EnhanceMed™ Quarterly Clinical Update

Highlighting Current Research and Market Updates Affecting Behavioral Health Medical Practitioners

MAGELLAN HEALTH SERVICES

WINTER 2013—VOL. 4, NO. 1

Overview of the Growing Problem of Opioid Abuse

A major problem in the United States has now reached epidemic proportions—the presence on our streets (and in the hands of drug abusers) of high-dose, extended-release oral formulations of opioids. These products increasingly are used to treat chronic non-cancer pain and are readily available in the black-market. In fact, prescription opioid abuse now exceeds the use of street narcotics here in the United States.

A multi-agency effort aimed at reducing the problem was unveiled in April 2011 by the White House. It is a collaborative effort involving the Departments of Justice, Health and Human Services, Veterans Affairs, Defense, and other agencies. The authors point out that nobody agrees on anything in the context of discussion of this topic—from the very definitions of terminology used in clinical practice to treatment guidelines and philosophies to what certifications should be required for a physician to qualify as a pain expert.

Points that the authors discuss include the following:

- Hydrocodone and oxycodone (extended- and immediate-release) are now the most abused drugs in the country.
- Rates of prescription opioid drug abuse have increased as the poverty rate and the unemployment rate increased.
- Significantly more men than women experienced lifetime use.
- Americans consume 80% of the global opioid supply, 99% of the global hydrocodone supply, and 66% of the world's illegal drugs.
- Approximately 20% of Americans report using prescription opioids for non-medical use.
- In 2007, retail sales of commonly used opioid medications increased overall by 149%, with ranges of 222% for morphine and 1,293% for methadone.
- The mean annual direct health care costs for patients who abuse opioids are 8.7 times higher than non-abusers. From 1998 to 2002, the mean per capita annual direct health care costs for commercially insured beneficiaries in the United States was $16,000 for abusers and $1,800 for non-abusers.
- Medical, economic, social, and criminal costs of this abuse total nearly half a trillion dollars.
- Between 1999 and 2004, the CDC reported a rise in prescription opioid-related deaths of 68%.
- Diversion was a factor in over 50% of overdose fatalities. The primary sources of prescription drugs on the street are the elderly, patients with pain, and doctor shoppers, as well as dealers who get their supplies from the former.
- Patients receiving more than a 450mg equivalent of morphine over a period of several months were disabled 69 days longer than those who received no opioids, had a 3 times increased risk for surgery, and had a 6 times greater risk of receiving late opioids.

Doctors Sehgal, Smith, and Manchikanti challenge all in the medical community to screen for opioid abuse potential, to monitor patients for opioid abuse, and to assist with regulatory agencies in tackling opioid abuse and diversion.

Sehgal N, et al. Prescription opioid abuse in chronic pain: a review of opioid abuse predictors and strategies to curb opioid abuse. *Pain Physician* 2012; 15:ES67-ES92.

New Drug Review - Quillivant XR

Quillivant XR is a new formulation of methylphenidate used to treat Attention Deficit Hyperactivity Disorder (ADHD). Methylphenidate, which has been in use since the 1960s to treat ADHD, is available in many formulations. Quillivant XR is unique in that it is formulated as once-daily extended-release suspension. Quillivant XR reaches peak plasma levels on average in 5 hours and has 95% bioavailability. Taking this medication with food will decrease the time to peak plasma concentrations to 4 hours. The suspension's concentration is 25mg/5ml and it is available in 60, 120, 150, and 180 ml bottles. It can only be dispensed by the pharmacy in the original bottle. The recommended starting dose for children over 6 years is 20mg per day—doses greater than 60mg per day are not recommended. The manufacturer provides an oral syringe and a bottle adapter to make administration easier. It is important to counsel parents on how the medication should be measured

Valproic Acid Can Significantly Lower Olanzapine Concentrations

Olanzapine, an atypical antipsychotic, prescribed for schizophrenia and bipolar disorder, is frequently used adjunctively with antiepileptic drugs (AEDs). This retrospective study on the effects of AEDs on olanzapine plasma levels and olanzapine metabolites was conducted at a hospital in Oslo, Norway.

Valproic acid, an AED, is metabolized by uridine diphosphate glycosyltransferase (UGT) enzymes and also acts as an inhibitor of these enzymes. Olanzapine is metabolized by several enzyme pathways, one of which is UGT1A4. While valproic acid is considered an inhibitor of UGT enzymes, which would tend to increase plasma levels of olanzapine, *decreases* in plasma levels up to 30% have also been observed. The actual mechanism by which this occurs was not found in this study. The decreased plasma levels of olanzapine were comparable to the observed levels in a patient who smokes. This reinforces the importance of taking factors such as smoking and concurrent use of valproic acid into account when titrating a patient's olanzapine dose.

From other studies, we also know that carbamazepine, another AED, can decrease serum concentrations of olanzapine by as much as 50%.

Haslemo T, et al. Valproic acid significantly lowers serum concentrations of olanzapine - an interaction effect comparable with smoking. *Ther Drug Monit*. 2012 Oct; 34(5):512-7.

EnhanceMed Quarterly Update is produced by Magellan Health Services

New Drug Review - Quillivant XR (cont)

so their child gets an accurate dose.

