Application for Inclusion to the 22nd Expert Committee on the Selection and Use of Essential Medicines:

METHYLPHENIDATE HYDROCHLORIDE

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Submitted by:

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1. Summary Statement of the Proposal for Inclusion of Methylphenidate

Methylphenidate (MPH), a central nervous system (CNS) stimulant, of the phenethylamine class, is proposed for inclusion in the WHO Model List of Essential Medications (EML) & the Model List of Essential Medications for Children (EMLc) for treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) under ICD-11, 6C9Z mental, behavioral or neurodevelopmental disorder, disruptive behavior or dissocial disorders. To date, the list of essential medications does not include stimulants, which play a critical role in the treatment of psychotic disorders. Methylphenidate is proposed for inclusion on the complimentary list for both children and adults. This application provides a systematic review of the use, efficacy, safety, availability, and cost-effectiveness of methylphenidate compared with other stimulant (first-line) and non-stimulant (second-line) medications.

Considerable evidence has accumulated over several decades that most patients with ADHD symptoms can be successfully treated by psychopharmacotherapies. Extensive research aligns with the general consensus across pharmacopeial standards around the world - MPH consistently proves to have the best comprehensive ranking in efficacy and tolerability. Methylphenidate has fewer reported side effects and studies show less occurrence of all-cause withdrawal. Although it is associated with weight loss and sleeping problems, the overall side effect profile of methylphenidate is encouraging when compared to other ADHD medications. Methylphenidate represents a class of medication, central nervous stimulants, that should be included in the essential medications list. Within its class, the choice of methylphenidate offers a uniquely good balance of efficacy, safety, minimal monitoring and cost-effectiveness. Methylphenidate is an important treatment option that can reduce the global disease burden of attention-deficit/hyperactivity disorder.
2. Focal Point Person(s) in the World Health Organization

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Evidence, Research and Action on Mental and Brain Disorders (MER)
Department of Mental Health And Substance Abuse
World Health Organization

Dr. Lorenzo Moja, Technical Officer
Policies, Access and Use (PAU) Team
Essential Medicines and Health Products (EMP)
World Health Organization

Dr. N Magrini, Medical Officer
Policies, Access and Use (PAU) Team
Selection and Rational Use, Group Lead
Essential Medicines and Health Products (EMP)
World Health Organization
3. **Name of the Organization(s) Consulted and Supporting the Application**

- Eleanor Bennett, PNP, Ministry of Health, Belize
- Sandip Shah, M.D. GMERS Medical College, Vadadora (Gujarat), India
- Doris Keens-Douglas, Ministry of Health, Grenada
- Dr. Evlyn Spencer, Ministry of Health, Grenada
- Dr. Omar Hernandez Rivero, Ministry of Health, Grenada

*SEE APPENDIX FOR LETTERS OF SUPPORT*
4. **International Nonproprietary Name (INN, generic name) of the medicine**

Methylphenidate Hydrochloride
ATC Code: N06BA04
5. Formulations of Methylphenidate Proposed for Inclusion

Methylphenidate (hydrochloride)
- Immediate release tablets, 10mg, 20mg
6. **International Availability**

<table>
<thead>
<tr>
<th>Brand Name</th>
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<tr>
<td>Adaphen</td>
<td>South Africa</td>
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<td>Addwize</td>
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<td>Cognil</td>
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<td>Concentra</td>
<td>Bangladesh</td>
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<tr>
<td>Equasym</td>
<td>Belgium, Switzerland, Spain, Ireland</td>
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<tr>
<td>Inspiral</td>
<td>India</td>
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<tr>
<td>Medikinet</td>
<td>Belgium, Switzerland, Germany, Denmark, Estonia, Great Britain, Ireland, Norway, Poland, Sweden</td>
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<tr>
<td>Methylin</td>
<td>Argentina</td>
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<td>Nebapul</td>
<td>Chile</td>
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<td>Penid</td>
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<td>Phenida</td>
<td>Pakistan</td>
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<td>Prohiper</td>
<td>Indonesia</td>
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<tr>
<td>Ritaline</td>
<td>Luxembourg</td>
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<tr>
<td>Ritalin</td>
<td>United Arab Emirates, Austria, Australia, Barbados, Burkina Faso, Bahrain, Benin, Switzerland, Cote D'Ivoire, Chile, Colombia, Cyprus, Czech Republic, Germany, Denmark, Ethiopia, Great Britain, Ghana, Gambia, Guinea, Hong Kong, Indonesia, Ireland, Israel, Iraq, Iran, Iceland, Jordan, Japan, Kenya, Kuwait, Lebanon, Sri Lanka, Liberia, Libya, Morocco, Mali, Mauritania, Malt, Mauritius, Malawi, Mexico, Malaysia, Niger, Nigeria, Norway, New Zealand, Oman, Peru, Pakistan, Qatar, Saudi Arabia, Seychelles, Sudan, Sweden, Singapore, Slovenia, Sierra Leone, Senegal, Syria, Tunisia, Taiwan, Tanzania, Uganda, Venezuela, Yemen, Zambia, Zimbabwe</td>
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<tr>
<td>Ritalina</td>
<td>Argentina, Brazil, Paraguay, Uruguay</td>
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<td>Ritaline</td>
<td>Belgium, France, Greece</td>
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Rubifen
Argentina, Spain, Sri Lanka, Malaysia, New Zealand, Portugal, Singapore, Thailand, Uruguay

Tradea
Costa Rica, Dominican Republic, Guatemala, Honduras, Mexico, Nicaragua, Panama, El Salvador

Sources
The above information was obtained from the following drug name databases:

Lexi-Comp ONLINE (1)
Up To Date (2)
7. Listing request

Listing for methylphenidate is requested as an individual medication for both children and adults.

Methylphenidate (hydrochloride), immediate release tablets, 10mg and 20mg.
8. Information Supporting the Public Health Relevance of Methylphenidate

Central nervous system stimulants have been shown to be efficacious in treating a range of mental illnesses, including attention-deficit hyperactivity disorder (ADHD) (3), narcolepsy (4), treatment resistant depression (5) and some formulations have been used for treating obesity (6).

Methylphenidate (MPH), a central nervous system (CNS) stimulant, of the phenethylamine class, is commonly used for pharmacological treatment of attention deficit disorder (ADD), attention deficit hyperactivity disorder (ADHD) and narcolepsy. The drug, first synthesized in 1944 and launched as Ritalin, was first used for the treatment of lethargy, narcolepsy, chronic fatigue, disorders associated with depression and what was then known as hyperactivity (7). However, its most impressive beneficial effect has been the decrease in symptoms noticed in ADHD, which is one of the most common behavioral disorders in childhood and may persist into adulthood, found in approximately 3% to 5% of the general population of school-aged children, occurring more frequently in boys (8). In 1990, when diagnosis of ADHD became more broadly accepted, MPH became the drug of choice for treatment and its prescription exceedingly increased (9). In general, it is effective, safe and widely prescribed.

The mental disorders that methylphenidate is approved to treat have a high global disease burden. In 2010, mental neurological and substance use disorders accounted for 10.4% of global disability-adjusted life years (DALYs) and 28.5% of years of life lost due to disability, illness, or premature death (YLDs), making them the leading cause of YLDs (10). The Global Burden of Disease Study 2010 (GBD 2010) is the first to include conduct disorder (CD) and attention-deficit/hyperactivity disorder (ADHD) for burden quantification (11). Globally, CD was responsible for 5.75 million YLDs/DALYs with ADHD responsible for a further 491,500 (12). Collectively, CD and ADHD accounted for 0.80% of total global YLDs and 0.25% of total global DALYs (12).

MPH is highly effective in improving the core symptoms of ADHD (13). Despite the high prevalence and recent increases in illicit use, prescription stimulants remain highly effective and safe medication for the majority of individuals with ADHD. Expert consensus recommends MPH as the first line medication to be used in a treatment algorithm for ADHD in children and adolescents (14).

In developing countries, more than 75% of people suffering from mental disorders in the developing world receive no treatment or care (15). In the majority of countries, less than 2% of health funds are spent on mental health (15). Despite the rumored notion that ADHD is the product of Western culture, the worldwide prevalence of this disorder if 5.2% (16). The finding of Polanczyk and colleagues of a uniform prevalence rate worldwide attests that ADHD is probably not caused by the avarice of the American psychiatric profession or by permissive Western culture and that reducing our avarice and permissiveness will not make ADHD disappear (16). Similarly, a multisite trial study reported that using a uniform diagnostic protocol yields ADHD patients who are highly similar across clinics in Africa, Australia, Europe, and North America (17).

The target population for methylphenidate includes children and adolescents as well as adults. Attention deficit hyperactivity disorder is a developmental disorder with an age onset prior to 12 years and can also affect adults. Children with ADHD have significantly lower ability to focus and sustain attention and also score higher on impulsivity and hyperactivity. Stimulants, such as methylphenidate, have remained the mainstay of ADHD treatment for decades with evidence supporting their use (3).
We evaluate the appropriateness of current prescription practices of methylphenidate in the Comparative Effectiveness section, drawing comparisons to stimulant and non-stimulant medications. Overall, we find methylphenidate to be advantageous in treating attention deficit hyperactivity disorder.
9. Treatment Details for Methylphenidate

9.1 Dosing and Duration

Methylphenidate Dosage Form (18)
- Immediate-release tablets 5mg, 10mg, 15mg, 20mg (Ritalin, generic methylphenidate)

Dosage Guidelines for Adult Patients (1)
ADHD: Oral:
- *Immediate release (IR) products (tablets, chewable tablets, and solution):* Initial: 5 mg twice daily, before breakfast and lunch; increase by 5 to 10 mg daily at weekly intervals; maximum dose: 60 mg/day (in 2 to 3 divided doses).
  - *IR methylphenidate:*
    - Patients taking IR methylphenidate 5 mg 2 to 3 times daily: 18 mg once every morning
    - Patients taking IR methylphenidate 10 mg 2 to 3 times daily: 36 mg once every morning
    - Patients taking IR methylphenidate 15 mg 2 to 3 times daily: 54 mg once every morning
    - Patients taking IR methylphenidate 20 mg 2 to 3 times daily: 72 mg once every morning

Dosage Guidelines for Pediatric Patients (1)
ADHD:
- *Oral, immediate release (IR) products (tablets, chewable tablets, and solution):* Children ≥6 years and Adolescents: Initial: 5 mg twice daily, before breakfast and lunch; increase by 5 to 10 mg daily at weekly intervals; maximum dose: 60 mg/day (in 2 to 3 divided doses).
  - *IR methylphenidate:*
    - Patients taking IR methylphenidate 5 mg 2 to 3 times daily: 18 mg once every morning
    - Patients taking IR methylphenidate 10 mg 2 to 3 times daily: 36 mg once every morning
    - Patients taking IR methylphenidate 15 mg 2 to 3 times daily: 54 mg once every morning
    - Patients taking IR methylphenidate 20 mg 2 to 3 times daily: 72 mg once every morning

Special Populations (18)
Renal Impairment
- No dose adjustment necessary
Hepatic Impairment
- No dose adjustment necessary
Cardiac Impairment
- Use with caution, particularly in patients with recent myocardial infarction or other conditions that could be negatively affected by increased blood pressure
  - Do not use in patients with structural cardiac abnormalities
Elderly
- Some patients may tolerate lower doses better
Children and Adolescents
- Safety and efficacy not established in children under age 6
- Use in young children should be reserved for the expert
- Methylphenidate has acute effects on growth hormone; long-term effects are unknown but weight and height should be monitored during long-term treatment
• Sudden death in children and adolescents with serious health problems has been reported
• American Heart Association recommends EKG prior to initiating stimulant treatment in children, although not all experts agree

Pregnancy
• Effective June 30, 2015, the US FDA requires changes to the content and format of pregnancy and lactation information in prescription drug labels, including the elimination of the pregnancy letter categories; the Pregnancy and Lactation Labeling Rule (PLLR or final rule) applies only to prescription drugs and will be phased in gradually for drugs approved on or after June 30, 2001
• Controlled studies have not been conducted in pregnant women
• Infants whose mothers took methylphenidate during pregnancy may experience withdrawal symptoms
• Racemic methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200mg/k/day throughout organogenesis
• Use in women of childbearing potential requires weighing potential benefits to the mother against potential risks to the fetus
• For ADHD patients, methylphenidate should generally be discontinued before anticipated pregnancies

Breast Feeding
• Unknown if methylphenidate is secreted in human breast milk, but all psychotropics assumed to be secreted in breast milk
• Recommended either to discontinue drug or bottle feed
• If infants show signs of irritability, drug may need to be discontinued

Pharmacokinetics (18)
• Average half-life in adults is 3.5 hours (1.3-7.7 hours)
• Average half-life in children is 2.5 hours (1.5-5 hours)
• First-pass metabolism is not extensive with transdermal dosing, thus resulting in notably higher exposure to methylphenidate and lower exposure to metabolites as compared to oral dosing

Onset of Action (18)
• Some immediate effects can be seen with first dosing
• Can take several weeks to attain maximum therapeutic benefit

Long-Term Use (18)
• Often used long-term for ADHD when ongoing monitoring documents continued efficacy
• Dependence and/or abuse may develop
• Tolerance to therapeutic effects may develop in some patients
• Long-term stimulant use may be associated with growth suppression in children (controversial)
• Periodic monitoring of weight, blood pressure, CBC, platelet counts, and liver function may be prudent

Overdose (18)
• Vomiting, tremor, coma, convulsion, hyperreflexia, euphoria, confusion, hallucination, tachycardia, flushing, palpitations, sweating, hyperpyrexia, hypertension, arrhythmia, mydriasis

Dependence or Abuse (18)
• High abuse potential, Schedule II drug
• Patient may develop tolerance, psychological dependence
• Drug abuse may actually be lower in ADHD adolescents treated with stimulants than in ADHD adolescents who are not treated

Discontinuation (18)
• Taper to avoid withdrawal effects
• Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder and may require follow-up and reinstatement of treatment
• Careful supervision is required during withdrawal from abusive use since severe depression may occur

Storage and Handling of Methylphenidate

Capsule:
Solution: Immediate-release (Methylin): Store at 20°C to 25°C (68°F to 77°F).

Tablet:
Immediate-release chewable (Methylin): Store at 20°C to 25°C (68°F to 77°F). Protect from light and moisture.
Immediate-release (Ritalin): Store at 25°C (77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). Protect from light and moisture.
9.2 Reference to Methylphenidate in Existing WHO & Other Clinical Guidelines

From the pharmacological interventions section of the World Health Organization’s, mhGAP Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings (19): “Consider methylphenidate for hyperkinetic disorder only if psychosocial interventions have failed, child has been carefully assessed and is at least 6 years old, and conditions whose management can be complicated by methylphenidate have been ruled out. Use of stimulant medication must always be part of a comprehensive treatment plan that includes psychological, behavioral and educational interventions”.

