MARK W. WILSON, MD
330 W58TH STREET, SUITE 313
NEW YORK, NEW YORK 10019

Treatment of ADHD: Stimulants

- General

Key Points: Stimulants

(Practice Parameter for Assessment and Treatment of ADHD, JAACAP, 2007; 46; 894-921)

- **Indications:** Attention Deficit Hyperactivity Disorder (ADHD), all presentations.
- Evidence base for ADHD pharmacotherapy is of the strongest in psychiatry or general medicine
- ***Stimulants*** are the most widely studied and efficacious agents in child psychiatry.
- Level A evidence based data.
- Response rate 70-80%
- ***All medications must be titrated to individual clinical response***

- History

Medical Stimulant History

- Amphetamine synthesized in 1887
- Charles Bradley in ADHD kids used Benzedrine 1932
- Methylphenidate synthesized 1944 – a cyclized derivative of amphetamine-
- Ritalin marketed for geriatric fatigue depression and hyperkinetic kids 1954
- Amphetamine Mixed Salts (Obetrol 1960, renamed Adderall 1996), Adderall XR 2000
- Cylert 1975
- OROS Methlyphenidate (Concerta) Metadate CD long-acting Methylphenidate (Ritalin LA) 2000
- Modafinil (Provigil) 1998 for narcolepsey
- Dexmethylphenidate (Focalin) 2001
- Lisdexamfetamine (Vyvanse) 2007

- Amphetamines first developed in 1887; used in the 1920's as alternative to ephedrine for asthma
- First used in hospitalized children with attention/behavior problems in 1937 at the Emma Pendleton Bradley Home for Children in Rhode Island
  - Charles Bradley, a psychiatrist, was working with children who had brain injuries and had received a pneumoencephalogram as part of a standard (at the time) diagnostic work-up; the procedure commonly caused severe headaches for which Benzedrine (an amphetamine) was used
- Benzadrine led to immediate cognitive and behavioral benefits

- Most studied treatment option

        - Over 60 years of data
        - Recent meta-analyses of stimulants (and other treatment options):
            - Cochrane review of methylphenidate in children (2015)
                - Efficacy
                    - Studies included
                        - 38 parallel studies (5,111 patients)
                        - 147 cross-over studies (7,134 patients)
                    - Results
                        - All positive
                        - Overall positive
                - Side effects
                    - Studies included
                        - 21 trials (3,132 patients)
                        - 18 out of 21 favored placebo
                        - Overall, favored placebo by a little bit
            - Cochrane review of methylphenidate in adults (2015)
            - Meta-analysis of stimulants and tics (2015)
            - Meta-analysis of stimulants and anxiety (2015)
            - Meta-analysis of neurocognitive therapy (2015)
            - Sonuga-Barke meta-analysis of non-stimulants (2014)
            - AHRQ review of stimulants (2011)
    - Most commonly used treatment option
    - Most effective treatment option
    - First line treatment option

Stimulants: Common Myths

- **Addictive when used as prescribed**
    - No, Except when inhaled or injected
- **Over Prescribed**
    - 11% prevalence rate, only 6.1% on stimulants
- **Creates Aggressive, Assaultive Behavior**
    - No, decreases aggression and antisocial actions
- **Increases the likelihood of Seizures**
    - Only at very very high doses
- **Causes Tourette's Syndrome**
    - Can increase tics in 30%; decreases it in 35%
- **Increases risk of later substance abuse**
- **Increase risk of BP disorder- Alexander Glassman, Steven Brill**

- Benefits of stimulants (per research studies) improve the following:
    - most prominent benefits are with tasks without an executive functioning component (Swanson et al, 2011)
    - less prominent benefits with tasks with an executive functioning component
        - response inhibition
        - working memory
        - set shifting
        - interference control
    - task behavior,
    - peer interactions
    - parent-child interactions
    - accuracy—errors of omission and errors of commission
    - academic compliance
    - classwork
    - computation skills
    - reaction time

- processing speed
- response variability
- short-term memory
- organizational deficits
- planning deficits
- time management deficits
- sense of time
- executive functions (which overlap with other benefits listed here)
- visual field perception
- fidgeting behaviors
- overt and covert aggression
- impulsive behaviors
- disruptive behavior
- attention
- distractibility
- IQ and achievement effect much less robust
- Grades (in college):

Stimulants do not raise Grades

Addict Behav. 2017 Feb;65:245-249. doi: 10.1016/j.addbeh.2016.07.016. Epub 2016 Jul 19.
Do college students improve their grades by using prescription stimulants nonmedically?
Arria AM[1], Caldeira KM[2], Vincent KB[3], O'Grady KE[4], Cimini MD[5], Geisner IM[6], Fossos-Wong N[7], Kilmer JR[8], Larimer ME[9].

INTRODUCTION:
Many college students engage in nonmedical use of prescription stimulants (NPS) because they believe it provides academic benefits, but studies are lacking to support or refute this belief.

METHODS:
Using a longitudinal design, 898 undergraduates who did not have an ADHD diagnosis were studied. Year 3 GPA (from college records) of four groups was compared: Abstainers (did not engage in NPS either year; 68.8%); Initiators (NPS in Year 3 but not Year 2; 8.7%); Desisters (NPS in Year 2 but not Year 3; 5.8%); and Persisters (NPS in both years; 16.7%). Generalized estimating equations regression was used to estimate the association between NPS and change in GPA, controlling for sex and Year 2 GPA.

RESULTS:
GPA increased significantly within Abstainers ($p<0.05$), but did not change significantly within the other groups. Overall, the relationship between NPS pattern group and change in GPA was not statistically significant ($p=0.081$). NPS was generally infrequent, but Persisters used more frequently than Desisters (11.7 versus 3.4days in Year 2) and Initiators (13.6 versus 4.0days in Year 3, both $ps<0.001$), controlling for sex and Year 2 GPA.

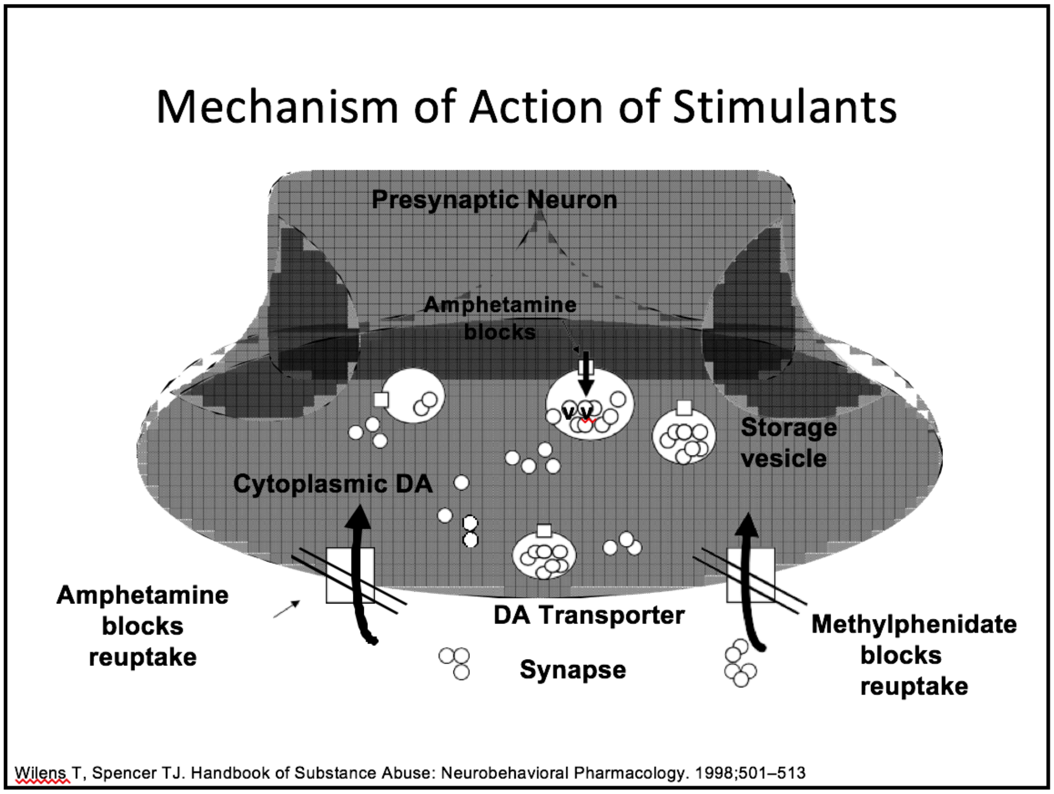
CONCLUSIONS:
We cannot rule out the possibility that NPS prevented declines in GPA, but we can conclude that students who engaged in NPS showed no increases in their GPAs and gained no detectable advantages over their peers. The results suggest that prevention and intervention strategies should emphasize that the promise of academic benefits from NPS is likely illusory.

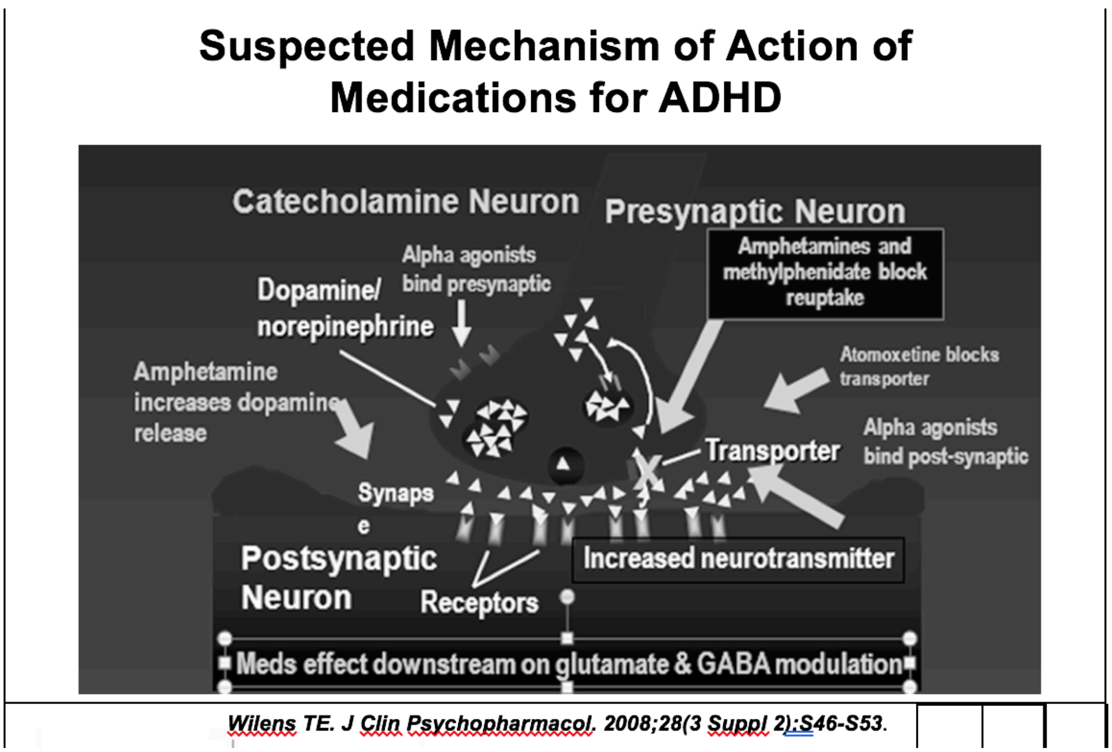
- may reduce the increased risk of substance abuse associated with untreated ADHD

o Thought to be among the safest and most effective psychotropic medications prescribed. Methylphenidate has a 100:1 margin of safety between a single dose in animals that approximates an effective dose in humans and a dose that produces lethality in two animal species; as such, methylphenidate is one of the safest medications used in the treatment of children if given within the appropriate dose range.

o Lack of response or tolerability
  - 1-3% of children with ADHD cannot tolerate any dose of stimulant medications
  - Children with poor response to stimulants when younger than 6 may respond in later years (older than 6)
  - Side effects are more likely and response rates lower (<65%) in children younger than 4.
  - Misdiagnosis or co-morbid diagnoses (e.g., anxiety, bipolar disorder)

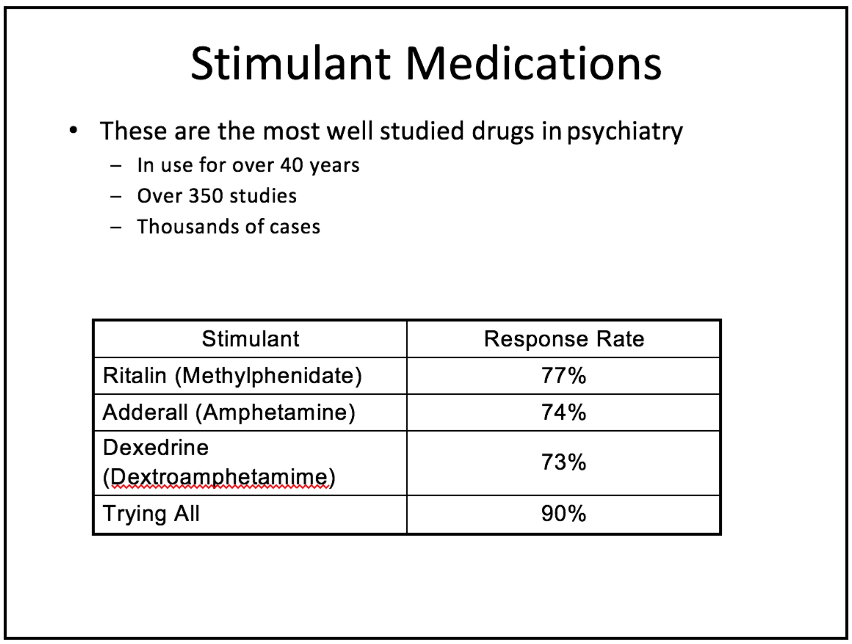
- Mechanism:





- Dopamine
  - Thought to work primarily by affecting the release and reuptake of dopamine in the striatum/basal ganglia, frontal lobes, and perhaps the cerebellum.
  - Increasing dopamine in the striatum is believed to decreased background firing rates and increase signal-to-noise ratio of striatal cells, enhancing task-related neuronal firing.
    - Increases saliency of important signals

        - Decreases noise from extraneous stimuli
    - Increasing dopamine in the nucleus accumbens may enhance the saliency of task by increasing the interest it elicits and thus improving attention and performance.
    - Enhanced cerebral blood flow in the striatum and the connections between the bilateral orbital-frontal and limbic regions; left sensorimotor and parietal areas.
  - Norepinephrine
    - Increases norepinephrine activity
    - Increases salience and strength of signal in prefrontal cortex
  - Methylphenidate products function by
    - increasing dopamine release into the synaptic cleft
    - blocking the reuptake of dopamine (and to a lesser extent norepinephrine)
    - releasing norepinephrine not dopamine from long term stores within neurons
    - working as agonist post-synaptically
  - Amphetamine products function by
    - causing release of dopamine into the synapse as amphetamine enters the pre-synaptic neuron
    - blocking uptake of dopamine into pre-synaptic cytoplasmic vesicles
    - releasing norepinephrine and dopamine from pre-synaptic cytoplasmic vesicles into the cytoplasm
    - blocks the reuptake of dopamine and norepinephrine
    - working as agonist post-synaptically.
- Stimulants investigated for over 60 years:



Stimulant	Response Rate
Ritalin (Methylphenidate)	77%
Adderall (Amphetamine)	74%
Dexedrine (Dextroamphetamime)	73%
Trying All	90%

  - Over 350 double-blind placebo controlled studies of stimulant medications involving over 5,768 subjects, over 3,000 of which have been children
  - Between 1962 and 1993 there have been over 3,000 articles published on stimulant effects, some of the important studies described below.
  - Response rates per any given stimulant ~60-80% vs. 20-35% (mode is 10%) placebo. Response rate approaches 95% if more than one stimulant is tried
  - Preschool
    - Slower clearance of methylphenidate so need lower doses
    - Seven short RCT, DB, placebo-controlled studies of methylphenidate, 3-8 weeks duration, all but one demonstrating efficacy of methylphenidate
      - NIMH PATS 2006:
        - Methylphenidate; 8-phase, 70-week study with 2 RCT double-blind phases, a crossover-titration trial followed by a placebo-controlled parallel trial
        - 303 preschoolers, 165 of which randomized into titration trial
        - Doses increased from ~14 mg/day to ~20 mg/day towards the end of the trial; average effective dose of methylphenidate 14.2 mg/day (effective dose range 6-24 mg/day)
        - 114 youth who improved with methylphenidate were randomized to methylphenidate continuation or placebo for double-blind 4-week trial.

- 144 youths, whose ADHD improved in an acute trial or methylphenidate, enter a 10-month, open-label maintenance treatment study
- 15-22% versus 8% response with placebo; 4% had no response; benefits were maintained throughout
- Increasing benefit as the dose increased
- Effect ratios (the higher the better) compared to the MTA trial with youth grade school or older
  - 0.35-0.66 for PATS
  - 0.52-1.31 for MTA
- Remission (this rate is always lower than response rates)
  - 21% on best-dose methylphenidate vs. 13% placebo
- Side effects
  - Decreased appetite: 25-50% vs 28% placebo
  - Difficulty falling asleep: 34-50% vs 30% on placebo
  - Stomach ache—17-20% vs 12% placebo
  - Dull, listless, tired—15-24% vs 13% placebo
  - Social withdrawal—10-22% vs 13% placebo
  - Uninterested in others: 12% on high dose, 0% on low dose, 0% on placebo
  - Talks less with others: 9% high dose, 3% low dose, 3% placebo
  - Tongue or jaw movements—6-7% vs 2.5% placebo
  - Sadness
  - Irritability: less than placebo
  - Anxiety: less than placebo
  - Emotional outbursts
  - Repetitive behaviors/thoughts
  - Skin picking
  - Transient pulse and blood pressure elevations in 5/165 patients

- % with side effect per dose

	Dose, in milligrams						
	Plac	1.25	2.5	5	7.5	10	15/20
Crabbiness (***LESS***)							
Trial, parents	30	--	--	25	--	22	22
Trial, teachers	27	--	--	17	--	13	10
Decreased appetite (***MORE***)							
Titration trial	1	0.5	2	<8	6	--	--
Trial, parents	15	--	--	22	--	27	36
Trial, teachers	6	--	--	6	--	11	15
Dulled (***MIXED-MORE***)							
Trial, parents	11	--	--	10	--	15	24
Trial, teachers	17	--	--	13	--	14	14
Worried (***LESS***)							
Trial, teachers	17	--	--	11	--	16	12
Trouble sleeping (***More***)							
Titration trial	<1	>2	>2	6	5.5	--	--
Trial	21	--	--	22	--	30	32
Emot'l outbursts (***MIXED***)	2	>2	>3	<8	<2	--	--
Abdom/stom upset	<1	>2	<2	4	0	--	--
Irritability	>2	<2	<2	>2	2	--	--

- Growth rates
  - 20.3% less than expected for height
  - 55.2% less than expected for weight (from 75-80th %'s pre-treatment to ~60th % after 540 days of treatment)
- Genetics
  - Specific dopamine 4 receptor allele associated with side effects of:
    - Picking
    - Irritability
    - Social withdrawal
  - Synaptosomal-associated protein 25 variant associated with side effects of:
    - Tics
    - Jaw/tongue movements
    - Irritability

- Follow-Up Studies of the PATS group (6 years later)
  - 63% have persistence of ADHD up to age 10 (Riddle, et al, 2011)
  - 64% remained on medication (Vitiello, et al, 2015)

- Grade school and adolescents:
  - 65-75% response rates overall
    - 55-65% response rate for inattentive type
    - 70-90% response rate for combined type
    - 50% response rate for clinic-referred adolescents
  - Effect size better than for preschool youth (0.94)
  - Wilens, 2005: 24 month open-label study of Concerta 18-54 mg/day in 407 kids (of which 229 completed the study):
    - Efficacy maintained throughout
    - Adverse events (overall) included:
      - Insomnia in 20% (7.7% in another study vs. 13.3% with transdermal methylphenidate vs. 4.7% placebo)
      - Decreased appetite in 18% (18.7% in another study vs. 25.5% with transdermal methylphenidate vs. 4.7% placebo)
      - Abdominal pain in 11%
      - Tics in 10% of which 33% had a history of tics, 7% with no history and 60% with unknown history (1.1% in another study vs. 7.1% with transdermal methyphenidate vs. 0% placebo)
      - 7.6% discontinued due to adverse effects, including
        - tics (2%)
        - decreased appetite (2%)
        - insomnia (1.5%)
        - "aggravation" (0.7%)
        - hostility (0.7%)
        - emotional lability (0.2%)
        - hallucinations (0.2%)
        - and many other others, all less than 0.7%
      - Absolute weight did not increase significantly during the first 4-6 months and then increased steadily; the mean weight was greater than expected for their age at start and somewhat less than expected for their age at 21 months.
      - Mean height was 0.23 cm (0.09 inches) less than expected at study end.
  - Multisite trial of mixed amphetamine salts (MAS, or Adderall XR) in adolescents (Spencer et al, 2006; 287 adolescents aged 13-17; 4 week, RCT, DB, placebo-controlled; 10-40 mg/day
    - 70% response vs. 27% placebo
    - Side effects
      - Decreased appetite: 26% vs. 2% on placebo
      - Insomnia: 12% vs. 3.7% on placebo
      - Weight loss: 9.4% vs. 0% on placebo
  - NIMH Multimodal Treatment Study of Children with ADHD (MTA study), 2004
    - Involves 579 subjects from 7 sites; studied subjects over 14 months (will continue to do so for another 22 months); studied the comparative efficacy of the following treatments: intensive medication management per clinical research protocol (MM), combined treatment of intensive, manualized behavior therapy and medication management (CT), intensive manualized behavior therapy alone (BT), and standard community care (CC)
    - Teacher/school important critical in MM, BT, and CT
    - <u>Overall, CT was as efficacious as MM, both of which were more effective than BT and CC (which were equivalent in efficacy)</u>
    - When subjects have co-occurring anxiety symptoms, CT was somewhat better than MM and BT is almost as effective as MM; CC is still the least efficacious
    - BT was slightly superior to MM for arguing, oppositionality, and defiance, and CT was somewhat better than both
    - CT may allow for less total daily dose of medication
    - When you compare the percentage of children who are "normalized" (no longer meeting criteria for the diagnosis of ADHD) **<u>after 14 months treatment, you see the following results: youth controls (no diagnosis, no treatment) 88%, CT 68%, MM 56%, BT 34%, CC 25%</u>**
    - When you compare the decrease in the number of other co-occurring diagnoses after 14 months treatment, you see the following decreases in the number of co-occurring diagnoses: CT and MM ¾, BT ½, CC 0.
    - When subjects have co-occurring oppositional defiant disorder or conduct disorder, CT or MM are better than BT or CC.
    - Factors that were predictive of good response to treatment include in descending order: the use of intensive medication management by provider, the absence of depression in parents, the severity of symptoms, and IQ <99.
    - Preliminary results that benefits continue at the 24 month end point (CT and MM more than BT and CC). Benefits diminish if medications are stopped.
    - Subjects in CT and MM gained weight at a slower rate and were about 2 cm less tall than subjects in BT and CC
    - Efficacy and efficacy by treatment differences maintained throughout 24 month study period
    - Results at 36 months (analyzed in Jensen et al, 2007)
      - 485 of the original 579 youth studied still participating in follow-up; mean age now 11.9 yo
      - All treatment groups demonstrated continued improvement
      - Efficacy by treatment type no longer significantly different
      - The following factors predicted at 36 months poor outcome at 36 months but not treatment response:

- Initial symptom severity
- Male gender
- Co-morbidity with other psychiatric diagnoses
- Public assistance (likely due to family stress)
- Parental ADHD
- Growth effects
  - Height decrements reached a plateau of 2 cm difference by 36 months
  - Weight decrements reached a plateau of ~6 pounds difference by 36 months
- Delinquent behavior and substance abuse
  - Compared to local normative comparative youth (with no formal diagnoses), children with ADHD in the MTA:
    - Higher rates of delinquency: 27.1% vs. 7.4% controls
    - Higher rates of substance abuse: 17.4% vs. 7.8% controls
    - Youth randomized to intensive behavior therapy reported less substance abuse at 24 months than youth in other MTA treatment groups
    - More days of prescribed medication were associated with serious delinquency but not substance abuse at 24 and 36 months
    - Cause-and-effect associations not clear
- Abikoff, 2004: smaller, 24-month, controlled, multicenter study of Ritalin; efficacy maintained throughou
- Gillberg, 1997: single site study of Adderall over 15 months; efficacy maintained.

