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6

Toward a Fresh Understanding of ADHD

The National Institutes of Health Attention-Deficit/ Hyperactivity Disorder Consensus Statement: Implications for Practitioners and Scientists

P. S. Jensen

Neurobiological Models of Attention-Deficit/Hyperactivity Disorder: A Brief Review of the Empirical Evidence

K. P. Schulz, J. Himelstein, J. M. Halperin, and J. H. Newcorn

The Predominantly Inattentive Subtype of Attention-Deficit/Hyperactivity Disorder

M. V. Solanto

Predictors of Physical Aggression in Children With Attention-Deficit/Hyperactivity Disorder

D. J. Marks, K. E. McKay, J. Himelstein, K. J. Walter, J. H. Newcorn, and J. M. Halperin

Neurocognitive Functioning in Adults With Attention-Deficit/Hyperactivity Disorder

J. Himelstein, J. H. Newcorn, and J. M. Halperin

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In mild to moderate Alzheimer's disease

You see it as maintaining cognitive

* *Individual responses to ARICEPT® may include improvement, stabilization, or decline.*

† The most common adverse events in pivotal clinical trials with ARICEPT® were nausea, diarrhea, insomnia, vomiting, muscle cramps, fatigue, and anorexia. Pivotal clinical trials of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. Nevertheless, cholinesterase inhibitors may be expected to increase gastric acid secretion. Therefore, patients (especially those at increased risk for developing ulcers—eg, having a history of ulcer disease, receiving concurrent nonsteroidal anti-inflammatory drugs) should be monitored closely for gastrointestinal bleeding. In pivotal clinical trials, syncopal episodes have been reported in association with ARICEPT® (2% vs 1% for placebo).

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function.

She sees it as a bedtime story.

ARICEPT®. Helping to make a difference for people living with Alzheimer's

- Slows the worsening of symptoms*
- Proven to maintain cognition in placebo-controlled studies
- Well tolerated†
- Proven safety profile
- Once-daily dosing
- 3 years of real-world use

ONCE-A-DAY

ARICEPT®

(donepezil HCl)

5-MG AND 10-MG TABLETS

THERAPY TO REMEMBER™

Please see brief summary of prescribing information on adjacent page.

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ARICEPT® (Donepezil Hydrochloride Tablets)

Brief Summary – see package insert for full prescribing information. **INDICATIONS AND USAGE** ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer's type. **CONTRAINDICATIONS** ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to piperidine derivatives. **WARNINGS** ***Anesthesia:*** ARICEPT®, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. ***Cardiovascular Conditions:*** Because of their pharmacological action, cholinesterase inhibitors may have vagotonic effects on heart rate (e.g., bradycardia). The potential for this action may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction conditions. Syncopal episodes have been reported in association with the use of ARICEPT®. ***Gastrointestinal Conditions:*** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those at increased risk for developing ulcers, e.g., those with a history of ulcer disease or those receiving concurrent nonsteroidal anti-inflammatory drugs (NSAIDS). Clinical studies of ARICEPT® have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea, nausea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose. In most cases, these effects have been mild and transient, sometimes lasting one to three weeks, and have resolved during continued use of ARICEPT®. ***Genitourinary:*** Although not observed in clinical trials of ARICEPT®, cholinomimetics may cause bladder outflow obstruction. ***Neurological Conditions:*** Seizures: Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity also may be a manifestation of Alzheimer's Disease. ***Pulmonary Conditions:*** Because of their cholinomimetic actions, cholinesterase inhibitors should be prescribed with care to patients with a history of asthma or obstructive pulmonary disease. **PRECAUTIONS Drug-Drug Interactions *Drugs Highly Bound to Plasma Proteins:*** Drug displacement studies have been performed *in vitro* between this highly bound drug (96%) and other drugs such as furosemide, digoxin, and warfarin. ARICEPT® at concentrations of 0.3-10 µg/mL did not affect the binding of furosemide (5 µg/mL), digoxin (2 ng/mL), and warfarin (3 µg/mL) to human albumin. Similarly, the binding of ARICEPT® to human albumin was not affected by furosemide, digoxin, and warfarin. ***Effect of ARICEPT® on the Metabolism of Other Drugs:*** No *in vivo* clinical trials have investigated the effect of ARICEPT® on the clearance of drugs metabolized by CYP 3A4 (e.g. cisapride, terfenadine) or by CYP 2D6 (e.g. imipramine). However, *in vitro* studies show a low rate of binding to these enzymes (mean K_I about 50-130 µM), that, given the therapeutic plasma concentrations of donepezil (164 nM), indicates little likelihood of interference. Whether ARICEPT® has any potential for enzyme induction is not known. ***Effect of Other Drugs on the Metabolism of ARICEPT®:*** Ketoconazole and quinidine, inhibitors of CYP450, 3A4 and 2D6, respectively, inhibit donepezil metabolism *in vitro*. Whether there is a clinical effect of these inhibitors *is not known. Inducers of CYP 2D6 and CYP 3A4 (e.g., phenytoin, carbamazepine, dexamethasone, rifampin, and phenobarbital)* could increase the rate of elimination of ARICEPT®. ***Use with Anticholinergics:*** Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. ***Use with Cholinomimetics and Other Cholinesterase Inhibitors:*** A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. **Carcinogenesis, Mutagenesis, Impairment of Fertility** Carcinogenicity studies of donepezil have not been completed. Donepezil was not mutagenic in the Ames reverse mutation assay in bacteria. In the chromosome aberration test in cultures of Chinese hamster lung (CHL) cells, some clastogenic effects were observed. Donepezil was not clastogenic in the *in vivo* mouse micronucleus test. Donepezil had no effect on fertility in rats at doses up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis). **Pregnancy *Pregnancy Category C:*** Teratology studies conducted in pregnant rats at doses up to 16 mg/kg/day (approximately 13 times the maximum recommended human dose on a mg/m² basis) and in pregnant rabbits at doses up to 10 mg/kg/day (approximately 16 times the maximum recommended human dose on a mg/m² basis) did not disclose any evidence for a teratogenic potential of donepezil. However, in a study in which pregnant rats were given up to 10 mg/kg/day (approximately 8 times the maximum recommended human dose on a mg/m² basis) from day 17 of gestation through day 20 postpartum, there was a slight increase in still births and a slight decrease in pup survival through day 4 postpartum at this dose; the next lower dose tested was 3 mg/kg/day. There are no adequate or well-controlled studies in pregnant women. ARICEPT® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nursing Mothers** It is not known whether donepezil is excreted in human breast milk. ARICEPT® has no indication for use in nursing mothers. **Pediatric Use** There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children. **ADVERSE REACTIONS Adverse Events Leading to Discontinuation** The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the ARICEPT® 5 mg/day treatment groups were comparable to those of placebo-treatment groups at approximately 5%. The rate of discontinuation of patients who received 7-day escalations from 5 mg/day to 10 mg/day, was higher at 13%. The most common adverse events leading to discontinuation, defined as those occurring in at least 2% of patients and at twice the incidence seen in placebo patients, are shown in Table 1.

Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group

Dose Group	Placebo	5 mg/day ARICEPT®	10 mg/day ARICEPT®
Patients Randomized	355	350	315
Event/%Discontinuing			
Nausea	1%	1%	3%
Diarrhea	0%	<1%	3%
Vomiting	<1%	<1%	2%

Most Frequent Adverse Clinical Events Seen in Association with the Use of ARICEPT® The most common adverse events, defined as those occurring at a frequency of at least 5% in patients receiving 10 mg/day and twice the placebo rate, are largely predicted by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, insomnia, vomiting, muscle cramp, fatigue and anorexia. These adverse events were often of mild intensity and transient, resolving during continued ARICEPT® treatment without the need for dose modification. There is evidence to suggest that the frequency of these common adverse events may be affected by the rate of titration. An open-label study was conducted with 269 patients who received placebo in the 15- and 30-week studies. These patients were titrated to a dose of 10 mg/day over a 6-week period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in the controlled clinical trials and were comparable to those seen in patients on 5 mg/day. See Table 2 for a comparison of the most common adverse events following one and six week titration regimens.

Table 2. Comparison of Rates of Adverse Events in Patients Titrated to 10 mg/day Over 1 and 6 Weeks

Adverse Event	Placebo (n=315)	No titration 5 mg/day (n=311)	One-week titration 10 mg/day (n=315)	Six-week titration 10 mg/day (n=269)
Nausea	6%	5%	19%	6%
Diarrhea	5%	8%	15%	9%
Insomnia	6%	6%	14%	6%
Fatigue	3%	4%	8%	3%
Vomiting	3%	3%	8%	5%
Muscle cramps	2%	6%	8%	3%
Anorexia	2%	3%	7%	3%

Adverse Events Reported in Controlled Trials The events cited reflect experience gained under closely monitored conditions of clinical trials in a highly selected patient population. In actual clinical practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behavior, and the kinds of patients treated may differ. Table 3 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled trials who received ARICEPT® and for which the rate of occurrence was greater for ARICEPT® assigned than placebo assigned patients. In general, adverse events occurred more frequently in female patients and with advancing age.

Table 3. Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving ARICEPT® (donepezil HCl) and at a Higher Frequency than Placebo-treated Patients

Body System/Adverse Event	Placebo (n=355)	ARICEPT® (n=747)
Percent of Patients with any Adverse Event	72	74
Body as a Whole		
Headache	9	10
Pain, various locations	8	9
Accident	6	7
Fatigue	3	5
Cardiovascular System		
Syncope	1	2
Digestive System		
Nausea	6	11
Diarrhea	5	10
Vomiting	3	5
Anorexia	2	4
Hemic and Lymphatic System		
Ecchymosis	3	4
Metabolic and Nutritional Systems		
Weight Decrease	1	3
Musculoskeletal System		
Muscle Cramps	2	6
Arthritis	1	2
Nervous System		
Insomnia	6	9
Dizziness	6	8
Depression	<1	3
Abnormal Dreams	0	3
Somnolence	<1	2
Urogenital System		
Frequent Urination	1	2

