Neuroscientific Approach to Emotions and Feelings: The Last Frontier of the New Millennium

Libido and Hormones
D. Canale and S. Pistoia

Psychobiology of Boredom
C. Maggini

Shame and Psychopathology
S. Pallanti and L. Quercioli

Emotions, Brain Development, and Psychopathologic Vulnerability
S. Galderisi and A. Mucci

Original Research
The Obsessive-Compulsive Spectrum: A Survey of 800 Practitioners
E. Hollander, R. Twersky, and C. Bienstock
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).
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.
ARICEPT® (Donepezil Hydrochloride Tablets)

Brief Summary – use package insert for full prescribing information. INDICATIONS AND USAGE ARICEPT® is indicated for the treatment of mild to moderate dementia of the Alzheimer type. CONTINUOUS use of ARICEPT® is contraindicated in patients with known hypersensitivity to donepezil hydrochloride or to pyridone derivatives. WARNINGS Anaphylaxis, Seizures, Hypersensitivity Reactions, Constipation, Increased Risk of Death, pneumonia, and Other Infections, Treatment with ARICEPT®, and in patients with nasal polyps. SYMPTOMATIC treatment with ARICEPT® has been reported in association with the use of ARICEPT®. Gastrointestinal: Conditions: In their presence, donepezil hydrochloride tablets may be more likely to cause increased gastric and duodenal ulceration due to the increased cholinergic activity. Therefore, patients should be monitored closely for signs of ulcer development. donepezil hydrochloride tablets are not indicated for the treatment of ulcer disease or gastrointestinal bleeding. ARICEPT®, as a predictable consequence of its pharmacological properties, has been shown to produce diarrhea and vomiting. These effects, when they occur, appear more frequently with the 10 mg/day dose than with the 5 mg/day dose and have been related to adverse effects having occurred during the titration period. The rates of common adverse events were lower than those seen in patients titrated to 10 mg/day over one week in controlled trials who received ARICEPT®, and the rates of occurrence were greater for ARICEPT® assigned thanPlacebo-treated patients. In regards to the highest dose of 10 mg/day, this population includes 650 patients treated for 3 months, 455 patients treated for 6 months and 116 patients treated over 1 year. The rate of patient exposure is not known. Effect of Other Drugs on the Metabolism of ARICEPT®: In vitro, human liver microsomal and human lung microsomal preparations were found to be susceptible to inhibition by donepezil hydrochloride. donepezil hydrochloride is not a substrate of the currently available human liver microsomal preparations. The frequency of adverse events seen in placebo patients, are shown in Table 1. There are no adequate and well-controlled trials to document the safety and efficacy of ARICEPT® in any illness occurring in children. ADVERSE REACTIONS Drug-Drug Interactions The rates of discontinuation from controlled clinical trials of ARICEPT® due to adverse events for the 2.5 mg, 5 mg and 10 mg treatment groups were comparable to those of placebo treatment groups at approximately 3.0%, 10% and 20%, respectively. 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 150 patients, are shown in Table 1. Table 1. Most Frequent Adverse Events Leading to Withdrawal from Controlled Clinical Trials by Dose Group

<table>
<thead>
<tr>
<th>Dose Group</th>
<th>Placebo</th>
<th>5 mg/day ARICEPT®</th>
<th>10 mg/day ARICEPT®</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients Randomized</td>
<td>355</td>
<td>350</td>
<td>315</td>
</tr>
<tr>
<td>Patients Discontinuing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>1%</td>
<td>1%</td>
<td>5%</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>1%</td>
<td>1%</td>
<td>3%</td>
</tr>
<tr>
<td>Nausea</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>5%</td>
<td>8%</td>
<td>8%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2%</td>
<td>5%</td>
<td>3%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>9%</td>
<td>7%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>6%</td>
<td>7%</td>
<td>6%</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2%</td>
<td>4%</td>
<td>3%</td>
</tr>
<tr>
<td>Pruritus</td>
<td>2%</td>
<td>5%</td>
<td>3%</td>
</tr>
</tbody>
</table>

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 predictable by ARICEPT®'s cholinomimetic effects. These include nausea, diarrhea, vomiting, urticaria, rash, conjunctivitis, muscle weakness, and fatigue. These adverse events were often of mild intensity and transiently 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 200 patients who received placebo in the 15- and 30-week studies. These patients were filated 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 nine weeks in the monophasic studies. The most common adverse event occurring in 5 patients. See Table 2 for a compilation of the most common adverse events following one and six week titration regimens.