- Adults
  - COMPASS (Comparison of Methylphenidate and Psychotherapy in adult ADHD Study; Phillipsen, et al, 2015
    - Stimulants + group therapy reduce ADHD symptoms
    - Stimulants + CBT helps reduce frequency of cocaine use
    - Vyvanse reduces frequency of binge eating
  - Effect size 0.9 across 16 studies uncluding 6 RCT, DB studies with methylphenidate, 2 RCT, DB studies with Adderall XR, and 1 RCT, DB study with Concerta (with 66% response rate vs. 39% placebo)
  - 80% response rate in another study with methylphenidate

Neural Correlates of Symptom Improvement Following Stimulant Treatment in Adults with Attention-Deficit/Hyperactivity Disorder
Zhen Yang, Clare Kelly, Francisco X Castellanos, Terry Leon, Michael P Milham, Lenard A Adler
Journal of Child and Adolescent Psychopharmacology 2016, 26 (6): 527-36

OBJECTIVE: The purposes of this study were to examine the impact of 3 weeks of amphetamine administration on intrinsic connectome-wide connectivity patterns in adults with attention-deficit/hyperactivity disorder (ADHD) and explore the association between stimulant-induced symptom improvement and functional connectivity alteration.
METHODS: Participants included 19 adults (age 20-55 years) diagnosed with ADHD using the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) criteria per the Adult Clinician Diagnostic Scale taking part in amphetamine trials. For each patient, two 6-minute resting-state functional magnetic resonance imaging (R-fMRI) scans were acquired at baseline and after treatment. A fully data-driven multivariate analytic approach (i.e., multivariate distance matrix regression [MDMR]) was applied to R-fMRI data to characterize the distributed pharmacological effects in the entire functional connectome. Clinical efficacy was assessed using ADHD rating scale with adult prompts and the Adult Self-Report Scale v1.1 Symptom Checklist. We linked stimulant-induced functional connectivity changes to symptom amelioration using Spearman's correlation.
RESULTS: Three weeks of administration of a stimulant significantly reduced ADHD symptoms. MDMR-based analyses on R-fMRI data highlighted the left dorsolateral prefrontal cortex (DLPFC, a key cognitive control region) and the medial prefrontal cortex (MPFC, the anterior core of default network) whose distributed patterns of functional connectivity across the entire brain were altered by psychostimulants. Follow-up intrinsic functional connectivity revealed that stimulants specifically decreased the positive functional connectivity between DLPFC-insula, DLPFC-anterior cingulate cortex, and MPFC-insula. Importantly, these functional connectivity changes are associated with symptom improvement.
CONCLUSION: These results suggested that ADHD is associated with increased functional integration or decreased functional segregation between core regions of cognitive control, default, and salience networks. The apparent normalization of intrinsic functional interaction in these circuits (i.e., increased functional segregation) may underlie the clinical benefits produced by 3 weeks of amphetamine treatment.

Intrinsic Brain Connectivity Following Long-Term Treatment with Methylphenidate in Children with Attention-Deficit/Hyperactivity Disorder
Lucas Battel, Renata R Kieling, Christian Kieling, Maurício Anés, Nathassia Kadletz Aurich, Jaderson Costa da Costa, Luis Augusto Rohde, Alexandre Rosa Franco
Journal of Child and Adolescent Psychopharmacology 2016, 26 (6): 555-61

INTRODUCTION: Although widely used for the treatment of attention-deficit/hyperactivity disorder (ADHD) across the life span, the effects of methylphenidate (MPH) on the brain are not completely understood. Functional neuroimaging techniques may help increase knowledge about the mechanisms of MPH action.
OBJECTIVE: To evaluate changes in functional connectivity patterns of the default mode network (DMN) in children with ADHD following long-term treatment with MPH.
METHODS: Twenty-three right-handed treatment-naïve boys with ADHD underwent a protocol of intrinsic functional connectivity before and after 6 months of treatment with MPH. Functional connectivity was analyzed using a region of interest (ROI) approach and independent component analysis (ICA).
RESULTS: ROI analyses showed no significant changes in connectivity between regions of the DMN following treatment, with a relatively small increase in the anterior-posterior connectivity of the network. ICA revealed a significant increase in connectivity between the left putamen and the DMN ($p<0.001$, corrected). There was a correlation between the reduction of symptoms and the increased connectivity between the putamen and the DMN after treatment ($rho=-0.65$, $p=0.017$).
CONCLUSION: Dysfunctions in cortical-subcortical circuits have often been associated with the pathophysiology of ADHD. Our findings suggest that effective treatment with MPH in children with ADHD may affect brain functioning by increasing connectivity between the DMN and subcortical nuclei.

- Quick Summary of Stimulants:
  - Methylphenidate group
    - Methylphenidate
      - Immediate release (4 hours)
        - Ritalin (methylphenidate); last 4 hours
        - Methylin; liquid; lasts 4 hours
        - Methylin tablets; last 4 hours
        - Desmethylphenidate
      - Extended release (8 hours)
        - Biphentin caps; lasts 8 hours; <50% immediate release
        - Methylin ER; lasts 8 hours
        - Ritalin SR; lasts 8 hours
        - Metadate CD; lasts 8 hours; 30% immediate release
        - Metadate ER; lasts 8 hours; 40% immediate release
        - Ritalin LA; lasts 8 hours; 50% immediate release; 50% at 4 hours
        - Focalin XR; lasts 8 hours; 50% immediate release; peak at 1.5 and 6 hours
        - Jornay; given at night; lasts 8 hours
      - Extended release (up to 12 hours)
        - Quillivant XR; lasts 8-12 hours; 20% immediate release; peak at 5 hours
        - Quillichew; lasts 8-12 hours; 20% immediate release; peak at 5 hours
        - Concerta; lasts 12 hours; 27% immediate release
        - Aptensio XR; last 12 hours; ~38% released right away
        - Daytrana; patch; lasts up to 12 hours; linear increase in dose
        - Cotempla XR-ODT (8-12 hours)
      - Extended release (more than 12 hours)
        - Adhansia XR (lasts 16 hours)

  - Amphetamine group
    - Dextroamphetamine
      - Immediate release (4 hours)
        - Dextroamphetamine immediate release; last 4 hours
        - Zenzedi immediate release tablet; lasts 4 hours
        - ProCentra immediate release liquid; lasts 4 hours
      - Extended release (6 hours)
        - Dextroamphetamine spansules; lasts ~6-8 hours
      - Extended release (12 hours)
        - Vyvanse; lasts 9-13 hours
    - Mixed amphetamine salts (3/4 of which consists of dextroamphetamine, ¼ of which consists of levoamphetamine)
      - Immediate release
        - Adderall (3/4 dextroamphetamine, ¼ levoamphetamine); lasts 4-8 hours
        - Evekeo (1/2 dextroamphetamine, ½ levoamphetamine); lasts 4-8 hours
      - Extended release (8-10 hours)
        - Adderall XR; lasts 8-12 hours; 50% immediate; peak at 6-8 hours
        - Adzenys XR-ODT orally disintegrating tablets
      - Extended release (up to 12+ hours)
        - Mydayis; lasts 12+ hours; 33% immediate release, 33% delayed release, 33% delayed extended release; mimics Adderall XR/am and equivalent dose of Adderall immediate release 8 hours later
        - Dynavel XR; lasts 8-12 hours; liquid; 20% immediate; peak at 4 hours
    - In development

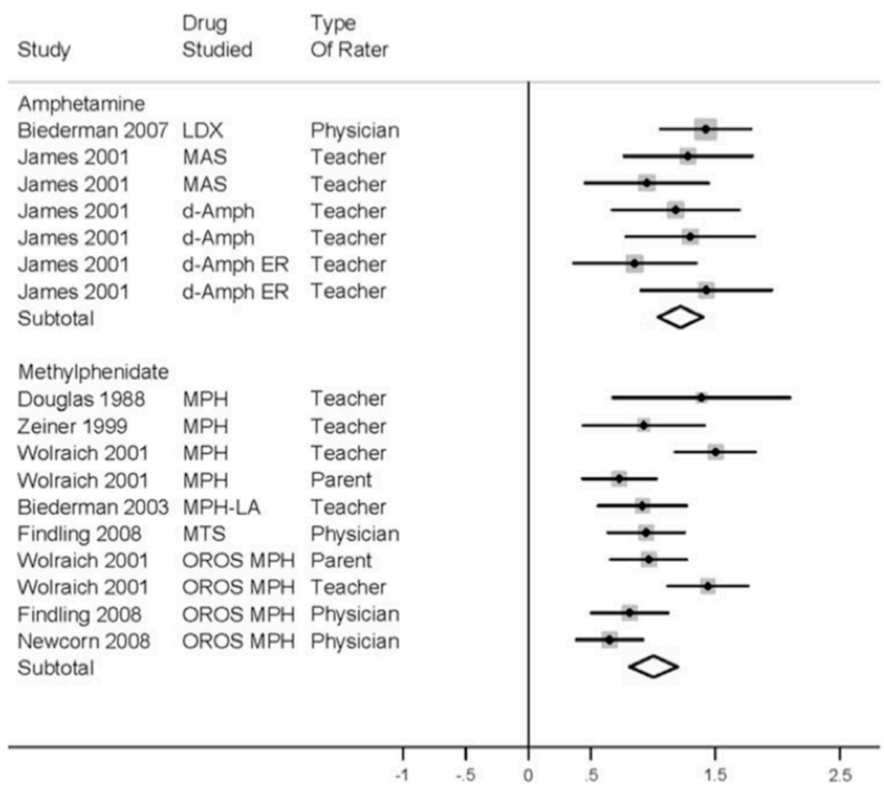
- **D-ATS:** amphetamine transdermal system
- **HLD-100:** amphetamine Delexis technology; nighttime dosing

Comparing Efficacy of Stimulants for ADHD in Children and Adolescents Using Meta-Analysis

(Faraone, S. Buitelaar, J. Eur Child Adolesc Psych; 2010; 19:353-364)

- **Method**: Literature search for double blind, placebo controlled studies of ADHD in children published after 1979.
- N=23 trials met criteria and were included in analysis.
- Trials used 11 drugs and 19 outcome measures.
- **Results:** Significant differences were found between amphetamines and methylphenidates (MPH), even after correcting for study design confounders.
- Effect sizes were significantly **greater in amphetamines vs. MPHs,** albeit moderately.
- **Conclusion:** Differences in effect size may be due to differences in compounds' impact on dopamine f(x)g

Fig. 3 Effect sizes and 95% confidence intervals (CIs) for hyperactivity-impulsivity. Note: see text for description of graph



Faraone, S. and Buitelaar, J. Eur Child Adolesc Psychiatry (2010) 19:353–364

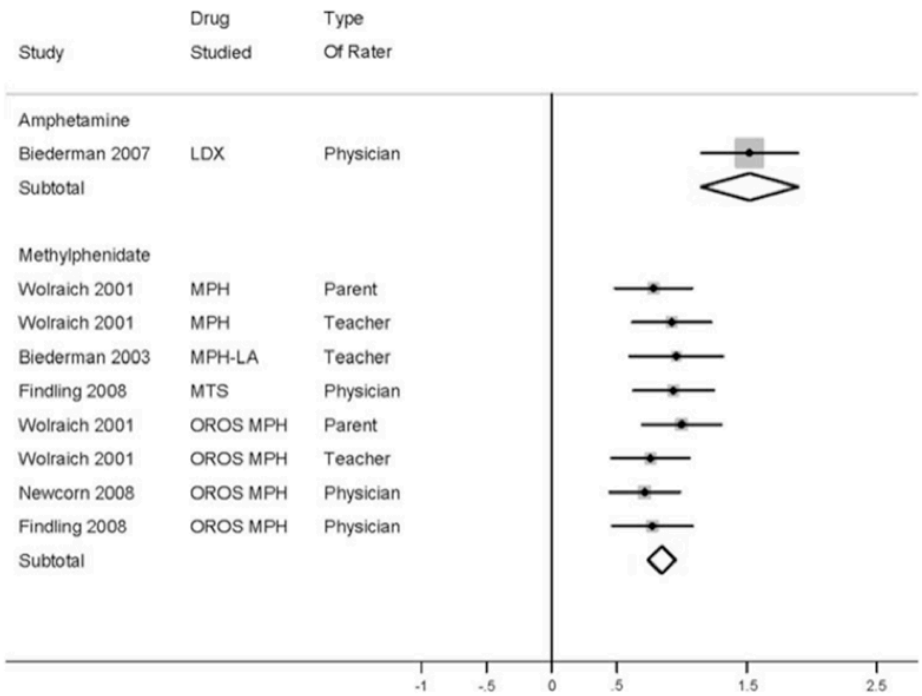
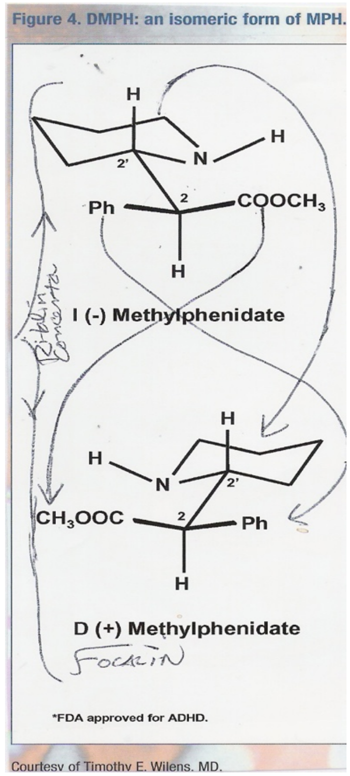


Fig. 4 Effect sizes and 95% confidence intervals (CIs) for inattention. Note: see text for description of graph

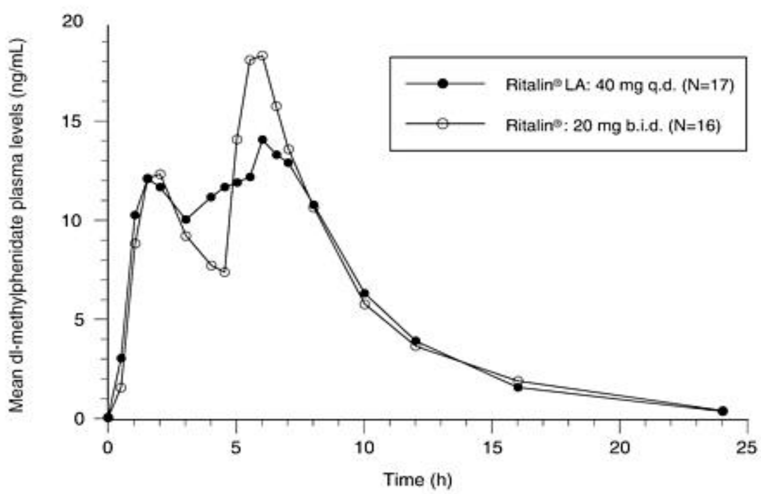
- **Methylphenidate** Group
  - FDA-approved for ADHD in folks aged 6 and up
  - Immediate release
    - **Methylphenidate/Ritalin** Hydrochloride Tablets (Novartis)
      - Tabs—5 mg, 10 mg, 20 mg, dose range 15-60 mg/d
        - Also: chewable tab from Gavis generic—2.5 mg, 5 mg, 10 mg; grape flavored
      - Initial target is 0.3 mg/kg per dose (0.15 mg/kg per dose for Focalin); usually start with 2.5-5 mg twice-a-day
      - Optimal dose range is 0.3-0.7 mg/kg/dose with maximum daily dose around 60 mg/day
      - Onset of action 20-60 minutes after a therapeutically active dose (usually 20-35 minutes)
      - Time to peak 1.9 hours (1.5-2.5)
      - Half-life 2-3.5 hours
      - Duration of effect 2-6 hours (methylphenidate may have shorter duration of action than Dexedrine); my experience: 3.5-4 hours
      - Administer every 3-4 hours; usually 3-4 times/d
      - Administration with food not only decreases risk of stomach ache but increases the bioavailability of methylphenidate although the peak may be delayed by one hour after a high fat meal.
      - Methylphenidate Has Superior Efficacy Over Parent-Child Interaction Therapy for Preschool Children with Disruptive Behaviors
        Lianne van der Veen-Mulders, Barbara J van den Hoofdakker, Maaike H Nauta, Paul Emmelkamp, Pieter J Hoekstra
        Journal of Child and Adolescent Psychopharmacology 2017 November 13
        OBJECTIVE: To compare the effectiveness between parent-child interaction therapy (PCIT) and methylphenidate in preschool children with attention-deficit/hyperactivity disorder (ADHD) symptoms and disruptive behaviors who had remaining significant behavior problems after previous behavioral parent training.
        METHODS: We included 35 preschool children, ranging in age between 3.4 and 6.0 years. Participants were randomized to PCIT (n = 18) or methylphenidate (n = 17). Outcome measures were maternal ratings of the intensity and number of behavior problems and severity of ADHD symptoms. Changes from pretreatment to directly posttreatment were compared between groups using two-way mixed analysis of variance. We also made comparisons of both treatments to a nonrandomized care as usual (CAU) group (n = 17) regarding intensity and number of behavior problems. All children who started one of the treatments were included in the analyses.
        RESULTS: Mothers reported a significantly more decreased intensity of behavior problems after methylphenidate (pre-post effect size d = 1.50) compared with PCIT (d = 0.64). ADHD symptoms reduced significantly over time only after methylphenidate treatment (d = 0.48) and not after PCIT. Changes over time of children in the CAU treatment were nonsignificant.
        CONCLUSIONS: Although methylphenidate was more effective than PCIT, both interventions may be effective in the treatment of preschool children with disruptive behaviors. Our findings are preliminary as our sample size was small and the use of methylphenidate in preschool children lacks profound safety data as reflected by its off-label status. More empirical support is needed from studies with larger sample sizes.
    - **Methylin** (methylphenidate HCL)
      - Oral solution (Alliant)—5 mg/5 ml and 10 mg/5 ml; grape
      - Tablets (Mallinckrodt)
      - Lasts 4 hours
    - **Desmethylphenidate/Focalin** (Novartis)
      - "the pharmacologically more active d-isomer of Ritalin"
      - one of four stereoisomers of methylphenidate
      - tabs—2.5 mg, 5 mg, 10 mg; dose range 2.5-20 mg/D
      - lasts 4-6 hours (4 hours in my experience)

- 

- Extended Release (~8 Hours)
  - **Biphentin**
    - Multilayer, biphasic release
    - Rapid initial release with peak at 1.7-2.5 hours; a little less than 50% of total medication
    - Second release at 4 hours
    - Lasts 8 hours
    - 10, 15, 20, 30, 40, 50, 60 and 80 mg caps
  - **Methylin ER** (Mallinkrodt)
    - Tablet, cannot split
    - Lasts 8 hours
  - **Ritalin SR** Tablets (Novartis)
    - tabs—20 mg (cannot split)
    - 8 hours
    - Time to peak 4.7 hours
    - 1/3 less potent then Ritalin immediate release; 20 mg Ritalin SR is equivalent to 7 mg Ritalin immediate release
  - **Metadate CD** Capsules (Celltech)
    - Caps—10 mg, 20 mg, 30 mg, 40 mg, 50 mg, 60 mg
    - **30% of beads in the Diffucaps is immediate release; 70% is extended release**
    - Can be opened and sprinkled on apple sauce as long as the beads within the capsule are not chewed
    - A high fat meal may increase absorption so that they are best taken prior to breakfast
    - Onset of action within 60 minutes
    - Peak clinical effect 1-3 hours
    - Half-life 2-12 hours
    - Duration of effect 8 hours
    - Administer 1-2X/D
    - Compared to Concerta, more exposure to methylphenidate in the first 4 hours but less later in the day
    - Can administer with immediate-release
  - **Metadate ER** Tablets (Medeva)
    - Once-daily, multilayer-release (MLR) methylphenidate bead formulation
    - **40% released immediately**
    - Blood levels in the first four hours
    - Similar to immediate release methylphenidate
    - Peak is ~80% of the peak of immediate release

    - Second peak occurs about 6-8 hours post-administration
    - Side effects:
        - Headache 26% vs. 24% with placebo
        - Anorexia 22% vs. 6% with placebo
        - Insomnia 22% vs. 8% with placebo
        - Nervousness 20% vs. 4% with placebo
        - Nausea 16% vs. 8% with placebo
        - Anxiety 14% vs. 0% with placebo
        - Dry mouth 12% vs. 2% with placebo
        - Emotionally lability 10% vs. 2% with placebo
        - Depression 8% vs. 2% with placebo
        - Physical lassitude 8% vs. 8% with placebo
        - Sweating 6% vs. 0% with placebo
- **Ritalin LA** (Novartis)
    - Extended release capsules—10 mg, 20 mg, 30 mg, 40 mg
    - **50% released in AM; 50% released 4 hours later**
    - Once daily dosing
    - Can sprinkle caps
    - Compared to immediate release Ritalin, first 3 hours are generally the same, but the four hour trough is less low and the second peak is less high
    - Compared to Concerta, leads to twice the exposure to methylphenidate in the first four hours; may be more effective than Concerta during the first 8 hours of use