The American Academy of Pediatrics (AAP) published a clinical practice guideline that provides recommendations based on the best available medical evidence (evidence-based) for the diagnosis and treatment of children with attention-deficit/hyperactivity disorder (ADHD) (20–22). The guideline contains the following recommendations by AAP for the treatment of ADHD: “For preschool-aged children (4–5 years of age), the primary care clinician may prescribe methylphenidate if the behavior therapy does not provide significant improvement and the child continues to have moderate to severe symptoms”.

The American Academy of Child and Adolescent Psychiatry (AACAP) published an ADHD Parents Medication Guide (23) which is intended to help parents, patients, and family members better understand the treatments used to care for children with ADHD. The guideline contains the following recommendations regarding types of effective treatments: “To help families make important decisions about treatment, the National Institute of Mental Health (NIMH) conducted the most in-depth study ever carried out for evaluating ADHD treatments. This study is called the Multi-Modal Treatment Study of Children with ADHD (or the MTA) (24). Data from this study showed that methylphenidate (a commonly used stimulant medication for ADHD) is “effective in treating the symptom of ADHD, either alone or in combination with behavioral therapy. It also found that treatment that includes medication is more effective for the symptoms of ADHD (such as hyperactivity) than behavioral therapy alone.”.
9.3 Need for Special Diagnostics, Treatment or Monitoring Facilities and Skills When Prescribing Methylphenidate

Prior to initiating methylphenidate therapy
Assess for presence of cardiac disease (history, family history, physical exam)

Monitoring while on methylphenidate therapy (1)
• Blood pressure should be monitored regularly
• In children, monitor weight and height
• Periodic complete blood cell and platelet counts may be considered during prolonged therapy (rare leukemia and/or anemia)

Methylphenidate is indicated as an integral part of a comprehensive treatment program for ADHD which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only of comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present, and a diagnosis of central nervous system dysfunction may or may not be warranted.

The specific etiology of ADHD is unknown, and there is no single, definitive diagnostic test. Diagnosis is usually reached via a combination of assessing the patient (and their caretaker in the case of children) with validated surveys or interview schedules and clinical judgment.

Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, especially psychotic illness. Educational accommodations and psychosocial interventions are often attempted before or in conjunction with medication trials. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician’s assessment of the chronicity and severity of the child’s symptoms.

Assessing Cardiovascular Status in Patients being Treated with Stimulant Medication
Children, adolescents or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for family history of sudden death or ventricular arrhythmia) and physical exam to assess for presence of cardiac disease and should receive further cardiac evaluation including an electrocardiogram if findings suggest such disease. Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

Long Term Suppression of Growth
Careful follow-up of weight and height should be monitored during treatment with stimulants, and patients who are not growing or gaining weight as expected may need to have their treatment interrupted.
Use in Children Under Six Years of Age
Methylphenidate should not be used in children under 6 years, since safety and efficacy in this age group have not been established.

Socioeconomic Status
In one study looking at factors related to the incidence of methylphenidate use by Canadian children, the composite individual-level measure of SES, which included income, education and occupation, predicted incidence of methylphenidate use, with the probability of methylphenidate use increasing as SES decreased (25).
10. Summary of the Comparative Effectiveness of Methylphenidate in a Variety of Clinical Settings

10.1 Identification of Clinical Evidence Regarding Methylphenidate

A systematic review conducted using PubMed and Cochrane databases (last search, Dec 5, 2018). These catalogues were searched for articles using keywords “methylphenidate” and “comparison” for PubMed and “methylphenidate” only for the Cochrane database search. Further data was obtained through cross-referencing and a hand search of relevant literature. There were no specifications on language.

A total of 423 abstracts in PubMed and 21 reviews in Cochrane databases were identified initially. Among these, 141 were relevant to comparative effectiveness for methylphenidate. Of the 141 relevant articles, 93 were excluded due to poor study design, small sample size, type of article (e.g. letter to the editor), and/or incomplete or non-available data. Of the 48 remaining, 19 studies focused on indications of methylphenidate (extended-release, osmotically released etc.) not being proposed for inclusion and therefore excluded. As a result, 29 studies and review articles were included in this summary.

10.2 Summary of Available Data on Methylphenidate

**Children and Adolescents**

**ATTENTION-DEFICIT HYPERACTIVITY DISORDER**

**Comparison with placebo/control:**

In a Cochrane review (26) comparing methylphenidate versus placebo, 38 parallel-group trials and 147 cross-over trials were included. Studies included were all randomized controlled trials comparing methylphenidate versus placebo or no intervention in children and adolescents aged 18 years and younger with a diagnosis of ADHD. The duration of methylphenidate treatment ranged from 1 to 425 days, with an average duration of 75 days. Seventeen review authors participated in data extraction and risk of bias assessment and two review authors independently performed all tasks. The study showed that methylphenidate may improve teacher-rated ADHD symptoms (SMD -0.77, 95% CI -0.90 to -0.64; 1698 participants). This corresponds to a mean difference (MD) of -9.6 points (95% CI -13.75 to -6.38) on the ADHD Rating Scale (ADHD-RS; range 0 to 72 points; DuPaul 1991a). A change of 6.6 points on the ADHD-RS is considered clinically to represent the minimal relevant difference. The results of meta-analyses suggest that methylphenidate may improve teacher-reported ADHD symptoms, teacher-reported general behavior, and parent-reported quality of life among children and adolescents diagnosed with ADHD.
Boys with attention-deficit/hyperactivity and reading disorders (n=25) between the ages of 7.9 and 11.7 years, with at least average intelligence and verbal processing abilities participated in double-blind, acute randomized, placebo-controlled crossover trial with a single dose of methylphenidate with weekly intervals between testing sessions (27). The test battery included tasks of attention/control functions and reading domain functions. Paired comparisons and first trial group comparison comparing performance under placebo and under methylphenidate were used. Methylphenidate selectively improved strategy/set shift (p=0.004) and facilitated improvement in both rapid naming (p=0.043) and word/nonword accuracy (p=0.028/p=0.035). These findings lend support to a possible influence of methylphenidate on cognitive attention functions related to reading skills in the comorbid group.

Visual scanning patterns were investigated in 32 children referred for symptoms of hyperactivity in a double-blind crossover comparison of methylphenidate and placebo treatments (28). Total errors, response latency and visual fixations were recorded as the child scanned computer-generated visual matching-to-sample problems. Results indicated that the number of fixations on the standard stimulus in the matching task was significantly larger in the methylphenidate state. Drug treatment also resulted in a significant increase in the number of systematic comparisons between the standard and the variants in the task. However, the increased selectivity of attention to the standard stimulus was not accompanied by a reduction of total errors. It was suggested that the stimulant drug may increase attentional selectivity even when such shifts fail to produce improvement in task performance.

Meta-analytic Comparison of methylphenidate with stimulant and non-stimulant medications:

In early literature on the subject, a double-blind crossover comparison of methylphenidate hydrochloride, dextroamphetamine sulfate, and caffeine after placebo washout in 29 children with minimal brain dysfunction (term in early 1960s to describe what is today Attention Deficit Hyperactivity Disorder) showed on six ratings that methylphenidate and dextroamphetamine were significantly better than placebo and caffeine (P<.05 to P<.001), but not significantly different from each other (P<.05) (29). The three drugs were compared in a randomized Latin-square crossover following placebo washout. Each of the drug conditions lasted three weeks with a minimum of three telephone consultations for adjustment of dosage. At each of the visits, including the pre-drug assessment, the following information was collected: a parent’s symptom checklist reported and factor-analyzed by Arnold and Smeltzer; a Conner’s Teacher’s Behavior Problem Checklist; a David’s Hyperkinetic Rating Scale completed by the parents; a David’s Hyperkinetic Rating Scale completed by the teacher; and a target symptom assessment in the manner described by Arnold and associates.

Three separate studies using uncrossed double-blind controls in which the effects of chlorpromazine, dextroamphetamine and methylphenidate on the behavior and intellectual functioning of chronically hyperactive children were evaluated (30). The subjects were children, aged 6 to 12 years, seen in the outpatient clinic of the Department of Psychiatry, Montreal Children’s Hospital. In all three studies, active drug or identical placebo was given, using an uncrossed double-blind technique with random allocation of subjects to one or the other of the two groups. In each study, medication was slowly increased for each child until maximal therapeutic benefit was achieved or side effects limited further increase of the dose. Drug effects were measured by completing a series of rating scales and tests including Wechsler Intelligence Scale for Children, Bender Visual-Motor Gestalt Test, Goodenough-Harris Draw-A-Man Test etc. The study found chlorpromazine, dextroamphetamine and methylphenidate to be significantly superior to placebo in producing overall improvement in the behavior of hyperactive children. Chlorpromazine was effective for the majority of children, but reduced only hyperactivity, having no demonstrable effect on distractibility, aggressivity or excitability. Both stimulants produced more goal-oriented behavior and reduced distractibility. Methylphenidate was the most effective of the drugs in producing exceptional improvement.
A conventional meta-analysis was performed to give direct comparisons and a network meta-analysis was used to show the combination of direct and indirect evidence for the analysis of efficacy and tolerability of different interventions for young patients (6-18 years old) with Attention Deficit Hyperactivity Disorder (ADHD) (31). Overall, 15,025 participants from 73 studies were involved comparing the efficacy and tolerability of six interventions: the stimulants lisdexamfetamine dimesylate (LDX) and methylphenidate (MPH); the adrenergic agonists clonidine hydrochloride (CLON) and guanfacine extended release (GXR); and the dopaminergic anti-depressant bupropion (BUP). The 73 studies consisted primarily of randomized controlled trials and systematic reviews or meta-analyses. The outcome measure of efficacy was evaluated by ADHD-RS as a continuous score, whereas adverse effects for tolerability were all cause withdrawals: withdraw due to adverse event, withdrawal due to lack of efficacy, nausea, abdominal pain, or fatigue for tolerability. The risk of bias was evaluated using the Cochrane Handbook for RCTs. Data of interest were blinding, durations, diagnostic criteria, treatment, age of patients, number of patients, and assessment criteria for patients conditions. Direct comparisons among these drugs, in the forms of mean deviation (MD) with the corresponding 95% confidence (CI) for the primary outcomes of ADHD-RS, and the pooled odds ratios (ORs) with 95% CI for the secondary outcomes of tolerability were performed. In comparison to placebo, ATX had significantly better ADHD-RS (MD = 6.95, 95% CI: 4.92–8.98) and decreasing withdrawal due to lack of efficacy (OR = 0.55, 95% CI: 0.40–0.74), but an increase the chance of adverse events (nausea: OR = 2.22, 95% CI: 1.61–3.03; abdominal pain: OR = 1.47, 95% CI: 1.16–1.85; fatigue: OR = 1.82, 95% CI: 1.33–2.50). There were no statistically significant results in the comparison of BUP versus placebo. CLON yielded great improvement in the primary outcome of ADHD-RS (MD = 8.10, 95% CI: 4.47–11.73) and less withdrawal was observed (all-cause withdrawal: OR = 0.65, 95% CI: 0.43–0.97; withdrawal due to lack of efficacy: OR = 0.37, 95% CI: 0.20–0.66). Compared to placebo, GXR was significantly more likely to cause adverse effects (abdominal pain: OR = 2.04, 95% CI: 1.37–3.13; fatigue: OR = 2.70, 95% CI: 1.89–3.85) and related withdrawal due to adverse events (OR = 2.94, 95% CI: 1.41–5.88), but the chance of withdrawal due to lack of efficacy was reduced (OR = 0.41, 95% CI: 0.30–0.56). LDX significantly resulted in less withdrawal (all-cause withdrawal: OR = 0.67, 95% CI: 0.47–0.96; withdrawal due to lack of efficacy: OR = 0.18, 95% CI: 0.06–0.48) versus placebo. MPH showed even less withdrawal (all-cause withdrawal: OR = 0.67, 95% CI: 0.50–0.91; withdrawal due to lack of efficacy: OR = 0.50, 95% CI: 0.33–0.77), plus an improvement in ADHD-RS (MD = 6.53, 95% CI: 4.91–8.15). In the direct comparisons among the seven interventions, LDX was associated with less withdrawal due to lack of efficacy (OR = 0.16, 95% CI: 0.04–0.73) than ATX. MPH showed slightly less effectiveness than LDX according to ADHD-RS (MD = −5.80, 95% CI: −8.93 to −2.67).

Data collected from 62 studies (n=12,930) were examined in another meta-analysis analyzing drugs widely used for ADHD treatment (ATX, BUP, CLON, GXR, LDX, and MPH) (32). Two independent reviewers screened articles separately, any disagreements were openly discussed until a consensus was reached. Certain/ specific criteria were included in the search terms: firstly, the patients in the studies should be accurately diagnosed with ADHD; secondly, studies were conducted based on children and adolescents (4-17 years old); thirdly, studies had to be randomized, controlled clinical trials (RCTs); finally, active medications had to be involved, which compared the drugs used in combination or singly, or with placebo (PBO). Efficacy of different drugs were evaluated by the ADHD Rating Scale-IV (ADHD-RS) and Connor’s Parents Rating Scale-Revised (CPRS). The changes of efficacy variables were calculated between the start and the end of treatment. LDX had the highest probability to rank first in terms of efficacy concerning both CPRS and ADHD-RS(-14.0 (-17.0,-12.0)) followed closely by MPH on ADHD-RS (-9.10 (-12.0,-6.4)).
Head-to-Head Comparison with first-line therapeutic strategies (stimulant drugs)

Nine randomized trials comparing methylphenidate and atomoxetine, totaling 2762 participants were included in a meta-analysis (33). The studies included were all published randomized, open-label and double-blind trials which compared efficacy of methylphenidate with atomoxetine in treatment of ADHD in children and adolescents diagnosed using DSM-IV criteria. The outcomes studied were ADHDRS-IV Parent: Inv and Turgay DSM-IV-Based Child and Adolescent Behavior Disorders Screening and Rating Scale (T-DSM-IV-S) scores. Meta-analysis did not find a significant difference in efficacy between methylphenidate and atomoxetine when standardized mean difference (SMD) was used as a measure of effect size 0.09 (95%CI -0.08-0.26) (Z1.06, p=0.29).

