# Application for Inclusion to the 23rd Expert Committee on the Selection and Use of Essential Medicines for Children: Methylphenidate Hydrochloride

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**Author Disclosures of Potential Conflicts of Interest**

In the past year, Dr. Faraone received income, potential income, travel expenses continuing education support and/or research support from Takeda, OnDosis, Tris, Otsuka, Arbor, Ironshore, Rhodes, Akili Interactive Labs, Sunovion, Supernus and Genomind. With his institution, he has US patent US20130217707 A1 for the use of sodium-hydrogen exchange inhibitors in the treatment of ADHD. He also receives royalties from books published by Guilford Press: Straight Talk about Your Child's Mental Health, Oxford University Press: Schizophrenia: The Facts and Elsevier: ADHD: Non-Pharmacologic Interventions. He is Program Director of www.adhdinadults.com.

Dr. Banaschewski served in an advisory or consultancy role for Lundbeck, Medice, Neurim Pharmaceuticals, Oberberg GmbH, Takeda, and Infectopharm. He received conference support or speaker's fee by Lilly, Medice, and Takeda. He received royalities from Hogrefe, Kohlhammer, CIP Medien, Oxford University Press.

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Dr. Newcorn is/has been an advisor and/or consultant for Adlon Therapeutics, Arbor, Eisai, Medice, Myriad Neuroscience, NLS, OnDosis, Rhodes, Shire/Takeda, and Supernus, and was a DSMB member for Sunovion. He has received research support from the National. Institute on Drug Abuse (NIDA), the Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD), Otsuka, Shire and Supernus. He also has received speaker fees from Shire/Takeda for disease-state presentations, and served as a consultant for the US National Football League.

Dr Cortese declares honoraria and reimbursement for travel and accommodation expenses for lectures from the following non-profit associations: Association for Child and Adolescent Central Health (ACAMH), Canadian ADHD Alliance Resource (CADDRA), British Association of Pharmacology (BAP), and from Healthcare Convention for educational activity on ADHD

Drs. Katz and Moscibrodzki have no potential conflicts of interest to declare.

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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 ADHD. Methylphenidate is proposed for inclusion on the complimentary list for children. 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.

Untreated ADHD is not a benign condition and pharmacological interventions such as methylphenidate have wide ranging beneficial effects for children world-wide, not just those in industrialized or western countries. For most patients, the impairing symptoms of ADHD persist into adulthood (Faraone et al., 2006). Annual incremental costs of ADHD have been estimated at $143-$266 billion in the US (Doshi et al., 2012), $12.8 billion in Australia (Australian ADHD Professionals Association, 2019) and (Sciberras et al., 2020) are substantial in other countries as well (Le et al., 2014). Because ADHD is a common neurodevelopmental disorder in childhood affecting 5% of children (Polanczyk et al., 2014) and 2.8% of adults (Fayyad et al., 2017) worldwide, limiting access to methylphenidate has profound repercussions.

In 2018 the European ADHD Guidelines Group (EAGG) published the most comprehensive meta-analysis of short-term RCTs of ADHD medications across the lifespan (Cortese et al., 2018). When assessing efficacy, the standardized mean differences (SMDs) comparing methylphenidate to placebo were 0.78 for children (95% CI: 0.62-0.93) and 0.49 for adults (0.35-0.64). Both SMDs were based on clinician ratings of outcome in double-blinded RCTs. These SMDs are not only statistically significant, they are among the highest in psychiatry and other areas of medicine (Leucht et al., 2012). Because long-term RCTs are not ethical, we rely on large, naturalistic population registry studies to assess longer term functional outcomes. These show that methylphenidate treatment for ADHD reduces accidental injuries, traumatic brain injury, substance abuse, cigarette smoking, educational underachievement, bone fractures, sexually transmitted infections, depression, suicide, criminal activity and teenage pregnancy Given this strong evidence for efficacy from RCTs and effectiveness, in the longer term, from naturalistic studies along with a profile of minor, adverse effects, methylphenidate warrants inclusion in WHO's list of Essential Medicines for Children.

In 2020, WHO rejected a request to place methylphenidate on the list of Essential Medicines for Children. The Expert Committee's decision to exclude methylphenidate from their list stands in stark contrast to the decisions of many regulatory agencies and professional groups around the world. As regards regulatory agencies, the safety and efficacy of methylphenidate have been approved by the US Food and Drug Administration, the European Medicine Agency, The Chinese National Medical Products Administration, Health Canada, the Australian Therapeutic Goods Administration, the Japanese Pharmaceuticals and Medical Devices Agency and the Israeli Ministry of Health, Pharmaceutical Division, Medical Preparations Registration Department.

The Expert Committee cited the meta-analysis of randomized controlled trials (RCTs) of methylphenidate for children with ADHD by Storebø et al. (2015) as a source supporting the notion that the evidence for the use of methylphenidate for ADHD is of poor quality, likely overestimates the positive effects of methylphenidate and underestimates its harms. However, relying on the Storebø et al. (2015) meta-analysis is problematic for several reasons. That meta-analysis is flawed due to its use of idiosyncratic methods to assess the quality of the evidence and factual errors, such as inappropriate study

inclusion, incorrect downgrading of the evidence based on the GRADE system, and incorrect data imputation. For further details, see Banaschewski et al. (2016) and Hoekstra et a. (2016),.

The 2018 European ADHD Guidelines Group (EAGG) meta-analysis of RCTs of ADHD across the lifespan (Cortese et al., 2018) was based on a more advanced and precise meta-analytic method (network meta-analysis) compared with the standard approach (pairwise) used by Storebø and colleagues. Cortese et al. concluded that, considering all the included outcomes related to efficacy/safety, methylphenidate should be considered the first line pharmacological option for ADHD in children and adolescents.

In Cortese et al.'s meta-analysis, the quality of the evidence of the RCTs on methylphenidate on the primary outcome (clinicians rating) was judged as moderate, as opposed to the very low quality of evidence reported by Storebø and colleagues. This difference stems from two sources. First, Storebø et al.'s use of the GRADE system for rating risk of bias in meta-analysis did not follow usual practice. For example, they rated overall study bias as 'high risk' if only one item was uncertain. Most guidelines for rating quality define 'high risk' if one item clearly indicates a high risk of bias, and this procedure was followed in Cortese et al. Second, the rating of the quality of the evidence is based on the information available to the researchers who perform the rating. Cortese et al. gathered unpublished data after systematically contacting study authors and drug manufacturers. After including this information, which was not available to Storebø et al., the overall number of uncertain quality items across all items of the Risk of Bias decreased from 63.5% to 35.2%. This suggests that what previous meta-analyses assessed as "very low" may refer more to the quality of the study reporting, rather than the evidence per se.

We acknowledge that there are gaps in the evidence for almost all medicines used to treat both physical and mental health problems. It is however important that the decision-making process about which treatments should be made available is applied consistently across different disorders and in such a way that ensures parity between physical and mental disorders. As pointed out by Leucht et al. (2012) medications for mental and behavioural disorders have a similar range of efficacies to those for physical health problems. For example, when investigating the effects of digoxin on atrial fibrillation and flutter Sethi and colleagues (Sethi et al., 2018) were unable to identify any trials with follow-up longer than 24 weeks. We also note that state-of-the-art tools to rate the quality of the evidence, such as GRADE used by Storebo et al. and Cortese et al., set the highest standards of reporting. Indeed, using GRADE, the UK National Institute for Clinical Care and Excellence failed to rate as high level most of the evidence from studies on the efficacy and tolerability of some commonly used treatments in general medicine, such as antihypertensive (https://www.nice.org.uk/guidance/ng136) and anti-asthmatic drugs (https://www.nice.org.uk/guidance/ng80), yet these drugs are still recommended for use.

The decision by the Expert Committee to not recommend the addition of methylphenidate to the complementary list of the EML and EMLc for the treatment of ADHD will continue to make access to methylphenidate challenging for millions of people around the world. Your decision will disproportionately affect the poorest and highest risk of children due to economic and educational disadvantages. This will increase morbidity, create chaos in families and drive up health care costs.

Considering the evidence given above, we urge the Expert Committee to reconsider their decision regarding the inclusion of methylphenidate in the complementary list of the EML and EMLc.

## 2. Relevant WHO technical department and focal point

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

## 3. Names of the Organization(s) Consulted and Supporting the Application

This application has been submitted by Stephen V. Faraone, President of the World Federation of ADHD, https://www.adhd-federation.org/, on behalf of the following organizations. See Appendix A for letters of support.

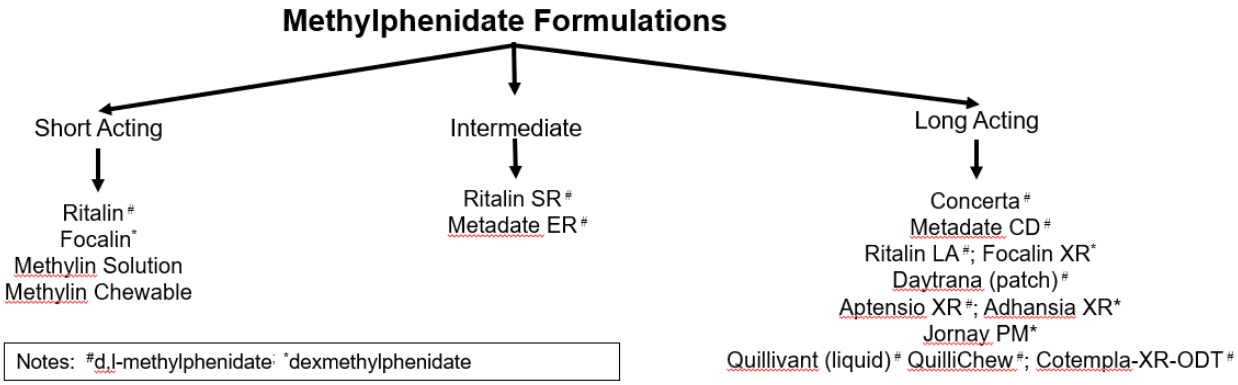
1. ADHD, ASC & LD, Belgium
2. ADHD Association Axarquia, Spain
3. ADHD Association Iceland
4. ADHD Association Palencia, Spain
5. ADHD Europe
6. ADHD Germany
7. ADHD Ireland
8. ADHD Malta, European Union
9. ADHD Solutions CIC, UK
10. ADHD Terres de L'Ebre, Spain
11. Andalusian Federation of Associations for Aid to Hyperkinetic Disorder and Attention Deficit, Spain
12. Asian Federation of ADHD
13. Association for Attention Deficit Hyperactivity, Spain
14. Association for ADHD, Spain
15. Association for Understanding ADHD, Croatia
16. Association of Mothers and Fathers of Children and Adolescents with ADHD, Spain
17. Association of Parents of Hyperactive Children, Spain
18. Association of People with ADH of Bizkaia, Spain
19. Australian ADHD Professionals Association
20. Bahía de Cádiz ADHD Association, Spain
21. Belize Ministry of Health, Mental Health Unit, Central America
22. Brazilian Association for Attention Deficit Disorder
23. Canadian ADHD Resource Alliance
24. Catalan Federation of Relatives and People Affected by ADHD, Catalonia, Spain
25. Centre for ADHD Awareness, Canada
26. Children and Adults with ADHD, USA
27. Chinese Society of Child and Adolescent Psychiatry
28. Danish ADHD Organization
29. Eunethydis Network, European Union
30. European Society for Child and Adolescent Psychiatry
31. Federation of ADHD Castilla y Leon Associations, Spain
32. Fundación Cultural Federico Hoth, A.C. (Proyectodah, seeks knowledge and solutions around ADHD in all Spanish-speaking countries)
33. Galician Federation of Associations for Attention Deficit and Hyperactivity, Spain
34. Geha Mental Health Center, Israel
35. German Society for Child and Adolescent Psychiatry, Psychosomatics, and Psychotherapy (DGKJP)
36. GMERS Medical College and Hospital, India
37. Grenada Ministry of Health
38. HyperSupers - ADHD France
39. Impuls en Woortblind, Organisation for Individuals with ADHD and Dyslexia, Netherlands
40. Israeli Society of ADHD
41. Italian Association of ADHD Families
42. Japanese Society of ADHD
43. Latin American League for the Study of ADHD
44. Latin American Federation and Association of Child and Adolescent Psychiatric and Related Professions
45. Madrid Association of ADHD, Spain
46. Meeting Point ADHD, Luxemburg
47. National Attention Deficit Disorder Information and Support Service, UK
48. Network of Child Adolescent Neuropsychopharmacology, European Union
49. Neurodevelopmental Disorders Across Lifespan, European Psychiatric Association
50. Paediatric Neurology and Development Association of South Africa
51. Possibilities Clinic for assessment and treatment of ADHD, Canada
52. PsyQ, Netherlands
53. Saudi ADHD Society, Saudi Arabia
54. Spanish Federation of Associations of Attention Deficit and Hyperactivity
55. Swiss Society for ADHD
56. The American Professional Society of ADHD and Related Disorders, International
57. The Icelandic Disability Alliance

## 4. International Nonproprietary Name (INN, generic name) of the medicine

Methylphenidate Hydrochloride, ATC Code: N06BA04

## 5. Dose forms(s) and strength(s) proposed for inclusion; including adult and age-appropriate paediatric dose forms/strengths (if appropriate).

