

New Tools Developed for End-of-Life Issues

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PHILADELPHIA — Two new ways of dealing with end-of-life issues—default surrogates and physician-ordered life-sustaining treatment orders—are becoming more common in hospitals, according to several legal experts.

So far, 37 states have passed default surrogate regulations, aimed at naming a person who can act on behalf of an incapacitated

hospital patient who does not have an advance directive, said Nina Kohn of Syracuse (N.Y.) University's College of Law. The vast majority of Americans—especially minorities, those with lower education levels, and younger patients—do not have an advance directive, noted Ms. Kohn, who spoke at a meeting of the American Society of Law, Medicine, and Ethics.

The states that have passed the default surrogate statutes “create a priority list saying if there is not an appointed surro-

gate, first the spouse does it, then the parent, then an adult sibling, and so on,” she explained. “The common justification is the idea that the statutes help protect wishes of the incapacitated person.”

But does that really work? Ms. Kohn and her associate Jeremy Blumenthal, also of Syracuse University, have been studying whether the laws result in the selection of the surrogates that incapacitated patients would have selected for themselves, and whether those surrogates made the deci-

sions that those patients would have made.

They found that Americans tend to favor close family members as surrogates, which is consistent with most of the state laws. On the other hand, said Ms. Kohn, “The priority lists don't account for a number of factors predictive of surrogate selection, such as surrogate gender. Women are disproportionately selected as surrogates.” In addition, the statutes “don't do a good job of accounting for nontraditional family structures such as same-sex couples, or [situations] where people have more inclusive or more intergenerational notions of families.” This is particularly true of African Americans, who are less likely than are members of other racial groups to select a spouse or adult child as a surrogate, according to studies, she said.

As to whether the surrogates are deciding things the same way the patients would have, “we can't know for sure ... because the patient is incapacitated,” she said. “But I think we can confidently say that there's real reason to be skeptical about the congruence levels being obtained.”

The literature on the subject shows that surrogates are very bad at predicting patient wishes; in addition, surrogates are not always willing to do what they know the patients would want them to do, Ms. Kohn continued.

Ms. Kohn had two suggestions for improving decision making by surrogates: First, move away from selecting surrogates based on familial relations and toward surrogates whose values are more consistent with those of the patient. And second, provide surrogates with information to better inform their decisions—for example, what a typical patient would do in a particular situation.

Another emerging tool for hospital-based end-of-life care is the physician orders for life-sustaining treatment (POLST) form, said Robert Schwartz, J.D., professor of law at the University of New Mexico, Albuquerque. These orders also go by other names: medical orders on life-sustaining treatment, medical orders on scope of treatment, or physician orders on scope of treatment.

“This is the next step from the advance directive,” he explained. “These are physician orders that go in the patient's chart and provide information about the kind of patient care that should be provided.”

Usually, a POLST form addresses resuscitation issues, the extent of appropriate medical intervention, use of antibiotics, provision of nutrition and hydration, desired place of treatment, and the identity of the authorized health care provider, Mr. Schwartz said. The forms all have a place for the physician's signature, and many have a place for the patient's or surrogate decision maker's signature.

He has some reservations about the concept. “My problem with all these documents is that it seems like it's a step backwards [because] doctors are deciding these things in the hospital [rather than] patients having the authority to make these decisions. On the other hand, if patients make these decisions and they're never honored, we haven't achieved a whole lot.”

Vyvanse™ (lisdexamfetamine dimesylate)

CII Rx Only

BRIEF SUMMARY: Consult the Full Prescribing Information for complete product information.

WARNING: POTENTIAL FOR ABUSE

AMPHETAMINES HAVE A HIGH POTENTIAL FOR ABUSE. ADMINISTRATION OF AMPHETAMINES FOR PROLONGED PERIODS OF TIME MAY LEAD TO DRUG DEPENDENCE. 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. MISUSE OF AMPHETAMINES MAY CAUSE SUDDEN DEATH AND SERIOUS CARDIOVASCULAR ADVERSE EVENTS.

INDICATIONS AND USAGE

Vyvanse™ is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). The efficacy of Vyvanse in the treatment of ADHD was established on the basis of two controlled trials in children aged 6 to 12 and one controlled trial in adults who met DSM-IV-TR criteria for ADHD.

