

Psychotropic Drugs in Children: Newer Perspectives on Therapy and Abuse

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ADHD and Stimulants

Hallucinations, Other Psychotic Symptoms in Children Linked to Use of ADHD Medications

- Current study rose from concerns voiced to the FDA regarding psychiatric adverse events related to the use of medications for ADHD
- Adverse events of interest in this study were hallucinations, delusions, schizophrenia, psychotic disorder, psychosis, paranoia, catatonia, mania, hypomania, and schizophreniform disorders.
- Researchers examined clinical trials of 9 medications for ADHD. In addition, they queried the FDA Adverse Event Reporting System safety database and manufacturers' databases for reports of psychiatric adverse events filed between 2000 and 2005.

Charles Vega, MD, FAAFP; Medscape CME
<http://www.medscape.com/viewarticle/587526>

Hallucinations, Other Psychotic Symptoms in Children Linked to Use of ADHD Medications

- 49 RCTs of ADHD treatment in 4028 pediatric patients for review. Atomoxetine, methylphenidate transdermal system, and dextromethylphenidate were the most common drugs studied.
- The rate of psychosis/mania events was 1.48 per 100 person-years in children receiving active treatment. In contrast, no such events were recorded in children receiving placebo.
- All ADHD medications were associated with psychosis/mania events in randomized clinical trials, except *Adderall XR*. However, *Adderall XR* was associated with psychosis in open-label trials.

Hallucinations, Other Psychotic Symptoms in Children Linked to Use of ADHD Medications

- There were 865 postmarketing case reports of psychosis and/or mania associated with ADHD medications in manufacturers' databases.
- Many of these cases (between 30% and 78%) were confirmed by a health professional.
- Symptoms resolved on cessation of treatment in 25% to 59% of these reports, but many files were incomplete with regard to follow-up.
- The vast majority of cases lacked risk factors that could confound a causative relationship between ADHD medications and psychosis/mania.
- Nearly half of postmarketing spontaneous reports of psychiatric events involved children 10 years old or younger.

Antipsychotics

Antipsychotics In Children And Adolescents: The Risks And Benefits

- Presented at the 21st Congress of the European College of Neuropsychopharmacology 2008, Barcelona, Spain
- From: Science News
<http://www.sciencedaily.com/releases/2008/09/080901205624.htm>

Antipsychotics In Children

• Efficacy

- Few well-controlled studies have assessed the efficacy, safety, and tolerability of antipsychotics in children and adolescents
- Antipsychotics have shown efficacy in the treatment of psychotic disorders in children and adolescents (schizophrenia, bipolar disorders), as well as conduct disorders, Tourette syndrome, and tics
- Antipsychotics have low rate of efficacy in children and adolescents with schizophrenia (< 50%)
- In some cases, first generation drugs may be as effective as SGAs

Antipsychotics In Children

• Metabolic and Hormonal Safety

In one study directly comparing weight gain and other metabolic and hormonal risk factors after treatment with 3 different new-generation antipsychotics in children and adolescents (mean age 15.2 years), it was shown that, after 6 months, body mass index scores and total cholesterol levels increased significantly, with 33 patients (50.0%) with no previous antipsychotic exposure showing significant weight gain

- The number of patients at risk for adverse health outcomes increased from 11 (16.7%) to 25 (37.9%).

Antipsychotics In Children

• Metabolic and Hormonal Safety

- Compared with children and adolescents not exposed to antipsychotic agents, a treatment cohort had twice the risk for obesity and triple the risk for type 2 diabetes mellitus.
- The prevalence of cardiovascular conditions and orthostatic hypotension/syncope was also increased in those treated with antipsychotic drugs.
- Pts given multiple antipsychotics had twice the risk for incident obesity or weight gain and type 2 diabetes mellitus and 5 times the risk for dyslipidemia.
- Conventional or multiple antipsychotics and mood stabilizers were linked to a greater incidence of cardiovascular events.

Antipsychotics In Children

• Metabolic and Hormonal Safety

In one cross-sectional study with 66 children, hyperprolactinemia was present in 78.6% and 48.5% in the short-term and longer-term treatment groups, respectively.

Antipsychotics In Children

• Abnormal involuntary movements

- In a cross-sectional study by our group, the presence of abnormal involuntary movements was compared in 60 children and adolescents who had taken antipsychotic medication for less than 1 month and 66 who had been receiving treatment with antipsychotics for more than 12 months
- The mean age of the total sample was 15.62 years. As many as 21.7% of short-term treatment group patients and 37.9% of longer-term treatment group patients presented mild dyskinetic movements.
- In a more recent study, a cohort of 110 early-onset psychosis patients followed for one year showed that neurological side effects (especially hypokinesia/akinesia) were more common with risperidone

Antipsychotics In Children

Study Author's Summary

- **What do we know?**

Early intervention with an effective and well-tolerated antipsychotic provides symptomatologic improvement in some mental disorders in children and adolescents that may modify the actual course of the disease associated with these disorders.