Alternatives to Quillivant XR include Concerta, Ritalin LA, Metadate CD, and Daytrana. Concerta is an extended-release tablet that reaches tmax in 6.8 hours. Ritalin LA is a capsule with a biphasic tmax designed to mimic immediate-release tablets taken twice a day; the first tmax is at 2 hours and the second occurs in about 6.6 hours. Metadate CD is similar to Ritalin LA in that it, too, is biphasic with tmaxs reached at 1.5 hours and 4.5 hours after the dose is taken. Both Metadate CD and Ritalin LA capsules can be opened and sprinkled for those patients who cannot swallow the capsules. Daytrana is a transdermal patch that reaches tmax in 8 hours with daily administration.

A clinical study was performed on Quillivant XR to confirm its extended release effectiveness. Forty-five pediatric patients were initially started on 20mg daily. The dose was titrated weekly to an optimum dose or until the maximum dose (60mg daily) was reached. The subjects were then randomized into a treatment and placebo group. At the end of each week, the subject's behavior and attention were rated using the SKAMP rating scale. The SKAMP scores were significantly improved over placebo at all time points measured.

Quillivant XR is an alternative for a small group of patients who cannot swallow pills, have difficulty reaching an effective dose because of side effects (some patients may experience less side effects with Quillivant due to a slower release rate), or are sensitive to the adhesive in the transdermal patch, or where other products are not lasting long enough to provide adequate relief of symptoms. Quillivant XR will be available in pharmacies beginning in January 2013.

Quillivant XR Package Insert, by Nextwave Pharmaceuticals, Inc.

Grapefruit and Medication Warning is Expanded

Twenty years after their original article, the authors have updated the list of medications interacting with grapefruit to include data on new drugs, bringing this topic into focus once again. Most psychotropic medications are not metabolized by CYP3A enzymes and grapefruit has little effect. Various surveys of the medications are available and many contradict one another. Of interest to behavioral health practitioners, Dr. Bailey and colleagues point out that lurasidone and ziprasidone are reported to have the potential for torsades when mixed with grapefruit and elderly patients on these medications should avoid grapefruit. Practitioners are encouraged to consider another neuroleptic agent such as risperidone, olanzapine, or haloperidol. Grapefruit and its juice cause irreversible inhibition of the CYP3A4 enzyme in the gut that normally metabolizes these medications. The interaction can occur even if grapefruit juice is consumed many hours before taking the medication because the metabolic pathway can be shut down for up to 72 hours. Drugs that suffer this fate are administered orally, have low bioavailability, and are metabolized in the GI tract by CYP3A4. The importance of an interaction will depend on what might be the clinical significance of increased drug exposure, the therapeutic index of the affected drug, and the quantity of grapefruit consumed. Elderly patients especially may be less able to tolerate increased drug levels.

What foods/juices to avoid:

- Fruit juice mixes (both concentrate and prepared)
- Fresh, canned, or frozen grapefruit
- Food items that contain the words "citrus blend," unless they specifically state they do not contain grapefruit
- Dietary supplements that contain grapefruit bioflavonoids
- Seville oranges and tangelos (may have cross-reactivity)

Bailey DG, et al. Grapefruit-medication interactions: forbidden fruit or avoidable consequences? *CMAJ* 2012;doi:10.1503/cmaj.120951 (published ahead of print).

Drug	Implications
Benzodiazepines, oral: Diazepam (Valium) Triazolam (Halcion)	Potential for increased sedation.
Buspirone (Buspar)	Potential for dizziness, sedation. Avoid grapefruit in elderly.
Carbamazepine (Tegretol)	Avoid grapefruit.
Clomipramine (Anafranil)	Potential for increased side effects, such as dry mouth, somnolence, dizziness, fatigue.
Lurasidone (Latuda)	Potential for torsades, orthostatic hypotension. Canadian product labeling advises avoiding grapefruit.
Quetiapine (Seroquel)	Potential for dizziness, drowsiness.
Ziprasidone (Geodon)	Potential for torsades. Avoid grapefruit in elderly.

FDA Recommends Lower Dose of Zolpidem

The Food and Drug Administration (FDA) announced it is requiring manufacturers of zolpidem, a sleeping medication, to lower current recommended doses. It has been found that blood levels of zolpidem may be high enough to cause impairment the morning following use. Women clear zolpidem slower than men; the FDA is recommending a labeling change for women and lower doses should be considered for men as well. The risk of impairment the morning following use of zolpidem is highest with extended release forms.

The FDA informed manufacturers that the recommended dosage of zolpidem for women should be lowered from 10mg to 5mg for immediate-release tablets and from 12.5mg to 6.25mg. The FDA also informed manufacturers that labeling should be changed to recommend prescribers apply these lower dosages to men as well.

The FDA reminded the public that morning impairment is not unique to zolpidem; other medications used for insomnia may also cause drowsiness the following morning.

This labeling change stems from driving simulation and laboratory studies that showed elevated blood levels of zolpidem capable of impairing some individuals' ability to drive safely. The FDA will continue to evaluate prescription and over-the-counter medications used for insomnia to examine their effects on mental alertness.

FDA News Release, Jan 10, 2013

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm334798.htm

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