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Bipolar Mood Disorder: Recent Developments Across the Spectrum

Guest Editor
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BRIEF SUMMARY. WELLBUTRIN XL™ (bupropion hydrochloride extended-release tablets) The following is a brief summary only; see full prescribing information for complete product information. **CONTRAINDICATIONS:** WELLBUTRIN XL is contraindicated in patients with a seizure disorder. WELLBUTRIN XL is contraindicated in patients treated with ZYBAN® (bupropion hydrochloride) Sustained-Release Tablets, WELLBUTRIN (bupropion hydrochloride) the immediate-release formulation, WELLBUTRIN SR (bupropion hydrochloride) the sustained-release formulation, or any other medications that contain bupropion because the incidence of seizure is dose dependent. WELLBUTRIN XL is contraindicated in patients with a current or prior diagnosis of bulimia or anorexia nervosa because of a higher *incidence of seizures noted in patients treated for bulimia with the immediate-release formulation of bupropion.* WELLBUTRIN XL is contraindicated in patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines). The concurrent administration of WELLBUTRIN XL Tablets and a monoamine oxidase (MAO) inhibitor is contraindicated. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with WELLBUTRIN XL Tablets. WELLBUTRIN XL is contraindicated in patients who have shown an allergic response to bupropion or the other ingredients that make up WELLBUTRIN XL Tablets. **WARNINGS: Patients should be made aware that WELLBUTRIN XL contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN XL should not be used in combination with ZYBAN, or any other medications that contain bupropion, such as WELLBUTRIN SR (bupropion hydrochloride), the sustained-release formulation or WELLBUTRIN (bupropion hydrochloride), the immediate-release formulation. Seizures: Bupropion is associated with a dose-related risk of seizures. The risk of seizures is also related to patient factors, clinical situations, and concomitant medications, which must be considered in selection of patients for therapy with WELLBUTRIN XL. WELLBUTRIN XL should be discontinued and not restarted in patients who experience a seizure while on treatment. As both WELLBUTRIN XL and the sustained-release formulation of bupropion (WELLBUTRIN SR) are bioequivalent to the immediate-release formulation of bupropion, the seizure incidence with WELLBUTRIN XL, while not formally evaluated in clinical trials, may be similar to that presented below for the immediate-release and sustained-release formulations of bupropion. Dose: At doses up to 300 mg/day of the sustained-release formulation of bupropion (WELLBUTRIN SR), the incidence of seizure is approximately 0.1% (1/1,000). Data for the immediate-release formulation of bupropion revealed a seizure incidence of approximately 0.4% (i.e., 13 of 3,200 patients followed prospectively) in patients treated at doses in a range of 300 to 450 mg/day. This seizure incidence (0.4%) may exceed that of some other marketed antidepressants. Additional data accumulated for the immediate-release formulation of bupropion suggested that the estimated seizure incidence increases almost tenfold between 450 and 600 mg/day. The 600 mg dose is twice the usual adult dose and one and one-third the maximum recommended daily dose (450 mg) of WELLBUTRIN XL Tablets. This disproportionate increase in seizure incidence with dose incrementation calls for caution in dosing. Patient factors: Predisposing factors that may increase the risk of seizure with bupropion use include history of head trauma or prior seizure, central nervous system (CNS) tumor, the presence of severe hepatic cirrhosis, and concomitant medications that lower seizure threshold. Clinical situations: Circumstances associated with an increased seizure risk include, among others, excessive use of alcohol or sedatives (including benzodiazepines); addiction to opiates, cocaine, or stimulants; use of over-the-counter stimulants and anorectics; and diabetes treated with oral hypoglycemics or insulin. Concomitant medications: Many medications (e.g., antipsychotics, antidepressants, theophylline, systemic steroids) are known to lower seizure threshold. *Recommendations for Reducing the Risk of Seizure:* Retrospective analysis of clinical experience gained during the development of bupropion suggests that the risk of seizure may be minimized if the total daily dose of WELLBUTRIN XL Tablets does *not* exceed 450 mg, the rate of incrementation of dose is gradual. WELLBUTRIN XL should be administered with extreme caution to patients with a history of seizure, cranial trauma, or other predisposition(s) toward seizure, or patients treated with other agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold. Hepatic Impairment: WELLBUTRIN XL should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients a reduced frequency and/or dose is required, as peak bupropion, as well as AUC, levels are substantially increased and accumulation is likely to occur in such patients to a greater extent than usual. The dose should not exceed 150 mg every other day in these patients (see PRECAUTIONS and CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION of full prescribing information). Potential for Hepatotoxicity:** In rats receiving large doses of bupropion chronically, there was an increase in incidence of hepatic hyperplastic nodules and hepatocellular hypertrophy. In dogs receiving large doses of bupropion chronically, various histologic changes were seen in the liver, and laboratory tests suggesting mild hepatocellular injury were noted. **PRECAUTIONS: General:** ***Agitation and Insomnia:*** Increased restlessness, agitation, anxiety, and insomnia, especially shortly after initiation of treatment, have been associated with treatment with bupropion. Patients in placebo-controlled trials receiving 300 mg/day (n = 376) and 400 mg/day (n = 114) of WELLBUTRIN SR, the sustained-release formulation of bupropion, experienced agitation (3% and 9%), anxiety (5% and 6%), and insomnia (11% and 16%), respectively, compared to 2%, 3%, and 6% of patients receiving placebo (n = 385). In clinical studies, these symptoms were sometimes of sufficient magnitude to require treatment with sedative/hypnotic drugs. Symptoms were sufficiently severe to require discontinuation of treatment in 1% and 2.6% of patients treated with 300 and 400 mg/day, respectively, of bupropion sustained-release tablets and 0.8% of patients treated with placebo. ***Psychosis, Confusion, and Other Neuropsychiatric Phenomena:*** Depressed patients treated with bupropion have been reported to show a variety of neuropsychiatric signs and symptoms, including delusions, hallucinations, psychosis, concentration disturbance, paranoia, and confusion. In some cases, these symptoms abated upon dose reduction and/or withdrawal of