Low-dose vs. Normal-dose MPH on EFs in Children With ADHD

This study is not yet open for participant recruitment. (see Contacts and Locations)

Verified June 2014 by University of British Columbia

Sponsor:
University of British Columbia

Information provided by (Responsible Party):
University of British Columbia

ClinicalTrials.gov Identifier:
NCT02167048

First received: June 11, 2014
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Last verified: June 2014

Purpose
This double-blind crossover study aims to compare cognitive performance (e.g., working memory, selective attention and cognitive flexibility) of children ages 9-16 years diagnosed with ADHD of the combined type (ADHD-C) or inattentive-type (ADHD-IA) and currently on > 20 mg/day of Methylphenidate (MPH) on: a) their current dose of MPH, vs. b) a lower-dose of MPH (half of their current dose).

The investigators hypothesize that the lower-dose MPH will result in better cognitive performance than moderate-to-high doses of MPH.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Intervention</th>
<th>Phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Attention Deficit Hyperactivity Disorders</td>
<td>Drug: Methylphenidate (MPH)</td>
<td>Phase 1 Phase 2</td>
</tr>
</tbody>
</table>

Study Type: Interventional

Study Design:
- Allocation: Randomized
- Intervention Model: Crossover Assignment
- Masking: Double Blind (Subject, Caregiver, Investigator, Outcomes Assessor)
- Primary Purpose: Treatment

Official Title: Effects of Low-dose Versus Normal-dose Methylphenidate on Executive Functions in Children
With Attention-Deficit Hyperactivity Disorder

Resource links provided by NLM:

MedlinePlus related topics: Attention Deficit Hyperactivity Disorder Memory

Drug Information available for: Methylphenidate Methylphenidate hydrochloride

U.S. FDA Resources

Further study details as provided by University of British Columbia:

Primary Outcome Measures:

- Executive Functions (difference in performance on the two MPH doses) [ Time Frame: Day 1 ]
  [ Designated as safety issue: No ]
  Executive Functions consist of selective attention, working memory, response inhibition, reasoning, and set switching. Each of those component abilities will be assessed, scores converted to z scores, and a composite score assigned to each subject for each test session.

- Executive Functions (difference in performance on the two MPH doses) [ Time Frame: 2 weeks ]
  [ Designated as safety issue: No ]
  Executive Functions consist of selective attention, working memory, response inhibition, reasoning, and set switching. Each of those component abilities will be assessed, scores converted to z scores, and a composite score assigned to each subject for each test session.

Estimated Enrollment: 52

Study Start Date: June 2014

Estimated Primary Completion Date: December 2015 (Final data collection date for primary outcome measure)

<table>
<thead>
<tr>
<th>Arms</th>
<th>Assigned Interventions</th>
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</thead>
<tbody>
<tr>
<td>Experimental: Normal-dose MPH, Low-dose MPH</td>
<td>Drug: Methylphenidate (MPH) Participants will be tested twice 2 weeks apart. All will continue on their normal MPH dose up until 3 days before the testing day. 3 days before their 1st testing session, half the participants will start on either their current-dose of MPH or half their current dose depending on the arm they were randomized to (we provide those pills). To control for different pharmacokinetics of the MPH</td>
</tr>
<tr>
<td>Normal-dose: Dose participants are currently taking as part of their prescription (on more than or equals to 20 mg/day of Methylphenidate [MPH]) Lose-dose: Half the normal dose</td>
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</tr>
</tbody>
</table>
medications, a given participant will be tested at roughly the peak time for his/her specific version of MPH and at the same time of day for his/her two testing sessions.

**EXAMPLE:**

1. Long-acting Concerta: 5-8 hours after dose, both testing sessions
2. Long-acting Ritalin: 5-7 hours after dose, both testing sessions
3. Short-acting Ritalin: 2-3 hours after dose, both testing sessions

**Other Names:**

- Ritalin
- Concerta
- Biphentin

| Active Comparator: Low-dose MPH, Normal-dose MPH
| Normal-dose: Dose participants are currently taking as part of their prescription (on more than or equals to 20 mg/day of Methylphenidate [MPH]) Lose-dose: Half the normal dose |

| Drug: Methylphenidate (MPH) |
| Participants will be tested twice 2 weeks apart. All will continue on their normal MPH dose up until 3 days before the testing day. 3 days before their 1st testing session, half the participants will start on either their current-dose of MPH or half their current dose depending on the arm they were randomized to (we provide those pills).