Other Adverse Events Observed During Clinical Trials ARICEPT® has been administered to over 1700 individuals during clinical trials worldwide. Approximately 1200 of these patients have been treated for at least 3 months and more than 1000 patients have been treated for at least 6 months. Controlled and uncontrolled trials in the United States included approximately 900 patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 475 patients treated for 6 months and 116 patients treated for over 1 year. The range of patient exposure is from 1 to 1214 days. Treatment emergent signs and symptoms that occurred during 3 controlled clinical trials and two open-label trials in the United States were recorded as adverse events by the clinical investigators using terminology of their own choosing. To provide an overall estimate of the proportion of individuals having similar types of events, the events were grouped into a smaller number of standardized categories using a modified COSTART dictionary and event frequencies were calculated across all studies. These categories are used in the listing below. The frequencies represent the proportion of 900 patients from these trials who experienced that event while receiving ARICEPT®. All adverse events occurring at least twice are included, except for those already listed in Tables 2 or 3, COSTART terms too general to be informative, or events less likely to be drug caused. Events are classified by body system and listed using the following definitions: *frequent adverse events* — those occurring in at least 1/100 patients; *Infrequent adverse events* — those occurring in 1/100 to 1/1000 patients. These adverse events are not necessarily related to ARICEPT® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. No important additional adverse events were seen in studies conducted outside the United States. **Body as a Whole:** *Frequent:* influenza, chest pain, toothache; *Infrequent:* fever, edema face, periorbital edema, hernia hiatai, abscess, cellulitis, chills, generalized coldness, head fullness, listlessness. **Cardiovascular System:** *Frequent:* hypertension, vasodilation, atrial fibrillation, hot flashes, hypotension; *Infrequent: angina pectoris, postural hypotension, myocardial infarction,* AV block (*first degree*), *congestive heart failure, arteritis,* bradycardia, peripheral vascular disease, supraventricular tachycardia, deep vein thrombosis. **Digestive System:** *Frequent:* fecal incontinence, gastrointestinal bleeding, bloating, epigastric pain; *Infrequent:* eructation, gingivitis, increased appetite, flatulence, periodontal abscess, cholelithiasis, diverticulitis, drooling, dry mouth, fever sore, gastritis, irritable colon, tongue edema, epigastric distress, gastroenteritis, increased transaminases, hemorrhoids, ileus, increased thirst, jaundice, melena, polydipsia, duodenal ulcer, stomach ulcer. **Endocrine System:** *Infrequent:* diabetes mellitus, goiter. **Hemic and Lymphatic System:** *Infrequent:* anemia, thrombocythemia, thrombocytopenia, eosinophilia, erythrocytopenia. **Metabolic and Nutritional Disorders:** *Frequent:* dehydration; *Infrequent:* gout, hypokalemia, increased creatine kinase, hyperglycemia, weight increase, increased lactate dehydrogenase. **Musculoskeletal System:** *Frequent:* bone fracture; *Infrequent:* muscle weakness, muscle fasciculation. **Nervous System:** *Frequent:* delusions, tremor, irritability, paresthesia, aggression, vertigo, ataxia, increased libido, restlessness, abnormal crying, nervousness, aphasia; *Infrequent:* cerebrovascular accident, intracranial hemorrhage, transient ischemic attack, emotional lability, neuralgia, coldness (localized), muscle spasm, dysphoria, gait abnormality, hypertonia, hypokinesia, neurodermatitis, numbness (localized), paranoia, dysarthria, dysphasia, hostility, decreased libido, melancholia, emotional withdrawal, nystagmus, pacing. **Respiratory System:** *Frequent:* dyspnea, sore throat, bronchitis; *Infrequent:* epistaxis, post nasal drip, pneumonia, hyperventilation, pulmonary congestion, wheezing, hypoxia, pharyngitis, pleurisy, pulmonary collapse, sleep apnea, snoring. **Skin and Appendages:** *Frequent:* pruritus, diaphoresis, urticaria; *Infrequent:* dermatitis, erythema, skin discoloration, hyperkeratosis, alopecia, fungal dermatitis, herpes zoster, hirsutism, skin striae, night sweats, skin ulcer. **Special Senses:** *Frequent:* cataract, eye irritation, vision blurred; *Infrequent:* dry eyes, glaucoma, earache, tinnitus, blepharitis, decreased hearing, retinal hemorrhage, otitis externa, otitis media, bad taste, conjunctival hemorrhage, ear buzzing, motion sickness, spots before eyes. **Urogenital System:** *Frequent:* urinary incontinence, nocturia; *Infrequent:* dysuria, hematuria, urinary urgency, metrorrhagia, cystitis, enuresis, prostate hypertrophy, pyelonephritis, inability to empty bladder, breast fibroadenosis, fibrocystic breast, mastitis, pyuria, renal failure, vaginitis. **Postintroduction Reports** Voluntary reports of adverse events temporally associated with ARICEPT® that have been received since market introduction that are not listed above, and that there is inadequate data to determine the causal relationship with the drug include the following: abdominal pain, agitation, cholecystitis, confusion, convulsions, hallucinations, heart block (all types), hemolytic anemia, hepatitis, hyponatremia, pancreatitis, and rash. **OVERDOSAGE Because strategies for the management of overdose are continually evolving, it is advisable to contact a Poison Control Center to determine the latest recommendations for the management of an overdose of any drug.** As in any case of overdose, general supportive measures should be utilized. Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for ARICEPT® overdosage. Intravenous atropine sulfate titrated to effect is recommended: an initial dose of 1.0 to 2.0 mg IV with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics such as glycopyrrolate. It is not known whether ARICEPT® and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included reduced spontaneous movement, prone position, staggering gait, lacrimation, clonic convulsions, depressed respiration, salivation, miosis, tremors, fasciculation and lower body surface temperature. **DOSAGE AND ADMINISTRATION** The dosages of ARICEPT® shown to be effective in controlled clinical trials are 5 mg and 10 mg administered once per day. Controlled clinical trials indicated that the 10 mg dose, with a one week titration, is likely to be associated with a higher incidence of cholinergic adverse events than the 5 mg dose. Because steady state is not achieved for 15 days and because the incidence of such effects may be influenced by the rate of dose escalation, treatment with a dose of 10 mg should not be contemplated until patients have been on a daily dose of 5 mg for 4 to 6 weeks. Whether or not to employ a dose of 10 mg is a matter of prescriber and patient preference. ARICEPT® should be taken in the evening, just prior to retiring, and may be taken with or without food.

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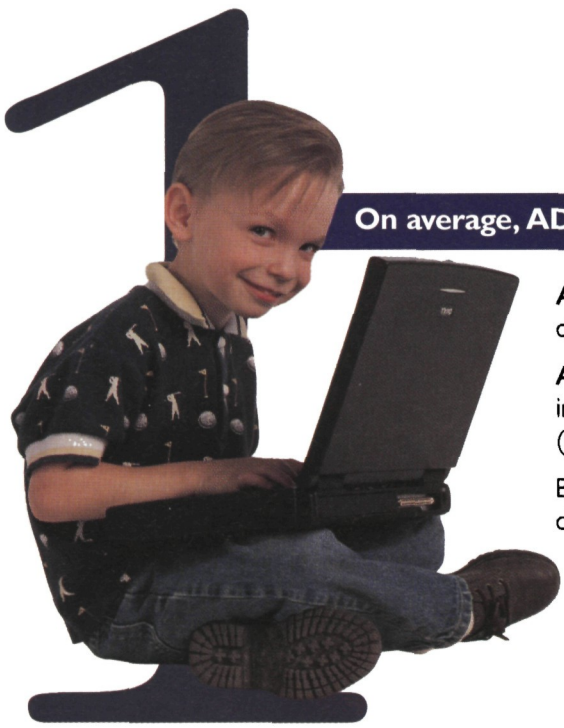
In the medical management of ADHD...

FIVE clinically *sound* reasons to *consider* ADDERALL® for the ADHD *patients* in *your* practice...



On average, ADDERALL is more effective than Ritalin® ($p<0.001$)[1]

ADDERALL is favored 3 to 1 compared to Ritalin® by clinical staff for continued medication[1]

ADDERALL produced significantly more improvement in most measures of behavior as compared to Ritalin ($p<0.05$)*[1]

Both drugs produced low and comparable levels of clinically significant side effects[1]

Pelham et al, 1999.[1]

ADDERALL achieved better scores than methylphenidate (MPH) in reducing inattentive and hyperactive symptoms ($p<0.05$)[2]

ADDERALL scored better than MPH ($p<0.05$) on Clinical Global Impression (CGI) improvement[2]

Children who obtained a CGI-improvement score of 1 or 2 were defined as "responders"—and there were significantly more responders in the **ADDERALL** group as compared to the MPH group ($p<0.01$)[2]

Side effects were no different than placebo[2]

Pliszka et al, 2000.[2]

*Except for complaining and positive peer behaviors, in which cases the degree of improvement with **ADDERALL** was equal to that of Ritalin.

ADDERALL is a registered trademark of Shire Richwood Inc. Ritalin is a registered trademark of Novartis Pharmaceuticals Corp.

Please see adjacent pages for references and summary prescribing information.

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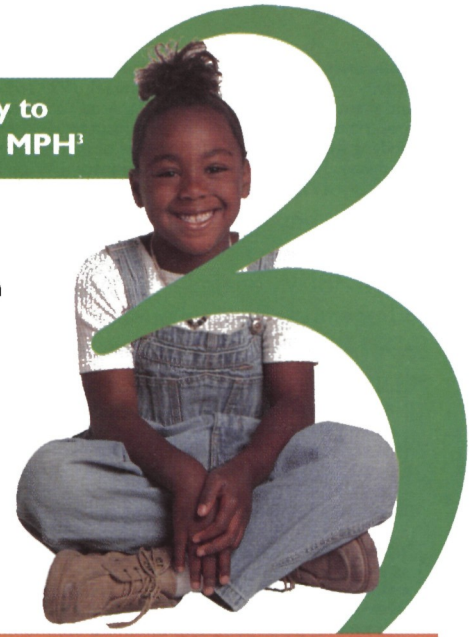
Children initially treated with ADDERALL were 4 times less likely to require a medication switch in the first 6 months compared with MPH[3]



Patients receiving **ADDERALL** remained on therapy significantly longer than those receiving MPH—average length of time on initial medication was 153 days for **ADDERALL** ($p<0.001$) and 130 days for MPH ($p=0.0003$)[3]

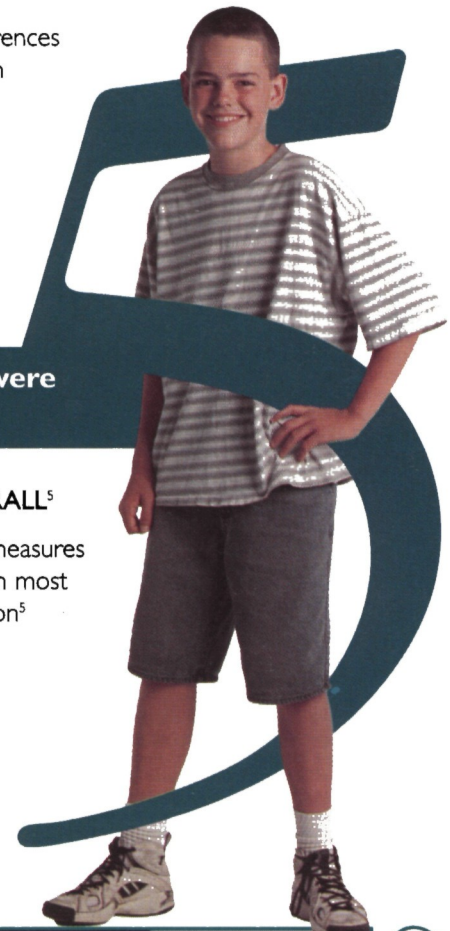
Grcevich et al, 1999.[3]

Single-dose treatments of ADDERALL (average 10.6 mg/day) appear to be as effective as 2 daily doses of MPH (average 19.5 mg/day)[4]

87% of MPH failures were successfully treated with **ADDERALL**[4]

Analysis of side effects data revealed no differences between placebo and best dose. Few children experienced any serious side effects their best dose week[4]

Manos et al, 1999.[4]



Overall effects of ADDERALL on attention and deportment were significant ($p<0.0001$)[5]

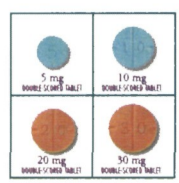
Duration of action increases with dose of **ADDERALL**[5]

No serious or unusual side effects were noted—measures of side effects were no more frequent or severe in most medication conditions than in the placebo condition[5]

Swanson et al, 1998.[5]

Adderall is generally well tolerated—adverse reactions have seldom been reported (most frequently reported adverse reactions include anorexia, insomnia, stomach pain, headache, irritability, and weight loss).