treatment. ***Activation of Psychosis and/or Mania:*** Antidepressants can precipitate manic episodes in bipolar disorder patients during the depressed phase of their illness and may activate latent psychosis in other susceptible patients. WELLBUTRIN XL is expected to pose similar risks. ***Altered Appetite and Weight:*** In placebo-controlled studies using WELLBUTRIN SR, the sustained-release formulation of bupropion, weight gain (>5 lbs) was reported by 3% and 2% of patients receiving bupropion at a dose of 300 mg/day (n = 339) and 400 mg/day (n = 112), respectively, compared to 4% of patients receiving placebo (n = 347). Weight loss (>5 lbs) in the same patient groups was reported by 14% and 19% of patients receiving bupropion at a dose of 300 mg/day and 400 mg/day of the sustained–release formulation, respectively, compared to 6% of patients receiving placebo. In studies conducted with the immediate-release formulation of bupropion, 35% of patients receiving tricyclic antidepressants gained weight, compared to 9% of patients treated with the immediate-release formulation of bupropion. If weight loss is a major presenting sign of a patient's depressive illness, the anorectic and/or weight-reducing potential of WELLBUTRIN XL Tablets should be considered. ***Suicide:*** The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Accordingly, prescriptions for WELLBUTRIN XL Tablets should be written for the smallest number of tablets consistent with good patient management. ***Allergic Reactions:*** Anaphylactoid/anaphylactic reactions characterized by symptoms such as pruritus, urticaria, angioedema, and dyspnea requiring medical treatment have been reported in clinical trials with bupropion. In addition, there have been rare spontaneous postmarketing reports of erythema multiforme, Stevens-Johnson syndrome, and anaphylactic shock associated with bupropion. A patient should stop taking WELLBUTRIN XL and consult a doctor if experiencing allergic or anaphylactoid/anaphylactic reactions (e.g., skin rash, pruritus, hives, chest pain, edema, and shortness of breath) during treatment. Arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity have been reported in association with bupropion. These symptoms may resemble serum sickness. ***Cardiovascular Effects:*** In clinical practice, hypertension, in some cases severe, requiring acute treatment, has been reported in patients receiving bupropion alone and in combination with nicotine replacement therapy. These events have been observed in both patients with and without evidence of pre-existing hypertension. Data from a comparative study of the sustained-release formulation of bupropion (ZYBAN® Sustained-Release Tablets), nicotine transdermal system (NTS), the combination of sustained-release bupropion plus NTS, and placebo as an aid to smoking cessation suggest a higher incidence of treatment-emergent hypertension in patients treated with the combination of sustained-release bupropion and NTS. In this study, 6.1% of patients treated with the combination of sustained-release bupropion and NTS had treatment-emergent hypertension compared to 2.5%, 1.6%, and 3.1% of patients treated with sustained-release bupropion, NTS, and placebo, respectively. The majority of these patients had evidence of pre-existing hypertension. Three patients (1.2%) treated with the combination of ZYBAN and NTS and 1 patient (0.4%) treated with NTS had study medication discontinued due to hypertension compared to none of the patients treated with ZYBAN or placebo. Monitoring of blood pressure is recommended in patients who receive the combination of bupropion and nicotine replacement. There is no clinical experience establishing the safety of WELLBUTRIN XL Tablets in patients with a recent history of myocardial infarction or unstable heart disease. Therefore, care should be exercised if it is used in these groups. Bupropion was well tolerated in depressed patients who had previously developed orthostatic hypotension while receiving tricyclic antidepressants, and was also generally well tolerated in a group of 36 depressed inpatients with stable congestive heart failure (CHF). However, bupropion was associated with a rise in supine blood pressure in the study of patients with CHF, resulting in discontinuation of treatment in 2 patients for exacerbation of baseline hypertension. ***Hepatic Impairment:*** WELLBUTRIN XL should be used with extreme caution in patients with severe hepatic cirrhosis. In these patients, a reduced frequency and/or dose is required. WELLBUTRIN XL should be used with caution in patients with hepatic impairment (including mild to moderate hepatic cirrhosis) and reduced frequency and/or dose should be considered in patients with mild to moderate hepatic cirrhosis. All patients with hepatic impairment should be closely monitored for possible adverse effects that could indicate high drug and metabolite levels (see WARNINGS and CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION of full prescribing information). ***Renal Impairment:*** No studies have been conducted in patients with renal impairment. Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and subsequently excreted by the kidneys. WELLBUTRIN XL should be used with caution in patients with renal impairment and a reduced frequency and/or dose should be considered as bupropion and its metabolites may accumulate in such patients to a greater extent than usual. The patient should be closely monitored for possible adverse effects that could indicate high drug or metabolite levels. **Information for Patients:** See the tear-off leaflet of full prescribing information for Patient Information. Patients should be made aware that WELLBUTRIN XL contains the same active ingredient found in ZYBAN, used as an aid to smoking cessation treatment, and that WELLBUTRIN XL should not be used in combination with ZYBAN or any other medications that contain bupropion hydrochloride (such as WELLBUTRIN SR, the sustained-release formulation, and WELLBUTRIN, the immediate-release formulation). Physicians are advised to discuss the following issues with patients: Patients should be told that WELLBUTRIN XL should be discontinued and not restarted if they experience a seizure while on treatment. Patients should be told that any CNS-active drug like WELLBUTRIN XL Tablets may impair their ability to perform tasks requiring judgment or motor and cognitive skills. Consequently, until they are reasonably certain that WELLBUTRIN XL Tablets do not adversely affect their performance, they should refrain from driving an automobile or operating complex, hazardous machinery. Patients should be told that the excessive use or abrupt discontinuation of alcohol or sedatives (including benzodiazepines) may alter the seizure threshold. Some patients have reported lower alcohol tolerance during treatment with WELLBUTRIN XL. Patients should be advised that the consumption of alcohol