To control for different pharmacokinetics of the MPH medications, a given participant will be tested at roughly the peak time for his/her specific version of MPH and at the same time of day for his/her two testing sessions.

**EXAMPLE:**

1. Long-acting Concerta: 5-8 hours after dose, both testing sessions
2. Long-acting Ritalin: 5-7 hours after dose, both testing sessions
3. Short-acting Ritalin: 2-3 hours after dose, both testing sessions

**Other Names:**

- Ritalin
- Concerta
- Biphentin
No Intervention: No intervention, No intervention  
This arm is completely no intervention, and is ONLY for healthy volunteers. We are testing healthy volunteers of the same age to give us an estimate of order effects to help us correct for better performance in the 2nd session due simply to taking the same tests twice (note: the tests are Version A and B).

Detailed Description:
Attention-deficit hyperactivity disorder (ADHD) is a neurodevelopmental disorder characterized by attention deficits, hyperactivity, or impulsive actions that are not appropriate for the individuals’ age (Barkley 1997). These behavioural issues arise relatively early in life, typically before the age of 12, and continue to persist into adulthood in many cases (Barkley 1997). In school-aged children, ADHD is associated with low academic achievement, poor school performance, anxiety and depression.

Symptoms are divided into inattention (e.g., easily distracted, difficulty focusing on & completing a task), hyperactivity (e.g., constantly in motion, fidgets, squirms, talks non-stop), and impulsivity (e.g., difficult waiting one's turn, interrupting others). Three subtypes of ADHD have been identified: predominantly inattentive (ADHD-I), predominantly hyperactive-impulsive (ADHD-H), and the combined type (ADHD-C).

Methylphenidate (MPH) in medium to high doses (roughly 20-40 mg/day; the doses most commonly prescribed for children and youths with ADHD) acts to inhibit re-uptake of dopamine by the dopamine transporter (DAT), resulting in increased dopamine concentrations in the synapse. DAT is abundant in the striatum, which is implicated in hyperactivity and impulsivity aspects of ADHD. However, DAT is sparse in prefrontal cortex (PFC), which plays a critical role in subserving executive functions. Executive functions (EFs; also called cognitive control or self-regulation) are a group of processes involved in concentration, focused attention, self-control, cognitive flexibility, problem-solving, and working memory (refs: Diamond, 2013; Jacques & Marcovitch, 2010). Thus the number of high risk alleles of the gene that codes for the dopamine transporter (DAT1) are associated with hyperactivity (which depends on the striatum) but not inattention or EF deficits (which depend on PFC; refs: Jucaite et al., 2005; Waldman et al., 1998.

The action of low doses of MPH (5-10 mg/day) has been shown to be different, however. At low doses MPH has been demonstrated to act preferentially on PFC, increasing dopamine release (refs: Berredge et al., 2006; Schmeichel & Berredge, 2013; Spencer et al, 2012). Thus, moderate to high doses of MPH (doses most often prescribed for children and youths with ADHD) probably do not improve PFC function or EFs, or worse, may actually impair cognitive function, leaving a patient feeling more in a daze.

Optimal dosing for MPH in children and youths with ADHD is usually determined by parents' reports of improved behaviour, almost never by performance on cognitive measures. We propose to look at cognitive performance on measures of attention, working memory, planning, etc. in children and youths with ADHD on their current dose of MPH and on half that much (order counterbalanced across participants).

Purpose/Objectives: This double-blind crossover study aims to compare cognitive performance (e.g., working memory, selective attention and cognitive flexibility) of children ages 9-16 years diagnosed with ADHD of the combined type (ADHD-C) or inattentive-type (ADHD-IA) and currently on > 20 mg/day of MPH on their current dose of MPH and on a lower-dose of MPH (half of their current dose), order counterbalanced across subjects.
To give us an estimate of order effects to help us correct for better performance in the 2nd session due simply to taking the same cognitive tests twice (note: the tests are Version A and B), we will also be recruiting healthy volunteers to serve as a control group. This control group will be strictly no intervention.