Children and adolescents seem to have a higher risk than adults for experiencing adverse events such as extrapyramidal symptoms, prolactin elevation, sedation, weight gain, and metabolic effects when taking antipsychotics.

Patients and their families should be included in a careful risk-benefit assessment before prescribing any specific antipsychotic.

Antipsychotics In Children

Study Author's Summary

- **What do we need to know?**
- There is a need for controlled studies in the case of disorders in which antipsychotics are being used without clinical evidence of

Depression

Lexapro

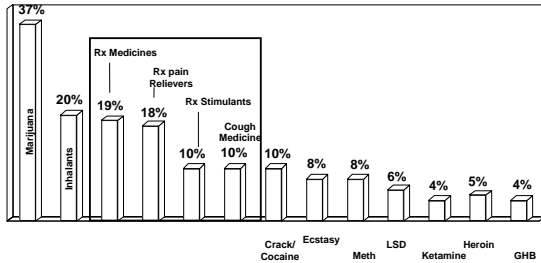
- Lexapro (escitalopram) approved for the acute and maintenance treatment of Major Depressive Disorder (MDD) in adolescents, 12 - 17 years of age (which affects approximately 2 million adolescents in the U.S.)
- The FDA's determination of the efficacy of Lexapro in the acute treatment of MDD in adolescents was established, in part, on the basis of extrapolation from this latter study. Interestingly, only Lexapro (escitalopram) and not generic citalopram (formerly Celexa) received the approval.

Comparing the SSRIs

- **Fluoxetine**
 - Affects 5HT and DA (NE)
 - “Activating”
 - Long half-life
 - Slow to steady-state
 - Good for reducing withdrawal likelihood
 - Potent Inhibitor of CYP 2D6
 - Potential for major drug interactions
- **Escitalopram**
 - 5HT reuptake only
 - May have faster clinical onset
 - Shorter half-life
 - No significant potential for interactions

Misuse and Abuse of Prescription Drugs: A Growing & Concerning Trend

The Good News . . . And the Bad!



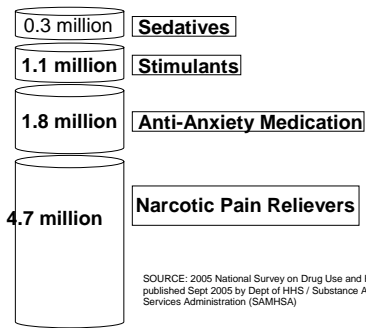
Abuse of Rx and OTC Medications

Partnership for a Drug-Free America Tracking Study (2005)

Scope of the Problem

- Unintentional poisoning deaths involving narcotics and hallucinogens grew 55 percent from 1999 to 2004.
 - Research suggests this is an increase attributed primarily to prescription painkillers. (CDC, 2007)
- Unintentional poisoning deaths involving psychotherapeutic drugs, such as sedative-hypnotics and anti-depressants, grew 84 percent from 1999 to 2004. (CDC, 2007)
- Between 1995 and 2005, treatment admissions for abuse of prescription pain relievers grew more than 300 percent. (TEDS, 2007)

In 2005, 6.4 million Americans Age 12+ used a prescription drug for non-medical purposes in past month



SOURCE: 2005 National Survey on Drug Use and Health (NSDUH), published Sept 2005 by Dept of HHS / Substance Abuse and Mental Health Services Administration (SAMHSA)

Prescription drug abusers

- Youth, elderly, women, pain patients
- Users with comorbid psychiatric conditions
- Substance abusers
 - Prescription drugs only
 - Prescription drugs plus other substances such as heroin (polydrug abusers)

Demographics ~ *Teens* “*Generation Rx*”

- In 2006, more than 2.1 million teens abused prescription drugs. (NSDUH, 2007)
- Every day, 2,500 youth (12-17) abuse a prescription pain reliever for the very first time. (SAMHSA, 2007a)
- One-third of all new abusers of prescription drugs in 2006 were 12- to 17-year-olds. (NSDUH, 2007)
- Three percent of teens (12-17) reported current abuse of prescription drugs in 2006 (< marijuana, > cocaine + ecstasy + meth + heroin. (NSDUH, 2007)
- Prescription drugs are the drug of choice among 12- to 13-year-olds. (NSDUH, 2007)

Why might there be an increase in prescription opioid abuse?

Increased availability of Rx Medications

Production quotas for prescription opioids have increased steadily across the last 10 years - due in part to a national movement to more aggressively treat pain

More prescriptions for therapy has direct correlation with greater amount of a abuse

Alternative to Other Illicit Drugs

- Post 9/11 decreased of imports of “illicit” drugs like Ecstasy”
- Perception that Rx drugs are safer

OTC Drug Misuse / Abuse

Dextromethorphan

- Dex
- Robo
- Skittles
- Triple CDM
- Rojo
- Velvet
- Red Devils

NIDA's "Monitoring the Future" 2006 Survey

Reports of intentional abuse of cough medicine by:

- 8th graders = 4% of all students
- 10th graders = 5% of all students
- 12th graders = 7% of all students

On par with abuse of other illicit drugs
among this population group

Why are they using Dextromethorphan?