should be minimized or avoided. Patients should be advised to inform their physicians if they are taking or plan to take any prescription or over-the-counter drugs. Concern is warranted because WELLBUTRIN XL Tablets and other drugs may affect each other's metabolism. Patients should be advised to notify their physicians if they become pregnant or intend to become pregnant during therapy. Patients should be advised to swallow WELLBUTRIN XL Tablets whole so that the release rate is not altered. Do not chew, divide, or crush tablets. Patients should be advised that they may notice in their stool something that looks like a tablet. This is normal. The medication in WELLBUTRIN XL is contained in a non-absorbable shell that has been specially designed to slowly release drug in the body. When this process is completed, the empty shell is eliminated from the body. **Laboratory Tests:** There are no specific laboratory tests recommended. **Drug Interactions:** Few systemic data have been collected on the metabolism of bupropion following concomitant administration with other drugs or, alternatively, the effect of concomitant administration of bupropion on the metabolism of other drugs. Because bupropion is extensively metabolized, the coadministration of other drugs may affect its clinical activity. In vitro studies indicate that bupropion is primarily metabolized to hydroxybupropion by the CYP2B6 isoenzyme. Therefore, the potential exists for a drug interaction between WELLBUTRIN XL and drugs that are substrates or inhibitors of the CYP2B6 isoenzyme (e.g., orphenadrine, thiotepa, and cyclophosphamide). In addition, in vitro studies suggest that paroxetine, sertraline, norfluoxetine, and fluvoxamine as well as nelfinavir, ritonavir, and efavirenz inhibit the hydroxylation of bupropion. No clinical studies have been performed to evaluate this finding. The threohydrobupropion metabolite of bupropion does not appear to be produced by the cytochrome P450 isoenzymes. The effects of concomitant administration of cimetidine on the pharmacokinetics of bupropion and its active metabolites were studied in 24 healthy young male volunteers. Following oral administration of two 150-mg tablets of the sustained-release formulation of bupropion with and without 800 mg of cimetidine, the pharmacokinetics of bupropion and hydroxybupropion were unaffected. However, there were 16% and 32% increases in the AUC and C_{max}, respectively, of the combined moieties of threohydrobupropion and erythrohydrobupropion. While not systematically studied, certain drugs may induce the metabolism of bupropion (e.g., carbamazepine, phenobarbital, phenytoin). Animal data indicated that bupropion may be an inducer of drug-metabolizing enzymes in humans. In one study, following chronic administration of bupropion, 100 mg 3 times daily to 8 healthy male volunteers for 14 days, there was no evidence of induction of its own metabolism. Nevertheless, there may be the potential for clinically important alterations of blood levels of coadministered drugs. ***Drugs Metabolized By Cytochrome P450IID6 (CYP2D6):*** Many drugs, including most antidepressants (SSRIs, many tricyclics), beta-blockers, antiarrhythmics, and antipsychotics are metabolized by the CYP2D6 isoenzyme. Although bupropion is not metabolized by this isoenzyme, bupropion and hydroxybupropion are inhibitors of CYP2D6 isoenzyme in vitro. In a study of 15 male subjects (ages 19 to 35 years) who were extensive metabolizers of the CYP2D6 isoenzyme, daily doses of bupropion given as 150 mg twice daily followed by a single dose of 50 mg desipramine increased the C_{max}, AUC, and $t_{1/2}$ of desipramine by an average of approximately 2-, 5-, and 2-fold, respectively. The effect was present for at least 7 days after the last dose of bupropion. Concomitant use of bupropion with other drugs metabolized by CYP2D6 has not been formally studied. Therefore, co-administration of bupropion with drugs that are metabolized by CYP2D6 isoenzyme including certain antidepressants (e.g., nortriptyline, imipramine, desipramine, paroxetine, fluoxetine, sertraline), antipsychotics (e.g., haloperidol, risperidone, thioridazine), beta-blockers (e.g., metoprolol), and Type 1C antiarrhythmics (e.g., propafenone, flecainide), should be approached with caution and should be initiated at the lower end of the dose range of the concomitant medication. If bupropion is added to the treatment regimen of a patient already receiving a drug metabolized by CYP2D6, the need to decrease the dose of the original medication should be considered, particularly for those concomitant medications with a narrow therapeutic index. ***MAO Inhibitors:*** Studies in animals demonstrate that the acute toxicity of bupropion is enhanced by the MAO inhibitor phenelzine (see CONTRAINDICATIONS). ***Levodopa and Amantadine:*** Limited clinical data suggest a higher incidence of adverse experiences in patients receiving bupropion concurrently with either levodopa or amantadine. Administration of WELLBUTRIN XL Tablets to patients receiving either levodopa or amantadine concurrently should be undertaken with caution, using small initial doses and gradual dose increases. ***Drugs That Lower Seizure Threshold:*** Concurrent administration of WELLBUTRIN XL Tablets and agents (e.g., antipsychotics, other antidepressants, theophylline, systemic steroids, etc.) that lower seizure threshold should be undertaken only with extreme caution (see WARNINGS). Low initial dosing and gradual dose increases should be employed. ***Nicotine Transdermal System:*** (see PRECAUTIONS: Cardiovascular Effects). ***Alcohol:*** In postmarketing experience, there have been rare reports of adverse neuropsychiatric events or reduced alcohol tolerance in patients who were drinking alcohol during treatment with bupropion. The consumption of alcohol during treatment with WELLBUTRIN XL should be minimized or avoided (also see CONTRAINDICATIONS). ***Carcinogenesis, Mutagenesis, Impairment of Fertility:*** Lifetime carcinogenicity studies were performed in rats and mice at doses up to 300 and 150 mg/kg/day, respectively. These doses are approximately 7 and 2 times the maximum recommended human dose (MRHD), respectively, on a mg/m^2 basis. In the rat study there was an increase in nodular proliferative lesions of the liver at doses of 100 to 300 mg/kg/day (approximately 2 to 7 times the MRHD on a mg/m^2 basis); lower doses were not tested. The question of whether or not such lesions may be precursors of neoplasms of the liver is currently unresolved. Similar liver lesions were not seen in the mouse study, and no increase in malignant tumors of the liver and other organs was seen in either study. Bupropion produced a positive response (2 to 3 times control mutation rate) in 2 of 5 strains in the Ames bacterial mutagenicity test and an increase in chromosomal aberrations in 1 of 3 in vivo rat bone marrow cytogenetic studies. A fertility study in rats at doses up to 300 mg/kg/day revealed no evidence of impaired fertility. **Pregnancy:** ***Teratogenic Effects:*** Pregnancy Category B. Teratology studies have been performed with bupropion immediate-release formulation at dosages up to 450 mg/kg in rats, and at doses up to 150 mg/kg in rabbits (approximately 7 to 11 and 7 times the MRHD, respectively, on a mg/m^2 basis), and have revealed no evidence of harm to the fetus due to bupropion. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. To monitor fetal outcomes of pregnant women exposed to WELLBUTRIN XL, GlaxoSmithKline maintains a Bupropion Pregnancy Registry. Health care providers are encouraged to register patients by calling (800) 336-2176. **Labor and Delivery:** The effect of WELLBUTRIN XL Tablets on labor and delivery in humans is unknown. **Nursing Mothers:** Like many other drugs, bupropion and its metabolites are secreted in human milk. Because of the potential for serious adverse reactions in nursing infants from WELLBUTRIN XL Tablets, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother. **Pediatric Use:** The safety and effectiveness of WELLBUTRIN XL Tablets in pediatric patients below 18 years old have not been established. The immediate-release formulation of bupropion was studied in 104 pediatric patients (age range, 6 to 16) in clinical trials of the drug for other indications. Although generally well tolerated, the limited exposure is insufficient to assess the safety of bupropion in pediatric patients. **Geriatric Use:** Of the approximately 6,000 patients who participated in clinical trials with bupropion sustained-release tablets (depression and smoking cessation studies), 275 were ≥65 years old and 47 were ≥75 years old. In addition, several hundred patients 65 and over participated in clinical trials using the immediate-release formulation of bupropion (depression studies). No overall differences in safety or effectiveness were observed between these subjects and younger subjects. Reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older individuals cannot be ruled out. A single-dose pharmacokinetic study demonstrated that the disposition of bupropion and its metabolites in elderly subjects was similar to that of younger subjects; however, another pharmacokinetic study, single and multiple dose, has suggested that the elderly are at increased risk for accumulation of bupropion and its metabolites (see CLINICAL PHARMACOLOGY of full prescribing information). Bupropion is extensively metabolized in the liver to active metabolites, which are further metabolized and excreted by the kidneys. The risk of toxic reaction to this drug may be greater in patients with impaired renal function. Because elderly patients are more likely to have decreased renal function, care should be taken in dose selection, and it may be useful to monitor renal function (see PRECAUTIONS: Renal Impairment and DOSAGE AND ADMINISTRATION of full prescribing information). **ADVERSE REACTIONS** (See also WARNINGS and PRECAUTIONS.) WELLBUTRIN XL has been demonstrated to have similar bioavailability to the immediate-release formulation of bupropion (see CLINICAL PHARMACOLOGY of full prescribing information). The information included under the Incidence in Controlled Trials subsection of ADVERSE REACTIONS *is based primarily on data from controlled clinical trials with* WELLBUTRIN SR *Tablets, the sustained-release formulation of bupropion.* WELLBUTRIN XL has not been studied in placebo-controlled trials, although it has been studied in non-placebo-controlled clinical bioavailability studies. Information on additional adverse events associated with the sustained-release formulation of bupropion in smoking cessation trials, as well as the immediate-release formulation of bupropion, is included in a separate section (see Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion). **Incidence in Controlled Trials With Bupropion:** ***Adverse Events Associated With Discontinuation of Treatment Among Patients Treated With Bupropion:*** In placebo-controlled clinical trials, 9% and 11% of patients treated with 300 and 400 mg/day, respectively, of the sustained-release formulation of bupropion and 4% of patients treated with placebo discontinued treatment due to adverse events. The specific adverse events in these trials that led to discontinuation in at least 1% of patients treated with either 300 mg/day or 400 mg/day of WELLBUTRIN SR, the sustained-release formulation of bupropion, and at a rate at least twice the placebo rate are listed as follows: **Treatment Discontinuations Due to Adverse Events in Placebo-Controlled Trials.** The adverse event term is followed by incidence in parenthesis for WELLBUTRIN SR 300 mg/day (n = 376), WELLBUTRIN SR 400 mg/day (n = 114), and placebo (n = 385), respectively: Rash (2.4%, 0.9%, 0.0%), nausea (0.8%, 1.8%, 0.3%), agitation (0.3%, 1.8%, 0.3%), migraine (0.0%, 1.8%, 0.3%). In clinical trials with the immediate-release formulation of bupropion, 10% of patients and volunteers discontinued due to an adverse event. Events resulting in discontinuation, in addition to those listed above for the sustained-release formulation of bupropion, include vomiting, seizures, and sleep disturbances. ***Adverse Events Occurring at an Incidence of 1% or More Among Patients Treated With Bupropion:*** Listed below are treatment-emergent adverse events that occurred among patients treated with 300 and 400 mg/day of the sustained-release formulation of bupropion and with placebo in controlled trials. Events that occurred in either the 300- or 400-mg/day group at an incidence of 1% or more and were more frequent than in the placebo group are included. Reported adverse events were classified using a COSTART-based Dictionary. Accurate estimates of the incidence of adverse events associated with the use of any drug are difficult to obtain. Estimates are influenced by drug dose, detection technique, setting, physician judgments, etc. The figures cited cannot be used to predict precisely the incidence of untoward events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. These incidence figures also cannot be compared with those obtained from other clinical studies involving related drug products as each group of drug trials is conducted under a different set of conditions. Finally, it is important to emphasize that the listing does not reflect the relative severity and/or clinical *importance of the events. A better perspective on the serious adverse events associated with the use of bupropion is* provided in the WARNINGS and PRECAUTIONS sections. **Treatment-Emergent Adverse Events in Placebo-Controlled Trials.** Adverse events are listed by body system followed by incidence in parenthesis for WELLBUTRIN SR 300 mg/day (n = 376), WELLBUTRIN SR 400 mg/day (n = 114), and placebo (n = 385), respectively. A hyphen denotes adverse