Table 2. Comparison of Adverse Events in Patients Titrated to 5 mg/day and 10 mg/day ARICEPT®

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (n=355)</th>
<th>No titration (n=10)</th>
<th>One-week titration (n=50)</th>
<th>Six-week titration (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>5%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>5%</td>
<td>5%</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2%</td>
<td>2%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Headache</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
</tr>
<tr>
<td>Insomnia</td>
<td>3%</td>
<td>3%</td>
<td>4%</td>
<td>5%</td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Body System/Adverse Event</th>
<th>ARICEPT® (n=747)</th>
<th>Placebo (n=355)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Patients with any Adverse Event</td>
<td>74%</td>
<td>72%</td>
</tr>
<tr>
<td>Body as a Whole</td>
<td>14%</td>
<td>14%</td>
</tr>
<tr>
<td>Headache</td>
<td>10%</td>
<td>10%</td>
</tr>
<tr>
<td>Nausea</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Dizziness</td>
<td>10%</td>
<td>7%</td>
</tr>
<tr>
<td>Fatigue</td>
<td>6%</td>
<td>5%</td>
</tr>
<tr>
<td>Cardiovascular System</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Constipation</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Skin</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>General Disorders and Administration Site Conditions</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Urogenital System</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Weight Decrease</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Musculoskeletal System</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>Muscle Cramps</td>
<td>2%</td>
<td>1%</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Sleep Disorders</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>Other Adverse Events</td>
<td>3%</td>
<td>3%</td>
</tr>
</tbody>
</table>

NOTICE: THIS DOCUMENT IS AN EXTRACT FROM THE PACKAGE INSERT FOR ARICEPT®. It is not a substitute for the complete information contained in the full prescribing information. For the most recent prescribing information, go to the U.S. Pharmaceuticals: http://www Eisai.com/Pharmaceuticals/ARICEPT for the U.S. version of the Package Insert. Revised September 1999.
**DISROBING LIBIDO**

"After this organizational and inductive role of androgens at puberty, their influence on sexual activity decreases with age. Sexuality becomes more mature, intellectual, more mind-induced, and less hormonally driven. Nevertheless, some aspects of sexuality remain linked to hormones. A reduction of central arousability—the neurophysiologic substrate of sexual desire and spontaneous nocturnal erections—is typical of the hypogonadal state. Davidson et al have clearly shown that libido, the number of coital attempts, and spontaneous erections are strictly correlated to the dose of androgens administered in hypogonadal men. Ansong and Punwaney showed that in men with erectile dysfunction, sexual drive was partially related to levels of circulating testosterone. It is still not clear, however, at what level of androgen deficiency the loss of libido begins. Clinical experience and the available scientific experience suggest that a personal susceptibility exists and that, in some cases, other central inducers can overcome the role of androgens. Even in ancient times, some castrated men were said to have sexual activity. Moreover, patients with a history of prostate carcinoma who take drugs, such as gonadotropin-releasing hormone analogues, that lower plasma testosterone to undetectable levels still show sexual interest even in the absence of erectile function. Among other androgens, dehydroepiandrosterone (DHEA) has recently attracted the attention of scientists and even mass media. A recent double-blind pilot study on men infected with the human immunodeficiency virus showed that DHEA treatment had a positive effect on libido, mood, and body mass, regardless of baseline serum DHEA level."

**THE COMPLEXITY OF BOREDOM**

"The study of the pharmacology of opiates has led to stimulating findings on the biology of boredom. These substances exert a reward effect through the stimulation of dopaminergic neurons of the ventral tegmental area (mainly the A10 group) mediated by \( \mu \) and \( \Delta \) receptors. Several studies have reported relationships between opiate dependence and chronic feelings of boredom. According to Zuckerman's model, low levels of endogenous opiates in high sensation seekers may explain why they are more prone to heroin and cocaine use, as demonstrated by negative correlations between boredom susceptibility subscale scores and endorphin levels. The negative correlations among endorphin levels, sensation seeking, and average evoked potential augmentation and the positive correlations between endorphin levels and average evoked potential reduction strengthen the hypothesis that endogenous opiates may have a protective effect against an excessive stimulation, causing a behavioral depression. Average evoked potential reduction is, in fact, involved in the defensive function from overstimulation. According to Sicueteri, the endogenous opiates also may work as a euphoriant mechanism activated by emotional factors and exciting external situations (eg, job, sex, sports, etc). When the subject gives up the pleasant activity, boredom may appear with its related phenomena, such as yawns, restlessness, autonomic disturbances, and headache—a state that resembles a mild opiate withdrawal syndrome."