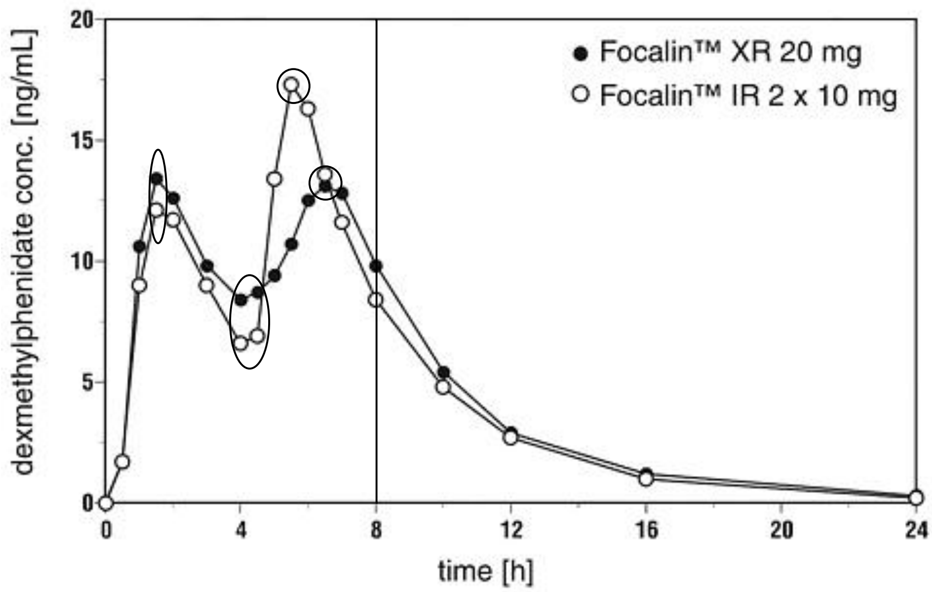
Figure 1. Mean plasma concentration time-profile of methylphenidate after a single dose of Ritalin® LA 40 mg q.d. and Ritalin® 20 mg given in two doses four hours apart



- **Focalin XR**
    - 5 mg, 10 mg, 20 mg caps
    - Capsule technology (SODA) is same as Ritalin LA and Adderall XR
    - Capsule can be opened and sprinkled on yogurt, etc, as long as beads not chewed
    - High fat meals may delay peak by one hour.
    - **50% released immediately and 50% released 4 hours later**
    - Compared to Focalin immediate release, the first 3 hours are similar but the 4 hour trough and the second peak are both less
    - Lasts 8-12 hours (8-9 hours in my experience)
    - Greenhill et al, 2006:
        - 67.3% response rate vs. 13.3% rate with placebo
    - Side effects
        - Gastrointestinal 38% vs. 19% placebo
        - Decreased appetite 30% vs. 9% placebo
        - Decreased weight by -0.5 (+/- 1.4) kg vs. 0.4 (+/- 1.3) kg for placebo
        - Headache 25% vs. 11% placebo
        - Anxiety 6% vs. 0 placebo
        - Cardiovascular

        - Systolic blood pressure increases by 3.5 (+/- 11.4) mmHg vs. -0.2 (+/-7.5) for placebo
        - Diastolic blood pressure increases by 1.8 (+/- 8) mmHg vs. 0.4 (+/- 7.5) for placebo
        - Pulse increases 2.7 (+/- 9.5) beats per minute vs. 1.3 (+/- 8.9) for placebo
        - Thought to be clinically insignificant

Figure 1. Mean Dexmethylphenidate Plasma Concentration-Time Profiles After Administration of 1 x 20 mg Focalin™ XR (n=24) Capsules and 2 x 10 mg Focalin™ Immediate-Release Tablets (n=25)



- **Jornay PM**
    - Delayed release (by 8 hours) AND extended release
        - Pill given at night, between 6:30-9:30 pm
        - Onset of action in the AM
        - Outer later delays release for up to 10 hours
        - Inner layer controls the rate of release throughout the day
    - **Time to max is**
        - **15.6 hours in adults (so 11 pm - MN dosing would peak the next day at ~2:30-3:30 pm)**
        - **17.1 hours in adolescents (so 10 pm – MN dosing would peak at ~2-4 pm)**
        - **17.7 in children (so 8-9 pm dosing would peak at ~1:45-2:45 pm)**
    - Dosing
        - Recommended starting dose is 20 mg in the evening
        - Dose range is 20-100 mg/day
        - Caps are 20 mg, 40 mg, 60 mg, 80 mg, and 100 mg
    - Side effects

	Placebo	Jornay PM
Insomnia	9%	33%
Initial	5%	14%
Middle	4%	11%
Late	1%	11%
Not specified	1%	4%
Mood swings	1%	6%
Decreased appetite	4%	19%
Headache	5%	10%
Hyperactivity	1%	5%
Diastolic BP inc	4%	7%
Vomiting	0	9%
Nausea	0	6%
Rash	0	2%

    - *August 10, 2018*

The FDA approved JORNAY PM, a new formulation of methylphenidate, for the treatment of attention deficit disorder (ADHD or ADD) in patients 6 years and older. Ironshore Pharmaceuticals plans to make the drug available commercially in the first half of 2019.

JORNAY PM is designed to be taken before going to sleep, instead immediately upon waking, to provide early-morning symptom control. It uses DELEXIS, a proprietary drug delivery technology, to provide long-acting coverage with two functional film coatings:

"Many parents of children with ADHD note that the early morning routine is often one of the most chaotic times of the day. The idea of dosing the medication the night before was our moon-shot solution to meeting this need," says Dr. Randy Sallee, Chief Medical Officer at Ironshore. "The approval of JORNAY PM is a welcome treatment option for healthcare providers, patients and their caregivers that may affect the way physicians think about ADHD treatment going forward."

The FDA granted approval after two separate Phase III studies, with 278 total participants, demonstrated statistically significant improvement of ADHD symptoms for children ages 6-12 taking JORNAY PM when compared to a placebo. The studies measured symptom control in two settings: a classroom and during the early morning hours before school. In the first study, all participants received JORNAY PM for six weeks. In the seventh week, participants were randomly selected to continue taking JORNAY PM or switch to a placebo. Teachers rated classroom symptoms using the Swanson, Kotkin, Agler, M-Flynn and Pelham (SKAMP) Scale. Parents rated early morning symptoms on the Parent Rating of Evening and Morning Behavior-Revised (PREMB-R AM) scale.

In the second study, randomized participants received JORNAY PM or placebo for three weeks. Symptom improvement was measured by the ADHD Rating Scale (ADHD-RS-IV) Total Score, and the Before School Functioning Questionnaire (BSFQ).

During the open-label JORNAY PM treatment phase of testing, the most common adverse reaction reported was insomnia (41%). Side effects were similar to other methylphenidate products, and in addition, Ironshore reports adverse reactions of headache, psychomotor hyperactivity, and mood swings.

JORNAY PM has been designated a Schedule II controlled substance, indicating that it has a high potential for abuse.

- **Efficacy and Safety of HLD200, Delayed-Release and Extended-Release Methylphenidate, in Children with Attention-Deficit/Hyperactivity Disorder; Steven R. Pliszka, et al, 2018**
  Objective: Evening-dosed HLD200 is a delayed-release and extended-release methylphenidate (DR/ER-MPH) formulation consisting of uniform, dual-layered microbeads with an inner drug-loaded core. DR/ER-MPH is designed to delay the initial release of drug by 8–10 hours, and thereafter, provide a controlled, extended drug release to target onset of effect upon awakening that lasts into the evening. This phase 3 study evaluated the safety and efficacy of DR/ER-MPH on symptoms and temporal at-home functional impairment in children with attention-deficit/hyperactivity disorder (ADHD).

  Methods: This 3-week, randomized, double-blind, multicenter, placebo-controlled, parallel-group, forced-dose titration trial evaluated DR/ER-MPH (40–80mg/day) in children aged 6–12 years with ADHD. Primary efficacy endpoint was the ADHD rating scale–IV (ADHD-RS-IV), and the key secondary endpoints were the Before-School Functioning Questionnaire (BSFQ), and Parent Rating of Evening and Morning Behavior-Revised, morning (PREMB-R AM) and evening (PREMB-R PM). Safety measures included spontaneously reported treatment-emergent adverse events (TEAEs) and two TEAEs of special interest, appetite suppression and insomnia (with direct questioning on sleep disturbance).

  Results: One hundred sixty-one participants were included in the intent-to-treat population (DR/ER-MPH, n=81; placebo, n=80). After 3 weeks, DR/ER-MPH achieved significant improvements versus placebo in ADHD symptoms (least-squares [LS] mean ADHD-RS-IV: 24.1 vs. 31.2; p=0.002), and at-home early morning (LS mean BSFQ: 18.7 vs. 28.4; p<0.001; LS mean PREMB-R AM: 2.1 vs. 3.6; p<0.001) and late afternoon/evening (LS mean PREMB-R PM: 9.4 vs. 12.2; p=0.002) functional impairment. Commonly reported TEAEs (≥10%) were insomnia and decreased appetite.

  Conclusions: DR/ER-MPH was generally well tolerated and demonstrated significant improvements versus placebo in ADHD symptoms and at-home functional impairments in the early morning, late afternoon, and evening in children with ADHD.

- Cotempla XR
  - Orally disintegrating tablet
  - Lasts ~12 hours
  - Dose range 17.3-51.8 mg/am
  - Tabs include 8.6 mg, 17.3 mg, and 25.9 mg
  - Time to max 4.6-5.31 hours
  - Half life 3.93-4.43 hours

- Plasma concentrations per dose about twice as high in children as observed in adults

Figure 2: Mean *d*-Methylphenidate Plasma Concentration-Time Profiles After Administration of COTEMPLA XR-ODT or Methylphenidate Hydrochloride Extended-Release Capsule in Healthy Volunteers Under Fasted Conditions

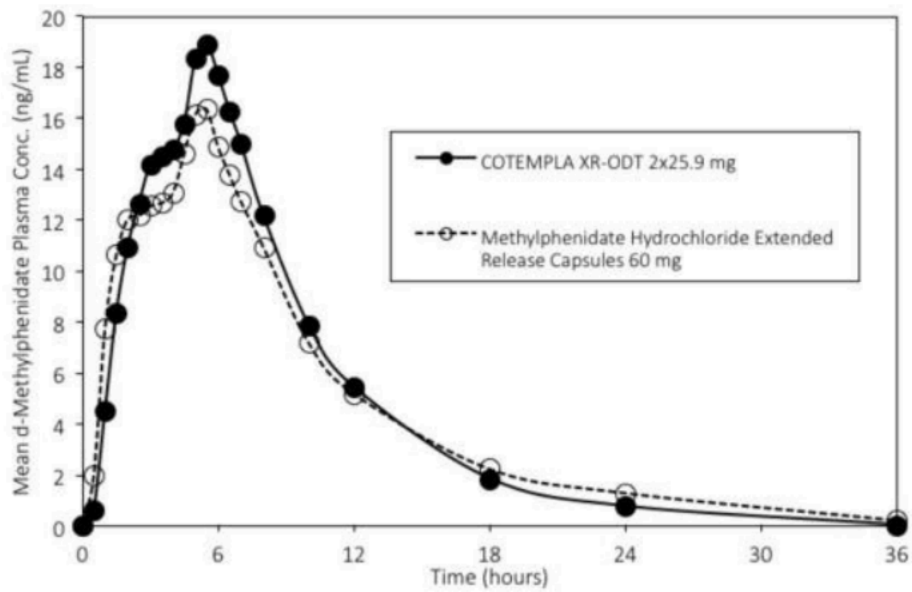


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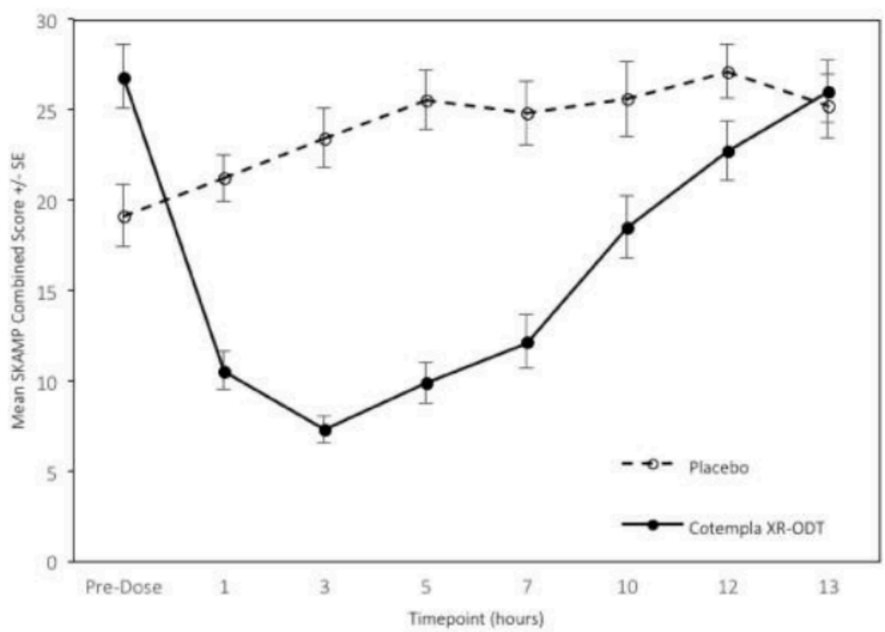
Figure 3: LS Mean SKAMP Combined Score After Treatment with COTEMPLA XR-ODT or Placebo During Classroom Day in Patients with ADHD



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- A Single-Dose, Single-Period Pharmacokinetic Assessment of an Extended-Release Orally Disintegrating Tablet of Methylphenidate in Children and Adolescents with Attention-Deficit/Hyperactivity Disorder
  Ann Childress, Jeffrey Newcorn, Jeffrey G Stark, Russ McMahen, Mark Tengler, Carolyn Sikes
  Journal of Child and Adolescent Psychopharmacology 2016, 26 (6): 505-12
  OBJECTIVE: To determine the pharmacokinetic (PK) profile of a proprietary formulation of methylphenidate (MPH) in children and adolescents with attention-deficit/hyperactivity disorder (ADHD) in a phase 1 study. Methylphenidate extended-release orally disintegrating tablets (MPH XR-ODTs) combine two technologies in a single-tablet formulation-an extended-release profile that was designed for once-daily dosing in an ODT that does not require water or chewing for ingestion.
  METHODS: This was a single-dose, open-label, single-period, single-treatment study, in which 32 children with ADHD who were receiving MPH in doses of 40 or 60mg before beginning the study each received a 60-mg dose (2×30mg) of MPH XR-ODT. The following plasma PK parameters of MPH were determined for participants grouped by age (6-7, 8-9, 10-12, and 13-17 years old): maximum concentration (Cmax), time to maximum concentration (Tmax), elimination half-

life (T½), area under the curve from 0 hours to infinity (AUCinf), oral clearance (CL/F), and volume of distribution in the terminal phase (Vz/F). Safety and tolerability were also assessed.
RESULTS: A total of 32 participants received the study drug. For all participants, plasma concentration-time profiles of MPH exhibited a broad peak after administration of MPH XR-ODT through ~8 hours, indicating extended release from the formulation, followed by an apparent first-order elimination phase. As age increased, MPH exposure decreased and mean estimates of CL/F increased; however, weight-normalized CL/F values were comparable across age groups. Similarly, mean estimates of Vz/F increased with age, but weight-normalization decreased differences across age groups, with the exception of the youngest age group, which had higher values. All adverse events (AEs) were mild.
CONCLUSION: This XR-ODT formulation of MPH demonstrated weight-normalized clearance rates that were consistent across all age groups, a PK profile consistent with once-daily dosing, and an AE profile consistent with this class of medication in children and adolescents with ADHD.

- Efficacy, Safety, and Tolerability of an Extended-Release Orally Disintegrating Methylphenidate Tablet in Children 6-12 Years of Age with Attention-Deficit/Hyperactivity Disorder in the Laboratory Classroom Setting
Ann C Childress, Scott H Kollins, Andrew J Cutler, Andrea Marraffino, Carolyn R Sikes
Journal of Child and Adolescent Psychopharmacology 2016 May 16
OBJECTIVE: Methylphenidate extended-release orally disintegrating tablets (MPH XR-ODTs) represent a new technology for MPH delivery. ODTs disintegrate in the mouth without water and provide a pharmacokinetic profile that is consistent with once-daily dosing. This study sought to determine the efficacy, safety, and tolerability of this novel MPH XR-ODT formulation in school-age children with attention-deficit/hyperactivity disorder (ADHD) in a laboratory classroom setting.
METHODS: Children aged 6-12 years with ADHD (n=87) were enrolled in this randomized, multicenter, double-blind, placebo-controlled, parallel, laboratory classroom study. The MPH XR-ODT dose was titrated to an optimized dose during a 4-week open-label period and maintained on that dose for 1 week. Participants (n=85) were then randomized to receive their optimized dose of MPH XR-ODT or placebo once daily for 1 week (double blind), culminating in a laboratory classroom testing day. Efficacy was evaluated using the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Attention, Deportment, and Combined scores along with Permanent Product Measure of Performance (PERMP; Attempted and Correct) assessments. Onset and duration of drug action were also evaluated as key secondary endpoints. Safety assessments included adverse events (AEs), physical examinations, electrocardiograms (ECGs), and the Columbia Suicide Severity Rating Scale (C-SSRS).
RESULTS: The average SKAMP-Combined score on the classroom study day was significantly better for the MPH XR-ODT group (n=43) than for the placebo group (n=39; p<0.0001). The effect was evident at 1 hour and lasted through 12 hours postdose. The average SKAMP-Attention, SKAMP-Deportment, PERMP-A, and PERMP-C scores were indicative of significantly greater ADHD symptom control for the MPH XR-ODT group. The most common AEs reported were decreased appetite, upper abdominal pain, headache, insomnia, upper respiratory tract infection, affect lability, irritability, cough, and vomiting.
CONCLUSIONS: MPH XR-ODT was effective and well tolerated for the treatment of children with ADHD in a laboratory classroom setting. Clinical Trial Registry: NCT01835548 (ClinicalTrials.gov).

- Extended Release (8-12 hours)
    - Quillivant XR
        - Extended release oral suspension
        - 25 mg/5 ml (5 mg/1 ml)
        - 20% released right away
        - Peak level 2-5 hours after dosing, earlier with food, later on an empty stomach
        - Half-life 5 hours
        - Benefits last 8-12 hours

12.3 Pharmacokinetics

Absorption

Following a single, 60 mg oral dose of QUILLIVANT XR in 28 healthy adult subjects in a crossover study under fasting conditions, *d*-methylphenidate (*d*-MPH) mean (± SD) peak plasma concentrations of 13.6 (± 5.8) ng/mL occurred at a median time of 5.0 hours after dosing (Figure 2). The relative bioavailability of QUILLIVANT XR compared to Methylphenidate IR oral solution (2×30 mg, q6h) is 95%.

Extended Release MPH Solution and Chewable Preparations (Wilens, T. 2018)

Quillivant XR

Suspension

12 hour duration

25 mg/5 cc (tsp)

