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Side Effects of Stimulants

- Summary

Stimulants: Side Effects

- Most tolerate well
  - 5% discontinue due to negative effects
- Side effects are dose dependent
- Most common side effects:
  - Insomnia (50% +)
  - Loss of Appetite (50% +)
  - Headaches (20-40%) or Stomach Aches (20-40%)
- Irritability, tearfulness (<10%)
- Nervous Habits & Mannerisms (<10%)
  - Tics (<3%) and Tourette's (Rare)
- Mild Weight Loss (Average 1-4 pounds; transient)
- Small effect on height during 1st year (Approx 1cm)
  Increased heart rate (3-10 bpm)
- Increased blood pressure (1.5-14 mmHg)
- Psychosis (<3%)

- Contraindicated in folks with
  - uncontrolled hypertension
  - other symptomatic forms of cardiac disease
  - hyperthyroidism
  - active seizures
  - narrow-angle glaucoma
  - during use of or within 14 days of discontinuation of MAOI antidepressants
- Growth:
  - General
    - Growth on weight and height curves tend to slow during stimulant treatment, but appear to return to normal when medicine stopped
    - Monitor weight and height with pediatrician and psychiatrist
  - Weight
    - Less appetite in 14-22% vs. 2-6.4% with placebo
    - Primarily within the first year of use
    - Usual loss of weight is 1 kg or less
    - To minimize effects on weight (data from Waxmonsky et al, 2020 suggests this may not help slowing of height velocity):
      - closely monitor weight and height with psychiatrist and pediatrician
      - give with or after meals
      - give high-protein, high calorie breakfast when possible
      - give high calorie snacks, especially in early morning and late evening; encourage grazing
      - use nutrient dense meals (e.g., yogurt, cottage cheese, peanut butter, turkey, granola)
      - may want to enlist the expertise of a nutritionist
      - try high-protein drinks/shakes/smoothies
      - avoid soft drinks and overly refined foods; fruit juice (but not too much) and water is better

- schedule outdoor play before meals when possible (even a quick walk)
- give a daily multivitamin
- drug holidays; no evidence of working in clinical research, but anecdotal evidence
- possible medications to help with appetite problems
  - cyproheptadine, 4-8 mg/day (4-20 mg/day in adults), may also be helpful; adverse effects: sleepiness, dry nasal mucosa (with bloody nose), facial swelling
  - mirtazapine, 3.75-15 mg/pm

◦ Height
- **Evidence indicates that children with ADHD may be somewhat smaller than their counterparts without ADHD prior to puberty and catch up with their peers during adolescence; this is not associated with stimulant use**
- Slowing of growth appears to be at least partly related to decreased appetite and food intake
- Stimulants do not affect growth hormone or pubertal development
- Height velocity, or yearly growth, typically slows for the first few years of stimulant therapy and then resumes at a nearly normal rate, and pubertal development is normal; adult height usually normal)
- There appears to be little to no significant impairment of height attained in adulthood (Kramer, 2000; Mannuzza, 1991)
  - With long term (2-3 years+) treatment, slowing of growth is usually minimal, though more significant slowing may occur in a subset of patients (?10%?)
  - There are NO published studies which have reported the final adult height of patients treated continuously from childhood through adulthood; the best estimate risk of decrement in height in long term use of stimulants is ~2 cm (0.2-3 cm range)
- Rebound in growth or habituation to this effect seems to occur with time
- Slowing of growth may be greater in:
  - Pre-pubertal children (vs. adolescents)
  - Boys (vs. girls)
  - Children who are tall (vs. average or short)
  - Children are overweight (vs. average or underweight)
  - Children treated with sustained release formulations (vs. immediate release/shorter acting meds)
  - Children treated with higher drug doses (controversial)
- More prevalent with dextroamphetamine

The Effects of Methylphenidate Treatment on Child Growth in Thai Children and Adolescents with Attention-Deficit/Hyperactivity Disorder

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Objectives: To determine the effects of methylphenidate treatment on child growth in Thai pediatric patients with attention-deficit/hyperactivity disorder (ADHD). Methods: The medical records of children and adolescents with ADHD, between 5 and 18 years of age, who received pharmacological treatment with methylphenidate as a sole psychiatric medication for ≥1 year between 2001 and 2018 at the Rajanagarindra Institute of Child Development, Thailand, were retrospectively reviewed. Data on anthropometric parameters and methylphenidate use were extracted. Height and weight were converted to age- and gender-corrected standard scores (z -scores) using norms from the Thai pediatric population. Changes in height and weight z -scores were assessed using a paired t -test or one-way repeated measures ANOVA with the Bonferroni correction. Results: In this retrospective observational study, 911 children and adolescents were eligible, with the mean age of 95.0 ± 19.5 months at baseline, the cumulative duration of methylphenidate treatment of 39.4 ± 23.5 months, and the average daily dosage of 14.1 ± 6.2 mg/day. **Comparative analysis found no statistically significant change in height z -scores between baseline and last recorded measurement** (mean difference = 0.0017, confidence interval [95% CI] = -0.0004 to 0.0038, p = 0.107), **while a slight, but significant increase in weight z -scores was observed** (mean difference = 0.0271, 95% CI = 0.0179-0.0362, p < 0.001). **Longitudinal analysis observed that weight z -scores were significantly decreased during the first year of therapy, but regained in the second year and continued to increase in subsequent years of therapy. Conclusion: Treatment with methylphenidate in our cohort of Thai pediatric patients with ADHD was not associated with growth deficits, except for a slightly significant decrease in weight during the first year of therapy.**

Psychostimulants: Influence on Body Mass Index and Height in a Pediatric Population with Attention-Deficit/Hyperactivity Disorder?

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Journal of Child and Adolescent Psychopharmacology 2018 May 16

OBJECTIVES: Attention-deficit/hyperactivity disorder (ADHD) is often treated with psychostimulants. Psychostimulants' adverse effects on body mass index standard deviation score (BMI-sds) and height in children/adolescents with ADHD have been reported. However, literature is inconsistent, and it is unclear whether the observed effects are dosage- and/or BMI-dependent. Therefore, the aim of this retrospective observational study is to evaluate the influence of psychostimulants on BMI-sds and height-sds in a pediatric cohort with ADHD from an outpatient clinic, and to study the correlation between psychostimulant dosage and BMI-sds and height-sds change.

METHOD: Participants ≤18 years of age diagnosed with ADHD who started with psychostimulants (methylphenidate) were studied. Changes in BMI-sds and height-sds over an 18-month treatment period were assessed in subgroups according to baseline BMI-sds, gender, and age. Furthermore, correlations between BMI-sds, height-sds, and psychostimulant dose were studied.

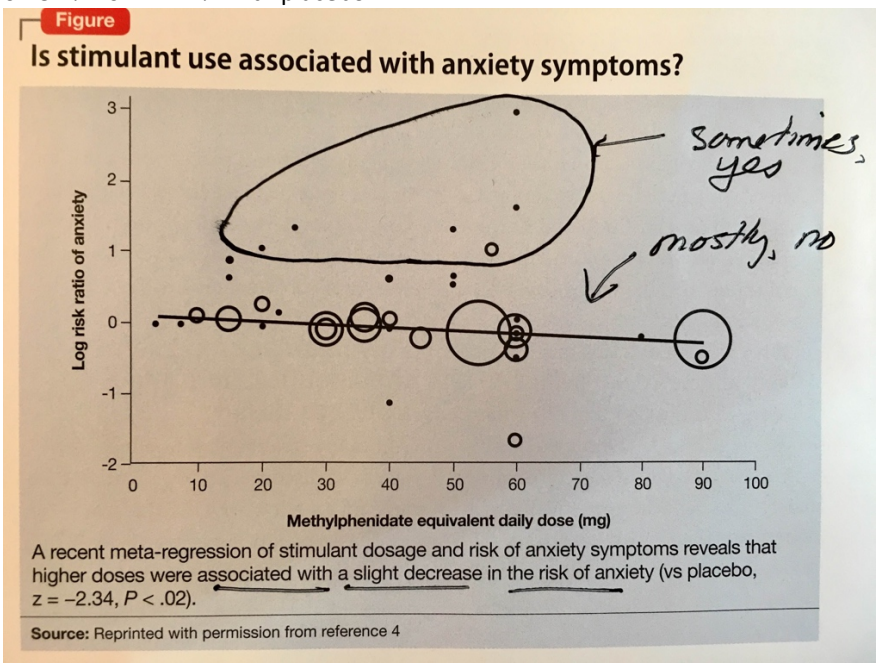
RESULTS: In total, 298 participants [median age 9.8 years, height-sds 0.0, BMI-sds 0.5, psychostimulant dosage 0.5 (0.2-1.4) mg/kg/day] were analyzed, with an underweight, overweight, and obesity prevalence of 5%, 21%, and 7%, respectively. After 18 months of treatment a significant decline in BMI-sds (-0.4) and height-sds (-0.2) was observed. These effects were consistent in all subgroups except for no change in BMI-sds in the underweight subgroup and no change in height-sds in

the overweight subgroup. Medication dosage was weakly correlated with change in BMI-sds [r = -0.3 (-0.9 to +0.5); p < 0.01] and height-sds [r = -0.2 (-0.4 to -0.1); p = 0.01].
CONCLUSION: After 18 months of psychostimulant treatment, a significant decline in BMI-sds and height-sds was observed. However, the correlation with psychostimulant dosage was weak, and the decline was not observed in all subgroups. Therefore, further studies on the etiology of BMI-change are warranted, particularly with regard to the ADHD symptoms.