**THE PSYCHOLOGY OF SHAME**

"The early recognition of innate factors gives rise to the hypothesis of the existence of some kind of innate central hardware involved in shame. Malin has hypothesized that a hard-wired pathway exists for nine basic affects: 'The positive affects of interest-excitement and enjoyment-joy, the neutral affect of surprise-startle, the negative affects of fear-terror, distinct-anguish, and anger-rage, as well as the negative affect auxiliaries of dismissal, disgust, and shame-humiliation.' The subjective experience of these affective states is not simply the result of the activation of these pathways. When analyzed in these terms, shame-humiliation is an innate reaction that functions primarily to reduce facial communication. It includes lowering the eyes and head, as well as blushing. In contrast, shame is a subjective experience that develops as other components render innate physical sensations of the affect meaningful. Malin prefers to change the first definition into inhibition-withdrawal to describe the innate response, and reserves the term emotion for describing the experience of shame."

**THE ATTACHMENT RELATIONSHIP: EMOTIONAL SHAPING OF THE BRAIN**

"A poor attachment relationship might create an unbalanced right/left hemisphere development, which in turn might play an important role in vulnerability to psychopathology. Hemispheric organization abnormalities have been found in several psychiatric disorders, such as schizophrenia, mania, and autism, as well as in individuals at risk for psychiatric disorders. Abnormalities of dopamine levels in the right hemisphere have been found in association with altered emotionality soon after birth following prenatal stress. Electrophysiologic data have shown abnormal right-frontal activation in 10-month-old infants with high levels of distress to maternal separation. In both infants and adults, this asymmetry is associated with vulnerability to psychopathology. A right hemisphere dysfunction has been reported in children with nonverbal learning disabilities and with a developmental right-hemisphere syndrome involving maladaptation to new situations, difficulties in relationships with peers, and extreme shyness. It has been found that an underactivation of the right and/or hyperactivation of the left brain is associated with a high degree of physical health complaints, alexithymia, and panic disorder."
Antidiuretic hormone secretion (SIADH) have been reported, usually in the elderly. The concomitant use of venlafaxine with a drug that potentially inhibits both CYP2D6 and CYP3A4, the concentrations of venlafaxine and decrease concentrations of ODV. However, since the composite plasma levels of smallest quantity of capsules consistent with good patient management to reduce the risk of overdose. The same pre-

Brief Summary

Postmarketing Spontaneous Drug Interaction Reports: See “ADVERSE REACTIONS.” Postmarketing Reports: See “ADVERSE REACTIONS.” Pharmacokinetics: See “PHARMACOKINETICS.” Nitrofurantoin (150 mg) decreased total oral-clearance (CLp) of haloperidol which resulted in a 45% decrease in Cmax. ODV increased 88% when coadministered with venlafaxine, but the haloperidol elimination half-life was unchanged.

Warnings

In clinical depression and GAD trials, Effexor XR was associated with a mean increase in pulse rate of 4 beats/min and increases in systolic and diastolic blood pressure of approximately 5 mm Hg. In short-term depression studies, 12% were 65 years of age or over. No overall differences in effectiveness or safety were noted between these two age groups. However, increased sensitivity of older individuals cannot be ruled out. As with other antidepressants, some cases of hypotension and syncope of antidepressants have been reported. During treatment with venlafaxine, they were not necessarily caused by it.

Carcinogenesis

Digestive:

Other Events Observed During the Premarking Evaluation of Effexor and Effexor XR—During pre-

Other Adverse Events Observed During Premarking Evaluation of Effexor XR—During pre-

Metabolic/Nutritional:

Digestive:

Psychomotor, cognitive, or complex behavior performance. However, caution patients about operating hazardous

Digestive:

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.¹²

Need proof? Call 1-888-EFFEXOR XR.

