



The DUR Discovery

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WHAT'S INSIDE!

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The last Pharmacy and Therapeutics (P&T) Committee Meeting held by Idaho Medicaid was August 15, 2008. Recommendations from the meeting can be found on the Medicaid website at: www.healthandwelfare.idaho.gov. Follow the Medical link to Prescription Drugs and then P&T Committee.

The next P&T Meeting will be held on January 16, 2009, at Idaho Medicaid, 3232 Elder Street, Boise, ID 83705

Treatment of Fibromyalgia

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Fibromyalgia (FM) is an idiopathic syndrome characterized by generalized fatigue and muscle pain and tenderness that is associated with a significant reduction in quality of life.¹ It is estimated that 2% of the U.S. population is affected with women age 20-50 reporting symptoms most frequently.²

Although diagnostic criteria were developed by the American College of Rheumatology (ACR) in 1990, fibromyalgia is still considered a diagnosis of exclusion by many practitioners. The ACR Criteria for Classification of Fibromyalgia includes the following: 1) widespread pain for at least three months (both sides of the body, above and below the waist, and axial skeleton involvement) and 2) pain on palpation in 11 of 18 specific tender points.³

Many FM patients often have comorbid conditions that can make diagnosis and treatment problematic. Such conditions include sleep disorders, anxiety, depression, headaches, cognitive difficulties, paresthesias, and irritable bowel syndrome.¹

Treatment of FM is primarily symptomatic, with non-pharmacologic modalities often demonstrating the best efficacy. **Low-impact regular exercise, cognitive-behavioral therapy, and participation in support groups have been shown to be helpful for many patients.⁴ These treatments should be considered the cornerstone of therapy and ought to be utilized even in patients for whom drug therapy is prescribed.⁵**

Pharmacologic treatments include antidepressants and several agents used for neuropathic pain (see table 1). **The drugs with the most supporting clinical evidence include low-dose amitriptyline (Elavil) and the structurally-related muscle relaxant, cyclobenzaprine (Flexeril).⁴** These agents are often viewed as first-line treatment options and are possibly the most efficacious drug treatments available for FM, although their adverse effect profile (especially drowsiness) may limit their tolerability in some patients.

Other antidepressants, such as selective serotonin reuptake inhibitors (fluoxetine, sertraline) as well as serotonin and norepinephrine reuptake inhibitors (venlafaxine, duloxetine) may also be effective and are better tolerated.⁵ Of note, duloxetine (Cymbalta) recently received FDA-approval for the treatment of FM.

Analgesics such as tramadol (Ultram) or opioids (hydrocodone, oxycodone) with or without acetaminophen may be necessary, but should be viewed as last resorts.⁵ **NSAIDs are not generally beneficial as FM is not thought to have an inflammatory component.⁵**

Gabapentin (Neurontin) has a long history of use in the management of a variety of neuropathic pain states and has some supporting data for FM.⁵ Although the related agent, pregabalin (Lyrica) is the first drug approved by the FDA for the management of FM, it is a schedule V controlled substance,⁶ is more expensive than other options (including generic gabapentin) and has less supporting clinical evidence than amitriptyline, cyclobenzaprine, or gabapentin.

References

- American College of Rheumatology. Patient education for fibromyalgia. http://www.rheumatology.org/public/factsheets/fibromya_new.asp#1. (Accessed March 27, 2007).
- Wolfe F, Ross K, Anderson J, Russell IJ, Hebert L. The prevalence and characteristics of fibromyalgia in the general population. *Arthritis Rheum* 1995;38:19-28.
- Wolfe F, Smythe HA, Yunus MB, Bennett RM, Bombardier C, Goldenberg DL, et al. The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum* 1990;33:160-72.
- Buckhardt CS, Goldenberg D, Crofford L, et al. Guideline for management of fibromyalgia syndrome pain in adults and children. *American Pain Society*, 2005. http://guidelines.gov/summary/summary.aspx?doc_id=7298&nbr=004342&string=fibromyalgia. (Accessed March 27, 2008).
- Arnold LM, Goldenberg DL, Stanford SB, et al. Gabapentin in the treatment of fibromyalgia: a randomized, double-blind, placebo-controlled, multicenter trial. *Arthritis Rheum* 2007 Apr;56(4):1336-44.
- Product information for Lyrica. Pfizer Inc, New York, NY 10017. June 2007.

Table 1: Pharmacologic Treatments for the Management of Fibromyalgia

Evidence for Efficacy	Drug Class/Drug	Dosing Range for Fibromyalgia	Average Monthly Cost*
Strong	Tricyclic antidepressant (TCA) Amitriptyline (Elavil)**	10-50 mg qhs	\$7.99 - 11.99
	Skeletal muscle relaxant Cyclobenzaprine (Flexeril)**	10-40 mg daily (qhs or divided doses)	\$13.99 - 25.30
Moderate	SSRIs Fluoxetine (Prozac)**	20-80 mg qd	\$14.99 - 35.99
	SNRIs Duloxetine (Cymbalta)	60-120 mg daily	\$123.99 - 247.99
	Non-opioid analgesic Tramadol (Ultram)	200-300 mg daily	\$63.96 - 95.94
	Anticonvulsants Pregabalin (Lyrica) Gabapentin (Neurontin)	300-450 mg daily in divided doses 1,200-2,400 mg daily in divided doses	\$69.54 - 139.08 \$72.99 - 92.99

*Approximate cost per www.drugstore.com. Accessed April 2008.