Effect of methylphenidate on height and weight in Korean children and adolescents with attention-deficit/hyperactivity disorder: a retrospective chart review
Hyo-Won Kim, Seon-Ok Kim, Seunghyun Shon, Jung-Sun Lee, Hyun-Jeong Lee, Jin-Ho Choi *Journal of Child and Adolescent Psychopharmacology 2014, 24 (8): 448-53*
OBJECTIVE: The purpose of this study was to investigate the effect of methylphenidate (MPH) on growth in Korean children and adolescents with attention-deficit/hyperactivity disorder (ADHD).
METHODS: The medical records of 157 subjects (mean age 8.9±2.2 years; 134 boys) with ADHD who received treatment with MPH for at least 1 year at the Department of Psychiatry at Asan Medical Center were retrospectively reviewed. Height and weight were prospectively obtained and retrospectively gathered. Height and weight were converted to age- and gender-corrected standard scores (z scores) using norms from the Korean population. Growth changes were analyzed from the starting to the end of treatment using random coefficients models with change in weight or height z score as the dependent variable.
RESULTS: Weight (β = -0.109, p<0.001) and height (β = -0.072, p<0.001) z scores significantly decreased during treatment. Weight z score decreased more in girls (β = -0.247, p<0.001) than in boys (β = -0.090, p<0.001). Weight z score decreased during the 1st year of medication (β = -0.327, p<0.001 for boys; β = -0.646, p<0.001 for girls), and did not change or increase after the 1st year. Height z score significantly decreased during treatment (β = -0.072, p<0.001) after controlling for the effect of age at treatment, gender, mean daily mg/kg dose, and comorbid depressive disorder. Height z score also decreased during the 1st year of medication (β = -0.089, p<0.001) but did not change after the 1st year.
CONCLUSIONS: These results suggest that MPH could be related to weight and height deficit in Korean children and adolescents, although the effects were minor, and disappeared after the 1st year. Because of the limitations of this study such as retrospective design, selection bias, and high attrition rate, further prospective studies are needed.

    - Swanson et al, 2007, 2013:
        - growth deficit found to persist in future years in continuously treated children
        - data from MTA study should eventually yield definitive information on youth treated continuously up to adulthood; so far, there is some data suggesting growth deficits of up to 1 inch persisting after 10-12 years of treatment (from age 8 to 18-20)
    - JAACAP, 2006 (2 studies): confirmed that stimulant treatment in children with ADHD for up to 3 years has a negligible effect on adult height and weight (drug holidays had no impact).
        - Spencer, et al, 2006: 178 children 6-13 yo taking Concerta for 21 months or longer; an average of 0.23 cm less than expected heights at 21 months; an average of 1.23 kg less than expected at month 21 (after a 4 month period of no growth in weight); drug holidays made no difference
        - Plizka, et al, 2006: children on methylphenidate vs. Adderall for 3 years; both had virtually no effect on height; Adderall had slightly greater effect on weight
    - MTA study, 2004: **youth on stimulants grew an average of 1.4 cm less than those not on stimulants**
        - **for those children who took stimulant medications (immediate release) for 24 months, there appeared to be a modest growth suppression of 1.7 cm in height and 1 kg in weight**
        - **after 2 years, the differences widened to 3.7 cm in height and nearly 5 kg in weight.**
        - **data on folks treated continuously have had a growth deficit of about 1 inch which has persisted after 10-12 years of treatment (from about ages 8 to 18-20).**
- Insomnia
    - 4-17% (up to 20% with Concerta) vs. 2-7.2% with placebo; the percentage is higher in my experience
    - compare to pre-medication sleeping pattern; patients with ADHD often have delayed sleep phase even in the absence of medication
    - often transient (not infrequently chronic)
    - Mick and Biederman, 2006: stimulant treatment either had no impact on insomnia or improved it
    - may need to adjust the timing or dose of the medication
    - may need to change stimulant medication
    - may need an additional medication for ADHD-related sleep disorders (e.g., melatonin, clonidine, gunafacine, Remeron, trazodone)
    - monitor level of energy during the day (and sleeping in class)
    - possible medications to help with insomnia
        - melatonin 1-10 mg/pm 1-3 hours prior to desired sleep time
            - Keijzer et al, 2011; melatonin 5 mg vs. placebo in 62 youth with ADHD aged 6-12, 40% of which we're on stimulants
                - Significant reduction in sleep latency by 17 minutes
                - Time of sleep onset 57 minutes earlier
                - Well tolerated
            - General
                - Plasma levels peak at 1 hour

        - Minimal effect on sleep architecture
        - Dosing
            - 0.1-1 mg for ages 6-8
            - 2.5-3 mg for ages 8-12
            - 3-5 mg for adolescents
            - 3-10 mg for adults
            - (or 0.5 mg 5-7 hours before traditional sleep onset time)
    - clonidine 0.05-0.2 mg/pm
    - tricyclic antidepressant imipramine 25-50 mg/pm
    - trazodone 25-100 mg/pm
    - mirtazapine 3.75-15 mg/pm 1-3 hours prior to desired sleep time
    - Benadryl 25-50 mg/pm
- Headache
    - 9-14% (up to 30% with Concerta) vs. 8.4% with placebo; less common in my experience
    - often transient
    - minimize by giving medicine during or right after meals
    - may need to adjust the timing or dose of the medication
    - may need to change the medication
- Stomach ache
    - 7-14% (11-18% if vomiting is included) vs. 7-10% with placebo
    - often transient
    - minimize by giving medicine during or right after meals
    - may need to adjust the timing or dose of the medication
    - may need to change the medication
- Irritability-agitation
    - irritability may improve as a beneficial effect of the medication or worsen as a side effect
    - may need to adjust the timing or dose of the medication
    - may need to change the medication
    - if part of rebound phenomena as the medication wears off, may need a small dose of medication in the afternoon
    - may be slightly more common with methylphenidate products in my experience, but only minimally so

- Moodiness, depression
  - keep in my that pre-treatment symptoms of moodiness and depression may improve as a beneficial effect of the medication or worsen as a side effect; the goal is either symptom improvement (if present pre-treatment) or minimization of these side effects
  - may be more common with amphetatine products
  - may need to adjust the timing or dose of the medication
  - may need to change the medication or add in another medication
  - if part of rebound phenomena as the medication wears off, may need a small dose of medication in the afternoon
- Suicidality
  - does not appear to be a risk in the absence of mood disorders
  - (Lack of causal) association of risk of of suicide attempts with methylphenidate treatment (Man et al, 2017)
    - 25,629 folks aged 6-25 years who were treated with methylphenidate between January 2001-12/31/2015.
    - 154 folks had their first recorded suicide attempt within the study period
    - Overall incidence of suicide attempts during methylphenidate treatment was 9.27 per 10,000 patient-years
    - An INCREASED risk of suicide attempts was detected during the 90-day period BEFORE methylphenidate was initiated, with an incident rate ratio (IRR) of 6.55 (range of 3.37-12.72).
    - The IRR remained elevated during the first 90 days of methylphenidate treatment at 3.91 (range of 1.62-9.42)
    - Then the IRR returned to baseline levels during ongoing treatment beyond the first 90 days at 1.35 (range 0.77-2.38)
    - The incidence of suicide attempts was NOT elevated during the first 90 days of methylphenidate treatment compared the to the 90 days PRECEDING first treatment; the IRR (for the first 90 days vs. the preceding 90 days) was 0.78.
    - The study does NOT support a causal association between methylphenidate and suicide attempts
  - Jacobs et al, 2006: review of studies involving Concerta
  - Double-blind database reveals no cases of suicidal ideation, attempted suicide, or completed suicide
  - Open-label database revealed 5 cases of suicidal ideation (3.6/1000 patient years) and 2 cases of suicide attempts (1.4/1000 patient years), both far below expected rates; there were no cases of completed suicide
- Anxiety-agitation
  - Meta-analysis (Coughlin, et al, 2015)
    - 23 studies
    - 2,959 children
    - Risk of anxiety LOWER with stimulants than with placebo
    - Higher doses of stimulants associated with LOWER risk of anxiety
  - No increase in irritability (Fernandez de la Cruz, 2015)
  - 6-13.4% vs. 2-17.4% with placebo
  - 

- may need to adjust the timing or dose of the medication
- may need to change the medication or add in another medication

Meta-Analysis: Reduced Risk of Anxiety with Psychostimulant Treatment in Children with Attention-Deficit/Hyperactivity Disorder
Catherine G Coughlin, Stephanie C Cohen, Jilian M Mulqueen, Eduardo Ferracioli-Oda, Zachary D Stuckelman, Michael H Bloch
Journal of Child and Adolescent Psychopharmacology 2015, 25 (8): 611-7

OBJECTIVE: Anxiety is a commonly reported side-effect of psychostimulant treatment. Our goal was to quantify the risk of anxiety as a side effect of psychostimulant treatment for attention-deficit/hyperactivity disorder (ADHD).
METHODS: We conducted a PubMed search to identify all double-blind, randomized, placebo-controlled trials examining the efficacy of psychostimulant medications in the treatment of children with ADHD. We used a fixed-effects meta-analysis to examine the risk ratio of anxiety reported as a side effect in children treated with psychostimulants compared with those treated with placebo. We used stratified subgroup analysis and meta-regression to examine the effects of stimulant type, dosage, duration of use, and trial design on the measured risk of anxiety.
RESULTS: We identified 23 studies involving 2959 children with ADHD for inclusion in our meta-analysis. The risk of anxiety associated with psychostimulant treatment was significantly lower than that experienced with placebo (relative risk [RR] = 0.86 [95% CI: 0.77, 0.95], $z = -2.90$, $p < 0.05$). Higher doses of psychostimulants were associated with a reduced measured risk of anxiety of psychostimulants when compared with placebo ($\beta = -0.0039$ [95% CI: -0.00718, -0.00064], $z = -2.34$, $p = 0.019$).
CONCLUSIONS: Meta-analysis suggests that treatment with psychostimulants significantly reduced the risk of anxiety when compared with placebo. This finding does not rule out the possibility that some children experience increased anxiety when treated with psychostimulants, but suggests that those risks are outweighed by the number of children who experience improvement in anxiety symptoms (possibly as a secondary effect of improved control of ADHD symptoms). Clinicians should consider rechallenging children with ADHD who report new-onset or worsening anxiety with psychostimulants, as these symptoms are much more likely to be coincidental rather than caused by psychostimulants.

