EnhanceMed™ Quarterly Clinical Update

Highlighting Current Research and Market Updates Affecting Behavioral Health Medical Practitioners

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Review and Pharmacotherapy of Akathisia Caused by Second Generation Antipsychotic Agents

Falling under the heading of acute extrapyramidal symtom (EPS), akathisia is a movement disorder characterized by unpleasant sensations of inner restlessness that manifests itself with an inability to sit still or remain motionless. There is an intense urge to move around, which is often seen as rocking while sitting or standing, marching in place or pacing. Patients can pace for hours because it seems that the pressure on the knees somewhat reduces the discomfort. Once their knees and legs become fatigued and they are unable to continue pacing, they sit or lie down, although this does not relieve the akathisia. This disorder may be seen as a side effect of antipsychotics, SSRI's and antiemetics, or may occur in patients with Parkinson's disease.

The exact pathophysiological mechanism of this is unclear, but Loonen and Stahl point out that evidence suggests that it can be attributed to an extensive decrease in dopaminergic (DA) stimulation. Because drugs that do not block DA have also been noted to cause the disorder, another effect might be the indirect stimulation of serotonin receptors, which would result in an inhibition of DA release. Akathisia is a psychological disorder and not just a movement disorder like Parkinson's and dyskinesias. It is very similar to restless leg syndrome, but occurs mostly in the daytime.

A meta-analysis of 54 studies ranked the following atypicals (from highest to lowest) as contributors of akathisia: aripiprazole, risperidone, paliperidone, ziprasidone, olanzapine, clozapine, quetiapine.

Akathisia can be reduced by withdrawing or decreasing the dose of the causative agent, or by administering other drugs, though the latter proves many times to be counter-productive. First-line treatment of akathisia is usually propranolol, initiating therapy at 10mg TID, which can be increased every few days to a maximum of 90-120mg/day. Benzodiazepines such as clonazepam at 0.5mg/day are also effective to a certain degree. Anticholinergics can also be used if other EPS are present, though a Cochrane review found no trial-based evidence for their use in the treatment of akathisia.

Rummel-Kluge C, et al. Second-Generation Antipsychotic Drugs and Extrapyramidal Side Effects: A Systematic Review and Meta-analysis of Head-to-Head Comparisons. *Schizophr Bull.* 2012 Jan; 38(1):67–177.
Loonen A, et al. The Mechanism of Drug-induced Akathisia. *CNS Spectr.* 2011;16(1):ePub Ahead of Print.
Rathbone J, et al. Anticholinergics for Neuroleptic-induced Acute Akathisia. *Cochrane Database Syst Rev.* 2006 Oct 18;(4):CD003727.
Kane JM, et al. Akathisia: An Updated Review Focusing on Second-Generation Antipsychotics. *J Clin Psychiatry*. 2009;70(5):627-643.

Antipsychotic Medications Are Not Significantly Helpful for Depression

An estimated 3.9 million treatment visits per year in the U.S. during 2007 and 2008 resulted in an antipsychotic medication being prescribed for depression, and 96% of those involved the prescription of an atypical antipsychotic. Two systematic reviews had been conducted previously but they did not assess changes in terms of symptom severity and safety was only assessed by examining drop-out rates.

A recent meta-analysis of measures of improvement of depression, of quality of life and of safety outcomes regarding the use of adjunctive atypical antipsychotics was published in March 2013. The literature search identified 14 short-term acute-phase trials (with 3549 participants) that compared aripiprazole, olanzapine/fluoxetine combination, quetiapine, or risperidone to placebo in treatment-resistant depression in adults. Published literature was supplemented with data from manufacturers' clinical trial registries and the U.S. Food and Drug Administration's New Drug Applications. In its conclusion, Dr. Spielmans, the lead author, suggested that "some of the trials…tried to boost the perception of the effectiveness of [that study's] drug and downplay its side

Pharmaceutical Abuse

Abuse of pharmaceuticals has grown to epic proportions. In 2010 there were 4.9 million drug-related emergency room visits. Of those, 46.8 percent were due to misuse or abuse of drugs. Narcotic pain relievers accounted for the most emergency room visits, with benzo-diazepines a close second. Oxycodone, followed by hydrocodone, are the preferred agents by 75 percent of medical patients; while methadone is preferred by 75 percent of street users. Americans consume 99 percent of the worlds hydrocodone produced and 80 percent of the global opioid supply.

The group of potential abusers is quite large, making prescribing opioids an increasingly tedious task. Risk factors for opioid abuse include pain, drug-related factors, genetics, psychosocial and family history, psychopathology, social and demographic factors, and the presence of other substance abuse disorders. Groups of individuals who may be at a larger risk include those with chronic pain and a substance abuse disorder and/or a mental health disorder. Young white men and women can be at an increased risk of opioid abuse due to emotional issues and affective distress.

A tool has been developed to analyze the risk of abuse of opioids in chronic pain patients. Patients who have 3 or more of the following criteria are predictive of abuse:

- Patient focus on opioids
- Opioid overuse
- Other substance abuse
- Low functional status
- Unclear etiology of pain
- Exaggeration of pain.