events occurring in greater than 0 but less than 0.5% of patients. **Body (General):** Headache (26%, 25%, 23%), infection (8%, 9%, 6%), abdominal pain (3%, 9%, 2%), asthenia (2%, 4%, 2%), chest pain (3%, 4%, 1%), pain (2%, 3%, 2%), fever (1%, 2%, –); **Cardiovascular:** Palpitation (2%, 6%, 2%), flushing (1%, 4%, –), migraine (1%, 4%, 1%), hot flashes (1%, 3%, 1%); **Digestive:** Dry mouth (17%, 24%, 7%), nausea (13%, 18%, 8%), constipation (10%, 5%, 7%), diarrhea (5%, 7%, 6%), anorexia (5%, 3%, 2%), vomiting (4%, 2%, 2%), dysphagia (0%, 2%, 0%); **Musculoskeletal:** Myalgia (2%, 6%, 3%), arthralgia (1%, 4%, 1%), arthritis, (0%, 2%, 0%), twitch (1%, 2%, –); **Nervous System:** Insomnia (11%, 16%, 6%), dizziness (7%, 11%, 5%), agitation (3%, 9%, 2%), anxiety (5%, 6%, 3%), tremor (6%, 3%, 1%), nervousness (5%, 3%, 3%), somnolence (2%, 3%, 2%), irritability (3%, 2%, 2%), memory decreased (–, 3%, 1%), paresthesia (1%, 2%, 1%), central nervous system stimulation (2%, 1%, 1%); **Respiratory:** Pharyngitis (3%, 11%, 2%), sinusitis (3%, 1%, 2%), increased cough (1%, 2%, 1%); **Skin:** Sweating (6%, 5%, 2%), rash (5%, 4%, 1%), pruritus (2%, 4%, 2%), urticaria (2%, 1%, 0%); **Special Senses:** Tinnitus (6%, 6%, 2%), taste perversion (2%, 4%, –), amblyopia (3%, 2%, 2%); **Urogenital:** Urinary frequency (2%, 5%, 2%), urinary urgency (–, 2%, 0%), vaginal hemorrhage [incidence based on number of female patients] (0%, 2%, –), urinary tract infection (1%, 0%, –). Additional events to those listed above that occurred at an incidence of at least 1% in controlled clinical trials of the immediate-release formulation of bupropion (300 to 600 mg/day) and that were numerically more frequent than placebo were: cardiac arrhythmias (5% vs 4%), hypertension (4% vs 2%), hypotension (3% vs 2%), tachycardia (11% vs 9%), appetite increase (4% vs 2%), dyspepsia (3% vs 2%), menstrual complaints (5% vs 1%), akathisia (2% vs 1%), impaired sleep quality (4% vs 2%), sensory disturbance (4% vs 3%), confusion (8% vs 5%), decreased libido (3% vs 2%), hostility (6% vs 4%), auditory disturbance (5% vs 3%), and gustatory disturbance (3% vs 1%). ***Incidence of Commonly Observed Adverse Events in Controlled Clinical Trials:*** Adverse events listed immediately above occurring in at least 5% of patients treated with the sustained-release formulation of bupropion and at a rate at least twice the placebo rate are listed below for the 300- and 400-mg/day dose groups. ***300 mg/day of the Sustained-Release Formulation:*** *Anorexia, dry mouth, rash,* sweating, tinnitus, and tremor. ***400 mg/day of the Sustained-Release Formulation:*** Abdominal pain, agitation, anxiety, dizziness, dry mouth, insomnia, myalgia, nausea, palpitation, pharyngitis, sweating, tinnitus, and urinary frequency. ***Other Events Observed During the Clinical Development and Postmarketing Experience of Bupropion:*** In addition to the adverse events noted above, the following events have been reported in clinical trials and postmarketing experience with the sustained-release formulation of bupropion in depressed patients and in nondepressed smokers, as well as in clinical trials and postmarketing clinical experience with the immediate-release formulation of bupropion. Adverse events for which frequencies are provided below occurred in clinical trials with the sustained-release formulation of bupropion. The frequencies represent the proportion of patients who experienced a treatment-emergent adverse event on at least one occasion in placebo-controlled studies for depression (n = 987) or smoking cessation (n = 1,013), or patients who experienced an adverse event requiring discontinuation of treatment in an open-label surveillance study with the sustained-release formulation of bupropion (n = 3,100). All treatment-emergent adverse events are included except those listed above, those events listed in other safety-related sections, those adverse events subsumed under COSTART terms that are either overly general or excessively specific so as to be uninformative, those events not reasonably associated with the use of the drug, and those events that were not serious and occurred in fewer than 2 patients. Events of major clinical importance are described in the WARNINGS and PRECAUTIONS sections of the labeling. Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions of frequency: Frequent adverse events are defined as those occurring in at least 1/100 patients. Infrequent adverse events are those occurring in 1/100 to 1/1,000 patients, while rare events are those occurring in less than 1/1,000 patients. Adverse events for which frequencies are not provided occurred in clinical trials or postmarketing experience with bupropion. Only those adverse events not previously listed for sustained-release bupropion are included. The extent to which these events may be associated with WELLBUTRIN XL is unknown. ***Body (General):*** Infrequent were chills, facial edema, musculoskeletal chest pain, and photosensitivity. Rare was malaise. Also observed were arthralgia, myalgia, and fever with rash and other symptoms suggestive of delayed hypersensitivity. These symptoms may resemble serum sickness (see PRECAUTIONS). ***Cardiovascular:*** Infrequent were postural hypotension, stroke, tachycardia, and vasodilation. Rare was syncope. Also observed were complete atrioventricular block, extrasystoles, hypotension, hypertension (in some cases severe, see PRECAUTIONS), myocardial infarction, phlebitis, and pulmonary embolism. ***Digestive:*** Infrequent were abnormal liver function, bruxism, gastric reflux, gingivitis, glossitis, increased salivation, jaundice, mouth ulcers, stomatitis, and thirst. Rare was edema of tongue. Also observed were colitis, esophagitis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, intestinal perforation, liver damage, pancreatitis, and stomach ulcer. ***Endocrine:*** Also observed were hyperglycemia, hypoglycemia, and syndrome of inappropriate antidiuretic hormone. ***Hemic and Lymphatic:*** Infrequent was ecchymosis. Also observed were anemia, leukocytosis, leukopenia, lymphadenopathy, pancytopenia, and thrombocytopenia. Altered PT and/or INR, infrequently associated with hemorrhagic or thrombotic complications, were observed when bupropion was coadministered with warfarin. ***Metabolic and Nutritional:*** Infrequent were edema and peripheral edema. Also observed was glycosuria. ***Musculoskeletal:*** Infrequent were leg cramps. Also observed were muscle rigidity/fever/rhabdomyolysis