- Behavioral activation-agitation
  - may indicate need for diagnostic and treatment re-assessment
- Psychosis/mania
  - McKenzie, et al, 2016
    - 62.5% of young adult inpatients who were offspring of parents with mood disorder and used stimulants
    - 27% of young adult inpatients with no prior history of stimulants
    - Is this because bipolar disorder symptoms are often misdiagnosed as ADHD?
  - Moran, et al, 2015
    - Younger onset of first psychosis (20.5 yo with use of stimulants vs. 24.6 without)
  - in patients with psychotic disorders or when high doses of stimulants are used
  - Ciccone et al, 2006: review of studies involving Concerta
  - Open-label database revealed 9 cases of psychosis/mania out of 2825 patients
  - Post-marketing database: 4.6/100,000 person years (160 cases in a total exposure of 3,486,586 person-years

World J Psychiatry. 2015 Dec 22;5(4):412-24. doi: 10.5498/wjp.v5.i4.412. eCollection 2015.

Risk for emerging bipolar disorder, variants, and symptoms in children with attention deficit hyperactivity disorder, now grown up.

Elmaadawi AZ[1], Jensen PS[1], Arnold LE[1], Molina BS[1], Hechtman L[1], Abikoff HB[1], Hinshaw SP[1], Newcorn JH[1], Greenhill LL[1], Swanson JM[1], Galanter CA[1].

Author information

Abstract

AIM:

To determine the prevalence of bipolar disorder (BD) and sub-threshold symptoms in children with attention deficit hyperactivity disorder (ADHD) through 14 years' follow-up, when participants were between 21-24 years old.

METHODS:

First, we examined rates of BD type I and II diagnoses in youth participating in the NIMH-funded Multimodal Treatment Study of ADHD (MTA). We used the diagnostic interview schedule for children (DISC), administered to both parents (DISC-P) and youth (DISCY). We compared the MTA study subjects with ADHD (n = 579) to a local normative comparison group (LNCG, n = 289) at 4 different assessment points: 6, 8, 12, and 14 years of follow-ups. To evaluate the bipolar variants, we compared total symptom counts (TSC) of DSM manic and hypomanic symptoms that were generated by DISC in ADHD and LNCG subjects. Then we sub-divided the TSC into **pathognomonic manic (PM**) and **non-specific manic (NSM) symptoms**. We compared the PM and NSM in ADHD and LNCG at each assessment point and over time. We also evaluated the irritability as category A2 manic symptom in both groups and over time. Finally, we studied the irritability symptom in correlation with PM and NSM in ADHD and LNCG subjects.

RESULTS:

DISC-generated BD diagnosis did not differ significantly in rates between ADHD (1.89%) and LNCG 1.38%). Interestingly, no participant met BD diagnosis more than once in the 4 assessment points in 14 years. However, on the symptom level, ADHD subjects reported significantly higher mean TSC scores: ADHD 3.0; LNCG 1.7; $P < 0.001$. ADHD status was associated with higher mean NSM: ADHD 2.0 vs LNCG 1.1; $P < 0.0001$. Also, ADHD subjects had higher PM symptoms than LNCG, with PM means over all time points of 1.3 ADHD; 0.9 LNCG; $P = 0.0001$. Examining both NSM and PM, ADHD status associated with greater NSM than PM. However, Over 14 years, the NSM symptoms declined and changed to PM over time (df 3, 2523; $F = 20.1$; $P < 0.0001$). Finally, Irritability (BD DSM criterion-A2) rates were significantly higher in ADHD than LNCG ($\chi(2) = 122.2$, $P < 0.0001$), but irritability was associated more strongly with NSM than PM (df 3, 2538; $F = 43.2$; $P < 0.0001$).

CONCLUSION:

Individuals with ADHD do not appear to be at significantly greater risk for developing BD, but do show higher rates of BD symptoms, especially NSM. The greater linkage of irritability to NSM than to PM suggests caution when making BD diagnoses based on irritability alone as one of 2 (A-level) symptoms for BD diagnosis, particularly in view of its frequent presentation with other psychopathologies.

- Overfocus/constriction of affect, attention/aloofness
  - overquiet, less responsive, more withdrawn
  - may be overfocused and perseverative, diminished flexibility in problem solving
  - especially at doses above 0.6 mg/kg, though many studies have not shown these effects at doses up to 0.9 mg/kg
  - most reasonable doses do not diminish creativity
  - responds well to reducing the dose of the stimulant
  - may need to change the medication
- Glaucoma
  - can worsen glaucoma; stimulants are contraindicated in glaucoma
- Obsessive-compulsive symptoms
  - may precipitate or worsen obsessive-compulsive symptoms
  - may need to adjust the timing or dose of the medication
  - may need to change the medication or add in another medication
- Tics
  - Tics/Tourette's syndrome are highly co-morbid with ADHD (regardless of treatment status)
  - Data
    - Meta-analysis (Cohen, et al, 2015)
      - 22 studies
      - 2,385 patients
      - Rate of new onset or worsening tics
        - 5.7% for those on stimulants
        - **6.5% for those on placebo pills**
        - No change with type of stimulant, dose, duration of treatment, or age
        - Overall risk of tics with stimulants = to that with placebo
    - Gadow et al, 2007: in ADHD with co-morbid chronic multiple tic disorder, Ritalin treated ADHD without exacerbating tics

        - Roessner et al, 2006: literature review looking at the association of tic onset and stimulants in youth with no pre-existing tics: 20% of those on stimulants and 17% in those on placebo; overall, including the study just noted, no evidence of a correlation/association.
        - Gadow et al, 1999, 1990: children with co-morbid ADHD and tic disorders, on average, show a decline in tics when treated with a stimulant; this remains true after more than 1 year of treatment
        - Law and Schachar, 1999: in large RCT, DB, placebo-controlled study, 1 year in duration: no association (using methylphenidate)
        - Castellanis et al, 1997: some correlation with exacerbation in motor tics in kids with co-morbid tics/Tourette's
            - at higher doses and with dextroamphetamine more than methylphenidate; often transient
        - Gadow et al, 1995: some correlation with exacerbation in motor tics in kids with co-morbid tics/Tourette's
        - Lowe et al, 1982: exacerbates tics; de novo tics
        - Shapiro et al, 1981: do not cause or exacerbate tics/Tourette's in kids with co-morbid tics/Tourette's
        - Denckla et al, 1976: exacerbated in 0.39%; de novo in 0.92%
    - may precipitate tics in 0.8-1% (up to 9% in some studies) of patients with ADHD
    - may worsen tics or Tourette Syndrome in 13% of patients with ADHD
    - tics may return to baseline over time (usually over 7-10 days)
    - tics tend to ebb and flow over time even in the absence of medication
    - may need to change the medication or add in another medication
    - methylphenidate may be less likely to cause tics than amphetamines
- Priapism (prolonged, painful erection)
    - risk associated with methylphenidate products
    - not clearly associated with amphetamine products
    - risk appears less than with Strattera
- Changes in brain chemicals
    - unlike methylphenidate, high dosage regimens of amphetamine (in animal studies) produce long-term (days to months) decrements in brain dopamine and serotonin
    - this appears to be transitory
    - the relevance to people chronically treated with stimulants is unclear.
- Hormones
    - Mattison et al, 2011: transient inhibition of testosterone and delay in puberty in monkeys
- Tumors
    - liver tumors in mice treated with ultra-high doses of methylphenidate (4-50X above normal) have been reported; these mice are susceptible to liver tumors
    - mice treated with amphetamine showed a decrease in spontaneous tumors
    - rats treated with methylphenidate or with amphetamine showed a decrease incidence of tumors
    - no liver tumors have been reported in children taking methylphenidate to date
    - Walitza et al, 2007: in a study of 28 previously unmedicated children with ADHD along with 9 children who had been receiving methylphenidate for 6-24 months were assessed; researchers found NO differences in the number of micronuclei pre-treatment vs. post-treatment or at any point after treatment was initiated vs. pretreatment values in a newly treated group
    - El-Zein et al, 2005: in a small study of 12 children (average age 8.2 years) treated with therapeutic doses (20-54 mg/day) of methylphenidate for 3 months were assessed; researchers found:
        - a three-fold increase in chromosome aberrations
        - a 4.3-fold increase in sister chromatid exchanges
        - a 2.4-fold increase in micronuclei.
- Hippocampal (brain) growth (Legace et al, 2006)
    - Juvenile exposure to high dose methylphenidate in young rodents (post-natal days 20-35) is associated with:
        - Later behavioral changes
        - Decreased response to rewards
        - Decreased response to cocaine
        - Decreased choice of cocaine (as reward)
        - Less neurogenesis in temporal hippocampus in adulthood (of rats)
- Stimulants do not change cortical thickness (Schweren, et al, 2015)
- Seizures
    - may lower the threshold for seizures; data does not back up this risk; appears to be a theoretical risk at this point
    - Gonzales-Heydri: Concerta 18-54 mg not associated with increased seizures when used in patients with epilepsy

- this effect appears to be minimal; not contraindicated in clients with well-controlled seizure disorders
- Adderall may actually enhance the anti-seizure effects of certain anticonvulsants
- Methylphenidate often the treatment of choice with well-controlled epilepsy
- Stimulants Do Not Increase the Risk of Seizure-Related Hospitalizations in Children with Epilepsy
  Xinyue Liu, Paul R Carney, Regina Bussing, Richard Segal, Linda B Cottler, Almut G Winterstein
  Journal of Child and Adolescent Psychopharmacology 2017 October 13
  OBJECTIVE: To evaluate the safety of stimulants in children with epilepsy.
  METHODS: In a retrospective cohort study based on Medicaid Analytic eXtract billing records from 26 U.S. states from 1999 to 2010, we identified incident stimulant use among children with epilepsy through outpatient encounter claims and pharmacy claims. We established a control group of nonusers and used frequency matching to generate index dates. We followed both cohorts for 12 months and calculated hazard ratios [HRs] of current and former use of stimulants versus no use on the outcome of seizure-related hospitalization using multivariate Cox proportional hazard models.
  RESULTS: We identified 18,166 stimulant users and 54,197 nonusers in children with epilepsy. The incidence of seizure-related hospitalization in current stimulant users, former users, and nonusers was 3.6, 3.5, and 4.3 per 100 patient-years. After adjustment for confounders, we found current and former use of stimulants did not increase seizure-related hospitalizations (HR 0.95, 95% confidence interval [CI]: 0.83, 1.09 and HR 0.99, 95% CI: 0.85, 1.15). Children with cerebral palsy, congenital nervous system anomalies, or intellectual disability did not have significantly higher HRs than those without the already mentioned comorbidities.
  CONCLUSION: This study has not identified any overall increase in the rate of seizure-related hospitalizations with the use of stimulants in children with epilepsy.