The Figure below gives an overview of current methylphenidate formulations:




*Doses Available for each Formulation (from [www.pdr.net](http://www.pdr.net)):*

- Adhansia XR/Aptensio XR/Jornay/Metadate CD/Methylphenidate Hydrochloride/Ritalin LA Oral Cap ER: 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg, 50mg, 55mg, 60mg, 70mg, 80mg, 85mg, 100mg
- Concerta/Metadate ER/Methylin/Methylphenidate Hydrochloride/RELEXXII/Ritalin SR Oral Tab ER: 10mg, 18mg, 20mg, 27mg, 36mg, 54mg, 72mg
- Daytrana Topical Film ER: 1h, 1.1mg, 1.6mg, 2.2mg, 3.3mg
- Methylin/Methylphenidate Hydrochloride Oral Sol: 5mL, 5mg, 10mg
- Methylin/Methylphenidate Hydrochloride Oral Tab Chew: 2.5mg, 5mg, 10mg
- Methylin/Methylphenidate Hydrochloride/Ritalin Oral Tab: 5mg, 10mg, 20mg
- Methylphenidate Oral Tab Orally Dis DR: 8.6mg, 17.3mg, 25.9mg
- QuilliChew ER Oral Tab Chew ER: 20mg, 30mg, 40mg
- Quillivant XR Oral Susp ER: 5mL, 25mg

Note: the above are names in the USA. Other countries may use different names for the same formulation.

## 6. Whether listing is requested as an individual medicine or as representative of a pharmacological class.

We request that methylphenidate be listed as a representative of a pharmacologic class. It represents all products containing methylphenidate approved for use by any government regulatory agency for the treatment of ADHD.

## 7. Treatment details (requirements for diagnosis, treatment and monitoring).

Diagnosis

ADHD can only be diagnosed by a licensed clinician who interviews the parent or caregiver and/or patient to document criteria for the disorder (American Psychiatric Association, 2013; Chinese Society of Psychiatry, 2001; Faraone et al., 2015; Feldman and Reiff, 2014; Pearl et al., 2001; Stein, 2008; World Health Organization, 2018a). It cannot be diagnosed by rating scales alone, neuropsychological tests or methods for imaging the brain. Professional associations have endorsed and published guidelines for diagnosing ADHD (Alliance, 2011; Banaschewski T, 2018; Bolea-Alamanac et al., 2014; Crunelle et al., 2018; Flisher, 2013; Graham et al., 2011; Kooij et al., 2019; National Collaborating Centre for Mental Health, 2018; National Institute for Health Care and Excellence, 2018; Pliszka, 2007; Schoeman and Liebenberg, 2017; Seixas et al., 2012; Taylor et al., 2004; Wolraich et al., 2011). The diagnosis requires: 1) the presence of developmentally inappropriate levels of hyperactive-impulsive and/or inattentive symptoms for at least 6 months; 2) symptoms occurring in different settings (e.g., home and school); 3) symptoms that cause impairments in living; 4) some of the symptoms and impairments first occurred in early to mid-childhood; and 4) no other disorder better explains the symptoms (American Psychiatric Association, 2013; World Health Organization, 2018a; Yi and Jing, 2015).

Treatment

As determined by governmental regulatory agencies around the world, methylphenidate is safe and effective for treating ADHD symptoms as determined by randomized controlled clinical trials that typically study patients for several weeks.

Dosage Guidelines for Pediatric Patients with ADHD from www.pdr.net

Children and Adolescents 6 years and older not currently taking methylphenidate

Initially, 18 mg PO once daily in the morning. Dose may be increased by 18 mg increments at weekly intervals. A 27-mg tablet is available for prescribers who wish to utilize a dosage between 18 to 36 mg. FDA-approved Max: 54 mg/day in children and 72 mg/day (not to exceed 2 mg/kg/day) in adolescents; however, some experts recommend doses up to 108 mg, which may be appropriate in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

Children and Adolescents 6 years and older currently taking 10 to 15 mg/day methylphenidate

Initially, 18 mg PO once daily in the morning. Titrate dose by 18 mg increments at weekly intervals as needed. A 27-mg tablet is available for patients who may benefit from a dosage between 18 to 36 mg. FDA-approved Max: 54 mg/day in children and 72 mg/day (not to exceed 2 mg/kg/day) in adolescents; however, some experts recommend doses up to 108 mg, which may be appropriate in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

Children and Adolescents 6 years and older currently taking 20 to 30 mg/day methylphenidate

Initially, 36 mg PO once daily in the morning. Titrate dose by 18 mg increments at weekly intervals as needed. FDA-approved Max: 54 mg/day in children and 72 mg/day (not to exceed 2 mg/kg/day) in adolescents; however, some experts recommend doses up to 108 mg, which may be appropriate in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

Children and Adolescents 6 years and older currently taking 30 to 45 mg/day methylphenidate

Initially, 54 mg PO once daily in the morning. Titrate dose by 18 mg increments at weekly intervals as needed and as clinically appropriate. FDA-approved Max: 54 mg/day in children and 72 mg/day (not to exceed 2 mg/kg/day) in adolescents; however, some experts recommend doses up to 108 mg, which may be appropriate in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

Adolescents currently taking 40 to 60 mg/day methylphenidate

Initially, 72 mg PO once daily in the morning. While the FDA-approved maximum dosage is 72 mg/day (not to exceed 2 mg/kg/day), some experts recommend doses up to 108 mg, which may be appropriate in patients weighing more than 50 kg. Titrate dosage by 18 mg increments no more frequently than weekly intervals as clinically appropriate. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

*Oral dosage (extended-release once-daily capsules; Metadate CD)*

Children and Adolescents 6 years and older not currently taking methylphenidate

Initially, 20 mg PO once daily in the morning. Dose may be increased by 10 to 20 mg increments at weekly intervals. FDA-approved Max: 60 mg/day; however, some experts recommend doses up to 100 mg/day for patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

Children and Adolescents 6 years and older currently taking other dosage forms of methylphenidate

Initially, 20 mg PO once daily in the morning. Alternatively, give no more than the equivalent total daily dose of the previous methylphenidate product, rounded to the nearest available capsule size, PO once daily. For example, patients already taking 10 mg of immediate-release methylphenidate twice daily (20 mg/day) should start with 20 mg Metadate CD once daily; those taking 20 mg twice daily (40 mg/day) could start with 40 mg Metadate CD once daily. Dose may be increased by 10 to 20 mg increments at weekly intervals. FDA-approved Max: 60 mg/day; however, some experts recommend doses up to 100 mg/day for patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

*Oral dosage (extended-release once-daily capsules; Ritalin LA)*

Children and Adolescents 6 years and older not currently taking methylphenidate

Initially, 20 mg PO once daily in the morning. If a lower initial dose is desired, 10 mg PO once daily may be used. Dose may be increased by 10 mg increments at weekly intervals. FDA-approved Max: 60 mg/day; however, some experts recommend doses up to 100 mg/day in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

Children and Adolescents 6 years and older currently taking other dosage forms of methylphenidate

Initially, give no more than the total daily dosage of the previous methylphenidate product PO once daily in the morning. For example, patients already taking 10 mg of immediate-release methylphenidate twice daily (20 mg/day) should start with 20 mg Ritalin LA once daily; those taking 20 mg of extended-release methylphenidate once daily (20 mg/day) should also start with 20 mg of Ritalin LA once daily. Dose may be increased by 10 mg increments at weekly intervals. FDA-approved Max: 60 mg/day; however, some experts recommend doses up to 100 mg/day in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

*Oral dosage (extended-release once-daily capsules; Aptensio XR)*

Children and Adolescents 6 years and older

Initially, 10 mg PO once daily in the morning. Dose may be increased by 10 mg increments at weekly intervals. FDA-approved Max: 60 mg/day; however, some experts have recommended doses up to 100 mg/day of other methylphenidate formulations in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

*Oral dosage (extended-release once-daily chewable tablets; QuilliChew ER)*

Children and Adolescents 6 years and older

Initially, 20 mg PO once daily in the morning. Dose may be titrated up or down in increments of 10 mg, 15 mg, or 20 mg at weekly intervals. The 10 mg and 15 mg doses can each be achieved by breaking in half the functionally scored 20 mg and 30 mg tablets, respectively. FDA-approved Maximum: 60 mg/day PO; however, some experts have recommended doses up to 100 mg/day of other methylphenidate formulations in patients weighing more than 50 kg. If switching from another methylphenidate product, discontinue that treatment and titrate with QuilliChew ER as previously described; do not substitute QuilliChew ER for other methylphenidate products on a mg-for-mg basis. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

*Oral dosage (extended-release once-daily suspension; Quillivant XR)*

Children and Adolescents 6 years and older

Initially, 20 mg PO once daily in the morning. Dose may be increased by 10 to 20 mg increments at weekly intervals. FDA-approved Max: 60 mg/day; however, some experts have recommended doses up to 100 mg/day of other methylphenidate formulations in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

*Oral dosage (extended-release orally disintegrating tablets; Cotempla XR-ODT)*

Children and Adolescents 6 years and older

Initially, 17.3 mg PO once daily in the morning; take consistently with or without food. Dose may be increased by 8.6 to 17.3 mg increments at weekly intervals. FDA-approved Max: 51.8 mg/day. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

*Transdermal dosage (transdermal system; Daytrana)*

Children and Adolescents 6 years and older

Initially, apply a 10 mg/9-hour patch topically once daily in the morning, 2 hours before an effect is needed, regardless of previous methylphenidate therapy. If response is not maximized after 1 week, titrate to the next available patch strength in weekly intervals. The suggested upward titration schedule is Week 1: apply 10 mg/9-hour patch once daily; Week 2: apply 15 mg/9-hour patch once daily; Week 3: apply 20 mg/9-hour patch once daily; Week 4: apply 30 mg/9-hour patch once daily. Dose titration, final dosage, and wear time should be individualized according to the needs and response of the patient. Maximum: 30 mg/9-hour patch once daily. In clinical trials, there was no additional benefit of increasing the patch dose from 20 mg/9-hours to 30 mg/9-hours. Remove the patch 9 hours after application or may remove earlier if late day side effects appear and shorter duration of effect is desired.

*Oral dosage (extended-release once-daily capsules; Jornay PM)*

Children and Adolescents 6 years and older

Initially, 20 mg PO once daily in the evening. Dose may be titrated in increments of 20 mg at weekly intervals. Max: 100 mg/day. If switching from another methylphenidate product, discontinue that treatment and titrate with Jornay PM as previously described; do not substitute Jornay PM for other methylphenidate products on a mg-for-mg basis. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse reactions occur, reduce dosage or discontinue the drug.

*Oral dosage (extended-release once-daily capsules; Adhansia XR)*

Children and Adolescents 6 years and older

Initially, 25 mg PO once daily in the morning. Dose may be titrated in increments of 10 to 15 mg at intervals of no less than 5 days. Max: 85 mg/day. Although 85 mg was efficacious in short-term controlled trials, dosages above 70 mg daily were associated with a disproportionate increase in the

incidence of certain adverse reactions. If switching from another methylphenidate product, discontinue that treatment and titrate with Adhansia XR as previously described; do not substitute Adhansia XR for other methylphenidate products on a mg-for-mg basis. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse reactions occur, reduce dosage or discontinue the drug.

*Oral dosage (immediate-release preparations; Ritalin, Methylin, Methylin oral solution, Methylin chewable tablets).*

Children and Adolescents 6 years and older

Initially, 5 mg PO twice daily before breakfast and lunch. Dose may be increased by 5 to 10 mg/day at weekly intervals; some patients may require dosing up to 3 times daily (administer last dose of day before 6 pm to limit sleep interference). Max: 60 mg/day per FDA-approved labeling; however, some experts state that doses up to 100 mg/day may be needed in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If no improvement within 1 month, discontinue methylphenidate and consider an alternative treatment/therapy. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

Children 3 to 5 years†

The National Institute of Mental Health's Preschool ADHD Treatment Study (PATS) provides clinical guidance for children with ADHD 3 to 5 years of age. In the PATS, the initial dose of immediate-release methylphenidate was 1.25 mg PO 3 times daily. Doses were increased gradually up to a maximum of 10 mg PO 3 times daily to reach optimum therapeutic response. The mean optimal total daily dose was 14.2 +/- 8.1 mg (0.7 +/- 0.4 mg/kg/day). Max: 30 mg/day. In all cases, treatment should start with a low dose and be titrated upward slowly. Use lowest effective dose. Higher doses have lead to social withdrawal in some children. Behavior therapy, parental training, and a structured preschool environment are considered first line treatment for preschool-aged children with ADHD; lack of significant improvement with such modalities may warrant the addition of methylphenidate.

*Oral dosage (extended-release tablets; Ritalin SR, Metadate ER, Methylin ER)*

The extended-release (ER) tablets have a duration of action of approximately 8 hours. Use in place of immediate-release (IR) tablets when the 8-hour dosage of the ER tablets corresponds to the previously titrated 8-hour dosage of the IR tablets. Alternatively, some experts recommend an initial dose of 10 mg PO once daily. Ritalin SR may be administered once or twice daily. Max: 60 mg/day per FDA-approved labeling; however, some experts state that doses up to 100 mg/day may be needed in patients weighing more than 50 kg. Individualize dosage based on psychosocial and comorbid factors; use lowest effective dose. If paradoxical aggravation of symptoms or other adverse effects occur, reduce dosage or discontinue the drug.

## Maximum Doses

(from www.pdr.net):

### Adolescents

85 mg/day PO for Adhansia XR; 72 mg/day (Max: 2 mg/kg/day) PO for Concerta (FDA-approved labeling); 60 mg/day PO for all other oral formulations excluding Cotempla XR-ODT and Jornay PM (FDA-approved labeling); 51.8 mg/day PO for Cotempla XR-ODT and 100 mg/day PO for

Jornay PM; however, doses up to 100 to 108 mg/day PO have been used in patients weighing more than 50 kg for some formulations. For the transdermal patch, 30 mg/9-hour patch per day is the maximum.