Dosing to 60 mg daily

Approved in pediatrics

QuilliChew ER

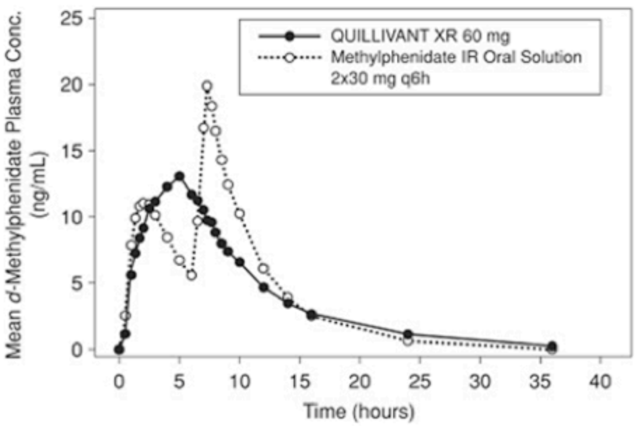
Chewable tablet

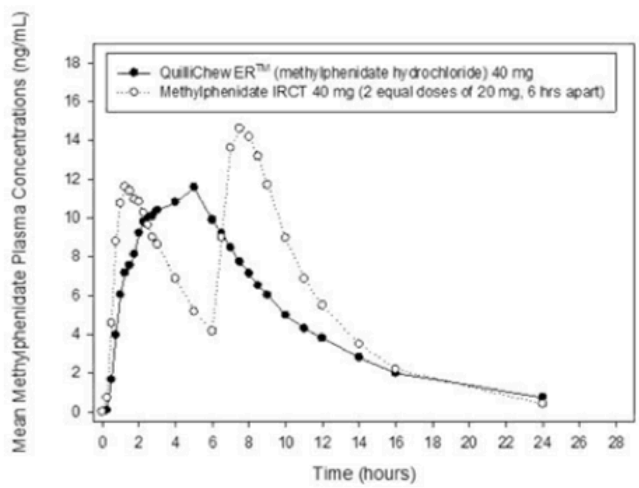
8 hour duration

20, 30, 40 mg tablets

Dosing to 60 mg daily

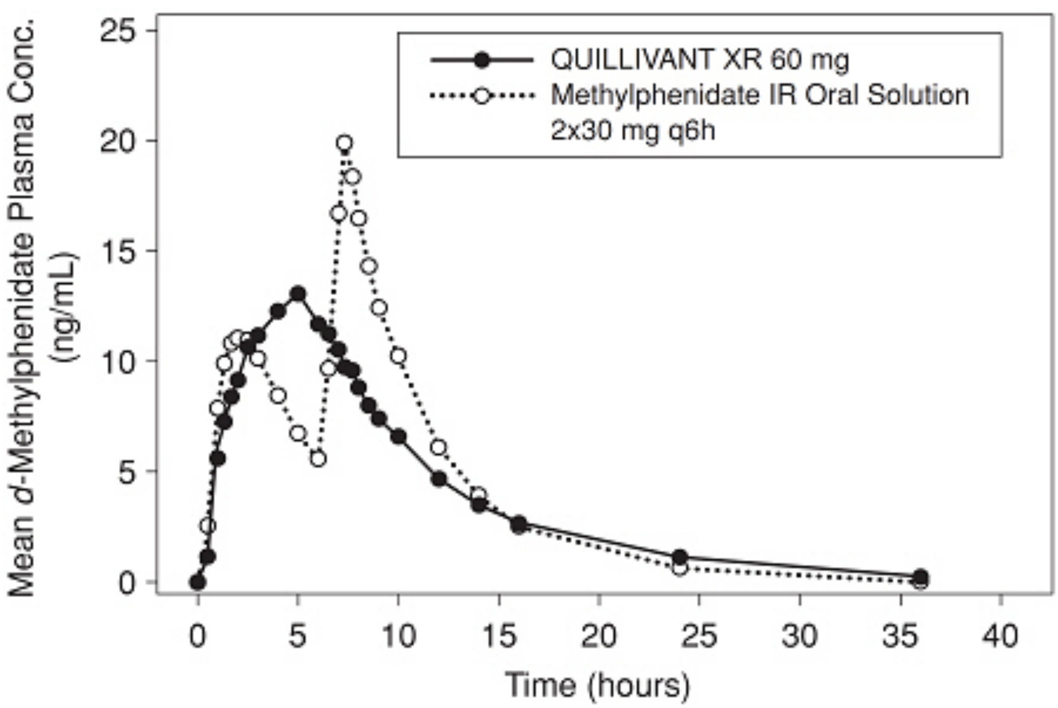
Approved in pediatrics

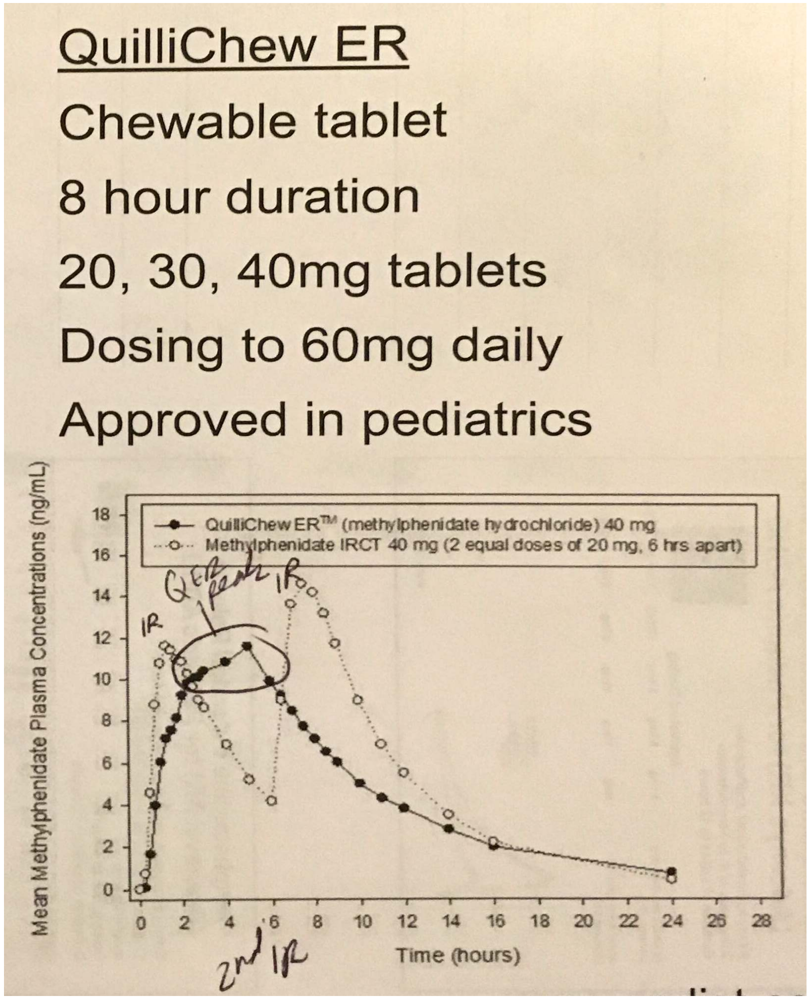




Rx list.com; Wilens,T. 2018

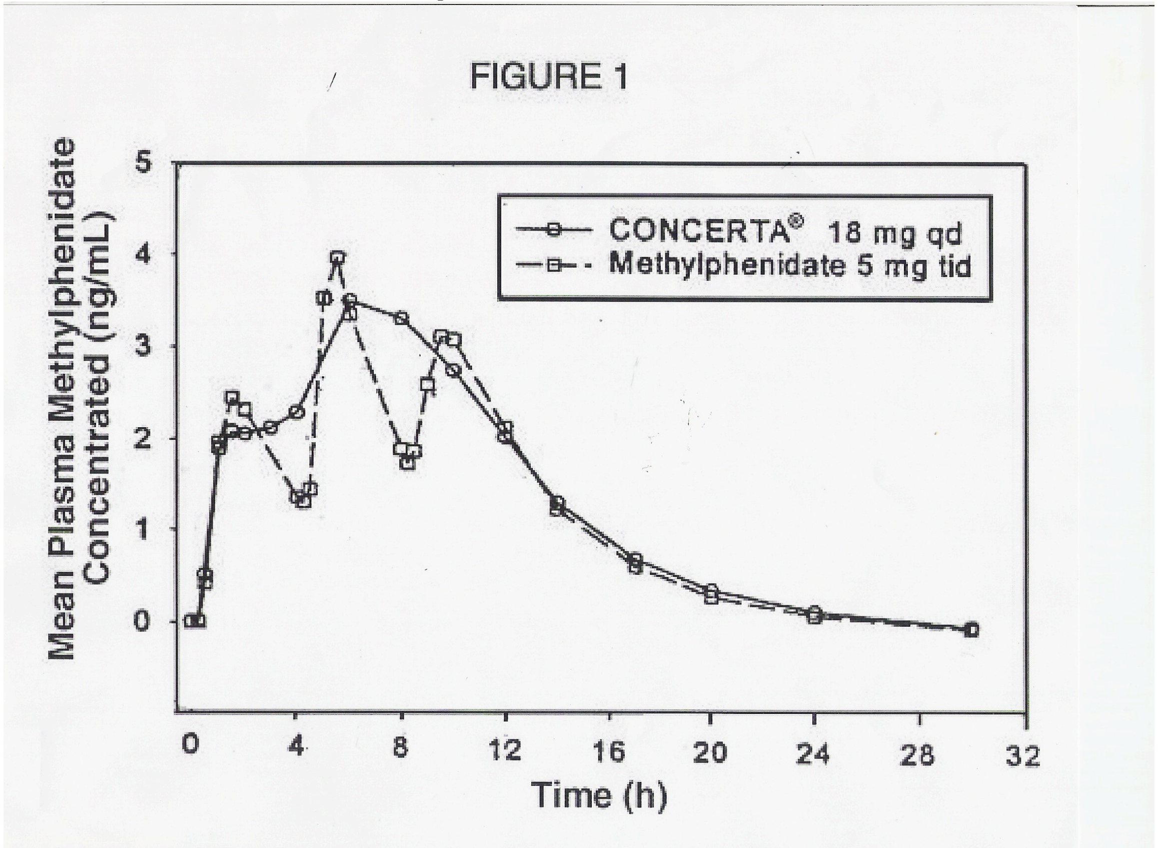
Figure 2. Mean *d*-Methylphenidate Plasma Concentration-Time Profiles



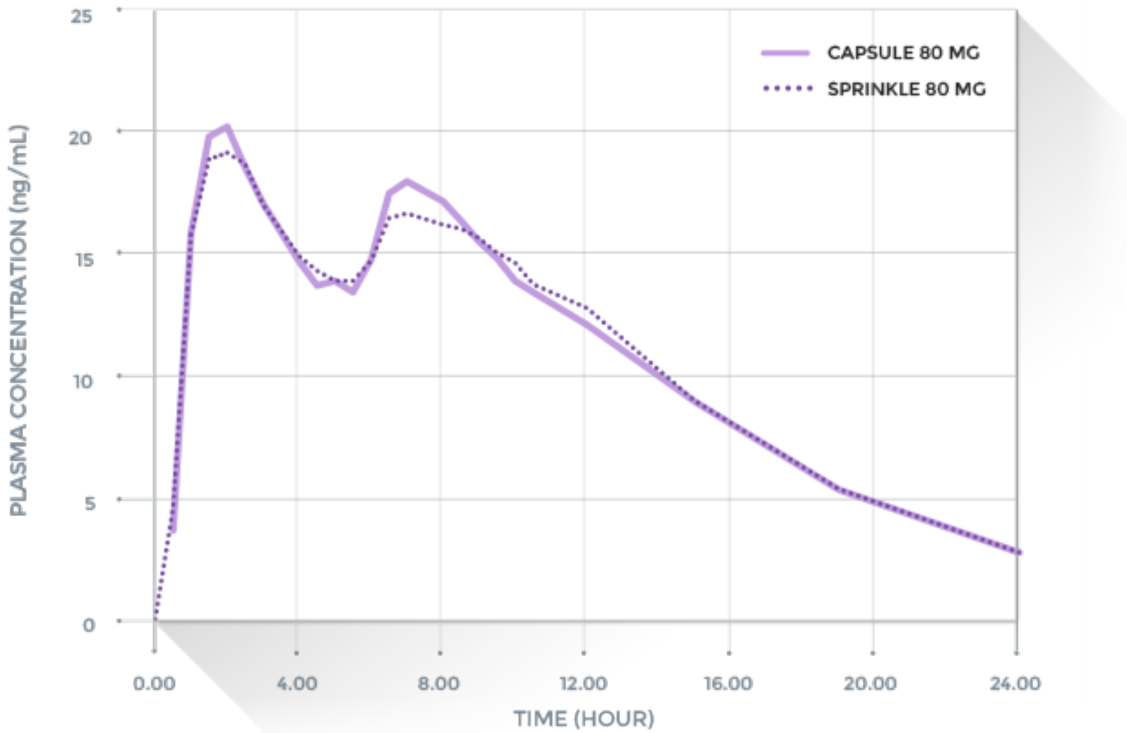
- Quillichew
    - Chewable
    - 20% released right away
    - Lasts 8-12 hours
    - Peak at 5 hours
    - 

- **Concerta** Tablets (Alza)
  - Tabs—18 mg, 27 mg, 36 mg, 54 mg; dose range 18-72 mg/d; can use higher doses if necessary
  - **22-33% released in AM; another 30-35% around 4 hours later, and 32-48% at around the 8 hour mark**
  - Initial peak in 1-2 hours; last peak 6-8 hours after which levels decline
  - Duration 8-14 hours; in my experience: 9-12 hour duration in kids, 8-10 hours in adults
  - Recent evidence from a 2-year study (Wilens) demonstrated continued safety (with no apparent decrement to weight and height by the end of the 2 years) and efficacy
  - Equivalencies
    - Concerta 18 mg is equivalent to
      - Ritalin 5 mg/5 mg/5 mg
      - Focalin OR Adderall 2.5/2.5/2.5
      - Adderall 2.5/2.5/2.5
      - Ritalin LA 20 mg (but 10 mg released immediately, 10 mg released 4 hours later)
      - Focalin XR OR Adderall XR 10 (but 5 mg released immediately, 5 mg released 4 hours later)
      - 4 mg is released immediately and 14 mg extended release
    - Concerta 27 mg is equivalent to
      - slightly more than Ritalin 5/5/5
      - Focalin OR Adderall 5/5/2.5
      - Ritalin LA 20 mg (but 10 mg released immediately, 10 mg released 4 hours later)
      - Focalin XR OR Adderall XR 15 mg (but 7.5 mg released immediately, 7.5 mg released 4 hours later)
      - 6 mg immediate, 21 mg delayed and extended
    - Concerta 36 mg is equivalent to
      - Ritalin 10/10/10
      - Focalin OR Adderall 5/5/5
      - Ritalin LA 30 mg (but 15 mg released immediately, 15 mg released 4 hours later)
      - Focalin XR OR Adderall XR 15-20 mg (but 7.5-10 mg released immediately, 7.5-10 mg released 4 hours later)
      - 8 mg immediate, 28 mg delayed and extended
    - Concerta 54 mg equivalent to
      - Ritalin 15/15/10-15
      - Focalin OR Adderall 7.5 mg/7.5 mg/5 mg - 7.5 mg
      - Ritalin LA 40 mg (but 20 mg released immediately, 20 mg released 4 hours later)
      - Focalin XR OR Adderall XR 20 mg (but 10 mg released immediately, 10 mg released 4 hours later)
      - 12 mg immediate, 42 mg delayed and extended
    - Concerta 63 mg equivalent to
      - Ritalin 15 – 20 mg/15 mg – 20 mg/15 mg
      - Focalin OR Adderall 10/10/10
      - Ritalin LA 50-60 mg (but 25-30 mg released immediately, 25-30 mg released 4 hours later)
      - Focalin XR OR Adderall XR 30 mg (but 15 mg released immediately, 15 mg released 4 hours later)
    - Concerta 72 mg equivalent to
      - Ritalin 20/20/20
      - Focalin OR Adderall 10 – 12.5 mg/10 – 12.5 mg/10 – 12.5 mg
      - Ritalin LA 60 mg (but 30 mg released immediately, 30 mg released 4 hours later)
      - Focalin XR OR Adderall XR 30-40 mg (but 15 – 20 mg released immediately, 15 – 20 mg released 4 hours later)
      - 16 mg immediate, 56 mg delayed and extended
  - Note on two particular generic brands: generics made by Mallinckrodt and Kudco are not bioequivalent to name brand, so do not use.
  - Side effects in adults
    - Decreased appetite 25% vs. 7% placebo
    - Headache 17-22% vs. 18% placebo
    - Nausea 13% vs. 4% placebo
    - Loss of appetite 13%
    - Dry mouth 12% vs. 2% placebo
    - Insomnia 11-13% vs. 7% placebo
    - Weight loss 7% vs. 5% placebo

- Increase in heart rate of 2-10.6 beats per minute



- **Aptensio XR** (methylphenidate extended release)
  - 12 hours duration
  - **~37-40% delivered as immediate release rapidly**
  - with decline over next 5 hours
  - ~60% delivered later as extended release at 7 hours
  - Comes in 10, 15, 20, 30, 40, 50, 60 mg caps

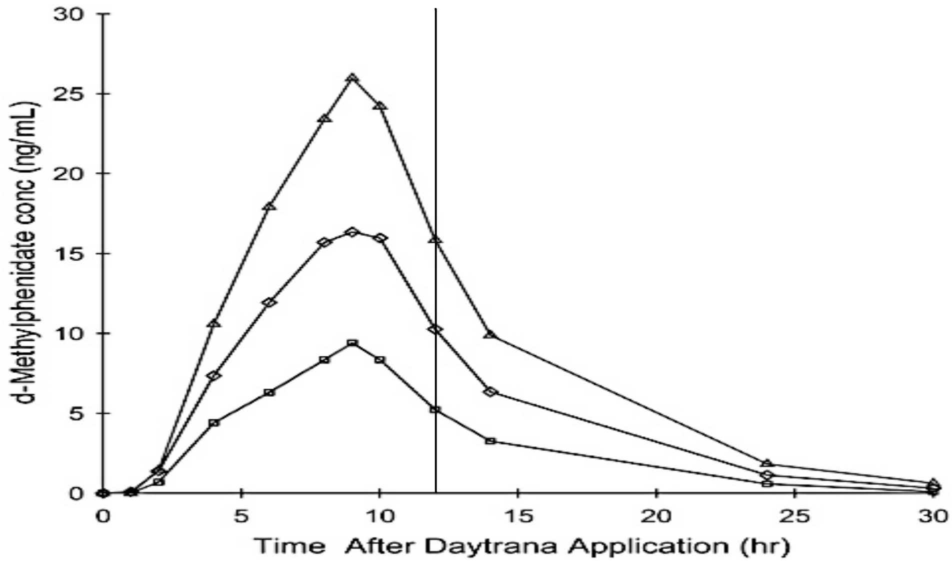


- A randomized placebo-controlled double-blind study evaluating the time course of response to methylphenidate hydrochloride extended-release capsules in children with attention-deficit/hyperactivity disorder
  Sharon B Wigal, Laurence L Greenhill, Earl Nordbrock, Daniel F Connor, Scott H Kollins, Akwete Adjei, Ann Childress, Annamarie Stehli, Robert J Kupper
  Journal of Child and Adolescent Psychopharmacology 2014, 24 (10): 562-9
  OBJECTIVE: The purpose of this study was to assess the time of onset and time course of efficacy over 12.0 hours of extended-release multilayer bead formulation of methylphenidate (MPH-MLR) compared with placebo in children 6-12 years of age with attention-deficit/hyperactivity disorder (ADHD) in a laboratory school setting.
  METHODS: This randomized double-blind placebo-controlled study included children 6-12 years of age with ADHD. Enrolled children went through four study phases: 1) Screening period (≤4 weeks) and a 2 day medication washout period; 2) open-label period with dose initiation of MPH-MLR 15mg daily and individual dose optimization treatment period (2-4 weeks); 3) double-blind crossover period in which participants were randomized to sequences (1 week each) of placebo and the optimized MPH-MLR dose given daily; and 4) follow-up safety call. Analog classroom time course evaluations were performed at the end of each double-blind week. The primary efficacy end-point was the mean of the on-treatment/postdose Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP)-Total scores over time points collected 1.0-12.0 hours after dosing. End-points were evaluated using a mixed-effects analysis of covariance.
  RESULTS: The evaluable population included 20 participants. The least-squares mean postdose SKAMP-Total score was higher for placebo than for MPH-MLR (2.18 vs. 1.32, respectively; $p=0.0001$), indicating fewer symptoms with MPH-MLR therapy than with placebo. No difference in SKAMP-Total score between participants who received sequence 1 or sequence 2 was noted. From each of hours 1.0-12.0, least-squares mean SKAMP-Total score was significantly lower for those receiving MPH-MLR than for those receiving placebo ($p \leq 0.0261$). Neither serious adverse events nor new or unexpected safety findings were noted during the study.
  CONCLUSIONS: MPH-MLR showed a significant decrease in SKAMP scores compared with placebo in children with ADHD 6-12 years of age, indicating a decrease in ADHD symptoms. The estimated onset was observed within 1.0 hour, and duration was measured to 12.0 hours postdose.
- Single-dose pharmacokinetics of methylphenidate extended-release multiple layer beads administered as intact capsule or sprinkles versus methylphenidate immediate-release tablets (Ritalin(®)) in healthy adult volunteers
  Akwete Adjei, Nathan S Teuscher, Robert J Kupper, Wei-Wei Chang, Laurence Greenhill, Jeffrey H Newcorn, Daniel F Connor, Sharon Wigal
  Journal of Child and Adolescent Psychopharmacology 2014, 24 (10): 570-8
  OBJECTIVES: The purpose of this study was to evaluate the relative bioavailability and safety of a multilayer extended-release bead methylphenidate (MPH) hydrochloride 80mg (MPH-MLR) capsule or sprinkles (37% immediate-release [IR]) versus MPH hydrochloride IR(Ritalin(®)) tablets, and to develop a pharmacokinetic (PK) model simulating MPH concentration-time data for different MPH-MLR dosage strengths.
  METHODS: This was a single-center, randomized, open-label, three-period crossover study conducted in 26 fasted healthy adults (mean weight±standard deviation, 70.4±11.7kg) assigned to single-dose oral MPH-MLR 80mg capsule or sprinkles with applesauce, or Ritalin IR 25mg (1×5mg and 1×20mg tablet) administered at 0, 4, and 8 hours.
  RESULTS: MPH-MLR 80mg capsule and sprinkles were bioequivalent; ratios for maximum concentration (C_{max}), area under plasma drug concentration versus time curve (AUC_{0-t}), and AUC_{0-inf} were 1.04 (95% confidence interval [CI], 96.3-112.4), 0.99 (95% CI, 95.3-102.8), and 0.99 (95% CI, 95.4-103.0), respectively. MPH-MLR capsule/sprinkles produced highly comparable, biphasic profiles of plasma MPH concentrations characterized by rapid initial peak, followed by moderate decline until 5 hours postdose, and gradual increase until 7 hours postdose, culminating in an attenuated second peak.

Based on 90% CIs, total systemic exposure to MPH-MLR 80mg capsule/sprinkles was similar to that for Ritalin IR 25mg three times daily, but marked differences in Cmax values indicated that MPH-MLR regimens were not bioequivalent to Ritalin. MPH Cmax and total systemic exposure over the first 4 hours postdose with MPH-MLR capsule/sprinkles was markedly higher than that associated with the first dose of Ritalin. All study drugs were safe and well tolerated. The PK modeling in adults suggested that differences in MPH pharmacokinetics between MPH-MLR and Ritalin are the result of dosage form design attributes and the associated absorption profiles of MPH.
CONCLUSIONS: MPH-MLR 80mg provides a long-acting biphasic pattern of plasma MPH concentrations with one less peak and trough than Ritalin IR.

- Effect of Aptensio XR (Methylphenidate HCl Extended-Release) Capsules on Sleep in Children with Attention-Deficit/Hyperactivity Disorder
  Judith Owens, Margaret Weiss, Earl Nordbrock, Greg Mattingly, Sharon Wigal, Laurence L Greenhill, Wei-Wei Chang, Ann Childress, Robert J Kupper, Akwete Adjei
  Journal of Child and Adolescent Psychopharmacology 2016 October 18
  OBJECTIVE: To evaluate measures of sleep (exploratory endpoints) in two pivotal studies of a multilayer bead extended-release methylphenidate (MPH-MLR) treatment of attention-deficit/hyperactivity disorder in children.
  METHODS: Study 1 evaluated the time course of response to MPH-MLR (n=26) patients in an analog classroom setting through four phases: screening (≤28 days), open label (OL) dose optimization (4 weeks), double-blind (DB) crossover (2 weeks; placebo vs. optimized dose), and follow-up call. Study 2 was a forced-dose parallel evaluation of MPH-MLR (n=230) in four phases: screening (≤28 days), DB (1 week; placebo or MPH-MLR 10, 15, 20, or 40mg/day), OL dose optimization (11 weeks), and follow-up call. Sleep was evaluated by parents using the Children's or Adolescent Sleep Habits Questionnaire (CSHQ or ASHQ) during the DB and OL phases. DB analysis: Study 1 (crossover), analysis of variance; Study 2, analysis of covariance. OL analysis: paired t-test.
  RESULTS: DB: treatments were significantly different in Study 1 only for CSHQ Sleep Onset Delay (MPH-MLR, 1.90 vs. placebo, 1.34; $p=0.0046$, placebo was better), and Study 2 for CSHQ Parasomnias (treatment, $p=0.0295$), but no MPH-MLR treatment was different from placebo (pairwise MPH-MLR treatment to placebo, all $p \geq 0.170$). OL: CSHQ total and Bedtime Resistance, Sleep Duration, Sleep Anxiety, Night Wakings, Parasomnias, and Sleep-disordered Breathing subscales decreased (improved, Study 1) significant only for CSHQ Night Wakings ($p<0.05$); in Study 2 CSHQ total and Bedtime Resistance, Sleep Duration, Night Wakings, Parasomnias, and Daytime Sleepiness, and ASHQ total, Bedtime, Sleep Behavior, and Morning Waking all significantly improved ($p<0.05$).
  CONCLUSIONS: In both studies, there was minimal negative impact of MPH-MLR on sleep during the brief DB phase and none during the longer duration OL phase. Some measures of sleep improved with optimized MPH-MLR dose.