As with most psychostimulants indicated for ADHD, the possibility of growth suppression and the potential for precipitating motor tics and Tourette's syndrome exist with Adderall treatment and, in rare cases, exacerbations of psychosis have been reported. Since amphetamines have a high potential for abuse, Adderall should only be prescribed as part of an overall multimodal treatment program for ADHD, with close physician supervision.



ADDERALL XR

5 mg, 10 mg, 20 mg & 30 mg TABLETS

(Mixed Salts of a Single-Entity Amphetamine Product)

Dextroamphetamine Sulfate *Amphetamine Sulfate*
Dextroamphetamine Saccharate Amphetamine Aspartate

May 2000

Shire

https://doi.org/10.1017/S1092852900006957 Published online by Cambridge University Press

References: 1. Pelham WE, Aronoff HR, Midlam JK, et al. A comparison of Ritalin and Adderall: efficacy and time-course in children with attention-deficit/hyperactivity disorder. *Pediatrics* [serial online]. 1999;103:e43. Available at: http://www.pediatrics.org/. 2. Pliszka S, Browne RG, Wynne SK, et al. Comparing Adderall and methylphenidate in ADHD. *J Am Acad Child Adolesc Psychiatry*. 2000. In press. 3. Grcevich S, Rowane WA, Marcellino B, et al. Assessing the clinical practice of prescribing Adderall vs. methylphenidate to children with attention-deficit disorder. APA Annual Meeting, May 15-20, 1999. Washington DC. 4. Manos MJ, Short EJ, Findling RL. Differential effectiveness of methylphenidate and Adderall® in school-age youths withattention-deficit/hyperactivity disorder. *J Am Acad Child Adolesc Psychiatry*. 1999;38(7):813-819. 5. Swanson J, Wigal S, Greenhill L, et al. Analog classroom assessment of Adderall in children with ADHD. *J Am Acad Child Adolesc Psychiatry*. 1998;37(5):519-525.

ADDERALL® II

5 mg, 10 mg, 20 mg & 30 mg TABLETS
(Mixed Salts of a Single-Entity Amphetamine Product)
Dextroamphetamine Sulfate Amphetamine Sulfate
Dextroamphetamine Saccharate Amphetamine Aspartate

ADDERALL® TABLETS II BRIEF SUMMARY

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE AND MUST BE AVOIDED. PARTICULAR ATTENTION SHOULD BE PAID TO THE POSSIBILITY OF SUBJECTS OBTAINING AMPHETAMINES FOR NON-THERAPEUTIC USE OR DISTRIBUTION TO OTHERS, AND THE DRUGS SHOULD BE PRESCRIBED OR DISPENSED SPARINGLY.

INDICATIONS: Attention Deficit Disorder with Hyperactivity: ADDERALL is indicated as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted. **In Narcolepsy: CONTRAINDICATIONS:** Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncrasy to the sympathomimetic amines, glaucoma. Agitated states. Patients with a history of drug abuse. During or within 14 days following the administration of monoamine oxidase inhibitors (hypertensive crises may result). **WARNINGS:** Clinical experience suggests that in psychotic children, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder. Data are inadequate to determine whether chronic administration of amphetamine may be associated with growth inhibition; therefore, growth should be monitored during treatment. **Usage in Nursing Mothers:** Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing. **PRECAUTIONS: General:** Caution is to be exercised in *prescribing amphetamines for patients with even mild hypertension. The least amount* feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. **Information for Patients:** Amphetamines may impair the ability of the patient to engage in potentially hazardous activities such as operating machinery or vehicles; the patient should therefore be cautioned accordingly. **Drug Interactions:** *Acidifying agents* - Gastrointestinal acidifying agents (guanethidine, reserpine, glutamic acid HCl, ascorbic acid, fruit juices, etc.) lower absorption of amphetamines. *Urinary acidifying agents* - (ammonium chloride, sodium acid phosphate, etc.) Increase the concentration of the ionized species of the amphetamine molecule, thereby increasing urinary excretion. Both groups of agents lower blood levels and efficacy of amphetamines. *Adrenergic blockers* - Adrenergic blockers are inhibited by amphetamines. *Alkalinizing agents* - Gastrointestinal alkalinizing *agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Urinary* alkalinizing agents (acetazolamide, some thiazides) increase the concentration of the non-ionized species of the amphetamine molecule, thereby decreasing urinary excretion. Both groups of agents increase blood levels and therefore potentiate the actions of amphetamines. *Antidepressants, tricyclic* - Amphetamines may enhance the activity of tricyclic or sympathomimetic agents; d-amphetamine with desipramine or protriptyline and possibly other tricyclics cause striking and sustained increases in the concentration of d-amphetamine in the brain; cardiovascular effects can be potentiated. *MAO inhibitors* - MAOI antidepressants, as well as a metabolite of furazolidone, slow amphetamine metabolism. This slowing potentiates amphetamines, increasing their effect on the release of norepinephrine and other monoamines from adrenergic nerve endings; this can cause headaches and other signs of hypertensive crisis. A variety of neurological toxic effects and malignant hyperpyrexia can occur, sometimes with fatal results. *Antihistamines* - Amphetamines may counteract the sedative effect of antihistamines. *Antihypertensives* - Amphetamines may antagonize the hypotensive effects of antihypertensives. *Chlorpromazine* - Chlorpromazine blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines, and can be used to treat amphetamine poisoning. *Ethosuximide* - Amphetamines may delay intestinal absorption of ethosuximide. *Haloperidol* - Haloperidol blocks dopamine and norepinephrine reuptake, thus inhibiting the central stimulant effects of amphetamines. *Lithium carbonate* - The anorectic and stimulatory effects of amphetamines may be inhibited by lithium carbonate. *Meperidine* - Amphetamines potentiate the analgesic effect of meperidine. *Methenamine therapy* - Urinary excretion of amphetamines is increased, and efficacy is reduced, by acidifying agents used in methenamine therapy. *Norepinephrine* - Amphetamines enhance the adrenergic effect of norepinephrine. *Phenobarbital* - Amphetamines may delay intestinal absorption of phenobarbital; co-administration of phenobarbital may produce a synergistic anticonvulsant action. *Phenytoin* - Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action. *Propoxyphene* - In cases of propoxyphene overdosage, amphetamine CNS stimulation is potentiated and fatal convulsions can occur. *Veratrum alkaloids* - Amphetamines inhibit the hypotensive effect of veratrum alkaloids. **Drug/Laboratory Test Interactions:** • Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greatest in the evening. • Amphetamines may interfere with urinary steroid determinations. **Carcinogenesis/Mutagenesis:** Mutagenicity studies and long-term studies in animals to determine the carcinogenic potential of amphetamine, have not been performed. **Pregnancy - Teratogenic Effects:** Pregnancy Category C. Amphetamine has been shown to have embryotoxic and teratogenic effects when administered to A/Jax mice and C57BL mice in doses approximately 41 times the maximum human dose. Embryotoxic effects were not seen in New Zealand white rabbits given the drug in doses 7 times the human dose nor in rats given 12.5 times the maximum human dose. While there are no adequate and well-controlled studies in pregnant women, there has been one report of severe congenital bony deformity, tracheoesophageal fistula, and anal atresia (vater association) in a baby born to a woman who took dextroamphetamine sulfate with lovastatin during the first trimester of pregnancy. Amphetamines should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. **Nonteratogenic Effects:** Infants born to mothers dependent on amphetamines have an increased risk of premature delivery and low birth weight. Also, these infants may experience symptoms of withdrawal as demonstrated by dysphoria, including agitation, and significant lassitude. **Pediatric Use:** Long-term effects of amphetamines in children have not been well established. Amphetamines are not recommended for use in children under 3 years of age with Attention Deficit Disorder with Hyperactivity described under INDICATIONS AND USAGE. Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome in children and their families should precede use of stimulant medications. Drug treatment is not indicated in all cases of Attention Deficit Disorder with Hyperactivity and should be considered only in light of the complete history and evaluation of the child. The decision to prescribe amphetamines should depend on the physician's assessment of the chronicity and severity of the child's symptoms and their appropriateness for his/her age. Prescription should not depend solely on the presence of one or more of the behavioral characteristics. When these symptoms are associated with acute stress reactions, treatment with amphetamines is usually not indicated. **ADVERSE REACTIONS: Cardiovascular:** Palpitations, tachycardia, elevation of blood pressure. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use. **Central Nervous System:** Psychotic episodes at recommended doses (rare), overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome. **Gastrointestinal:** Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances. Anorexia and weight loss may occur as undesirable effects when amphetamines are used for other than the anorectic effect. **Allergic:** *Urticaria.* ***Endocrine:*** *Impotence, changes in libido.* ***DRUG ABUSE AND DEPENDENCE:*** Dextroamphetamine sulfate is a Schedule II controlled substance. Amphetamines have been extensively abused. Tolerance, extreme psychological dependence, and severe social disability have occurred. There are reports of patients who have increased the dosage to many times that recommended. Abrupt cessation following prolonged high dosage administration results in extreme fatigue and mental depression; changes are also noted on the sleep EEG. Manifestations of chronic intoxication with amphetamines include severe dermatoses, marked insomnia, irritability, hyperactivity, and personality changes. The most severe manifestation of chronic intoxication is psychosis, often clinically indistinguishable from schizophrenia. This is rare with oral amphetamines. **OVERDOSAGE:** Individual patient response to amphetamines varies widely. While toxic symptoms occasionally occur as an *idiosyncrasy at doses as low as 2 mg, they are rare with doses of less than 15 mg; 30 mg* can produce severe reactions, yet doses of 400 to 500 mg are not necessarily fatal. In rats, the oral LD_{50} of dextroamphetamine sulfate is 96.8 mg/kg. **Symptoms:** Manifestations of acute overdosage with amphetamines include restlessness, tremor, hyperreflexia, rapid respiration, confusion, assaultiveness, hallucinations, panic states, hyperpyrexia and rhabdomyolysis. Fatigue and depression usually follow the central stimulation. Cardiovascular effects include arrhythmias, hypertension or hypotension and circulatory collapse. Gastrointestinal symptoms include nausea, vomiting, diarrhea, and abdominal cramps. Fatal poisoning is usually preceded by convulsions and coma. **Treatment:** Consult with a Certified Poison Control Center for up to date guidance and advice. Management of acute amphetamine intoxication is largely symptomatic and includes gastric lavage, administration of activated charcoal, administration of a cathartic and sedation. Experience with hemodialysis or peritoneal dialysis is inadequate to permit recommendation in this regard. Acidification of the urine increases amphetamine excretion, but is believed to increase risk of acute renal failure if myoglobinuria is present. If acute, severe hypertension complicates amphetamine overdosage, administration of intravenous phentolamine (Regitine®, Novartis) has been suggested. However, a gradual drop in blood pressure will usually result when sufficient sedation has been achieved. Chlorpromazine antagonizes the central stimulant effects of amphetamines and can be used to treat amphetamine intoxication. **DOSAGE AND ADMINISTRATION:** Regardless of indication, amphetamines should be administered at the lowest effective dosage and dosage should be individually adjusted. Late evening doses should be avoided because of the resulting insomnia. **Attention Deficit Disorder with Hyperactivity:** Not recommended for children under 3 years of age. In children from 3 to 5 years of age, start with 2.5 mg daily; daily dosage may be raised in increments of 2.5 mg at weekly intervals until optimal response is obtained. In children 6 years of age and older, start with 5 mg once or twice daily; daily dosage may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. Only in rare cases will it be necessary to exceed a total of 40 mg per day. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. Where possible, drug administration should be interrupted occasionally to determine if there is a recurrence of behavioral symptoms sufficient to require continued therapy. **Narcolepsy:** Usual dose 5 mg to 60 mg per day in divided doses, depending on the individual patient response. Narcolepsy seldom occurs in children under 12 years of age; however, when it does, dextroamphetamine sulfate may be used. The suggested initial dose for patients aged 6-12 is 5 mg daily; daily dose may be raised in increments of 5 mg at weekly intervals until optimal response is obtained. In patients 12 years of age and older, start with 10 mg daily; daily dosage may be raised in increments of 10 mg at weekly intervals until optimal response is obtained. If bothersome adverse reactions appear (e.g., insomnia or anorexia), dosage should be reduced. Give first dose on awakening; additional doses (1 or 2) at intervals of 4 to 6 hours. **Rx only.**

