ADHD medications

History

In an attempt to alleviate headaches, psychiatrist Charles Bradley administered Benzedrine sulfate, an amphetamine, to children at the Emma Pendleton Bradley Home in Rhode Island in 1937. This institution provided care for children with behavioral disorders. The drug had no effect on the headaches, but caused a remarkable change in the children's behavior. The children exerted "more conscious control over their activities and the expression of their emotions" and conducted "themselves with increased consideration and regard for the feelings" of others. In addition to improved emotional responses, the children showed improved social interactions and school performance. At the time, the study did not gain much attention because makers of the drug wanted to market the drug to a larger audience of healthy schoolchildren for cognitive enhancement. Research on Benzedrine was soon abandoned altogether when reports of abuse and addiction reached the media. Stimulants would not be used as a regular treatment of behavioral disorders until the 1950's, when the medical community began to focus on hyperactivity.

Strohl, M. P. (2011). Bradley's Benzedrine Studies on Children with Behavioral Disorders. *The Yale Journal of Biology and Medicine, 84*(1), 27–33.

Yet the first edition of the Diagnostic and Statistical Manual of Mental Disorders, published 1952, does not mention anything related to ADHD symptoms. In 1955 Ritalin was approved by the FDA for treatment of hyperactivity. In 1964 Conners published a study showing it reduced impulsivity in "emotionally disturbed children." When the second edition of the DSM came out in 1968 it included the disorder hyperkinetic reaction of childhood. In 1970 a Washington Post article spurred controversy around the diagnosis of the disorder and use of stimulants. The story discussed how 5-10% of all schoolchildren in Omaha, Nebraska were receiving stimulants to control their behavior. However, the statistics actually only referred to kids in special education programs. In 1975 the controversy grew. The belief that ADHD isn't a real diagnosis or was created by drug companies to make money emerged. Then in 1980, the third edition of the DSM came out, including diagnostic criteria for Attention Deficit Disorder. Also in 1980 the American Academy of Pediatrics published their first statement about ADHD symptoms, *Medication for Hyperkinetic Children*. It stated "there is a place for stimulant drugs in the treatment of hyperkinetic children." The fourth edition of the DSM described three types of ADHD: combined type, predominantly inattentive type, and predominantly hyperactive-impulsive type.

Iannelli, V. (2016). The History of ADHD. Very Well. www.verywell.com/adhd-history-of-adhd-2633127

Medication use in children

Data from 2011-2012 National Survey of Children's Health for children aged 4-17

- 69% of children with current ADHD were taking medication for ADHD (6.1%, 3.5 million children)
- The proportion of children taking medication for ADHD increased with ADHD severity: 59.6% for "mild" ADHD, 73.3% for "moderate" ADHD, and 82.4% for "severe" ADHD

- Prevalence of medicated ADHD increased by 28% from 2007 to 2011 (from 4.8% to 6.1%)

Visser, S. N., Danielson, M. L., Bitsko, R. H., Holbrook, J. R., Kogan, M. D., Ghandour, R. M., & ... Blumberg, S. J. (2014). Trends in the parent-report of health care provider-diagnosed and medicated attention-deficit/hyperactivity disorder: United States, 2003-2011. *Journal Of The American Academy Of Child And Adolescent Psychiatry, 53*(1), 34-46.

Medication use in children under 6

- Nearly 1/3 of children with ADHD (approximately 2 million) received the diagnosis before age 6
- 30% of children aged 3-5 taking ADHD medications experience adverse effects:
    - most commonly appetite suppression and sleep problems, but also upper abdominal pain ("stomach ache"), emotional outbursts, irritability, lack of alertness, repetitive behaviors and thoughts, social withdrawal, and irritability when the medication wears off
    - >10% discontinue treatment because of side effects
    - they experience annual growth rates that are 20% lower for height (-0.6 inches/year) and 55% lower for weight (-2.9 pounds/year)

Visser, S. N., Danielson, M. L., Wolraich, M. L., Fox, M. H., Grosse, S. D., Valle, L. A., & ... Peacock, G. (2016). Vital Signs: National and State-Specific Patterns of Attention Deficit/Hyperactivity Disorder Treatment Among Insured Children Aged 2-5 Years -- United States, 2008-2014. MMWR: *Morbidity & Mortality Weekly Report, 65*(17), 443-450.