and muscle weakness. ***Nervous System:*** Infrequent were *abnormal coordination, decreased libido, depersonalization, dysphoria, emotional lability, hostility, hyperkinesia,* hypertonia, hypesthesia, suicidal ideation, and vertigo. Rare were amnesia, ataxia, derealization, and hypomania. Also observed were abnormal electroencephalogram (EEG), akinesia, aphasia, coma, delirium, dysarthria, dyskinesia, dystonia, euphoria, extrapyramidal syndrome, hallucinations, hypokinesia, increased libido, manic reaction, neuralgia, neuropathy, paranoid reaction, and unmasking tardive dyskinesia. ***Respiratory:*** Rare was bronchospasm. Also observed was pneumonia. ***Skin:*** Rare was maculopapular rash. Also observed were alopecia, angioedema, exfoliative dermatitis, and hirsutism. ***Special Senses:*** Infrequent were accommodation abnormality and dry eye. Also observed were deafness, diplopia, and mydriasis. ***Urogenital:*** Infrequent were impotence, polyuria, and prostate disorder. Also observed were abnormal ejaculation, cystitis, dyspareunia, dysuria, gynecomastia, menopause, painful erection, salpingitis, urinary incontinence, urinary retention, and vaginitis. **DRUG ABUSE AND DEPENDENCE: Controlled Substance Class:** Bupropion is not a controlled substance. **Humans:** Controlled clinical studies of bupropion (immediate-release formulation) conducted in normal volunteers, in subjects with a history of multiple drug abuse, and in depressed patients showed some increase in motor activity and agitation/excitement. In a population of individuals experienced with drugs of abuse, a single dose of 400 mg of bupropion produced mild amphetamine-like activity as compared to placebo on the Morphine-Benzedrine Subscale of the Addiction Research Center Inventories (ARCI), and a score intermediate between placebo and amphetamine on the Liking Scale of the ARCI. These scales measure general feelings of euphoria and drug desirability. Findings in clinical trials, however, are not known to reliably predict the abuse potential of drugs. Nonetheless, evidence from single-dose studies does suggest that the recommended daily dosage of bupropion when administered in divided doses is not likely to be especially reinforcing to amphetamine or stimulant abusers. However, higher doses that could not be tested because of the risk of seizure might be modestly attractive to those who abuse stimulant drugs. **Animals:** Studies in rodents and primates have shown that bupropion exhibits some pharmacologic actions common to psychostimulants. In rodents, it has been shown to increase locomotor activity, elicit a mild stereotyped behavioral response, and increase rates of responding in several schedule-controlled behavior paradigms. In primate models to assess the positive reinforcing effects of psychoactive drugs, bupropion was self-administered intravenously. In rats, bupropion produced amphetamine-like and cocaine-like discriminative stimulus effects in drug discrimination paradigms used to characterize the subjective effects of psychoactive drugs. **OVERDOSAGE: Human Overdose Experience:** There has been very limited experience with overdosage of the sustained-release formulation of bupropion (WELLBUTRIN SR Tablets); 3 cases were reported during clinical trials. One patient ingested 3,000 mg of the sustained-release formulation of bupropion and vomited quickly after the overdose; the patient experienced blurred vision and lightheadedness. A second patient ingested a "handful" of WELLBUTRIN SR Tablets (the sustained-release formulation) and experienced confusion, lethargy, nausea, jitteriness, and seizure. A third patient ingested 3,600 mg of the sustained-release formulation of bupropion and a bottle of wine; the patient experienced nausea, visual hallucinations, and "grogginess." None of the patients experienced further sequelae. There has been extensive experience with overdosage of the immediate-release formulation of bupropion. Thirteen overdoses occurred during clinical trials. Twelve patients ingested 850 to 4,200 mg and recovered without significant sequelae. Another patient who ingested 9,000 mg of the immediate-release formulation of bupropion and 300 mg of tranylcypromine experienced a grand mal seizure and recovered without further sequelae. *Since introduction, overdoses of up to 17,500 mg of the immediate-release formulation of bupropion* have been reported. Seizure was reported in approximately one third of all cases. Other serious reactions reported with overdoses of the immediate-release formulation of bupropion alone included hallucinations, loss of consciousness, and sinus tachycardia. Fever, muscle rigidity, rhabdomyolysis, hypotension, stupor, coma, and respiratory failure have been reported when the immediate-release formulation of bupropion was part of multiple drug overdoses. Although most patients recovered without sequelae, deaths associated with overdoses of the immediate-release formulation of bupropion alone have been reported rarely in patients ingesting massive doses of the drug. Multiple uncontrolled seizures, bradycardia, cardiac failure, and cardiac arrest prior to death were reported in these patients. **Overdosage Management:** Ensure an adequate airway, oxygenation, and ventilation. Monitor cardiac rhythm and vital signs. EEG monitoring is also recommended for the first 48 hours post-ingestion. General supportive and symptomatic measures are also recommended. Induction of emesis is not recommended. Gastric lavage with a large-bore orogastric tube with appropriate airway protection, if needed, may be indicated if performed soon after ingestion or in symptomatic patients. Activated charcoal should be administered. There is no experience with the use of forced diuresis, dialysis, hemoperfusion, or exchange transfusion in the management of bupropion overdoses. No specific antidotes for bupropion are known. Due to the dose-related risk of seizures with WELLBUTRIN XL, hospitalization following suspected overdose should be considered. Based on studies in animals, it is recommended that seizures be treated with intravenous benzodiazepine administration and other supportive measures, as appropriate. In managing overdosage, consider the possibility of multiple drug involvement. The physician should consider contacting a poison control center for additional information on the treatment of any overdose. Telephone numbers for certified poison control centers are listed in the *Physicians' Desk Reference* (PDR).

