Diagnosis & Assessment in Pediatric Psychopharmacology

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• 50% of adults with a mental disorder reported onset by 14 years or younger

• In terms of burden of illness, mental and substance abuse disorders are, in fact, the predominant noncommunicable disorders of young people
2013 CDC Major Report on Mental Illness in Youth

• 1 in 5 youth has a mental illness
• Estimated yearly cost: $247 billion
• Because of their high prevalence, early onset, their impact on the child, family, and community, and its associated enormous cost Mental and behavioral disorders of the young represent a major public-health issue in the US (and across the world)
Most Prevalent Mental Illnesses in Youth

• ADHD (11%)
• Conduct disorder (3%)
• Anxiety disorders (3-5%)
• Depression (2%-4%)
• ASD (1%-2%)
• SUD (in prior yr 5%)
• Alcohol abuse (in prior yr 4%)
• Cigarette Dependence (prior month 3%)
• Suicide remains a leading cause of death in youth
Problem: Limited Manpower

• There are less than 7000 fully trained child and adolescent psychiatrists currently practicing in the US, despite estimates that over 30,000 would be required to meet the current demand.

• The need for services is projected to increase 100% by the year 2020, highlighting a growing mental health crisis.

• Increasing importance of the PCP in the management of children’s mental health problems
Problem: Prejudices and Misconceptions

- Pervasiveness of psychosocial and psychological hypotheses to explain childhood mental disorders
- Poor public acceptance for using pharmacotherapy in children
  - Bad Press
  - Frequent “alarming statistics” on the use of psychotropics in children
  - Diagnostic Conundrums (i.e., DSM-V Temper Dysregulation Disorder)
  - Diagnostic biases in the medical community (mental illnesses do not exist; they are accounted by other conditions; their treatment not necessary; “cosmetic” pharmacotherapy)
The Selling of Attention Deficit Disorder

By ALAN SCHWARZ

After more than 50 years leading the fight to legitimate attention deficit hyperactivity disorder, Keith Conners could be celebrating.

Severely hyperactive and impulsive children, once shunned as bad seeds, are now recognized as having a real neurological problem. Doctors and parents have largely accepted drugs like Adderall and Concerta to temper the traits of classic A.D.H.D., helping youngsters succeed in school and beyond.

But Dr. Conners did not feel triumphant this fall as he addressed a group of fellow A.D.H.D. specialists in Washington. He noted that recent data from the Centers for Disease Control and Prevention show that the diagnosis had been made in 15 percent of high school-age children, and that the number of children on medication for the disorder had soared to 3.5 million from 600,000 in 1990. He questioned the rising rates of diagnosis and called them “a national disaster of dangerous proportions.”

“The numbers make it look like an epidemic. Well, it’s not. It’s preposterous,” Dr. Conners, a psychologist and professor emeritus at Duke University, said in a subsequent interview. “This is a concoction to justify the giving out of medication at unprecedented and unjustifiable levels.”

The rise of A.D.H.D. diagnoses and prescriptions for stimulants over the years coincided with a remarkably successful two-decade campaign by pharmaceutical companies to publicize the syndrome and promote the pills to doctors, educators and parents. With the children’s market booming, the industry is now employing similar marketing techniques as it focuses on adult A.D.H.D., which could become even more profitable.
In April, 2000, Steven Hyman, a psychiatrist who at the time was the director of the National Institute of Mental Health, convened a meeting of nineteen prominent psychiatrists and psychologists in order to discuss bipolar disorder in children. The disorder has long been recognized as a serious psychiatric illness in adults, characterized by recurring episodes of mania and depression. (It is sometimes called manic depression.) People with bipolar disorder are often unable to hold down jobs; require lifelong treatment with powerful medications, many of which have severe side effects; and have high suicide rates. The disorder is thought to afflict between one and four percent of Americans and tends to run in families, although no genes for it have been identified. At the time of the meeting, few children had been given a diagnosis of the illness, and it was considered to begin, typically, in adolescence or early adulthood.