The CDC compared Medicaid and employer-sponsored insurance claims for ADHD medication among children aged 2-5 years receiving clinical care for ADHD

- nearly 150,000 insured children aged 2-5 years received clinical care for ADHD
- over 75% received ADHD medication for treatment
- only about 50% received psychological services (including parent training in behavior therapy)

Visser, S. N., Danielson, M. L., Wolraich, M. L., Fox, M. H., Grosse, S. D., Valle, L. A., & ... Peacock, G. (2016). Vital Signs: National and State-Specific Patterns of Attention Deficit/Hyperactivity Disorder Treatment Among Insured Children Aged 2-5 Years -- United States, 2008-2014. MMWR: *Morbidity & Mortality Weekly Report, 65*(17), 443-450.

Limitations of medications

Stimulant formulas have advanced over the years in hopes of providing a longer duration of treatment benefit throughout the day. However, 280 of 290 primary caregivers surveyed could identify at least one period of the day when their child's/adolescent's ADHD symptoms were inadequately controlled. All the children in the study were currently taking stable doses of stimulant medications. Symptoms of ADHD were rated as most severe during the early morning routine and evening homework times of day. 60% of caregivers reported overall ADHD symptoms throughout the day as moderate to severe. Caregivers were also asked about their satisfaction with their child's/adolescent's current ADHD medication in providing meaningful

symptom relief, specifically during the early morning routine time of day. Most (39%) reported that they were only somewhat satisfied, 11% were not very satisfied, and 3% were not at all satisfied.

Sallee, F. R. (2015). Early morning functioning in stimulant-treated children and adolescents with attention-deficit/hyperactivity disorder, and its impact on caregivers. *Journal Of Child And Adolescent Psychopharmacology,* (7), 558.

Emerging Side Effects
Recent research has uncovered differences in bone health for children on ADHD medications.

- Data from NHANES on 5,315 children 8-17
- Bone health measured using DXA scans
- children on ADHD medication had lower bone mineral density in the femur (-0.4855 standardized BMD), femoral neck (-0.4671), and lumbar spine (-0.3947), relative to their peers not on ADHD drugs
- significantly more children on ADHD medications (38.3%) versus a match cohort not on ADHD medication had BMD in the osteopenic range (21.6%)
- stimulant medications can cause GI problems such as reduced appetite and upset stomach, which may contribute to poor nutrition and reduced calcium intake

Similar findings when researchers looked at adolescents.

- 4,303 NHANES participants aged 12-20 (mean age 15)
- completed a DXA scan
- SSRI use was an independent predictor of bone mass
- total femur BMC was 8.8% lower among SSRI users versus non-users, while total femur BMD was 6.1% lower
- lumbar spine BMC was 7% lower among SSRI users and BMD was 3.2% lower compared to nonusers

Feuer, A. J., Demmer, R. T., Thai, A., & Vogiatzi, M. G. (2015). Use of selective serotonin reuptake inhibitors and bone mass in adolescents: An NHANES study. *Bone, 78*, 28-33.

United States vs. other countries

About 11% of children in the U.S. have been diagnosed with ADHD, while only 4% of children in France have been diagnosed with ADHD (CFFS, 2016). The difference in prescription rates between the U.S. and France stems from scientific and cultural disparities. In the U.S., one health professional utilizes the American Psychiatric Association's Diagnostic and Statistical Manual to diagnose ADHD. The professional gets inputs from parents and teachers regarding a child's symptoms. A diagnosis can be made over a short period of time. In France, professionals more often consider a child's underlying social circumstances. In the U.S. ADHD is recognized as a biological disorder. In France, ADHD symptoms are initially viewed as a reaction to environmental factors (e.g. trauma) or attributed to other diagnostic categories such as behavioral expression of internalized disorders. Thus professionals in France consider lifestyle, environment, and family situation, in addition to a behavioral checklist. The average time between first appointment for symptoms and diagnosis is 2.8 years. (In Italy it is 3.1 years!)

(Purper-Ouakil & Cortese, 2008). Health professionals receive feedback from parents and teachers across 6 months to 1 year. Medication in France is not the cultural norm as it in the U.S. In fact, it is illegal to prescribe stimulants to children under age 6 (CFFS, 2016).