- Rebound effects
  - symptoms of ADHD and moodiness may worsen in the afternoons or over the weekend (if stimulants are not taken over the weekend) as part of a withdrawal phenomenon
  - may need to add a larger afternoon dose
  - may need to switch to a longer-acting stimulant, to another stimulant, or to another medication
- Drug-drug interactions
  - minimize
    - caffeine
    - nicotine
    - alcohol
  - do not take with
    - decongestants (e.g., pseudoephedrine)
    - MAOI's
- Stimulant dependence
  - using stimulants every day can produce a small degree of physiologic dependence, which means that one develops some degree of tolerance to the medication benefits and side effects and that one can experience some rebound/withdrawal symptoms when the medicine wears off (lasting about 20-60 minutes)
- Substance abuse/substance abuse

J Am Acad Child Adolesc Psychiatry. 2013 Mar;52(3):250-63. doi: 10.1016/j.jaac.2012.12.014. Epub 2013 Feb 8.
Adolescent substance use in the multimodal treatment study of attention-deficit/hyperactivity disorder (ADHD) (MTA) as a function of childhood ADHD, random assignment to childhood treatments, and subsequent medication.

Molina BS1, Hinshaw SP, Eugene Arnold L, Swanson JM, Pelham WE, Hechtman L, Hoza B, Epstein JN, Wigal T, Abikoff HB, Greenhill LL, Jensen PS, Wells KC, Vitiello B, Gibbons RD, Howard A, Houck PR, Hur K, Lu B, Marcus S; MTA Cooperative Group.
Collaborators (27)

To determine long-term effects on substance use and substance use disorder (SUD), up to 8 years after childhood enrollment, of the randomly assigned 14-month treatments in the multisite Multimodal Treatment Study of Children with Attention-Deficit/Hyperactivity Disorder (MTA; n = 436); to test whether medication at follow-up, cumulative psychostimulant treatment over time, or both relate to substance use/SUD; and to compare substance use/SUD in the ADHD sample to the non-ADHD childhood classmate comparison group (n = 261).
METHOD:

Mixed-effects regression models with planned contrasts were used for all tests except the important cumulative stimulant treatment question, for which propensity score matching analysis was used.
RESULTS:

The originally randomized treatment groups did not differ significantly on substance use/SUD by the 8-year follow-up or earlier (mean age = 17 years). Neither medication at follow-up (mostly stimulants) nor cumulative stimulant treatment was associated with adolescent substance use/SUD. Substance use at all time points, including use of two or more substances and SUD, were each greater in the ADHD than in the non-ADHD samples, regardless of sex.
CONCLUSIONS:

Medication for ADHD did not protect from, or contribute to, visible risk of substance use or SUD by adolescence, whether analyzed as randomized treatment assignment in childhood, as medication at follow-up, or as cumulative stimulant treatment over an 8-year follow-up from childhood. These results suggest the need to identify alternative or adjunctive adolescent-focused approaches to substance abuse prevention and treatment for boys and girls with ADHD, especially given their increased risk for use and abuse of multiple substances that is not improved with stimulant medication. Clinical trial registration information-Multimodal Treatment Study of Children With Attention Deficit and Hyperactivity Disorder (MTA); http://clinical trials.gov/; NCT00000388.

International Consensus Statement on Screening, Diagnosis and Treatment of Substance Use Disorder Patients with Comorbid Attention Deficit/Hyperactivity Disorder. Eur Addict Res. 2018;24(1):43-51. Crunelle CL[1,2], et al

- Adult attention deficit/hyperactivity disorder (ADHD) often co-occurs with substance use disorders (SUD) and is associated with early onset and more severe development of SUD and with reduced treatment effectiveness.
- Screening tools allow for a good recognition of possible ADHD in adults with SUD and should be used routinely, followed by an ADHD diagnostic process initiated as soon as possible.
- Simultaneous and integrated treatment of ADHD and SUD, using a combination of pharmaco- and psychotherapy, is recommended. Long-acting methylphenidate, extended-release amphetamines, and atomoxetine with up-titration to higher dosages may be considered in patients unresponsive to standard doses. This paper includes evidence- and consensus-based recommendations developed to provide guidance in the screening, diagnosis and treatment of patients with ADHD-SUD comorbidity.

- occasionally, adolescents and adults may overuse or abuse stimulants; certainly, there is a good deal of misuse on college campuses
- the side effects of abuse (as opposed to appropriate use) depend on many factors, but the cardiac and central nervous system side effects are likely greater and more dangerous
- appropriate use of stimulant medications lowers the long term risk of substance use and dependence; unmedicated or undermedicated patients with ADHD may be at higher risk of substance abuse and dependence
- ADHD medication and substance-related problems (Quinn et al, 2017)
  - 2,993,887 health claims from adolescents and adults during period 2005-2014 analyzed

- Use of ADHD meds (compared to periods where ADHD meds were not used) associated with 35% LOWER odds of concurrent substance-related events in male patients and 31% LOWER odds in female patients
- Men had 19% LOWER odds of substance-related events 2 years after medication periods and female patients has 14% lower odds.

◦ Data
- In smokers
  - Evidence of increased risk
    - Stimulant administration has been found to increase smoking behaviors in unstructured lab settings (Rush et al, 2005; Stoops et al, 2011; Varsickel et al, 2007; Varsickel et al, 2009; Varsickel et al, 2011)
    - Stimulant administration has been found to increase smoking behaviors following demanding cognitive tasks (Sigmon et al, 2003)
    - Stimulant administration has been found to increase smoking behaviors in choice tasks in which smokers can choose smoking versus money (Tidey et al, 2000)
    - Evidence for increased risk of smoking following stimulant treatment
      - Lambert et al, 1998; looked at children identified as "hyperactive" by teachers in the 1970's
        - 41% of children treated with stimulants for a year or more reported daily smoking in their mid-20's
        - 37% of children not treated with stimulants reported the same
        - See Barkley et al, 2003 for critical analysis of the study
        - Correlation may be between conduct disorder and smoking (as seen in Flory et al, 2003; Milberger et al, 1997)
        - Follow-up study on the same kids (in Lambert, 1998) in their mid-30's found that the severity of ADHD and conduct disorder symptoms predicted higher rates of smoking (Lambert, 2005)
    - The link may be in reverse, which is that increased severity of ADHD is linked to both increased likelihood of using stimulant medication AND to increased risk of smoking
  - Evidence for decreased risk of smoking following stimulant treatment
    - Stimulant use in ADHD associated with significant reduction in rates of substance abuse (Chang, et al, 2014)
    - Higher dose Adderall XR in folks with ADHD and cocaine use disorder is helpful for both ADHD and cocaine abuse (Levin, et al, 2015)
    - Strattera (a non-stimulant) improves outcomes in recently abstinent adults (Wilens, et al, 2009; Adler, et al, 2009)
    - Youth who maintained a consistent regimen of stimulant medication during the study period had lower rates of smoking than youth who discontinued their medication (Ercan et al, 2012, Monuteaux et al, 2007)
    - Youth who maintained a consistent regimen of stimulant medication during the study period had lower rates of smoking than youth who were not treated (Whalen et al, 2003)
    - Progression to regular smoking coincides temporally with youths' discontinuation of stimulant treatment (Lambert, 2005; Huss et al, 2008)
    - Reduced risk of smoking amongst stimulant-treated girls over a 5-year period compared to untreated peers, regardless of length of stimulant treatment (Wilens et al, 2008)
  - Evidence of no effect of stimulant treatment on smoking outcomes
    - No effect (Barkley et al, 2003; Biederman et al, 1999; Biederman et al, 2008; Winters et al, 2011) (accounting for co-morbidity with conduct disorder often rendered non-significant (in either direction) any correlation between stimulant use and smoking, as analyzed in Burke et al, 2001 and Hammerness et al, 2013)
- Other drugs
  - MTA Study (looking at over 8 years of follow-up data); Molina et al, 2013
    - Medication for ADHD did not protect from or contribute to risk of substance abuse/dependence
  - Grabowski, 2006: Dexedrine treatment of ADHD reduced cocaine use in patients with ADHD and cocaine dependence
  - Santosh et al, 2006: appropriate treatment of ADHD with stimulants reduces the risk of substance abuse
  - Manuzza, Klein and Moulton (2003) demonstrated no increase in substance abuse 16 years after treatment of pediatric ADHD with stimulants.
  - a 2005 study of more than 5,500 patients demonstrated that ADHD (and NOT stimulant treatment) is associated with a 6-fold increased risk of a record of alcohol or drug abuse

- 14 other studies prior to 2005, only one showed any evidence of increased risk of substance abuse