A multi-country, multicenter, randomized double-blind study was conducted in 6-16-year old outpatients (n=300) with ADHD in China, Korea and Mexico (34). The study examined whether atomoxetine is non-inferior to methylphenidate in treating symptoms of ADHD in pediatric patients and to determine the tolerability of the two drugs. Patients were randomly assigned to once-daily atomoxetine (n=164) or twice-daily methylphenidate (n=166) for approximately 8 weeks. Primary efficacy assessment was the comparison of response rates on Attention Deficit Hyperactivity Disorder Rating Scale IV Parents Version: Investigator-Administered and Scored. The study found that atomoxetine was non-inferior to methylphenidate in improving ADHD symptoms based on response rates in the improvement of ADHD symptoms in pediatric outpatients (atomoxetine, 77.4% [123/159]; methylphenidate, 81.5% [128/157]; one-sided 95% lower confidence limit = − 11.7%; p = 0.404). The overall study completion rate was high (87.9%), although the methylphenidate group had a significantly higher completion rate compared with atomoxetine group due to treatment-emergent adverse events.

A within-subject, double-blind, placebo-controlled, crossover design study compared two doses of Ritalin and Adderall in the treatment of ADHD in children and assessed the medications time courses (35). Twenty-one children participated in the study which was conducted during an 8-week Summer Treatment Program at the State University of New York at Buffalo. The children were all diagnosed with ADHD, according to the Diagnostic and Statistical Manual of Mental Disorders before participating. To examine the comparability of a single administration of Adderall with twice-daily methylphenidate, the study included a within-subject, placebo-controlled, daily crossover design of 0.3 mg/kg of MPH given twice-daily (7:30 am and 11:30am), 0.3 mg/kg of Adderall given once-daily (7:30am), and a single 7:30 am dose of 0.3 mg/kg of MPH— included as a condition for direct time course comparisons with Adderall given once in the morning. Both drugs were routinely superior to placebo and produced dramatic improvements in the rate of negative behavior, academic productivity, and staff/parent ratings of behavior. There were no differences between twice-daily MPH and once-daily Adderall on any measures taken during a typical school-day period (8:00 am to 3:30 pm). Time course results showed that a single 7:30am dose of 0.3 mg/kg of Adderall and 0.3 mg/kg of MPH twice-daily (7:30 and 11:30 am) had very similar time courses and seemed to be effective for an entire program day (until 4:45 pm) and perhaps longer.

Head-to-Head Comparison with second-line therapeutic strategies (non-stimulant drugs)

There are several second-line agents for treating ADHD. These include buspirone, venlafaxine, imipramine, desipramine, nortriptyline, guanfacine, pemoline and modafinil. A few comparative studies are available and included below.

In one meta-analysis, forty-eight trials were identified, of which 12 were used in a head-to-head double-blind randomized controlled trial on the efficacy of available treatments for attention deficit hyperactivity disorder (ADHD) in children and adolescents (36). The following drugs were included in the analyses: methylphenidate, (MPH); atomoxetine (ATX); bupropion; buspirone (BSP); dexamphetamine; edivoxetine (EDX); guanfacine (GXR); lisdexamfetamine (LDX); mixed amphetamine salts; modafinil; pindolol
A double-blind randomized clinical trial compared the efficacy of methylphenidate with buspirone in children with attention-deficit/hyperactivity disorder (ADHD) (37). A total of 34 children with ADHD as defined by SDM-IV-TR were randomized to buspirone or methylphenidate dosed on weight-adjusted basis at buspirone and methylphenidate for a 6-week double-blind clinical trial. The principal outcome measures were the teacher and parent ADHD rating scales (ADHD-RS). The subjects were assessed by a child and adolescent psychiatrist at baseline 2, 4 and 6 weeks after the medications started. No significant differences were observed between the two protocols on the total scores of parent and teacher ADHD Rating Scale \((t = -0.45, df = 32, p = 0.66)\), but methylphenidate was superior to buspirone in decreasing the symptoms of inattention \((F = 6.27, df = 1, p = 0.018)\).

A double-blind, randomized, parallel group comparison of Ginkgo biloba and methylphenidate was conducted for the treatment of ADHD. Fifty outpatients (39 boys and 11 girls) with a DSM-IV-TR diagnosis of ADHD were study population of this trial. Subjects were recruited from an outpatient child and adolescent clinic (38). All study subjects were randomly assigned to receive treatment using tablet of Ginko T.D. at a dose of 80-120mg/day on weight or methylphenidate at a dose of 20-30mg/day depending on weight. The principal measure of outcome was the Teacher and Parent ADHD Rating Scale-IV. Patients were assessed at baseline and at 21 and 42 days after the medication started. The changes at the endpoint compared to baseline were: -6.52+/-11.43 (mean+/-S.D.) and -15.92+/-11.44 (mean+/-S.D.) for Ginko T.D. and methylphenidate, respectively for Parent ADHD Rating Scale.

Significant differences were observed between the two groups showing that G. biloba is less effective than methylphenidate in the treatment of ADHD.

A 6-week, double-blind clinical trial evaluated the efficacy of the norepinephrine reuptake inhibitor reboxetine in comparison with methylphenidate in the treatment of children and adolescents with ADHD using Teacher and Parent ADHD Rating Scale (39). Thirty-three outpatient children and adolescents with ADHD participated in the study. Patients were randomized to receive reboxetine or methylphenidate in a 1:1 ratio using a computer-generated code. Reboxetine was started at a dose of 1mg twice a day and gradually (every 2 weeks) increased based on the therapeutic response and the tolerance observed in patients. The optimal dose of reboxetine was 6mg/day. Methylphenidate was started at a dose of 5mg twice a day and gradually (every 2 weeks) increased based on therapeutic response and the tolerance observed. The optimal dose of methylphenidate was 50mg/day. There was a 34% reduction of parent ADHD rating scale 4 weeks post treatment and 42% 6 weeks post treatment in Reboxetine group. A 36% reduction of Parent ADHD Rating Scale 4 weeks post treatment and 49% reduction 6 weeks post treatment in Methylphenidate group were observed. Mauchly’s Test revealed a significant difference between the two groups \((P < 0.05)\). Therefore, epsilon correction was used to interpret the results where the within subject effect was significant but interaction and between subject effect was not significant \((F = 0.001 \ df = 1, 12 P = 0.97\) observed power \(5\%\) partial \(\eta^2 = 0.00)\).

Forty subjects, aged 6-15 years who were diagnosed as having ADHD, were randomly assigned to receive either selegiline or MPH for 60 days (40). The design was a double-blind, randomized clinical trial. All participants were randomly assigned by a pharmacist to either a 5mg/bid MPH or a 2.5mg/bid selegiline starting treatment; the doses were titrated to the highest dose level. The average daily doses of selegiline and MPH were 7.6 and 25.5mg, respectively. Treatment outcomes were assessed using the Attention Deficit Hyperactivity Scale (ADHS) administered at baseline and on days 14, 28, 42 and 60. Both groups showed a significant improvement over the 60 days of treatment results from the teachers and parent’s ADHS scores across treatment. Using the Friedman tests showed a significant improvement of treatments by MPH, as
reported by teachers (p=0.003), parents (p<0.001), and by selegiline, as again reported by teachers (p<0.001) and parents (p<0.001). MPH did not result in greater mean improvement compared to selegiline.

A prospective double-blind placebo-controlled study compared pindolol and methylphenidate in the treatment of children with ADHD (41). Fifty-two ADHD children, 7-13 years old participated. The outcome was assessed on the basis of the Abbreviated Connors Rating Scales (ACRS) completed by parents, teachers, and by a psychologist during psychological testing. Pindolol proved to be just as effective as MPH in decreasing hyperactivity and conduct problems at home, and hyperactivity problems at school. Pindolol, however, had less therapeutics effects than MPH during psychological testing and failed to affect conduct problems in school.

An eight-week double-blind comparison between pemoline, methylphenidate and placebo was carried out on 60 hyperactive children (42). Patients for the study were randomly assigned to one of three treatment regimens: pemoline, methylphenidate or placebo. The basic drug trial was eight weeks in duration. After the nine-week period, patients were withdrawn from all medications for two weeks, with a final clinical rating made at the end of ten weeks. The final mean dosages of the two active medications used in the study were 2.25mg/kg/day for pemoline and 0.82mg/kg/day for methylphenidate. Outcomes were assessed by a variety of tests including: Parent and Teacher Connor’s Tests; Abbreviated Parent and Teacher Questionnaires; Psychological tests such as Wechsler’s Intelligence Scale for Children, Porteus maze test, Wide Range Achievement test, Golman-Fristoe-Woodcock Test for Auditory and others. Measurements of home, school, achievement, cognitive function, and global clinical status were made at baseline, mid-treatment, end of treatment, and posttreatment. Both drugs produced improvement in all areas except the achievement measures. One major difference between drugs was the apparently longer action of pemoline, since its effects at home and school tended to persist when the drug was withdrawn, whereas the patients receiving methylphenidate tended to regress to their baseline levels.

A double-blind outpatient study comparing imipramine hydrochloride, methylphenidate hydrochloride and placebo treatments of 76 hyperactive grade-school boys utilized several tests including the Connors rating scale (43). Medication was coded and administered in a double-blind fashion, utilizing a non-crossover design. Patients were started on one morning and one evening capsule and dosage was increased individually, according to clinical improvement or appearance of side effects. The maximum dose was 30mg methylphenidate or 150mg imipramine. Physicians global ratings of improvement were made after three and six weeks of treatment. Although global judgements of psychiatrists, psychologists, and pediatrician indicated the superiority of both drugs to placebo, all measures favored the stimulant drug, methylphenidate.

**ADHD & TIC DISORDER**

A Cochrane review included eight randomized controlled trials (n=510) to assess the effects of pharmacological treatments for ADHD in children with comorbid tic disorder symptoms (44). Two reviewers independently selected studies, extracted data using standardized forms, assessed risk of bias and graded the overall quality of the evidence by using the GRADE approach. Risk of bias of included studies was low for blinding; low or unclear for random sequence generation, allocation concealment, and attrition bias; and low or high for selective outcome reporting. Medications assessed included methylphenidate, clonidine, desipramine, dextroamphetamine, guanfacine, atomoxetine, and deprenyl. ADHD and tic symptom severity were measured by validated clinician, teacher or parent report scales. Specifically, ADHD symptom were evaluated by Conners Abbreviated Symptom Questionnaire for Parents & Teachers or ADHD Rating Scale, tic severity was assessed with the Yale Global Tic Severity Scale or Tourette Syndrome Severity Scale. All studies, with the exception of a study using deprenyl, reported improvement in symptoms of ADHD. Tic symptoms also improved in children treated with guanfacine, desipramine, methylphenidate, clonidine and a combination of methylphenidate and clonidine.
**ADHD & MENTAL RETARDATION**

In a 4-week, single-blind, parallel-group trial, 45 subjects with moderate mental retardation and ADHD were randomized to risperidone or methylphenidate and assessed using objective rating scales for efficacy (SNAP [Swanson, Nolan, and Pelham]-IV and Nisonger Child Behavior Rating Form) (45). Subjects enrolled in the study were between the ages of 6 and 16. The study was a 28 day randomized single-blind, parallel-group clinical trial. Subjects were randomly assigned to either risperidone or MPH for 4 weeks. An individualized flexible titration procedure was used to adjust the dose for optimal efficacy and tolerability. Risperidone was titrated to a maximum tolerable dose with a minimum target dose of 0.5 mg/day at the beginning of the trial. The overall upper dose limit was 4 mg/day. MPH was titrated to a maximum daily dose of 0.7 mg/kg/day at the end of the trial administered twice daily (8 A.M. and noon). At the end of any of the 4 weeks, the principal investigator could increase the dose of either medicine, depending on efficacy and tolerability. Compliance was checked by returning the blister packs used each week, when pills were counted. Both groups had reduced ADHD symptoms during trial, but findings suggested that risperidone is associated with greater reductions in ADHD total score \( (F = 3.26; p = .05) \) than methylphenidate in children with moderate mental retardation and ADHD. Comorbidity and side effects profile might be of importance in choosing between medications, although it is usually prudent to try stimulants before antipsychotics in such children.

**ADHD & AUTISM SPECTRUM DISORDER**

A Cochrane systematic review investigated the effects of methylphenidate for symptoms of ADHD and autistic spectrum disorder (ASD) in children and adolescents aged 6 to 18 years (46). Four cross-over randomized clinical trials were included with a total of 113 children. The primary outcome was clinical efficacy, defined as an improvement in ADHD-like symptoms (inattention, impulsivity and hyperactivity) and in the core symptoms of ASD (impaired social interaction, impaired communication, and stereotypical behaviors) and overall ASD. The meta-analysis suggested that high-dose methylphenidate had a significant and clinically relevant benefit on hyperactivity as rated by teachers (SMD −0.78, 95% confidence interval (CI) −1.13 to −0.43; 4 studies, 73 participants; \( P < 0.001; \) low-quality evidence) and parents (mean difference (MD) −6.61 points, 95% CI −12.19 to −1.03, rated on the hyperactivity subscale of the Aberrant Behavior Checklist, range 0 to 48; 2 studies, 71 participants; \( P = 0.02; \) low-quality evidence) and a significant but not clinically relevant benefit on teacher-rated inattention (MD −2.72 points, 95% CI −5.37 to −0.06, rated on the inattention subscale of the Swanson, Nolan and Pelham, Fourth Version questionnaire, range 0 to 27; 2 studies, 51 participants; \( P = 0.04; \) low-quality evidence). There was no evidence that methylphenidate worsens the core symptoms of ASD or benefits social interaction (SMD −0.51, 95% CI −1.07 to 0.05; 3 studies, 63 participants; \( P = 0.07; \) very low-quality evidence), stereotypical behaviors (SMD −0.34, 95% CI −0.84 to 0.17; 3 studies, 69 participants; \( P = 0.19; \) low-quality evidence), or overall ASD (SMD −0.53, 95% CI −1.26 to 0.19; 2 studies, 36 participants; \( P = 0.15; \) low-quality evidence), as rated by teachers.

**ADHD & OPPOSITIONAL DEFIENT DISORDER AND AGGRESSION**

In an open-label comparative study, children with DSM-IV-TR ADHD, aged 8-18 years with (n=30) and without (n=30) oppositional defiant disorder (ODD) received MPH treatment for 12 weeks (47). The severity of ODD symptoms was assessed by the Kiddie-Schedule for Affective Disorders and Schizophrenia. The severity of ADHD symptoms was assessed by the ADHD-Rating Scale-IV and suspiciousness was assessed at baseline and at endpoint by a scale designed especially for assessment of suspiciousness and named Suspiciousness Rating Scale (SRS). Significant reductions in SRS scores were detected in both groups following MPH treatment (before and after: \( p = .0012 \) and \( p = .0273 \), respectively).
Only in the ADHD/ODD group a significant correlation was found between the rate of improvement in ADHD, as assessed by the ADHD-RS, and the reduction in suspiciousness, as assessed by the SRS (Spearman r = 0.48, p = .0066). In addition to the beneficial effect of MPH treatment on ADHD and ODD symptoms it also diminishes suspiciousness.

