; *Infrequent* – cystitis, urinary frequency, leukorrhea, urinary retention, hematuria, dysuria, amenorrhea, abnormal ejaculation, vaginal hemorrhage, vaginal moniliasis, kidney failure, uterus hemorrhage, menorrhagia, albuminuria, kidney calculus, nocturia, polyuria, urinary urgency; *Rare* – breast pain, cervicitis, female lactation, anorgasmy, urinary burning, glycosuria, gynecomastia, urolithiasis, priapism.

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%.

DRUG ABUSE AND DEPENDENCE

Controlled Substance: ABILIFY (aripiprazole) 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).

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