In the late nineteen-nineties, however, there was an increase in awareness of bipolar disorder in children, first in medical journals and then in places like BPParents, a list serf founded by the mother of an eight-year-old boy who had been diagnosed with the disorder. Hyman himself had been consulted by parents of children who, he told me, were “really suffering and extremely disruptive, having violent outbursts at school and at home, and hard to contain under any circumstances.” Many of the parents told Hyman that they believed their child had bipolar disorder, and they cited a book called BPParents, whose several hundred members are parents who suspect that their children have the disorder. “These children seem to burst into life and are on a different time schedule from the rest of the world right from the beginning,” the Papalos wrote. “Many are extremely precocious and bright—doing everything early and with gusto. They seem like magical children, their creativity can be astounding—"
In February, the American Psychiatric Association released draft revisions for the next iteration of its diagnostic manual (the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders [DSM-V]). As reported by Moreno and colleagues, the number of children with a diagnosis of bipolar disorder visiting outpatient clinics increased by a factor of 40. These children, some preschoolers, were...
The statistics are staggering: a sixfold spike, between 1993 and 2002, in the number of doctor visits in which kids and adolescents were prescribed antipsychotic drugs. Total tally in '02: 1.2 million. Antipsychotics are powerful drugs, typically used to treat severe mental illnesses like schizophrenia in adults—and they're not FDA-approved for children. But increasingly, doctors are prescribing newer generations of antipsychotics "off label" for a range of conditions in young people, from mood disorders to behavioral problems and ADHD.
Problem: Lack of FDA Approval for the Use of Many Psychotropics in Youth

- Absence of FDA approval is not synonymous with proscription of use
- Lack of FDA approval only denotes that the drug was not adequately studied for the particular condition, at a particular dose or for a particular age group
- When used off-label, risks, potential benefits and informed consent should be carefully documented
Black Box Fatigue

• Cardiovascular risk/sudden death for stimulants
• Suicidality/activation for antidepressants and anticonvulsants
• Metabolic syndrome/ TD for neuroleptics
• General uncertainties about long-term effects of psychotropics
ADHD Drugs and Cardiovascular Risk
Steven E. Nissen, M.D.

On February 9, 2006, the Drug Safety and Risk Management Advisory Committee of the Food and Drug Administration (FDA) voted by a narrow margin — eight to seven — to recommend a “black-box” warning describing the cardiovascular risks of stimulant drugs used to treat attention deficit–hyperactivity disorder (ADHD). This action was unexpected, largely because the FDA had not requested a review of current labeling for this class of drugs; it had merely asked for recommendations of approaches to studying the cardiovascular risks associated with these drugs. The committee, however, decided to take an independent course. As a consultant to this committee, I introduced two motions, one recommending the black-box warning and the other proposing the development of a guide for patients, which was approved by a vote of 15 to 0. The guides are handouts that are required to be provided at the time prescriptions are dispensed; they contain information, written in nontechnical language, about the potential hazards of the medication.

The drugs under review were primarily amphetamines (Adderall and other brands) and methylphenidate (Ritalin, Concerta, and other brands). These agents are closely related members of the class of sympathomimetic amines, the structures of several of which are shown in the diagram. These compounds exert potent stimulant effects on the cardiovascular and central nervous systems. One of the oldest such agents, methamphetamine, was originally synthesized in 1891 and first widely used during World War II in Nazi Germany to enhance the ability of Luftwaffe pilots to stay alert during extended hours of combat. Medical use of this agent is now limited, but illicit use has grown rapidly and now represents an increasing public health problem. When smoked or injected intravenously, methamphetamine (“speed”) is associated with hyperthermia, rhabdomyolysis, myocardial infarction, stroke, and sudden death — effects well known to coroners in regions of the United States where abuse is common. Beginning in the 1950s, the stereoisomer dextroamphetamine and related agents were introduced as appetite suppressants.