Another study aimed to assess the effectiveness of monotherapy with stimulant MPH and risperidone in a consecutive sample of 40 drug-naïve male youths diagnosed as having ADHD-combined presentation, comorbid with ODD and aggression, without psychiatric comorbidities (48). Twenty males treated with MPH (mean age, 8.95 ± 1.67 years) and 20 males treated with risperidone (mean age, 9.35 ± 2.72 years) followed up to 6 months, were assessed according to efficacy measures, Child Behavior Checklist (CBCL), Clinical Global Impression-Severity (CGI-S) and Improvement (CGI-I) and Children Global Assessment Scale. At the end of follow-up, both medications were similarly effective based on subscales of aggression and rule-breaking behaviors, but only MPH was effective on attention problems (8.44 ± 2.55 (P < 0.001)) and attention-deficit/hyperactivity problems (7.83 ± 2.36 (P < 0.001)).

**Adults**

**ATTENTION-DEFICIT HYPERACTIVITY DISORDER**

*Comparison with placebo/control:*

A randomized, 7-week, placebo-controlled, crossover study of methylphenidate using 25 outpatient adults of both sexes with ADHD, between the ages of 18 and 60 (49). There were two 3-week treatment periods with 1 week of washout between to avoid carryover effect of medication. The order of treatment was randomized. To assess change during treatment, three main domains of symptoms were examined; ADHD, depression and anxiety. Overall severity in each of the domains was assessed with the Clinical Global Impressions Scale (CGI). The results found a marked therapeutic response for methylphenidate treatment of ADHD symptoms that exceeded the placebo response (78% vs 4%, P<.0001). Response to methylphenidate was independent of gender, psychiatric comorbidity with anxiety or moderate depression, or family history of psychiatric disorders.

*Meta-analytic Comparison of methylphenidate with stimulant and non-stimulant medications:*

A meta-analysis aimed to evaluate the efficacy, acceptability, and tolerability of lisdexamfetamine (LDX), mixed amphetamine salts (MASs), modafinil (MDF) and methylphenidate (MPH) in comparison with placebo on adults diagnosed with ADHD (50). Published reports were the sole source for data extraction. Improvement in ADHD symptoms were the primary outcome, where investigator rating scales were the preferred method of symptoms assessment. Random-effects model meta-analysis was applied to calculate the standardized mean differences (SMD) with 95% CIs. Two reviewers independently assessed the risk of bias utilizing the Cochrane Collaborations tool criteria, differences were resolved through consensus. The search retrieved 701 records, of which 20 randomized, double-blind, placebo-controlled, parallel-group clinical trials were eligible and included. The findings showed a high effect size in reducing ADHD symptoms for LDX (-0.89; 95% CL = -.109, -0.70), whereas MASs (-0.64; 95% CI = -0.83, -0.45) and MPH (-0.50; 95%CI = -0.58, -0.41) reduced symptoms moderately compared with placebo.

A systematic review assessed the comparative benefits and harms of competing medications for adult ADHD using indirect comparison meta-analysis. Eligible studies were randomized controlled trials comparing ADHD drugs to placebo, of which twenty-two trials (n=2,203) were included (51). Two reviewers independently assessed full-text articles of potentially relevant abstracts, and a second review for
inclusion was conducted by reapplying the inclusion criteria. All disagreements were resolved through consensus. Internal validity (quality) of trials was assessed using predefined criteria based on US Preventative Services Task Force and the National Health Service Centre for Reviews and Dissemination (UK) criteria. Efficacy outcomes were incidence of clinical response and change from baseline in ADHD symptom scores. The ADHD Rating Scale (ADHD-RS) was most commonly used to measure symptoms, and clinical response was most commonly defined as the proportion of patients with a 30% or greater improvement in ADHD-RS total score. According to drug type, we grouped trials into four categories including atomoxetine, longer-acting forms of bupropion, shorter-acting stimulants, and longer-acting stimulants. For all outcomes, the investigators combined data from placebo-controlled trials for each drug type to calculate pooled relative risks (RR) with 95% confidence intervals. As a way to test the sensitivity of our inferences to variation in statistical method, we also calculated risk differences (RD) for all outcomes. Overall the outcome of clinical response was more likely for all drug treatment groups compared to placebo. Indirect comparison of the estimated RRs showed significant differences among drug types ($\chi^2 = 24.15; p = 0.0001$), with shorter-acting stimulants favored over longer-acting forms of bupropion ($p = 0.008$) and longer-acting stimulants ($p < 0.001$) for the outcome of clinical response. The relative benefit of clinical response for shorter-acting stimulants, primarily immediate release methylphenidate was 3.26 times greater than for patients taking longer-acting stimulants and 2.24 times greater than for patients taking longer-acting forms of bupropion.

Impairments of error monitoring are common in many psychiatric disorders including schizophrenia, attention deficit hyperactivity, obsessive compulsive disorder and substance abuse (52). A randomized, double-blinded, placebo-controlled, crossover design using methylphenidate, atomoxetine and citalopram in comparison to placebo was employed. Forty individuals (mean age =24.3 years, SD=5.6years) participated in the study. Each participant attended four sessions, each at the same time of day, spaced at least 1 week apart. At each session, a single blue gelatin capsule containing methylphenidate, atomoxetine, citalopram, or placebo was administered. Cognitive testing began 90min following drug administration to allow peak plasma concentrations of drug. Participants underwent EEG recording while performing a standard Eriksen flanker task. A flanker test was used because of its reliability in eliciting errors and its extensive use in previous research that has characterized the error-related negativity (ERN) and the error positivity (Pe). Accuracy and reaction time measures were obtained, and congruent and incongruent stimulus conditions were compared. Repeated measures ANOVA’s with factors of drug (methylphenidate, atomoxetine, citalopram, placebo) and congruency (congruent, incongruent) were performed. Pos hoc analyses were Bonferroni-corrected. Only methylphenidate produced significant improvement in performance accuracy ($p=0.001$ compared to placebo), which was without concomitant slowing of reaction time.

**ADHD & ALZHEIMERS DISEASE**

A Cochrane review included 21 double-blind, randomized, placebo-controlled trials investigating the efficacy of pharmacotherapies including methylphenidate for the treatment of apathy in Alzheimer’s patients (53). Three review authors extracted data; risk of bias is very low to moderate; all studies reported appropriate methods of randomization and blinding; most studies reported appropriate methods of allocation concealment. In three studies, methylphenidate was shown to improve apathy compared to placebo. This finding was present when apathy was assessed using the apathy evaluation scale (AES) which was used by all three studies investigating methylphenidate MD -4.99, 95% CI -9.55 to -0.43, n = 145, 3 studies, low quality of evidence, but not when assessed with the neuropsychiatric inventory (NPI)-apathy subscale, which was used by two of the three studies investigating methylphenidate: MD -0.08, 95% CI -3.85 to 3.69, n = 85, 2 studies, low quality of evidence. As well as having potential benefits for apathy, methylphenidate probably also slight improves cognition (MD 1.98, 95% CI 1.06 to 2.91, n = 145, 3 studies,
moderate quality of evidence), and probably improves instrumental activities of daily living (MD 2.30, 95% CI 0.74 to 3.86, P = 0.004, n = 60, 1 study, moderate quality of evidence) compared to placebo.

10.3 Summary of Available Estimates of Comparative Effectiveness of Methylphenidate

In the treatment of attention deficit hyperactivity disorder, methylphenidate has shown similar efficacy to amphetamine-based drugs with varying results on different psychometric scales. Some individual studies have demonstrated superiority of MPH over AMF, some have found superiority of AMF over MPH, and others have shown no difference between the two types of medications. Given the currently available evidence, it has not been demonstrated that one stimulant is more efficacious than any other at a population level. It should be noted, however, that the frequency and severity of adverse events maybe somewhat greater with AMF than with MPH products and will be highlighted in the section below.

In comparison of methylphenidate with non-stimulant medications for treatment of attention deficit hyperactivity disorder, all non-stimulant medications appear to have a lower efficacy though some studies show equivalent efficacy with atomoxetine.

Methylphenidate is effective in reducing fatigue in palliative care patients when compared to placebo. There is also evidence of methylphenidate being effective in reducing symptoms in patients with ADHD comorbid with Oppositional Defiant Disorder and Aggression.
11. Summary of Comparative Evidence on Safety of Methylphenidate

11.1 Identification of Clinical Evidence of Regarding Methylphenidate

A systematic review was conducted using PubMed and Cochrane databases (last search, Dec 5, 2018). These catalogues were searched for articles using keywords “methylphenidate” and “comparison” for PubMed and “methylphenidate” only for the Cochrane database search. There were no specifications on language.

A total of 423 abstracts in PubMed and 21 reviews in Cochrane databases were identified initially. Among these, 74 were relevant to comparative evidence on safety for methylphenidate. Of the 74 relevant articles, 34 were excluded due to poor study design, small sample size, type of article (e.g. letter to editor), and/or incomplete or non-available data. Of the 40 remaining, 12 studies focused on indications of methylphenidate (extended-release, osmotically released etc.) not being proposed for inclusion and therefore excluded. As a result, 28 studies and review articles were included in this summary.

Estimate of Total Patient Exposure to Date

Methylphenidate was first approved by the United States Food and Drug Administration in 1955 (1). There is no available data estimating the total patient exposure of methylphenidate worldwide to date. In the United States, methylphenidate continues to be one of the most commonly prescribed stimulant medications. In 2015, there were 14.52 million US prescriptions for methylphenidate (54).

Common Adverse Effects (2)

Common side effects include erythema, weight loss, decrease in appetite, loss in appetite, nausea, vomiting, headache, insomnia, mild labile mood, nasal congestion, and nasopharyngitis.

Serious side effects include contact dermatitis, decreased body growth, lowered convulsive threshold, tic, mania, psychotic disorder and drug dependence.

11.2 Summary of Available Data on Methylphenidate

Children and Adolescents

Attention Deficit Hyperactivity Disorder

Comparison with placebo or controls

In a Cochrane review comparing methylphenidate versus placebo, 38 parallel-group trials and 147 cross-over trials were included to assess the beneficial and harmful effects in for children and adolescents with ADHD (26). All studies included were randomized controlled trials. Seventeen review authors participated in data extraction and risk of bias assessment, and two review authors independently performed all tasks. The duration of methylphenidate treatment ranged from 1 to 425 days, with an average duration of 75 days.
Among those prescribed methylphenidate, 526 per 1000 (range 448 to 615) experienced non-serious adverse events, compared with 408 per 1000 in the control group. This equates to a 29% increase in the overall risk of any non-serious adverse events (RR 1.29, 95% CI 1.10 to 1.51; 21 trials, 3132 participants; very low-quality evidence). The Trial Sequential Analysis-adjusted intervention effect was RR 1.29 (CI 1.06 to 1.56). The most common non-serious adverse events were sleep problems and decreased appetite. Children in the methylphenidate group were at 60% greater risk for trouble sleeping/sleep problems (RR 1.60, 95% CI 1.15 to 2.23; 13 trials, 2416 participants), and 266% greater risk for decreased appetite (RR 3.66, 95% CI 2.56 to 5.23; 16 trials, 2962 participants) than children in the control group.

**Comparison of methylphenidate with stimulant and non-stimulant medications:**

An analysis of multiple publications was undertaken to assess the comparable efficacy and tolerability of six interventions in young patients (6–18 years old) suffering from attention deficit hyperactivity disorder (ADHD) (31). Overall, 15,025 participants from 73 studies were involved in an analysis assessing comparable efficacy and tolerability of six interventions: lisdexamfetamine dimesylate (LDX), atomoxetine (ATX), methylphenidate (MPH), clonidine hydrochloride (CLON) guanfacine extended release (GXR), and bupropion. The articles included consisted of randomized controlled trials with a minimum of 3-week duration. The outcome measures for safety were all cause withdrawals, withdrawal due to an adverse event, withdrawal due to lack of efficacy, nausea, abdominal pain or fatigue. In comparison to placebo, there was less occurrence for all-cause withdrawal by LDX and MPH, with MPH having the least withdrawal due to adverse events (1.31 (0.70, 2.25). LDX is an effective medication, but its level of toxicity is generally attracted additional attention because it frequently results in adverse events. Results suggested that MPH is a highly recommended candidate, especially with regards to fatigue and the rate of withdrawal, which makes MPH the routine therapy clinically. LDX is used for patients with ADHD who have an inadequate response to MPH.

In a head-to-head double blind randomized-controlled trial, forty-eight trials were identified (n=4169 participants), of which 12 were used for efficacy analysis and 33 for safety analysis of patients (aged 0-18 years) with ADHD (36). These 33 articles (n=3493) were evaluated for at least one safety outcome reporting data on: any adverse event, sleep disturbance, decreased appetite or behavior events (e.g. irritability, crying, anxiety, nervousness, aggression and restlessness). A network of comparisons was built for each outcome of interest. For the outcome of any adverse event, MPH was ranked 6 out of 8, where ranking 1 is the worst therapy (more likely to lead to the onset of the adverse event), suggesting MPH was considered one of the safest medications among those compared (BUP bupropion, GXR guanfacine, MAS mixed amphetamine salts, LDX lisdexamfetamine, ATX atomoxetine, EDX edivoxetine, RBX reboxetine, BSP buspirone, DEX dexamphetamine, MOD modafinil, MPH methylphenidate, PDL pindolol, SLG selegiline, and VEN venlafaxine). According to drug rankings LDX was ranked worst all three analyses: sleep disorders (39% chance of being the worst option) as well as loss of appetite (65%) and behavior problems such as irritability (60%). BSP and VEN were the best options against sleep disorders, being ranked with 62, 31% of chances, respectively. For behavioral effects, PDL was considered safest (50%). BUP was more likely to cause any adverse event (54%), while RBX (89%) followed by EDX (39%) were considered safer options for this outcome. All networks for safety outcomes were subjected to analysis by the node splitting method. All analyses revealed p values superior to 0.05, ensuring the robustness of the networks.

