Pain Medicine

Antidepressant Better Than Bulking Agent in IBS

BY TIMOTHY F. KIRN

Sacramento Bureau

SAN FRANCISCO — An antidepressant often is better than a high-fiber bulking agent as first-line treatment for irritable bowel syndrome, at least for the diarrheapredominant form of the disorder, Philip S. Schoenfeld, M.D., said at the annual meeting of the American College of Physicians.

Results from 14 well-designed clinical tri-

als of the use of bulking agents for irritable bowel syndrome (IBS) "consistently show ... that they are no better than placebo," said Dr. Schoenfeld, chief of the division of gastroenterology at the Ann Arbor (Mich.) Veterans Affairs Medical Center.

Worse, bulking agents usually cause uncomfortable bloating. In one study of psyllium (Metamucil), placebo patients actually did better than treated patients, said Dr. Schoenfeld, who was a member of the American College of Gastroenterology's task force that reviewed treatment evidence in 2002.

The only time to try a bulking agent is with a patient with constipation-predominant IBS who does not normally have bloating discomfort with the constipation,

Tricyclic antidepressants, on the other hand, are good agents for pain control. Several studies have shown that tricyclics reduce abdominal pain. The most recent study-which met the criteria for good study design spelled out by the International Congress of Gastroenterology's Rome guidelines—showed a significant reduction of symptoms, Dr. Schoenfeld said.

The study used low-dose desipramine, which Dr. Schoenfeld said he prefers to use first. He uses it in patients with diarrheapredominant IBS because tricyclics can cause constipation.

About one-quarter of patients don't tolerate tricyclic therapy; they can be switched to a selective serotonin-reuptake inhibitor (SSRI), with advice to use loperamide as needed.

Of the three well-designed trials that have tested the use of an SSRI, one showed significant symptom improvement, one showed a trend to improvement, and one showed decreased health care utilization, he said.

Although IBS has been called a diagnosis of exclusion, in practice it does not re-

Tricyclic antidepressants are good agents for pain control. The most recent study showed a significant reduction in symptoms of abdominal pain. ally need to be. That approach leads to a lot of expensive tests-40% of IBS patients, for example, get endoscopy at the time of initial diagnosis, Dr. Schoenfeld said.

In the absence of specific danger signs, such as fecal

blood, the incidence of other serious conditions in patients with IBS-like symptoms is generally about the same as in the general population (less than 1%). The exception is celiac sprue, which occurs about 10 times more often in patients with diarrhea-predominant IBS-like symptoms than it does in the general population.

Dr. Schoenfeld said that he prefers to test for serum celiac sprue using the tissue transglutaminase antibody test, because its sensitivity is almost 100%. There are false positives, but a negative test rules out the

In clinical trials, tegaserod maleate (Zelnorm) was effective in about 40% of patients. Yet about 30% of placebo patients had improvement, as they often do in IBS trials, so the absolute difference was only about 10%.

Tegaserod is worth a try in constipationpredominant, female patients; when it works, symptoms improve rapidly. But Dr. Schoenfeld does not continue a trial for very long because the drug is expensive. "It's not a miracle drug, and if they haven't improved in about a month they are unlikely to improve," he said.

He usually stops the drug after 8 weeks, as specified on the product label. IBS patients generally have flares and quiescent periods, and studies have shown the average flare lasts 6-8 weeks. Moreover, evidence indicates that response to the drug, when reinitiated, is exactly the same as the initial response.

Novartis Pharmaceuticals Corp., the maker of Zelnorm.

References: I. Ambrosini PJ. Lopez FA, Chandler MC, et al. An open-label community assessment of ADDERALL XR in pediatric ADHD. Poster presented at: 155th Annual Meeting of the American Psychiatric Association; May 22, 2002: Philadelphia, Pa. 2. Data on file, Shire US Inc., 2005. 3. Biederman J. Lopez FA, Boellner SW, Chandler MC. A randomized, double-blind, placebo-controlled, parallel-group study of SLI3BI (AdDERALL XR), in children with attention-deficit/hyperactivity disorder. Pediatrics. 2002; IDD Jam Acad Child Adders Association; May 22, 2002: Philadelphia, Pa. 2. Data on file, Shire US Inc., 2005. 3. Biederman J. Lopez FA, Boellner SW, Chandler MC, A randomized, double-blind, placebo-controlled, parallel-group study of SLI3BI (ADDERALL XR) in children with a Delta Child Adders Association; Annotani PJ. Chandler MC, et al. ADDERALL XR) in pediatric ADHD: quality of life measures from an open-label community assessment trial. Poster presented at: 14th Annual CHADD International Conference, October 17, 2002; Mlami Beach, Fla.

REF SUMMARY: Consult the full prescribing information for complete product information.

**ADDERALL XR: on pediatric ADHD: quality of life measures from an open-label community assessment of a once-daily mixed Parallel Annual CHADD International Conference, October 17, 2002; Mlami Beach, Fla.

***ADDERALL XR: on pediatric ADHD: Poster presented at: 155th Annual Meeting of the American Psychiatric Association; May 22, 2002; Plandler MC. A randomized, double-blind, placebo-controlled, parallel-group study of SLI3BI (ADDERALL XR) in children with Annual CHADD International Conference, October 17, 2002; Mlami Beach, Fla.

