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THE PREMIER MONTHLY FORUM ABOUT THE USE OF PSYCHOTROPIC MEDICATIONS IN THE YOUNG

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Highlights...

Our page 1 stories this month focus on two hot-button topics: the dangers of relapse and overdose for young people coming out of drug-free rehab, and a caution about off-label use of antipsychotics in youth.

Inside

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SUBSTANCE USE DISORDERS

Dangers of overdose after coming out of drug-free rehab

précis

- The opioid epidemic is affecting young people, with many progressing to heroin.
- While the gold standard of treatment for adults is a medication, many young people get drug-free treatment instead.
- Young people are at high risk for relapse in the days and weeks immediately following treatment.
- Relapse could be fatal because they have lost tolerance.

It has been known for years that people formerly dependent on opioids who have been abstinent for a few weeks after inpatient treatment are at increased risk for overdose during that period. This was first proven in studies of people who had been incarcerated, and therefore abstinent. The seminal article on deaths after release from incarceration was published by Ingrid A. Binswanger and colleagues in *The New England Journal of Medicine* in 2007; at that time, drug overdoses — about half from cocaine and half from opioids — were the leading cause of death after release from incarceration (http://www.nejm.org/doi/full/10.1056/NEJMsa064115).

Increasingly, overdoses related to opioids upon release from incarceration have been blamed on people returning to their former doses. Likewise, many patients who go to drug-free treatment are at high risk for overdose upon release, again because it is assumed that they are returning to their

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DISRUPTIVE BEHAVIOR

Article warns against using antipsychotic medications for nonpsychotic children

Disruptive behavior and aggression are increasingly being treated with antipsychotic medications, prescribed off-label to control behaviors, especially in vulnerable children, like those in foster care. While antipsychotics are approved to treat pediatric psychotic disorders, as well as aggressive behaviors in children with autism, their off-label use, especially considering the largely unstudied developmental risks, raises questions.

For example, there are other therapies that are safer and equally effective, the authors write. These therapies should be considered first.

précis

- Antipsychotic use in children for off-label use to control disruptive behavior is on the increase.
- There are risks of adverse side effects of these medications on developing children, which should be balanced against benefits.
- Vulnerable children in foster care and the juvenile justice system are most likely to be prescribed antipsychotics off-label.
- Evidence-based psychotherapeutic interventions exist for disruptive behaviors but are not being utilized due to various barriers.

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expected to have a lower symptom severity than a clinical sample, but still be valuable to examining dimensions of psychopathology. They hypothesized that there would be both common and separable deficits in executive activation depending on the dimension of psychopathology; specifically, they predicted that, in general, psychopathology would be associated with hypoactivation, and that specific dimensions would have regional impairments within the executive network.

For the research, 1,129 youths, with a mean age of 15.5 years, completed a working memory task during functional magnetic resonance imaging (fMRI) as part of the Philadelphia Neurodevelopmental Cohort. A screening interview determined overall psychopathology, as well as four dimensions of symptoms: anxious misery (mood and anxiety), behavioral disturbance (ADHD and conduct disorder), psychosis-spectrum symptoms, and fear (phobias). The researchers examined the effect of psychopathology on behavioral performance and executive function.

Results

Psychopathology was associated with abnormal patterns of activation and a failure to activate executive regions within the cingulo-opercular control network, including the frontal pole, cingulate cortex, and anterior insula, which are associated with overall psychopathology. Psychosis-spectrum symptoms were associated with hypoactivation of the left dorsolateral prefrontal cortex, while behavioral symptoms were associated with hypoactivation of the frontoparietal cortex and cerebellum a different part of the brain. Anxious-misery symptoms were associated with hyperactivation of the executive network.

Increasing working memory load was associated with fewer correct responses and increased false-positive responses to foils, as expected. Higher levels of overall psychopathology and behavior symptoms were associated with lower working memory performance. In contrast, higher levels of anxious-misery symptoms were associated with better working memory performance. There was no relationship between fear or psychosis and working memory performance.

Implications

The findings show for the first time that there are common and separable deficits within the executive system of the brain that are present in youth with psychopathology.

The most robust finding shows that there are executive deficits that are attributable to psychopathology, present across diagnoses. The researchers used a bifactor analysis of item-level responses from the screening interview, which avoids the obstacles to estimating deficits across traditional diagnoses.

The orthogonal (statistically independent) dimensions were also associated with diminished activation in the case of behavioral symptoms related to externalizing disorders such as ADHD, conduct disorder, and oppositional defiant disorder. Anxious-misery symptoms, on the other hand, were associated with hyperactivation.

Limitations included the fact that this nonclinical sample had diminished symptom severity, and longitudinal data were not included. Substance use, which is known to affect executive function, was not included.

However, the data provide evidence that executive dysfunction is present across traditional psychiatric diagnoses, underscoring the relevance of executive function to conceptualization of psychiatric disorders. This is what the National Institute of Mental Health is encouraging with its Research Domain Criteria. The results suggest that interventions to improve executive function may not match existing diagnostic categories, and that it may be beneficial to use these interventions across diverse syndromes. Early interventions that mitigate executive dysfunction before negative outcomes accrue may be facilitated by this research. ■

The study was supported by the National Institute of Mental Health. Two authors declared relationships with pharmaceutical companies.