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REACHING A CONSENSUS: WHAT THE SCIENCE SAYS

page 29

"In several areas, the statement reached conclusions that can now be modified to accommodate new findings in these areas. For example, the statement noted that medication treatments yielded little improvements in social skills, yet a good body of evidence, including findings from the MTA as well as previous short-term, placebo-controlled studies, suggests that children treated with careful medication management receive higher peer nomination scores and likeability rankings from their classmates and are rated as having better social skills by parents and teachers than children who are not treated with medication. In addition, the panelists noted that it had not been shown whether children treated with combined (multimodal) treatments could do as well or better on lower doses of medication than medication-only subjects. This issue has now been partly addressed by the MTA study, with evidence suggesting that children treated with combined therapies can be successfully maintained over time on lower stimulant doses than those treated with medication alone."

ATTENTION-DEFICIT/HYPERACTIVITY DISORDER: THE MASQUERADE

page 34

"Overall, morphological and functional imaging studies have implicated localized abnormalities in the PFC and basal ganglia in the etiology of ADHD. The PFC and the basal ganglia are part of a complex neural system that regulates behavior via working memory. The PFC exerts inhibitory control over motor functions through connections with the caudate nucleus, which in turn projects to the globus pallidus. The globus pallidus provides feedback to the PFC via thalamic nuclei. Consequently, the findings of smaller PFC, caudate, globus pallidus, and anterior callosal regions in children with ADHD suggests: (1) fewer corticostriatal fibers linking the PFC and caudate; (2) less pallidal feedback to the PFC; and (3) less interhemispheric fibers in the PFC. Importantly, functional abnormalities in the PFC and the basal ganglia have been tentatively linked with executive function deficits in children with ADHD."

THE CHALLENGE OF THE PREDOMINANTLY INATTENTIVE SUBTYPE

page 45

"Early work suggested that children with the IN subtype of ADHD were more likely to have a comorbid learning disability. A higher prevalence of clinically diagnosed arithmetic and/or reading disorders was found in the IN and ADD without hyperactivity subgroups, respectively, in two small studies. However, there were no subgroup differences in two larger studies, one of which employed objective criteria for diagnosis of specific learning disabilities. More recent studies using *DSM-IV* criteria have found no differences between the IN and CB subtypes in Wechsler Intelligence Scale for Children-Revised (WISC-R) IQ scores or in performance in arithmetic, reading, or spelling on the Wide Range Achievement Test. However, WISC-R scores and achievement scores were depressed in both the CB and IN subtypes compared with normal controls. In addition, children with CB, but not those with IN, were more likely than controls to have a comorbid language disability. A comprehensive study of the prevalence of learning disabilities across subtypes remains to be conducted."

VERBAL AGGRESSION: A STABLE AND ACCURATE PREDICTOR OF LATER PHYSICAL AGGRESSION

page 52

"Loeber and Hay have suggested that aggression, like personality features, may become more stable with age. The present findings suggest that verbal aggression (ie, cursing, threatening, etc) represents a highly stable, temperamental characteristic that may be of greater value than early physical aggression for predicting later aggressive acts. Consistent with these findings, verbally aggressive temperamental characteristics have been shown to be both longitudinally stable and predictive of later behavioral problems. The severity of aggression is influenced by sociocultural antecedents or consequences; verbal hostility may represent a more socially tolerated (and, thus, indirectly reinforced/perpetuated) response pattern."

NEUROCOGNITIVE DIFFICULTIES IN ADULTS

page 58

"This study assessed orientation to target, motor output/response organization, encoding speed, and sustained attention in adults with and without ADHD using distinct measures of each construct. It was hypothesized that adults with ADHD may have impairments in one or several of these areas of neurocognitive functioning. The fact that significant main effects were found for all manipulations indicates that the tasks are sensitive to the processes they target. The differential performance of the ADHD participants vs controls on the two measures of the TOT, as indicated by significant interactions on the TOT, suggests that this test targets processes that are deficient in adults with ADHD. On the other hand, the absence of an interaction on the CPT indicates that the two processes that were targeted by the task (ie, encoding speed and sustained attention) are not areas of impairment for adults with ADHD. The absence of an interaction on the CMPT may have been due to the small sample sizes, as two of the ADHD adults were unable to complete this task."

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Table of Contents

Feature Articles

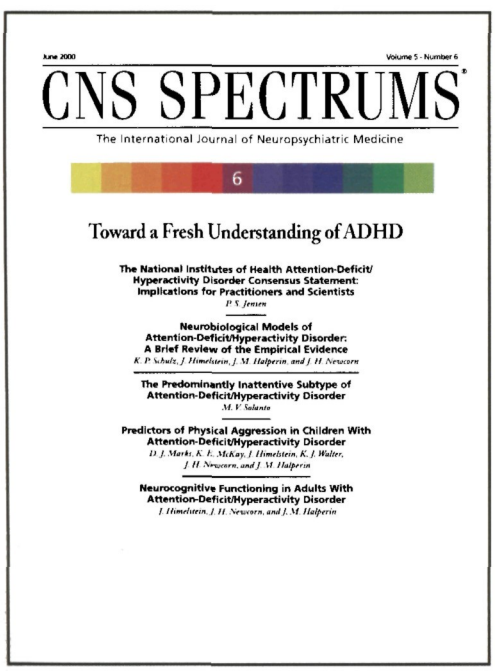

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Table of Contents

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INDICATIONS AND USAGE

RISPERDAL® (risperidone) is indicated for the management of the manifestations of psychotic disorders.

CONTRAINDICATIONS

RISPERDAL® (risperidone) 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 antipsychotic drugs. 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. Whether antipsychotic drug products differ in their potential to cause tardive dyskinesia is unknown.

If signs and symptoms of tardive dyskinesia appear in a patient on RISPERDAL®, drug discontinuation should be considered. However, some patients may require treatment with RISPERDAL® despite the presence of the syndrome.

Potential for Proarrhythmic Effects: Risperidone and/or 9-hydroxyrisperidone appears to lengthen the QT interval in some patients, although there is no average increase in treated patients, even at 12-16 mg/day, well above the recommended dose. Other drugs that prolong the QT interval have been associated with the occurrence of torsades de pointes, a life-threatening arrythmia. Bradycardia, electrolyte imbalance, concomitant use with other drugs that prolong QT, or the presence of congenital prolongation in QT can increase the risk for occurrence of this arrhythmia.

PRECAUTIONS

General

Orthostatic Hypotension: RISPERDAL® (risperidone) may induce orthostatic hypotension associated with dizziness, tachycardia, and in some patients, syncope, especially during the initial dose-titration period, probably reflecting its alpha-adrenergic antagonistic properties. Syncope was reported in 0.2% (6/2607) of RISPERDAL® treated patients in phase 2-3 studies. The risk of orthostatic hypotension and syncope may be minimized by limiting the initial dose to 2 mg total (either QD or 1 mg BID) in normal adults and 0.5 mg BID in *the elderly and patients with renal or hepatic impairment* (See DOSAGE AND ADMINISTRATION). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern. A dose reduction should be considered if hypotension occurs. RISPERDAL® should be used with particular caution in patients with known cardiovascular disease (history of myocardial infarction or ischemia, heart failure, or conduction abnormalities), cerebrovascular disease, and conditions which would predispose patients to hypotension e.g., dehydration and hypovolemia. Clinically significant hypotension has been observed with concomitant use of RISPERDAL® and antihypertensive medication.

Seizures: RISPERDAL® should be used cautiously in patients with a history of seizures.

Dysphagia: Esophageal dysmotility and aspiration have been associated with antipsychotic drug use. Aspiration pneumonia is a common cause of morbidity and mortality in patients with advanced Alzheimer's dementia. RISPERDAL® and other antipsychotic drugs should be used cautiously in patients at risk for aspiration pneumonia.

Hyperprolactinemia: As with other drugs that antagonize dopamine D_2 receptors, risperidone elevates prolactin levels and the elevation persists during chronic administration. Neither clinical studies nor epidemiologic studies conducted to date have shown an association between chronic administration of this class of drugs and tumorigenesis in humans; the available evidence is considered too limited to be conclusive at this time.