Children

6 to 12 years: 85 mg/day PO for Adhansia XR; 54 mg/day PO for Concerta (FDA-approved labeling); 60 mg/day PO for all other oral formulations excluding Cotempla XR-ODT and Jornay PM (FDA-approved labeling); 51.8 mg/day PO for Cotempla XR-ODT and 100 mg/day PO for Jornay PM; however, doses up to 100 to 108 mg/day PO have been used in patients weighing more than 50 kg for some formulations. For the transdermal patch, 30 mg/9-hour patch per day is the maximum.

3 to 5 years: Safety and efficacy have not been established. Maximum doses have not been adequately studied; however, The Preschool ADHD Treatment Study (PATS) has suggested immediate-release doses up to 30 mg/day PO.

1 to 2 years: Safety and efficacy have not been established.

Infants

Safety and efficacy have not been established.

Neonates

Safety and efficacy have not been established.

Elderly

Some patients may tolerate lower doses better

## Special Populations (Stahl, 2018)

**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 heart rate and/or blood pressure
- Do not use in patients with structural cardiac abnormalities or outflow obstructions
-

**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/kg/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

## Other Issues (Stahl, 2018)

**Pharmacokinetics** (Stahl, 2018)

- Average half-life in adults is 3.5hours (1.3-7.7hours)
- Average half-life in children is 2.5hours (1.5-5hours)
- There is considerable inter-individual variability in metabolism and dosing by weight (mg/kg) is not generally recommended
- First-pass metabolism is not extensive with transdermal dosing, thus resulting in notably higher exposure to l-methylphenidate and lower exposure to metabolites as compared with oral dosing

**Onset of Action** (Stahl, 2018)

- Some immediate effects can be seen with first dosing
- Can take several weeks to attain maximum therapeutic benefit

**Long-Term Use** (Stahl, 2018)

- Often used long-term for ADHD when ongoing monitoring documents continued efficacy
- Dependence and/or abuse may develop. However, the best current information, controlling for confounding factors, suggests that the therapeutic use of stimulant medications such as methylphenidate decreases the risk for substance use disorders (Chang et al., 2014c).
- 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** (Stahl, 2018)

- Vomiting, tremor, coma, convulsion, hyperreflexia, euphoria, confusion, hallucination, tachycardia, flushing, palpitations, sweating, hyperpyrexia, hypertension, arrhythmia, mydriasis

**Dependence or Abuse** (Stahl, 2018)

- Schedule II drug
- Patient may develop tolerance, psychological dependence
- Treatment with methylphenidate and other stimulants reduces the risk for substance use, abuse and dependence (Chang et al., 2014c; Schoenfelder et al., 2014).

**Discontinuation** (Stahl, 2018)

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

Storage and Handling of Methylphenidate (from: www.pdr.net)

Generic:

- Protect from moisture
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

Adhansia XR:

- Protect from light
- Protect from moisture
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

Aptensio XR:

- Store at controlled room temperature (between 68 and 77 degrees F)

Concerta:

- Avoid excessive humidity
- Store at controlled room temperature (between 68 and 77 degrees F)

Cotempla XR:

- Product should always be stored in the blister and only removed immediately before use
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

Daytrana:

- Do not freeze
- Do not refrigerate
- Product should be used within 2 months after opening
- Store at 77 degrees F; excursions permitted to 59-86 degrees F
- Store unused product in foil pouch

Jornay:

- Store at controlled room temperature (between 68 and 77 degrees F)

Metadate CD:

- Store at controlled room temperature (between 68 and 77 degrees F)

Metadate ER:

- Protect from moisture
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

Methylin:

- Protect from moisture
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

QuilliChew ER:

- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

Quillivant XR:

- Store and dispense in original container
- Store reconstituted product in accordance with package insert instructions
- Store unreconstituted product at 77 degrees F; excursions permitted to 59-86 degrees F

RELEXXII:

- Avoid excessive humidity
- Store at 77 degrees F; excursions permitted to 59-86 degrees F

Ritalin:

- Protect from light

- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

Ritalin LA:

- Store at controlled room temperature (between 68 and 77 degrees F)

Ritalin SR:

- Protect from moisture
- Store between 68 to 77 degrees F, excursions permitted 59 to 86 degrees F

## Need for Special Diagnostics, Treatment or Monitoring Facilities and Skills When Prescribing Methylphenidate

### Assessing Cardiovascular Status (Torres-Acosta et al., 2020)

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 baseline heart rate and blood pressure, and an electrocardiogram if personal or family history, or findings on physical exam suggest risk for cardiac 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. Heart rate and blood pressure should be monitored regularly.

### Growth (Faraone et al., 2008)

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 adjusted or interrupted.

### Other Considerations

Before prescribing methylphenidate, appropriate attention needs to be given to the psychosocial environment. In children, attention should be paid as to whether the family is intact or separated, whether both parents are supportive of the child's treatment, and whether any concerns exist about abuse or maltreatment. Additionally, legal concerns, psychopathology and substance use in the parents, psychosocial stressors (such as financial and medical distress), access to firearms, and the intellectual abilities of the parents are assessed because treatments may not be effective in chaotic or dangerous environments. Access to medications may be an issue due to lack of health insurance or restrictive policies by some governments or managed care formularies. Pharmacotherapy for ADHD will not address these issues, but they can be targeted by appropriate social services or non-pharmacologic treatments. It is important to educate parents and patients about ADHD and its treatments to help them understand the value of treatment options.

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 of inattention, hyperactivity and impulsivity. The diagnosis of

this syndrome should not be made without evidence of impairment in two or more settings and onset prior to age 12 (Faraone et al., 2015; National Institute for Health Care and Excellence, 2018).

Methylphenidate treatment is not indicated for all children with this syndrome. Methylphenidate is not intended for use in the child who exhibits symptoms secondary to environmental factors and/or other primary psychiatric disorders, especially psychotic illness. Psychoeducation should form the foundation of all treatment for ADHD (National Institute for Health Care and Excellence, 2018). 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. Methylphenidate should be used cautiously or not at all in patients at risk for diversion or misuse (Faraone et al., 2020).

## 8. Information Supporting the Public Health Relevance of Methylphenidate

Epidemiological information on disease burden

ADHD is a disorder associated with serious distress and/or impairments in living. Although significant impairment across at least two settings is a prerequisite for a diagnosis of ADHD and, as documented below, many severe adverse outcomes have been associated with ADHD, the typical patient does not experience all, or even most, of these problems and many patients live enjoyable and productive lives, especially if they receive treatment. Much of the following comes from the International Consensus Statement on ADHD (Faraone et al., 2020 Submitted).

Quality of Life

1. A meta-analysis of seven studies with over 5,000 youths and their parents reported large impairments in the quality of life of youths with ADHD relative to typically developing peers, regardless of whether evaluated by the youths themselves or by their parents. Physical functioning was only moderately impaired, but emotional, social and school functioning were strongly impaired. As youths with ADHD grew older, their quality of life, when compared with typically developing peers, grew worse in physical, emotional, and school domains. (Lee et al., 2016b).

2. A meta-analysis of six studies encompassing 647 families evaluated the quality of life of parents whose children had ADHD relative to parents with typically developing children. Parents of the former reported a moderate deficit in quality of life relative to parents of the latter (Dey et al., 2019).

Emotional and Social Impairment

3. A study of over 8,600 youths from the US National Health Interview Survey found that those with ADHD were six times as likely to have a high level of emotional, conduct, and peer problems, and nine times as likely to manifest a high level of impairment including interference with home life, friendships, classroom learning, and leisure activities (Strine et al., 2006).

4. A meta-analysis of 22 studies with almost 22,000 participants found that youth with ADHD were strongly impaired in the ability to modulate their reactivity to novel or stressful events. ADHD was also associated with medium-to-large impairments identifying emotions and expressing empathy (Graziano and Garcia, 2016). Another meta-analysis, combining four studies with over 600 adults, reported a very strong correlation between ADHD symptom severity and emotional dysregulation (Beheshti et al., 2020).

5. A meta-analysis of 109 studies of over a hundred thousand participants found that children with ADHD had medium-to-large impairments in socializing with peers as measured by rejection/likability, popularity, and friendships. They also had medium impairments in social skills (e.g., sharing, cooperating, turn-taking, reciprocity) and social-information processing (e.g., recognizing social cues, identifying problems, generating solutions, and avoiding biases) (Ros and Graziano, 2018).

6. A study of over 53,000 U.S. children from the National Survey of Children's Health found that those with ADHD were 2.4 times as likely to engage in bullying (Montes and Halterman, 2007). A more recent study of some 64,000 children using the same database confirmed this finding, reporting that those with ADHD were 2.8 times more likely to engage in bullying (Benedict et al., 2015).

Accidental Injuries

7. A nationwide cohort study of over 50,000 youths with ADHD and an equal number of age-, sex-, and comorbidity-matched controls drawn from Taiwan's National Health Insurance Research Database reported that having ADHD was associated with a more than three-quarters greater likelihood of burn injury. For those under six years old, the risk was doubled. For youths between six and seventeen years old, the increase in risk was about 70 percent. There were no significant differences between boys and girls (Yeh et al., 2020).

8. A meta-analysis of 32 studies covering more than four million people found that those with ADHD had a 40 to 50% greater risk of accidental physical injuries (Ruiz-Goikoetxea et al., 2018a).

9. A Swedish national registers study followed 17,408 individuals with ADHD from 2006 to 2009 and found that patients with ADHD had an almost 50% greater risk of serious transport accidents (Chang et al., 2014b).

10. A U.S. study of over 8,000 high school and collegiate athletes (predominantly male football players) found that those with ADHD were three times as likely to have had three or more reported concussions (Nelson et al., 2016).

11. A meta-analysis of 32 studies encompassing over 175,000 people estimated that controlling for mileage driven, those with ADHD were 23% more likely to be involved in vehicular crashes (Vaa, 2014).

12. A retrospective cohort study of over 18,000 New Jersey drivers found that the crash risk for those with ADHD was a third greater than for those without (Curry et al., 2017).

13. A meta-analysis of five studies, comprising over three thousand patients with minor traumatic brain injury (mTBI) and over nine thousand controls found that those with mTBI were twice as likely to have ADHD than those without mTBI (Adeyemo et al., 2014).

Premature Death and Suicide

14. A Danish study of almost two million people found ADHD is associated with a small risk for premature death, mostly due to accidents. When ADHD was accompanied by other psychiatric and substance use disorder, the chances of premature death increased (Dalsgaard et al., 2015b).

15. A cohort study of more than 2.2 million Taiwanese found no increased risk of death from natural-causes associated with ADHD. But people with ADHD had twice the rate of suicide, twice the rate of death by homicide, and a 30% greater rate of death from unintentional injury (Chen et al., 2019).

16. Using nationwide registers in Denmark, a cohort study of 2.9 million people reported a fourfold higher rate of suicide attempts and deaths in patients with ADHD. The risk was over tenfold in those with ADHD plus another psychiatric diagnosis (Fitzgerald et al., 2019).

17. A meta-analysis of 57 studies with over 330,000 people found that those with ADHD attempted suicide at twice the rate of typically developing people, had over three times the rate of suicidal ideation, and over six times the rate of completed suicide (Septier et al., 2019).

18. A Taiwanese study of over 20,000 adolescents and young adults with ADHD and over 61,000 age- and sex-matched non-ADHD individuals found that those with ADHD were almost four times as likely to attempt suicide, and over six times as likely to repeat suicide attempts. Methylphenidate or atomoxetine treatment did not increase the risk of suicide attempts or repeated suicide attempts. Long-term methylphenidate treatment was associated with a lower risk for repeated suicide attempts among men (Huang et al., 2018).

19. In a prospective cohort study of more than 2.6 million Swedes, adults with ADHD had a small increase in premature death, mostly due to accidents and suicide. There was no significant association for children with ADHD (Sun et al., 2019b).

Crime and Delinquency

20. A study of the Danish population using nationwide registers found that, compared with other youth, those diagnosed with ADHD were more than twice as likely to be convicted of criminal offenses and were three times as likely to be incarcerated. After adjusting for other risk factors, those with ADHD were 60% more likely to have been convicted of a crime, and 70% more likely to have been incarcerated (Mohr-Jensen et al., 2019).

21. A meta-analysis reported the prevalence of ADHD among adolescents in juvenile detention to be just over 17%, both for males (24 studies, over 24,000 individuals) and females (12 studies, over 3,900 individuals), which is much higher than the prevalence in the population (Beaudry et al., 2020). Another meta-analysis comprising 21 studies and 19,575 prison inmates found that the prevalence of ADHD in prisons was 20.5% with no differences observed between males and females or adolescents and adults (Young et al., 2015).

22. A study using a nationally representative American sample of over 5,000 adults found that those with ADHD were over twice as likely to be perpetrators of physical dating violence, and 65% more likely to be victims of such violence (McCauley et al., 2015).

23. In a nationwide study of over 21,000 Icelandic adolescents and young adults, 14% reported having been interrogated at a police station. Of these, 15% reported making a false confession. Those with ADHD were twice as likely to make a false confession (Gudjonsson et al., 2016).

24. A study using the Danish national registries looked at violent crimes against youth aged 7-18 years, among a total of 678,000 individuals. Children with ADHD were 2.7 times more likely to be victims of violent crimes than their typically developing peers, after adjusting for confounding risk factors (Christoffersen, 2019).