- Rare cases of bone marrow suppression and neutropenia thrombocytopervia anemia
- Lethal dose
  - no data on deaths could be directly attributable to the use of acute toxic doses of stimulants in humans
  - the margin of safety is at least 100:1 between a single dose representing the high end of the human clinical dose range (1 mg/kg) and lethal doses in small mammals.
- Pregnancy
  - 2017
    - "Pregnant women who take drugs like Ritalin and Concerta for attention deficit hyperactivity disorder (ADHD) are more likely than those who don't to have babies with heart deformities and other birth defects, a recent study suggests. Researchers examined data on more than 1.8 million pregnancies in the U.S., including 2,072 women who used methylphenidate (Ritalin, Concerta, Daytrana) and 5,571 who took an amphetamine (Adderall) during their first trimester. Overall, women who took methylphenidate were 11 percent more likely to have a baby with birth defects and 28 percent more likely to have infants with heart malformations than women who didn't take stimulants for ADHD during pregnancy"
  - Pottegard et al, 2014
    - Exposure to methylphenidate during the first trimester of pregnancy not associated with major congenital malformations in population-based cohort study
    - 22 live births followed
    - Major malformations
      - 3.2% (7 children) of those exposed to methylphenidate (1.4% (3 children) with cardiac malformations)
      - 3.9% (86 children) of those not exposed (1.4% (32 children) with cardiac malformations)
- Cardiac/Sympathetic Nervous System effects
  - Generally thought to be safe in terms of cardiac effects (SEE FURTHER ANALYSIS OF 2005/2006 CONTROVERSIES BELOW)
  - May have mild increases in heart rate: 6-15 beats per minute (average 11); outweighed by other normal physiological stresses (e.g., digestion)
    - Vitiello et al, 2012: 579 youth aged 7-9, stimulant treatment vs. behavioral vs. both vs. community treatment over 14 months: 1) no treatment effect on blood pressure, 2) ~5 bpm average increase in heart rate which normalized after treatment; 3) no increased risk of tachycardia
  - Methyphenidate's effect may attenuate over time
  - No electrocardiogram irregularities with any of the stimulants
  - Heart rate variability is reduced by methylphenidate, as is heart rate deceleration to a reaction time task
  - Dexedrine may be less likely to increase heart rate
  - May have mild increases in blood pressure
  - Adderall XR appears safe in patients with high blood pressure.
  - African-American adolescents may be more sensitive to increases in diastolic blood pressure
  - May have cold clammy extremities
  - May reduce the effectiveness of antihypertensive medications; may need to adjust the dose or type of medication
  - Data

Stimulants and Pediatric Cardiovascular Risk: A Review

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OBJECTIVE: Concerns about serious cardiovascular (CV) events among stimulant-treated youth have led to clinical and policy debates. Accordingly, several population-based empirical studies have assessed the risk of CV events in children and adolescents treated with stimulants. The main objective of this review was to summarize findings and to evaluate the strengths and weaknesses of these population-based studies. In addition, we discuss the CV monitoring and policy implications for a clinically focused audience.

METHODS: A computerized literature search of Medline and PsycINFO was conducted for the calendar years 1990-2015 to identify population-based studies assessing stimulant treatment-emergent CV events in youth. Additional reports, peer-reviewed or gray literature, for example, government reports, were also included.

RESULTS: Nine population-based studies (one case-control and eight retrospective cohort designs) were included in this review. The case-control study compared sudden unexplained death cases to age-matched controls (motor vehicle passenger deaths) with respect to prior stimulant use and found a significant association (odds ratio = 7.4 [95% CI: 1.4-74.9]). By contrast, most retrospective cohort studies

assessed the risk of serious CV events (i.e., sudden death, myocardial infarction, and stroke) and did not find an association with current stimulant exposure. The absolute rate for these serious events was low, but other data support risk. For example, cardiac-related emergency department visits showed a 20% increased risk for current stimulant users compared with nonusers in one study, and another study showed a 64% and 90% increased risk for concurrent use of stimulants with antidepressants and antipsychotics, respectively. Similarly, in another study, compared with nonusers, stimulant users had twofold greater odds of CV-related inpatient or outpatient services.

CONCLUSION: In the face of mixed results from population-based safety studies, this review supports the inclusion of baseline and ongoing monitoring of cardiac status to assure a favorable benefit risk profile for stimulant users, particularly in concomitant regimens with antipsychotics and antidepressants.

-
- Kelly, et al, 2015
  - Kids with ADHD on stimulants (85 kids) vs. siblings without ADHD (53 kids)
  - Kids treated with stimulants
    - Altered cardiac autonomic function
      - Increased sympathetic tone
    - Evidence of arterial stiffening
    - Long term risks unknown at this time
- Dalsgaard, 2014
  - Prospective study of 714,258 born in Denmark from 1990-1999
  - 4,511 stimulant treated
  - 2,203 controls
  - 9.5 years of observation
  - 111 cardiac events
  - Risk: 1.83 (1.1-3.04; increased)
  - Higher dose associated with higher risk
  - Risk of fast heart rate (considered an "event") is 2.2 (increased)
- 10 Year Follow-Up of MTA (Vitello, 2012)
  - 579 children with ADHD
  - 288 controls
  - Heart rate on medication: 84
  - Heart rate on behavioral treatment: 79
- Olfson et al, 2012:
  - Privately insured people aged 6-21 without known cardiovascular risk factors (171,126 people)
  - Compared to no stimulant use, the current or past use of stimulant medicine was not associated with increased cardiovascular risk
- AJP, 2/2012
  - Methylphenidate in adults
  - 43,999 new methylphenidate users vs. 175,9555 nonusers.
  - No association between use and heart attack or stroke
  - Some association with sudden death/ventricular arrhythmia, but association was not dose-related and therefore may be not causally related
  - In fact, the risk was higher with lower doses, with less risk at higher doses, suggesting the possibility that lower doses were used in people with confounding factors (e.g., medical issues) that may be causally linked to death/arrhythmias
- AJP, 4/2012
  - "Blood pressure and Heart Rate Over 10 Years in the MTA Study"
  - No increased risk of hypertension
- Tai and Gau, 3/2012
  - Nested matched case control study in Taiwan
  - No association between cardiovascular events and exposure to methylphenidate
  - Using data on 2,124 folks aged 3-25 yo compared to 8,496 controls
  - Prior studies in Taiwan were similar
- Habel, et al, 2012:
  - 150,359 current users of stimulants, aged 25-64

- 292,839 nonusers of stimulants
- Covered 806,182 person-years of follow-up, 1986-2005
- Relative risk of heart attacks, sudden cardiac deaths, and strokes: 0.83 (which means the risk was actually LESS in users of stimulants than in nonusers.

- Schelleman et al, 2012:
  - 43,999 new adult users of methylphenidate compared to 175,955 nonusers:
    - 1.84-fold increased risk of sudden death OR ventricular arrhythmyia
    - Dosage was inversely correlated with risk (so that the higher the dose, the less the risk), suggesting the association may not be causal
    - No increased risk for stroke, myocardial infarction
- Cooper, et al, 2011:
  - Risk of sudden cardiac death in users of stimulants
    - Current user: 0.88 (reduced)
    - Former user: 1.52 (increased)
  - Risk of acute myocardial infarction
    - Current user: N/A (no cases)
    - Former user: 0.88 (reduced)
  - Risk of stroke
    - Current user: 0.93 (reduced)
    - Former user: 0.80 (reduced)
- Pediatrics, 2011
  - 241,417 youth aged 3-17 (for every one child with a prescription for amphetamine, methylphenidate, or Strattera (a non-stimulant), they were matched with 4 youth not taking such medications
  - Risk was essentially equal (not increased in youth on these medications
- Florida Medicaid claims database, 2007:
  - 55,000 patients aged 3-20 (average age 8 yo) from 7/94-6/04, new diagnosis of ADHD
  - 32,807 patients had used a stimulant, translating to 42,612 person-years of stimulant use
  - Deaths
    - No one died while on stimulants
    - 4 per 100,000 died of circulatory system disease (5 total, none on stimulants)
  - Hospitalizations
    - 21.6 per 100,000 person-years hospitalized for cardiac reasons; the rate was too low to assess the risk with stimulant use
  - Emergency room visits
    - 10.9 per 1,000 person-years in those who were on stimulants
    - 9.3 per 1,000 person-years in those who were not on stimulants but had been on stimulants
    - 9.1 per 1,000 person-years in those who were not on stimulants
    - The risk was 20% higher with stimulant use (which was statistically significant)
  - Physician office visits for heart-related symptoms or problems
    - 13.1 visits per 1,000 person-years in those who were on stimulants
    - 10.4 visits per 1,000 person-years in those who were not on stimulants but had been on stimulants
    - 10.8 visits per 1,000 person-years in those who were not on stimulants
    - The risk was 20% higher with stimulant use (which was statistically significant)
- Biederman, 2005: 10-40 mg Adderall XR; occasional fast heart rate, occasional higher blood pressure
- Wilens, 2005: 10-60 mg Adderall, Adderall XR, short and long term, in 327 adolescents
  - changes in blood pressure and QTc not statistically different from placebo
  - pulse increased by 5-8.5 bpm
  - increase in systolic blood pressure: 1.7 mm Hg
- Connor, 2005: 10-40 mg Adderall XR, 4 weeks, in 308 children with ADHD

- change in systolic blood pressure: -0.2 to 1.1 mm Hg; placebo change: -0.6
- change in diastolic blood pressure: -1 to 2.1 mm Hg; placebo change: -0.4
- mean end point pulse: 80.8-84.7; placebo 81.8
- change in QTc: 0.5-3.0 ms.