Special Diagnostic Considerations

Specific etiology of this syndrome is unknown, and there is no single diagnostic test. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

Need for Comprehensive Treatment Program

Vyvanse is indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social) for patients with this syndrome.

Long-Term Use

The effectiveness of Vyvanse for long-term use, i.e., for more than 4 weeks, has not been systematically evaluated in controlled trials. Therefore, the physician who elects to use Vyvanse for extended periods should periodically re-evaluate the long-term usefulness of the drug for the individual patient.

CONTRAINDICATIONS

Advanced arteriosclerosis, symptomatic cardiovascular disease, moderate to severe hypertension, hyperthyroidism, known hypersensitivity or idiosyncratic reaction to 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 AND PRECAUTIONS

Serious Cardiovascular Events

Sudden Death and Pre-existing Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents

Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Adults

Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and Other Cardiovascular Conditions

Stimulant medications cause a modest increase in average blood pressure (about 2-4 mm Hg) and average heart rate (about 3-6 bpm) and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with pre-existing hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients Being Treated with Stimulant Medications

Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Psychiatric Adverse Events

Pre-existing Psychosis

Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a pre-existing psychotic disorder.

Bipolar Illness

Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder. Such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder and depression.

Emergence of New Psychotic or Manic Symptoms

Treatment-emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in children and adolescents without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) or stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression

Aggressive behavior or hostility is often observed in children and adolescents with ADHD, and has been reported in clinical trials and the post marketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment of ADHD should be monitored for the appearance of, or worsening of, aggressive behavior or hostility.

Seizures

There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

Visual Disturbance

Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

Tics

Amphetamines have been reported to exacerbate motor and phonic tics and Tourette's syndrome. Therefore, clinical evaluation for tics and Tourette's syndrome should precede use of stimulant medications.

Long-Term Suppression of Growth

Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. In a controlled trial of amphetamine (d- to l-enantiomer ratio of 3:1) in adolescents, mean weight change from baseline within the initial 4 weeks of therapy was -1.1 lbs. and -2.8 lbs., respectively, for patients receiving 10 mg and 20 mg of amphetamine. Higher doses were associated with greater weight loss within the initial 4 weeks of treatment. In a controlled trial of Vyvanse in children ages 6 to 12 years, mean weight loss from baseline after 4 weeks of therapy was -0.9, -1.9, and -2.5 lb, respectively, for patients receiving 30 mg, 50 mg, and 70 mg of Vyvanse, compared to a 1 lb weight gain for patients receiving placebo. Higher doses were associated with greater weight loss with 4 weeks of treatment. Careful follow-up for weight in children ages 6 to 12 years who received Vyvanse over 12 months suggests that consistently medicated children (i.e. treatment for 7 days per week throughout the year) have a slowing in growth rate, measured by body weight as demonstrated by an age- and sex-normalized mean change from baseline in percentile, of -13.4 over 1 year (average percentile at baseline and 12 months, were 60.6 and 47.2, respectively). Therefore growth should be monitored during treatment with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.

Prescribing and Dispensing

The least amount of amphetamine feasible should be prescribed or dispensed at one time in order to minimize the possibility of overdosage. Vyvanse should be used with caution in patients who use other sympathomimetic drugs.

ADVERSE REACTIONS

Clinical Studies Experience

The premarketing development program for Vyvanse included exposures in a total of 762 participants in clinical trials (348 pediatric patients, 358 adult patients and 56 healthy adult subjects). The information included in this section is based on data from the 4-week parallel-group controlled clinical studies in pediatric and adult patients with ADHD.

Adverse Reactions Associated with Discontinuation of Treatment in Clinical Trials

In the controlled pediatric (aged 6 to 12) trial, 10% (21/218) of Vyvanse-treated patients discontinued due to adverse reactions compared to 1% (1/72) who received placebo. The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e. leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were ECG voltage criteria for ventricular hypertrophy, tic, vomiting, psychomotor hyperactivity, insomnia, and rash (2/218 each; 1%). In the controlled adult trial, 6% (21/358) of Vyvanse-treated patients discontinued due to adverse events compared to 2% (1/62) who received placebo. The most frequent adverse events leading to discontinuation and considered to be drug-related (i.e. leading to discontinuation in at least 1% of Vyvanse-treated patients and at a rate at least twice that of placebo) were insomnia (8/358; 2%), tachycardia (3/358; 1%), irritability (2/358; 1%), hypertension (4/358; 1%), headache (2/358; 1%), anxiety (2/358; 1%), and dyspnea (3/358; 1%).