ADHD is a disorder commonly diagnosed in school-age boys (less commonly in girls) and is characterized by increased activity, an inability to concentrate, and poor school performance. The effectiveness of stimulants in...
CONCLUSIONS

This large study showed no evidence that current use of an ADHD drug was associated with an increased risk of serious cardiovascular events, although the upper limit of the 95% confidence interval indicated that a doubling of the risk could not be ruled out. However, the absolute magnitude of such an increased risk would be low. (Funded by the Agency for Healthcare Research and Quality and the Food and Drug Administration.)
Conclusions  Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events. Apparent protective associations likely represent healthy-user bias.

Results  During 806,182 person-years of follow-up (median, 1.3 years per person), 1357 cases of MI, 296 cases of SCD, and 575 cases of stroke occurred. There were 107,322 person-years of current use (median, 0.33 years), with a crude incidence per 1000 person-years of 1.34 (95% CI, 1.14-1.57) for MI, 0.30 (95% CI, 0.20-0.42) for SCD, and 0.56 (95% CI, 0.43-0.72) for stroke. The multivariable-adjusted rate ratio (RR) of serious cardiovascular events for current use vs nonuse of ADHD medications was 0.83 (95% CI, 0.72-0.96). Among new users of ADHD medications, the adjusted RR was 0.77 (95% CI, 0.63-0.94). The adjusted RR for current use vs remote use was 1.03 (95% CI, 0.86-1.24); for new use vs remote use, the adjusted RR was 1.02 (95% CI, 0.82-1.28); the upper limit of 1.28 corresponds to an additional 0.19 events per 1000 person-years at ages 25-44 years and 0.77 events per 1000 person-years at ages 45-64 years.

Conclusions  Among young and middle-aged adults, current or new use of ADHD medications, compared with nonuse or remote use, was not associated with an increased risk of serious cardiovascular events. Apparent protective associations likely represent healthy-user bias.
FDA issues Black Box Warning: Suicide Risk with Antidepressant

- 78 out of 4,400 cases in controlled clinical trials on all antidepressants in pediatric patients suffered increases in suicidal ideation and/or self-harm
  - 52 patients (3.8%) randomized to medications
  - 26 patients (2.1%) randomized to placebo

- No patients committed suicide or seriously harmed self

AACAP Joint Meeting of the Psychopharmacologic Drugs Advisory Committee and the Pediatric Advisory Committee September 28, 2004
% of high school students who felt sad or hopeless, who seriously considered attempting suicide, who made a suicide plan, and who attempted suicide

Antidepressant Medication and Suicide in Adolescents

\[ \beta = -0.23 \quad \text{(t}=5.14, \text{ } P<.001) \]

\( AD = \text{Antidepressant rate per 1000 Medication Users} \)

\[ AD = 11.54 \quad \text{and} \quad \text{Suicide} = 6.51 \]

\( Olfson \text{ et al., (2003) AGP 60 (10): 978-982} \)
Rates of Suicide Attempts During the 3 Months Before and the 6 Months After Initial Antidepressant Prescription

Pediatric Depression Treatment Declines After FDA Advisory on Antidepressants

Diagnoses of new cases of major depression in children and adolescents, and their antidepressant treatment, declined sharply over the 2 years following the first Food and Drug Administration (FDA) advisory about suicidality risk for pediatric patients taking selective serotonin reuptake inhibitors (SSRIs). Decreases in SSRIs and non-SSRI antidepressants for depressed patients ages 5–18 are shown by claims in a national database of managed health care plans analyzed by Libby et al. (p. 884). Psychotherapy did not increase after the advisory. This comparison of the 5 years before the FDA advisory in October 2003 with the 2 years afterward encompassed more than 65,000 children and adolescents with a new diagnosis of major depressive disorder. In addition, population-level depression rates fell in 2005 after steadily increasing. Dr. Cynthia Pfeffer comments on these trends in an editorial on p. 843.
Trends in the prescribing of psychotropic medications to preschoolers