▪ Recent FDA analysis regarding risk of heart attack/sudden death and cerebrovascular accidents (stroke)
- **The population rate of sudden unexplained death (in general population, irrespective of stimulant use)**
  - 0.6-6/100,000 children per year (some estimates go as high as 8.5/100,000)
  - 6/100 children with congenital heart disease per year
  - 1/1000 adults per year
  - >1/1000 in adult competitive athletes
- **The rate of sudden death in people taking Adderall/Adderall XR or other stimulants:**
  - **0.25/100,000 (calculated based on data). THIS IS 2-10 FOLD LESS THAN IN GENERAL POPULATION)**
  - **0.2/100,000 per year for methylphenidate**
  - **0.3/100,000 per year for amphetamine**
  - **0.5/100,000 per year (assuming 50% underreporting)**
  - **0.5/100,000 per year with Strattera**
- **Nonetheless, great caution must accompany use of Adderall or other stimulants in folks at risk for or with current cardiovascular problems.**
- 676,000 adults studied
  - Higher-than-expected number of strokes; 401 strokes (versus 164 expected)
  - Higher-than-expected number of heart attacks; 732 heart attacks (versus 218 expected)
    - This is 7.6 extra heart attacks out of every 10,000 adult patients taking the medication which is an increased risk of 0.08%
    - The death rate from heart attacks is 50% so the increased risk of death due to increased risk of heart attack, per this analysis, is 0.038%
- THE INCREASED RISK OF ACCIDENTAL DEATH FROM MOTOR VEHICLE ACCIDENTS IN ADULTS WITH ADHD ***NOT*** TAKING STIMULANTS IS 250%--THIS INCREASED RISK IS >6,600 TIMES GREATER THAN THE INCREASED RISK OF DEATH BY HEART ATTACK.
- Now, consider what the increased risk of smoking cigarettes and abusing marijuana, alcohol or other recreational drugs, associated with untreated or undertreated ADHD—one could wisely assume that there is an increased risk of death associated with this increase risk of substance use.
- Studies like this are confusing—one could look at 676,000 patients with diabetes and conclude that insulin increases the risk of death when it is in fact the diabetes that increases the risk of death.
- Youth
  - higher-than-expected number of strokes
  - lower-than-expected number of heart attacks (but see below which contradicts this statement); 49 cases overall (versus 12 heart attacks expected
  - ***2005 CONTROVERSY WITH STIMULANTS (and the March 2006 Pediatric Advisory Committee): Data Summary from the FDA (UPDATED WITH INFORMATION FROM 1/2006)***
    - A review of the data from the FDA's Adverse Event Reporting System database for the years 1999 through 2003 identified 12 cases of sudden death in pediatric patients out of 30 million Adderall prescriptions who were being treated for ADHD with Adderall or Adderall XR. (More specifically, there were 431 reported cases of severe adverse reactions possibly connected to amphetamine products between 1969 and 2003).
    - The four most commonly reported reactions include psychotic disorder, overdose, cardiac arrest, and convulsion.
    - Of the 431 reported cases of reactions, there were 149 fatalities, 114 of which involved other medications enough to exclude their analysis), leaving 35 fatalities associated with amphetamine, biphetamine, Dexedrine or dextroamphetamine.

- 4 of the 35 fatalities were suicides, leaving 31 cases, 28 of which occurred during the period between 1/1/99 and 12/31/03.
- 17 of these 28 met criteria for "sudden death" possibly connected to Adderall products, 5 of which were adults, 12 youth
- ***Specific Details***
  - The ages of the pediatric patients were 7-16 years (mean 12.5 years)
  - Gender breakdown: 12 male patients; 0 female patients
  - Suspect drug: Adderall or Adderall XR
  - The total daily dose was as follows: 10 mg in 1 case; 20 mg in 5, 30 mg in 1, 40 mg in 1, 50 mg in 1, not reported in 3
  - Duration of treatment was 1 day to 8 years.
  - Autopsy done in 11 cases, not mentioned or not done in 1 case
  - Risk factors:
    - History of heart murmur in 3 cases
    - Abberrant origin of coronary artery in 1 case
    - Idiopathic hypertrophic subaortic stenosis in 1 case
    - Biscupid aortic valve in 1 case
    - Cardiac hypertrophy in 3 cases
    - Diabetes in at least 1 case
    - Previous heart attack in at least one case
    - Extreme exercise and dehydration in 1 case
    - Family history of ventricular arrhythmia in 1 case
    - Unexplained increase or toxic amphetamine level in 3 cases
    - None mentioned in 4 cases
  - Concomitant meds:
    - 1 medication in 3 cases
    - none mentioned in 9 cases
  - Year reported:
    - 1999: no cases
    - 2000: 2 cases
    - 2001: 6 cases
    - 2002: 2 cases
    - 2003: 2 cases
  - Narrative summaries of the 12 pediatric cases
    - 7 yo, history of heart murmur, passed away while sleeping, dose/duration of Adderall not reported, tox screen negative for amphetamines, autopsy showed bicuspid aortic valve.
    - 10 yo, dose/duration Adderall not reported (?8 years duration), collapsed on soccer field.
    - 11 yo, insulin-dependent diabetes mellitus, passed away while sleeping, 4 years of Adderall up to 10 mg twice daily, last dose two days prior to death, was taking insulin, amphetamine level 900-1000 (units not clear; abnormal is considered >150 ng/ml).
    - 11 yo, Adderall 20 mg daily, duration not reported, collapsed during activities at camp, blood level Adderall 210 ng/ml, did not appear to take extra tablets of Adderall, concentration within each tablet normal.
    - 12 yo, died suddenly after taking a single dose of Adderall XR 10 mg for ADHD, prior treatment Ritalin for 4 years, at 4 pm, the day of the first and only capsule of Adderall, he collapsed after running 1-2 miles cross country, family history positive for ventricular arrhythmia treated with implanted debrillator and ablation.

- 17 boy, collapsed mid-afternoon while working at his computer after taking a single dose of Adderall 20 mg at 10:30 am for ADHD, he had seen a physician for a physical exam the day before (blood pressure, heart rate, weight were all normal); he was active in sports; he had idiopathic hypertrophic subaortic stenosis (IHSS), an enlarged heart; did not appear to take extra tablets of Adderall.
- 14 yo, died of complications from heat exhaustion, dehydration, and near-drowning after several weeks of Adderall 30 mg/day for ADHD; was also taking Depakote for post-traumatic stress disorder, depression with possible psychotic symptoms, weight 205 lb; was living at tent-based facility boot camp for troubled youth; the temperature that day was 109-111 degree F; given 50 mg Adderall that day (not 30 mg. Was being punished and forced to sit in dirt for 2-3 hours. Water was restricted. He became delirious, ate dirt and passed out (his heart rate was 160-180). He was taken to a hotel and placed in a bathtub. He was later found face down, passed away, in the water.
- 14 yo, developed shortness of breath while running as part of his ROTC exercises, collapsed and passed away, on Adderall for 4 years (dose not reported) for ADHD, prior history of Ritalin, heart enlarged, blood amphetamine 0.22 mg/L (higher than expected for therapeutic dose), past history of heart murmur.
- 15 yo, collapse while playing basketball, Adderall 20 mg/day for ADHD for 3 years, appeared healthy in recent sports physical, ?increased density of muscle around the heart, history of heart murmur
- 15 yo, Adderall 20 mg/day for ADHD for 18 months, toxicology screen negative, post-mortem finding of neutropenia (low white blood cells of a certain type), no prior history of neutropenia.
- 16 yo, Adderall 40 mg/day for ADHD for 2 years, 1-2 years Zyprexa 5 mg for ADHD and personality disorder, autopsy showed hepatic steatosis.
- 12 yo, history of bipolar disorder, oppositional defiant disorder, collapsed while playing basketball, fatal myocardial infarction (leading to ventricular wall rupture), Adderall 15 mg twice-a-day, duration not reported, dose increased to 30 mg/day several months prior to death; child had reportedly experienced palpitations and dizziness at the lower dose with one or more episodes of fast hear rate.

- Narrative Summaries of Adult Cases
  - 22 yo female, found dead in the community home where she lived, Adderall 20 mg/day for ADHD for 4 months and Wellbutrin 225 mg/day for one year,.
  - 28 yo patient developed flu-like symptoms and chest pain and died suddenly, Adderall and Celexa.
  - 42 yo male with history of high blood pressure, obstructive sleep apnea, and dysrhythymia; developed chest pain, ventricular fibrillation, asystole, and then died; Adderall XR 15 mg, intermittent treatment for 9 months, weight 239, was also on hydrochlorthiazide and quinapril.
  - 62 yo male, shoveling snow, fatal heart attack, 13 days of therapy with Adderall 15 mg/day for ADHD, had not taken Adderall on the day of his death, last dose had been taken the previous day at 3:30 pm; prior physical exam showed blood pressure of 155/95 and weight of 210 pounds.
  - 76 yo female, history of irritable bowel syndrome, urinary incontinence, osteoarthritis, hypertension, headaches, hiatal hernia, depression, anxiety, memory deficits, chronic fatigue syndrome, deep vein thrombosis, pulmonary embolus, peptic ulcer disease, and obesity, developed dizziness and later was found dead after 4 months of Lotronex for diarrhea/IBS and Dexedrine t mg twice-a-day for fatigue (duration not reported). Physician had recently advised the patient to reduce her dose of Dexedrine due to high blood pressure. Was also taking Celexa,

Effexor, Zantac, lansoprazole, doneprazil, methylcellulose, oxybutynin, verapamil, warfarin, allopurinol, thyroxin, losartan, Celecoxib, and Excedrin. She also had coronary artery disease.

- ***2006 CONTROVERSY WITH RITALIN/METHYLPHENIDATE PRODUCTS:***
  - There have been 494 cases of serious adverse reactions associated with use of methylphenidate products between 1969 through 2003.
  - The four most commonly reported adverse reactions include non-accidental overdose, drug dependence, convulsion, and psychotic disorder.
  - 160 of the 494 cases involved a fatal outcome, with 3 additional cases likely as well.
  - 117 of the 163 cases were excluded based on the involvement of multiple drugs or duplicate reports.
  - 16 of the remaining 46 cases were received between 1/1/99 and 12/31/03.
  - 8 of the 16 met criteria for sudden death, 7 of which involved youths and 1 of which an adult.
  - Specific details:
    - Narrative Summary of Fatalities
      - 10 yo male, Ritalin 10 mg twice-a-day with clonidine patch (0.2 mg every 5 days for ADHD and tics since kindergarten; started clonidine within six months of death; history of exercise-induced fainting woth normal ECG, EEG, and head CT; while swimming, felt faint; then passed out and had ? seizure, on autopsy had congenital cardiac malformation—left coronary artery originated in the right sinus of Valsalva and was subject to compression by the aortic root. The left coronary artery was stenotic.
      - 11 yo female taking Ritalin for ADHD for 4 years, 3 months; one day prior to her death, her doctor changed her dose from 20 mg/AM and 15 mg/lunch to 25 mg/am and 15 mg/lunch; she was out of it on the first morning of the dose increase but seemed fine after school; the following morning she was found dead in her bed.
      - 12 yo girl on Concerta for ADHD (unknown duration); history of migraine' skating accident with head trauma 11 months prior to death, patient found in bathtub 20 minutes after entering it submerged in water; history of seizures after the accident?
      - 13 yo male, ADHD, sudden cardiac death while at camp; started on Concerta 18 mg for one month and then increased to 36 mg/day; fainted after 6 months on this regimen; ECG that day was normal; 3 months later, at camp as above, he suffered polymorphic ventricular tachycardia from which he could not be revived.
      - 13 yo female with ADHD and seasonal allergies died in her sleep due to cardiac arrhythmia; on Concerta 36 mg/day for 9 months and Zyrtex for unknown period of time; no prior cardiac history.
      - 14 yo obese male, 198 pounds, Ritalin 20 mg three times-a-day for 10 years, small vessel damage of the heart, heart enlarged, complained of chest pain for an unknown period of time prior to death; methylphenidate level was 6.5 ng/ml (3.6-6.8 is therapeutic range).
      - 9 yo female with ADHD, asthma, chronic otitis media, surgical placement of tubes in ears nine days prior, admitted to hospital for sinusitis, vomiting, increasing respiratory symptoms; given intravenous fluids; 3 hours later experienced cardiopulmonary arrest and died; was on Concerta, cefuroxime, ceftriaxone, albuterol, loratadine, fluticasone. Concerta 18 mg/day had been started 2 months prior for ADHD. At the time of hospital admission the methylphenidate level was 156 ng/ml (therapeutic range 3.6-6.8 ng/ml), blood glucose was high at 402 (should be well under 200), and liver enzymes were modestly elevated. Appears to have taken prescribed amount and no more.