- Friends are doing it
- It's legal (therefore more accessible)
- It's low-cost or free
- It's seen as being safer than other forms of illicit drug abuse

Source: 2006 CADCA Leadership Focus Group on OTC Cough Medicine Abuse

Dextromethorphan

- Pharmacology
 - D-isomer of levorphanol
 - Antagonist at glutamate (NMDA) receptors
 - Similar in mechanism to ketamine / Phencyclidine
 - "Recreational" Doses > 100 - 200 mg
 - Dissociative "high"
 - Mild distortions of color and sound
 - Strong visual hallucinations
 - "Out-of-body" sensations
 - Confusion
 - Incoordination

Dextromethorphan . . . the "dark" side

- Drowsiness and dizziness
- Delusions
- Panic attacks
- Memory problems
- Blurred vision
- Stomach pain, nausea, and vomiting
- High blood pressure and rapid heart beat
- Numbness of fingers and toes
- Fever and headaches
- Rashes and itchy skin
- Loss of consciousness

Additional problems from OTC DXM-containing products

Other active ingredients in DXM OTC products can be harmful when ingested in quantities above the recommended dosage.

Chlorpheniramine: Increased heart rate, lack of coordination, seizures

Guaifenesin: Vomiting

Acetaminophen: Liver damage



Where are these drugs coming from?

Source of Rx medications for non-medical uses or abuse

- Household Medicine cabinet
- Peers and family
 - Males obtain from peers
 - Females from family
- Inappropriate prescribing
- Fraudulent prescriptions
- Employee theft / Pharmacy theft
- Doctor shopping
- Rogue Internet “Pharmacies”
- Foreign diversion & smuggling into the U.S.

“Pharming”

- Practice of sharing, trading and mixing medicines
- Often mixed with alcohol
- Common among teenagers to have “pharming parties”
- Taken from family medicine cabinet
- Also share their own prescriptions in exchange for other pills

Combinations that could cause Serotonin Syndrome

Prescription Drugs

- SSRIs
- SNRIs
- Tricyclics
- Meridia
- Lithium
- Buspirone
- Meperidine
- Tramadol
- Methadone
- Triptans

OTC Drugs

- Dextromethorphan
- Chlorpheniramine

Illicit Drugs

- Ecstasy (MDMA)
- LSD, mescaline
- Methamphetamine
- cocaine

Other

- St John’s wort
- 5-HTP

Serotonin Syndrome Clinical Presentation

- Anxiety, restlessness, delirium
- Autonomic dysfunction
 - **Tachycardia**, HTN, diaphoresis, **hyperthermia**, vomiting, diarrhea
- Neuromuscular hyperactivity
 - Tremor, rigidity, **hyperreflexia**, clonus,
 - Usually more pronounced in lower extremities

Combinations that could cause Excessive CNS Depression

Prescription Drugs

- Antipsychotics
- Antiepileptics
- Anticholinergics
- Benzodiazepines
- Buspirone
- Lithium
- Opioids
- Sedative-hypnotics
- TCAs

OTC Drugs

- Antihistamines
- Sleep aids
- Dextromethorphan

Illicit Drugs

- GHB
- Ketamine

Other

- Alcohol
- Inhalants

Combinations that could increase risk of cardiovascular side effects

(Arrhythmias, tachycardia, high blood pressure, cardiac arrest, QT prolongation, etc)

Prescription Drugs

Tricyclic antidepressants

Stimulants

Atomoxetine

Bupropion

Many others

OTC Drugs

- Antihistamines
- Decongestants
- Energy supplements
- Diet supplements

Illicit Drugs

- Cocaine
- Ketamine
- Meth
- Ecstasy



Prevention

Preventing prescription drug abuse/misuse

School-based prevention

- Educate parents, school nurses, social workers, counselors, and principals about prescription drug misuse.
- Solicit school administrators such as school nurses, social workers, etc. to help monitor which students are prescribed medications and may be at risk for prescription drug diversion.

Preventing prescription drug abuse/misuse

Increasing the role of the provider

- Prescription drug abuse prevention is an important part of total patient care.
- Accurate screening and increases in select medication should be carefully monitored by providers as well as the patient receiving the medication.

Preventing prescription drug abuse/misuse

Increasing the role of the Parent

- Parents should make attempts to store their medications (particularly those that may be abused) in a safe and private place and be aware of missing doses or whole bottles of drugs.
- Parents should know where their children's medicines are kept and how many pills are in the bottle.

Conclusion:

Prescription Drug Abuse

- A real problem and it is growing
- Teens are the fastest rising population
- Perception that Rx and OTC meds are "legal" and safer.
- Many who abuse one drug, also combine and abuse others
- Adverse effects and interactions are causing increasing number of ER visits and deaths
- OTC drugs like dextromethorphan and Alcohol are also big players in the equation
- Prevention has many layers and can be complex at the political, societal, logistical, emotional and other levels.
- Education is critical