- Daytrana; methylphenidate transdermal system MTS; Shire, Noven
  - FDA-approved 4/06; in pharmacies 7/06
  - Patches:
    - Most common use: wear for 9 hours during which methylphenidate is increasingly released to a peak at the (9 hour) point at which the patch is removed; the methylphenidate level then decreases over the next three hours so that the duration of efficacy (when removed after 9 hours) is 12 hours
    - The patch can be removed at any point after which the level/efficacy will always decrease over the subsequent 3 hours from the removal of the patch
    - Available in patches of the following strengths and the corresponding amount of methylphenidate delivered when the particular patch is worn for 9 hours:
      - 10 mg--> 27.5 mg
      - 15 mg--> 41.3 mg
      - 20 mg--> 55 mg
      - 30 mg--> 82.5 mg
  - Pharmacodynamics (Daytrana vs Ritalin three times-a-day)
    Time to peak 9 hours (7-11 hours) vs 8 hours (6-10 hours) for Ritalin three times-a-day
    - Plasma peak levels are higher for Daytrana; plasma levels are smooth (bell shaped)
  - Side effects
    - Decreased appetite or decreased eating or weight decrease 39% (vs. 5% placebo)
    - Decreased appetite alone: 5-15%
    - Nausea or vomiting 22% (vs. 6% placebo)
    - Insomnia (4% placebo)
    - Difficulty falling asleep 0-5.6%
    - Other sleep problems: 2.6-11.1
    - Headache 5.6-8% (23% for 30 mg/day dose)
    - Tic 7% (vs. 0% placebo)
    - Affect lability 6% (vs. 0% placebo)
    - Upper abdominal pain 3-7% (13% for 30 mg/day dose)
    - Skin irritation



Oculomotor Abnormalities in Children with Attention-Deficit/Hyperactivity Disorder Are Improved by Methylphenidate
Maria Pia Bucci, Coline Stordeur, Mathilde Septier, Eric Acquaviva, Hugo Peyre, Richard Delorme
Journal of Child and Adolescent Psychopharmacology 2016 December 15
BACKGROUND: There are relatively few studies of saccadic eye movements in children with attention-deficit/hyperactivity disorder (ADHD). The aim of this study was to examine inhibitory abilities of eye movements in children with ADHD and to explore the effect of methylphenidate (MPH) on eye movement performance.
METHODS: Thirty-one children with ADHD (mean age 9.9±0.4 years) and 31 sex-, age-, and IQ-matched children with normal development were examined. Saccades elicited not only by the gap, step, overlap, and antisaccade paradigms but also a simple fixation paradigm have been recorded using an eye tracker. The latency of each type of saccade, the error rate of antisaccades, and the number of saccades made during fixation have been measured.
RESULTS: Children with ADHD and naive to treatment with respect to controls showed significantly shorter mean latency of voluntary saccades (overlap paradigm), more frequent errors during the antisaccade paradigm, and higher number of saccades made during fixation. After 1 month of MPH treatment, all these parameters changed significantly and reached control values.
CONCLUSION: Taken together, these results suggest that oculomotor abilities are poor in children with ADHD, which may correlate with deficits in inhibitory mechanisms. Treatment with MPH improves oculomotor performances through adaptive strategies, which may involve brain structures related to cognitive inhibition.

- Adhansia XR
  - Pharmacology
    - Two peaks
      - First is at about 1.5 hours (1-2.5 hour range)
        - ~2 hours in pediatric patients
      - Second is about 12 hours (8.5-16 hour range)
        - ~10-11 hours in pediatric patients
      - Time to peaks reduced by ~1 hour if taken with a high fat meal
  - The capsules contain multilayered beads, composed of an immediate-release (IR) layer which contains approximately 20% of the methylphenidate dose, and a controlled release layer which contains approximately 80% of the methylphenidate dose
  - Each extended-release capsule contains 25 mg, 35 mg, 45 mg, 55 mg, 70 mg, or 85 mg of methylphenidate hydrochloride (HCl), which is equivalent to 21.6 mg, 30.3 mg, 38.9, mg, 47.6 mg, 60.5 mg, and 73.5 mg of methylphenidate
  - The recommended starting dose of ADHANSIA XR for patients 6 years or older is 25 mg once daily. Titrate the dose in increments of 10 to 15 mg at intervals of no less than 5 days. Dosages higher than 100 mg daily in adults and 85 mg daily in pediatric patients have not been evaluated in clinical trials and are not recommended. Although efficacy was demonstrated in short-term controlled trials in adults at dosages of 100 mg daily, dosages above 85 mg daily were associated with a disproportionate increase in the incidence of certain adverse reactions. In short-term controlled trials in pediatric patients, efficacy was demonstrated at dosages of 70 mg daily, but dosages 70 mg daily and higher were associated with a disproportionate increase in the incidence of certain adverse reactions
  - ADHANSIA XR may be taken whole or the capsule may be opened and the entire contents sprinkled onto a tablespoon of applesauce or yogurt. The entire mixture should be consumed immediately or within 10 minutes. If the mixture is not consumed within 10 minutes after mixing, it should be discarded and not stored. Patients

should take the entire contents of the capsule sprinkled on the chosen food in its entirety, without chewing. The dose of a single capsule should not be divided. Patients should not take anything less than one capsule per day.

- The total number of patients exposed to ADHANSIA XR during 1 to 4-week long, controlled treatment periods is 883; this included 434 adult patients and 449 pediatric patients [156 (6 to 12 years); 293 (12 to 17 years)], from two clinical trials in adults, one in pediatric patients ages 12 to 17 years, and one in pediatric patients ages 6 to 12 years

Figure 1: Mean Concentration-Time Profiles for d,l-Methylphenidate on Day 5 After Daily Dosing

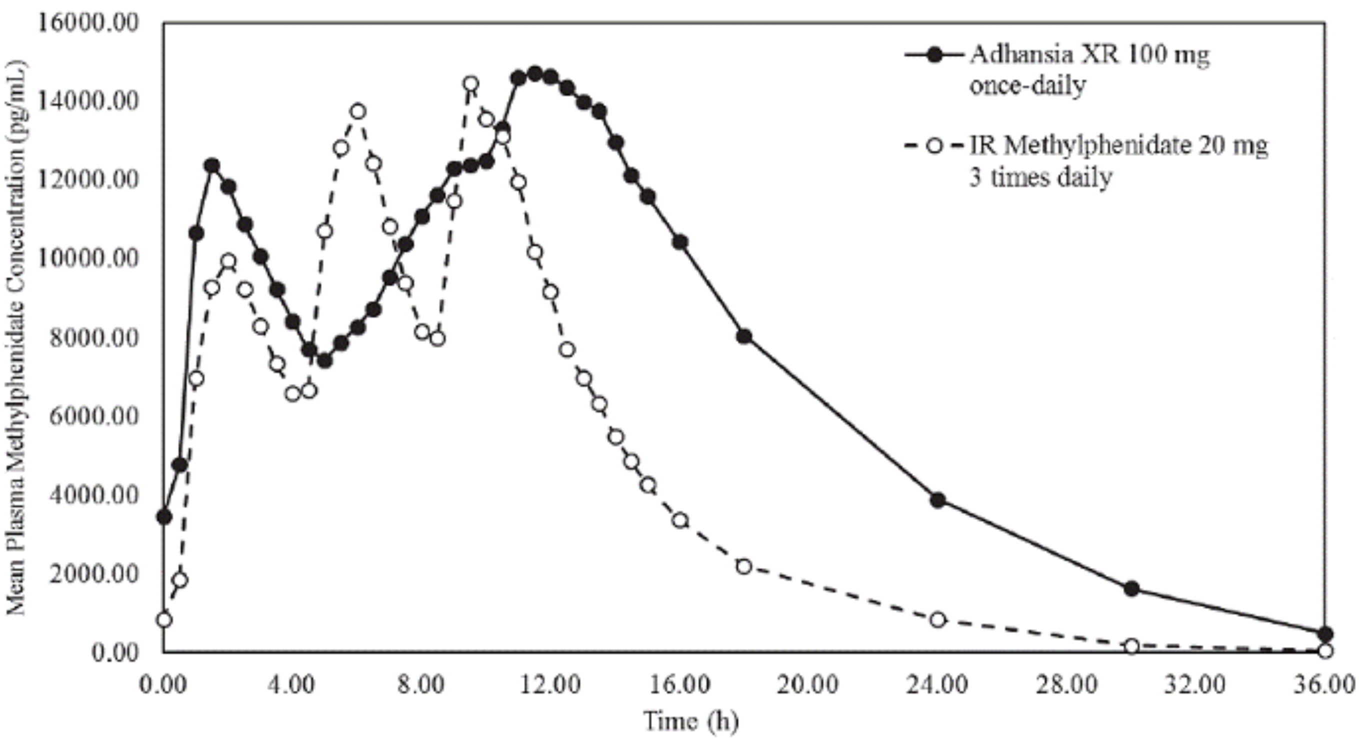


Table 1: Adverse Reactions Occurring in ≥2% of Adult Patients with ADHD on ADHANSIA XR and Greater than Patients Taking Placebo in a 4-week Clinical Trial

Adverse Reaction N=375	ADHANSIA XR				All doses ADHANSIA XR (N=297)	Placebo (N=78)
	25 mg (N=77)	45 mg (N=73)	70 mg (N=73)	100 mg (N=100)		
Initial Insomnia	4%	8%	6%	7%	5%	1%
Insomnia.	17%	11%	16%	19%	13%	4%
Dry mouth	8%	8%	7%	14%	8%	4%
Nausea	4%	6%	4%	11%	5%	3%
Diarrhea	1%	3%	7%	5%	3%	1%
Decreased appetite	4%	7%	15%	19%	9%	3%

Feeling jittery	1%	3%	8%	4%	4%	1%
Weight decreased	3%	4%	3%	5%	3%	1%
Upper respiratory tract infection	0%	4%	3%	3%	2%	1%

Pediatric Patients (12 to 17 years) With ADHD

Table 2: Adverse Reactions Occurring in ≥2% of Pediatric Patients (12 to 17 years) with ADHD Taking ADHANSIA XR and Greater than Placebo in a 4-week Clinical Trial

Adverse Reaction	ADHANSIA XR				All doses ADHANSIA XR (N=293)	Placebo (N=74)
	25mg (N=73)	45 mg (N=72)	70 mg (N=76)	85 mg (N=72)		
Decreased appetite	7%	19%	28%	26%	20%	0%
Insomnia	4%	0%	9%	13%	6%	1%
Initial Insomnia	4%	7%	5%	4%	5%	1%
Weight decreased	1%	3%	8%	13%	7%	0%
Abdominal pain upper	5%	1%	5%	4%	4%	1%
Nausea	3%	6%	7%	8%	6%	4%
Dizziness	3%	0%	4%	4%	3%	0%
Dry mouth	1%	0%	5%	4%	3%	1%
Vomiting	1%	1%	3%	6%	3%	0%

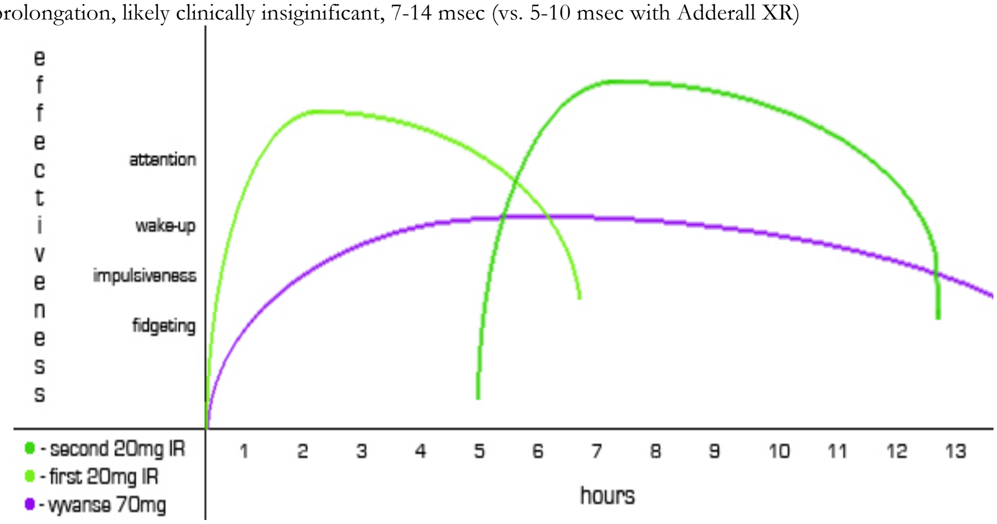
Pediatric Patients (6 to 12 years) With ADHD

- Study 4, conducted in pediatric patients 6 to 12 years of age, was comprised of a 6-week open-label dose-optimization phase in which all patients received ADHANSIA XR (n=156; mean dose 48 mg), followed by a 1-week, double-blind controlled phase in which patients were randomized to continue ADHANSIA XR (n=75) or switch to placebo (n=73). During the open-label ADHANSIA XR treatment phase, adverse reactions reported in > 5% of patients included: decreased appetite (35%), upper abdominal pain (15%), affect lability (13%), nausea or vomiting (13%), weight decreased (12%), insomnia (10%), irritability (10%), headache (10%), and heart rate increased (5%). Because of the trial design (6-week open-label active treatment phase followed by a 1-week, randomized, double-blind, placebo-controlled withdrawal), the adverse reaction rates described in the double-blind phase are lower than expected in clinical practice. No difference occurred in the incidence of adverse reactions between ADHANSIA XR and placebo during the 1-week, double-blind, placebo-controlled treatment phase.

- **Amphetamine Group**
  - NB: Agents that alter urinary pH can impact urinary excretion and alter blood levels of amphetamine. Acidifying agents (e.g., ascorbic acid) decrease blood levels, while alkalinizing agents (e.g., sodium bicarbonate) increase blood levels. Adjust dosage accordingly
  - **Dextroamphetamine** products
    - General
      - The d-isomer of amphetamine is more potent and has a more rapid onset of action than the l-isomer of amphetamine.
      - Onset of action 30-60 minutes
      - Peak plasma level within 2-3 hours
      - Peak clinical effect 1-2 hours
      - Duration of effect 2-6 hours
      - Half-life 4-8 hours in children, 10-12 hours in adults; elsewhere: 12-20 hours; my experience: 4 hours
      - Administer immediate release tabs every 4-6 hours
    - **Dextroamphetamine** Tablets (Dexedrine, SmithKline Beecham)
      - Tabs—5 mg, 10 mg (generic only); 2-4X as potent as methylphenidate (e.g., 5 mg of Dexedrine is equivalent to 10 mg of Ritalin immediate release in my experience)
      - Elixir—5 mg/5 ml
      - Initial target 0.15 mg/kg per dose
      - Time to max 2-3 hours
      - Half-life 7 hours
      - Duration 4 hours
    - **Zenzedi**
      - Dextroamphetamine immediate release
      - 2.5, 7.5, 15, 20, 30 mg tabs
    - **ProCentra**
      - Immediate release liquid
    - **Dextroamphetamine Sulfate ER Capsules** CII
      - 5 mg, 10 mg, 15 mg caps
      - Peak at ~8 hours (but benefits lasts 6-8 hours)
      - **Dexedrine (dextroamphetamine) Spansule**s (SmithKline Beecham)
      - Capsules—10 mg, 15 mg
      - Can be opened and sprinkles
    - **Vyvanse (lisdexamfetamine dimesylate)**
      - Dextroamphetamine conjugated to an amino acid (l-lysine)
      - Reduced potential for addiction; not considered a controlled substance
      - FDA-approved for ADHD in kids aged 6-12
      - FDA-approved for ADHD in adults in 2/2012
      - Begins to work in about an hour
      - Evidence
        - Biederman et al, 2007, 285 youth aged 6-12 years
          - Symptom scores declined 4-fold to 5-fold more than placebo
          - 70 mg dose was most effective per parent report
          - All doses were statistically more effective than placebo, and 70 mg was statistically more effective than 30 mg
        - Two short-term RCT's, 6-12 yo's, demonstrating safety and efficacy
          - Lopez et al, 2006
            - NRP104 vs. Adderall XR vs. placebo
            - Former two equivalent; both more effective than placebo
          - Second study—safe and effective
            - Childress et al, 2006: multicenter, open-label extension up to one year
            - At 6 months, 82% response rate
      - 20 mg, 30 mg, 40 mg, 50 mg, 60 mg and 70 mg caps
      - Comparison of **Adderall XR vs. Vyvanse**:
        - Adderall XR 10mg has 6.3mg of amphetamine base, and Vyvanse 30mg has 8.9mg of amphetamine base.
        - Adderall XR 20mg has 12.5mg of amphetamine base, and Vyvnase 50mg has 14.8mg of amphetamine base.
        - Adderall XR 30mg has 18.8mg of amphetamine base, and Vyvanse 70mg has 20.8mg of amphetamine base.
        - Adderall XR has 4 different amphetamine salts which are in this salt format so that it could be made into a solid form; d-amphetamine appears to be a bit more potent than the l form, and the ratio is 3:1.

- This means that a given amount of d-amphetamine base is more potent than the same amount of d/l amphetamine base, so comparing the 2 drugs simply in terms of the amount of amphetamine base may not be exactly correct.
- Vyvanse is a pro-drug of dextroamphetamine (just the d form); Dexedrine is d-amphetamine. D-amphetamine sulfate 10mg has 7.28 mg of d-amphetamine base.
- ***So based on this, a total of 40mg of Dexedrine/day would actually probably be closer to Vyvanse 100mg, or Adderall XR 50mg, or Adderall IR (immediate release) 25mg bid.***

- Pharmacokinetics
  - Once-a-day; lasts 10-13 hours
  - Half-life 9.5 hours (17 hours in adults)
  - Peak at 3.5 hours (4.4 hours in adults)
  - Food doesn't affect absorption but delays peak by 60 minutes or less
  - Side effects
    - Decreased appetite 39% (37% at 30 mg; 31% at 50 mg; 49% at 70 mg) vs. 4% placebo
    - Insomnia 19% (16% at 30 or 50 mg; 25% at 70 mg) vs. 3% placebo
    - Headaches 12% (10% at 30 mg or 50 mg; 16% at 70 mg) vs. 10% placebo
    - Upper abdominal pain 12% (14% at 30 mg; 7% at 50 mg; 15% at 70 mg) vs. 6% placebo
    - Irritability 10% (11% at 30 mg; 8% at 50 mg; 10% at 70 mg) vs. 0% placebo
    - Vomiting 9% (7% at 30 mg; 5% at 50 mg; 14% at 70 mg) vs. 4% placebo
    - Weight loss 9% (6% at 30 mg; 3% at 50 mg; 19% at 70 mg) vs. 1% placebo
    - QTc prolongation, likely clinically insiginificant, 7-14 msec (vs. 5-10 msec with Adderall XR)



Parent-Reported Improvements in Family Functioning in a Randomized Controlled Trial of Lisdexamfetamine for Treatment of Parental Attention-Deficit/Hyperactivity Disorder
Dara E Babinski, James G Waxmonsky, Daniel A Waschbusch, Hugh Humphery, William E Pelham
Journal of Child and Adolescent Psychopharmacology 2016 December 19

OBJECTIVE: This study examines the effects of parental stimulant medication treatment on parent ratings of parent-child functioning. Ratings of parent-child functioning in the home setting and immediately following a laboratory-based parent-child interaction were collected.
METHOD: Participants were 20 parents who along with their children (ages 5-12 years) were diagnosed with Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV) attention-deficit/hyperactivity disorder (ADHD). Parents completed an open-label titration to determine their optimal dose of lisdexamfetamine (30, 50, or 70mg/day) and then completed a month-long double-blind randomized pharmacological intervention for parental ADHD. Effects of parental stimulant medication administered for an extended duration were assessed by parent ratings of parent-child functioning in the home setting and immediately following a laboratory parent-child interaction task conducted at an academic mental health center. Data were collected from September 2010 to June 2013.
RESULTS: Stimulant medication versus placebo was associated with larger reductions in parental ADHD (d=1.01-1.09), impairment (d=0.67-0.82), and executive dysfunction (d=0.74-0.94) in the home setting. No significant benefits of stimulant medication emerged in measures of parenting or child behavior at home. In the laboratory setting, parents treated with stimulant medication versus placebo reported fewer ADHD symptoms (d=1.01-1.05) and their interaction was more successful (d=0.83) and pleasant (d=0.92). Several additional trends emerged showing beneficial effects of stimulant medication on parent-child functioning.
CONCLUSION: Parents treated with stimulant medication evidenced some improvements in parent-child functioning, which support the use of pharmacological intervention to improve functioning in families with parent-child ADHD.

Pharmacokinetic and Pharmacodynamic Properties of Lisdexamfetamine in Adults with Attention-Deficit/Hyperactivity Disorder
Lenard A Adler, Samuel Alperin, Terry Leon, Stephen V Faraone
Journal of Child and Adolescent Psychopharmacology 2016 December 9

BACKGROUND: Lisdexamfetamine (LDX) is a prodrug and consists of an active moiety, d-amphetamine, bound to lysine. Clinically, d-amphetamine becomes available postcleavage of the prodrug in the blood stream. Clinical effects of LDX in attention-deficit/hyperactivity disorder (ADHD) have been shown to persist up to 14 hours; however, pharmacokinetic (PK) data of LDX and amphetamine in ADHD adults are not currently available.

OBJECTIVES: (1) To examine PK data of LDX and d-amphetamine in plasma and (2) to compare such PK data with Time-Sensitive ADHD Symptom Scale (TASS) ratings (PK vs. pharmacodynamic [PD]).
METHODS: Plasma d-amphetamine/LDX levels and TASS ratings were obtained immediately before morning dosing and then 0.5, 1, 2, 4, 6, 8, 10, and 12 hours postdosing in 21 adults with ADHD treated with 5 weeks of single-blind LDX up to 70mg/day (after 1 week single-blind placebo). ADHD Rating Scale scores were obtained at the beginning of the visit, before morning dosing.
RESULTS: LDX levels peaked at 1.5 hours after administration (Tmax) and then rapidly declined (levels were negligible at 6 hours and area under the plasma concentration versus time curve, AUC=45.9, Cmax=25.0, and half-life [t1/2]=0.5 hours). Levels of d-amphetamine peaked at (Tmax) 4.4 hours and then slowly declined (AUC=641.6, Cmax=67.9, and t1/2=17.0 hours). No statistically significant correlations were seen between d-amphetamine levels and TASS scores.
CONCLUSIONS: (1) Prodrug LDX levels peaked fairly rapidly and declined, while d-amphetamine levels peaked 3 hours later than LDX levels and persisted throughout the day and (2) the absence of PK/PD correlations between PK data and TASS ratings may be due to the subjects being tested in a controlled nonattention demanding environment.

JAMA Psychiatry. 2015 Mar;72(3):235-46. doi: 10.1001/jamapsychiatry.2014.2162.

Efficacy and safety of lisdexamfetamine for treatment of adults with moderate to severe binge-eating disorder: a randomized clinical trial.

McElroy SL[1], Hudson JI[2], Mitchell JE[3], Wilfley D[4], Ferreira-Cornwell MC[5], Gao J[5], Wang J[6], Whitaker T[5], Jonas J[7], Gasior M[5].

Author information

Abstract

IMPORTANCE:
Binge-eating disorder (BED), a public health problem associated with psychopathological symptoms and obesity and possibly with metabolic syndrome, lacks approved pharmacotherapies.

OBJECTIVE:
To examine the efficacy and safety of lisdexamfetamine dimesylate, a dextroamphetamine prodrug, to treat moderate to severe BED.