- 42 yo female with unknown medical history found unresponsive; she was seizing upon arrival to ER; Xanax and Dilantin failed to control the seizures; pt was on Wellbutrin SR, methylphenidate, Librium/clinidium; Singulair, and levothyroxine.

- Adverse effects in Pediatric Patients taking Concerta/Methylphenidate following Market Approval (12/03-1/4/05):
  - CONCERTA: 1 death, 39 hospitalizations, 5 life-threatening events
  - OTHER METHYLPHENIDATE : 1 death, 15 hospitalizations, 2 life-threatening events
  - 13 yo, Zyrtec/Concerta, died in sleep, heart arrhythmia
  - 13 yo, Concerta, history of passing out, sudden heart death with polymorphic ventricular tachycardia
  - 3 suicides by overdose (other medications involved too)
- ***May, 2006: FDA determined that a "black box warning" is not necessary for stimulant medications.***

April, 2008 recommedatins from American Heart Association

Children with attention-deficit/hyperactivity disorder (ADHD) should receive careful cardiac evaluation—including an electrocardiogram (ECG) (this recommendation has since been modified)—before starting treatment with stimulant drugs, a new **American Heart Association** statement recommends [1].

The statement, published online April 21, 2008 in *Circulation*, notes that stimulant medications used to treat ADHD can increase heart rate and blood pressure, and although these side effects are insignificant for most children with ADHD, they are an important consideration for children who have certain forms of congenital heart disease or arrhythmias with a predisposition for sudden cardiac arrest. The statement says that these new recommendations "are not intended to limit the appropriate use of stimulants in children with ADHD, to label children with heart disease, or to limit their participation in athletic activities but to add clarity to who has or does not have heart disease and the extent of the risk."

Some conditions undetected by physical exam

It advises that after a diagnosis of ADHD has been made, but before therapy with a stimulant or other medication is initiated, a thorough evaluation should be performed, with special attention to symptoms that can indicate a cardiac condition, such as palpitations, near syncope, or syncope. All additional medications, including prescribed and over-the-counter medications, should be determined, and a complete family history should be obtained. Because "some of the cardiac conditions associated with sudden cardiac death might not be detected on a routine physical examination, we are suggesting that an ECG be added to increase the likelihood of identifying significant cardiac conditions that might place the child at risk," the authors write.

Head of the statement-writing committee, **Dr Victoria Vetter** (University of Pennsylvania School of Medicine, Philadelphia), commented to **heart*wire***: "The FDA has issued medication guidelines for stimulant drugs used to treat ADHD that state that you should tell your doctor if you have any heart condition, but there are many children who have structural heart disease that could lead to sudden cardiac death who don't know they have it until a significant event occurs. It is possible that using a stimulant medication could be a trigger for such an event. While there are patients who have had sudden cardiac arrest and strokes on these drugs, there are no large studies that have proven that the drugs have caused these events. However, it is thought that if adrenergic stimulation is increased, something these drugs do, this could trigger sudden cardiac arrest in susceptible patients."

Vetter explained that the committee has therefore recommended that physicians consider ordering an ECG to aid them in deciding whether or not underlying heart disease is present before prescribing these drugs for ADHD

and, if there is any indication of heart disease, the child should be referred to a pediatric cardiologist for a full examination, because ECGs can give false-positive results.

She added that children with underlying heart disease can still take drugs for ADHD if they are stable and under the care of a pediatric cardiologist. "Even if an underlying disorder is confirmed by the cardiologist, these children can still take stimulant drugs, but they should be monitored very carefully. We know that many children with structural heart disease have ADHD, and we still want them to take the drugs because ADHD has a huge emotional and social impact on children and affects the way they grow up and their ability to be successful. The drugs do work in helping this; we don't want to limit people from getting these medications. We just want them to be used as safely as possible," Vetter told **heart*wire***.

Class 2a recommendation

She stressed that if a child does not have access to an ECG or to a pediatric cardiologist who can evaluate an ECG or perform a cardiology consultation, this does not mean that they should not receive treatment for ADHD. "This is a class 2a recommendation—we feel it is useful, helpful, and reasonable, but it is has not been proven to be of benefit. We recommend that doctors use family history, a physical exam, and an ECG to make a decision about possible heart disease in children before prescribing stimulant drugs and, although we feel that an ECG is reasonable and helpful as a tool in identifying children with cardiac conditions that can lead to sudden cardiac death, if, in the view of the physician, a child requires immediate treatment with stimulant medications, this recommendation is not meant to keep them from getting that treatment," she said.

The statement adds that once stimulant treatment begins, all children should have their heart health monitored periodically, with a blood-pressure check one to three months after starting medication and during routine follow-ups every six to 12 months thereafter. Because some heart conditions do not appear until adolescence, it is recommended that if the initial ECG was obtained when the child was younger than 12 years of age, a repeat ECG should be done when the child is older than 12 years.

In 2003, an estimated 2.5 million children in the US took medication for ADHD. Surveys indicate that ADHD affects an estimated 4% to 12% of all school-aged children in the US, and it appears more common in children with heart conditions. Studies report that, depending on the specific cardiac condition, 33% to 42% of pediatric cardiac patients have ADHD, Vetter said. The number of undiagnosed children with heart conditions is unknown because routine heart screening is not performed. However, Vetter said, in a recent pilot study, up to 2% of healthy school-aged children had potentially serious undiagnosed cardiac conditions identified by an ECG.

Source

1. Vetter VL, Elia J, Erickson C, et al. Cardiovascular monitoring of children and adolescents with heart disease receiving stimulant drugs. A scientific statement from the American Heart Association Congenital Cardiac Defects Committee of the Council on Cardiovascular Disease in the Young and the Council on Cardiovascular Nursing. *Circulation*. 2008; published online April 21. DOI:10.1161/CIRCULATIONAHA.107.189473.

Clinical Context

Concerns expressed by the US Food and Drug Administration regarding potential cardiovascular risks for stimulant medications used for ADHD, and requirements for specific heart-related labeling and medication guides, have posed several dilemmas for the clinician intending to prescribe stimulant medications to children with ADHD. These include how to know if the child has heart disease, a heart problem, or heart defect and what to do if these conditions are identified.

The goal of this statement from the American Heart Association Congenital Cardiac Defects Committee of the Council on Cardiovascular Disease in the Young and the Council on Cardiovascular Nursing was to provide the clinician with some tools to help identify these children, determine whether the use of stimulant medications is appropriate in a particular child, and monitor and follow up on children receiving these medications to lower the cardiovascular risks.

Study Highlights

1. Evaluation of children with ADHD being considered for treatment with stimulant medications should include patient history focusing on symptoms of fainting or dizziness, particularly with exercise; seizures; rheumatic fever; exercise-induced chest pain or shortness of breath; unexplained change in exercise tolerance; palpitations, increased heart rate, or extra or skipped beats; high blood pressure; significant heart murmur or heart problems; and intercurrent viral illness with chest pains or palpitations.
2. Use of medications and health supplements should be elicited.
3. Family history should ask about sudden or unexplained death at an early age; sudden cardiac death (SCD) or "heart attack" in relatives younger than 35 years; sudden death during exercise; cardiac arrhythmias; hypertrophic cardiomyopathy (HCM) or other cardiomyopathy (eg, dilated cardiomyopathy, right ventricular cardiomyopathy); long-QT syndrome (LQTS), short-QT syndrome, or Brugada's syndrome; Wolff-Parkinson-White (WPW) or similar rhythm abnormalities; syncope or other event requiring resuscitation in those younger than 35 years; and Marfan's syndrome.
4. Physical examination should look for abnormal heart murmur, other cardiovascular abnormalities, and physical features of Marfan's syndrome.
5. Baseline ECG can often detect cardiovascular abnormalities (eg, HCM, LQTS, WPW anomaly) if read by a pediatric cardiologist or a cardiologist or clinician with expertise in reading pediatric ECGs.
6. A second ECG may be useful after the child is older than 2 years if baseline ECG was done at younger than 12 years or if new symptoms or family history develops.
7. Pediatric cardiology consult is recommended if the above evaluation shows any significant findings.
8. Once stimulant drugs are started, the clinician should monitor cardiovascular status at each visit with physical examination and with questions concerning potential cardiac symptoms and new family history.
9. Blood pressure and pulse should be monitored every 1 to 3 months during routine follow-up for all medications and more often during titration and weaning of alpha-agonists.
10. Appropriate referral and testing are indicated for any cardiac symptoms.
11. In patients with congenital heart disease that is not repaired or repaired but without current hemodynamic or arrhythmic concerns, or congenital heart disease that is considered to be stable, it is reasonable to consider the use of stimulant medication unless the patient's pediatric cardiologist has specific concerns.
12. After other methods of treatment of ADHD have been considered or used, it is reasonable to use stimulants with caution in patients with:
    1. Heart condition associated with SCD
    2. History of arrhythmia requiring resuscitation, direct-current cardioversion or defibrillation, or overdrive pacing
    3. History of arrhythmia associated with death or SCD
    4. Previous aborted SCD
    5. Other clinically significant, untreated, or uncontrolled arrhythmia
    6. Corrected QT interval on ECG of more than 0.46 second
    7. Heart rate or blood pressure more than 2 SD above means for age.
13. After stimulant medications are started in such patients, these patients should be carefully monitored.
14. If any of the listed conditions are diagnosed during treatment, discontinuation of the stimulant medication should be considered, at least until further testing and treatment are performed.
15. ***Once arrhythmias are treated and controlled, the patient can be restarted on medication if the pediatric cardiologist approves.***