Educational Underachievement

25. A study of a U.S. sample of almost 30,000 adults found that those with ADHD were twice as likely not to have graduated from high school on time, after adjusting other psychiatric disorders (Breslau et al., 2011).

26. A nationwide cohort study of over 750,000 Scottish school children using linked national registers identified those who had been prescribed medicine for ADHD. Even while receiving medication, these children were more than three times as likely as typically developing peers to have low educational achievement, more than twice as likely to drop out of school before age 16, more than eight times as likely to have a record of special educational needs, 50% more likely to get injured, 40% more likely to

be unemployed. These results were adjusted for socioeconomic confounders and other psychiatric conditions (Fleming et al., 2017).

27. A meta-analysis of ten studies and 830 youths found that ADHD was strongly associated with poorer performance on measures of overall, expressive, receptive, and pragmatic language (Korrel et al., 2017).

Substance Use Disorders

28. A meta-analysis of twelve studies covering over 5,400 people found that those with ADHD were almost three times more likely to be nicotine-dependent. Combining eleven studies with almost 2,400 participants, those with ADHD were 50% more likely to develop a drug or alcohol use disorder than those without ADHD (Lee et al., 2011).

29. A meta-analysis of 23 studies with over 22,000 participants found that ADHD was associated with a more than twofold greater risk of addiction, alcohol-related disorders, drug-related disorder, and nicotine-related disorder (Groenman et al., 2017).

30. A Swedish study of over half a million people found a more than threefold association between ADHD and subsequent drug use disorders after adjusting for sex and parental education (Sundquist et al., 2015).

Other

31. Studies of 2.7 million girls from Denmark (Ostergaard et al., 2017), 380,000 from Sweden (Skoglund et al., 2019) and 7,500 from Taiwan (Hua et al., 2020) found that those with ADHD were more likely to have teen pregnancies than those without ADHD. Consistent with these results, large studies from Sweden (Chang et al., 2014a), Finland (Chudal et al., 2015) and a consortium of eight European countries (Pohlabeln et al., 2017) each found ADHD to be more likely among children of teenage mothers than among children of older mothers.

32. A study of over 36,000 people from the US reported that ADHD increased the risks for problem gambling, spending too much money, reckless driving, and quitting a job without a plan for what to do next (Bernardi et al., 2012).

33. A nationwide study using Taiwan's National Health Insurance Research Database compared 675 adults with ADHD and 2,025 without ADHD, matched by age and sex. After adjusting for other psychiatric disorders, urbanization level of residence, and monthly income, those with ADHD had 3.4 times the risk of developing dementia (Tzeng et al., 2019).

34. A meta-analysis of nine studies encompassing almost a million and a half people found that ADHD is associated with a threefold greater risk of poisoning in children (Ruiz-Goikoetxea et al., 2018b). In a study from Taiwan comparing 3,685 children with ADHD with 36,000 controls, those with ADHD had a more than fourfold greater risk of deliberate self-poisoning (Chou et al., 2014).

35. A longitudinal study of some 15,000 U.S. adolescents reported that those with ADHD had a 12% reduction in employment and a 34% reduction in earnings relative to non-ADHD siblings (Fletcher, 2014).

36. Using Danish registers, a nationwide population study of over 675,000 youths between the ages of 7 and 18 found that youths with ADHD were 3.7 times as likely to be reported as victims of sexual crimes than normally developing controls. After adjusting for covariates, such as parental violence, parental inpatient mental illness, parental suicidal behavior or alcohol abuse, parental long-term unemployment, family separation, and child in public care outside the family, youths with ADHD remained almost twice as likely to be reported as victims of sexual crimes (Christoffersen, 2020).

The Economic Burden of ADHD

1. A nationwide population study of over 83,000 persons with ADHD and 334,446 non-ADHD controls matched by age and sex used Danish national registries to calculate the net socioeconomic cost of ADHD. Relative to controls, and summing net direct health costs and net losses from lower income and employment, the yearly average cost per individual with ADHD came to just over €16,000. Including additional social transfers, the total rose to just over €23,000. For partners of persons with ADHD, the additional yearly average cost per individual was almost €5,500. With additional social transfers, the total rose to €8,000 (Jennum et al., 2020).

2. A systematic review of seven European studies of hundreds of thousands of participants estimated total ADHD-related costs in the Netherlands as €9,860 to €14,483 per patient per year, with annual national costs more than €1 billion (Le et al., 2014).

3. A review of the costs of child, youth and adult ADHD in Australia estimated the total annual costs to be over $20 billion Australian dollars, or $25,000 per person with ADHD. This includes financial costs of $12.8 billion, well-being losses of $7.6 billion, and productivity losses of $10.2 billion (Australian ADHD Professionals Association, 2019).

4. A systematic review of 19 U.S. studies of hundreds of thousands of people found that ADHD was associated with overall national annual costs from $143 to $266 billion, mostly associated with adults ($105 to $194 billion). Costs borne by family members of people with ADHD ranged from $33 - $43 billion (Doshi et al., 2012).

5. A study with over 7,000 workers in ten nations found that those with ADHD had an average of 22 annual days of lost role performance compared with those without ADHD (de Graaf et al., 2008).

6. A study of a U.S. national Fortune 100 company's database of over 100,000 beneficiaries compared healthcare costs for youths with ADHD with matched controls without ADHD. The annual average cost per family member was $2,728 for non-ADHD family members of ADHD patients, almost double the $1,440 for family members of matched controls (Swensen et al., 2003).

7. German health insurance records, including over 25,000 patients with ADHD, indicate that patients with ADHD cost roughly €1,500 more annually than those without ADHD. Main cost drivers were inpatient care, psychiatrists, and psychotherapists. Mood, anxiety, substance use disorders, and obesity were significantly more frequent in patients with ADHD. The additional costs resulting from these conditions added as much as €2,800 per patient (Libutzki et al., 2019).

8. Using the National Health Insurance Service claims data for the population aged 19 years or younger in South Korea (69,353 diagnosed with ADHD), the total annual economic burden due to ADHD was estimated to be $47.55 million (Hong et al., 2020).

9. Using the Danish national registers, over 5,000 adults with a diagnosis of ADHD in adulthood who had not received a diagnosis in childhood were identified. Excluding cases with missing data, other psychiatric diagnoses, and cases without a same-sex sibling free of any diagnosed psychiatric diagnoses, a final cohort was formed consisting of 460 sibling pairs. On average, adults with ADHD had an annual economic burden of just over €20,000 compared with their normally developing siblings (Daley et al., 2019).

10. A nationwide cohort study of over 445,000 people in the Swedish national registers compared healthcare costs for three groups: those with childhood ADHD that persisted into adulthood, those whose ADHD remitted in adulthood, and those who never had ADHD. Those who never had ADHD had average annual healthcare costs of €304. Those in remission had double the cost, and those with persistent ADHD over triple the cost (Du Rietz et al., 2020).

## Assessment of current use

Methylphenidate is recommended as a first line treatment for ADHD in many treatment guidelines for ADHD from around the world. (Alliance, 2011; Banaschewski T, 2018; Bolea-Alamanac et al., 2014; Crunelle et al., 2018; Flisher, 2013; Graham et al., 2011; Kooij et al., 2019; National Collaborating Centre for Mental Health, 2018; National Institute for Health Care and Excellence, 2018; Pliszka, 2007; Schoeman and Liebenberg, 2017; Seixas et al., 2012; Taylor et al., 2004; Wolraich et al., 2011). As a result, it is widely used in many countries.

**Table 10. Methylphenidate: rates of consumption in the 20 countries and territories reporting the highest consumption in 2018, compared with 2016 and 2017**

| | (S-DDD per 1,000 inhabitants per day) | | |
|---|---|---|---|
| *Country or territory* | *2016* | *2017* | *2018* |
| Iceland | 25.10 | 31.94 | 29.05 |
| Israel | 16.14 | 13.95 | 11.75 |
| Canada | 8.21 | 8.09 | 9.49 |
| Sweden | 8.35 | 7.83 | 8.00 |
| Netherlands | 7.97 | 7.40 | 7.98 |
| United States | 7.91 | 6.82 | 7.60 |
| Denmark | 6.60 | 7.04 | 7.31 |
| Switzerland | 3.85 | 3.90 | 4.11 |
| New Zealand | 4.56 | 2.62 | 3.92 |
| Finland | 2.38 | 2.73 | 3.23 |
| Belgium | 2.71 | 2.36 | 2.86 |
| Germany | 1.84 | 1.26 | 1.68 |
| Chile | 2.14 | 1.61 | 1.60 |
| *Falkland Islands (Malvinas)* | — | 1.70 | 1.46 |
| South Africa | 1.04 | 1.22 | 1.45 |
| *Sint Maarten* | 1.59 | 0.94 | 1.04 |
| Portugal | — | 0.98 | 1.02 |
| Turkey | 0.83 | 0.00 | 0.96 |
| *Gibraltar* | 0.88 | 0.99 | 0.89 |
| *Turks and Caicos Islands* | — | 0.92 | 0.83 |

The following Table was extracted from a Technical Publication of the International Narcotics Control Board. It lists methylphenidate rates of consumption in the 20 countries and territories reporting the highest rates of consumption in 2018 and compares those rates with rates in 2016 and 2017. Rates are expressed in 'defined daily dose for statistical purposes' (S-DDD) per 1,000 inhabitants per day. DDD is the assumed average maintenance dose per day for a drug used for its main indication.

By comparison and although its dosing range is different than methylphenidate, another controlled substance already among the psychotropic medications on the EML is diazepam. Historically the most produced benzodiazepine in the world, the consumption of diazepam was reported by 92 countries in 2018. Rates of reported consumption were higher than 10 S-DDD by Uruguay, Montenegro, Brazil, Serbia, Portugal and Ghana. A further 27 countries, most of them in Europe, reported rates of consumption higher than 2 S-DDD.

## Target population(s)

The target population for methylphenidate comprises all patients diagnosed with ADHD. In guidelines, it is typically recommended as a first line treatment (Alliance, 2011; Banaschewski T, 2018; Bolea-Alamanac et al., 2014; Crunelle et al., 2018; Flisher, 2013; Graham et al., 2011; Kooij et al., 2019; National Collaborating Centre for Mental Health, 2018; National Institute for Health Care and Excellence, 2018; Pliszka, 2007; Schoeman and Liebenberg, 2017; Seixas et al., 2012; Taylor et al., 2004; Wolraich et al., 2011; Zheng and Liu, 2015) except for children younger than six for whom a trial of behavior therapy is recommended first.

## Likely impact of treatment on the disease

As determined by governmental regulatory agencies around the world, methylphenidate is safe and effective for treating ADHD symptoms as determined by randomized controlled clinical trials that

typically study patients for several weeks. Methylphenidate is as efficacious, or more efficacious, than many medications used in physical medicine (Leucht et al., 2012).

Randomized Controlled Clinical Trials Comparing Methylphenidate and Placebo in Patients with ADHD

A network meta-analysis of 133 RCTs including more than 24,000 participants found stimulants to be highly effective in reducing the symptoms of ADHD. Compared with placebo, methylphenidate treatment led to large improvements in youths with a mean standardized mean difference of -0.78 (-0.93 to -0.62) (Cortese et al., 2018).

A meta-analysis of 19 parallel group trials with over 1,600 participants, found methylphenidate produced moderate to large improvements in teacher-rated ADHD symptoms, teacher-rated behavior and parent-rated quality of life. There was no evidence of serious adverse events, and just a slightly elevated risk of non-serious side effects (Storebo et al., 2015).

A meta-analysis of 21 studies with over 2,300 adult participants found that methylphenidate led to small-to-moderate reductions in symptoms of emotional dysregulation (Lenzi et al., 2018).

A meta-analysis of eight studies with 423 participants reported moderate-to-strong improvements in ADHD symptoms with methylphenidate in ADHD patients with borderline intellectual functioning or intellectual disability. It was equally effective for hyperactivity and inattention. It also led to small-to-moderate improvements on a continuous performance test (Sun et al., 2019a).

Clinical Trials Comparing Methylphenidate and Placebo in 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 (Osland et al., 2018). 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 be 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.

Clinical Trials Comparing Methylphenidate and Placebo in 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) (Correia Filho et al., 2005). 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 methylphenidate 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. methylphenidate 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.

Clinical Trials Comparing Methylphenidate and Placebo in ADHD & Autism Spectrum Disorders

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 (Sturman et al., 2017). 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.

Clinical Trials Comparing Methylphenidate and Placebo in ADHD & Oppositional Defiant Disorder and Aggression

In an open-label comparative study, children with DSM-IV-TR ADHD, aged 8-18years with (n=30) and without (n=30) oppositional defiant disorder (ODD) received methylphenidate treatment for 12 weeks (Golubchik and Weizman, 2018).. 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 methylphenidate 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 methylphenidate treatment on ADHD and ODD symptoms it also diminishes suspiciousness.

Another study aimed to assess the effectiveness of monotherapy with stimulant methylphenidate 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 (Masi et al., 2017). Twenty males treated with methylphenidate (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 methylphenidate was effective on attention problems ($8.44 \pm 2.55$ ($P < 0.001$)) and attention-deficit/hyperactivity problems ($7.83 \pm 2.36$ ($P < 0.001$)).