DESIGN, SETTING, AND PARTICIPANTS:
We performed a randomized, double-blind, parallel-group, forced dose titration, placebo-controlled clinical trial at 30 sites from May 10, 2011, through January 30, 2012**. Safety and intention-to-treat analyses included 259 and 255 adults with BED**, respectively.

INTERVENTIONS:
Lisdexamfetamine dimesylate at dosages of 30, 50, or 70 mg/d or placebo were provided to study participants (1:1:1:1). Dosages were titrated across 3 weeks and maintained for 8 weeks. We followed up participants for a mean (SD) of 7 (2) days after the last dose.

MAIN OUTCOMES AND MEASURES:
We assessed the change in binge-eating (BE) behaviors measured as days per week (baseline to week 11) with a mixed-effects model using transformed log (BE days per week) + 1. Secondary measures included BE cessation for 4 weeks. Safety assessments included treatment-emergent adverse events, vital signs, and change in weight.

RESULTS:
At week 11, log-transformed BE days per week decreased with the 50-mg/d (least squares [LS] mean [SE] change, -1.49 [0.066]; P = .008) and 70- mg/((LS mean [SE] change, -1.57 [0.067]; P < .001) treatment groups but not the 30-mg/d treatment group (LS mean [SE] change, -1.24 [0.067]; P = .88) compared with the placebo group. Nontransformed mean (SD) days per week decreased for placebo and the 30-, 50-, and 70-mg/d treatment groups by -3.3 (2.04), -3.5 (1.95), -4.1 (1.52), and -4.1 (1.57), respectively. The percentage of participants achieving 4-week BE cessation was lower with the placebo group (21.3%) compared with the 50-mg/d (42.2% [P = .01]) and 70-mg/d (50.0% [P < .001]) treatment groups. The incidence of any treatment-emergent adverse events was 58.7% for the placebo group and 84.7% for the combined treatment group. In the treatment groups, 1.5% of participants had serious treatment-emergent adverse effects. Events with a frequency of at least 5% and changes in heart rate were generally consistent with the known safety profile. The mean (SD) change in body weight was -0.1 (3.09), -3.1 (3.64), -4.9 (4.43), -4.9 (3.93), and -4.3 (4.09) kg for the placebo group, the 30-, 50-, and 70-mg/d treatment groups, and the combined treatment groups, respectively (P < .001 for each dose vs placebo group comparison in post hoc analysis).

CONCLUSIONS AND RELEVANCE:
The 50- and 70-mg/d treatment groups demonstrated efficacy compared with the placebo group in decreased BE days, BE cessation, and global improvement. The safety profile was generally consistent with previous findings in adults with attention-deficit/hyperactivity disorder. Further investigation of lisdexamfetamine in BED is ongoing

Expert Opin Pharmacother. 2015;16(10):1463-78. doi: 10.1517/14656566.2015.1053465. Epub 2015 Jun 4.
Pharmacological treatment of binge eating disorder: update review and synthesis.
Reas DL[1], Grilo CM.
Author information
Abstract
INTRODUCTION:
Binge eating disorder (BED), a formal eating disorder diagnosis in the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), is characterized by recurrent binge eating, marked distress about binge eating, and the absence of extreme weight compensatory behaviors. BED is more prevalent than other eating disorders, with broader distribution across age, sex and ethnic/racial groups, and is associated strongly with obesity and heightened risk for psychiatric/medical comorbidities.
AREAS COVERED:
This article provides an overview of pharmacotherapy for BED with a focus on Phase III randomized controlled trials (RCTs). The search with minimal methodological inclusion requirements yielded 22 RCTs investigating several different medication classes; most were pharmacotherapy-only trials with 8 trials testing combination approaches with psychological-behavioral methods.
EXPERT OPINION:
The evidence base regarding pharmacotherapy for BED remains limited, although this year the FDA approved the first medication **(i.e., lisdexamfetamine dimesylate; LDX**) specifically for moderate-to-severe BED. Data from RCTs suggest certain medications are superior to placebos for reducing binge eating over the short term; almost no data exist regarding longer-term effects of pharmacotherapy for BED**. Except for topiramate, which significantly reduces both binge eating and weigh**t, tested medications yield minimal weight loss and LDX is not indicated for weight loss. Psychological-behavioral and combination approaches with certain medications yield superior outcomes to pharmacotherapy-only acutely and over longer-term follow-up.

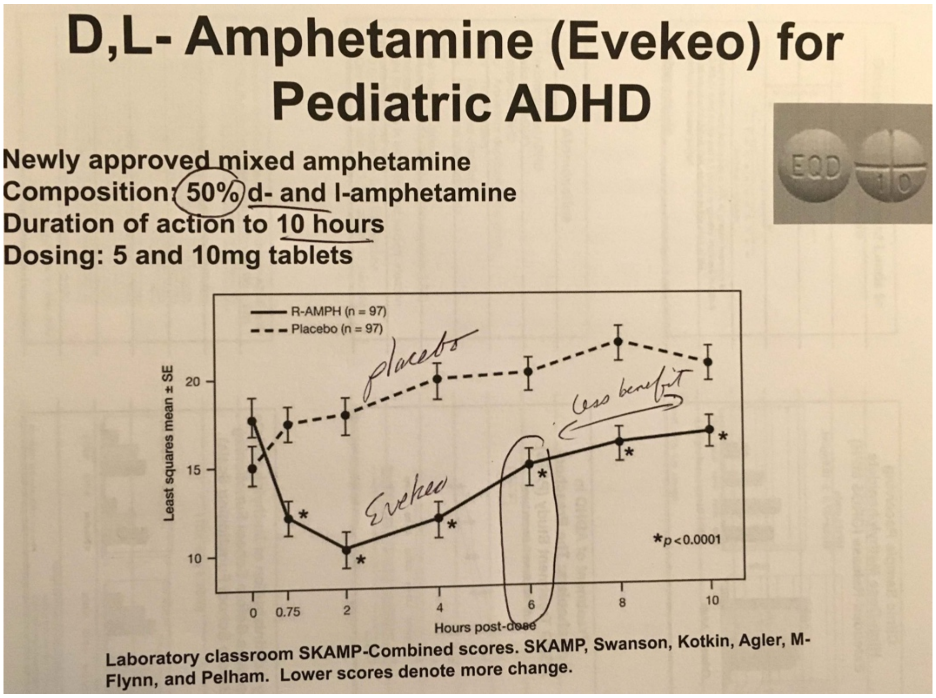
1/3 of Binge eating disorder patients met criteria for ADHD

BMC Psychiatry. 2017 Jan 17;17(1):19. doi: 10.1186/s12888-016-1093-1.
Symptoms of Attention Deficit Hyperactivity Disorder (ADHD) among adult eating disorder patients.
Svedlund NE[1,2], Norring C[3,4], Ginsberg Y[3,5], von Hausswolff-Juhlin Y[3,4].

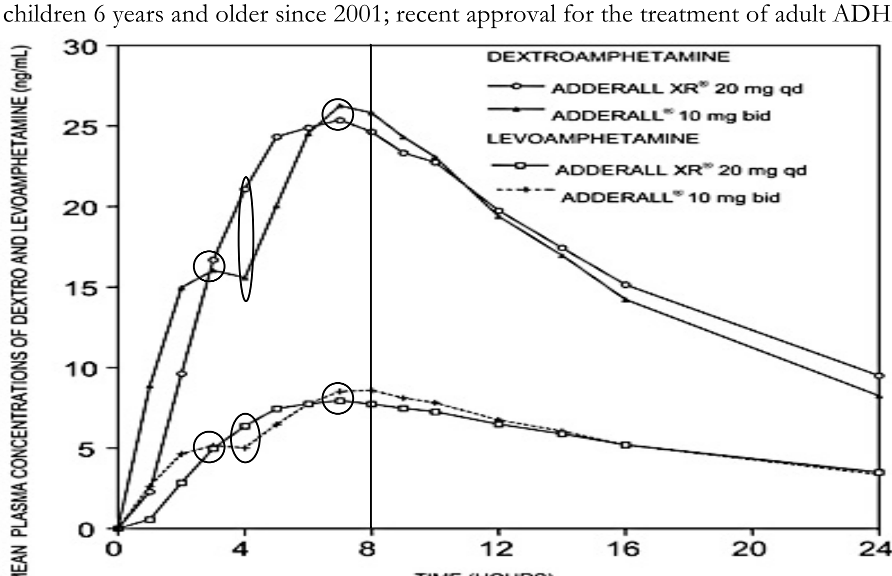
BACKGROUND:
Very little is known about the prevalence of ADHD symptoms in Bulimia Nervosa and Binge Eating Disorder and even less in other eating disorders. This knowledge gap is of clinical importance since stimulant treatment is proven effective in Binge Eating Disorder and discussed as a treatment possibility for Bulimia Nervosa. The objective of this study was to explore the prevalence and types of self-reported ADHD symptoms in an unselected group of eating disorder patients assessed in a specialized eating disorder clinic.
METHODS:
In total 1165 adults with an eating disorder were assessed with a battery of standardized instruments, for measuring inter alia ADHD screening, demographic variables, eating disorder symptoms and psychiatric comorbidity. Chi-square tests were used for categorical variables and Kruskal-Wallis tests for continuous variables.
RESULTS:
Almost one third (31.3 %) of the patients scored above the screening cut off indicating a possible ADHD. The highest prevalence rates (35-37 %) were found in Bulimia Nervosa and Anorexia Nervosa bingeing/purging subtype, while Eating Disorder Not Otherwise Specified type 1-4 and Binge Eating Disorder patients reported slightly below average (26-31 %), and Anorexia Nervosa restricting subtype patients even lower (18 %). Presence of binge eating, purging, loss of control over eating and non-anorectic BMI were related to results indicating a possible ADHD. Psychiatric comorbidity correlated to ADHD symptoms without explaining the differences between eating disorder diagnoses. **CONCLUSIONS:**
There is a high frequency of ADHD symptoms in patients with binge eating/purging eating disorders that motivates further studies, particularly concerning the effects of ADHD medication. The finding that the frequency of ADHD symptoms in anorexia nervosa with binge eating/purging is as high as in bulimia nervosa highlights the need also for

- Mixed amphetamine salts products
  - General
    - Peak level ~3 hours, 7 hours for XR caps
    - Duration 6-8 hours
    - Half-life 7-8 hours
    - Administer immediate release form every 4-6 hours
  - Adderall (mixed amphetamine salts, (75% of which is dextroamphetamine); Shire US
    - Tabs—5 mg, 7.5 mg, 10 mg, 12.5 mg, 15 mg, 20 mg, 30 mg—all scored
    - dose range 0.1-1mg/kg/d
    - usually 10-40 mg/D, occasionally up to 60 mg/day necessary
    - lasts 4-6 hours
    - Available since 1996
  - Evekeo
    - Begins working at 45 minutes
    - Lasts 4-8 hours
    - ½ dextroamphetamine and ½ levoamphetamine
    - The Efficacy and Safety of Evekeo, Racemic Amphetamine Sulfate, for Treatment of Attention-Deficit/Hyperactivity Disorder Symptoms: A Multicenter, Dose-Optimized, Double-Blind, Randomized, Placebo-Controlled Crossover Laboratory Classroom Study
      Ann C Childress, Matthew Brams, Andrew J Cutler, Scott H Kollins, Jo Northcutt, Americo Padilla, John M Turnbow
      Journal of Child and Adolescent Psychopharmacology 2015, 25 (5): 402-14
      OBJECTIVE: The study goal was to determine the efficacy and safety of an optimal dose of Evekeo, racemic amphetamine sulfate, 1:1 d-amphetamine and l-amphetamine (R-AMPH), compared to placebo in treating children with attention-deficit/hyperactivity disorder (ADHD) in a laboratory classroom setting.
      METHODS: A total of 107 children ages 6-12 years were enrolled in this multicenter, dose-optimized, randomized, double-blind, placebo-controlled crossover study. After 8 weeks of open-label dose optimization, 97 subjects were randomized to 2 weeks of double-blind treatment in the sequence of R-AMPH followed by placebo (n=47) or placebo followed by R-AMPH (n=50). Efficacy measures included the Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale and Permanent Product Measure of Performance (PERMP) administered predose and at 0.75, 2, 4, 6, 8, and 10 hours postdose on 2 laboratory classroom days.

Safety assessments included physical examination, chemistry, hematology, vital signs, and treatment-emergent adverse events (TEAEs).
RESULTS: Compared to placebo, a single daily dose of R-AMPH significantly improved SKAMP-Combined scores ($p<0.0001$) at each time point tested throughout the laboratory classroom days, with effect onset 45 minutes postdose and extending through 10 hours. R-AMPH significantly improved PERMP number of problems attempted and correct ($p<0.0001$) throughout the laboratory classroom days. During the twice-daily dose-optimization open-label phase, improvements were observed with R-AMPH in scores of the ADHD-Rating Scale IV and Clinical Global Impressions Severity and Improvement Scales. TEAEs and changes in vital signs associated with R-AMPH were generally mild and not unexpected. The most common TEAEs in the open-label phase were decreased appetite (27.6%), upper abdominal pain (14.3%), irritability (14.3%), and headache (13.3%).
CONCLUSIONS: Compared to placebo, R-AMPH was effective in treating children aged 6-12 years with ADHD, beginning at 45 minutes and continuing through 10 hours postdose, and was well tolerated.



- **Adderall (mixed amphetamine salts) XR**; Shire US
  - Capsules—5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg
  - Dose range— 0.1-1mg/kg/d; 10-40 mg/D
  - **50% released right away and 50% released 4 hours later**
  - Lasts 8 hours, occasionally longer
  - Can open the capsules and sprinkle onto apple sauce as long as the beads are not chewed
  - More than 20 clinical studies involving 5,200 patients
  - Approved for children 6 years and older since 2001; recent approval for the treatment of adult ADHD since 2004.

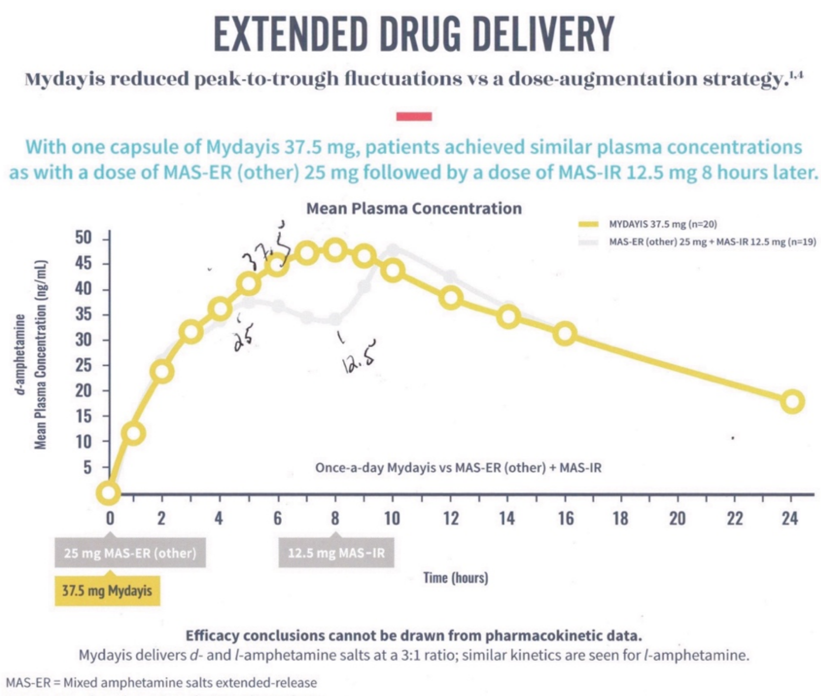


- Mydayis

Amphetamine Extended-Extended Release (Mydayis) for Adult/ Adolescent ADHD

"Very" extended mixed amphetamine (e.g. XR[2])
Composition: mixed-amphetamine salts
Dosing: 12.5 to 25 mg QD ($\geq$13) or 50 mg (adults)
Capsules: 12.5, 25, 37.5, 50 mg
Duration of action: 16 hours (onset at 2-4 hours)

  - Three types of beads: 33% immediate release; 33% delayed release; 33% delayed extended release
  - Lasts 12+ hours
  - Release mimics Adderall XR/AM and an equivalent amount of Adderall immediate release 8 hours later
  - Cap sizes: 12.5 mg, 25 mg, 37.5 mg, 50 mg
  - Side effects
    - Insomnia 41%
    - Decreased appetite 30.6%
    - Dry mouth 26.4%
    - Headache 21.5%
    - Pharmacology
  - Initial target 0.15 mg/kg per dose; optimal dose falls between 0.15-0.5 mg/kg/dose

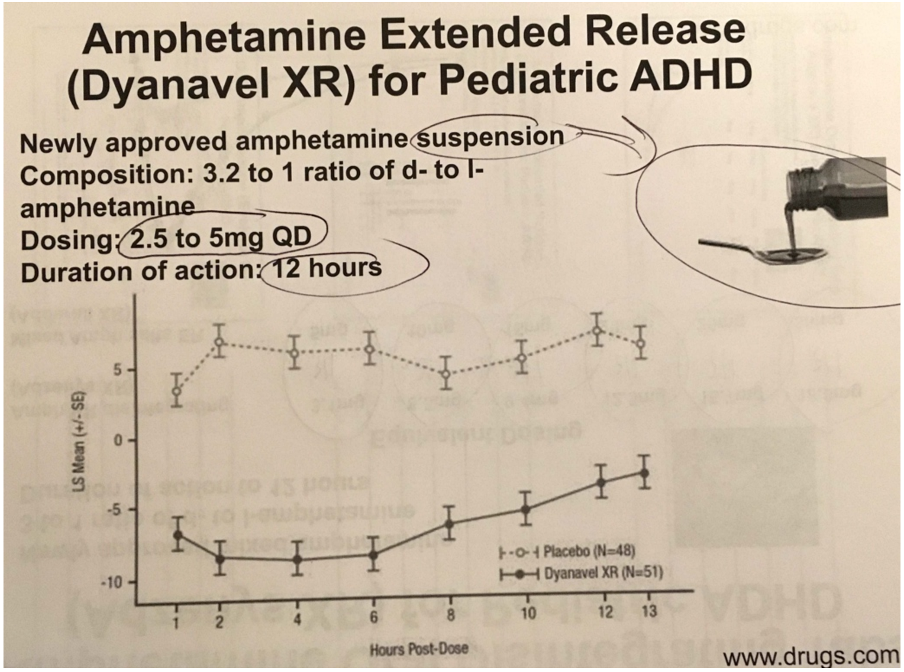


- Dynavel (amphetamine) XR
  - General

Amphetamine suspension (Dynavel XR) for Pediatric ADHD

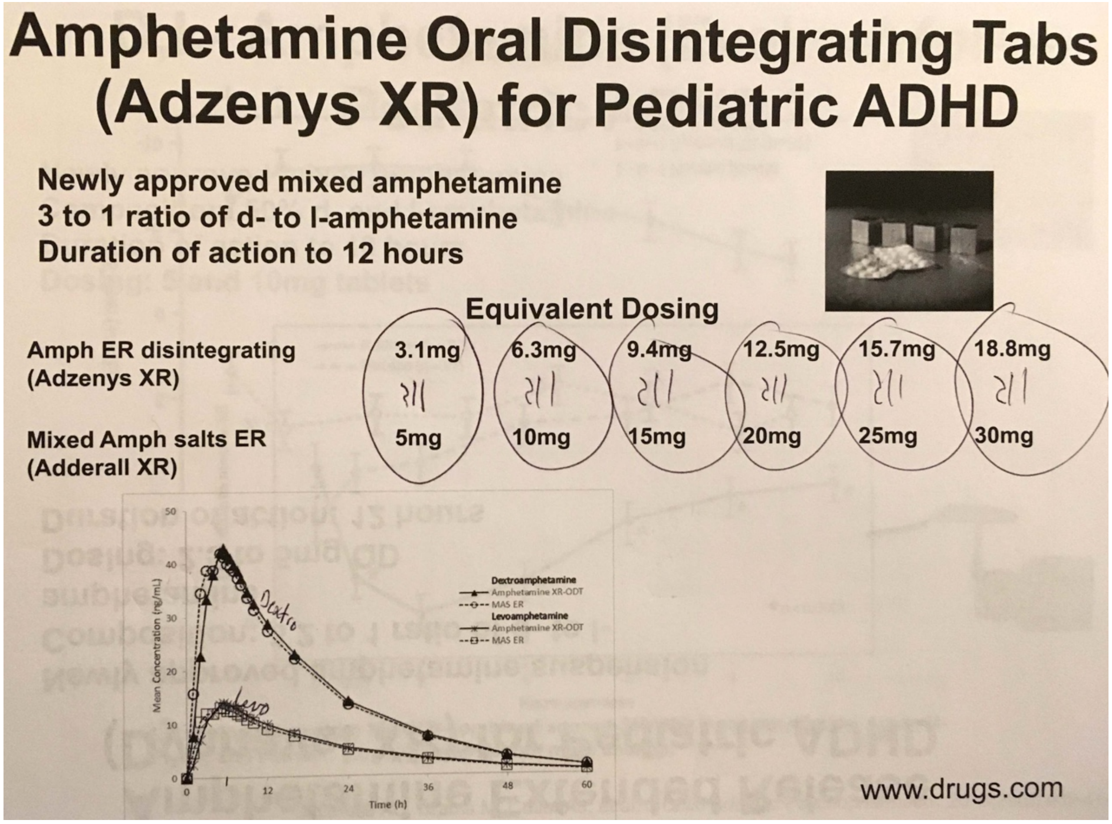
Amphetamine suspension
Composition: 3.2 to1 ratio of d- to l-amphetamine
Dosing: 2.5 to 5 mg QD
Duration of action: 12 hours

    - Once daily, extended release oral liquid suspension, bubble-gum flavored, in bottles of 464 mL; 2.5 mg/mL (max 20 mg)
    - 2.5-5 mg/day
    - Extended-release oral suspension containing 2.5 mg amphetamine base per 1 mL, which is the same as the amount of amphetamine (base equivalent) found in a 4 mg strength amphetamine mixed salts product.
    - 3.2 to1 ratio of d- to l-amphetamine
    - FDA-approved for ADHD in children aged 6 years and older
    - 20% released right away
    - Onset of efficacy at 1 hour, which persisted through 13 hours post dosing
    - Peak level at ~4 hour (2-7 hours in adults); a high fat meal delays the peak by an hour
    - Lasts 8-12 hours
    - Most common side effects (great or equal to 2% in the Dyanavel XR group and more than placebo)
        - Bloody nose (3.8% vs. 0% in placebo)
        - Allergic rhinitis (3.8% vs. 0% in placebo)
        - Upper abdominal pain (3.8% vs. 2.1% in placebo)
    - utilizes an ion exchange resin where the drug is bound to the resin (sodium polystyrene sulfonate) through an ionic binding reaction. DYANAVEL XR contains immediate release and extended release components. The extended-release component is coated with an aqueous, pH-independent polymer. After drug release the ion-exchange resin is excreted in the feces.
- Dosing and administration
    - Before administering the dose, shake bottle
    - May be taken with or without food
    - In children 6 years of age and older, recommended starting dose is 2.5 mg or 5 mg once daily in the morning
    - Dosage may be increased in increments of 2.5 mg to 10 mg per day every 4 to 7 days until optimal response is obtained
    - Daily dose above 20 mg is not recommended
    - Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine base compositions and differing pharmacokinetic profiles

- 

- Pharmacokinetics of a New Amphetamine Extended-Release Oral Suspension in Children with Attention-Deficit/Hyperactivity Disorder
  Carolyn R Sikes, Russ L McMahen, Jeffrey G Stark, Dorothy Engelking
  Journal of Child and Adolescent Psychopharmacology 2017 September 21
  OBJECTIVE: An extended-release amphetamine (AMP) oral suspension has been developed to facilitate medication ingestion and dose titration. This study sought to determine the pharmacokinetic (PK) profile of this new formulation in children with attention-deficit/hyperactivity disorder (ADHD).
  METHODS: This was an open-label, single-period, PK study in 29 pediatric participants with ADHD. Participants were stratified into age groups 1 (6-7 years), 2 (8-9 years), and 3 (10-12 years), and dosed with 15mL extended-release AMP liquid suspension (equivalent to 30mg mixed AMP salts) after an overnight fast. Blood samples were collected at prespecified time points and analyzed for d- and l-AMP concentrations. Key PK parameters included maximum plasma concentration (Cmax), time to maximum plasma concentration, half-life (T1/2), area under the curve from time 0 to last quantifiable concentration (AUClast) and to infinity (AUCinf), oral clearance (CL/F), and volume of distribution (Vz/F). The 95% confidence intervals (CIs) about the geometric means of the weight-normalized CL/F, Vz/F, and AUClast were determined. Safety was also assessed.
  RESULTS: All participants completed the study. As age increased, mean maximum and total exposure to AMP decreased; weight-normalized CL/F slightly increased, resulting in decreasing T1/2 values with age. For d- and l-AMP, the 95% CIs for the geometric means of weight-normalized CL/F/kg and Vz/F/kg were within the 60%-140% range for groups 2 and 3, while those of weight-normalized AUClast were within range for all age groups. Adverse events were mild and consistent with the safety profile of AMP.