Potential for Cognitive and Motor Impairment: Somnolence was a commonly reported adverse event associated with RISPERDAL® treatment, especially when ascertained by direct questioning of patients. This adverse event is dose related. Patients should be cautioned about operating hazardous machinery, including automobiles, until they are reasonably certain that RISPERDAL® therapy does not affect them adversely.

Priapism: Rare cases of priapism have been reported.

Thrombotic Thrombocytopenic Purpura (TTP): A single case of TTP was reported in a 28 year-old female patient receiving RISPERDAL® in a large, open premarketing experience (approximately 1300 patients). She experienced jaundice, fever, and bruising, but eventually recovered after receiving plasmapheresis. The relationship to RISPERDAL® therapy is unknown.

Antiemetic effect: Risperidone has an antiemetic effect in animals; this effect may also occur in humans, and may mask signs and symptoms of overdosage with certain drugs or of conditions such as intestinal obstruction, Reye's syndrome, and brain tumor.

Body Temperature Regulation: Disruption of body temperature regulation has been attributed to antipsychotic agents. Caution is advised when prescribing for patients who will be exposed to temperature extremes.

Suicide: The possibility of a suicide attempt is inherent in schizophrenia, and close supervision of high risk patients should accompany drug therapy.

Use in Patients with Concomitant Illness: Clinical experience with RISPERDAL® in patients with certain concomitant systemic illnesses is limited. Caution is advisable in using RISPERDAL® in patients with diseases or conditions that could affect metabolism or hemodynamic responses.

Because of the risks of orthostatic hypotension and QT prolongation, caution should be observed in cardiac patients (See WARNINGS and PRECAUTIONS).

Increased plasma concentrations of risperidone and 9-hydroxyrisperidone occur in patients with severe renal impairment and in patients with severe hepatic impairment. A lower starting dose should be used in such patients.

Information for Patients

Physicians are advised to consult full prescribing information to review issues to be discussed with patients for whom they prescribe RISPERDAL®.

Drug Interactions

The interactions of RISPERDAL® and other drugs have not been systematically evaluated. Given the primary CNS effects of risperidone, caution should be used when RISPERDAL® is taken in combination with other centrally acting drugs and alcohol. RISPERDAL® may antagonize the effects of levodopa and dopamine agonists. Chronic administration of carbamazepine with risperidone may increase the clearance of risperidone. Chronic administration of clozapine with risperidone may decrease the clearance of risperidone.

Fluoxetine may increase the plasma concentration of the anti-psychotic fraction (risperidone plus 9-hydroxyrisperidone) by raising the concentration of risperidone, although not the active metabolite, 9-hydroxyrisperidone.

Drugs that Inhibit Cytochrome $P_{450}IID_6$ and Other P_{450} Isozymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome $P_{450}IID_6$, an enzyme that is polymorphic in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that reduce the metabolism of risperidone to 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a modest number of poor metabolizers (n≈70) does not suggest that poor and extensive metabolizers have different rates of adverse effects. No comparison of effectiveness in the two groups has been made.

In vitro studies showed that drugs metabolized by other P_{450} isozymes, including 1A1, 1A2, IIC9, MP, and IIIA4, are only weak inhibitors of risperidone metabolism.

Drugs Metabolized by Cytochrome $P_{450}IID_6$: In vitro studies indicate that risperidone is a relatively weak inhibitor of cytochrome $P_{450}IID_6$. Therefore, RISPERDAL® is not expected to substantially inhibit the clearance of drugs that are metabolized by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis: *Carcinogenicity studies were conducted in Swiss albino mice* and Wistar rats. Risperidone was administered in the diet at doses of 0.63, 2.5, and 10 mg/kg for 18 months to mice and for 25 months to rats. These doses are equivalent to 2.4, 9.4 and 37.5 times the maximum human dose (16 mg/day) on a mg/kg basis or 0.2, 0.75 and 3 times the maximum human dose (mice) or 0.4, 1.5, and 6 times the maximum human dose (rats) on a mg/m² basis. There were statistically significant increases in pituitary gland adenomas, endocrine pancreas adenomas and mammary gland adenocarcinomas.

These findings are considered to be prolactin medicated. The relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown (See Hyperprolactinemia under PRECAUTIONS, GENERAL).

Mutagenesis: No evidence of mutagenic potential for risperidone was found.

Impairment of Fertility: Risperidone (0.16 to 5 mg/kg) was shown to impair mating, but not fertility, in Wistar rats in three reproductive studies at doses 0.1 to 3 times the maximum recommended human dose on a mg/m² basis.

Pregnancy

Pregnancy Category C: There are no adequate and well-controlled studies in pregnant women.

RISPERDAL® should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labor and Delivery

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

Nursing Mothers

It is not known whether or not risperidone is excreted in human milk. Women receiving RISPERDAL® should not breast feed.

Pediatric Use

Safety and effectiveness in children have not been established.

Geriatric Use

Clinical studies of RISPERDAL® did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently from younger patients. Other reported clinical experience has not identified differences in responses between elderly and younger patients. In general, a lower starting dose is recommended for an elderly patient, reflecting a decreased pharmacokinetic clearance in the elderly, as well as a greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy (See CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). While elderly patients exhibit a greater tendency to orthostatic hypotension, its risk in the elderly may be minimized by limiting the initial dose to 0.5 mg BID followed by careful titration (See PRECAUTIONS). Monitoring of orthostatic vital signs should be considered in patients for whom this is of concern.

This drug is known to be substantially excreted by the kidney, and the risk of toxic reactions 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 DOSAGE AND ADMINISTRATION).

ADVERSE REACTIONS

Associated with Discontinuation of Treatment

Approximately 9% percent (244/2607) of RISPERDAL® (risperidone)-treated patients in phase 2-3 studies discontinued treatment due to an adverse event, compared with about 7% on placebo and 10% on active control drugs. The more common events (≥ 0.3%) associated with discontinuation and considered to be possibly or probably drug-related included: extrapyramidal symptoms, dizziness, hyperkinesia, somnolence, and nausea.

Incidence in Controlled Trials

Commonly Observed Adverse Events in Controlled Clinical Trials: In two 6- to 8-week placebo-controlled trials, spontaneously-reported, treatment-emergent adverse events with an incidence of 5% or greater in at least one of the RISPERDAL® groups and at least twice that of placebo were: anxiety, somnolence, extrapyramidal symptoms, dizziness, constipation, nausea, dyspepsia, rhinitis, rash, and tachycardia.

Adverse events were also elicited in one of these two trials (i.e., in the fixed-dose trial comparing RISPERDAL® at doses of 2, 6, 10, and 16 mg/day with placebo) utilizing a checklist for detecting adverse events, a method that is more sensitive than spontaneous reporting. By this method, the following additional common and drug-related adverse events were present at least 5% and twice the rate of placebo: increased dream activity, increased duration of sleep, accommodation disturbances, reduced salivation, micturition disturbances, diarrhea, weight gain, menorrhagia, diminished sexual desire, erectile dysfunction, ejaculatory dysfunction, and orgastic dysfunction.

The following adverse events occurred at an incidence of 1% or more, and were at least as frequent among RISPERDAL® treated patients treated at doses of ≤10 mg/day than among placebo-treated patients in the pooled results of two 6- to 8-week controlled trials: ***Psychiatric Disorders:*** insomnia, agitation, anxiety, somnolence, aggressive reaction. ***Nervous System:*** extrapyramidal symptoms[1], headache, dizziness. ***Gastrointestinal System:*** constipation, nausea, dyspepsia, vomiting, abdominal pain, saliva increased, toothache. ***Respiratory System:*** rhinitis, coughing, sinusitis, pharyngitis, dyspnea. ***Body as a Whole:*** back pain, chest pain, fever. ***Dermatological:*** rash, dry skin, seborrhea. ***Infections:*** upper respiratory. ***Visual:*** abnormal vision. ***Musculo-Skeletal:*** arthralgia. ***Cardiovascular:*** tachycardia.

[1] Includes tremor, dystonia, hypokinesia, hypertonia, hyperkinesia, oculogyric crisis, ataxia, abnormal gait, involuntary muscle contractions, hyporeflexia, akathisia, and extrapyramidal disorders.

Dose Dependency of Adverse Events:

Data from two fixed dose trials provided evidence of dose-relatedness for extrapyramidal symptoms associated with risperidone treatment. These symptoms include: sleepiness, increased duration of sleep, accommodation disturbances, orthostatic dizziness, palpitations, weight gain, erectile dysfunction, ejaculatory dysfunction, orgastic dysfunction, asthenia/lassitude/increased fatiguability, and increased pigmentation.

Vital Sign Changes: RISPERDAL® is associated with orthostatic hypotension and tachycardia (See PRECAUTIONS).

Weight Changes: A statistically significantly greater incidence of weight gain for RISPERDAL® (18%) compared to placebo (9%).

Laboratory Changes: A between group comparison for 6- to 8-week placebo-controlled trials revealed no statistically significant RISPERDAL®/placebo differences in the proportions of patients experiencing potentially important changes in routine serum chemistry, hematology, or urinalysis parameters. Similarly, there were no RISPERDAL®/placebo differences in the incidence of discontinuations for changes in serum chemistry, hematology, or urinalysis. However, RISPERDAL® administration was associated with increases in serum prolactin (See PRECAUTIONS).

ECG Changes: The electrocardiograms of approximately 380 patients who received RISPERDAL® and 120 patients who received placebo in two double-blind, placebo-controlled trials were evaluated and revealed one finding of potential concern; i.e., 8 patients taking RISPERDAL® whose baseline QTc interval was less than 450 msec were observed to have QTc intervals greater than 450 msec during treatment (See WARNINGS). Changes of this type were not seen among about 120 placebo patients, but were seen in patients receiving haloperidol (3/126).

Other Events Observed During the Pre-Marketing Evaluation of RISPERDAL®

During its premarketing assessment, multiple doses of RISPERDAL® (risperidone) were administered to 2607 patients in phase 2 and 3 studies and the following reactions were reported: (Note: frequent adverse events are those occurring in at least 1/100 patients. *Infrequent* adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients. It is important to emphasize that, although the events reported occurred during treatment with RISPERDAL®, they were not necessarily caused by it.)

Psychiatric Disorders: *Frequent:* increased dream activity*, diminished sexual desire*, nervousness. *Infrequent:* impaired concentration, depression, apathy, catatonic reaction, euphoria, increased libido, amnesia. *Rare:* emotional lability, nightmares, delirium, withdrawal syndrome, yawning.

Central and Peripheral Nervous System Disorders: *Frequent:* increased sleep duration*. *Infrequent:* dysarthria, vertigo, stupor, paraesthesia, confusion. *Rare:* aphasia, cholinergic syndrome, hypoesthesia, tongue paralysis, leg cramps, torticollis, hypotonia, coma, migraine, hyperreflexia, choreoathetosis.