• Main Findings
  – Psychotropic medications prescribed for preschoolers increased dramatically from 1991-1995 with the preponderance of medications with off-label (unlabeled) indications.
  – <2% of preschoolers receive various psychotropics

Zito et al JAMA. Feb 23;283(8):1025-30
MGH Study of Preschoolers

Types of Psychiatric Disorders in Preschoolers (N=200)

- Multiple Anxiety: 28%
- Mood: 43%
- Disruptive: 61%
- ADHD: 86%

MGH Study of Preschoolers: Preliminary Study of Psychopathology

Mean age at referral = 5.2 years

Diagnostic Categories

- ADHD
- Mood
- Disruptive
- Multiple Anxiety

Emerging evidence makes it possible to diagnose and manage ADHD in children from ages 4 to 18 (the previous AAP guidelines, from 2000 and 2001, covered children ages 6 to 12). The new guidelines describe the special considerations involved in diagnosing and treating preschool children and adolescents. They also include interventions to help children with hyperactive/impulsive behaviors that do not meet the full diagnostic criteria for ADHD.

“Treating children at a young age is important, because when we can identify them earlier and provide appropriate treatment, we can increase their chances of succeeding in school,” said Mark Wolraich, MD, FAAP, lead author of the report. “Because of greater awareness about ADHD and better ways of diagnosing and treating this disorder, more children are being helped.”
General Principles

• A successful pharmacotherapeutic intervention requires realistic expectations and initial diagnostic hypotheses with careful definition of target symptoms
  – i.e., the treatment of insomnia is very different if driven by existential concerns, mania, psychosis or depression

• While psychotropics can be highly beneficial, their use is not universally successful
General Principles

• The use of psychotropics should follow a careful evaluation of the child and the family
• Before beginning treatment, the family and the child need to be familiarized with the risks and benefits of such an intervention
General Principles

• Treatment should be started at the lowest possible dose with frequent reevaluation during the initial phase of treatment.
• Following a sufficient period of clinical stabilization (i.e., 6-12 months) it is prudent to reevaluate the need for continued psychopharmacologic intervention.
• This approach needs to be considered when the clinical picture has fully stabilized.
General Issues: Adverse Effects

• Certain adverse effects can be anticipated based on known pharmacologic properties of the drug (i.e., the anticholinergic effects of tricyclic antidepressants), while others, generally rare, are unexpected (idiosyncratic) and are difficult to anticipate
Components of the Diagnostic Process

- Psychiatric Assessment
- Cognitive Assessment
- Assessment of School Functioning
- Psychosocial Assessment
- Laboratory Assessments (when indicated)
Diagnostic Process: Cognitive Assessment

• Estimates of IQ
• Estimates of EFDs (i.e., working memory, processing speed)
• Estimates of academic performance: Achievement in math and reading
• Search for discrepancies between expected and actual functioning
• Distinguish Low achievement from Underachievement
  – Example: a brilliant child that is performing averagely in school may be underachieving
Diagnostic Process: Psychosocial Evaluation

– Evaluation of the family environment
  • Marital discord
  • Parenting difficulties
  • Separation and divorce
  • Custodial parent
  • Guardianship
  • Potential issues of abuse and neglect
Psychosocial Adversity

- Low SES (poverty)
- Family conflict
- Single parent homes
- Parental psychopathology
Findings from Rutter Study

Risk for Childhood Mental Disturbance

The Challenge of Psychopathology vs. Stress Reaction

- Normal Reaction
- Adjustment Disorder
- Major Psychiatric Disorders (such as Major Depressive Disorder or Anxiety Disorder)

Stress
Diagnostic Process: Psychosocial Evaluation

• Social Functioning
  – Relationship with peers
  – Relationship with parents
  – Use of leisure time
Diagnostic Process: Psychosocial Evaluation

• Social Functioning Assessment
  – Anamnesis
  – Questionnaires and Rating Scales
Diagnostic Process: School Functioning

- School Functioning
  - School and grade placement
  - Teacher information
  - Parent-based school information
Diagnostic Process: School Functioning

