EnhanceMed™ Quarterly Clinical Update

Highlighting Current Research and Market Updates Affecting Behavioral Health Medical Practitioners

MAGELLAN PHARMACY SOLUTIONS | MAGELLAN MEDICAID ADMINISTRATION

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Women Are Dying of Opioid Overdose at Unprecedented Rates

The Centers for Disease Control (CDC) has just published a brochure on the growing epidemic of prescription painkiller overdoses among women. A review of the statistics from 1999 through 2010 highlights several important observations:

- There has been a 400 percent increase in the number of deaths of women from prescription painkiller overdoses (from 1,287 in 1999 to 6,631 in 2010). Men still top the chart with 10,000 deaths per year.
- Nearly 48,000 women died of prescription opioid or narcotic pain reliever overdoses between 1999 and 2010. (See graph following this discussion.)
- For every woman who dies of a prescription painkiller overdose, 30 women go to the emergency department for painkiller misuse or abuse.

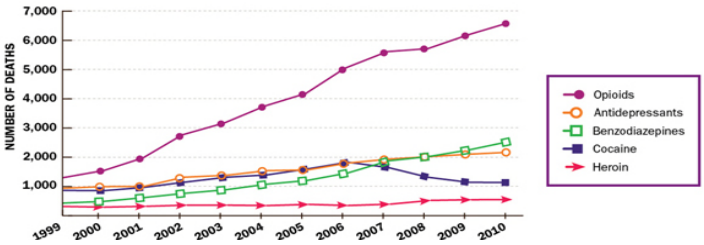
Women are affected in different ways from men because

- Women are more likely to have chronic pain, be taking prescription painkillers, be given higher doses, and use them for longer time periods compared to men; and
- Abuse of prescription painkillers by pregnant women can put an infant at risk. Cases of neonatal abstinence syndrome, a group of problems a baby experiences when withdrawing from exposure to narcotics or other drugs while in the womb, grew by almost 300 percent in the United States between 2000 and 2009.

Health care providers are asked to do the following to aid in containing the epidemic:

- Recognize that there is a risk of overdose with each prescription for opioids
- Discuss pain treatment options, including those that do not involve prescription drugs
- Discuss the risks and benefits of taking prescription painkillers, especially during pregnancy
- Follow guidelines for responsible painkiller prescribing, including
  - Screening and monitoring for substance abuse and mental health problems and prescribing only the quantity needed based on appropriate pain diagnosis;
  - Using patient-provider agreements combined with urine drug tests for people using long-term prescription painkillers;
  - Teaching patients how to safely use, store, and dispose of drugs; and
  - Avoiding combinations of prescription painkillers and benzodiazepines.
- Talk with pregnant women who are dependent on prescription painkillers about treatment options, such as opioid agonist therapy
- Use prescription drug monitoring programs or electronic databases that track controlled substance prescriptions in your state to identify patients who may be improperly using prescription painkillers and other drugs

Death by Overdose of Prescription Painkillers among Women



SOURCE: National Vital Statistics System, 1999-2010 (deaths include suicides)
www.cdc.gov/VitalSigns/pdf/2013-07-vitalsigns.pdf (accessed 070813)

In Arizona, A.R.S. § 36-2606 *requires* each medical practitioner who is licensed under Title 32 and who possesses a DEA registration to also possess a current controlled substances prescription monitoring program registration issued by the AZ State Board of Pharmacy. The Controlled Substances Prescription Monitoring Program (CSPMP) is a free program developed by the Board to promote the public health and welfare by detecting diversion, abuse, and misuse of prescription medications classified as controlled substances under the Arizona Uniform Controlled Substances Act. Providers must sign up with the AZ Board of Pharmacy to gain access to the program. Information can be accessed at this website: http://www.azpharmacy.gov/pmp/default.asp

New Indications for Latuda®

Sunovion Pharmaceuticals' lurasidone (Latuda®) is now approved as mono-therapy and adjunctive therapy with lithium or valproate for the treatment of adult patients with major depressive episodes associated with Bipolar I Disorder. Latuda received an indication for the treatment of patients with schizophrenia in 2010.