Longer Term Outcomes Associated with Methylphenidate Treatment in Youth with ADHD

Because methylphenidate has been used for many decades, it has been feasible for researchers to study its longer-term effects using naturalistic study designs. Much of the following comes from the International Consensus Statement on ADHD (Faraone et al., 2020 Submitted)

A Swedish registry study of over 650,000 students found that treatment with ADHD medication for three months resulted in a more than nine-point gain in grade point sum (on a scale of 0 to 320); treatment was associated with an increase in the probability of completing upper secondary school by two-thirds (Jangmo et al., 2019).

A Swedish national register study of over 61,000 youths with ADHD found that their test scores were higher during periods they were taking medication vs non-medicated periods (Lu et al., 2017). A Danish study of over half a million children (over 6,400 with ADHD) found that discontinuation of ADHD medication was associated with a small but significant decline in grade point averages (Keilow et al., 2018). A meta-analysis of nine RCTs comprising 1,463 patients found that discontinuing medications led to a worsening in quality of life for children and adolescents but not adults (Tsujii et al., 2020).

A Swedish cohort study of over 25,000 ADHD patients found a one-third reduction in criminality among men receiving ADHD medication, and a 40% reduction for women (Lichtenstein et al., 2012). A Danish national registry study of over 4,200 individuals with childhood ADHD found that crime rates in adulthood were 30-40% lower during periods of taking ADHD medication (Mohr-Jensen et al., 2019).

A Danish cohort study of over 700,000 people, including 4,557 with ADHD, found that among teenagers with ADHD, stimulant treatment was associated with a decrease in rates of injuries (30% for ten-year olds and 40% for twelve-year olds) (Dalsgaard et al., 2015a).

Using the Swedish national registries, a study followed 9,421 youths with ADHD and 2,986 youths with both ADHD and other psychiatric diagnoses from 2006 to 2013. It compared periods when they were taking ADHD medication with periods when they were not. During medicated periods both groups had a greater than 10% reduction in unintended injuries, and a greater than 70% reduction in traumatic brain injuries (Ghirardi et al., 2020).

A Taiwanese study of over 124,000 youths with ADHD found that methylphenidate treatment decreased the risk for traumatic brain injuries, after adjusting for confounders (Liao et al., 2018).

A nationwide study compared 7,200 Taiwanese youths with ADHD with 36,000 children without ADHD. After adjusting by age, sex, urbanization level, and geographic region, boys with ADHD were almost 40% more likely and girls with ADHD 60% more likely to suffer bone fractures (Guo et al., 2016). Another study from Taiwan identified over 6,200 youths newly diagnosed with ADHD and assessed the effect of methylphenidate treatment. The risk of bone fractures was 20% lower in those who had over half a year of methylphenidate treatment (Chen et al., 2017).

A population-based, electronic medical records database in Hong Kong identified over 17,000 individuals aged 6-19 years who had been prescribed methylphenidate. Of these, almost 5,000 had at least one trauma-related emergency room admission. Researchers found a 9% reduction in such admissions during periods covered by a methylphenidate prescription compared with periods with no active prescription (Man et al., 2015).

A meta-analysis of five studies with over 13,000 participants found that ADHD medications (primarily stimulants) were associated with a greater than 10% reduction in unintentional injuries (Ruiz-Goikoetxea et al., 2018a).

Using Swedish national registers, a study of over 17,000 people with ADHD found that medication for ADHD was associated with a greater than 50% reduction in the risk of serious transport accidents among males but not females. Over 40% of crashes by male patients would have been avoided if they had been receiving treatment during the entire period (Chang et al., 2014b). A U.S. national cohort study of 2.3 million people with ADHD examined emergency room visits for motor vehicle crashes over ten years. Males with ADHD had a 38% lower risk of crashes in months when receiving ADHD medication compared with months when not receiving medication, and females a 42% lower risk in months when receiving ADHD medication. About a fifth of crashes would have been avoided if they had been on medication throughout the period of the study (Chang et al., 2017).

A longitudinal study using the Taiwan Health Insurance Research Database compared almost 18,000 adolescent and young adults with ADHD with over 70,000 age- and sex-matched controls. Short-term use of ADHD medications was associated with a 30% reduction in sexually transmitted infections, and long-term use with a 40% reduction, though these reductions were only among males (Chen et al., 2018).

A nationwide longitudinal cohort study using the Swedish national registers found that among more than 38,000 individuals with ADHD, ADHD medication was associated with a greater than 40% reduction in the risk for depression three years later. The risk decreased with the duration of ADHD medication use. Depression was 20% less common when patients received ADHD medication compared with periods when they did not (Chang et al., 2016).

A Swedish population-based study of 38,000 people with ADHD found a 20% decline in suicide related events among those prescribed stimulants during periods when they were under treatment as opposed to during periods when they were not under treatment. No such benefit was found for non-stimulant medications (Chen et al., 2014).

A Taiwanese study identified 85,000 youths with ADHD using National Health Insurance data to examine whether methylphenidate use affected suicide attempts. After adjusting for relevant variables, it found a 60% lower risk of suicide in those using methylphenidate for 3 months to half a year, and a 70% reduction among those using methylphenidate for more than half a year (Liang et al., 2018b).

A study using the Swedish national registers investigated the association between prescription stimulant medication for ADHD in 2006 and substance abuse during 2009 among all 38,753 people born between 1960 and 1998 and diagnosed with ADHD. After controlling for relevant variables, it found a greater than 30% reduction in indicators of substance abuse among those prescribed stimulants. The longer the duration of medication, the lower the rate of substance abuse (Chang et al., 2014c). A meta-analysis of 14 studies with over 2,300 participants found that people with ADHD were half as likely to smoke cigarettes when regularly treated with stimulant medications (Schoenfelder et al., 2014). A meta-analysis of 15 studies with over 2,500 participants found that stimulants did not increase the risk for alcohol, nicotine, cocaine, or cannabis abuse or dependence (Humphreys et al., 2013).

A nationwide study of over 7,500 Taiwanese adolescents with ADHD and over 30,000 matched controls found that long-term use of ADHD medication use was associated with a 30% decrease in teenage pregnancy (Hua et al., 2020).

A nationwide population-based cohort using Taiwan's National Health Insurance Research Database identified over 68,000 children and adolescents with a diagnosis of ADHD and who were prescribed methylphenidate and compared them with an identical number of controls matched on age, gender and year of first ADHD diagnosis. After controlling for potential confounders, ADHD individuals

prescribed methylphenidate had a one-fifth lower rate of all-cause mortality than ADHD individuals not prescribed methylphenidate. Delayed use of methylphenidate, on the other hand, was associated with slightly higher (5%) mortality. Long-term methylphenidate use was associated with a one-sixth lower rate of all-cause mortality. The authors caution, however, that "information lacking in the database precluded the measurement of other possible confounders, such as family history, psychosocial stressors, effect of behavioural therapy or severity of comorbidities," and thus unmeasured confounding cannot be excluded (Chen et al., 2020a).

A nationwide population-based cohort using Taiwan's National Health Insurance Research Database identified over 90,000 individuals younger than 18 years with a diagnosis of ADHD, and compared risk of burn injury between those not on methylphenidate, those on methylphenidate for less than 90 days, and this on methylphenidate for more than 90 days. The data suggested that fully half the incidence of burn injuries could have been prevented by taking methylphenidate. Compared with patients not taking methylphenidate, those taking it for less than 90 days had a 30% lesser risk of burn injuries, and those taking it for 90 days or more a 57% reduction in risk, after adjusting for confounders (Chen et al., 2020b).

## 9. Review of benefits: summary of evidence of comparative effectiveness

Identification of Clinical Evidence for Short Term Efficacy from Randomized Controlled Trials (RCTs)

A recent meta-review (Cortese et al., 2019) sought to identify available network meta-analyses (NMAs) aimed at assessing the comparative effectiveness of medications used in child and adolescent psychiatry. The following electronic databases, with no restrictions in terms of date, language, and type of document (e.g., full text paper, conference proceeding, or dissertation, among others): Pubmed (Medline), Ovid databases (PsycInfo, Embase+Embase classic, OVID Medline), and Web of Knowledge Databases (Web of science (science citation index expanded), Biological abstracts, Biosis, Food science and technology abstracts), from inception to 9 January, 2018. Reference lists of relevant retrieved papers were hand-searched to find any additional pertinent NMA. The quality of each included NMA was appraised using the AMSTAR-2 tool. The following NMAs were identified for ADHD medications, including methylphenidate

| First author (year) | N trials | Type of included trials | Participants | Eligible treatments | Outcomes |
|---|---|---|---|---|---|
| Roskell (2014) | 32 | Parallel RCTs | Children and/or adolescents with ADHD, with or without comorbid ODD | MPH, LDX ATX, DEX | Efficacy: changes in ADHD-RS, CGI-I<br><br>Safety: all-cause and AE discontinuations |
| Locatelli (2016) (conference proceeding only) | 34 | Parallel double blind RCTs > 2 weeks | Children and/or adolescents with ADHD; no further information | MPH (MPH-I and MPH-MR), LDX ATX, BUP | Efficacy: clinical improvement (decline in ADHD-RS questionnaire score by at least 25% or improved CGI-I) |
| Catala-Lopez (2017) | 190 | Parallel RCTs ≥ 3 weeks. (crossover included if they reported pre crossover results) | Children and/or adolescents with ADHD (< 18 y), as per DSM or ICD | Pharmacological treatments: Stimulants; Non-stimulants Antipsychotics Other unlicensed drugs<br><br>Non-pharmacological interventions: Behavioral therapy Cognitive training Neurofeedback Complementary and alternative medicine interventions | Primary: treatment response (ADHD symptoms or global functioning) and all-cause treatment dis-continuation rates. Secondary outcomes: tolerability, serious AEs and specific adverse events |
| Joseph (2017) | 36 | Parallel RCTs, (crossover included if they reported pre crossover results) | Children and/or adolescents aged 6-17 | d-AMPH, ATX, CIR, GIR, GXR, LDX, MPH-IR, or MPH-ER/OROS | Efficacy: change in ADHD-RS, CGI-S, CPRSs, or SNAP-IV; achievement of response at the CGI<br><br>Safety: all cause discontinuation and discontinuation due to AEs |
| Li (2017) | 62 | RCTs, regardless of level of blinding | Children and adolescents with ADHD aged 4-17 | ATX, BUP, CLON, GXR, LDX, MPH | Efficacy: changes on validated ADHD scales |

| | | | | | |
|---|---|---|---|---|---|
| | | | | | Safety: Withdrawals due to all-cause, or AEs and lack of efficacy |
| Luan (2017) | 73 | RCTs, regardless of level of blinding, > 3 weeks | Children and adolescents with ADHD as per DSM-I, aged 6-18 | ATX, CLON, GXR, BUP, LDX, MPH | Efficacy: changes on ADHD-RS<br><br>Safety: all cause withdrawals, withdraw due to AEs, withdrawal due to lack of efficacy |

Abbreviation for Medications: AMPH: Amphetamines; BUP: Bupropion; CLON: Clonidine; GUA: Guanfacine; GXR: Guanfacine Extended Release LDX: Lisdexamfetamine; MAS: Mixed Amphetamine Salts; MODA: Modafinil; MPH: Methylphenidate (ER: Extended release: SR: sustained release); PBO: Placebo.

Abbreviation for Comorbidity: AD: Aggression/Defiance; A/D: Abuse/Dependence; Adj Dis: Adjustment Disorder with mixed disturbance of emotions and conduct; ASD: Autism Spectrum Disorder; ASPD: Antisocial Personality Disorder; BD: Bipolar Disorder; CD: Conduct Disorder; Comm: Communications Disorder; DD: Depression Disorder; Disr Beh: Disruptive Behavior Disorder; GAD: Generalized Anxiety Disorder; LD: Learning disorder; MD: Major Depression; MOOD: Mood disorder; MSD: Motor Skills Disorder; OCD: Obsessive–Compulsive Disorder; ODD: Oppositional Defiant Disorder; PD: Personality disorder; PHO: Phobia; SAD: Separation anxiety disorder; SPD: Seasonal pattern disorders; SUD: substance use disorder; TD: Tic Disorders.

An additional NMA was published after the search date of this meta-review. The quality of the NMAs identified in the meta-review by Cortese et al. (2018) is described in the accompanying Table.