Gastro-intestinal Disorders: *Frequent:* anorexia, reduced salivation*. *Infrequent:* flatulence, diarrhea, increased appetite, stomatitis, melena, dysphagia, hemorrhoids, gastritis. *Rare:* fecal incontinence, eructation, gastro-esophageal reflux, gastroenteritis, esophagitis, tongue discoloration, cholelithiasis, tongue edema, diverticulitis, gingivitis, discolored feces, GI hemorrhage, hematemesis.

Body as a Whole/General Disorders: *Frequent:* fatigue. *Infrequent:* edema, rigors, malaise, influenza-like symptoms. *Rare:* pallor, enlarged abdomen, allergic reaction, ascites, sarcoidosis, flushing.

Respiratory System Disorders: *Infrequent:* hyperventilation, bronchospasm, pneumonia, stridor. *Rare:* asthma, increased sputum, aspiration.

Skin and Appendage Disorders: *Frequent:* increased pigmentation*, photosensitivity*. *Infrequent:* increased sweating, acne, decreased sweating, alopecia, hyperkeratosis, pruritus, skin exfoliation. *Rare:* bullous eruption, skin ulceration, aggravated psoriasis, furunculosis, verruca, dermatitis lichenoid, hypertrichosis, genital pruritus, urticaria.

Cardiovascular Disorders: *Infrequent:* palpitation, hypertension, hypotension, AV block, myocardial infarction. *Rare:* ventricular tachycardia, angina pectoris, premature atrial contractions, T wave inversions, ventricular extrasystoles, ST depression, myocarditis.

Vision Disorders: *Infrequent:* abnormal accommodation, xerophthalmia. *Rare:* diplopia, eye pain, blepharitis, photopsia, photophobia, abnormal lacrimation.

Metabolic and Nutritional Disorders: *Infrequent:* hyponatremia, weight increase, creatine phosphokinase increase, thirst, weight decrease, diabetes mellitus. *Rare:* decreased serum iron, cachexia, dehydration, hypokalemia, hypoproteinemia, hyperphosphatemia, hypertriglyceridemia, hyperuricemia, hypoglycemia.

Urinary System Disorders: *Frequent:* polyuria/polydipsia*. *Infrequent:* urinary incontinence, hematuria, dysuria. *Rare:* urinary retention, cystitis, renal insufficiency.

Musculo-skeletal System Disorders: *Infrequent:* myalgia. *Rare:* arthrosis, synostosis, bursitis, arthritis, skeletal pain.

Reproductive Disorders, Female: *Frequent:* menorrhagia*, orgastic dysfunction*, dry vagina*. *Infrequent:* nonpuerperal lactation, amenorrhea, female breast pain, leukorrhea, mastitis, dysmenorrhea, female perineal pain, intermenstrual bleeding, vaginal hemorrhage.

Liver and Biliary System Disorders: *Infrequent:* increased SGOT, increased SGPT. *Rare:* hepatic failure, cholestatic hepatitis, cholecystitis, cholelithiasis, hepatitis, hepatocellular damage.

Platelet, Bleeding and Clotting Disorders: *Infrequent:* epistaxis, purpura. *Rare:* hemorrhage, superficial phlebitis, thrombophlebitis, thrombocytopenia.

Hearing and Vestibular Disorders: *Rare:* tinnitus, hyperacusis, decreased hearing.

Red Blood Cell Disorders: *Infrequent:* anemia, hypochromic anemia. *Rare:* normocytic anemia.

Reproductive Disorders, Male: *Frequent:* erectile dysfunction*. *Infrequent:* ejaculation failure.

White Cell and Resistance Disorders: *Rare:* leukocytosis, lymphadenopathy, leucopenia, Pelger-Huet anomaly.

Endocrine Disorders: *Rare:* gynecomastia, male breast pain, antidiuretic hormone disorder.

Special Senses: *Rare:* bitter taste.

* Incidence based on elicited reports.

Postintroduction Reports: Adverse events reported since market introduction which were temporally (but not necessarily causally) related to RISPERDAL® therapy, include the following: anaphylactic reaction, angioedema, apnea, atrial fibrillation, cerebrovascular disorder, diabetes mellitus aggravated, including diabetic ketoacidosis, intestinal obstruction, jaundice, mania, pancreatitis, Parkinson's disease aggravated, pulmonary embolism. There have been rare reports of sudden death and/or cardiopulmonary arrest in patients receiving RISPERDAL®. A causal relationship with RISPERDAL® has not been established. It is important to note that sudden and unexpected death may occur in psychotic patients whether they remain untreated or whether they are treated with other antipsychotic drugs.

DRUG ABUSE AND DEPENDENCE

Controlled Substance Class: RISPERDAL® (risperidone) is not a controlled substance.

For information on symptoms and treatment of overdosage, see full prescribing information.

More detailed professional information is available upon request.

US Patent 4,804,663

July 1998, May 1999

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JANSSEN · PHARMACEUTICA · RESEARCH FOUNDATION ·

Titusville, NJ 08560

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Depression
or
Generalized Anxiety Disorder

to better

to well

I got my playfulness back

Get your patients beyond better

- Working on both serotonin and norepinephrine, the unique formulation of EFFEXOR XR offers more of your patients the ability to achieve remission—full symptom resolution.[1,2]

Need proof? Call 1-888-EFFEXOR XR.

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Please see brief summary of Prescribing Information on the next page.

ONCE-DAILY

VENLAFAXINE HCl

EFFEXOR® XR *EXTENDED RELEASE CAPSULES*

Beyond better.

The efficacy and safety of EFFEXOR XR for pediatric use have not been established.

EFFEXOR XR is contraindicated in patients taking monoamine oxidase inhibitors (MAOIs). EFFEXOR XR should not be used in combination with an MAOI or within at least 14 days of discontinuing treatment with an MAOI; at least 7 days should be allowed after stopping EFFEXOR XR before starting an MAOI.

The most common adverse events reported in EFFEXOR XR placebo-controlled depression trials (incidence ≥10% and ≥2× that of placebo) were nausea, dizziness, somnolence, abnormal ejaculation, sweating, dry mouth, and nervousness; and in GAD trials were nausea, dry mouth, insomnia, abnormal ejaculation, anorexia, constipation, nervousness, and sweating.

Treatment with venlafaxine is associated with sustained increases in blood pressure (BP) in some patients. Three percent of EFFEXOR XR patients in depression studies (doses of 75 to 375 mg/day) and 0.4% in GAD studies (doses of 75 to 225 mg/day) had sustained BP elevations. Less than 1% discontinued treatment because of elevated BP. Regular BP monitoring is recommended.

References: 1. Data on file, Wyeth-Ayerst Laboratories, Philadelphia, Pa. **2.** Ferrier IN. Treatment of major depression: is improvement enough? *J Clin Psychiatry.* 1999;60(suppl 6):10-14.