- Adzenys XR-ODT
  - Pharmacology
    - 50% immediate release, 50% extended release
    - Tmax is 5-7 hours (7 hours with food)
    - T-1/2 is 11.3 hours
    - Lasts up to 12 hours
  - Tab sizes
    - 3.1 mg; equivalent to Adderall XR 5 mg
    - 6.3 mg; equivalent to Adderall XR 10 mg
    - 9.4 mg; equivalent to Adderall XR 15 mg
    - 12.5 mg; equivalent to Adderall XR 20 mg
    - 15.7 mg; equivalent to Adderall XR 25 mg
    - 18.8 mg; equivalent to Adderall XR 30 mg

- 

  Pharmacokinetics of a Novel Amphetamine Extended-Release Orally Disintegrating Tablet in Children with Attention-Deficit/Hyperactivity Disorder
  Jeffrey G Stark, Dorothy Engelking, Russ McMahen, Carolyn Sikes
  Journal of Child and Adolescent Psychopharmacology 2016 December 12
  BACKGROUND: A novel formulation for treating attention-deficit/hyperactivity disorder (ADHD) has recently been developed-amphetamine extended-release orally disintegrating tablets (AMP XR-ODTs). In this study, we assessed the rate of absorption and exposure of AMP XR-ODT under fasted conditions in children with ADHD.
  METHODS: Children (6-12 years) with ADHD were enrolled in a single-dose, open-label, single-period pharmacokinetic (PK) study. Patients were stratified by age (6-7, 8-9, and 10-12 year olds) and were dosed with 18.8-mg AMP XR-ODT under fasted conditions. Plasma samples were analyzed for d-and l-amphetamine. Maximum plasma concentration (Cmax), time to maximum plasma concentration (Tmax), area under the concentration-time curve from time zero-infinity (AUCinf), weight-normalized clearance (CL/F), and weight-normalized volume of distribution (Vz/F) were assessed. The geometric mean and 95% confidence intervals (CIs) were calculated for weight-normalized CL/F and Vz/F in each age group to determine if the 95% CIs were within the target range of 60%-140%.
  RESULTS: A total of 28 children completed the study. The 95% CIs for the geometric mean CL/F/kg and Vz/F/kg for both d- and l-amphetamine fell within the target range of 60%-140% for each age group, thus meeting the primary end point. Four participants experienced treatment-related adverse events, including vomiting (n=3), abdominal pain (n=2), dry mouth (n=1), and insomnia (n=1).
  CONCLUSIONS: AMP XR-ODT, a novel formulation that does not require swallowing an intact tablet or capsule, was well tolerated and demonstrated a PK profile consistent with once-daily dosing in children with ADHD.

- **D-ATS:** transdermal amphetamine
- **HLD-100:** nighttime Delexis amphetamine dosing

Randomized, 6-Week, Placebo-Controlled Study of Treatment for Adult Attention-Deficit/Hyperactivity Disorder: Individualized Dosing of Osmotic-Release Oral System (OROS) Methylphenidate With a Goal of Symptom Remission
David W Goodman, H Lynn Starr, Yi-Wen Ma, Anthony L Rostain, Steve Ascher, Robert B Armstrong
Journal of Clinical Psychiatry 2016 August 2
OBJECTIVE: To evaluate the efficacy and safety of individualized dosing within the approved dose range for osmotic-release oral system (OROS) methylphenidate hydrochloride in adults with attention-deficit/hyperactivity disorder (ADHD).
METHODS: A double-blind, 6-week trial was conducted between July 2009 and February 2010 at 35 US sites. Adults with ADHD (DSM-IV diagnostic criteria) and a screening ADHD Investigator Symptom Rating Scale (AISRS) score > 24 were randomly assigned to OROS methylphenidate 18 mg or matching placebo. Treatment dose could be increased at 18 mg increments, up to 72 mg/d, until an optimal dose was achieved. AISRS score changes from baseline to end point (primary outcome) were analyzed using analysis of covariance.
RESULTS: At baseline, the intent-to-treat population of 169 OROS methylphenidate and 172 placebo subjects (mean age = 35.8 years) had mean (standard deviation [SD]) AISRS scores of 37.8 (6.94) and 37.0 (7.51), respectively. OROS methylphenidate-treated subjects exhibited a significantly greater mean (SD) AISRS score improvement than placebo subjects (-17.1 [12.44] vs -11.7 [13.30]; P < .001). In general, OROS

methylphenidate-treated subjects experienced greater improvements than placebo subjects in secondary measures of symptom frequency, cognitive function, work productivity, and quality-of-life. Little effect of OROS methylphenidate was observed in exploratory sleep assessments. The adverse event pattern was similar to previous reports of stimulants in adults with ADHD.
CONCLUSIONS: OROS methylphenidate treatment with individualized doses titrated to achieve symptom remission demonstrated greater ADHD symptom reduction than placebo treatment. These data support the overall efficacy of OROS methylphenidate treatment in the management of adults with ADHD and provide new possibilities for additional intervention.
TRIAL REGISTRATION: ClinicalTrials.gov identifier: NCT00937040.

Methylphenidate in pregnancy: a multicenter, prospective, comparative, observational study
Orna Diav-Citrin, Svetlana Shechtman, Judy Arnon, Rebecka Wajnberg, Cornelia Borisch, Evelin Beck, Jonathan Luke Richardson, Pina Bozzo, Irena Nulman, Asher Ornoy
Journal of Clinical Psychiatry 2016 May 24
INTRODUCTION: Methylphenidate is a central nervous system stimulant medicinally used in the treatment of attention-deficit disorder with or without hyperactivity (ADD/ADHD). Data on its use in human pregnancy are limited. The primary objective of the study was to evaluate the risk of major congenital anomalies after pregnancy exposure to methylphenidate for medical indications.
METHODS: In a prospective, comparative, multicenter observational study performed in 4 participating Teratology Information Services (in Jerusalem, Berlin, Newcastle upon Tyne, and Toronto) between 1996 and 2013, methylphenidate-exposed pregnancies were compared with pregnancies counseled for nonteratogenic exposure (NTE) after matching by maternal age, gestational age, and year at initial contact.
RESULTS: 382 methylphenidate-exposed pregnancies (89.5% in the first trimester) were followed up. The overall rate of major congenital anomalies was similar between the groups (10/309 = 3.2% [methylphenidate] vs 13/358 = 3.6% [NTE], P = .780). The rates of major congenital anomalies (6/247 = 2.4% [methylphenidate] vs 12/358 = 3.4% [NTE], P = .511) and cardiovascular anomalies (2/247 = 0.8% [methylphenidate] vs 3/358 = 0.8% [NTE], P = .970) were also similar after exclusion of genetic or cytogenetic anomalies and limiting methylphenidate exposure to the period of organogenesis (weeks 4-13 after the last menstrual period). There was a higher rate of miscarriages and elective terminations of pregnancy in the methylphenidate group. Significant predictors for the miscarriages using Cox proportional hazards model were methylphenidate exposure (adjusted hazard ratio [HR] = 1.98; 95% CI, 1.23-3.20; P = .005) and past miscarriage (adjusted HR = 1.35; 95% CI, 1.18-1.55; P < .001).
CONCLUSIONS: The present study suggests that methylphenidate does not seem to increase the risk for major malformations. Further studies are required to establish its pregnancy safety and its possible association with miscarriages.

Behavioral Effects of Neurofeedback Compared to Stimulants and Physical Activity in Attention-Deficit/Hyperactivity Disorder: A Randomized Controlled Trial
Katleen Geladé, Tieme W P Janssen, Marleen Bink, Rosa van Mourik, Athanasios Maras, Jaap Oosterlaan
Journal of Clinical Psychiatry 2016 September 13
OBJECTIVE: The efficacy of neurofeedback as a treatment for attention-deficit/hyperactivity disorder (ADHD), and whether neurofeedback is a viable alternative for stimulant medication, is still an intensely debated subject. The current randomized controlled trial compared neurofeedback to (1) optimally titrated methylphenidate and (2) a semi-active control intervention, physical activity, to account for nonspecific effects.
METHODS: A multicenter 3-way parallel-group study with balanced randomization was conducted. Children with a DSM-IV-TR diagnosis of ADHD, aged 7-13 years, were randomly allocated to receive neurofeedback (n = 39), methylphenidate (n = 36), or physical activity (n = 37) over a period of 10-12 weeks. Neurofeedback comprised theta/beta training on the vertex (Cz). Physical activity consisted of moderate to vigorous intensity exercises. Neurofeedback and physical activity were balanced in terms of number (~30) and duration of sessions. A double-blind pseudorandomized placebo-controlled crossover titration procedure was used to determine an optimal dose in the methylphenidate intervention. Parent and teacher ratings on the Strengths and Difficulties Questionnaire (SDQ) and Strengths and Weaknesses of ADHD Symptoms and Normal Behavior (SWAN) were used to assess intervention outcomes. Data collection took place between September 2010 and March 2014.
RESULTS: Intention-to-treat analyses revealed an improvement in parent-reported behavior on the SDQ and the SWAN Hyperactivity/Impulsivity scale, irrespective of received intervention ($\eta p^2 = 0.21$-0.22, $P \leq .001$), whereas the SWAN Inattention scale revealed more improvement in children who received methylphenidate than neurofeedback and physical activity ($\eta p^2 = 0.13$, $P \leq .001$). Teachers reported a decrease of ADHD symptoms on all measures for methylphenidate, but not for neurofeedback or physical activity (range of $\eta p^2 = 0.14$-0.29, $P < .001$).
CONCLUSIONS: The current study found that optimally titrated methylphenidate is superior to neurofeedback and physical activity in decreasing ADHD symptoms in children with ADHD.

Impact of Stimulant Medication Use on Heart Rate and Systolic Blood Pressure During Submaximal Exercise Treadmill Testing in Adolescents
Arthur N Westover, Paul A Nakonezny, Bryon Adinoff, Edson Sherwood Brown, Ethan A Halm
Journal of Child and Adolescent Psychopharmacology 2016 September 14
OBJECTIVES: Inappropriately decreased heart rate (HR) during peak exercise and delayed heart rate recovery (HRR) has been observed in adult users of stimulant medications who underwent exercise testing, suggesting autonomic adaptation to chronic stimulant exposure. In the

general population, this pattern of hemodynamic changes is associated with increased mortality risk. Whether the same pattern of hemodynamic changes might be observed in adolescent stimulant medication users undergoing exercise testing is unknown.
METHODS: Among adolescents (aged 12 to 20 years) that underwent submaximal exercise treadmill testing from 1999 to 2004 in the National Health and Nutrition Examination Survey, propensity score matching of stimulant medication users (n = 89) to matched nonusers (n = 267) was conducted. Testing consisted of a 3-minute warm-up period, two 3-minute exercise stages, and three 1-minute recovery periods, with the goal of reaching 75% of the predicted HR maximum. A linear mixed model analysis was used to evaluate the effect of stimulant exposure on each of the exercise outcomes.
RESULTS: Stimulant medication users compared to matched nonusers had a lower peak HR in Stage 2 (154.9 vs. 158.3 beats/minute [bpm], $p = 0.055$) and lower HR at 1-minute recovery (142.2 vs. 146.4 bpm, $p = 0.030$). However, submaximal HRR at 1 minute did not differ between stimulant users and matched nonusers (13.0 vs. 12.1 bpm, $p = 0.38$). Duration of stimulant use was not related to these outcomes.
CONCLUSION: Adolescent stimulant medication users compared to matched nonusers demonstrated a trend toward decreased HR during submaximal exercise, which is potential evidence of chronic adaptation with stimulant exposure. There was no evidence for delayed HRR in this study, and thus, no evidence for decreased parasympathetic activity during initial exercise recovery. Exercise testing outcomes may have utility in future research as a method to assess stimulant-associated autonomic nervous system adaptations.

Neural Correlates of Symptom Improvement Following Stimulant Treatment in Adults with Attention-Deficit/Hyperactivity Disorder
Zhen Yang, Clare Kelly, Francisco X Castellanos, Terry Leon, Michael P Milham, Lenard A Adler
Journal of Child and Adolescent Psychopharmacology 2016, 26 (6): 527-36
OBJECTIVE: The purposes of this study were to examine the impact of 3 weeks of amphetamine administration on intrinsic connectome-wide connectivity patterns in adults with attention-deficit/hyperactivity disorder (ADHD) and explore the association between stimulant-induced symptom improvement and functional connectivity alteration.
METHODS: Participants included 19 adults (age 20-55 years) diagnosed with ADHD using the Diagnostic and Statistical Manual of Mental Disorders, 4th ed., Text Revision (DSM-IV-TR) criteria per the Adult Clinician Diagnostic Scale taking part in amphetamine trials. For each patient, two 6-minute resting-state functional magnetic resonance imaging (R-fMRI) scans were acquired at baseline and after treatment. A fully data-driven multivariate analytic approach (i.e., multivariate distance matrix regression [MDMR]) was applied to R-fMRI data to characterize the distributed pharmacological effects in the entire functional connectome. Clinical efficacy was assessed using ADHD rating scale with adult prompts and the Adult Self-Report Scale v1.1 Symptom Checklist. We linked stimulant-induced functional connectivity changes to symptom amelioration using Spearman's correlation.
RESULTS: Three weeks of administration of a stimulant significantly reduced ADHD symptoms. MDMR-based analyses on R-fMRI data highlighted the left dorsolateral prefrontal cortex (DLPFC, a key cognitive control region) and the medial prefrontal cortex (MPFC, the anterior core of default network) whose distributed patterns of functional connectivity across the entire brain were altered by psychostimulants. Follow-up intrinsic functional connectivity revealed that stimulants specifically decreased the positive functional connectivity between DLPFC-insula, DLPFC-anterior cingulate cortex, and MPFC-insula. Importantly, these functional connectivity changes are associated with symptom improvement.
CONCLUSION: These results suggested that ADHD is associated with increased functional integration or decreased functional segregation between core regions of cognitive control, default, and salience networks. The apparent normalization of intrinsic functional interaction in these circuits (i.e., increased functional segregation) may underlie the clinical benefits produced by 3 weeks of amphetamine treatment.

Intrinsic Brain Connectivity Following Long-Term Treatment with Methylphenidate in Children with Attention-Deficit/Hyperactivity Disorder
Lucas Battel, Renata R Kieling, Christian Kieling, Maurício Anés, Nathassia Kadletz Aurich, Jaderson Costa da Costa, Luis Augusto Rohde, Alexandre Rosa Franco
Journal of Child and Adolescent Psychopharmacology 2016, 26 (6): 555-61
INTRODUCTION: Although widely used for the treatment of attention-deficit/hyperactivity disorder (ADHD) across the life span, the effects of methylphenidate (MPH) on the brain are not completely understood. Functional neuroimaging techniques may help increase knowledge about the mechanisms of MPH action.
OBJECTIVE: To evaluate changes in functional connectivity patterns of the default mode network (DMN) in children with ADHD following long-term treatment with MPH.
METHODS: Twenty-three right-handed treatment-naïve boys with ADHD underwent a protocol of intrinsic functional connectivity before and after 6 months of treatment with MPH. Functional connectivity was analyzed using a region of interest (ROI) approach and independent component analysis (ICA).
RESULTS: ROI analyses showed no significant changes in connectivity between regions of the DMN following treatment, with a relatively small increase in the anterior-posterior connectivity of the network. ICA revealed a significant increase in connectivity between the left putamen and the DMN ($p < 0.001$, corrected). There was a correlation between the reduction of symptoms and the increased connectivity between the putamen and the DMN after treatment (rho = -0.65, $p = 0.017$).
CONCLUSION: Dysfunctions in cortical-subcortical circuits have often been associated with the pathophysiology of ADHD. Our findings suggest that effective treatment with MPH in children with ADHD may affect brain functioning by increasing connectivity between the DMN and subcortical nuclei.

Stimulant Treatment of Young People in the United States
Mark Olfson, Marissa King, Michael Schoenbaum
Journal of Child and Adolescent Psychopharmacology 2016, 26 (6): 520-6
OBJECTIVE: To describe national stimulant treatment patterns among young people focusing on patient age and prescribing specialty.
METHODS: Stimulant prescriptions to patients aged 3-24 were analyzed from the 2008 IMS LifeLink LRx Longitudinal Prescription database (n = 3,147,352), which includes 60% of all U.S. retail pharmacies. A subset of young people from 2009 with service claims (n = 197,654) were also analyzed. Denominators were adjusted to generalize estimates to the U.S.
POPULATION: Population percentages filling ≥1 stimulant prescription during the study year by sex and age group (younger children, 3-5 years; older children, 6-12 years; adolescents, 13-18 years; and young adults, 19-24 years) were determined. Percentages prescribed stimulants by psychiatrists, child and adolescent psychiatrists, pediatricians, and other physicians were also determined along with percentages that were treated for a long or short duration; coprescribed other psychotropic medications; used psychosocial services; and received clinical psychiatric diagnoses.
RESULTS: Population percentages with any stimulant use varied across younger children (0.4%), older children (4.5%), adolescents (4.0%), and young adults (1.7%). Among children and adolescents, males were over twice as likely as females to receive stimulants. Percentages of stimulant-treated young people with ≥1 stimulant prescription from a child and adolescent psychiatrist varied from younger children (19.1%), older children (17.1%), and adolescents (18.2%) to young adults (10.1%), and these percentages increased among those who were also prescribed other psychotropic medications: young children (31.0%), older children (37.9%), adolescents (35.1%), and young adults (15.8%). Antipsychotics were the most commonly coprescribed class to stimulant-treated younger (15.0%) and older children (11.8%), while antidepressants were most commonly coprescribed to adolescents (17.5%) and young adults (23.9%).
CONCLUSIONS: Stimulant treatment peaks during middle childhood, especially for boys. For young people treated with stimulants, including younger children, low rates of treatment by child and adolescent psychiatrists highlight difficulties with access to specialty mental health services.

Impact of Stimulant Medication Use on Heart Rate and Systolic Blood Pressure During Submaximal Exercise Treadmill Testing in Adolescents
Arthur N Westover, Paul A Nakonezny, Bryon Adinoff, Edson Sherwood Brown, Ethan A Halm
Journal of Child and Adolescent Psychopharmacology 2016 September 14
OBJECTIVES: Inappropriately decreased heart rate (HR) during peak exercise and delayed heart rate recovery (HRR) has been observed in adult users of stimulant medications who underwent exercise testing, suggesting autonomic adaptation to chronic stimulant exposure. In the general population, this pattern of hemodynamic changes is associated with increased mortality risk. Whether the same pattern of hemodynamic changes might be observed in adolescent stimulant medication users undergoing exercise testing is unknown.
METHODS: Among adolescents (aged 12 to 20 years) that underwent submaximal exercise treadmill testing from 1999 to 2004 in the National Health and Nutrition Examination Survey, propensity score matching of stimulant medication users (n = 89) to matched nonusers (n = 267) was conducted. Testing consisted of a 3-minute warm-up period, two 3-minute exercise stages, and three 1-minute recovery periods, with the goal of reaching 75% of the predicted HR maximum. A linear mixed model analysis was used to evaluate the effect of stimulant exposure on each of the exercise outcomes.
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CONCLUSION: Adolescent stimulant medication users compared to matched nonusers demonstrated a trend toward decreased HR during submaximal exercise, which is potential evidence of chronic adaptation with stimulant exposure. There was no evidence for delayed HRR in this study, and thus, no evidence for decreased parasympathetic activity during initial exercise recovery. Exercise testing outcomes may have utility in future research as a method to assess stimulant-associated autonomic nervous system adaptations.

Effectiveness and Side Effect Profile of Stimulant Medication for the Treatment of Attention-Deficit/Hyperactivity Disorder in Youth with Epilepsy
Mary C Kral, Michelle D Lally, Andrea D Boan
Journal of Child and Adolescent Psychopharmacology 2017 April 6
OBJECTIVES: This clinical case series examined the effectiveness and potential side effects associated with stimulant medication for the treatment of attention-deficit/hyperactivity disorder (ADHD) in 20 youth with epilepsy.
METHODS: Response to stimulant medication was examined through symptom reduction on the Conners-Third Edition: Parent Rating Scale, Short Form [Conner 3-P(S)], which was administered to caregivers before initiation of treatment and following dosage titration to achieve therapeutic efficacy. Stimulant medication side effects were examined with the Side Effect Rating Scale before treatment and following dosage titration. Repeated measures mixed model approach was used to compare symptom reduction and side effects between the two time points.
RESULTS: Repeated measures ANOVA revealed significant ADHD symptom reduction as measured by the Conner 3-P(S). Review of patient medical records and caregiver report did not reveal seizure exacerbation. Caregivers, in fact, reported fewer side effects following treatment for ADHD compared with baseline.
CONCLUSION: These results contribute to growing evidence in support of the effectiveness of stimulant medication, without seizure exacerbation or medication side effects, for treatment of ADHD in youth with epilepsy.

