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

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

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

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

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

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

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

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

Finally, I want to remind our readers that CNS Spectrums is now accepting letters to the editor. Please send them in!
A different path to success in your continuing treatment of schizophrenia

ABILIFY (aripiprazole)

DISCOVER PROVEN EFFICACY, TOLERABILITY, AND SAFETY FOR THE ROAD AHEAD

FROM BRISTOL-MYERS SQUIBB COMPANY AND OTSUKA AMERICA PHARMACEUTICAL, INC.
Unique Pharmacology Sets Abilify Apart

Abilify is a partial agonist that uniquely modulates dopamine activity.\textsuperscript{1,2}

- Functional \textit{antagonist} activity at D\textsubscript{2} receptors in a \textit{hyperdopaminergic} environment\textsuperscript{1}

- Functional \textit{agonist} activity at D\textsubscript{2} receptors in a \textit{hypodopaminergic} environment\textsuperscript{1}

Serotonin \textit{antagonist} activity at 5-HT\textsubscript{2A} receptors and \textit{partial agonist} activity at 5-HT\textsubscript{1A} receptors

Abilify has \textit{moderate affinity} for alpha\textsubscript{1}-adrenergic and histamine (H\textsubscript{1}) receptors

Abilify has \textit{no appreciable affinity} for cholinergic muscarinic receptors

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

Abilify is indicated for the treatment of schizophrenia.

Please see Brief Summary of Prescribing Information on last page of this insert.
Effect of Abilify on weight, long term

A prospective 52-week, double-blind trial. For Abilify, BMI <23 (n=314); BMI 23 to 27 (n=265); and BMI >27 (n=260).
The percentage of patients with ≥7% increase in body weight was 30% for those with BMI <23, 19% for those with BMI 23 to 27,
and 8% for those with BMI >27.
†Last observation carried forward.

Because patients’ overall health is important

Abilify is comparable to placebo on§3:

- Glucose
- HDL
- LDL
- Triglycerides

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

Please see Brief Summary of Prescribing Information on last page of this insert.
Few patients discontinue due to adverse events with Abilify

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

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

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

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

- Significant improvement as early as Week 1

![Graph showing PANSS Total Score over time](image)

Abilify 15 mg (n=202), 20 mg (n=195), 30 mg (n=196), and placebo (n=312). Analysis included data from all fixed-dose trials.

*Last observation carried forward.

†P<0.05 vs placebo.

‡P<0.01 vs placebo.

In efficacy studies, 88% of responders did not experience sedation

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

**Abilify** (aripiprazole)
A course with few detours

Tolerability and Safety for the Road Ahead

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

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

In a 52-week study, the percentage of patients with ≥7% increase in body weight was 30% for those with BMI (Body Mass Index [kg/m²]) <23, 19% for those with BMI 23 to 27, and 8% for those with BMI >27.

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

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

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

Visit www.abilify.com
Please see Brief Summary of Prescribing Information on last page of this insert.

References:

Marketed by Otsuka America Pharmaceutical, Inc., Rockville, MD 20850 USA and Bristol-Myers Squibb Co., Princeton, NJ 08543 USA.
Manufactured by Otsuka Pharmaceutical Co., Ltd., Tokyo, 101-8535 Japan.
Distributed by Bristol-Myers Squibb Co., Princeton, NJ 08543.
U.S. Patent Nos. 4,734,416 and 5,006,528.

©2003, Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan
D6-K0047 A423205-03 June 2003 Printed in USA Printed on recycled paper.
The only adverse event to have a possible dose response relationship, and then most prominent only with 30 mg, was dizziness. Some patients had dizziness with placebo or no treatment. The incidence of dizziness was significantly lower in patients with Schizophrenia (13% of patients), than in healthy volunteers (29% of patients). Aripiprazole in short-term placebo-controlled trials revealed a significantly lower incidence of dizziness compared to placebo in patients with Schizophrenia (13% of patients), than in healthy volunteers (29% of patients). Aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in vital signs or laboratory tests at baseline were similar except in the treatment of patients with Nightmares in the elderly. Discontinuation of Aripiprazole in the double-blind phase of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study. Nonserotonergic antidepressants and other antipsychotics have been associated with rare cases of hyponatremia and SIADH in elderly patients. In particular those with advanced Alzheimer’s disease. Aripiprazole is not an anticholinergic agent and therefore is not expected to aggravate or cause anticholinergic side effects as a result of anticholinergic drug administration. The incidence of dizziness was significantly lower in patients with Schizophrenia (13% of patients), than in healthy volunteers (29% of patients). Aripiprazole in short-term placebo-controlled trials revealed a significantly lower incidence of dizziness compared to placebo in patients with Schizophrenia (13% of patients), than in healthy volunteers (29% of patients). Aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in vital signs or laboratory tests at baseline were similar except in the treatment of patients with Nightmares in the elderly. Discontinuation of Aripiprazole in the double-blind phase of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study. Nonserotonergic antidepressants and other antipsychotics have been associated with rare cases of hyponatremia and SIADH in elderly patients. In particular those with advanced Alzheimer’s disease. Aripiprazole is not an anticholinergic agent and therefore is not expected to aggravate or cause anticholinergic side effects as a result of anticholinergic drug administration. The incidence of dizziness was significantly lower in patients with Schizophrenia (13% of patients), than in healthy volunteers (29% of patients). Aripiprazole in short-term placebo-controlled trials revealed a significantly lower incidence of dizziness compared to placebo in patients with Schizophrenia (13% of patients), than in healthy volunteers (29% of patients). Aripiprazole and placebo in the proportions of patients experiencing potentially clinically significant changes in vital signs or laboratory tests at baseline were similar except in the treatment of patients with Nightmares in the elderly. Discontinuation of Aripiprazole in the double-blind phase of the study (causes of death were pneumonia, heart failure, and shock). The fourth patient (age 78 years) died following hip surgery while in the double-blind portion of the study.