By contrast, the quality of the NMA by Cortese et al. (2018) was rated as HIGH in another recent meta-review (Boaden et al., 2020). As such, data on comparative effectiveness of methylphenidate from the network meta-analysis by (Cortese et al., 2018) are presented here as deriving from the highest quality NMA currently available.

| **Quality of Network Meta Analyses** | |
|---|---|
| **Author (Year)** | **AMSTAR-2 Rating** |
| Roskell (2014) | Low |
| Catala-Lopez (2017) | Moderate |
| Joseph (2017) | Critically Low |
| Li (2017) | Critically Low |
| Luan (2017) | Critically Low |

## Summary of Available Data from RCTs

The following table summarizes the comparative efficacy of methylphenidate on ADHD core symptoms rated by clinicians in the short term (average 12 weeks) in relation to placebo and other medications used to treat ADHD

| | Atomoxetine | | Bupropion | | Clonidine | | Guanfacine | | Methylphenidate | | Modafinil | | Placebo | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Children | Adults | Children | Adults | Children | Adults | Children | Adults | Children | Adults | Children | Adults | Children | Adults |
| **Amphetamines** | | | | | | | | | | | | | | |
| Clinicians | **−0·46 (−0·65 to −0·27)*** | **−0·34 (−0·58 to −0·10)*** | −0·06 (−0·81 to 0·68)† | −0·33 (−0·77 to 0·11)* | −0·31 (−0·81 to 0·18)* | .. | **−0·35 (−0·59 to −0·10)*** | .. | **−0·24 (−0·44 to −0·05)*** | **−0·29 (−0·54 to −0·05)*** | **−0·39 (−0·67 to −0·12)*** | **−0·94 (−1·43 to −0·46)‡** | **−1·02 (−1·19 to −0·85)‡** | **−0·79 (−0·99 to −0·58)‡** |
| Teachers | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. |
| **Atomoxetine** | | | | | | | | | | | | | | |
| Clinicians | .. | .. | 0·40 (−0·34 to 1·14)* | 0·01 (−0·41 to 0·42)* | 0·15 (−0·33 to 0·63)* | .. | 0·11 (−0·09 to 0·32)* | .. | **0·22 (0·05 to 0·39)*** | 0·04 (−0·14 to 0·23)‡ | 0·07 (−0·17 to 0·31)* | **−0·61 (−1·06 to −0·15)*** | **−0·56 (−0·66 to −0·45)*** | **−0·45 (−0·58 to −0·32)*** |
| Teachers | .. | .. | 0·00 (−0·90 to 0·90)† | .. | .. | .. | 0·31 (−0·79 to 1·42)† | .. | 0·50 (−0·11 to 1·10)* | – | 0·44 (−0·19 to 1·07)* | – | −0·32 (−0·82 to 0·18)† | .. |
| **Bupropion** | | | | | | | | | | | | | | |
| Clinicians | .. | .. | .. | .. | −0·25 (−1·12 to 0·62)† | .. | −0·28 (−1·04 to 0·47)† | .. | −0·18 (−0·90 to 0·54)† | 0·04 (−0·38 to 0·45)* | −0·33 (−1·10 to 0·43)† | **−0·62 (−1·20 to −0·03)*** | **−0·96 (−1·69 to −0·22)‡** | **−0·46 (−0·85 to −0·07)*** |
| Teachers | .. | .. | .. | .. | .. | .. | 0·31 (−0·92 to 1·55)† | .. | 0·50 (−0·17 to 1·17)* | – | 0·44 (−0·38 to 1·26)* | – | −0·32 (−1·07 to 0·43)† | .. |
| **Clonidine** | | | | | | | | | | | | | | |
| Clinicians | .. | .. | .. | .. | .. | .. | −0·03 (−0·53 to 0·46)† | .. | 0·07 (−0·42 to 0·56)† | – | −0·08 (−0·59 to 0·43)† | – | **−0·71 (−1·17 to −0·24)‡** | .. |
| **Guanfacine** | | | | | | | | | | | | | | |
| Clinicians | .. | .. | .. | .. | .. | .. | .. | .. | 0·11 (−0·13 to 0·34)* | – | −0·05 (−0·32 to 0·23)* | – | **−0·67 (−0·85 to −0·50)‡** | .. |
| Teachers | .. | .. | .. | .. | .. | .. | .. | .. | 0·18 (−0·86 to 1·22)† | – | 0·12 (−0·93 to 1·18)† | – | **−0·63 (−1·62 to 0·35)†** | .. |
| **Methylphenidate** | | | | | | | | | | | | | | |
| Clinicians | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | −0·15 (−0·41 to 0·10)* | **−0·65 (−1·11 to −0·19)*** | **−0·78 (−0·93 to −0·62)‡** | **−0·49 (−0·64 to −0·35)‡** |
| Teachers | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | −0·06 (−0·53 to 0·42)† | – | **−0·82 (−1·16 to −0·48)*** | .. |
| **Modafinil** | | | | | | | | | | | | | | |
| Clinicians | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | **−0·62 (−0·84 to −0·41)*** | 0·16 (−0·28 to 0·59)* |
| Teachers | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | .. | **−0·76 (−1·15 to −0·37)†** | .. |

Data are standardised mean difference (95% CI) between treatments. Results in bold are significant. Negative values favour the treatment in the row and positive values favour the treatment in the column. Drugs are reported in alphabetical order. Results are based on network estimates. No data for clonidine and guanfacine in adults are reported because no studies identified by our search tested these two drugs in adults. No teacher ratings were available for clonidine. ADHD=attention-deficit hyperactivity disorder. *Low quality of evidence. †Very low quality of evidence. ‡Moderate quality of evidence.

***Table 1:*** **Effect of ADHD drugs in children and adults at timepoints closest to 12 weeks in terms of efficacy, as rated by clinicians and teachers**

In summary, methylphenidate showed higher SMDs compared with placebo and was slightly inferior to amphetamines in terms of efficacy on ADHD core symptoms rated by clinicians

The quality of the evidence from RCTs of methylphenidate, rated with the GRADE system, was deemed of moderate level for the comparison methylphenidate vs placebo, clinicians ratings.

## Identification of Clinical Evidence for Longer Term Effectiveness Observational Studies

Due to lack of randomization, observational, naturalistic studies may be prone to bias. A systematic review focused on within-individual design studies, that account for confounding by indication Chang et al. (2019). They performed a systematic search in PubMed and Embase for studies that investigated the association between ADHD medications and behavioral or neuropsychiatric outcomes using population-based prescription databases between January 1, 2008, and February 1, 2019, with no language restrictions. They used terms related to ADHD (attention-deficit/hyperactivity disorder, ADHD) and medication (medication, stimulant*, treatment) and type of data (regist*, claim*, record*, population*) in combination. They followed the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement

## Summary of Available Data for Longer Term Effectiveness from Observational Studies

These studies reviewed by Chang et al. (2019) showed a significant decrease in negative outcomes, such as unintentional physical injuries, motor vehicle accidents (among male patients), substance use disorder, and criminal acts, as well as an improvement in academic functioning. All of their results are shown in the following Figure, reproduced from their article.

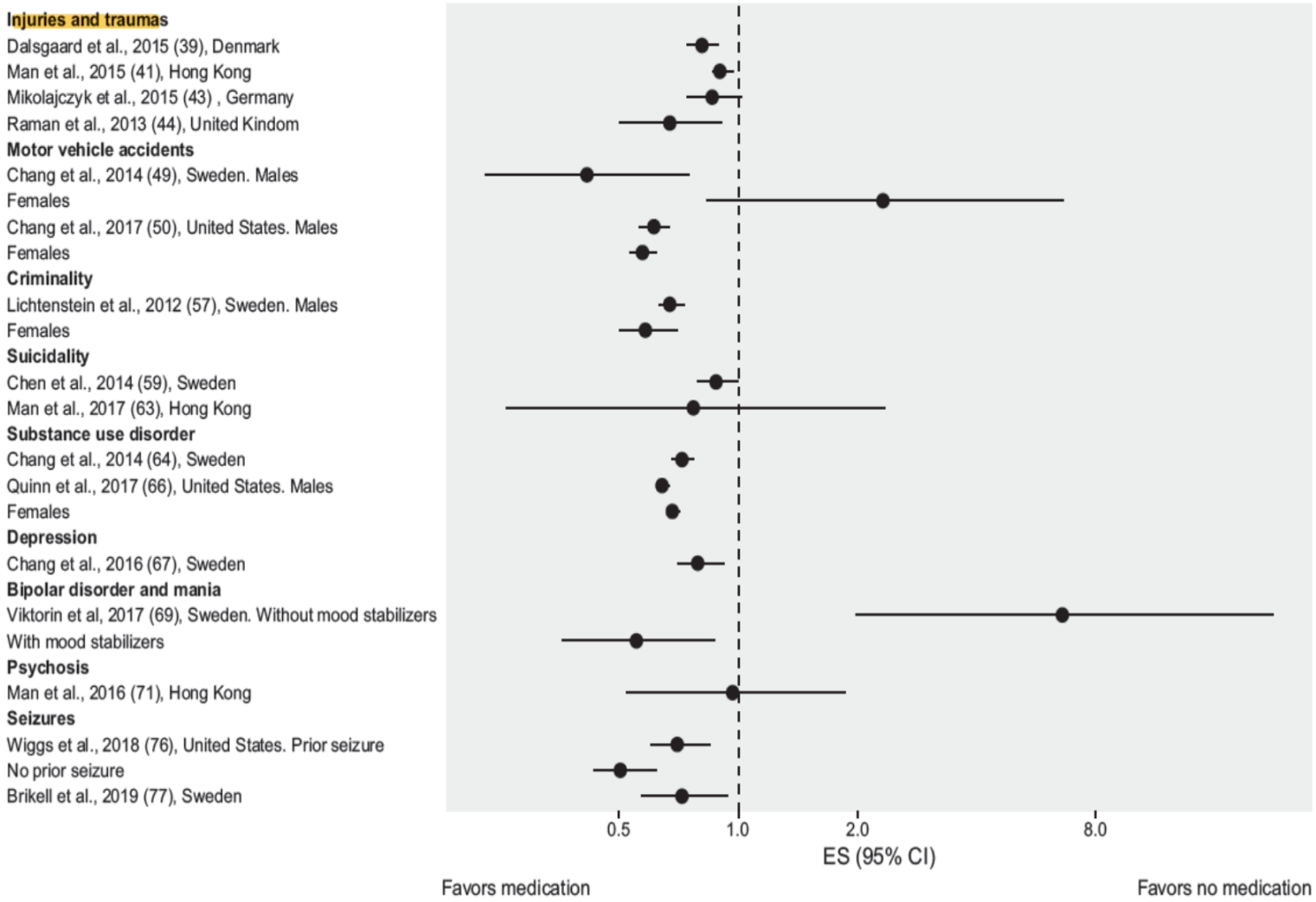



**Figure 1.** Forest plot of within-individual studies for short-term effects of attention-deficit/hyperactivity disorder medications. Note: Studies on educational outcomes were not included because they used continuous measures of outcome. CI, confidence interval; ES, effect size.

## 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 (World Health Organization, 2018b): "Consider methylphenidate for hyperkinetic disorder only if psychosocial interventions have failed, the 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"

Key recommendations from other recent guidelines are summarized in the table below from the New England Journal of Medicine (Cortese, 2020).

**Table 2. Recommendations for ADHD Treatment from Recent Clinical Guidelines.**

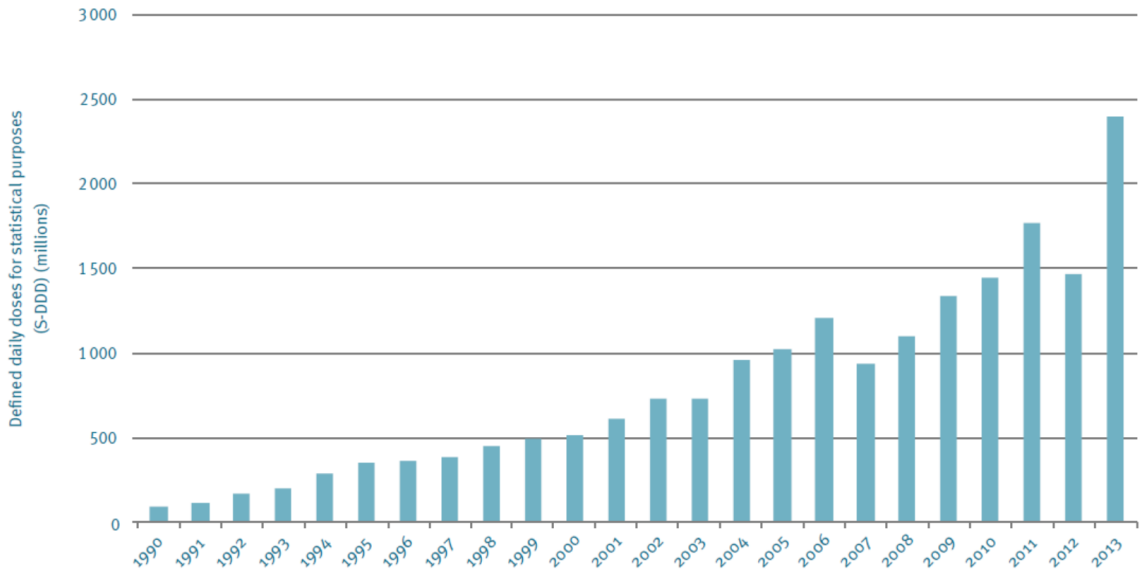
| Organization and Patient Age | Treatment Recommendations |
|---|---|
| **American Academy of Pediatrics**[3] | |
| Preschool children (4–5 yr old) | First line: parental training in behavior management, behavioral classroom interventions, or both<br>Second line: methylphenidate (off-label) |
| Children 6–11 yr old | FDA-approved medications (in descending order according to strength of evidence: stimulants, atomoxetine, extended-release guanfacine, extended-release clonidine) with parental training in behavior management, behavioral classroom interventions, or preferably both; educational interventions |
| Adolescents 12–17 yr old | FDA-approved medications; training or behavioral interventions, if available, or both; educational interventions |
| Adults | Recommendations are not included in the guideline |
| **National Institute for Health and Care Excellence, United Kingdom**[4] | |
| Children <5 yr old | First line: ADHD-focused group training for parents<br>Second line: medication only after second specialist opinion |
| Children ≥5 yr old and young people | ADHD-focused support (e.g., education and information on the causes and effects of ADHD, advice on parenting strategies, and liaison with school)<br>If ADHD symptoms persist in at least one area of functioning after environmental modification, start medication (in descending order of preference): methylphenidate, lisdexamfetamine (or dexamphetamine if unacceptable side effects with lisdexamfetamine), atomoxetine or guanfacine<br>For symptoms of oppositional defiant disorder or conduct disorder: parental training<br>Cognitive behavioral therapy for young people if symptoms still impairing at least one area of functioning after pharmacologic treatment |
| Adults | If ADHD symptoms persist in at least one area of functioning after environmental modification: medication (in descending order of preference): methylphenidate or lisdexamfetamine (or dexamphetamine if lisdexamfetamine associated with unacceptable side effect profile), atomoxetine<br>Supportive psychological intervention if medication is ineffective or associated with unacceptable side effects |
| **ADHD German Guidelines**[5] | |
| Children <6 yr old | First line: ADHD-focused group or individual training for parents or teachers<br>Second line: medication only after specialist advice for children >3 yr old |
| Children ≥6 yr old and young people | |
| Mild-to-moderate ADHD | After psychoeducation, first line: parental training or family-based interventions; if needed, patient-, school-, and workplace-based interventions<br>After psychoeducation, second line: medication (in descending order of preference): stimulants, atomoxetine or guanfacine |
| Moderate-to-severe ADHD | After psychoeducation, first line: medication (in descending order of preference): stimulants, atomoxetine or guanfacine<br>After psychoeducation, second line: parental training or family-based interventions; if needed, patient-based and school- or workplace-based interventions |
| Adults | After psychoeducation, first-line: medication; nonpharmacologic treatment if patient chooses it or if medication ineffective or associated with unacceptable side effects |

## 10.Review of harms and toxicity: summary of evidence of safety

Estimate of Total Patient Exposure to Date

According to the 2015 report from the International Narcotics Control Board http://www.incb.org/documents/Publications/AnnualReports/AR2014/English/methylphenidate.pdf, the United States accounted for more than 80% of global consumption. Iceland had the highest per capita consumption of methylphenidate in the world. Other countries with high per capita use were Norway, Sweden, Australia, Belgium, Germany and Canada. Their Figure below shows total consumption has been increasing from 1990 to 2013.