Abilify® Maintena™ approved

A new injectable depot formulation of the atypical antipsychotic aripiprazole was approved by the Food and Drug Administration (FDA) for the treatment of schizophrenia. The new formulation is a monthly intramuscular (IM) injection in the gluteal muscle that must be administered by a health care professional. It is available as 300mg and 400mg lyophilized powder for reconstitution.

Two Bioequivalents for Pristiq®

The FDA has approved two companies, Ranbaxy and Osmotica, to market desvenlafaxine as the free-base form; it will be available as 50mg and 100mg tablets. These two products will be bioequivalent to Pristiq, but will not be substitutable as the generic to Pristiq which is the only desvenlafaxine extended release tablet in succinate salt form. These newer products will be developed as extended release drug delivery technologies and plans are to have them on the market by third or fourth quarter 2014. Pristiq's patent expires on August 29, 2015.

Zubsolv®

Zubsolv® (buprenorphine/naloxone) sublingual tablet (C-III), indicated for the maintenance treatment of opioid dependence, received approval from the FDA. Orexo U.S. believes that this new tablet formulation will deliver more active ingredient to the bloodstream. This will allow patients to use a lower strength thereby reducing the amount of available drug for potential misuse and diversion. It should be available in fourth quarter 2013.

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The Treatment of Schizophrenia: Which Antipsychotic Is Best?

A comparison of 15 antipsychotic drugs used in the acute treatment of schizophrenia and related disorders was published recently. The study is a complex meta-analysis that uses both direct and indirect comparisons of randomized controlled trials, a process that the authors have used before in two previous multiple-treatments meta-analyses of major depressive disorder and bipolar mania. The group of scientists from Europe and the U.S. aimed to compare haloperidol and chlorpromazine with the atypical agents amisulpride, aripiprazole, asenapine, clozapine, iloperidone, lurasidone, olanzapine, paliperidone, quetiapine, risperidone, sertindole, ziprasidone, and zotepine to provide evidence-based hierarchies of the comparative efficacy, risk of all-cause discontinuation, and major side-effects of antipsychotic drugs. The analysis included both published and unpublished randomized controlled trials that were at least single-blinded—a total of 212 studies reported between October, 1955, and September, 2012, with 43,049 participants. The mean duration of illness was 12.4 years and the mean age of trial participants was 38.4 years.

The primary outcome was the mean overall change in schizophrenia symptoms, which was assessed in the first instance by change in the Positive and Negative Syndrome Scale (PANSS) or, if that information was not available, the Brief Psychiatric Rating Scale (BPRS). Secondary outcomes were all-cause discontinuation, weight gain, use of antiparkinson drugs as a measure of extrapyramidal side-effects, prolactin increase, QTc prolongation, and sedation. Studies in which antiparkinson drugs were given prophylactically were excluded from the analysis of extra-pyramidal side effects.

Conclusions reached by the authors can be summarized as follows:

- Clozapine was significantly more **effective** than all the other drugs and all drugs were superior to placebo. Amisulpride, olanzapine, and risperidone were significantly effective, followed by paliperidone and zotepine. The authors state that the hierarchy reported in this section was robust against many sources of bias, including various dose-related analyses. They suggest that there have been changes in study populations because the four most effective second-generation antipsychotic medications were the first to be developed. Also noted is that "clozapine was not more effective than any other second-generation antipsychotic in direct pairwise comparisons."
- All-cause discontinuation was used as a **measure of acceptability** because it encompasses efficacy and tolerability. All drugs, except zotepine, were significantly better than placebo. Amisulpride, olanzapine, clozapine, paliperidone, and risperidone had lower all-cause discontinuation than other drugs. These results paralleled the efficacy findings in that the "the most effective drugs also had the lowest discontinuation rates."
- All drugs caused more **weight gain** than placebo. Haloperidol, ziprasidone, and lurasidone produced less weight gain than other drugs. Olanzapine and zotepine produced the most significant weight gain, followed by clozapine, iloperidone, chlorpromazine, and sertindole.
- Clozapine produced fewer **extrapyramidal side effects** than all other drugs and placebo followed in ranking by sertindole, olanzapine, and quetiapine. Haloperidol topped the list even with doses lower than 12mg per day, followed by zotepine and chlorpromazine. Chlorpromazine did not produce significantly more side-effects than did most of the second-generation antipsychotics.
- Paliperidone and risperidone were associated with a more significant **prolactin increase** than all other drugs – more than one standard deviation from placebo. Aripiprazole, quetiapine, asenapine, chlorpromazine, and iloperidone did not cause significantly increased prolactin concentrations compared with placebo. Of note in this category is that there was no usable data for clozapine, zotepine, or amisulpride.
- Lurasidone, aripiprazole, paliperidone, and asenapine were not associated with significant **QTc prolongation**. Haloperidol was marginal and sertindole was almost one standard deviation worse than placebo. QTc data were not available for clozapine, chlorpromazine, and zotepine.
- Amisulpride, paliperidone, sertindole, and iloperidone were similar in **sedation** to placebo, followed by aripiprazole, lurasidone, risperidone, haloperidol, asenapine, olanzapine, quetiapine, and ziprasidone. Clozapine was the most sedating.

This article includes tables comparing all the medications, showing their effect sizes, Standard Mean Deviations (SMD), odds ratios, Numbers Needed to Treat (NNT), Numbers Needed to Harm (NNH), and the dosing used in the studies.

Leucht S, et al. Comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia: a multiple-treatments meta-analysis. *The Lancet*. Published online June 27, 2013. http://dx.doi.org/10.1016/S0140-6736(13)60733-3

Clozapine Solution

Versacloz,™ a new oral suspension formulation of clozapine, was approved for treatment of resistant schizophrenia and reducing suicidal behavior in adult patients with schizophrenia or schizoaffective disorder. Clozapine suspension, 50mg/ml in 100ml bottles, a product of Jazz Pharmaceuticals, is planned for launch in late Fall 2013.

Fetzima,™ a New Serotonin - Norepinephrine Reuptake Inhibitor (SNRI)

Levomilnacipran is the fourth SNRI in the U.S. with an indication for the treat-ment of major depressive disorder in adults. It is the L-enantiomer of the drug milnacipran, currently approved for the treatment of fibromyalgia, and it is marketed by Forest Laboratories. Studies have shown it to be the most nor-adrenergically active of the SNRI class, with a two-fold greater potency for norepinephrine relative to serotonin reuptake inhibition. Fetzima,™ which is taken once daily, will be available in 20, 40, 80, and 120mg dosages. The medication release is planned for fourth quarter 2013.

Zyprexa® Relprevv™ Deaths

The FDA is investigating two unexplained deaths in patients who received an intramuscular injection of the atypical antipsychotic olanzapine pamoate (Zyprexa Relprevv). The patients died three and fours days after receiving an appropriate dose of the drug, well after the three hour post-injection monitoring period required under the Zyprexa Relprevv Risk Evaluation and Mitigation Strategy (REMS). Both patients were found to have very high olanzapine serum levels after death. Patients are required to receive the injection at a REMS-certified health care facility, to be continuously monitored at the facility for at least three hours following an injection, and to be accompanied home from the facility. The labeling contains warnings about the risk of post-injection delirium sedation syndrome, a serious condition in which the drug enters the blood too fast following an IM injection, causing greatly elevated blood levels with marked sedation (possibly including coma) and/or delirium. Health care providers should follow the REMS requirements and label recommen-dations if therapy with olanzapine pamoate is started or continued. The FDA is continuing to evaluate these deaths and will provide an update as more information is available.