A systematic literature review was conducted to identify randomized controlled trials (RCTs) of pharmacological monotherapies among children and adolescents (6-17years) with ADHD (55). Thirty-six RCTs were included in the study. Safety outcomes considered were all-cause discontinuation and discontinuation due to adverse events (AEs). The feasibility of forming a connected network for each outcome was assessed based on data availability in the systematic literature review results. Different outcomes were not combined in any way in the analyses. The quality of studies was assessed according to
ADHD medication may be associated with cardiovascular effects. To evaluate potential cardiovascular effects of ADHD medication, a systematic review and meta-analysis was conducted for methylphenidate MPH, amphetamines AMP, and atomoxetine ATX on diastolic and systolic blood pressure (DBP, SBP) and heart rate (HR) in children and adolescents with ADHD (56). Eighteen clinical trials (n=5837) were included. Studies with an open-label design or a double-blind randomized control design of any duration were included. Statistical analysis involved calculating differences between pre- and post-treatment measurements for the various cardiovascular parameters divided by the pooled standard deviation. All three medications were associated with a small, but statistically significant pre-post increase of SBP (MPH: standard mean difference [SMD] 0.25, 95% confidence interval [CI] 0.08-0.42, p < 0.01; AMP: SMD 0.09, 95% CI 0.03-0.15, p < 0.01; ATX: SMD 0.16, 95% CI 0.04-0.27, p = 0.01). MPH did not have a pre-post effect on DBP and HR. AMP treatment was associated with a small but statistically significant pre-post increase of DBP (SMD 0.16, CI 0.03-0.29, p = 0.02), as was ATX treatment (SMD 0.22, CI 0.10-0.34, p < 0.01). AMP and ATX were associated with a small to medium statistically significant pre-post increase of HR (AMP: SMD 0.37, CI 0.13-0.60, p < 0.01; ATX: SMD 0.43, CI 0.26-0.60, p < 0.01). Statistically significant pre-post increases of SBP, DBP and HR were associated with AMP and ATX treatment in children and adolescents with ADHD, while MPH treatment had a statistically significant effect only on SBP in these patients.

Data collected from 62 studies (n=12,930) were used in a meta-analysis analyzing drugs widely used for ADHD treatment (ATX, BUP, CLON, GXR, LDX, and MPH) (32). Two independent reviewers screened articles separately, any disagreements were openly discussed until a consensus was reached. Certain/specific criteria were included in the search terms: firstly, the patients in studies should be accurately diagnosed with ADHD; secondly, studies were conducted based on children and adolescents (4–17 years old); thirdly, studies had to be randomized, controlled clinical trials (RCTs); finally, active medications had to be involved, which compared the drugs used in combination or singly, or with placebo (PBO). An output of validated and sufficient data was also needed for credible evaluation. Withdrawals due to all-cause, adverse effects and lack of efficacy were defined as primary outcomes evaluating the safety of such medications. When it came to evaluation of safety, MPH could be considered as the drug with the least adverse effect (20.00 % in cumulative ranking probabilities). Analyzing the results of patients’ withdrawals due to lack of efficacy, it was observed that LDX had the highest ranking among the drugs (91.50 % for cumulative ranking probabilities) combining LDX being confirmed as the drug with the highest efficacy.

Double-blind crossover comparison of methylphenidate hydrochloride, dextroamphetamine sulfate, and caffeine after placebo washout in 29 children with minimal brain dysfunction (term in early 1960s to describe what is today Attention Deficit Hyperactivity Disorder) showed significant weight loss (P<.05) and cardiovascular side effects for all three drugs (29). The three drugs were compared in a randomized
Latin-square crossover following placebo washout. Each of the drug conditions lasted three weeks with a minimum of three telephone consultations for adjustment of dosage. At each of the visits, including the pre-drug assessment, the following information was collected: a parent’s symptom checklist reported and factor-analyzed by Arnold and Smeltzer; a Conner’s Teacher’s Behavior Problem Checklist; a David’s Hyperkinetic Rating Scale completed by the parents; a David’s Hyperkinetic Rating Scale completed by the teacher; and a target symptom assessment in the manner described by Arnold and associates.

**Comparison with other first-line therapeutic strategies**

A double-blind study was conducted in 6-to-16-year-old outpatients with ADHD in China, Korea and Mexico (34). The study examined whether atomoxetine is non-inferior to methylphenidate in treating symptoms of ADHD in pediatric patients and to determine the tolerability of the two drugs. Patients were randomly assigned to once-daily atomoxetine (0.8-1.8 mg kg(-1) day(-1); n = 164) or twice-daily methylphenidate (0.2-0.6 mg kg(-1) day(-1); n = 166) for approximately 8 weeks. Tolerability measures included, but were not limited to, the assessment of treatment-emergent adverse events (TEAEs) and weight. Treatment-emergent adverse effects experienced significantly more frequently in the atomoxetine group, compared with the methylphenidate group, included anorexia (37.2% vs. 25.3%; p = 0.024), nausea (20.1% vs. 10.2%; p = 0.014), somnolence (26.2% vs. 3.6%; p <0.001), dizziness (15.2% vs. 7.2%; p = 0.024) and vomiting (11.6% vs. 3.6%; p = 0.007), most of which were of mild or moderate severity. Atomoxetine-treated patients experienced a small but significantly greater mean weight loss from baseline to end point than methylphenidate-treated patients (-1.2 kg vs. -0.4 kg; p <0.001).

**Comparison with second therapeutic strategies (non-stimulant drugs)**

A double-blind clinical trial randomized subjects to receive methylphenidate or buspirone over the course of 6 weeks (37). A total of 34 children with ADHD as defined by DSM-IV-TR were randomized to buspirone or methylphenidate dosed on weight-adjusted basis at buspirone (0.5 mg/kg/day) and methylphenidate (0.3-1 mg/kg/day). The side effects were assessed by the special side effect checklist of each drug. No serious drug effects were observed during the trial. The most common side effects in the buspirone group were tic and dizziness while in the MPH group, decreased appetite and sleep were the most common adverse effects. But there was no statistically significant difference between the two groups in the rate of any single adverse event.

A double-blind, randomized, parallel group comparison of Ginkgo biloba and methylphenidate was conducted for the treatment of ADHD (38). Fifty outpatients (39 boys and 11 girls) with a DSM-IV-TR diagnosis of ADHD were study population of this trial. Subjects were recruited from an outpatient child and adolescent clinic for a 6-week clinical trial. All study subjects were randomly assigned to receive treatment using tablet of Ginko T.D. at a dose of 80-120 mg/day depending on weight (80 mg/day for <30 kg and 120 mg/day for >30 kg) (group 1) or methylphenidate at a dose of 20-30 mg/day depending on weight (20 mg/day for <30 kg and 30 mg/day for >30 kg (group 2). Ten side effects were observed (abdominal pain, nervousness, decreased appetite, sadness, insomnia, weight loss, nausea, dry mouth, headaches and anxiety) over the trial that all of them were mild to moderate and tolerable. The difference between the Ginko T.D.™ and methylphenidate groups in the frequency of side effects was not significant except for decreased appetite, headache and insomnia that were observed more frequently in the methylphenidate group.

A 6-week, double-blind clinical trial evaluated the tolerability of reboxetine in comparison with methylphenidate in the treatment of children and adolescents with ADHD (39). Thirty-three children, 7-16 years of age, diagnosed with ADHD, participated in a 6-week, double-blind clinical trial with reboxetine
(4–6 mg/d) and methylphenidate (20–50 mg/d) in two divided doses. Side effects of drugs were assessed using the Side Effects Form for Children and Adolescents, New York State Psychiatric Institute. Side effects of the medications used in the two protocols was compared using Fisher’s exact test (two sided). Reboxetine was relatively well tolerated. Twelve out of seventeen (70.5%) participants completed the course of treatment within 6 weeks and nine (52.5%) did not suffer from any adverse effects. Two out of seventeen (11.76%) had intolerable immediate—onset adverse effects (severe drowsiness and pallor). The other three patients who discontinued the treatment did not report any side effects. In the Methylphenidate group twelve of sixteen (75%) participants accomplished the treatment and four (25%) discontinued the treatment after one or two weeks. Eight out of sixteen (50%) participants did not report any adverse effects. One patient complaining from severe anorexia and pallor discontinued the drug in the first week and another discontinued the medication after two weeks of treatment due to noncompliance related to lack of beneficial effects. In the two other dropouts of this group, no specific side effect was reported.

A prospective double-blind placebo-controlled study compared pindolol and methylphenidate in the treatment of children with ADHD (41). Fifty-two ADHD children, 7-13 years old participated. Active treatment was pindolol and MPH: pindolol 20 mg b.i.d. or MPH 10 mg b.i.d. for 4 weeks. Adverse effects were rated by the parents after 2 and 4 weeks of treatment on a checklist encompassing 20 possible side-effects of methylphenidate and beta-blockers. This checklist was modified from the Stimulant Drug Side Effects Rating Scale. Ratings included the presence of a symptom as well as a severity estimate (0 = no distress, 1 = mild distress, 2 = severe distress). Treatment-emergent adverse effects were further assessed systematically at end-point by the research psychiatrist. Pindolol treatment was associated with a higher incidence of paraesthesias and with more intense nightmares and hallucinations from MPH or placebo treatment. For all other adverse effects, the frequencies did not differ significantly across drug status. However, when the severity of the adverse effects was considered, pindolol side-effects caused significantly greater distress in the children and their parents. Methylphenidate did not exert a significant influence on heart rate (mean ± SD at baseline 72.6 ± 10.2 and at endpoint 75.6 ± 12.0) and blood pressure (mean ± SD in mm Hg, systolic blood pressure at baseline 104.2 ± 9.4, and at endpoint 108.1 ± 8.0, diastolic blood pressure at baseline 73.8 ± 5.4, and at endpoint 75.5 ± 6.0). Pindolol was associated with a slight decrease in heart rate (mean ± SD at baseline 72.2 ± 9.6 and at endpoint 66.6 ± 8.7, contrast to placebo, p< .05), but did not influence blood pressure (mean ± SD in mm Hg, systolic blood pressure at baseline 110.3 ± 8.4, and at endpoint 104.0 ± 6.9, diastolic blood pressure at baseline 74.7 ± 5.6, and at endpoint 69.5 ± 6.5). It should be noted that pindolol did not result in bradycardia (heart rate below 60) or a tension below 90/60 in any of the subjects treated.

Pertinent literature was reviewed on cardiovascular changes induced by psychostimulant medication treatment of hyperactive children (57). An assessment of 15 controlled studies using test doses of methylphenidate were examined. A major finding of this review showed that methylphenidate commonly causes a small dose-dependent increase in heart rate and a smaller increase in blood pressure in previously unmedicated hyperactive children. However, these effects become minimal to nonexistent within a matter of months as tolerance to this medication develops, a phenomenon noted following the prolonged use of a host of central nervous system stimulants. Among the three stimulant drugs used to treat hyperactivity in children, dextroamphetamine has the most potential to impair the cardiovascular system – as evidenced by studies of adult drug abusers. On the basis of long-term stimulant treatment of hyperactive children, methylphenidate has clearly the most reassuring data.
ADHD & OPPOSITIONAL DEFIANTR DISORDER AND AGGRESSION

In a study consisting of 40 drug-naïve male youth diagnosed as having ADHD comorbid with Oppositional Defiant Disorder ODD and aggression, twenty males were treated with MPH (mean age, 8.95 ± 1.67 years) and twenty males treated with risperidone (mean age, 9.35 ± 2.72 years) (48). All the 40 patients were drug naïve and were treated in monotherapy during the follow-up. The starting dose of MPH was 5 to 10mg, according to age and weight, with subsequent titrations of 5 to 10mg no more frequently than at 5-day intervals, with flexible titration, depending on age and weight, clinical outcome and occurrence of adverse effects, based on weekly monitoring visits during the first month, then monthly. The starting dose of risperidone was 0.25mg/d, with subsequent titration of 0.25mg no more frequently than at 2-day intervals, with flexible titration depending on weight, clinical outcome, and occurrence of adverse effects, based on monitoring visits. No patients discontinued treatment due to adverse effects. Health concerns for significant weight gain (3.60±2.24kg) and prolactin increase were associated with risperidone (increased from 8.80±6.83ng/mL to 19.88±10.20ng/mL). Regarding cardiovascular measures, data showed that in the MPH group the change of some measures (systolic blood pressure and QTc interval) were statistically significant, but clinically not relevant, because all values were within the reference range.

ADHD IN CANCER SURVIVORS

To investigate the effect of stimulant medication, methylphenidate, on growth patterns among survivors of childhood cancer, a case-matched comparison design study compared childhood cancer survivors in a 12-month open-label MPH trial with childhood cancer survivors not taking MPH (58). Study participants were treated for ALL or malignant BT with chemotherapy and/or CNS-directed radiation therapy, completed treatment at least 12 months prior to study enrollment with no evidence of recurrent disease, were between 6 and 18 years of age and were primary English speakers. Exclusion criteria included a premorbid ADHD diagnosis, uncontrolled seizures, uncorrected hypothyroidism, severe sensory loss, patient or family history of Tourette syndrome, glaucoma, substance abuse history or current use of psychotropic medication. Patients participated in a randomized, double-blind, placebo-controlled three-week home trial consisting of placebo (inert substance; bid), low-dose MPH (0.3 mg/kg; maximum dose, 10 mg bid), and moderate-dose MPH (0.6 mg/kg; maximum dose, 20 mg bid). Measures of body mass index (BMI), height, and weight were obtained at hospital visits and corrected for gender and age using Centers for Disease Control normative data. The findings showed that childhood cancer survivors taking MPH experience significant, though modest, deceleration of BMI and weight across the first year of MPH intervention (MPH group slope = -0.038, SE = 0.007, p < 0.001). The absence of height deceleration, and the presence of only modest BMI and weight deceleration, suggest that MPH is reasonably well tolerated by childhood cancer survivors with respect to growth. Such findings are encouraging in light of increasing evidence that MPH mitigates some of the cognitive late-effects of cancer treatments. Nevertheless, on a case-by-case basis, clinicians should balance the intended benefits of MPH with potential growth effects in this vulnerable population.

ADHD & TIC DISORDER

A Cochrane review included eight randomized controlled trials to assess the effects of pharmacological treatments for ADHD in children with comorbid tic disorder on symptoms of ADHD and tics (44). Standard methodological procedures of Cochrane were utilized, in that two review authors independently selected studies, extracted data using standardized forms, assessed risk of bias, and graded the overall quality of the evidence by using the GRADE approach. Risk of bias of included studies was low for blinding; low or unclear for random sequence generation, allocation concealment, and attrition bias; and low or high for selective outcome reporting. Meta-analysis was unable to performed due to important clinical heterogeneity and unit-of-analysis issues. Participants in these studies were children with both ADHD and a chronic tic disorder (n=500; 443 boys and 67 girls). Medications assessed included methylphenidate, clonidine, desipramine, dextroamphetamine, guanfacine, atomoxetine, and deprenyl. Safety was evaluated by adverse
effects including: cardiovascular effects such as changes in heart rate, blood pressure or electrocardiogram; and weight changes. There was appetite suppression or weight loss in association with methylphenidate, dextroamphetamine, atomoxetine, and desipramine. There was insomnia associated with methylphenidate and dextroamphetamine, and sedation associated with clonidine.