Association Between Medication Use for Attention-Deficit/Hyperactivity Disorder and Risk of Motor Vehicle Crashes
Zheng Chang, Patrick D Quinn, Kwan Hur, Robert D Gibbons, Arvid Sjolander, Henrik Larsson, Brian M D'Onofrio
JAMA Psychiatry 2017 May 10
Importance: Motor vehicle crashes (MVCs) are a major public health problem. Research has demonstrated that individuals with attention-deficit/hyperactivity disorder (ADHD) are more likely to experience MVCs, but the effect of ADHD medication treatment on the risk of MVCs remains unclear.
Objective: To explore associations between ADHD medication use and risk of MVCs in a large cohort of patients with ADHD.
Design, Setting, and Participants: For this study, a US national cohort of patients with ADHD (n = 2 319 450) was identified from commercial health insurance claims between January 1, 2005, and December 31, 2014, and followed up for emergency department visits for MVCs. The study used within-individual analyses to compare the risk of MVCs during months in which patients received ADHD medication with the risk of MVCs during months in which they did not receive ADHD medication.
Exposures: Dispensed prescription of ADHD medications.
Main Outcomes and Measures: Emergency department visits for MVCs.
Results: Among 2 319 450 patients identified with ADHD, the mean (SD) age was 32.5 (12.8) years, and 51.7% were female. In the within-individual analyses, male patients with ADHD had a 38% (odds ratio, 0.62; 95% CI, 0.56-0.67) lower risk of MVCs in months when receiving ADHD medication compared with months when not receiving medication, and female patients had a 42% (odds ratio, 0.58; 95% CI, 0.53-0.62) lower risk of MVCs in months when receiving ADHD medication. Similar reductions were found across all age groups, across multiple sensitivity analyses, and when considering the long-term association between ADHD medication use and MVCs. Estimates of the population-attributable fraction suggested that up to 22.1% of the MVCs in patients with ADHD could have been avoided if they had received medication during the entire follow-up.
Conclusions and Relevance: Among patients with ADHD, rates of MVCs were lower during periods when they received ADHD medication. Considering the high prevalence of ADHD and its association with MVCs, these findings warrant attention to this prevalent and preventable cause of mortality and morbidity.

The Possible Effect of Methylphenidate Treatment on Empathy in Children Diagnosed with Attention-Deficit/Hyperactivity Disorder, Both With and Without Comorbid Oppositional Defiant Disorder
Pavel Golubchik, Abraham Weizman
Journal of Child and Adolescent Psychopharmacology 2017, 27 (5): 429-432
OBJECTIVE: To assess the Empathizing Quotient (EQ) of patients diagnosed with attention-deficit/hyperactivity disorder (ADHD) only or comorbid with oppositional defiant disorder (ODD) and compare the two groups' responses to methylphenidate (MPH) treatment.
METHODS: Fifty-two children (8-18 years) diagnosed with ADHD, 26 of whom were also diagnosed with comorbid ODD (ADHD/ODD), were treated with MPH for 12 weeks. The level of EQ was assessed with the Children's version of the Empathizing Quotient (EQ-C) and the severity of ADHD symptoms with the ADHD Rating Scale (ADHD-RS). Assessments were done at baseline and at end point.
RESULTS: A significant increase in EQ scores was obtained in both groups following MPH treatment (p = 0.003 for ADHD/ODD; p = 0.002 for ADHD). Significant correlation was found in the ADHD group between the changes in ADHD-RS and those in EQ, following MPH treatment (p = 0.015), but not in the ADHD/ODD group (p = 0.48).
CONCLUSIONS: A correlation exists between MPH-related improvement in ADHD symptoms and between more empathy in children with ADHD not comorbid with ODD.

Empathy and Facial Expression Recognition in Children With and Without Attention-Deficit/Hyperactivity Disorder: Effects of Stimulant Medication on Empathic Skills in Children with Attention-Deficit/Hyperactivity Disorder
Funda Gumustas, Ibrahim Yilmaz, Yasemin Yulaf, Sebla Gokce, Osman Sabuncuoglu
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OBJECTIVE: The aim of this study was to compare children and adolescents with attention-deficit/hyperactivity disorder (ADHD) to healthy children and adolescents in terms of state and trait empathy and emotion expression recognition skills. The goal was also to determine whether there are changes in emotion recognition and empathy measures in children with ADHD after methylphenidate (MPH) treatment.
METHODS: The research sample consisted of outpatient drug-naive children and adolescents between the age of 8 and 14 years (n = 65) with ADHD according to the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. criteria, and healthy children and adolescents of the same age (n = 61). Scores of the oppositional problems (OPs) and conduct problems (CPs) were obtained to evaluate their impact on children's empathy skills with the Child Behavior Checklist. Self-reported (Bryant Index of Empathy, BEI) and parent-reported (Griffith Empathy Measurement-Parent Rating, GEM-PR) scales were used to evaluate trait empathy. The Empathy Response Task (ERT) was used to evaluate state empathy, and the Diagnostic Analysis of Nonverbal Accuracy-2 (DANVA-2) was used to evaluate facial expression recognition skills. The scales and tests were repeated after 12 weeks of MPH treatment in the ADHD group.
RESULTS: There were no significant statistical differences in trait empathy skills evaluated by parent-reported and self-reported measures, ERT, and DANVA-2 scores. In self-reported measures, the girls had higher scores than boys. From the results of the regression analysis, it was concluded that OPs were not associated with the measures. However, CPs were associated with the scores of the BEI, GEM-PR, and the match scores of the ERT. The average dosage of MPH in the group with ADHD was 0.83 ± 0.21 mg/(kg·d). While there was no change in the BEI and GEM-PR scores after 12 weeks of treatment, there was a significant increase in the ERT interpretation subscore and a significant decrease in the recognition error of anger and sadness expressions in the DANVA-2.

CONCLUSIONS: The findings of our study suggest that children with ADHD have similar levels of trait and state empathy skills and facial expressions as healthy controls and CPs negatively affect their empathy skills. MPH treatment does not change trait empathy skills, yet there are some improvements in state empathy skills.

Improvements in Irritability with Open-Label Methylphenidate Treatment in Youth with Comorbid Attention Deficit/Hyperactivity Disorder and Disruptive Mood Dysregulation Disorder
Drew E Winters, Sadaaki Fukui, Ellen Leibenluft, Leslie A Hulvershorn
Journal of Child and Adolescent Psychopharmacology 2018 April 30
OBJECTIVE: The purpose of this open-label study was to examine the effects of long-acting methylphenidate (MPH) treatment on irritability and related emotional symptoms associated with disruptive mood dysregulation disorder (DMDD) in youth with comorbid attention-deficit/hyperactivity disorder (ADHD).
METHODS: The sample included 22 medication-free male and female subjects (ages 9-15) who met criteria for both DMDD and ADHD. Participants underwent a 4-week trial of long-acting MPH treatment (Concerta®), with weekly dosing increases until a therapeutic dose was reached. Repeated measures t-tests were used to compare pre- and posttreatment ratings of primary and secondary measures. The primary outcome was self-report irritability. Secondary outcomes included parent and child ratings of emotional frequency, emotional lability, and negative affect (NA). Multiple regression was used to examine the impact baseline hyperactivity, age, gender, race, socioeconomic status, or comorbid diagnosis had on treatment outcomes.
RESULTS: Significant improvements (medium to large effect sizes) in child-rated irritability as well as parent and child ratings of emotional lability, NA, and anger were found. As anticipated, ADHD symptoms also improved. While a majority of the sample saw improvement in child-rated irritability (71%), symptoms worsened a small proportion (19%), and an even smaller portion experienced no change (10%). No demographics, psychiatric comorbidities, or severity of ADHD symptoms influenced treatment outcomes.
CONCLUSIONS: Study findings suggest that MPH treatment significantly improved mood and emotional symptoms associated with DMDD comorbid with ADHD. These findings, coupled with good tolerability in this open-label pilot study supports further research into the use of MPH as a first-line treatment for DMDD. Future work examining MPH treatment of youth with DMDD with and without comorbid ADHD is needed.

Relationship Between Aggravation of Seizures and Methylphenidate Treatment in Subjects with Attention-Deficit/Hyperactivity Disorder and Epilepsy

Objectives: We aimed to investigate the effectiveness and safety of methylphenidate (MPH), and especially its influence on seizures, in subjects with attention-deficit/hyperactivity disorder (ADHD) and epilepsy through a retrospective chart review of subjects treated with MPH in a clinical setting. We also evaluated factors that could affect seizure aggravation during MPH treatment.

Methods: From April 2004 to July 2011, MPH was prescribed to 105 subjects with ADHD and epilepsy. The demographic characteristics, psychiatric and medical history, and electroencephalography (EEG) results were reviewed. Two pediatric neurologists reviewed seizure type, epilepsy diagnosis, changes in seizure frequency, and EEG parameters during MPH treatment. Pediatric neurologists and psychiatrists determined the temporal relationship between seizure aggravation and MPH treatment.

Results: The mean age of the subjects was 14.8 ± 3.4 years (range: 7–24 years). Sixty-five (61.9%) of the subjects were male. The mean duration of MPH treatment was 22 months (range: 2 weeks to 89 months) and the mean dose of MPH was 0.84 mg/kg/day. MPH was effective in controlling ADHD symptoms in both the seizure aggravation and nonaggravation groups. However, 21 (20%) subjects had aggravated seizures and 32 (32.3%) subjects had worsened EEG findings. Subjects with uncontrolled seizure or anxiety disorders at baseline were more likely to show aggravated seizures. Subjects who had epileptiform discharges, anxiety disorders, or were free of antiepileptic drug use at baseline experienced EEG worsening more frequently. The median duration of MPH treatment was significantly longer in subjects who did not show seizure aggravation than in those who did ($p < 0.001$).

Conclusions: MPH treatment may be related to aggravation of seizures or significant worsening of EEG findings in subjects with ADHD and epilepsy. Thus, clinicians should closely monitor seizure aggravation after MPH administration, especially for high-risk subjects with uncontrolled seizures or anxiety disorders at baseline.

Single-Dose Pharmacokinetics of HLD200, a Delayed-Release and Extended-Release Methylphenidate Formulation, in Healthy Adults and in Adolescents and Children with Attention-Deficit/Hyperactivity Disorder; Ann Childress, et al, 2018

Objective: Current extended-release (ER) formulations of psychostimulants used for treatment of attention-deficit/hyperactivity disorder (ADHD) provide an extended duration of ADHD symptom control; however, the onset of efficacy can be protracted and variable, leaving the early morning untreated. The primary objective was to characterize the single-dose pharmacokinetics and tolerability of HLD200, an evening-dosed, delayed-release (DR) and ER formulation of methylphenidate (MPH), in healthy adults and in adolescents and children with ADHD.

Methods: The pharmacokinetics and tolerability of a single, oral evening dose of HLD200 (54 mg) were evaluated in two single-center open-label studies: the first in healthy adults (n = 12) and the second in adolescents (n = 18) and children (n = 11) with ADHD. Primary pharmacokinetic endpoints were the rate and extent of MPH absorption (C_{max} and area under the curve [AUC]) and time to peak concentration (T_{max}). These parameters were calculated using noncompartmental analysis.

Results: HLD200 produced a pharmacokinetic profile characterized by an 8- to 10-hour delay in MPH release, followed by a period of extended controlled release, resulting in an ascending absorption profile that coincided with the early morning and afternoon. Mean values (coefficient of variation [CV]%) of weight-adjusted pharmacokinetic parameters were similar in adults and in adolescents and children with ADHD: C_{max} ([ng/mL]/[mg/kg]) was 9.1 (35.2), 8.8 (34.5), and 7.4 (30.1); AUC_{0-t}([ng · h/mL]/[mg/kg]) was 126.5 (35.5), 129.4 (34.8), and 129.7 (27.3); and T_{max} (hours) was 15.6 (11.1), 17.1 (14.5), and 17.7 (14.1), respectively. Intersubject variability in the mean time to achieve ascending plasma MPH concentrations of 2, 3, 4, and 5 ng/mL was low (CV: 7.8%–17.7%).

Conclusions: Evening-dosed HLD200 produces the intended DR and ER pharmacokinetic profile that provides a consistent predictable delay in initial MPH release until the early morning, followed by extended release across the day. The body weight-adjusted pharmacokinetics of HLD200 were similar between adults and adolescents and children with ADHD.

Effects of Long-Term Use of Prescription Methylphenidate on Myocardial Performance in Children with Attention-Deficit/Hyperactivity Disorder: A Tissue Doppler Imaging Study
Tayfun Kara, Ajda Mutlu Mıhçıoğlu, Semra Yılmaz, İsmail Akaltun
Journal of Child and Adolescent Psychopharmacology 2018 November 2

OBJECTIVE: Many children diagnosed with attention-deficit/hyperactivity disorder are treated with methylphenidate (MPH). The purpose of this study was to evaluate the relationship between long-term use of osmotic-release oral system methylphenidate (OROS MPH) and cardiac functions.

METHODS: The study involved 116 subjects 6-18 years of age. Fifty-eight of these were in the case group and were using OROS MPH (extended-release capsules). Fifty-eight children not receiving treatment were included in the control group. Participants were also assessed using 12-channel electrocardiography (ECG), transthoracic 2D echocardiography, Doppler echocardiography, and tissue Doppler imaging (TDI). The findings obtained were compared using statistical methods.

RESULTS: No significant differences were determined between the case and control groups in terms of systolic blood pressure and diastolic blood pressure or 12-channel ECG findings. There was also no difference in 2D and M-mode measurements among the echocardiography findings. Of the TDI parameters obtained, only E' septal values differed significantly between the case and control groups. However, this was not at such a level as to indicate cardiac function impairment.

CONCLUSIONS: The study data showed that the echocardiographic parameters we measured resulted in no clinical difference between the children using MPH and the healthy controls. We conclude that MPH use in children does not impair cardiovascular functions at short-term follow-up.

Effects of Methylphenidate During Fear Learning in Antisocial Adolescents: A Randomized Controlled fMRI Trial

Van Lith et al, 2018

Methylphenidate normalizes amygdala reactivity

Testicular Function After Long-Term Methylphenidate Treatment in Boys with Attention-Deficit/Hyperactivity Disorder
Liang-Jen Wang, Sheng-Yu Lee, Wen-Jiun Chou, Min-Jing Lee, Ching-Shu Tsai, Tung-Liang Lee, Chun-Ju Yang, Kang-Chung Yang, Chih-Ken Chen, Yu-Chiau Shyu
Journal of Child and Adolescent Psychopharmacology 2018 December 21

OBJECTIVE: Treating attention-deficit/hyperactivity disorder (ADHD) with methylphenidate (MPH) has become increasingly common, while both animal studies and case reports have previously suggested that MPH may exert adverse effects on the reproductive system or gonadal hormones. This study aims to investigate whether long-term MPH treatment of boys with ADHD can induce testicular dysfunction (TD).
METHODS: A nationwide cohort that included 59,746 boys diagnosed with ADHD and 52,008 healthy subjects retrieved from the National Health Insurance database in Taiwan was also observed between 1999 and 2011. TD was defined by the International Classification of Diseases, 9th revision, Clinical Modifications codes (257.0, 257.1, 257.2, 257.8, or 257.9). Cumulative time of MPH use was categorized into

nonuse, short-term use (1-365 days), and long-term use (>365 days). We compared the rate of TD diagnosis between ADHD patients and controls and analyzed the risk of developing a TD after MPH treatment.
RESULTS: Compared with the control group (0.06%), the ADHD group had a higher comorbidity rate of TD (0.14%) (adjusted odds ratio [aOR] = 1.95, 95% confidence interval [95% CI]: 1.26-3.04, p = 0.003). However, MPH did not significantly influence the risk of developing TD (adjusted hazard ratio = 1.40, 95% CI: 0.77-2.54, p = 0.272). Compared with ADHD boys without MPH treatment, patients who were prescribed short-term MPH (aOR = 0.96, 95% CI: 0.51-1.82, p = 0.900) and long-term MPH (aOR = 1.40, 95% CI: 0.69-2.83, p = 0.351) showed no significance associated with an increased risk of developing TD.
CONCLUSIONS: Our nationwide cohort showed that long-term treatment with MPH has no harmful effect on the testosterone function of ADHD patients. However, due to the increased comorbidity rate of ADHD and TD, early recognition and detection of TD in ADHD children have the potential to change the trajectory of TD morbidity later in life.

Comparative Efficacy of Methylphenidate and Atomoxetine on Emotional and Behavioral Problems in Youths with Attention-Deficit/Hyperactivity Disorder
Hsien-Hsueh Shih, Chi-Yung Shang, Susan Shur-Fen Gau
Journal of Child and Adolescent Psychopharmacology 2018 November 17

OBJECTIVE: Methylphenidate and atomoxetine are efficacious in reducing core symptoms of attention-deficit/hyperactivity disorder (ADHD), but little is known about their efficacy in improving emotional/behavioral problems among youths with ADHD.
METHODS: One hundred sixty drug-naïve youths with DSM-IV-defined ADHD, aged 7-16 years, were recruited and randomly assigned to osmotic-release oral system methylphenidate (OROS-methylphenidate; n = 80) and atomoxetine (n = 80) in a 24-week, open-label, head-to-head clinical trial. The primary efficacy measure was parent-reported Child Behavior Checklist (CBCL), and the secondary efficacy measures included Youth Self Report (YSR) and Strengths and Difficulties Questionnaire (SDQ), which was based on the ratings of parents, teachers, and subjects.
RESULTS: For CBCL, both methylphenidate and atomoxetine groups showed significant improvement in all scores at weeks 8 and 24 except Somatic Complaints in the atomoxetine group. For SDQ, both treatment groups showed significant improvements in the Hyperactive and Conduct subscales for parent ratings, and the Externalizing subscale for teacher ratings at week 24. Methylphenidate was associated with greater improvements in Aggressive Behavior and Somatic Complaints of CBCL and in Conduct subscale of self-reported SDQ at week 24 compared with atomoxetine.
CONCLUSIONS: Our findings provide evidence to support that both methylphenidate and atomoxetine were effective in improving a wide range of emotional/behavioral problems in youths with ADHD after 24 weeks of treatment, with greater improvement in aggressive behavior, somatic complaints, and conduct problems in the methylphenidate group.

Changes in Sleep Problems Across Attention-Deficit/Hyperactivity Disorder Treatment: Findings from the Multimodal Treatment of Attention-Deficit/Hyperactivity Disorder Study
Emily J Ricketts, Alexandra Sturm, Dana L McMakin, Joseph F McGuire, Patricia Z Tan, Fallon B Smalberg, James T McCracken, Christopher S Colwell, John Piacentini
Journal of Child and Adolescent Psychopharmacology 2018 November 2
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OBJECTIVE: Stimulant medication and behavior therapy are efficacious for youth with attention-deficit/hyperactivity disorder (ADHD). However, research suggests that stimulants may start and/or worsen sleep problems for youth. Further, the impact of behavior therapy for ADHD on sleep is unknown. This study examined the frequency of sleep problems and effects of stimulant medication, behavior therapy, and their combination on sleep problems in youth with ADHD. This study also explored the influence of dimensional baseline ratings of ADHD symptom subtype and psychiatric comorbidity on sleep outcomes.
METHODS: Participants were 576 children (aged 7-9 years) with ADHD-Combined type from the Multimodal Treatment of ADHD study that compared methylphenidate, behavior therapy, and their combination to community care. Before treatment, parents completed the Child Behavior Checklist used to derive a total sleep problems score. Parents also completed ratings of oppositionality and ADHD symptom severity, whereas youth completed ratings of depression and anxiety. These ratings were readministered after treatment.
RESULTS: General linear mixed-effects models were used to assess change in total sleep problems across treatment. The combined group exhibited a statistically significant reduction in total sleep problems ($z = -5.81$, $p < 0.001$). Reductions in total sleep problems in methylphenidate ($z = -3.11$, $p = 0.05$), behavior therapy ($z = -2.99$, $p = 0.08$), or community care ($z = -1.59$, $p > 0.99$) did not reach statistical significance. Change in psychiatric symptoms did not significantly moderate change in total sleep problems by treatment assignment. Greater baseline oppositional defiant disorder severity predicted less reduction in total sleep problems, $\chi 2\ (1) = 3.86$, $p < 0.05$.
CONCLUSIONS: Findings suggest that combination of methylphenidate and behavior therapy is efficacious for reducing parent-reported sleep problems in young children with ADHD-Combined type relative to community care. However, potential ameliorative effects of monotherapy treatments (i.e., methylphenidate, behavior therapy) should be examined. Future replication is needed to confirm findings.

Methylphenidate-Induced Nocturnal Bruxism Alleviated by Adjunctive Clonidine
Ahmed Naguy, Dalal Elsori, Bibi Alamiri
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Stimulants-related bruxism has been previously reported; both diurnal and nocturnal. Here, authors report on a case of methylphenidate (MPH)-treated attention-deficit/hyperactivity disorder that developed nocturnal bruxism and failed multiple pharmacologic trials. Add-on clonidine has successfully helped with bruxisms while augmenting MPH response. This was achieved with great tolerability. This remains a viable option to deploy in such unusual clinical scenarios.

Influence of Psychopharmacotherapy on the Quality of Life of Children with Attention-Deficit/Hyperactivity Disorder
Hanife Temizsoy, Zeliha Özlü-Erkilic, Susanne Ohmann, Petra Sackl-Pammer, Christian Popow, Türkan Akkaya-Kalayci
Journal of Child and Adolescent Psychopharmacology 2019 March 29

OBJECTIVE: Attention-deficit/hyperactivity disorder (ADHD) may have a lasting effect on the quality of life (QoL) of children and their parents. Children with ADHD as well as their parents report a lower QoL compared with healthy children and children with chronic diseases such as bronchial asthma. The primary objective of this study was to investigate the changes of QoL of children with ADHD and their parents' subjective well-being before and after starting pharmacotherapy. We used the appropriate KINDL questionnaire for assessing the children's QoL and the World Health Organization (WHO) Big Five Questionnaire for assessing parental well-being.
METHODS: We assessed the QoL and the parental well-being in 60 children and adolescents with ADHD between the ages of 6 and 12 years [mean age 8.7 years, (standard deviation = 1.8)], treated at the Department of Child and Adolescent Psychiatry of the Medical University of Vienna. QoL was rated using the KINDL questionnaires, and parental well-being was assessed using the WHO Big Five Questionnaire (WHO-5) before and after starting pharmacotherapy. We used t-tests and three-way GLM-ANOVA (SPSS, version 22; IBM Corp.) for evaluating the statistical significance of pre-post differences.
RESULTS: The QoL of the children with ADHD and the subjective well-being of the parents improved significantly after introducing pharmacotherapy.
CONCLUSIONS: Pharmacotherapy is recommended in children with clinically significant ADHD not only because it helps to improve the symptoms of ADHD, but also their QoL and the well-being of their parents.