Figure I. Global consumption of methylphenidate, 1990-2013




Raman et al. reported a retrospective, observational study using population-based databases from 13 countries and one Special Administrative Region: four in Asia and Australia, two in North America, five in northern Europe, and three in western Europe. They reported their results as follows: "154·5 million individuals were included in the study. ADHD medication use prevalence in 2010 (in children aged 3–18 years) varied between 0·27% and 6·69% in the countries and SAR assessed (0·95% in Asia and Australia, 4·48% in North America, 1·95% in northern Europe, and 0·70% in western Europe). The prevalence of ADHD medication use among children increased over time in all countries and regions, and the absolute increase per year ranged from 0·02% to 0·26%. Among adults aged 19 years or older, the prevalence of any ADHD medication use in 2010 varied between 0·003% and 1·48% (0·05% in Asia and Australia, 1·42% in North America, 0·47% in northern Europe, and 0·03% in western Europe). The absolute increase in ADHD medication use prevalence per year ranged from 0·0006% to 0·12%. Methylphenidate was the most commonly used ADHD medication in most countries." (Raman et al., 2018)

Description of Adverse Effects/Reactions and Estimates of Frequency and Summary of Available Data

The review on this section is based on a) the relevant meta-analyses and within-subject cohort studies identified by the International Consensus Statement on ADHD (Faraone et al., 2020 Submitted),

b) a recent qualitative systematic review of studies that investigated risks and benefits of ADHD medication using linked prescription databases, including 18 within-individual designs accounting for confounding by indication (Chang et al., 2019), c) a recent large scale systematic meta-review of 78 adverse effects of psychotropic medications in children and adolescents with psychiatric disorders (Solmi et al., 2020), d) the most comprehensive network meta-analysis on the tolerability of ADHD medication (Cortese et al., 2018), e) the work of the EU-funded ADDUCE project, that investigated the long-term effects of stimulants on growth, the neurological system, psychiatric states and the cardiovascular system, and f) a systematic review of the PubMed and Cochrane databases (http://adhd-adduce.org/page/view/2/Home).

PubMed and Cochrane catalogues were searched for meta-analyses on the safety of methylphenidate using keywords "methylphenidate", "adverse" and "meta-analysis*" for PubMed and "methylphenidate" and "ADHD" for the Cochrane database search (last search, Nov 10, 2020). There were no specifications on language. A total of 75 abstracts in PubMed and 11 reviews in Cochrane databases were identified initially. Among these, 25 were relevant to comparative evidence on safety for methylphenidate in children and adolescents. Of the 25 relevant articles, 5 were excluded due to being outdated or methodological flaws.

Common side effects of methylphenidate include erythema, weight loss, decrease in appetite, loss in appetite, nausea, vomiting, headache, insomnia, mild labile mood, nasal congestion, and nasopharyngitis with loss of appetite and sleep difficulties being most common (Coghill et al., 2014; Cortese et al., 2013; Faraone et al., 2019; Graham and Coghill, 2008; UpToDate, 2018).

## Adverse Effects in Randomized Controlled Clinical Trials

a. In an comprehensive systematic review and network meta-analysis on the tolerability (study drop-outs) of medications for ADHD comparing amphetamines (including lisdexamfetamine), atomoxetine, bupropion, clonidine, guanfacine, methylphenidate, and modafinil with each other or placebo at timepoints closest to 12 weeks, 26 weeks, and 52 weeks, (Cortese et al., 2018) included 82 published and unpublished double-blind randomised controlled trials (11,018 children and adolescents). Summary odds ratios (ORs) and standardised mean differences (SMDs) were estimated using pairwise and network meta-analysis with random effects. Risk of bias of individual studies was assessed with the Cochrane risk of bias tool and confidence of estimates with the Grading of Recommendations Assessment, Development, and Evaluation approach for network meta-analyses. With respect to tolerability, methylphenidate was not statistically different from placebo (OR 1.44, 95% CI 0.90-2.31). Use of methylphenidate was associated with a significantly increased diastolic blood pressure (SMD: 0.24, CI: 0.14–0.33) and decreased weight (SMD: –0.77, CI: –1.09 to –0.45). There was no significant increase in systolic blood pressure (SMD: 0.09, CI: -0.01–0.19).

b. A Cochrane review by (Storebø et al., 2018) on adverse events of methylphenidate to treat ADHD concluded, in contrast to all other meta-analyses, that methylphenidate may be associated with psychotic disorders and arrhythmia. This conclusion was based on two non-randomised comparative studies. One was a Taiwanese cohort study conducted by Shyu et al. (Shyu et al., 2015), which reported that the risk for any psychotic disorder (RR 1.36; CI 1.17 to 1.57; 71,771 participants) was increased. The other study by (Shin et al., 2016) reported increased risk for arrhythmia (RR 1.61, 95% CI 1.48 to 1.74; 1 study, 1224 participants) compared with no intervention. However, according to (Storebø et al., 2018), both studies had serious (Shin et al., 2016) or critical (Shyu et al., 2015) risk for bias due to confounding factors, such as confound by indication to treatment or comorbid disorders. In contrast, two large population-based cohort studies using within-person designs from Swedish and Hong-Kong registries by (Hollis et al., 2019) and (Man et al., 2016) and found no evidence that methylphenidate was associated with psychotic disorders and the Cochrane review on the efficacy of methylphenidate by (Storebø et al.,

2015) found no evidence for an increase in serious adverse events. These latter studies are more convincing because the use of a within-person design eliminates confounding by indication.

c. According to a more recent, comprehensive meta-review on network meta-analyses and meta-analyses of randomized controlled trials (RCTs), individual RCTs, and cohort studies reporting on 78 a priori selected adverse events across 19 categories of 80 psychotropic medications in children and adolescents with mental disorders including data from nine network meta-analyses, 39 meta-analyses, 90 individual RCTs, and eight cohort studies with a total of 337,686 children and adolescents included (Solmi et al., 2020), methylphenidate was associated with significantly worse anorexia (RR: 3.21; 95% confidence interval [CI] 2.61-3.94; (Holmskov et al., 2017), insomnia (OR: 4.66; CI 1.99-10.9; (Ching et al., 2019), weight loss (standard mean difference [SMD] –0.77;CI –1.09 to –0.45; (Cortese et al., 2018), nausea (RR: 1.38; CI 1.04-1.84; (Holmskov et al., 2017)) and abdominal pain (RR: 1.50; CI = 1.26-1.79; (Holmskov et al., 2017)) than placebo. Details are in the following Table from Solmi et al. (2020) (reference citations in the table are in their published paper).

**Table 3** Safety of anti-attention-deficit/hyperactivity (ADHD) medications in children and adolescents with any mental illness (adverse events significantly worse than with placebo/controls)

| Medication | Adverse events covered by literature | Adverse events worse than placebo | Adverse event | Type of effect size | Effect size | 95% CI | Source | Quality | N |
|---|---|---|---|---|---|---|---|---|---|
| Mixed anti-ADHD medications | 19 (24.4%) | 7 (9.0%) | Abdominal pain[155] | RR | 1.44 | 1.03-2.00 | MA | H | 2,155 |
| | | | Anorexia[155] | RR | 6.31 | 2.58-15.5 | MA | H | 2,467 |
| | | | Discontinuation due to adverse event[144] | OR | 2.30 | 1.36-3.89 | NMA | H | 14,346 |
| | | | Hypertension[144] | SMD | 0.09 | 0.01-0.18 | NMA | H | 14,346 |
| | | | Insomnia[155] | RR | 3.80 | 2.12-6.83 | MA | H | 2,429 |
| | | | Nausea/vomiting[155] | RR | 1.63 | 1.04-2.56 | MA | H | 1,579 |
| | | | Weight loss[144] | SMD | –0.71 | –1.15 to –0.27 | NMA | H | 14,346 |
| Mixed α-2 agonists | 5 (6.4%) | 1 (1.3%) | Discontinuation due to adverse event[49] | Log OR | –29.6 | –95.5 to –2.6 | NMA | M | 2,623 |
| Atomoxetine | 20 (25.6%) | 5 (6.4%) | Anorexia[147] | RR | 2.51 | 1.77-3.57 | MA | M | 2,179 |
| | | | Gastrointestinal symptoms[147] | RR | 1.76 | 1.51-2.07 | MA | M | 3,712 |
| | | | Hypertension[144] | SMD | 0.12 | 0.02-0.22 | NMA | H | 14,346 |
| | | | Nausea/vomiting[156] | RR | 1.91 | 1.24-2.94 | MA | L | 193 |
| | | | Weight loss[144] | SMD | –0.84 | –1.16 to –0.52 | NMA | H | 14,346 |
| Clonidine | 10 (12.8%) | 2 (2.6%) | Hypotension[149] | Hedges' g | 0.52 | 0.15-0.89 | MA | M | 119 |
| | | | Sedation[164] | OR | 7.67 | 2.92-20.1 | RCT | M | 230 |
| d-amphetamine | 6 (7.7%) | 3 (3.8%) | Anorexia[170] | NA | Sig | Sig | RCT | L | 81 |
| | | | Insomnia[170] | NA | Sig | Sig | RCT | L | 81 |
| | | | Irritability[170] | NA | Sig | Sig | RCT | L | 81 |
| Guanfacine | 16 (20.5%) | 4 (5.1%) | Abdominal pain[166] | OR | 4.51 | 1.34-15.2 | RCT | M | 455 |
| | | | Discontinuation due to adverse event[144] | OR | 2.64 | 1.20-5.81 | NMA | H | 14,346 |
| | | | QT prolongation[149] | Hedges' g | 0.33 | 0.12-0.54 | MA | M | 785 |
| | | | Sedation[149] | RR | 2.43 | 1.06-5.58 | MA | M | 1,059 |
| Lisdexamphetamine | 14 (17.9%) | 5 (6.4%) | Anorexia[155] | RR | 9.83 | 5.08-19.0 | MA | H | 1,081 |
| | | | Discontinuation due to adverse event[145] | RR | 3.11 | 1.20-3.76 | NMA | M | 6,931 |
| | | | Dry mouth[169] | OR | 8.63 | 1.13-66.0 | RCT | H | 547 |
| | | | Hypertension[144] | SMD | 0.14 | 0.03-0.25 | NMA | H | 14,346 |
| | | | Insomnia[155] | RR | 5.91 | 2.84-12.3 | MA | H | 1,081 |
| Methylphenidate | 25 (32.1%) | 5 (6.4%) | Abdominal pain[154] | RR | 1.50 | 1.26-1.79 | MA | M | 5,983 |
| | | | Anorexia[154] | RR | 3.21 | 2.61-3.94 | MA | M | 5,983 |
| | | | Insomnia[148] | OR | 4.66 | 1.99-10.9 | MA | M | 749 |
| | | | Nausea/vomiting[154] | RR | 1.38 | 1.04-1.84 | MA | M | 2,630 |
| | | | Weight loss[144] | SMD | –0.77 | –1.09 to –0.45 | NMA | H | 14,346 |
| Modafinil | 13 (16.7%) | 3 (3.8%) | Anorexia[153] | RR | 5.02 | 2.55-9.89 | MA | M | 921 |
| | | | Insomnia[153] | RR | 6.16 | 3.40-11.2 | MA | M | 921 |
| | | | Weight loss[144] | SMD | –0.93 | –1.59 to –0.26 | NMA | H | 14,346 |

OR – odds ratio, RR – risk ratio, Log OR – log odds ratio, SMD – standardized mean difference, NMA – network meta-analysis, MA – meta-analysis, RCT – randomized controlled trial, NA – not available, H – high quality, M – medium quality, L – low quality (lower score of either AMSTAR or AMSTAR-Content), Sig – significant difference between medication and placebo without effect size available