**ADHD & BIPOLAR DISORDER**

Retrospective studies have indicated a high prevalence of ADHD comorbidity among the bipolar disorder (BD) population (59). A nationwide cohort of patients (children and youth) newly diagnosed with ADHD (n=144,920) and age-and gender-matching controls (n=144,920) were found in Taiwan’s National Health Insurance database from January 2000 to December 2011. To determine the effect that the duration of methylphenidate and atomoxetine exposure had on BD, the difference in the risk of developing BD was compared among non-users, short-terms users (≤365 days), and long-term users (>365 days). In comparison to the control group, the ADHD group showed a significantly increased risk of developing BD and had a younger mean age at the time of first diagnosis. Compared to ADHD patients that had never taken methylphenidate, patients with long-term use of MPH were less likely to be diagnosed with BD. However, the duration of exposure to atomoxetine did not have a significant relationship to a BD diagnosis, suggesting that MPH has protective effects.

**ADHD & DEPRESSION**

An increasing amount of research has shown that ADHD and depression can often co-exist in a child. The goal of this study was to clarify the relationship between ADHD, its drug treatments, and subsequent diagnoses of depressive disorders (60). A group of patients (children and youths) newly diagnosed with ADHD (n=71,080) and age-and gender-matching controls (n=71,080) were chosen from Taiwan’s National Health Insurance database during the period of January 200 to December 2011. The ADHD patients showed a significantly increased probability of developing a depressive disorder when compared to the control group. ADHD patients who received longer MPH treatment were found to be at a lower risk for developing any depressive disorder (aOR, 0.91; 99% CI, 0.88–0.94), dysthymic disorder (aOR, 0.89; 99% CI, 0.85–0.94) or major depressive disorder (aOR, 0.82; 99% CI, 0.73–0.93). However, treatment duration with ATX was not significantly correlated with the probability of developing a depressive disorder. Regarding treatment with MPH, a longer MPH use demonstrates significant protective effects against developing a depressive disorder.

**ADHD & SUBSTANCE USE DISORDER**

A study examined whether age at initiation of stimulant treatment in children with ADHD is related to subsequent development of substance use disorders (61). The prospective longitudinal study of 176 methylphenidate-treated male children (ages 6 to 12) with ADHD but without conduct disorder were evaluated at mean ages 18 (94% retention) and 25 (85%), and 178 comparisons diagnosed by blinded clinicians. Cox proportional hazards model was used to assess the relationship between age of methylphenidate treatment initiation in childhood and later development of substance use disorder (SUD). Four survival analyses were conducted with the following non-mutually exclusive outcome measures: Any SUD, Alcohol SUD, Non-Alcohol SUD (cannabis, opiates, cocaine, etc.), and Stimulant SUD (cocaine, amphetamines, etc.). Since age at first exposure to methylphenidate treatment was not a random characteristic, we considered whether other factors might account for the development of substance use disorder. The following were included in the analyses: treatment exposure (dosage and duration); childhood IQ; socioeconomic status and parent psychopathology. Among the 176 treated participants, 80 (45%) fulfilled criteria for SUD at some time in their lives. Of those, 49 (28%) had an Alcohol SUD, 65 (37%) met criteria for a Non-Alcohol SUD, and 43 (24%) of those individuals in the latter category fulfilled criteria.
for Stimulant SUD. The findings indicate that early age of initiation of methylphenidate treatment in children with ADHD does not increase the risk for negative outcomes and may have beneficial long-term effects

**ADHD & MENTAL RETARDATION**

In a 4-week, single-blind, parallel-group trial, 45 subjects with moderate mental retardation and ADHD were randomized to risperidone or methylphenidate and assessed using objective rating scales for efficacy and side effects (45). Patients were between the ages of 6-16 and diagnosed with both moderate mental retardation and ADHD. An individualized flexible titration procedure was used to adjust the dose for optimal efficacy and tolerability. Risperidone was titrated to a maximum tolerable dose with a minimum target dose of 0.5 mg/day at the beginning of the trial. The overall upper dose limit was 4 mg/day. MPH was titrated to a maximum daily dose of 0.7 mg/kg/day at the end of the trial administered twice daily (8 A.M. and noon). At the end of any of the 4 weeks, the principal investigator could increase the dose of either medicine, depending on efficacy and tolerability. Compliance was checked by returning the blister packs used each week, when pills were counted. Parents were interviewed weekly for side effects of MPH using the Barkley's Side Effects Rating Scale (SERS). To assess side effects related to risperidone, a scale created to assess side effects of antipsychotics, the Udvalg for Kliniske Undersøgelser (UKU), was also completed by parents weekly. In the MPH group, no significant difference was detected between baseline and end point scores in the SERS total scores ($t = −0.24, df = 23, p = .82$), the SERS-N ($z = −0.43, p = .67$), and the SERS-S ($z = −0.97, p = .33$). Because previous investigations have demonstrated that decreased appetite and insomnia are the two main side effects when using MPH we also assessed the effect of MPH on these side effects. A significant increase in the scores of insomnia ($z = −2.75, p < .01$) and loss of appetite ($z = −2.62, p < .01$) were detected between baseline and end point assessments. Although no significant difference was detected between baseline and end point scores on any UKU subscale scores in the risperidone group ($p > .05$), a trend for an increase in neurological effects (extrapyramidal effects) was detected during the trial ($z = −1.91, p = .06$). We also specifically assessed somnolence because it is one of the most frequent symptoms associated with risperidone in clinical trials A significant increase in somnolence ($z = −3.64, p < .001$) was detected between baseline and end point assessments. Although a mean weight reduction of 0.53 kg was detected in the MPH group, a significant increase was found in the risperidone group (mean weight increase = 1.01 kg). Comorbidity and side effects profile might be of importance in choosing between medications, although it is usually prudent to try stimulants before antipsychotics in such children.

**Adults**

**ATTENTION DEFICIT HYPERACTIVITY DISORDER**

**Comparison with placebo or controls**

In a Cochrane review investigating adverse events associated with methylphenidate, a total of 260 studies were included: 7 comparative cohort studies, 6 of which compared 968 patients who were exposed to methylphenidate to 166 controls, and 1 which assessed 1224 patients that were exposed or not exposed to methylphenidate during different time periods; 4 patient-control studies (53,192 exposed to methylphenidate and 19,906 controls); 177 non-comparative cohort studies (2,207,751 participants); 2 cross-sectional studies (96 participants) and 70 patient reports/series (206 participants) (62). Participants' ages ranged from 3 years to 20 years. Risk of bias in the included comparative studies ranged from moderate to critical, with most studies showing critical risk of bias. We evaluated all non-comparative studies at
critical risk of bias. The GRADE quality rating of the evidence was very low. In the comparative studies, methylphenidate increased the risk ratio of serious adverse events (RR 1.36, 95% confidence interval (CI) 1.17 to 1.57; 2 studies, 72,005 participants); any psychotic disorder (RR 1.36, 95% CI 1.17 to 1.57; 1 study, 71,771 participants) and arrhythmia (RR 1.61, 95% CI 1.48 to 1.74; 1 study, 1224 participants) compared to no intervention. In the comparative studies, methylphenidate, compared to no intervention, increased the RR of insomnia and sleep problems (RR 2.58, 95% CI 1.24 to 5.34; 3 studies, 425 participants) and decreased appetite (RR 15.06, 95% CI 2.12 to 106.83; 1 study, 335 participants). The certainty in the evidence is very low, and accordingly, it is not possible to accurately estimate the actual risk of adverse events.

A cohort analysis compared the prevalence proportion of malformations in pregnancies exposed to methylphenidate (n=222) in the first trimester to a propensity score-matched cohort of pregnancies during which the mother had never used psychostimulants (n=2,220) (63). Exposure was defined as having redeemed 1 or more prescriptions for methylphenidate within a time window defined as 14 days before the beginning of the first trimester up to the end of the first trimester. Each exposed subject was propensity score-matched to 10 unexposed subjects with respect to maternal age, smoking status, body mass index, length of education, calendar year of completion of pregnancy, and concomitant use of antipsychotics, antidepressants, anxiolytics, and nonsteroidal anti-inflammatory drugs. There was no statistically significant increase in major malformations (point prevalence ratio = 0.8; 95% CI 0.3-1.8) or cardiac malformations (point prevalence ratio = 0.9; 95% CI, 0.2-3.0). Sensitivity analyses using different definitions of exposure or previous users of methylphenidate as the unexposed comparison cohort yielded comparable results. First-trimester in utero exposure to methylphenidate does not appear to be associated with a substantially (ie, more than 2-fold) increased overall risk of major congenital malformations.

A two-group comparison and open-label therapy study was used to assess objective and subjective sleep parameters in adults with ADHD and the impact of stimulant medication on sleep (64). Thirty-four nonmedicated patients with ADHD were enrolled, of whom 24 were without current comorbid psychiatric disorders, and 34 sex- and gender-matched control subjects without current psychiatric disorders or psychotropic medication. Ten patients were treated with methylphenidate over ≥26 days with a mean daily dose of 36.7 ± 11.2 mg. Polysomnographic recording over 2 consecutive nights as well as assessments of subjective sleep parameters were performed in all patients and controls before treatment and reassessed in those patients receiving MPH. To determine subjective sleep parameters, the study administered the self-rated questionnaires Schlaffragebogen A and B, which are well-validated instruments widely used in Germany for scientific and clinical purposes. Compared to the control group, all subjects in our ADHD sample (n = 34) displayed reduced sleep efficiency, with longer sleep onset latency and more nocturnal awakenings; they had altered sleep architecture, with a higher percentage of stage 1 and reduced percentage of REM sleep. Patients also showed a trend toward a reduced total REM density and elevated percentage of wakefulness after sleep onset. When treated with methylphenidate patients showed a significant reduction in sleep onset latency and improved sleep efficiency. All other sleep parameters remained unchanged. Under treatment with methylphenidate patients reported improved evening mood, less psychosomatic symptoms while falling asleep, reduced sleep latency, and fewer nocturnal awakenings during the night spent in our sleeping laboratory (SF-A), though statistically significant only at the trend. Overall, the study found that sleep problems in patients with ADHD continue from childhood to adulthood, with similar objective sleep characteristics in adults and children with ADHD. Medication with methylphenidate appears to have beneficial effects on sleep parameters in adults with ADHD.

A double-blind, placebo-controlled, cross-over medication trial investigated the parameters of sleep, activity, and circadian rhythm, as well as the effects of methylphenidate on these variables, in adults with ADHD (65). Thirty-nine normal controls and 31 adults with ADHD were included in the study. Actigraphy and sleep log data were collected for 7 consecutive nights and days to obtain baseline values for ADHD and normal controls. Repeated measurements during placebo and methylphenidate treatment were
conducted for the ADHD group. The data suggests that sleep problems are inherent in adults with ADHD and that methylphenidate reduced total sleep time but improved sleep quality by consolidating sleep as the mean duration of within-night periods of uninterrupted sleep increased.

**Comparison with other first-line therapeutic strategies**

A meta-analysis was performed on studies that examined the relationships between methylphenidate or atomoxetine and heart rate (HR), systolic blood pressure (SBP), as well as a number of adverse cardiac events (66). These studies were either placebo-controlled or comparison studies between methylphenidate and atomoxetine. Meta-analysis was performed on studies that examined the relationships between methylphenidate or atomoxetine and HR, SBP, as well as a number of adverse cardiac events. Twenty-two studies were included and the total number of participants was 46,107. Children/adolescents and adults treated with methylphenidate had more significant increases in post- vs. pre-treatment HR (p < 0.001) and SBP (p < 0.001) than those treated by placebo. Children and adolescents treated with atomoxetine had more significant increases post- vs. pre-treatment HR (p = 0.025) and SBP (p < 0.001) than those treated with methylphenidate.

**ADHD & SUBSTANCE USE DISORDER**

Data from four Danish national registers covering a total of 20,742 patients with ADHD, their dispensed medications, co-morbid mental disorders, and associated substance use disorders (SUD) between 1994 and 2010 was analyzed (67). The analyses considered the risk of various medications (methylphenidate only, antidepressants only, antipsychotic only, mixed medication) in comparison to a control group of non-medicated patients with ADHD, various co-morbid disorders, duration of medication, age at diagnosis, year of birth, and sex for developing SUD. The patients included 15,648 (75.44%) males and 5094 (24.56%) females and the mean age at diagnosis was 15.20 (SD=10.08) years. In the total sample of N=20,742 patients with an ADHD diagnosis, N=14,372 patients had at least one dispensed prescription of the above-mentioned medications. N=7314 (35.26%) received MPH only, N=30 (0.14%) amphetamines only, N=99 (0.48%) other ADHD-specific drugs only, N=952 (4.59%) antidepressants only, N=483 (2.33%) antipsychotics only, and N=5494 (26.49%) mixed medication. In the mixed medication subgroup, methylphenidate was the most frequently prescribed drug (N=4588, 83.51%) followed by antidepressants (N=3444, 62.69%), antipsychotics (N=3266, 59.45%), other ADHD-specific drugs (N=1799, 32.74%), and amphetamines (N=187, 3.40%). The results showed that SUD rates were significantly higher prior to, compared to following the onset of medication in the methylphenidate and the mixed medication subgroup, whereas they were significantly higher following onset of medication in the antidepressants and the antipsychotics subgroup. Except MPH, all medication subtypes and co-morbid mood, anxiety, personality, and conduct disorders were risk factors for the development of SUD.

**ADHD & SUICIDE**

Untreated ADHD is recognized as an independent risk factor for suicide-related events and deliberate self-harm and is reported more commonly in these populations (68). Suicide-related events were retrospectively mapped to the suicide-related event assessment instrument recommended by the FDA, the Columbia Classification Algorithm for Suicide Assessment (C-CASA). Five double-blind placebo controlled comparative studies of ATX and MPH were evaluated (n=1024) of 6 to 9 weeks duration. All data included derives from prospectively collected data as part of a clinical trial. Patient summaries were reviewed blinded by two medical staff with training and expertise in adverse event reporting and pharmacovigilance, at least one a physician. With any discrepancy a third reviewer was used. Cases were then mapped to the relevant FDA codes. Data was collected during the trial into case report forms with subsequent further additional
data collected and incorporated into a patient narrative. Meta-analytic comparisons were made using the Mantel-Haenszel risk ratio. Two variables were reported: (1) the Mantel-Haenszel risk ratio (MHRR) which estimates the percentage risk of the specific adverse event amongst ATX treated patients over the percentage among methylphenidate treated patients; and (2) the Mantel-Haenszel incidence difference (MHID) which estimates the percentage risk of the specific adverse event amongst ATX treated patients minus the percentage among methylphenidate treated patients in percentage units. In total there were 5 suicide-related events, atomoxetine (ATX) 3/559 and methylphenidate (MPH) 2/465. There were no suicide attempts nor completed suicides. Meta-analysis finds no difference of a difference in risk between ATX and MPH with a Mantel-Haenszel risk ratio of 0.52 (95% CI; 0.06, 4.54).