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INTRODUCING ONCE-DAILY

Because

† Studies were conducted with the sustained-release formulation of bupropion HCl. WELLBUTRIN XL has been proven bioequivalent to both WELLBUTRIN® (bupropion HCl) Tablets and WELLBUTRIN SR® (bupropion HCl) Sustained-Release Tablets.[4]

Important safety considerations

WELLBUTRIN XL is contraindicated in patients who have or had a seizure disorder, patients being treated with ZYBAN® (bupropion HCl) Sustained-Release Tablets, WELLBUTRIN SR® (bupropion HCl) Sustained-Release Tablets, or any other medications that contain bupropion, patients who have or had bulimia or anorexia nervosa, patients undergoing abrupt discontinuation of alcohol or sedatives (including benzodiazepines), and patients taking MAO inhibitors. At least 14 days should elapse between discontinuation of an MAO inhibitor and initiation of treatment with WELLBUTRIN XL.

When treating depression, physicians should be aware that bupropion is associated with a risk of seizure, which is dose related. While WELLBUTRIN XL has not been formally evaluated in clinical trials, its incidence of seizure may be similar to that of the immediate-release and the sustained-release formulations of bupropion, since it has demonstrated bioequivalence to both. At doses of up to 300 mg/day of the sustained-release formulation (WELLBUTRIN SR), the incidence of seizure is approximately 0.1%. At doses of 300 mg/day to 450 mg/day of the immediate-release formulation (WELLBUTRIN), the incidence of seizure is approximately 0.4%. To reduce the risk of seizures, please see WARNINGS in the Prescribing Information for patient selection considerations, including concomitant medications and dosing recommendations.

When treating patients with severe hepatic cirrhosis, extreme caution should be exercised, and a reduced dosage and/or frequency is required to avoid accumulation.

The weight loss potential of WELLBUTRIN XL should be considered if weight loss is a major presenting sign of the depressive illness.

There have been reports of hypertension, in some cases severe, in patients receiving bupropion alone and in combination with nicotine replacement therapy.

Adverse events reported in at least 10% of patients treated with WELLBUTRIN SR 300 mg/day or 400 mg/day and at a rate at least twice that of placebo were dry mouth, nausea, insomnia, dizziness, weight loss, and pharyngitis. Similar adverse events would be expected with WELLBUTRIN XL.