Child and Family Support Services. (2016). ADHD in France and the United States. https://cfss.com/adhd-in-france-and-the-united-states

Purper-Ouakil, D. & Cortese, S. (2008). Delay of Attention-deficit-Hyperactivity Disorder Diagnosis in France - Reasons and Resolutions. *European Psychiatric Review*. www.touchophthalmology.com/sites/www.touchoncology.com/files/migrated/articles_pdfs/cortese.pdf

- More than 90% of Shire's sales of ADHD medications (Adderall and Vyvanse) come from the U.S., where the illness is diagnosed 25x more frequently than in the U.K.
- Shire had $1.8 billion in ADHD drug revenue in 2012
- Adderall and its generic equivalents are not approved in Europe
    - But account for 41% of U.S. prescriptions
- Most ADHD medications are sold in the U.S., but other countries are catching up
    - In 2007, the United States consumed 83% of the global supply of stimulant medication
    - In 2013 this dropped to 66%
    - Scandinavian countries now outpace the U.S. in growth of prescriptions
- Concerta is the most commonly prescribed ADHD medication in Europe
    - Sales grew 7% in 2012

Kelley, T. (2013). ADHD Pill Faces High Hurdle in Europe as Stigma Persists. Bloomberg. www.bloomberg.com/news/articles/2013-10-01/adhd-pill-faces-high-hurdle-in-europe-as-stigma-persists

Costs

Data from the IMS Health database across 10 years (1994-2003)

- U.S. expenditures for ADHD medications increased 594%, sales volume rose by 80%, and price increased by 285%
    - expenditures went from $304 million in 1994, to $658 million in 1999, and to $2.11 billion by 2003
    - the sales volume was 851 million standard units in 1994, 1.5 billion standard units in 1999, and 1.53 billion standard units in 2003
    - the real average price per standard units was $0.36 in 1994, it rose to $0.44 in 1999 and to $1.38 in 2003
- In countries with a lower per capita GDP, expenditures increased 149%, sales volume 464%, however price decreased by 37%

Possible reasons for these statistics:

- Prior to 1994, the U.S. market was already dominant, and there was relatively little room for increase

    - helps explain why the increase in the rate of volume growth in the U.S. was lower compared to that of countries with a lower per capita GDP
- The U.S. adopted the new DSM diagnosis criteria earlier than most European OECD countries, which might explain the high market share in ADHD medication spending
- The National Institute for Clinical Excellence of the UK recommends that medication be reserved for use in children with severe symptoms
- International Statistical Classification of Diseases and Related Health Problems (ICD) has narrower diagnostic criteria than the DSM

Lang, H., Scheffler, R. M., & Hu, T. (2010). The discrepancy in attention deficit hyperactivity disorder (ADHD) medications diffusion: 1994–2003—A global pharmaceutical data analysis. *Health Policy, 97*, 71-78.

Effects of untreated childhood ADHD → effects into adulthood

Untreated ADHD is among the most debilitating disorders to live with. Symptoms can negatively affect:

- school and academic achievement
- self-esteem and satisfaction
- sexual behavior (unwanted pregnancies, STDs)
- family and social relationships
- criminal activity
- eating habits
- occupational status, job performance
- driving ability

childhood:

- Up to 58% of children who were not medicated for their ADHD failed a grade in school - 46% had been suspended from school[1]
- when comparing treated ADHD patients to untreated ADHD patients, improvement in both achievement tests and academic performance outcomes have been observed
- children with ADHD are 12x more likely to have loss of control eating syndrome than kids without ADHD[2]

adolescence:

- Up to 30% of adolescents with untreated ADHD fail to complete high school, compared with 10% of those without ADHD[1]
- 38% of young adults with unmedicated ADHD have been pregnant or have caused an unwanted pregnancy vs. 4% of those without ADHD[1]
- 17% of young adults with ADHD have contracted a sexually transmitted disease vs. 4% of those without[1]
- young drivers with untreated ADHD have 2-4x as many motor vehicle crashes as their peers without ADHD[1]
    - their risk of destroying a car may be even higher than that of an adult who is legally drunk[1]

    - stimulants used to alleviate ADHD can reduce symptoms such as inattention, distractibility, and impulsiveness that have implications on driving skills[2]
- adolescents with untreated ADHD face 3-4x the rate of substance use disorder vs. medicated ADHD patients[2]

adulthood:

- Adults with unmedicated ADHD are 78% more likely to be addicted to tobacco and 58% more likely to use illegal drugs than those without ADHD[1]
- 79% of adults with ADHD who were not treated as children experience symptoms of anxiety, depression, and physical ailments vs. 51% of adults without ADHD[1]
- 25% of individuals in prison in the United States have ADHD (like due to impulsivity and poor self-regulation)[2]
    - as rates of antidepressant and stimulant prescriptions rose in the United States from 1997 to 2004, the rate of violent crime dropped[2]
- increased difficulty getting jobs and keeping them
    - make $8,900 to $15,400 per year less than non-ADHD employees[2]
    - less likely to be currently employed (52% vs. 72%)[2]
    - had more job changes over a 10-year period (5.4 vs. 3.4 jobs)[2]
- Adults with untreated ADHD are nearly twice as likely to get separated or divorced from their spouses[2]

1. Kessler, E. Based on a presentation by Alan Wachtel, MD. Smart Kids with Learning Disabilities. www.smartkidswithld.org/getting-help/adhd/untreated-adhd-lifelong-risks
2. Williams, P. (2015). Children Who Don't Get ADHD Treatment Can Have Problems Into Adulthood. Healthline. www.healthline.com/health-news/children-who-dont-get-adhd-treatment-can-have-long-lasting-problems-into-adulthood-051215

Rising emergency department visits

Between 2005 and 2010, the number of emergency department visits involving ADHD stimulant medications:

- Increased from 13,379 to 31,244 visits overall
- Increased from 2,131 to 8,148 visits among persons aged 18 to 25
- Increased from 5,212 to 15,585 visits involving nonmedical use
- Increased from 5,085 to 9,181 visits involving adverse reactions

Substance Abuse and Mental Health Services Administration (SAMHSA), Center for Behavioral Health Statistics and Quality. (January 24, 2013). The DAWN Report: Emergency Department Visits Involving Attention Deficit/Hyperactivity Disorder Stimulant Medications. Rockville, MD.

Stimulant abuse among college students

- 2012 National Survey on Drug Use and Health interviewed 37,869 adults

- About 4% said they have used methylphenidate
- Two-thirds of the adults who said they have taken methylphenidate were aged 18-25

"I think since it's so prevalent now that people aren't scared to take it anymore. It's just like candy around here. It's like eating skittles" (Cutler, 2014). The Yale Daily News, the Harvard Crimson, the Daily Princetonian, and the Stanford Daily are among the college newspapers that have recounted the growing use of stimulants on campus. Stimulants are attractive to college students especially during exam time because they can reduce the feeling of fatigue and increase alertness. This may help students increase concentration, study longer, and complete assignments. Students also cite desire to lose weight, party longer, and get high as other motivational factors. The prevalence of misuse of prescription stimulants among college students ranges from about 4-11%. Caucasian race, affiliation with a fraternity or sorority, having a prescription for the medication, abuse of alcohol or other drugs, and use of energy drinks and tobacco products have been associated with stimulant misuse (Gallucci & Martin, 2015).

Data from 682 students at a private Southwestern university revealed that 95 (13.9%) students admitted to misusing stimulants in the past year. Of those 95, 19 had misused medication from their own prescription, 73 had misused someone else's medication and 1 had done both. The majority of those reporting the misuse of someone else's medication reported receiving the medication from a friend. However, other sources included parents and drug dealers. The most common motivational factors reported were to concentrate better while studying (77.4%), to study longer or to complete major assignments (68.8%), and to improve mental focus (52.7%) (Gallucci & Martin, 2015).

Due to the high potential for abuse, in 1972 that the U.S. Food and Drug Administration classified amphetamines and methylphenidate as Schedule II medications, the strictest form of control for legal substances. Although the misuse of stimulants can lead to unintended consequences such as cardiac events, dehydration, insomnia, substance dependence, and even death, students do not often worry about the negative side effects. Students from a large northwestern university divulged that there is an overall sense of safety and normalization surrounding prescription stimulant misuse. "When participants were asked to check off what prescription drugs that they had used for nonmedical purposes, many students forgot to mention Adderall and other ADHD medications all together because they simply do not view these drugs as 'drugs.'" In fact, students compared taking prescription stimulants to consuming coffee or energy drinks (Cutler, 2014).

Cutler, K. A. (2014). Prescription Stimulants Are "A Okay": Applying Neutralization Theory to College Students' Nonmedical Prescription Stimulant Use. *Journal Of American College Health, 62*(7), 478-486.

Gallucci, A. R., & Martin, R. J. (2015). Misuse of prescription stimulant medication in a sample of college students: Examining differences between varsity athletes and non-athletes. *Addictive Behaviors, 51*, 44-50.