Visit us at www.EFFEXORXR.com

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

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.

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INDICES
70 By subject and author
In two 6- to 8-week placebo-controlled clinical 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.

EPS with RISPERDAL, while dose-dependent, are comparable to placebo at doses ≤6 mg/day and differ significantly from placebo at doses >6 mg/day. Prescribing should be consistent with the need to minimize the risk of tardive dyskinesia; if its signs and symptoms appear, discontinuation of RISPERDAL should be considered.

Orthostatic hypotension was reported infrequently (<1%) in clinical trials; its risk may be minimized by following the recommended RISPERDAL dose titration regimen.

Reference:
1. IMS America, 12/99.

Please see brief summary of Prescribing Information on adjacent page.

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The #1 prescribed antipsychotic

01-RS-708 July 2000
Drugs that Inhibit Cytochrome P450 and Other Enzymes: Risperidone is metabolized to 9-hydroxyrisperidone by cytochrome P450 (CYP3A4), an enzyme that is polymorphically expressed in the population and that can be inhibited by a variety of psychotropic and other drugs (See CLINICAL PHARMACOLOGY). Drug interactions that result in increased plasma concentrations of 9-hydroxyrisperidone would increase the plasma concentrations of risperidone and lower the concentrations of 9-hydroxyrisperidone. Analysis of clinical studies involving a number of antidepressants and antipsychotics suggests that patients taking one or both agents may have increased plasma concentrations of 9-hydroxyrisperidone and other metabolites. It is not known whether patients who take cytochrome P450 inhibitors will have a relative increase in the plasma concentration of 9-hydroxyrisperidone. Therefore, caution is advisable when administering risperidone to patients known to be taking these agents. In vitro studies showed that drugs metabolized by other P450 isozymes, including CYP1A2, 2C9, 2C19, and 2D6, may be weak inhibitors of risperidone metabolism. Drug Metabolism and Pharmacokinetics: Risperidone is extensively metabolized to a variety of metabolites that are modified by this enzymatic pathway. However, clinical data to confirm this expectation are not available.

Drug Interactions: The potential for drug interactions with RISPERDAL* is limited. Caution is advisable in using RISPERDAL* in patients with diseases or conditions that may alter hepatic or renal function, care should be taken in dose selection, and it may be useful to monitor clinical response. In vitro studies indicate that RISPERDAL* is a relatively weak inhibitor of cytochrome P450. Therefore, care should be taken when RISPERDAL* is administered in combination with other agents that are metabolized by this pathway. These interactions may be drug specific and may not be observed with all drugs that prolong QT, or the presence of concomitant proarrhythmic conditions that may increase the proarrhythmic potential of this antiarrhythmic.

PREGNANCY

General

Oral Hypothyroidism: RISPERDAL* (risperidone) may induce oral hypothyroidism associated with dizziness, tachycardia, and, in some patients, prominent signs of hypothyroidism in the form of weight gain and lid edema. Recovery occurs upon withdrawal of the drug. The dose of thyroid hormone may need to be increased in patients receiving RISPERDAL* as the dose is increased. Appropriate monitoring of TSH and thyroid-stimulating hormone levels should be performed when RISPERDAL* is administered to patients with certain concomitant systemic illnesses.

Diabetes Mellitus: Patients with diabetes mellitus may experience changes in glucose intolerance during treatment with RISPERDAL*. Therefore, careful individual assessment and management of diabetes mellitus in patients with pre-existing diabetes is recommended. Serum glucose concentrations should be monitored in all patients receiving RISPERDAL*.

Drug Interactions: The potential for drug interactions with RISPERDAL* is limited. Caution is advisable in using RISPERDAL* in patients with diseases or conditions that may alter hepatic or renal function. In some cases, serum glucose levels may increase or become unstable in patients receiving RISPERDAL*. This change should be closely monitored and appropriate intervention, including dosage adjustments, should be performed.

Drug Interactions: The potential for drug interactions with RISPERDAL* is limited. Caution is advisable in using RISPERDAL* in patients with diseases or conditions that may alter hepatic or renal function. In some cases, serum glucose levels may increase or become unstable in patients receiving RISPERDAL*. This change should be closely monitored and appropriate intervention, including dosage adjustments, should be performed.