• Indices of school dysfunction
  – Repeated grades
  – Placement in special classes
  – Need for Tutoring
Diagnostic Process: School Functioning

- Parent-based school information
  - Parent-teacher conferences
  - Teacher reports
  - Teacher complaints
  - Observation
Indications for Major Drug Classes

- Stimulants
- Antidepressants
- Antipsychotics
- Mood stabilizers
- Anxiolytics
- Alpha adrenergic compounds
- Beta blockers
Indications for Major Drug Classes

• Stimulants
  – ADHD
  – Narcolepsy
  – Tx resistant depression
Indications for Major Drug Classes

• Antidepressants
  – Depressive disorders
  – Anxiety disorders
  – OCD (serotonergic)
  – ADHD (noradrenergic, dopaminergic)
  – Enuresis (TCAs)
Antidepressants Best for Anxiety Disorders

Treatment of Adolescent Depression
Effect Size for CDRS (ITT)

• Yet, the FDA did not provide any guidance for dosing limitations in pediatric patients
• If children were to be at the same or higher risk for Citalopram associated QTc prolongations as adults, such risk would require EKG monitoring in children prescribed doses >0.5 mg/kg 940 mg for an 80 kg adult).

SSRIs and QTc Prolongations: Summary of Pediatric Data

- Using an electronic medical record, mean QTc intervals were in the normal range for all antidepressants
- No single antidepressant was associated with a significantly greater QTc than others
SSRIs and QTc Prolongations: Conclusions

• Results suggest that:
  – Most antidepressants do not meaningfully and consistently prolong QTc at doses typically prescribed for children
  – Citalopram is not associated with significantly prolonged QTc at doses typically prescribed in children
Indications for Major Drug Classes

• Antipsychotics (atypical)
  – Psychotic disorders
  – Tourette’s disorder
  – Bipolar disorder
  – Dysphoric dyscontrol
  – Augmentation of antidepressants
Indications for Major Drug Classes

• Mood stabilizers
  – Bipolar disorder
  – Tx refectory depression
  – Dysphoric dyscontrol
Indications for Major Drug Classes

• Anxiolytics
  – Anxiety disorders
  – Augmentation of treatments for other disorders (BPD, depression, TS)
  – Severe situational anxiety
  – Tourette’s syndrome (high potency BZDs)
  – Stimulant induced anxiety
  – Insomnia
Indications for Major Drug Classes

- Alpha Adrenergic Compounds (clonidine, guanfacine)
  - TS/Tics
  - ADHD
  - Dyscontrol
  - SIB
  - Augmentation
  - Treatment emergent adverse effects (i.e., stimulant-induced insomnia)
Indications for Major Drug Classes

• Beta Blockers
  – Akathisia
  – Stage fright
  – Tremor
  – Dyscontrol
  – SIB
Indications for Combined Pharmacotherapy

- Comorbidity
- Treatment resistant cases: Augmentation
- Treatment emergent adverse effects
- Poor tolerability with therapeutic doses of individual medicines

Combined Pharmacotherapy

• Treatment resistant cases
  – Augmentation
  – Less than satisfactory response to a single agent
  – Potential synergy of combined agents for certain disorders
    • Combined Tx may permit the use of lower doses of two agents reducing the adverse effect profile associated with higher doses of a single agent
Combined Pharmacotherapy

• Comorbidity
  – High rates of psychiatric comorbidity in childhood psychiatric disorders
  – Irrespective of etiology, different disorders require different treatments
Combined Pharmacotherapy

• Vast array of potential combinations
• Clinicians should become familiar with potential psychopharmacological combination regimens
  – adverse effects [i.e., excessive sedation]
  – drug-drug interactions [i.e., fluoxetine plus TCAs]
Combined Pharmacotherapy

- Simple cases: monotherapy could be sufficient and should be preferred
- Complex cases: monotherapy may be insufficient and combined pharmacotherapy needs to be considered