Hypotheses: The investigators hypothesize that lower-dose MPH will result in better cognitive performance than moderate-to-high doses of MPH.

**Eligibility**

Ages Eligible for Study: 9 Years to 16 Years  
Genders Eligible for Study: Both  
Accepts Healthy Volunteers: Yes  

**Criteria**

Inclusion Criteria:

- Between the chronological ages of 9 and 16 years
- Average to above-average IQ (Parental report of an IQ above 90; we will take their word for it)
- Meet DSM-V criteria for ADHD (Combined type or Inattentive type)
- Currently treated with and responding to oral methylphenidate >= 20 mg/day and not on a "drug holiday"
- Stable on current MPH dose for at least 6 months and not on MPH for more than 2 years
- Able to communicate (understand, speak, and write) in English without the aid of an interpreter
- Able to execute simple manual response (button-press) as required for our tasks
- The child and parent give assent and consent respectively for the child's participation in this study

Exclusion Criteria:

- Patients with significant prior or current medical conditions that could impact neuropsychological performance such as traumatic brain injury, hypoxia, or unstable diabetes.
- Have any medical condition that could markedly increase sympathetic nervous system activity (e.g. catecholamine-secreting neural tumor), or who are taking a medication on a daily basis (e.g. pseudoephedrine, oral steroids) that has sympathomimetic activity. Note: regular on-label use of inhalers for asthma (e.g., albuterol, steroidal) is permitted
- Taking any psychotropic medication other than MPH
- Have a major, uncorrected sensory impairment (e.g. significant hearing impairment despite hearing aids)
- Lack sufficient English language skills to perform our tasks
- Are taking medications other than MPH that may affect cognitive skills
- Have a documented history of Dyslexia (this may skew results on our cognitive measures), Bipolar I or II, psychosis, Depression, Autism Spectrum Disorders, or Disruptive Mood Dysregulation Disorder
- Have a past history of any severe adverse reaction to lowering of MPH dose
- Patient has been non-compliant with MPH or is on a "drug holiday"
- Parental report of an IQ below 90 (we will take their word for it)

**Contacts and Locations**

Choosing to participate in a study is an important personal decision. Talk with your doctor and family members or friends about deciding to join a study. To learn more about this study, you or your doctor may contact the study research staff using the Contacts provided below. For general information, see Learn About Clinical Studies.
Please refer to this study by its ClinicalTrials.gov identifier: NCT02167048

Contacts

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Locations

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Principal Investigator: Adele Diamond, Ph.D.

Sponsors and Collaborators

University of British Columbia

Investigators

Principal Investigator: Adele Diamond, Ph.D. Department of Psychiatry, University of British Columbia

More Information

Publications:

Responsible Party: University of British Columbia

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Health Authority: Canada: Health Canada

Keywords provided by University of British Columbia:

**Attention Deficit Hyperactivity Disorders**
- Executive Function
- Methylphenidate
- Child
- Adolescent

Inhibition
- Working Memory
- Prefrontal Cortex
- Attention
- Cognitive Function

Additional relevant MeSH terms:

**Attention Deficit Disorder** with **Hyperactivity Hyperkinesis**

**Attention Deficit and Disruptive Behavior Disorders**

Mental Disorders Diagnosed in Childhood

Mental Disorders

Nervous System Diseases

Dyskinesias

Neurologic Manifestations

Signs and Symptoms

Methylphenidate

Dopamine Uptake Inhibitors
- Dopamine Agents
- Neurotransmitter Agents
- Molecular Mechanisms of Pharmacological Action
- Pharmacologic Actions
- Neurotransmitter Uptake Inhibitors
- Physiological Effects of Drugs
- Central Nervous System Stimulants
- Central Nervous System Agents
- Therapeutic Uses

ClinicalTrials.gov processed this record on June 17, 2014