**May be available at lower cost on some pharmacies' promotional (\$4 or \$5) generic drug list

Table 2: Comparison of Selected Dosage Forms of Oral Stimulants for ADHD^{4,6,7}

Stimulant	Onset (min)	Duration (hrs)	Typical Dosage Regimens	Monthly Cost*
Immediate-Release				
Methylphenidate (generic for Ritalin)	20-60	2-4	5, 10 or 20 mg bid	\$ 18-37
Dextroamphetamine (generic for Dextrostat or Dexedrine tablets)	20-60	3-6	5 or 10 mg q day to bid	\$ 8-21
Dextroamphetamine/Amphetamine (generic for Adderall)	30-60	3-6	5, 7.5, 10, 12.5, 15, 20 or 30 mg q day	\$ 12-43
Sustained-Release				
Methylphenidate ER (Methylin ER)	60-90	6-8	20 mg q day	\$ 34
Dextroamphetamine (generic for Dexedrine Spansules or capsules)	60-90	4-8	5, 10, or 15 mg q day	\$ 24-38
Extended-Release				
Methylphenidate (Metadate CD)	30-120	6-8	10, 20, 30, 40, 50 or 60 mg q day	\$ 112-189
Methylphenidate (Ritalin LA)	30-120	6-8	10, 20, 30 or 40 mg q day	\$ 112-118
Dexmethylphenidate (Focalin XR)	60	12	5, 10, 15 to 20 mg q day	\$ 128-133
Methylphenidate (Concerta)	30-120	12	18, 27, 36 or 54 mg q day	\$ 133-153
Dextroamphetamine/Amphetamine (Adderall XR)	60-120	8-12	5, 10, 20 or 30 mg q day	\$ 155
Lisdexamfetamine (Vyvanse)	120 [†]	10	20, 30, 40, 50, 60 or 70 mg q day	\$ 137

* Monthly (30-day) cost represents Federal Upper Limit⁸ or AWP (according to Cardinal Health, Inc., July 2008) with no dispensing fee or discounts added for the range of dosage regimens specified. Costs have been rounded to the nearest dollar.

[†] Quickest onset reported⁴

Vyvanse: Place in ADHD Therapy

By John Erramouspe, PharmD, MS and Nicole Baker, PharmD

Initial approval of lisdexamfetamine (Vyvanse) by the FDA was in February 2007 for the treatment of attention-deficit/hyperactivity disorder (ADHD) in children 6 to 12 years of age.¹ In April of 2008, Vyvanse received FDA approval for use in adults. Its manufacturer, Shire Pharmaceuticals, is marketing Vyvanse preferentially over its own Adderall XR which will go off patent in 2009.²

Vyvanse is a prodrug requiring oral ingestion to be hydrolyzed to its active form, dextroamphetamine. Vyvanse was designed to have less potential for abuse than older stimulant formulations via a decrease in the early release of active drug. Abuse by inhalation or injection may be minimized due to impeded hydrolysis by these routes. Despite this, capsules of Vyvanse may be opened and the contents dissolved in water for administration and the drug is nevertheless classified as a Schedule II controlled substance similar to other stimulants used for ADHD.³

The duration of action of Vyvanse (Table 2) is approximately 10 hours, similar to newer extended-release dosage forms. However, Vyvanse's quickest reported onset of action is approximately 2 hours which is slower than most newer extended-release products. Since the onset of action of stimulants is critical in improving early daytime performance/behavior of many ADHD patients, additional studies are needed to better define how Vyvanse's onset compares to other once daily stimulant dosage forms.

The recommended daily starting dose of Vyvanse is 30 mg in the morning with dosage increments thereafter of 20 mg/day, increased at weekly intervals to a maximum of 70 mg.¹ Two randomized controlled trials in children with ADHD (344 children total) found greater improvement in ADHD rating scales with Vyvanse versus placebo.^{4,5} The smaller of these two trials (54 children) was crossover in design and included Adderall XR as an additional active treatment.⁴ Importantly, there

was no difference in clinical improvement between Adderall XR and Vyvanse when assessed over a 12-hour period following administration.

Vyvanse is priced comparable to newer extended-release, rapid onset stimulant dosage forms (e.g. Metadate CD, Ritalin LA, Concerta), but higher than many older immediate- and sustained-release stimulant dosage forms (Table 2). **There is no proven evidence that Vyvanse is more effective or safer than other stimulants.** Although it may have a place in treating patients at risk for abuse, newer extended-release stimulant dosage forms are also useful in treating this subpopulation of ADHD patients. At present it is reasonable to **reserve Vyvanse for ADHD patients who have failed or are intolerant to other stimulants.** Although the drug is still under review by Idaho Medicaid, at present the drug is non-preferred and will be approved only after documented failure of a preferred agent.