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VENLAFAXINE HCl

EFFEXOR XR EXTENDED RELEASE CAPSULES

Brief Summary
See package insert for full prescribing information.
Indications and Usage: Effexor XR is indicated for the treatment of depression and for the treatment of Generalized Anxiety Disorder (GAD).
Contraindications: Effexor XR is contraindicated in patients known to be hypersensitive to venlafaxine hydrochloride. Concomitant use in patients taking monoamine oxidase inhibitors (MAOIs) is contraindicated (see **"Warnings"**).
Warnings: POTENTIAL FOR INTERACTION WITH MONOAMINE OXIDASE INHIBITORS—**Adverse reactions, some of which were serious, have been reported in patients who have recently been discontinued from an MAOI and started on venlafaxine, or who have recently had venlafaxine therapy discontinued prior to initiation of an MAOI. These reactions have included tremor, myoclonus, diaphoresis, nausea, vomiting, flushing, dizziness, hyperthermia with features resembling neuroleptic malignant syndrome, seizures, and death. In patients receiving antidepressants with pharmacological properties similar to venlafaxine in combination with an MAOI, there have also been reports of serious, sometimes fatal, reactions. For a selective serotonin reuptake inhibitor, these reactions have included hyperthermia, rigidity, myoclonus, autonomic instability with possible rapid fluctuations of vital signs, and mental status changes that include extreme agitation progressing to delirium and coma. Some cases presented with features resembling neuroleptic malignant syndrome. Severe hyperthermia and seizures, sometimes fatal, have been reported in association with the combined use of tricyclic antidepressants and MAOIs. These reactions have also been reported in patients who have recently discontinued these drugs and have been started on an MAOI. The effects of combined use of venlafaxine and MAOIs have not been evaluated in humans or animals. Therefore, because venlafaxine is an inhibitor of both norepinephrine and serotonin reuptake, it is recommended that Effexor XR (venlafaxine hydrochloride) extended release capsules not be used in combination with an MAOI, or within at least 14 days of discontinuing treatment with an MAOI. Based on the half-life of venlafaxine, at least 7 days should be allowed after stopping venlafaxine before starting an MAOI.**
SUSTAINED HYPERTENSION—Venlafaxine is associated with sustained increases in blood pressure in some patients. Among patients treated with 75-375 mg per day of Effexor XR in premarketing depression studies, 3% experienced sustained hypertension (defined as treatment-emergent supine diastolic blood pressure (SDBP) ≥ 90 mm Hg and ≥ 10 mm Hg above baseline for 3 consecutive on-therapy visits). Among patients treated with 75-225 mg per day of *Effexor XR in premarketing GAD studies, 0.4% (2/476) experienced sustained hypertension. Experience with immediate* release venlafaxine showed that sustained hypertension was dose related, increasing from 3-7% at 100-300 mg per day to 13% at doses above 300 mg per day. An insufficient number of patients received mean doses of Effexor XR >300 mg/day to fully evaluate the incidence of sustained blood pressure at these higher doses. In premarketing depression and GAD studies, 0.7% and 0.4% of the Effexor XR-treated patients, respectively, discontinued treatment because of elevated blood pressure. It is recommended that patients receiving Effexor XR have regular monitoring of blood pressure. For patients who experience a sustained increase in blood pressure, either dose reduction or discontinuation should be considered.
Precautions: GENERAL—*Insomnia and Nervousness*: Treatment-emergent insomnia and nervousness have been reported for patients treated with Effexor XR. Insomnia and nervousness each led to drug discontinuation in 0.9% of the patients treated with Effexor XR in Phase 3 depression studies. In Phase 3 GAD trials, insomnia and nervousness led to drug discontinuation in 5% and 3%, respectively, of the patients treated with Effexor XR.
Changes in Appetite/Weight: Treatment-emergent anorexia has been reported in short-term depression and anxiety studies. A loss of 5% or more of body weight occurred in 7% of Effexor XR-treated and 2% of placebo-treated patients in placebo-controlled depression trials. A loss of 7% or more of body weight occurred in 3% of the Effexor XR-*treated and 0% of the placebo-treated patients in placebo-controlled GAD trials.*
Activation of Mania/Hypomania: Mania or hypomania has occurred during short-term depression studies. Effexor XR should be used cautiously in patients with a history of mania.
Seizures: No seizures occurred among Effexor XR-treated patients in short-term trials. In all premarketing depression trials with Effexor, seizures were reported in 0.3% of venlafaxine-treated patients. Use Effexor XR cautiously in patients with a history of seizures. Discontinue in any patient who develops seizures.
Suicide: The possibility of a suicide attempt is inherent in depression and may persist until significant remission occurs. Closely supervise high-risk patients during initial drug therapy. Prescriptions for Effexor XR should be written for the smallest quantity of capsules consistent with good patient management to reduce the risk of overdose. The same precautions observed when treating patients with depression should be observed when treating patients with GAD.
Use in Patients With Concomitant Illness: Premarketing experience with venlafaxine in patients with concomitant systemic illness is limited. Use Effexor XR cautiously in patients with diseases or conditions that could affect hemodynamic responses or metabolism. Venlafaxine has not been evaluated in patients with recent history of MI or unstable heart disease. In short-term depression studies electrocardiographic changes in corrected QT interval (QTc) for Effexor XR-treated patients showed an increase of 4.7 msec. In these same trials, the mean change from baseline *heart rate for Effexor XR-treated patients was 4 beats per minute. In short-term GAD studies, mean changes in QTc* for Effexor XR-treated patients did not differ significantly from placebo. The mean change from baseline heart rate for Effexor XR-treated patients in anxiety studies was 3 beats per minute. The clinical significance of these changes is unknown. In patients with renal impairment (GFR=10-70 mL/min) or cirrhosis of the liver, the clearances of venlafaxine and its active metabolites were decreased, thus prolonging the elimination half-lives. A lower dose may be necessary; use with caution in such patients.
INFORMATION FOR PATIENTS—Clinical studies in healthy individuals revealed no clinically significant impairment of psychomotor, cognitive, or complex behavior performance. However, caution patients about operating hazardous machinery, including automobiles, until they are reasonably sure that venlafaxine does not adversely affect their abilities. Tell patients to 1) notify their physician if they become pregnant or intend to become pregnant during therapy, or if they are nursing; 2) inform physician about other prescription or over the counter medications they are taking or plan to take; 3) avoid alcohol while taking Effexor XR; 4) notify their physician if they develop a rash, hives, or related allergic phenomena.
LABORATORY TESTS: There are no specific laboratory tests recommended.
DRUG INTERACTIONS—*Cimetidine*: Use with caution when administering venlafaxine with cimetidine to patients with *pre-existing hypertension or hepatic dysfunction, and the elderly.*
Haloperidol: Venlafaxine (150 mg/day) decreased total oral-dose clearance (CL/F) of haloperidol which resulted in a 70% increase in haloperidol AUC. The haloperidol C_{max} increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life was unchanged.
Drugs Inhibiting Cytochrome P4502D6 Metabolism: Venlafaxine is metabolized to its active metabolite, O-desmethylvenlafaxine (ODV), via cytochrome P4502D6. Drugs inhibiting this isoenzyme have the potential to increase plasma concentrations of venlafaxine and decrease concentrations of ODV. However, since the composite plasma levels of venlafaxine and ODV are essentially unchanged in CYP2D6 poor metabolizers, no dosage adjustment is required when venlafaxine is coadministered with a CYP2D6 inhibitor.
The concomitant use of venlafaxine with a drug treatment(s) that potentially inhibits both CYP2D6 and CYP3A4, the primary metabolizing enzymes for venlafaxine, has not been studied. Therefore, caution is advised should a patient's therapy include venlafaxine and any agent(s) that produce simultaneous inhibition of these two enzyme systems.
Drugs Metabolized by Cytochrome P450 Isoenzymes: Studies indicate that venlafaxine is a relatively weak inhibitor of CYP2D6. Venlafaxine did not inhibit CYP1A2 and CYP3A4 (*in vitro* and *in vivo*), CYP2C9 (*in vitro*), or CYP2C19 (*in vivo*).
Imipramine—Venlafaxine did not affect the pharmacokinetics of imipramine and 2-OH-imipramine. However, desipramine AUC, C_{max} and C_{min} increased by about 35% in the presence of venlafaxine. The 2-OH-desipramine AUC's increased by 2.5-4.5 fold. Imipramine did not affect the pharmacokinetics of venlafaxine and ODV. The clinical significance of elevated 2-OH-desipramine levels is unknown.
Risperidone—Venlafaxine administered under steady-state conditions at 150 mg/day slightly inhibited the CYP2D6-mediated metabolism of risperidone (administered as a single 1 mg oral dose) to its active metabolite, 9-hydroxy-risperidone, resulting in an approximate 32% increase in risperidone AUC. However, venlafaxine coadministration did not significantly alter the pharmacokinetic profile of the total active moiety (risperidone plus 9-hydroxyrisperidone).
Monoamine Oxidase Inhibitors: See **"Contraindications"** and **"Warnings."**
CNS-Active Drugs: Use of venlafaxine with CNS-active drugs has not been systematically evaluated; use caution when administering Effexor XR with such drugs.
Postmarketing Spontaneous Drug Interaction Reports: See **"ADVERSE REACTIONS," "Postmarketing Reports."**
CARCINOGENESIS, MUTAGENESIS, IMPAIRMENT OF FERTILITY—*Carcinogenesis*: There was no increase in tumors in 18-month studies in mice given up to 120 mg/kg/day [1.7 times the maximum recommended human dose (MRHD) mg/m² basis] or in 24-month studies in rats given up to 120 mg/kg/day.
Mutagenesis: Venlafaxine and ODV were not mutagenic in the Ames reverse mutation assay in Salmonella bacteria or the Chinese hamster ovary/HGPRT mammalian cell forward gene mutation assay. Venlafaxine was not clastogenic in several assays. ODV elicited a clastogenic response in the *in vivo* chromosomal aberration assay in rat bone marrow.
Impairment of Fertility: No effects on reproduction or fertility in rats were noted at oral doses of up to 2 times the MRHD on a mg/m² basis.
PREGNANCY—*Teratogenic Effects—Pregnancy Category C.* Reproduction studies in rats given 2.5 times, and rabbits given 4 times the MRHD (mg/m² basis) revealed no malformations in offspring. However, in rats given 2.5 times the MRHD, there was a decrease in pup weight, an increase in stillborn pups, and an increase in pup deaths during the first 5 days of lactation when dosing began during pregnancy and continued until weaning. There are no adequate *and well-controlled studies in pregnant women; use Effexor XR during pregnancy only if clearly needed.*
LABOR, DELIVERY, NURSING—The effect on labor and delivery in humans is unknown. Venlafaxine and ODV have been reported to be excreted in human milk. Because of the potential for serious adverse reactions in nursing infants from Effexor XR, 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—Safety and effectiveness in pediatric patients have not been established.
GERIATRIC USE—Approximately 4% and 3% of Effexor XR-treated patients in placebo-controlled premarketing depression and GAD trials, respectively, were 65 years of age or over. Of 2,897 Effexor-treated patients in premarketing phase depression studies, 12% were 65 years of age or over. No overall differences in effectiveness or safety were observed between geriatric patients and younger patients. However, greater sensitivity of some older individuals cannot be ruled out. As with other antidepressants, several cases of hyponatremia and syndrome of inappropriate antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly.
Adverse Reactions: ASSOCIATED WITH DISCONTINUATION OF TREATMENT—Approximately 11% and 23% of Effexor XR patients in placebo-controlled clinical depression and GAD trials, respectively, discontinued treatment due to an adverse event. The most common events leading to discontinuation in at least 1% of patients and at least twice that of placebo in depression trials included: nausea, anorexia, dry mouth, dizziness, **insomnia, and somnolence**; in U.S. placebo-controlled depression trials included: hypertension, diarrhea, paresthesia, tremor, abnormal (mostly blurred) vision, and abnormal (mostly delayed) ejaculation; in GAD trials included: headache, asthenia, vasodilation, nausea, anorexia, dry mouth, dizziness, insomnia, nervousness, somnolence, thinking abnormal, tremor, and abnormal vision.