***ADDERALL XR: on pediatric ADHD: Parallel Annual CHADD International Conference, October 17, 2002; Mlami Beach, Fla.

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**ADRABLA XR:

MISUSE OF AMPHETAMINE MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

WARNINGS

Psychosis: Clinical experience suggests that, in psychotic patients, administration of amphetamine may exacerbate symptoms of behavior disturbance and thought disorder.

Long-Term Suppression of Growth: Data are inadequate to determine whether chronic use of stimulants in children, including amphetamine, may be causally asso-ciated with suppression of growth. Therefore, growth should be monitored during treatment, and patients who are not growing or gaining weight as expected should have their treatment interrupted.

Sudden Death and Pre-existing Structural Cardiac Abnormalities: Sudden death has been reported in association with amphetamine treatment at usual doses in children with structural cardiac abnormalities. Adderall XR® generally should not be used in children or adults with structural cardiac abnormalities.

PRECAUTIONS

Ties: Amphetamines have been reported to exacerbate motor and phonic ties and Tourette's syndrome. Therefore, clinical evaluation for ties and Tourette's syndrome in children and their families should precede use of stimulant medications.

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 (quasterlinding, reserpine, glutamic acid HCI, ascorbic acid, etc.) lower absorption of amphetamines. Uninary acidifying agents—These agents (ammonium chiorides, 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. Advantage and activation of Aborea-Adrenergic blockers—Adrenergic blockers are inhibited by amphetamines. Advantaging agents—Gastrointestinal alkalinizing agents (sodium bicarbonate, etc.) increase absorption of amphetamines. Co-administration of Aborea-Adrenergic blockers are inhibited by amphetamines. Advantaging 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. Antilepressants. tricyclic—Amphetamines may enhance the activity of tricyclic antidepressants or sympathorimetic agents; ca-amphetamine with designamine 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. AMO 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 fo

Amphetamines may delay intestinal absorption of phenytoin; co-administration of phenytoin may produce a synergistic anticonvulsant action. *Proposyphene*—Incases of proposyphene overdosage, amphetamine CNS stimulation is potentiated and statal convulsions can occur. *Veratrum alkaloids*—Amphetamines mihibit the hypotensive effect of veratrum alkaloids.

Drug/Laboratory Test Interactions: Amphetamines can cause a significant elevation in plasma corticosteroid levels. This increase is greates in the evening. Amphetamines may interfere with urinary steroid determinations. Carcinogenesis/Mutagenesis and Impairment of Fertility: No evidence of carcinogenicity was found in studies in which of J-amphetamine (enaminer ratio of 1-1) was administered to moic and ratis in the elief to 2 years at doses of up to 30 mg/kg/day in male mice. 19 mg/kg/day in female mice, and 5 mg/kg/day in male and female rats. These doses are approximately 24. 1-5, and 0.8 times, respectively, the maximum recommended human dose of 30 mg/day (child) on a mg/m² body surface area basis.

Amphetamine, in the enantiomer ratio present in ADDERALL® (immediate-release)(d- to 1- ratio of 3-1), was not clastogenic in the mouse bone marrow micronucleus test *in vivo* and was negative when tested in the *E. coli* component of the Ames test in vivor. all Amphetamine (1-1) manimomer ratio) has been reported to produce a positive response in the mouse bone marrow micronucleus test. *in vivo* and was negative when tested in the *E. coli* component of the Ames test in vivor. all Amphetamine, 1-1 manimomer ratio present in ADDERALL® (immediate-release) (d- to 1- ratio of 3-1), did not adversely affect fertility or early rester to the ratio or activersely affect fertility or early rester to the proposition of the propos

% of pediatric patients discontinuing (n=595)

Adverse events

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Body System	Preferred Term	ADDERALL XR® (n=374)	Placebo (n=210)
General	Abdominal Pain (stomachache)	14%	10%
	Accidental Injury	3%	2%
	Asthenia (fatique)	2%	0%
	Fever	5%	2%
	Infection	4%	2%
	Viral Infection	2%	0%
Diaestive	Loss of Appetite	22%	2%
System	Diarrhea	2%	1%
	Dyspepsia	2%	1%
	Nausea	5%	3%
	Vomiting	7%	4%
Nervous System	Dizziness	2%	0%
	Emotional Lability	9%	2%
	Insomnia	17%	2%
	Nervousness	6%	2%

Table 2 Adverse Events Reported by 5% or More of Adults Receiving ADDERALL XR® with Higher Incide Than on Placebo in a 255 Patient Clinical Except Weekly Receiving ADDERALL XR® with Higher Incide

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Body System	Preferred Term	ADDERALL XR® (n=191)	Placebo (n=64)	
General	Asthenia	6%	5%	
	Headache	26%	13%	
Digestive System	Loss of Appetite	33%	3%	
	Diarrhea	6%	0%	
	Dry Mouth	35%	5%	
	Nausea	8%	3%	
Nervous System	Agitation	8%	5%	
•	Anxiety	8%	5%	
	Dizziness	7%	0%	
	Insomnia	27%	13%	
Cardiovascular System	Tachycardia	6%	3%	
Metabolic/Nutritional	Weight Loss	11%	0%	
Urogenital System	Urinary Tract Infection	5%	0%	

Dr. Schoenfeld has a consultantship with