References: 1. Coleman CC, Cunningham LA, Foster VJ, et al. Sexual dysfunction associated with the treatment of depression: a placebo-controlled comparison of bupropion sustained release and sertraline treatment. *Ann Clin Psychiatry.* 1999;11:205-215. **2.** Croft H, Settle E Jr, Houser T, Batey SR, Donahue RMJ, Ascher JA. A placebo-controlled comparison of the antidepressant efficacy and effects on sexual functioning of sustained-release bupropion and sertraline. *Clin Ther.* 1999;21:643-658. **3.** Coleman CC, King BR, Bolden-Watson C, et al. A placebo-controlled comparison of the effects on sexual functioning of bupropion sustained-release and fluoxetine. *Clin Ther.* 2001;23:1040-1058. **4.** Data on file, GlaxoSmithKline. **5.** Croft H, Houser TL, Jamerson BD, et al. Effect on body weight of bupropion sustained-release in patients with major depression treated for 52 weeks. *Clin Ther.* 2002;24:662-672.

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CNS Spectrums' *editorial mission is to address relevant neuropsychiatric topics, including the prevalence of comorbid diseases among patients, and original research and reports that emphasize the profound diagnostic and physiologic connections made within the neurologic and psychiatric fields. The journal's goal is to serve as a resource to psychiatrists and neurologists seeking to understand and treat disturbances of cognition, emotion, and behavior as a direct consequence of central nervous system disease, illness, or trauma.*

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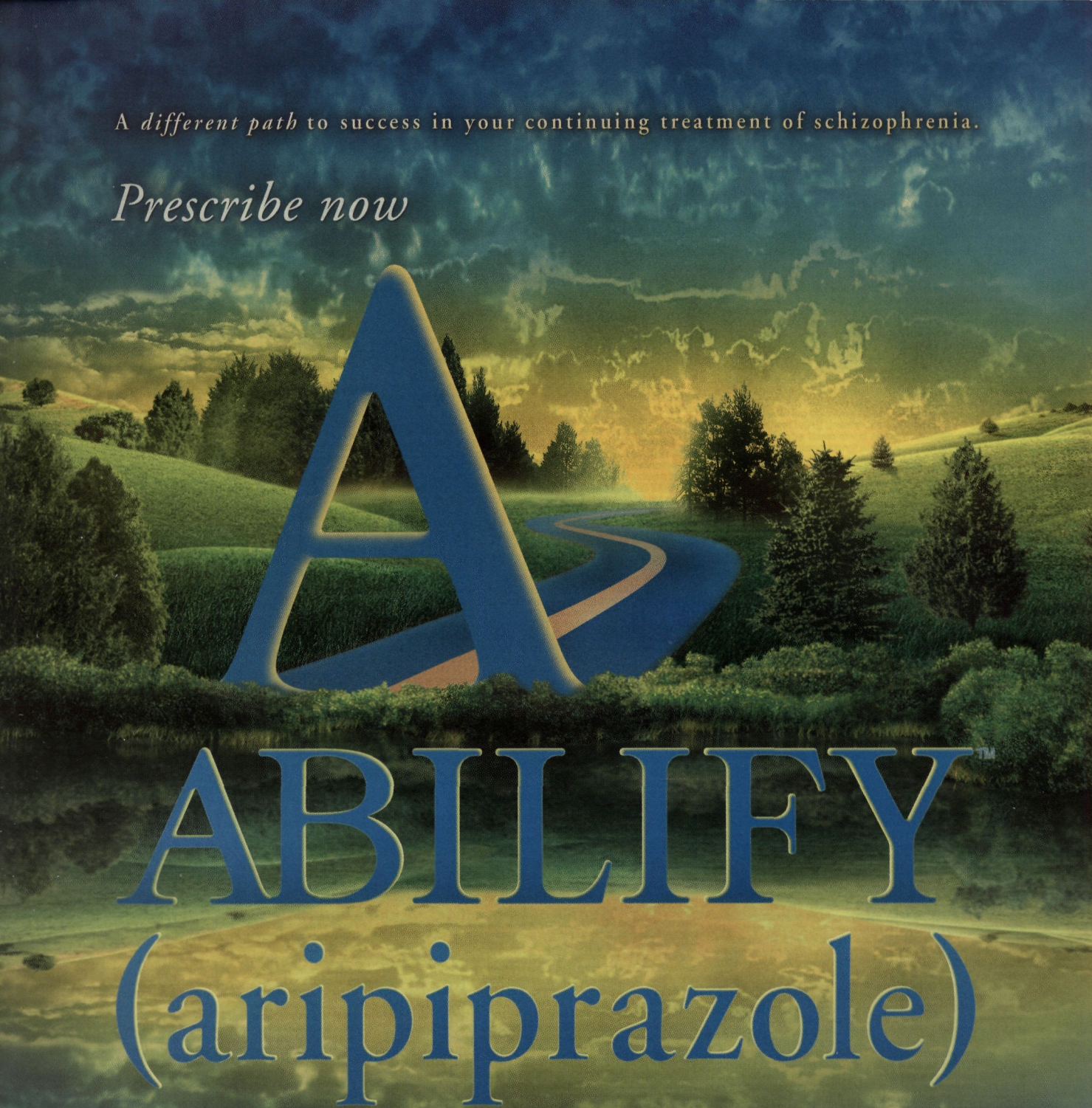

Abilify is indicated for the treatment of schizophrenia.

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. Seizures occurred in 0.1% of Abilify-treated patients in short-term, placebo-controlled trials. 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.

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

Please see Brief Summary of Prescribing Information on adjacent page. For more information, visit our web site at www.abilify.com.

Marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA and Bristol-Myers Squibb Co., Princeton, NJ 08543.
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ABILIFY™ Rx only
(aripiprazole) Tablets

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 (aripiprazole) 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.

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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