Shanmugan S, Wolf DH, Calkins ME, et al. Common and dissociable mechanisms of executive system dysfunction across psychiatric disorders in youth. *Am J Psychiatry* 2016 Jan 22. doi: 10.1176/appi.ajp.2015.15060725. Epub ahead of print.
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Antipsychotics

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Off-label use of antipsychotics in children is the predominant use, the authors wrote. For example, the most common diagnosis among children and adolescents receiving antipsychotics in one 2009 study was attention-deficit hyperactivity disorder (ADHD). Over the past 15 years, prescriptions for off-label antipsychotic use have increased dramatically, leveling off in young children in 2010 but continuing to rise in adolescents.

Randomized controlled trials have shown that antipsychotics are effective for children with bipolar manic symptoms, self-injurious and disruptive behavior in children with autism, and aggressive behavior in general. However, these trials have been brief, and most have been sponsored by the pharmaceutical industry, according to the article.

Risks

Short-term studies have provided most of the data on side effects of antipsychotic use by children. The side effects depend on the medication but have included somnolence, sedation, gastrointestinal problems, and excessive weight gain; other side effects include metabolic syndrome and hormonal effects (abnormal breast development, galactorrhea, amenorrhea, and hyperprolactinemia). Weight gain and hormonal effects are greater in children than adults. There are also neurological effects such as muscle rigidity, restlessness, and tardive dyskinesia, although these are less common with second-generation antipsychotics. The potentially fatal neuroleptic malignant syndrome is also rare with second-generation antipsychotics.

What concerns the authors is that the risk has not been assessed in longitudinal follow-up studies conducted with larger samples. They are also concerned about poor compliance with guidelines calling for monitoring children for metabolic and neurologic side effects.

It's possible that the more serious side effects persist after medication use. Furthermore, the long-term metabolic

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effects, whether the medication is continued or not, are mainly unknown in children. It is known that in young adults, antipsychotic use has led to obesity, diabetes, and heart disease.

Alternative therapies

There are few studies that have compared the effects of alternative therapies with antipsychotics, but several have shown that alternatives — either pharmacologic or psychotherapeutic — are effective. A recent trial found that children with ADHD and aggression that did not respond to methylphenidate or a stimulant often did well when a stimulant from a different group was titrated upward and combined with behavioral therapy. In addition, nonstimulant medications such as atomoxetine and extended-release formulations of guanfacine and clonidine are now approved for ADHD. And other medications that are not antipsychotics are also approved for pediatric bipolar disorder, such as lithium and divalproex sodium; however, these have possibly serious side effects requiring laboratory and clinical monitoring.

There are several short-term psychosocial interventions for disruptive behaviors and aggression that have well-established effects that are equal to medications:

- Manualized parent training (such as parent-child interaction therapy and parent training management—Oregon model).
- Cognitive behavioral techniques (such as problem-solving skills therapy).
- Multifocused interventions for adolescents (such as multisystemic therapy).

For children with autism spectrum disorders, the American Academy of Child and Adolescent Psychiatry work group has recommended psychosocial rather than pharmacological interventions as the first-line treatment for aggression.

Why are antipsychotics being used instead of these other interventions? The authors suggest several possible answers: advertising and marketing by manufacturers, increased diagnoses, difficulties obtaining hospitalization, difficulties obtaining other psychosocial treatments, lack of education, the willingness of prescribers and parents "to control behavior quickly despite potential side effects," and lack of access to mental health professionals who can deliver psychosocial interventions.

The researchers add that disruptive behaviors in children "are often related to disruptive parenting and stressful environments, which deserve primary attention." Children are vulnerable to the effects of medications because of their developing brains and bodies, but also because children with mental illness are already affected by high rates of economic disadvantage and stigma, the authors write. The most vulnerable — those in foster care or the juvenile justice system — are the most likely to receive antipsychotics. Finally, children, especially those with developmental disabilities or autism, already have difficulty describing their thoughts and feelings, and antipsychotics can further interfere with their ability to express themselves, the authors wrote.

Solutions

The authors recommend several solutions.

- **Prevention:** Extended maternal leave and family supports would be helpful. Many children receiving antipsychotics come from situations of family disruption, trauma, parenting changes, poverty, and other stressors, which can be addressed by prevention and early intervention.
- **Education:** Many mental health professionals are unaware of, or unable to provide, nonpharmacological interventions. Training should include education on safer medication strategies, and education of psychotherapists to use interventions for disruptive behaviors that are evidence-based.
- **Monitoring prescribing:** After training prescribers, compliance with guidelines needs to be monitored, as many clinicians don't follow the guidelines even in the cases in which they are aware of them. Monitoring can be done by prior authorization and other quality improvement strategies.
- **Shared decision-making:** Parents (and other guardians) and clinicians need more information about, and involvement in, deciding whether prescriptions should be used. Aids to promote discussions of benefits and harms would be helpful.
- **Courts and foster care:** Those charged with protecting vulnerable children, including state agencies, need to be better educated about these issues. "Decisions should not rest with public officials uninformed about the dangers of antipsychotics and unaware of the availability of safer alternatives," the authors wrote.

The authors conclude by calling on the National Institutes of Health, private foundations, and the pharmaceutical industry to study long-term clinical and developmental effects of antipsychotic use by children, and to support research on potentially safer pharmacological interventions, as well as psychosocial interventions for disruptive behavior and emotional disorders of children. "Clinicians have an ethical obligation to provide evidence-based treatment — but also to do no harm," the authors wrote. ■

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Daviss WB, Barnette E, Neubacher K, Drake RE. Use of antipsychotic medications for nonpsychotic children: Risks and implications for mental health services. *Psychiatr Serv* 2016 Jan 4. doi: 10.1176/appi.ps.201500272. Epub ahead of print