References

1. Product information. Vyvanse (lisdexamfetamine dimesylate) New River Pharmaceutical Inc. Blacksburg, VA. February 2007.
2. New drug: Vyvanse (lisdexamfetamine dimesylate). Pharmacist's Letter/Prescriber's Letter 2007;23(5):230507.
3. Drug Enforcement Administration, Department of Justice. Schedules of controlled substances: placement of lisdexamfetamine into schedule II. Final rule. Fed Regist. 2007 May 3;72(85):24532-4.
4. Biederman J. Lisdexamfetamine dimesylate and mixed amphetamine salts extended-release in children with ADHD: a double-blind, placebo-controlled, crossover analog classroom study. Biol Psychiatry. 2007;62:970-6.
5. Biederman J, Krishnan S, Zhang Y, McGough JJ, Findling RL. Efficacy and tolerability of lisdexamfetamine dimesylate (NRP-104) in children with attention-deficit/hyperactivity disorder: A Phase III, multicenter, randomized, double-blind, forced-dose, parallel-group study. Clin Ther. 2007 Mar;29(3):450-63.
6. Biederman J. New-generation long-acting stimulants for the treatment of attention-deficit/hyperactivity disorder, Medscape Psychiatry & Mental Health 8(2), 2003. Available at: <http://www.medscape.com/viewarticle/464377> (cited 12/13/07).
7. Product Information: Focalin XR, dexamethylphenidate hydrochloride extended-release capsules. Novartis Pharmaceuticals Corporation, East Hanover, NJ, 2005.
8. 2008 Drug topic red book. Montvale, NJ: Medical Economics, 2008.

Judicious Use of Benzodiazepines in Anxiety and Insomnia

By Christine Lee, PharmD and Brooke Pugmire, PharmD, BCPS

Benzodiazepines (BZDs) are frequently used in the management of anxiety disorders and insomnia due to their anxiolytic and hypnotic properties. BZDs share similar pharmacologic properties, but have different durations of action. In addition, there are established clinical "niches" for different agents (e.g. clonazepam (Klonopin®) for restless legs and muscle spasms). Despite this, use of multiple agents is not recommended, even for different indications.

Benzodiazepines are best used only short-term for these disorders. Some individuals may require long-term BZD therapy; however, such use is controversial owing to their potential for tolerance, dependence, and abuse. While abuse potential may be low in appropriately managed patients with clear indications, caution when prescribing these drugs long-term is still warranted, especially in individuals with a substance abuse history.¹

The manufacturers of sedative-hypnotic BZDs, including triazolam (Halcion®), temazepam (Restoril®), and estazolam (Prosom®), recommend short courses (7-10 days). Because insomnia is often transient and available data is limited to clinical trials of short duration, these drugs are most appropriately used as needed for durations of up to 4 weeks. Drug therapy may be indicated for chronic insomnia after ruling out medical/drug causes and non-pharmacologic options have been attempted.² Eszopiclone (Lunesta®), controlled-release zolpidem (Ambien CR®), and ramelteon (Rozerem®) are FDA-labeled for chronic insomnia; however, little guidance exists regarding the optimal agent, dosage, and duration for patients who require long-term drug therapy.

Generalized anxiety disorder (GAD) is typically chronic in nature and often requires long-term therapy.³ First-line chronic treatment options for GAD include selective-serotonin reuptake inhibitors (SSRIs) and serotonin-norepinephrine reuptake inhibitors (SNRIs), as they are also effective against comorbid psychiatric disorders. These antidepressants and buspirone (Buspar®) are suitable for long-term use but often take weeks to months for full effect. For this reason, BZDs are best used short-term as bridge therapy with chronic treatments such as antidepressants or buspirone or as occasional adjunctive therapy in patients whose anxiety symptoms or specific clinical needs warrant their use.³

Long-term use of BZDs for anxiety may be clinically warranted, but should be closely monitored and re-evaluated regularly. It is also important to assess repeat prescribing of short-course BZDs, as it may be that the patient has GAD and requires chronic treatment. Because anxiety is often a component of a number of psychiatric conditions, an individualized approach to treatment with BZDs is appropriate.

References

1. Kaplan EM, DuPont RL. Benzodiazepines and Anxiety Disorders: a Review for the Practicing Physician. Curr Med Res Opin 2005;21:941-50.
2. NIH State-of-the-Science Conference Statement on Manifestations and Management of Chronic Insomnia in Adults. NIH Consensus State Sci Statements 2005;22:1-30. Available at: <http://consensus.nih.gov/2005/2005InsomniaSOS026main.htm>.
3. Ballenger JC, et al. Consensus Statement on Generalized Anxiety Disorder From the International Consensus Group on Depression and Anxiety. J Clin Psychiatry 2001;62 (suppl 11):53-8.