11.3 Summary of Available Estimates of Comparative Safety of Methylphenidate

There is considerable overlap in the adverse event profiles of MPH- and AMF-based ADHD medications. Both have been associated with insomnia and appetite suppression as the most common adverse events. Overall, studies suggest that the frequency and severity of adverse events maybe somewhat greater with AMF than with MPH products.

In comparison to other non-stimulant medications, methylphenidate was associated with less sleeping problems and higher tolerability.

As methylphenidate is a controlled Schedule II substance under the 1971 Convention on Psychotropic Substances, the prevalence of misuse must be addressed. MPH nonmedical use is a microcosm of stimulant medications (MPHs and AMPs) misuse in general, with MPH-specific data generally mimicking results of studies looking at stimulant medication misuse in general. Thus, for example, while there are limited data on malingering specifically for MPH, studies of malingering for stimulants in general are likely generally applicable (69). Intoxication effects and potential health risks that can be associated with MPH abuse include feelings of exhilaration, increased energy, mental alertness, increased heart rate, increased or decreased blood pressure, increased metabolism, digestive problems, loss of appetite, weight loss, nervousness, insomnia, and perhaps even seizures, heart attack and stroke (70). Even if not abusing MPH in regard to quantity or frequency, someone taking nonprescribed MPH is likely to be unaware of its safety profile. MPH can increase systolic blood pressure (3–8 mm Hg), diastolic blood pressure (2–14 mm Hg), and pulse (3–10 beats/min), although epidemiological studies have shown stimulant use is not associated with cardiovascular symptoms, events, or sudden death (71–74). Child growth inhibition has been a historic concern, but it is debated, and evidence suggests that stimulant use is not associated with differences in growth over a 10- to 11-year follow-up (75), and in cases of observed growth deficit, it tends to attenuate after stimulant discontinuation (76). Tic development or worsening has been linked to MPH use, but the data are controversial, contrasting, and confounded by the fact that tics are a common comorbidity with ADHD (74). Thus, while cardiovascular events, growth inhibition, or tics generally may not be of major concern, there are common adverse events associated with MPH use that include abdominal pain, decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, decreased weight, irritability, and hyperhidrosis; patients should be made aware of these potential effects.

Overall, the misuse of MPH raises legitimate safety concerns for overdose and drug interactions with other medications or nonmedical use drugs, particularly since illicit users are generally unaware of these issues and often use MPH with other recreational drugs. It is also important to note that amphetamine-based drugs (AMPs) in recent years have been used more often than MPH for nonmedical use, particularly AMP immediate-release formulations (77). In a survey of students reporting stimulant NMU in the previous year (5.9 %), more students (75.8 %) reported the use of AMP misuse compared with MPH misuse (24.5 %),
suggesting that college students tend to misuse AMPs more than MPH (78). Several other studies support the finding that AMPs are misused more frequently than MPHs (79,80).

Being diagnosed with ADHD is associated with an elevated likelihood of also using nicotine, alcohol, and marijuana and other illicit drugs, regardless of age (81–85). Moreover, multiple studies have shown a linkage between ADHD and an increased risk of SUD (81,86–90), with a high comorbidity rate of SUD in patients with ADHD (91). In contrast to what one might hypothesize, studies have shown that use of MPH in patients with ADHD can actually reduce the likelihood of a later SUD by as much as twofold (92–97), and may even reduce the risk of SUD relapse (98). In a study mentioned above in our analysis, the younger the age of a child when receiving an ADHD prescription for MPH, the less likely he or she was of having a subsequent SUD (61).

Despite the necessary examination of MPH misuse, it is important to note that the misuse issue must be addressed in the context of the overall benefit-risk assessment for using MPH in the treatment of ADHD. In most circumstances, the potential benefit likely outweighs the risk of misuse, with a plethora of evidence supporting the efficacy of MPH for the treatment of child and adult ADHD. As evidenced in a subsequent section below on the Regulatory Status of Methylphenidate, the issue of misuse has been investigated across the various governing medical bodies and the consensus has been that the benefits of methylphenidate continue to outweigh the risks when used to treat children aged six years and above and adolescents with attention deficit/hyperactivity disorder (ADHD). Instead, governing bodies have opted to revise prescribing information for these medicines to make them consistent and in order to maximize their safe usage.
12. Summary of Available Data on Comparative Cost and Cost-Effectiveness of Methylphenidate within its Pharmacological Class/Therapeutic Group

12.1 Range of Costs

All cost information was obtained from the International Drug Price Indicator Guide for 2015. ¹

<table>
<thead>
<tr>
<th>Source</th>
<th>Package</th>
<th>Package Price</th>
<th>Unit Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>OECS/PPS</td>
<td>100 Tab-cap (Tablets)</td>
<td>$4.68</td>
<td>0.0468/tab-cap</td>
</tr>
<tr>
<td>SAFRICA</td>
<td>30 Tab-cap (Tablets)</td>
<td>$2.01</td>
<td>0.0670/tab-cap</td>
</tr>
<tr>
<td>PERU</td>
<td>1 Tab-cap (Tablets)</td>
<td>$0.31</td>
<td>0.3112/tab-cap</td>
</tr>
</tbody>
</table>

Median Price: 0.0670/tab-cap ↑23%     Lowest Price: 0.0468/tab-cap
High/Low Ratio: 6.65                  Highest Price: 0.3312/tab-cap

Supplier Information:
OECS/PPS: Organisation of Eastern Caribbean States Pharmaceutical Procurement Service
SAFRICA: South Africa Department of Health
PERU: Peru Ministerio de Salud (MINSA) ‘Peru Ministry of Health’

¹ (99)

12.2 Comparative Cost-Effectiveness

A systematic review of the cost-effectiveness literature on methylphenidate was conducted (last search, Dec 5, 2018). A PubMed search using the keywords “methylphenidate cost effectiveness” yielded 44 articles. Of these, 29 were deemed relevant based on criteria that they expressed cost-effectiveness as a range of cost per routine outcome. 18 of the relevant articles were excluded based on small sample size and/or poor study design. A search of the Cochrane Database of Systematic Reviews using the same keywords yielded 5 articles, all of which were deemed irrelevant based on analyses that only mentioned methylphenidate but did not include as a comparator therapy.

The overall evidence suggests that methylphenidate can be recommended from a cost-effectiveness standpoint, as it is at worst cost-neutral compared to other stimulant and non-stimulant medications for the treatment of attention deficit hyperactivity disorder.
ATTENTION DEFICIT HYPERACTIVITY DISORDER

A Markov model was constructed to compare MPH-IR to no treatment from the perspective of the Brazilian Unified Health System as payer, and the time horizon was 6 years (100). Considering the MPH-IR monthly cost of IS$38, the incremental cost-effectiveness ratio (ICER) of treatment was IS$9,103/QALY for children and IS$11,883/QALY for adolescents. In two-way sensitivity analysis, considering one Gross National Product per capita (IS$11,530) as willingness-to-pay, a cost of no-treatment lower than IS$45/month would render MPH-IR a cost-saving strategy.

A systematic review of the literature was to describe the cost-effectiveness analyses of medications launched in Spain for the treatment of ADHD (101). A search was made in PubMed/MEDLINE, SCOPUS, databases of the Centre for Reviews and Dissemination, and the websites of technology assessment agencies from Canada, the United Kingdom and the Spanish Platforms AUnETS. Eleven studies that considered at least methylphenidate or atomoxetine as pharmacological treatment alternatives in children/adolescents with ADHD were examined. Both MPH and ATX were presented as cost-effective alternatives over placebo or no treatment in all studies. However, the incremental cost-effectiveness reasons varied greatly in the various studies. The few direct comparisons between MPH and ATX presented contradictory results according to the source of funding for the study: ATX was shown to be cost-effective over MPH in 2 evaluations associated with the manufacturer or ATX, while MPH-ER was cost-effective over ATX in the evaluation associated with the manufacturer of MPH.

A systematic literature review of economic evaluations of pharmacotherapies for ADHD was conducted in MEDLINE, the National Health Services (NHS) Economic Evaluation database and EMBASE (102). For inclusion in this review, studies had to compare two or more ADHD interventions with at least one pharmacotherapy, assess both costs and outcomes, and be conducted between 1990 and 2011 in North America, Europe, Australia or New Zealand. Thirteen papers met the inclusion/exclusion criteria and were included in the review. Identified pharmacotherapies including methylphenidate were found to be cost-effective compared with no treatment, placebo, behavioral therapy or community care among children and adolescents with ADHD. When comparing stimulants with stimulants, there were varied results. A Zupancic et al. study showed that methylphenidate dominated dexamfetamine (with $Can 7 lower costs, i.e. $US8 in 2010 and a 2-point decrease in CTRS) and pemoline (with $Can29 lower costs, i.e. $US35 in 2010, and a 2.7-point decrease in CTRS) (103). Finally, a Marchetti et al. study found that branded methylphenidate had the lowest annual expected cost per patient among all medications considered ($US1487/patient in 2001) and branded SA amfetamine/dexamfetamine salts had the highest expected cost ($US2232/patient in 2001) (104).

An economic model with Markov processes was developed to estimate the costs and benefits of atomoxetine versus other current ADHD treatment options for the perspective of the United Kingdom (105). For stimulant-naive patients, the incremental cost per QALY gained for the atomoxetine algorithm compared with the immediate-release methylphenidate hydrochloride was £15,224 (£13,241 compared with extended-release MPH).

A systematic review with a total of 65 papers that met inclusion criteria were examined to assess the clinical and cost-effectiveness of oral methylphenidate (MPH), dexamfetamine (DEX) and atomoxetine (ATX) in children and adolescents diagnosed with ADHD (106). Given the lack of available evidence for statistically significant differences in efficacy between the alternative drugs, the results of the economic model were largely driven by drug cost, in which there are marked differences. The economic evaluation clearly suggests an optimal treatment strategy that is DEX first-line, followed by IR-MPH for treatment failures.
followed by ATX for repeat treatment failures. If DEX is considered not suitable as a first-line therapy, the optimal strategy is IR-MPH first-line, followed by DEX as second-line and ATX again as third-line.

In a multi-modal treatment study, five hundred seventy-nine children with ADHD were assigned to 14 months of medication management (including methylphenidate), behavioral treatment, both combined or community care (107). In summary, findings suggest that carefully monitored medication treatment, although not quite as effective as combination of medication and behavioral treatment, is likely to be more cost-effective in routine treatments for children with ADHD, particularly those without comorbid disorders.

A literature search was performed using MEDLINE to identify all published articles on the economic implications of ADHD, and in total, 22 relevant items were located including published original studies, economic review articles, conference presentations, and reports available on the internet (108). Three published studies utilized decision-analytic modeling techniques to assess the cost-effectiveness of drug therapy, methylphenidate, for ADHD. Overall, results of the three modeling analyses indicated that MPH is a cost-effective treatment option for children with ADHD. The cost per QALY gained ranged from $15,509 to $19,281 when considering short- and medium-term benefits of MPH.

A comprehensive literature review was conducted using HEALTHSTAR and MEDLINE regarding the use of AMP/DEX mixed salts, MPH and DEX in the treatment of ADHD, as well as relevant ADHD studies on cost-effectiveness and quality of life (109). A cost-effectiveness model was constructed from a societal perspective encompassing both direct and indirect cost, and using a cost per quality-adjusted life year outcomes metric. Decision-tree analysis was utilized to construct a 1-year model using probability-weighted utility and cost outcomes for each outcome branch. The results showed that methylphenidate treatment is dominated by amphetamine/dextroamphetamine therapy in the base case, yet when varying response rates, it can be seen that AMP/DEX no longer remains the dominant strategy. It is difficult to generalize about incremental cost effectiveness between stimulant therapies given the essentially equal efficacy and similar-side effect profiles between the agents. Thus, treatment with either amphetamine/dextroamphetamine or methylphenidate is quite cost effective compared with no treatment. Stimulant therapy is estimated to have an incremental cost per quality-adjusted life year ranging from US$14,758 to 73,162/QALY.

A meta-analysis of randomized controlled trails was performed from a health sector perspective in Australia to determine cost-effectiveness of dexamphetamine and methylphenidate interventions to treated childhood ADHD (110). Effect sizes were translated into utility values and a simulation modelling technique was used to present a 95% uncertainty interval around the incremental cost-effectiveness ratio (ICER) which is calculated in cost per DALY averted. The findings found that MPH and DEX are cost-effective interventions for childhood ADHD. The ICER For DEX is A$4100/DALY saved and for MPH is A$15,000/DALY saved. DEX is more costly than MPH for the government but much less costly for the patient. Therefore, DEX is more cost-effective than MPH, although if MPH were listed at a lower price as it is in Canada, then it would become more cost-effective.

A comprehensive literature search was undertaken in 1997 to identify randomized controlled or crossover trials that evaluated effects of methylphenidate in children (111). The cost-utility analysis was performed from NHS rather than a societal perspective according to methodology developed by the former South and West Development Evaluation Committee. The number of Quality Adjusted Life Years (QALYs) gained was estimated by using the Index of Health-Related Quality of Life to model treatment effects. Evidence from good and medium quality randomized controlled trials shows benefits of methylphenidate over weeks and months respectively. Evidence beyond 6 months is poorer and it is uncertain whether effects of methylphenidate persist into adolescence and adulthood. Methylphenidate is of reasonable cost-
effectiveness when considering short- and medium-term benefits with an estimated cost per QALY of £7,400 to £9,200 at 1997 prices.

According to the review papers identified, the comparative cost-effectiveness literature favors methylphenidate or is at least cost-neutral relative to both stimulant and non-stimulant treatments among treatments for ADHD.
13. Summary of the Regulatory Status of Methylphenidate

Methylphenidate hydrochloride – immediate release, is approved for use in various jurisdictions as follows:

**US Food and Drug Administration (FDA):**

Methylphenidate hydrochloride – generic immediate release 5mg, 10mg, 20mg and several brand name counterparts are licensed in the United States for the treatment of Attention Deficit Disorders as an integral part of a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity. The diagnosis of this syndrome should not be made with finality when these symptoms are only a comparatively recent origin. Nonlocalizing (soft) neurological signs, learning disability, and abnormal EEG may or may not be present and a diagnosis of central nervous system dysfunction may or may not be warranted.