INCIDENCE IN CONTROLLED TRIALS—Commonly Observed Adverse Events in Controlled Clinical Trials: The most commonly observed adverse events associated with the use of Effexor XR in placebo-controlled depression trials (incidence of 5% or greater and incidence for Effexor XR at least twice that for placebo): **nausea (31% vs. 12%)**, dizziness (20% vs. 9%), somnolence (17% vs. 8%), abnormal ejaculation (16% vs. <1%), **sweating (14% vs. 3%)**, dry mouth (12% vs. 6%), nervousness (10% vs. 5%), anorexia (8% vs. 4%), abnormal **dreams (7% vs. 2%)**, and tremor (5% vs. 2%). In U.S. placebo-controlled depression trials, the following were also reported with an incidence of at least 5% and at least twice that for placebo: impotence, anorgasmia, **decreased libido, constipation, flatulence**, insomnia, nervousness, tremor, abnormal vision, hypertension, vasodilation, and yawning. The most commonly observed adverse events associated with the use of Effexor XR in placebo-controlled GAD **trials** (incidence of 5% or greater and incidence for Effexor XR at least twice that for placebo): nausea (43% vs. 11%), dry mouth (23% vs. 5%), insomnia (22% vs. 11%), abnormal ejaculation (17% vs. 0%), anorexia (13% vs. 2%), constipation (12% vs. 5%), nervousness (12% vs. 5%), sweating (11% vs. <1%), abnormal vision (8% vs. 0%), yawn (6% vs. <1%), impotence (6% vs. 1%), decreased libido (6% vs. 2%), vasodilation (6% vs. 2%), vomiting (6% vs. 2%).
Adverse Events Occurring at an Incidence of 2% or More Among Effexor XR-Treated Patients: The following occurred in short-term, placebo-controlled depression trials (up to 12 weeks) with doses of 75 to 225 mg/day, at a frequency of 2% or more and greater than placebo. **Body as a Whole:** asthenia. **Cardiovascular:** vasodilation, hypertension. **Digestive:** nausea, constipation, anorexia, vomiting, flatulence. **Metabolic/Nutritional:** weight loss. **Nervous System:** dizziness, somnolence, insomnia, dry mouth, nervousness, abnormal dreams, tremor, depression, paresthesia, decreased libido, agitation. **Respiratory System:** pharyngitis, yawn. **Skin:** sweating. **Special Senses:** abnormal vision. **Urogenital System:** abnormal ejaculation, impotence, anorgasmia (female). The following occurred in short-term, placebo-controlled GAD trials (up to 8 weeks), with doses of 75 to 225 mg/day, at a frequency of 2% or more and greater than placebo. **Body as a Whole:** asthenia, infection, abdominal pain, fever, neck pain, chills. **Cardiovascular:** vasodilation, tachycardia. **Digestive:** nausea, anorexia, diarrhea, constipation, vomiting, flatulence. **Musculoskeletal System:** myalgia. **Nervous System:** dry mouth, insomnia, dizziness, somnolence, nervousness, decreased libido, abnormal dreams, tremor, paresthesia, thinking abnormal, trismus, twitching. **Respiratory System:** rhinitis, yawn, cough increased. **Skin:** sweating. **Special Senses:** abnormal vision. **Urogenital System:** abnormal ejaculation, impotence, dysmenorrhea, orgasmic dysfunction (female), urinary frequency.
Vital Sign Changes: In clinical depression and GAD trials, Effexor XR was associated with a mean increase in pulse rate of about 2 beats/min. (See the **"Sustained Hypertension"** section of **"Warnings"** for effects on blood pressure.)
Laboratory Changes: In clinical depression and GAD trials, Effexor XR was associated with a mean increase in serum *cholesterol concentration of about 1.5 mg/dL and 2.5 mg/dL, respectively; clinical significance is unknown.*
ECG Changes: (See the *"Use in Patients With Concomitant Illnesses"* section of **"Precautions"**.)
OTHER EVENTS OBSERVED DURING THE PREMARKETING EVALUATION OF EFFEXOR AND EFFEXOR XR—During premarketing assessment, multiple doses of Effexor XR or Effexor were administered to 4174 patients, and the following adverse events were reported. Note: "frequent" = events occurring in at least 1/100 patients; "infrequent" = 1/100 to 1/1000 patients; "rare" = fewer than 1/1000 patients. It is important to emphasize that although the events occurred during treatment with venlafaxine, they were not necessarily caused by it.
Body as a whole - **Frequent:** chest pain substernal; **Infrequent:** face edema, intentional injury, malaise, moniliasis, neck rigidity, pelvic pain, photosensitivity reaction, suicide attempt; **Rare:** appendicitis, carcinoma, cellulitis, withdrawal syndrome. Cardiovascular system - **Frequent:** migraine, postural hypotension; **Infrequent:** angina pectoris, arrhythmia, extrasystoles, hypotension, peripheral vascular disorder (mainly cold feet and/or cold hands), syncope, thrombophlebitis; **Rare:** arteritis, first-degree atrioventricular block, bigeminy, bradycardia, bundle branch block, cerebral ischemia, coronary artery disease, congestive heart failure, heart arrest, mitral valve disorder, mucocutaneous hemorrhage, myocardial infarct, pallor. Digestive system - **Frequent:** eructation, increased appetite; **Infrequent:** bruxism, colitis, dysphagia, tongue edema, esophagitis, gastritis, gastroenteritis, gastrointestinal ulcer, gingivitis, glossitis, rectal *hemorrhage, hemorrhoids, melena, stomatitis, mouth ulceration*; **Rare:** *cheilitis, cholecystitis, cholelithiasis*, hematemesis, gastrointestinal hemorrhage, gum hemorrhage, hepatitis, ileitis, jaundice, intestinal obstruction, oral moniliasis, proctitis, increased salivation, soft stools, tongue discoloration. Endocrine system - **Rare:** goiter, hyperthyroidism, hypothyroidism, thyroid nodule, thyroiditis. Hemic and lymphatic system - **Frequent:** ecchymosis; **Infrequent:** anemia, leukocytosis, leukopenia, lymphadenopathy, thrombocythemia, thrombocytopenia; **Rare:** basophilia, cyanosis, eosinophilia, lymphocytosis. Metabolic and nutritional - **Frequent:** edema, weight gain; **Infrequent:** alkaline phosphatase increased, glycosuria, hypercholesteremia, hyperglycemia, hyperuricemia, hypoglycemia, hypokalemia, SGOT increased, thirst; **Rare:** alcohol intolerance, bilirubinemia, BUN increased, creatinine increased, diabetes mellitus, dehydration, gout, hemochromatosis, hypercalciuria, hyperkalemia, hyperlipemia, hyperphosphatemia, hyponatremia, hypophosphatemia, hypoproteinemia, SGPT increased, uremia. Musculoskeletal system - **Frequent:** arthralgia; **Infrequent:** arthritis, arthrosis, bone pain, bone spurs, bursitis, leg cramps, myasthenia, tenosynovitis; **Rare:** pathological fracture, myopathy, osteoporosis, osteosclerosis, rheumatoid arthritis, tendon rupture. Nervous system - **Frequent:** amnesia, confusion, depersonalization, emotional lability, hypesthesia, vertigo; **Infrequent:** apathy, ataxia, circumoral paresthesia, CNS stimulation, euphoria, hallucinations, hostility, hypereslhesia, hyperkinesia, hypotonia, incoordination, libido increased, manic reaction, myoclonus, neuralgia, neuropathy, paranoid reaction, psychosis, seizure, abnormal *speech, stupor*; **Rare:** *akathisia, aklnesia, alcohol abuse*, aphasia, bradykinesia, buccoglossal syndrome, *cerebrovascular accident*, loss of consciousness, delusions, dementia, dystonia, facial paralysis, abnormal gait, Guillain-Barré Syndrome, hypokinesia, neuritis, nystagmus, psychotic depression, reflexes decreased, reflexes increased, suicidal ideation, torticollis. Respiratory system - **Frequent:** dyspnea; **Infrequent:** asthma, chest congestion, epistaxis, hyperventilation, laryngismus, laryngitis, pneumonia, voice alteration; **Rare:** atelectasis, hemoptysis, hypoventilation, hypoxia, pleurisy, pulmonary embolus, sleep apnea. Skin and appendages - **Frequent:** rash, pruritus; **Infrequent:** acne, alopecia, brittle nails, contact dermatitis, dry skin, eczema, skin hypertrophy, maculopapular rash, psoriasis, urticaria; **Rare:** erythremia moclosum, exfoliative dermatitis, lichenoid dermatitis, hair discoloration, skin discoloration, furunculosis, hirsutism, leukoderma, pustular rash, vesiculobullous rash, seborrhea, skin atrophy, skin striae. Special senses - **Frequent:** abnormality of accommodation, mydriasis, taste perversion; **Infrequent:** cataract, conjunctivitis, corneal lesion, diplopia, dry eyes, exophthalmos, eye pain, hyperacusis, otitis media, parosmia, photophobia, taste loss, visual field defect; **Rare:** blepharitis, chromatopsia, conjunctival edema, deafness, glaucoma, retinal hemorrhage, subconjunctival hemorrhage, keratitis, labyrinthitis, miosis, papilledema, decreased pupillary reflex, otitis externa, scleritis, uveitis. Urogenital system - **Frequent:** metrorrhagia,* prostatitis,* urination impaired, vaginitis*; **Infrequent:** albuminuria, amenorrhea,* cystitis, dysuria, hematuria, female lactation,* leukorrhea,* menorrhagia,* nocturia, bladder pain, *breast pain, polyuria, pyuria, urinary incontinence, urinary retention, urinary urgency, vaginal hemorrhage*; **Rare:** abortion,* anuria, breast engorgement, breast enlargement, fibrocystic breast, calcium crystalluria, cervicitis,* ovarian cyst,* prolonged erection,* gynecomastia (male),* hypomenorrhea,* kidney calculus, kidney pain, kidney function abnormal, mastitis, menopause,* pyelonephritis, oliguria, salpingitis,* urolithiasis, uterine hemorrhage,* uterine spasm.* (*Based on the number of men and women as appropriate.)
Postmarketing Reports: Voluntary reports of other adverse events temporally associated with the use of Effexor (the immediate release form of venlafaxine) that have been received since market introduction and that may have no causal relationship with the use of Effexor include the following: agranulocytosis, anaphylaxis, aplastic anemia, catatonia, congenital anomalies, CPK increased, deep vein thrombophlebitis, delirium, EKG abnormalities (such as atrial fibrillation, supraventricular tachycardia, ventricular extrasystoles, ventricular tachycardia), epidermal necrosis/Stevens-Johnson Syndrome, erythema multiforme, extrapyramidal symptoms (including tardive dyskinesia), hemorrhage (including eye and gastrointestinal bleeding), hepatic events (including GGT elevation; abnormalities of unspecified liver function tests; liver damage, necrosis, or failure; and fatty liver), involuntary movements, LDH increased, neuroleptic malignant syndrome-like events (including a case of a 10-year-old who may have been taking methylphenidate, was treated and recovered), pancreatitis, panic, prolactin increased, renal failure, serotonin syndrome, shock-like electrical sensations (in some cases, subsequent to the discontinuation of Effexor or tapering of dose), and syndrome of inappropriate antidiuretic hormone secretion (usually in the elderly).
There have been reports of elevated clozapine levels that were temporally associated with adverse events, including seizures, following the addition of venlafaxine. There have been reports of increases in prothrombin time, partial thromboplastin time, or INR when venlafaxine was given to patients receiving warfarin therapy.
Drug Abuse and Dependence: Effexor® XR is not a controlled substance. Evaluate patients carefully for history of drug abuse and observe such patients closely for signs of venlafaxine misuse or abuse (e.g., development of tolerance, incrementation of dose, drug-seeking behavior).
OVERDOSAGE: In premarketing evaluation of Effexor XR for depression, there were 2 reports of acute overdosage (6 g of Effexor XR with 2.5 mg of lorazepam, and 2.85 g of Effexor XR). Both recovered without sequelae. In premarketing evaluation of Effexor, there were 14 reports of acute overdosage (highest dose was 6.75 g). All patients recovered without sequelae. Most patients reported no symptoms. Symptoms observed included somnolence, generalized convulsions, prolongation of QTc to 500 msec (compared with 405 msec at baseline) in one case, and mild sinus tachycardia. In premarketing evaluation of Effexor XR for GAD, there were 2 reports of acute overdosage (0.75 g of Effexor XR and 200 mg of paroxetine and 50 mg of zolpidem, and 1.2 g of Effexor XR). Both recovered without sequelae.
In postmarketing experience, there have been reports of fatalities in patients taking overdoses of venlafaxine, predominantly in combination with alcohol and/or other drugs.
Treatment should consist of those general measures employed in the management of overdosage with any antidepressant. Ensure an adequate airway, oxygenation and ventilation. Monitor cardiac rhythm and vital signs. 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. Due to *the large volume of distribution of this drug, forced diuresis, dialysis*, hemoperfusion, and exchange transfusion are unlikely to be of benefit. No specific antidotes for venlafaxine are known. 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).
SWITCHING PATIENTS TO OR FROM A MONOAMINE OXIDASE INHIBITOR: At least 14 days should elapse between discontinuation of an MAOI and initiation of therapy with Effexor XR. In addition, at least 7 days should be allowed after stopping Effexor XR before starting an MAOI (See **"Contraindications"** and **"Warnings"**).
Please consult full prescribing information for detailed dosing instructions.
This brief summary is based on the circular 4876-4, issued March 22, 1999.

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