The public health community needs to raise awareness to the potential for serious consequences of the dangers of prescription and over-the-counter medications. The public generally views

effects. Studies were sometimes designed in a biased manner that may have slanted the results. Data were sometimes reported in a way that likely made the drugs appear more effective than they actually were."

Regarding atypical antipsychotics for the adjunctive treatment of depression, the research team reported that: 1. there is only a small-to-moderate-sized benefit to the patient; 2. there is a lack of benefit with regards to quality of life or functional impairment; 3. there is abundant evidence of potential treatment-related harm; and 4. that clinicians should interpret the reduction of observer-rated depressive symptoms cautiously. The authors explicitly described set-up, calculations, adjustments used, and limitations of this well-documented research.

Spielmans GI, et al. Adjunctive Atypical Antipsychotic Treatment for Major Depressive Disorder: A Meta-Analysis of Depression, Quality of Life, and Safety Outcomes. *PLoS Med* 2013. 10(3): e1001403

Behavioral Health Medications Requiring Dose-Adjustment in Hepatic Disease

Hepatic disease can affect the pharmacokinetics of many medications. Absorption can be delayed because of vascular congestion resulting from cirrhosis and distribution can be increased due to fluid retention of ascites and peripheral edema. Many psychotropic medications are highly protein-bound, but because of a reduction in albumin and alpha$_1$-acid-glycoprotein production caused by liver failure, some drugs might have increased levels of free pharmacologically-active drug, which can cause increased side effects (e.g., benzodiazepines and increased sedation).

The table below displays the recommendations for dosing in hepatic disease. If a medication is not listed in the table, the literature reports that no dosage adjustment is necessary in mild to moderate disease. Particularly if your patient has a Child-Pugh score of C, a review of the medication literature is needed.

	Medication	Protein Binding	CYP 450 metabolizing enzyme	Recommendations
Benzos	Alprazolam	80%	3A	Decrease dose by 1/2
	Diazepam	95%	3A	Decrease dose by 1/2
Antidepressants	Bupropion	84%	2B6	Lower dose or longer intervals between doses
	Desvenlafaxine	30%	3A4	The recommended dose in patients with hepatic impairment is 50 mg/day.
	Duloxetine	>90%	2D6, 1A2	Do not use with any liver insufficiency.
	Fluoxetine	95%	2D6	Lower dose or longer intervals between doses
	Fluvoxamine	77%	2D6	Lower dose or longer intervals between doses
	Paroxetine	95%	2D6	Decrease dose by 1/2 (initial dose: 10mg)
	Sertraline	98%	2D6, 2C9	Lower dose or longer intervals between doses (initial dose: <50mg)
	Trazodone	~90%	3A4	Should be used with caution.
	Venlafaxine	~27%	2D6	Reduce dose by 50% in patients with mild to moderate disease.
Antipsychotics	Iloperidone	95%	2D6, 3A4	Not recommended for patients with hepatic impairment.
	Lurasidone	99%	3A4	Moderate impairment max daily dose is 80mg and 40mg for severe impairment (initial dose: 20mg)
	Olanzapine	93%	minor 1A2, 2D6	Caution should be exercised; may be expected to reduce the clearance of olanzapine.
	Quetiapine	83%	3A4	Lower dose or longer intervals between doses
	Risperidone	90%	2D6	Max dose of 4mg QD; use caution
	Ziprasidone	>99%	3A4	Not clinically significant in mild-to-moderate hepatic impairment. Decrease dose with severe disease.

Information was obtained from *Facts and Comparisons* and the product package inserts.

Crone CC, et al. An Overview of Psychiatric Issues in Liver Disease for the Consultation-liaison Psychiatrist. *Psychosomatics*. 2006 May-Jun;47(3):188-205.

pharmaceuticals as safe because they are legally produced and dispensed and approved by the FDA.

Education, behavioral interventions, and monitoring will all help to limit prescription medication abuse and diversion. Prescription monitoring programs have been initiated in 38 states to track prescription medications. Physicians may opt to utilize an opioid treatment agreement with their patients. This agreement will inform the patients about the risks and benefits of opioid treatment, form a mutually agreed upon course, improve the patient-provider relationship, improve patient compliance by documenting treatment goals, and establish remedies if problems arise. It is important for providers to have a firm understanding of pain management and to keep up to date about the advances in opioid medication formulations to effectively treat pain while limiting abuse potential.

Sehgal N, Manchikanti L, Smith H. Prescription Opioid Abuse in Chronic Pain: A Review of Opioid Abuse Predictors and Strategies to Curb Opioid Abuse. *Pain Physician Journal*. 2012, 15:ES67-ES92

The DAWN Report. Highlights of the 2010 Drug AbuseWarning Network (DAWN) Findings on Drug-Related Emergency Department Visits. Available at http://www.samhsa.gov/data/DAWN.aspx Accessibility verified March 30, 2013.

Vayarin ®– new product

Vayarin®, a combination of three fatty acids essential to the brain, was clinically shown to reduce several ADHD symptoms including restlessness and impulsivity, hyperactivity and inattention. Vayarin is a medical food available by prescription only, but not evaluated by the FDA. It is important to note that insurance coverage for medical foods varies greatly. A study has shown Vayarin to be well-tolerated but the outcome of the study is that it may be effective for certain patient populations. Overall improvements were not statistically significant.

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