The U.S. Food and Drug Administration (FDA) is updating the public that a large, recently-completed study in children and young adults treated with medication for Attention-Deficit/Hyperactivity Disorder (ADHD) has not shown an association between use of certain ADHD medications and adverse cardiovascular events. These adverse cardiovascular events include stroke, heart attack (myocardial infarction or MI), and sudden cardiac death. Healthcare professionals should take special note that:

- Stimulant products and atomoxetine should generally not be used in patients with serious heart problems, or for whom an increase in blood pressure or heart rate would be problematic.
- Patients treated with ADHD medications should be periodically monitored for changes in heart rate or blood pressure.

Patients should continue to use their medicine for the treatment of ADHD as prescribed by their healthcare professional.

**European Medicines Agency (EMA) (112):**

The European Medicines Agency (EMEA) completed a review of the safety of medicines containing methylphenidate in 2009. The Agency’s Committee for Medicinal Products for Human Use (CHMP) has concluded that the benefits of these medicines continue to outweigh their risks when used to treat children aged six years and above and adolescents with attention deficit/hyperactivity disorder (ADHD). Thus, methylphenidate hydrochloride – generic immediate release 5mg, 10mg, 20mg and several brand name counterparts are licensed in in the EU.

The Committee concluded that new recommendations on prescribing the medicines on pre-treatment screening and ongoing monitoring of patients are needed to maximize the safe use of these medicines. Because the information provided to doctors on the safety of methylphenidate is not consistent across the EU, the Committee concluded that the product information of all methylphenidate-containing medicines authorized in the Member States should contain the following information:

- before treatment, all patients should be screened to see if they have any problems with their blood pressure or heart rate. The family history of cardiovascular problems should also be checked. Any patients with these problems should not be treated without specialist evaluation;
- during treatment, blood pressure and heart rate should be monitored regularly. Any problems that develop should be investigated promptly;
- there is a lack of information on the long-term effects of methylphenidate. For patients who take methylphenidate for more than a year, doctors should interrupt treatment at least once a year to...
determine whether continued treatment with methylphenidate is necessary;
- the use of methylphenidate could cause or worsen some psychiatric disorders such as depression, suicidal thoughts, hostility, psychosis and mania. All patients should be carefully screened for these disorders before treatment and monitored regularly for psychiatric symptoms during treatment;
- the height and weight of patients treated with methylphenidate should be monitored during treatment.

Australian Government, Department of Health, Therapeutic Goods Administration (113):

Methylphenidate hydrochloride – generic immediate release 10mg and several brand name counterparts are licensed in the Australia for the treatment of Attention Deficit Hyperactivity Disorder. Methylphenidate hydrochloride is indicated as part of a comprehensive treatment program which typically includes other remedial measures (psychological, educational, social) for achieving a beneficial effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate to severe distractibility, short attention span, hyperactivity (not always present) and impulsivity. The diagnosis of this syndrome should not be made when these symptoms are only of recent origin. Non-localizing (soft) neurological signs, emotional lability, learning disability and an abnormal electroencephalogram (EEG) may or may not be present, and a diagnosis of CNS dysfunction may or may not be warranted. Special diagnostic considerations for ADHD. The etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use not only of medical but also of psychological, educational and social resources. Characteristics commonly reported include chronic history or short attention span, distractibility, emotional lability, impulsivity, moderate to severe hyperactivity, minor neurological signs and an abnormal EEG. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the child and not solely on the presence of one or more of these characteristics. Drug treatment is not indicated for all children with this syndrome. Stimulants are not intended for use in children who exhibit symptoms secondary to environmental factors (eg. child abuse in particular) or primary psychiatric disorders. Appropriate educational placement is essential and psychosocial intervention is generally necessary. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the doctor's assessment of the chronicity and severity of the child's symptoms.

Japanese Pharmaceuticals and Medical Devices Agency (114):

Methylphenidate hydrochloride, immediate release 10mg and brand name counterparts are licensed in Japan for the treatment of Attention Deficit Hyperactivity Disorder. Most recently, in 2016, a revision of precaution for adverse reactions was amended and the inclusion of the following text was added to packaged inserts (115).

Hepatic failure and hepatic function disorder: Hepatic failure (including acute hepatic failure) or hepatic function disorder may occur. Patients should be carefully monitored. If any abnormalities are observed, administration of this drug should be discontinued and appropriate measures should be adopted.

Health Canada (116):

Methylphenidate hydrochloride, immediate release 5mg, 10mg, 20mg and brand name counterparts are licensed in Canada for the treatment of Attention Deficit Hyperactivity Disorder. Most recently, the NIHB Program introduced a dose coverage limit for stimulants on February 25, 2015 as part of a strategy to deal with the potential misuse and abuse of these medications. The stimulant dose coverage limit is set at 100mg.
of methylphenidate equivalents for all other stimulants per day, for adults and children. This limit is calculated based on the total dose of all stimulants that patients are receiving from NIHB. The Program will continue to monitor the utilization of stimulants and adjust the eligible dose limit as required.
14. Availability of Pharmacopoeial Standards for Methylphenidate

British Pharmacopoeia: Yes
European Pharmacopoeia: Yes
Indian Pharmacopoeia: Yes
International Pharmacopoeia: No
United States Pharmacopoeia: Yes

British Pharmacopoeia: https://www.pharmacopoeia.com
Last accessed: Sept 21, 2018

Last accessed Sept 21, 2018

Indian Pharmacopoeia: https://www.indianpharmacopoeia.in
Last accessed Sept 21, 2018

International Pharmacopoeia: http://apps.who.int/phint/en/p/docf/
Last accessed Sept 21, 2018

Last accessed Sept 21, 2018
15. Proposed New Text for the WHO Model Formulary

-------- INDICATIONS AND USAGE --------

Methylphenidate hydrochloride, is a mild central nervous system (CNS) stimulant indicated for:
  • Attention Deficit Disorders in children, adolescents and adults
  • Integration into a total treatment program which typically includes other remedial measures (psychological, educational, social) for a stabilizing effect in children with a behavioral syndrome characterized by the following group of developmentally inappropriate symptoms: moderate-to-severe distractibility, short attention span, hyperactivity, emotional lability, and impulsivity.

Adults

*Tablets:* Administer in divided doses 2 or 3 times daily, preferably 30 to 45 minutes before meals. In rare instances it can be dosed once daily.

Average dosage is 20 to 30mg daily. Some patients may require 40 to 60mg daily. In others, 10 to 15mg daily will be adequate.

Children (6 years and over)

Methylphenidate should be initiated in small doses, with gradual weekly increments. Daily dosage above 60mg is not recommended.

*Tablets:* Start with 5mg twice daily (before breakfast and lunch) with gradual increments of 5 to 10mg weekly.

-------- DOSAGE FORMS AND STRENGTHS --------

  • Tablets: 5mg, 10mg, 20mg

-------- CONTRAINDICATIONS --------

  • Patients with marked anxiety, tension and agitation
  • Patients known hypersensitivity to drug
  • Patients with glaucoma
  • Patients with motor tics or with family history or diagnosis of Tourette’s syndrome
  • Methylphenidate is contraindicated during treatment with monoamine oxidase inhibitors and within minimum of 14 days following discontinuation of a monoamine oxidase inhibitor
WARNINGS AND PRECAUTIONS

- Serious cardiovascular events, sudden death, stroke, and myocardial infarction. Stimulant products should not be used in children, adolescents or adults with known preexisting serious structural cardiac abnormalities or other serious health problems.
- Stimulant medications cause modest increase in average blood pressure and average heart rate. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate e.g., those with preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.
- Children, adolescents or adults who are being considered for treatment with stimulant medications should have a careful history and physical exam to assess presence of cardiac disease and should receive further cardiac evaluation if findings suggest such disease.
- Psychiatric adverse events including:
  - Preexisting psychosis
  - Bipolar illness
  - Emergence of new psychotic or manic symptoms
  - Aggression
  - Long-term suppression of growth
  - Seizures
  - Priapism
  - Peripheral Vasculopathy, including Raynaud’s Phenomenon
  - Visual Disturbance

ADVERSE REACTIONS

Nervousness and insomnia are the most common adverse reactions but are usually controlled by reducing dosage and omitting the drug in the afternoon or evening. Other reactions include hypersensitivity (including skin rash, urticaria, fever, arthralgia, exfoliative dermatitis, erythema multiforme with histopathological findings of necrotizing vasculitis, and thrombocytopenic purpura); anorexia; nausea; dizziness; palpitations; headache; dyskinesia; depression; blood pressure and pulse changes, both up and down; tachycardia; angina; cardiac arrhythmia; abdominal pain; weight loss during prolonged therapy; libido changes. There have been rare reports of Tourette’s syndrome. Toxic psychosis has been reported.

In children, loss of appetite, abdominal pain, weight loss during prolonged therapy, insomnia, and tachycardia may occur more frequently; however, any of the other adverse reactions listed above may also occur.

DRUG INTERACTIONS

- Methylphenidate is metabolized primarily to ritalnic acid by de-esterification and not through oxidative pathways.
- Methylphenidate should not be used in patients being treated with MAO inhibitors.
- Due to possible effects on blood pressure, methylphenidate should be used cautiously with pressor agents.
• Methylphenidate may decrease effectiveness of drugs used to treat hypertension.
• Human pharmacologic studies have shown that racemic methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants. Downward dose adjustments of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust dosage and monitor plasma drug concentration when initiating or discontinuing methylphenidate.

------- USE IN SPECIFIC POPULATIONS -------

• Methylphenidate should not be used in children under 6 years of age
• It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if Ritalin is administered to nursing woman.
• Methylphenidate should be used during pregnancy only if potential benefit justifies the potential risk to the fetus. (Pregnancy Category C)

(Adapted from www.fda.gov, last accessed on Sept 12, 2018: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/010187s087lbl.pdf#page=11)
References


24. A 14-Month Randomized Clinical Trial of Treatment Strategies for Attention-Deficit/Hyperactivity Disorder. Arch Gen Psychiatry. 1999 Dec 1;56(12):1073–86.


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APPENDIX

Letters of Support
11 May 2018

The Secretary of the 22nd Expert Committee on the Selection and Use of Essential Medicines - Medicine Access and Rational Use (MAR)

Department of Essential Medicines and Health Products (EMP)

World Health Organization

20 Avenue Appia

CH-1211 Geneva 27

Switzerland

Dear Secretariat,

I am writing to you on behalf of the GMERS Medical College and Hospital, Gorvi, Vadodara, INDIA in support of the application being made by Dr. Craig Katz and his colleagues at the Mount Sinai School of Medicine to have Methylphenidate added to the List of Essential Medications. We have collaborated with them for over 8 years on meeting mental health needs in our own country and see their decision to make this application on behalf of people around the world as showing great initiative and wisdom. We have much experience with Methylphenidate.

We believe that at least one central nervous system stimulant should be considered an essential part of any formulary, and our experience definitely supports that it should be Methylphenidate. I would like to make a special appeal that it be included in its immediate-release formulations.

Respectfully,

[Signature]

Dr. Sandip H. Shah MD

Professor and Head of Department of Psychiatry,

GMERS Medical College and Hospital, Gorvi, Vadodara, INDIA

Email: hod.psy.gorvi@gmail.com
May 14, 2018

The Secretary of the 22nd Expert Committee on the
Selection and Use of Essential Medicines
Medicine Access and Rational Use (MAR)
Department of Essential Medicines and Health Products (EMP)
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland

Dear Secretariat,

I am writing to you on behalf of the Ministry of Health, Belize in support of the application
being made by Dr. Craig Katz and his colleagues at the Mount Sinai School of Medicine to have
Methylphenidate added to the List of Essential Medications. We have collaborated with them
for over 10 years on meeting mental health needs in our own country and see their decision to
make this application on behalf of people around the world as showing great initiative and
wisdom. We have much experience with Methylphenidate.

We believe that at least one central nervous system stimulant should be considered an essential
part of any formulary, and our experience definitely supports that it should be Methylphenidate.
I would like to make a special appeal that it be included in its immediate-release formulations.

Respectfully,

ELEANOR BENNETT (Mrs.), MMHPS
Head, Mental Health Unit
Belize Ministry of Health
Belize, Central America
October 1, 2018

The Secretary of the 22nd Expert Committee on the Selection and Use of Essential Medicines
Medicine Access and Rational Use (MAR)
Department of Essential Medicines and Health Products (EMP)
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland

Dear Secretariat,

I am writing to you on behalf of the Mr. Gay Mental Hospital in support of the application being made by Dr. Craig Karp and his colleagues at the Mount Sinai School of Medicine to have Methylphenidate added to the List of Essential Medications. We have collaborated with them for over 3 years on meeting mental health needs in our own country and see their decision to make this application on behalf of people around the world as showing great initiative and wisdom. We have much experience with Methylphenidate.

We believe that at least one central nervous system stimulant should be considered an essential part of any formulary, and our experience definitely supports that it should be Methylphenidate. I would like to make a special appeal that it be included in its immediate-release formulations.

Respectfully,

Dr. Doris Keena Douglas MD, MPH
Senior Registrar
Mr. Gay Psychiatric Hospital

Tel: 1 (473) 440 - 3154/3272  Fax: 1 (473) 425 - 4160  rhinstitutions@gmail.com
October 1, 2018

The Secretary of the 22nd Expert Committee on the Selection and List of Essential Medicines: Medicine Access and Rational Use (MAR)
Department of Essential Medicines and Health Products (EMP)
World Health Organization
20 Avenue Appia
CH-1211 Geneva 27
Switzerland

Dear Secretariat,

I am writing to you on behalf of the Mt. Gay Mental Hospital in support of the application being made by Dr. Craig Katz and his colleagues at the Mount Sinai School of Medicine to have Methylphenidate added to the List of Essential Medications. We have collaborated with them for over 3 years on meeting mental health needs in our own country and see their decision to make this application on behalf of people around the world as showing great initiative and wisdom. We have much experience with Methylphenidate.

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Respectfully,

Dr. Evon Spencer
Senior House Officer
Mt. Gay Psychiatric Hospital

Tel: 1 (473) 410 - 3154/3272  Fax: 1 (473) 485 - 4160  rhinstituions@gmail.com
October 1, 2018

The Secretary of the 22nd Expert Committee on the Selection and Use of Essential Medicines
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Department of Essential Medicines and Health Products (EMP)
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Respectfully,

Dr. Omar Hernández Rivero
Consultant Psychiatrist
Mt. Gay Psychiatric Hospital

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