June, 2009 Statement from American Academy of Child and Adolescent Psychiatry

Madelyn Gould, Ph.D., M.P.H. and coauthors have published a matched case-control epidemiological study on the risk of sudden unexplained death (SUD) in youth taking stimulant medication. Working with state vital statistics offices across the United States, the authors identified 564 cases of sudden unexplained death (SUD) occurring at ages 7 through 19 years across the United States along with an group of 564 youth who died as passengers in motor vehicle accidents, who were matched to the cases on age, gender, year of death and data sources available (1). Parents' reports, death certificates, medical examiner records and toxicology reports were evaluated to determine exposure to psychostimulant medications, including amphetamines, dextroamphetamine, methamphetamine, and methylphenidate. Ten (1.8%) of the group experiencing SUD versus only two (0.4%) of the motor vehicle fatality group showed evidence of stimulant use. An exact conditional logistic regression (odds ratio = 7.4 (CI, 1.4 to 74.9) showed a significant association between SUD and treatment with stimulant medication.

The authors of the article were careful to point out the limitations of the study and tried to exclude or adjust for several potential confounding factors, such as asthma, that are associated with both ADHD and sudden death. Nevertheless, the authors acknowledged that while case-control studies are a powerful method to detect an association, they cannot establish causality. Moreover, despite the differences between the two groups, the number of exposed children was extremely small. The dates of data collection, between 1985 and 1996, were at a time when stimulants were being used far less than they are today, making it more difficult to precisely determine the strength of the association. The study cannot determine if ADHD as a medical disorder increases the risk of death, nor can it address the controversy about the value of pretreatment electrocardiographic (ECG) screening before stimulant treatment. This is because most of the children reported in the study had no record of an ECG before death.

For these caveats to the interpretation of the article, the Food and Drug Administration (FDA) has promulgated a statement that there will be no change in the current benefit to risk ratio for stimulant medications used to appropriately treat children with ADHD. Similarly, the AACAP will not change its most recent practice parameters for ADHD. Using the metrics of evidence- based medicine for describing the benefit to risk ratio, it only takes two children to show that stimulants have beneficial effects on the symptoms of ADHD, but it requires treating 250,000 children before one might encounter sudden unexpected death associated with stimulant treatment. However, it is important that child and adolescent psychiatrists actively discuss this article with families they treat who receive stimulant medications for their children.

Benedetto Vitiello, M.D. and **Kenneth Towbin, M.D.** have provided an accompanying editorial to discuss the clinical implications of the study's findings (2). They noted that stimulants are not innocuous, but that it is clear that sudden unexplained death is a rare event. Their comments support the standard practice parameters from the FDA and from the American Heart Association/American Academy of Pediatrics, shown below:

FDA - Recommendations for Healthcare Professionals:
Follow all the current prescribing information for use of these medications, including:

- Take a medical history for cardiovascular disease in the child and family.
- Perform a physical exam with special focus on the cardiovascular system (including examination for the signs of Marfan syndrome).

AAP/AHA – Recommendation from May 2008, endorsed by AACAP

- Continue a careful assessment of all children, including those starting stimulants, using a targeted cardiac history (eg, patient history of previously detected cardiac disease, palpitations, syncope, or seizures; a family history of sudden death in children or young adults; hypertrophic cardiomyopathy; long QT syndrome) and a physical examination, including a careful cardiac examination. (Evidence Quality: C; Strength: Recommendation).

- Continue currently recommended treatment for ADHD, including stimulant medications, without obtaining routine ECGs or routine subspecialty cardiology evaluations for most children before starting therapy with these medications.

- Support further research on risk factors for sudden cardiac death among all children and adolescents, including those with ADHD treated with stimulant medications. Improved methods to detect children with hidden cardiac disease should be another focus of such research efforts.

Footnotes:

1. Gould MS, Walsh BT, Munfakh JL, Kleinman N, Naihua D, Olfson M, Greenhill L, Cooper T, Sudden Death and Use of Stimulant Medications in Youth Am J Psychiatry (published online June 15, 2009; doi:10.1176/appi.ajp.2009.09040472).

2. Vitiello B, Towbin K. Commentary on Sudden Death and Use of Stimulant Medications in Youth. Am J Psychiatry (published online June 15, 2009; doi:10.1176/appi.ajp.2009.09050619)

STIMULANT DRUG SIDE EFFECTS RATING SCALE AND CHECK LIST ***(Barkley, 1981)***

(make copies of this scale, complete and bring to each appointment):

Name:_____ Date:_____ Person Completing this form:_____
Current Medications/Doses:_____

Instructions: Please rate each behavior from 0 (absent) to 9 (serious). Circle only one number beside each item. A zero means you have not seen the behavior in this child during the past week, and a 9 means that you have noticed it and believe it to be either very serious or to occur very frequently.

Behavior	***Absent***									***Serious***	***Timing*** (AM, noon, PM)
Insomnia or trouble sleeping	0	1	2	3	4	5	6	7	8	9	_____
Nightmares	0	1	2	3	4	5	6	7	8	9	_____
Stares a lot or daydreams	0	1	2	3	4	5	6	7	8	9	_____
Talks less with others	0	1	2	3	4	5	6	7	8	9	_____
Uninterested in others, social withdrawal	0	1	2	3	4	5	6	7	8	9	_____
Decreased appetite	0	1	2	3	4	5	6	7	8	9	_____
Irritable	0	1	2	3	4	5	6	7	8	9	_____
Stomachaches	0	1	2	3	4	5	6	7	8	9	_____
Headaches	0	1	2	3	4	5	6	7	8	9	_____
Drowsiness	0	1	2	3	4	5	6	7	8	9	_____
Dark circles under eyes sad/unhappy	0	1	2	3	4	5	6	7	8	9	_____
Prone to crying	0	1	2	3	4	5	6	7	8	9	_____
Anxious, fearful	0	1	2	3	4	5	6	7	8	9	_____
Bites fingernails	0	1	2	3	4	5	6	7	8	9	_____
Euphoric/unusually happy	0	1	2	3	4	5	6	7	8	9	_____
Dizziness	0	1	2	3	4	5	6	7	8	9	_____
Tics or nervous movements	0	1	2	3	4	5	6	7	8	9	_____
Rashes	0	1	2	3	4	5	6	7	8	9	_____
Other:_____	0	1	2	3	4	5	6	7	8	9	_____
Other:_____	0	1	2	3	4	5	6	7	8	9	_____
Other:_____	0	1	2	3	4	5	6	7	8	9	_____
Other:_____	0	1	2	3	4	5	6	7	8	9	_____

Please elaborate:_____

TARGET SYMPTOMS	***Improved***	***No Change***	***Worse***
Motor restlessness/hyperactivity			
Attention span/focus			
Distractibility			
Finishing tasks			
Impulse control			
Frustration tolerance			
Mood			
Accepting limits			
Peer relations			
Others			

CHECKLIST

- Have you spoken with the child's teacher lately? How is classwork, homework, grades, academic performance, behavior, mood?
- Did your child complain about taking the medication or avoid its use?
- Have there been any problems in giving the medication at school?
- Does the medication seem to be helping the child as much this month as it did last month? If not, what seems to have changed?
- When was your child last seen by the pediatrician? Have child seen every 6 months.

Exfoliative Skin Reactions with Methylphenidate and Desensitization Procedures in Two Cases

Yagmur Karakus, Tuna Cak Esen

Journal of Child and Adolescent Psychopharmacology 2019 January 7

Pre-Existing Comorbid Emotional Symptoms Moderate Short-Term Methylphenidate Adverse Effects in a Randomized Trial of Children with Attention-Deficit/Hyperactivity Disorder

Tanya E Froehlich, William B Brinkman, James L Peugh, Alexandra N Piedra, Daniel J Vitucci, Jeffery N Epstein

Journal of Child and Adolescent Psychopharmacology 2019 December 16

Objective: We sought to ascertain whether baseline anxiety/depression and oppositional defiant disorder (ODD) symptoms impacted the experience of short-term methylphenidate (MPH) adverse effects (AEs) in 7- to 11-year-old children with attention-deficit/hyperactivity disorder (ADHD) (n = 171) undergoing a double-blind MPH crossover trial. Method: The Vanderbilt ADHD Diagnostic Parent Rating Scale measured baseline child anxiety/depression and ODD symptomology. The parent-completed Pittsburgh Side Effect Rating Scale assessed the AEs of anxiety, sadness, and irritability at baseline, on placebo, and on three MPH dosages. For each AE, we evaluated comorbidity main effects, dose main effects, and comorbidity × dose interactions. Results: Baseline anxiety/depression × dose and ODD × dose interactions were significant for the AEs of anxiety, sadness, and irritability. Compared with premedication baseline, these AEs attenuated on MPH for children with initially higher comorbidity symptoms, whereas those with initially lower comorbidity symptoms tended toward no change or increasing AE levels. Conclusion: Premedication anxiety/depressive and ODD symptoms may be important predictors of short-term MPH emotional AEs.