Pediatric

Table 1 Adverse Reactions Reported by 2% or More of Pediatric Patients Taking Vyvanse in a 4-Week Clinical Trial

Body System	Preferred Term	Vyvanse (n=218)	Placebo (n=72)
Gastrointestinal Disorders	Abdominal Pain Upper	12%	6%
	Vomiting	9%	4%
	Nausea	6%	3%
	Dry Mouth	5%	0%
General Disorder and Administration Site Conditions	Pyrexia	2%	1%
	Investigations	Weight Decreased	9%
Metabolism and Nutrition	Decreased Appetite	39%	4%
	Nervous System Disorders	Dizziness	5%
	Somnolence	2%	1%
	Psychiatric Disorders	Insomnia	19%
Irritability		10%	0%
Initial Insomnia		4%	0%
Affect lability		3%	0%
Tic		2%	0%
Skin and Subcutaneous Tissue Disorders	Rash	3%	0%

Note: This table includes those reactions for which the incidence in patients taking Vyvanse is at least twice the incidence in patients taking placebo.

Adult

Table 2 Adverse Reactions Reported by 2% or More of Adult Patients Taking Vyvanse in a 4-Week Clinical Trial

Body System	Preferred Term	Vyvanse (n=358)	Placebo (n=62)
Gastrointestinal Disorders	Dry Mouth	26%	3%
	Diarrhea	7%	0%
	Nausea	7%	0%
General Disorder and Administration Site Conditions	Feeling Jittery	4%	0%
	Investigations	Blood Pressure Increased	3%
Heart Rate Increased		2%	0%
Metabolism and Nutrition Disorders	Anorexia	5%	0%
	Decreased Appetite	27%	3%
Nervous System Disorders	Tremor	2%	0%
	Psychiatric Disorders	Insomnia	27%
Anxiety		6%	0%
Agitation		3%	0%
Restlessness		3%	0%
Respiratory Thoracic and Mediastinal Disorders	Dyspnea	2%	0%
	Skin and Subcutaneous Tissue Disorders	Hyperhidrosis	3%

Note: This table includes those events for which the incidence in patients taking Vyvanse is at least twice the incidence in patients taking placebo.

Vital Signs

Weight Loss – In the controlled adult trial, mean weight loss after 4 weeks of therapy was 2.8 lbs, 3.1 lbs, 4.3 lbs, for patients receiving final doses of 30 mg, 50 mg and 70 mg of Vyvanse, respectively, compared to a mean weight gain of 0.5 lbs for patients receiving placebo.

Adverse Reactions Associated with the Use of Amphetamine

Cardiovascular
Palpitations, tachycardia, elevation of blood pressure, sudden death, myocardial infarction. There have been isolated reports of cardiomyopathy associated with chronic amphetamine use.

Central Nervous System

Psychotic episodes at recommended doses, overstimulation, restlessness, dizziness, insomnia, euphoria, dyskinesia, dysphoria, depression, tremor, headache, exacerbation of motor and phonic tics and Tourette's syndrome, seizures, stroke.

Gastrointestinal

Dryness of the mouth, unpleasant taste, diarrhea, constipation, other gastrointestinal disturbances.

Allergic

Urticaria, rashes, and hypersensitivity reactions, including angioedema and anaphylaxis. Serious skin reactions, including Stevens Johnson Syndrome and Toxic Epidermal Necrolysis have been reported.

Endocrine

Impotence, changes in libido.

USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

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

Labor and Delivery

The effects of Vyvanse on labor and delivery in humans is unknown.

Nursing Mothers

Amphetamines are excreted in human milk. Mothers taking amphetamines should be advised to refrain from nursing.

Pediatric Use

Vyvanse has not been studied in children under 6 years of age or adolescents. Amphetamines are not recommended for use in children under 3 years of age.

Geriatric Use

Vyvanse has not been studied in the geriatric population.

DRUG ABUSE AND DEPENDENCE

Vyvanse is classified as a Schedule II controlled substance.

OVERDOSAGE

Toxic symptoms may occur idiosyncratically at low doses.

Treatment: Consult with a Certified Poison Control Center for up-to-date guidance and advice.

The prolonged release of Vyvanse in the body should be considered when treating patients with overdose.

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