## Adverse Effects in Observational Studies: Somatic Effects

Much of the following comes from the International Consensus Statement on ADHD (Faraone et al., 2020 Submitted).

a. Children treated with stimulants may show delays in expected height gains averaging two centimeters over one or two years. These sometimes attenuate over time and often reverse when treatment is stopped (Faraone et al., 2008). A medical records study from the USA comparing 32,999 stimulant-treated ADHD children with 11,515 controls found continuing declines in expected height over a four-year period.

b. Carucci et al. (Carucci et al., 2020) conducted a meta-analysis of association of long-term (> six months) methylphenidate exposure with height, weight and timing of puberty, including 18 studies (n = 4868). methylphenidate was associated with consistent statistically significant pre-post difference for both height (SMD = 0.27, CI= 0.16-0.38) and weight (SMD = 0.33, CI= 0.22-0.44) Z scores, with prominent impact on weight during the first 12 months and on height within the first 24-30 months. No significant effects of dose, formulation, age and drug-naive condition as clinical moderators were found.

c. A study using Danish national registers followed over 700,000 individuals for an average period of almost a decade. Looking at 8,300 people with ADHD, stimulant users had more than twice the rate of cardiovascular events (primarily hypertension) than nonusers. These events were rare (Dalsgaard et al., 2014).

d. A recent meta-analysis by Liang et al. (Liang et al., 2018a) found that children and adolescents treated with methylphenidate had more significant post- vs. pretreatment increases in heart rate (11 studies; SMD: 1.56, CI: 0.71–2.41, $z = 3.59$, $p < 0.001$) and systolic blood pressure (10 studies; SMD: 1.61, 95% CI: 0.81–2.41, $z = 3.96$, $p < 0.001$) than those treated by placebo.

e. In a meta-analysis of three studies with over 1.4 million people of all ages methylphenidate was not associated with a higher risk of all-cause death, heart attack or stroke (three studies, over half a million people) (Liu et al., 2019).

f. A cohort study of over 1.8 million pregnancies in the United States and over 2.5 million pregnancies in the health registries of Denmark, Finland, Sweden, Norway, and Iceland reported that use of methylphenidate (but not amphetamines) by pregnant woman was associated with a higher risk for cardiac malformations from 12.9 per thousand infants to 16.5 per thousand infants (Huybrechts et al., 2018). A meta-analysis of four studies of three million women also found that intrauterine exposure to methylphenidate was associated with a higher risk of cardiac malformations (Koren et al., 2020).

## Adverse Effects in Observational Studies: Other Psychiatric and Neurological Effects

a. The Hong Kong Clinical Data Analysis & Reporting System, a population-based, electronic medical records database, was used to examine over 25,000 people receiving methylphenidate for ADHD. During the 90-day period prior to initiation of treatment, individuals with ADHD were greater than six times more likely to attempt suicide than after treatment. After ongoing treatment, the risk for attempted suicide was no longer elevated among patients with ADHD (Man et al., 2017).

b. In line with this, a Swedish cohort study examining including 37,936 patients with ADHD found no evidence for an increased risk of suicidal events, regardless of sex or type of medication. Among stimulant users, a reduced within patient rate of suicide related events was seen during treatment periods (0.81, 0.70 to 0.94) (Chen et al., 2014).

c. Another nationwide Swedish longitudinal cohort study including 38,752 patients with ADHD found that ADHD medication was associated with a reduced long-term risk (i.e., 3 years later) for

depression (hazard ratio = 0.58; 95% confidence interval, 0.51-0.67) and 20% reduced rate of unplanned hospital visits due to depression (Chang et al., 2016).

d. Studying children and youths newly diagnosed with ADHD (n=71,080) and age-and gender-matching controls (n=71,080) chosen from Taiwan's National Health Insurance database during the period of January 200 to December 201, Lee and colleagues investigated whether methylphenidate and atomoxetine influence the risk of depression (Lee et al., 2016a). ADHD patients who received longer methylphenidate 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 atomoxetine was not significantly correlated with the probability of developing a depressive disorder. Regarding treatment with methylphenidate, a longer duration of methylphenidate use demonstrates significant protective effects against developing a depressive disorder.

e. Using the Hong Kong Clinical Data Analysis & Reporting System, the risk for psychosis did not differ between periods when patients were on and off methylphenidate treatment (Man et al., 2016). A Swedish registry study of over 23,000 adolescents and young adults treated with methylphenidate for ADHD found no evidence for an association between psychosis and methylphenidate treatment. A year after initiation of methylphenidate treatment, the incidence of psychotic events was 36% lower in in those with a history of psychosis and 18% lower in those without a history of psychosis relative to the period immediately before the beginning of treatment (Hollis et al., 2019).

f. Two studies investigating short-term effects reported that ADHD medication was associated with up to 35% reduced risk of substance use disorder (Chang et al., 2014; Quinn et al., 2017). Using Swedish national registers, Chang and colleagues studied all individuals born between 1960 and 1998 and diagnosed with ADHD (38,753 patients) concerning an association between stimulant ADHD medication in 2006 and substance abuse during 2009 and found that ADHD medication was not associated with increased rate of substance abuse (hazard ratio: 0.69; CI=0.57-0.84).

g. The other study adopted a within-individual design using commercial health care claims from 2,993,887 patients (2005-2014) and found statistically significant negative associations for previous treatment and treatment duration with the risk of substance-related events during months in which patients received medication (Quinn et al., 2017). In adjusted within-individual comparisons, relative to periods in which patients did not receive ADHD medication, male patients had 35% lower odds of concurrent substance-related events when receiving medication (odds ratio=0.65, CI=0.64-0.67), and female patients had 31% lower odds of concurrent substance-related events (odds ratio=0.69, 95% CI=0.67-0.71). Moreover, male patients had 19% lower odds of substance-related events 2 years after medication periods (odds ratio=0.81, CI=0.78-0.85), and female patients had 14% lower odds of substance-related events 2 years after medication periods (odds ratio=0.86, 95% CI= 0.82-0.91). If anything, the data suggested a long-term protective effect on substance abuse.

Summary of comparative safety against comparators

a. In the comprehensive systematic review and network meta-analysis on the tolerability, Cortese et al. (2018) no statistically significant differences in tolerability, were noted between active drugs, although amphetamines (odds ratio [OR] 2.30, 95% CI 1.36-3.89) and guanfacine were less well tolerated than placebo (2.64, 1.20-5.81) and tolerability for methylphenidate was not statistically different from placebo (OR 1.44, 95% CI 0.90-2.31). No statistically significant differences were found between methylphenidate and other active drugs regarding effects on systolic blood pressure, diastolic blood pressure (except more increase than modafinil (SMD: 0.09, CI: 0.26-0.45)) and weight (except more loss than guanfacine (SMD: 0.86, CI: 0.26-1.47)).

b. A systematic review and meta-analysis (Hennissen et al., 2017) compared the effects of methylphenidate, amphetamines, and atomoxetine on diastolic and systolic blood pressure (DBP, SBP) and heart rate (HR). Based on 18 clinical trials (n=5837) the investigators found small, but statistically significant pre-post increase of SBP (methylphenidate: SMD 0.25, CI 0.08-0.42, $p < 0.01$; amphetamine: SMD 0.09, 95% CI 0.03-0.15, $p < 0.01$; atomoxetine: SMD 0.16, 95% CI 0.04-0.27, $p = 0.01$) for all medications. methylphenidate did not have a pre-post effect on DBP and HR. amphetamine 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 atomoxetine treatment (SMD 0.22, CI 0.10-0.34, $p < 0.01$). amphetamine and atomoxetine were associated with a small to medium statistically significant pre-post increase of HR (amphetamine: SMD 0.37, CI 0.13-0.60, $p < 0.01$; atomoxetine: SMD 0.43, CI 0.26-0.60, $p < 0.01$).

c. The meta-analysis by (Liang et al., 2018a) compared the effects of atomoxetine and methylphenidate on heart rate, systolic blood pressure, and a number of adverse cardiac events. Children and adolescents treated with atomoxetine had more significant post- vs. pre-treatment increases in heart rate (4 studies; 0.86, 95% CI: 0.11–1.62, $z = 2.24$, $p = 0.025$) and systolic blood pressure (3 studies; SMD: 0.366, 95% CI: 0.23–0.51, $z = 5.09$, $p < 0.001$) than those treated with methylphenidate. There was no difference in the number of adverse cardiac events between the participants treated with methylphenidate and atomoxetine (5 studies; OR = 0.88, 95% CI: 0.51–1.51, $z = -0.47$, $p = 0.64$).

d. In a fixed-effects meta-analysis of all double-blind, randomized, placebo-controlled trials examining the risk ratio of irritability reported as an adverse event in children treated with stimulants compared with placebo (32 trials, 3,664 children), the relative risk of irritability significantly differed between stimulant classes (Stuckelman et al., 2017). Methylphenidate derivatives was associated with a significantly decreased risk of irritability compared with placebo (risk ratio [RR] = 0.89 [95% CI, 0.82 to 0.96], $z = -2.87$, $P = .004$, $k = 32$, $I(2) = 50\%$), whereas amphetamine derivatives were associated with a significantly increased risk of irritability (RR = 2.90 [95% CI, 1.26 to 6.71], $z = 2.5$, $P = .01$, $k = 5$, $I(2) = 0\%$).

e. A meta-analysis of ten studies and more than 2,500 participants found that methylphenidate was more than twice as likely to induce insomnia as atomoxetine, but about half as likely to cause nausea and vomiting, and about a sixth as likely to cause drowsiness (Liu et al., 2017).

f. The umbrella systematic review by Solmi et al. (2020) concluded: “Among anti-ADHD medications with '20% of adverse events covered, methylphenidate had the best safety/coverage ratio (5/25 adverse events covered significantly worse), while guanfacine and atomoxetine had the worst safety/coverage ratio (4/16 and 5/20, respectively). Five anti-ADHD medications were associated with significantly worse anorexia (atomoxetine, d-amphetamine, lisdexamphetamine, methylphenidate, modafinil), four with insomnia (d-am-phetamine, lisdexamphetamine, methylphenidate, modafinil), three with weight loss (atomoxetine, methylphenidate, modafinil), two each with abdominal pain (methylphenidate, guanfacine), discontinuation due to adverse event (lisdexamphetamine, guanfacine), hypertension (atomoxetine, lisdexamphetamine), and sedation (clonidine, guanfacine), and one with QT prolongation (guanfacine). (page 218)”

## Identification of variation in safety that may relate to health systems and patient factors

### ADHD & tic disorder

a. A Cochrane review on the safety of various pharmacological treatments in children with ADHD and a comorbid chronic tic disorder (n=500; 443 boys and 67 girls) with regard to cardiovascular effects and weight changes included eight randomized controlled trials (Osland et al., 2018). 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. The authors found

appetite suppression or weight loss in association with methylphenidate, dextroamphetamine, atomoxetine, and desipramine, insomnia associated with methylphenidate and dextroamphetamine, and sedation associated with clonidine.

b. Another fixed effects meta-analysis of 22 double-blind, randomized, placebo-controlled trials involving 2,385 children with ADHD examined the risk ratio of new onset or worsening tics in children treated with stimulants compared with placebo (Cohen et al., 2015). The risk of new onset or worsening of tics associated with psychostimulant treatment was similar to that observed with placebo (risk ratio = 0.99, 95% CI = 0.78-1.27, z = -0.05, p = .962). Type of psychostimulant, dose, duration of treatment, recorder, and participant age did not affect risk of new onset or worsening of tics.

ADHD & epilepsy

a. Results from two studies on seizures that used a within-individual design suggest a possible protective short-term effect of ADHD medication in individuals both with and without a history of seizures. Wiggs and colleagues (Wiggs et al., 2018) followed a sample of 801,838 patients with ADHD who had prescribed drug claims from the Truven Health MarketScan Commercial Claims and Encounters databases. In adjusted within-individual comparisons, ADHD medication was associated with lower odds of seizures among patients with (OR = 0.71, 95% CI = 0.60-0.85) and without (OR = 0.71, 95% CI = 0.62-0.82) prior seizures. Long-term within-individual comparisons suggested no evidence of an association between medication use and seizures among individuals with (OR = 0.87, 95% CI = 0.59-1.30) and without (OR = 1.01, 95% CI = 0.80-1.28) a seizure history.

b. Using Swedish population registers including a total of 21 557 individuals with a seizure history (Brikell et al., 2019) found that ADHD medication periods were associated with a reduced rate of acute seizures (hazard ratio [HR] 0.73, 95% confidence interval [CI] 0.57-0.94), compared with non-medication periods within the same individual.

ADHD & autism spectrum disorder

a. A Cochrane review on randomised controlled trials including four cross-over studies (Sturman et al., 2017), with a total of 113 children diagnosed with ASD or pervasive developmental disorder (aged 5 to 13 years) found no evidence that methylphenidate worsens the core symptoms of ASD or benefits social interaction. The only adverse effect that was significantly more likely with treatment was reduced appetite as rated by parents (risk ratio 8.28, 95% CI 2.57 to 26.73; 2 studies, 74 participants; $P < 0.001$; very low-quality evidence).

b. A more recent systematic review and meta-analysis by Rodrigues et al. (Rodrigues et al., 2020) pooling evidence from four randomized controlled trials children and youth with autism spectrum disorder found a non-significant elevated risk of dropout due to adverse events associated with methylphenidate.

ADHD & intellectual impairment

a. There is a paucity of data on tolerability of methylphenidate in children with intellectual impairment (ID). The most recent meta-analysis of 8 studies (average Jadad score = 2.5) by Sun et al. (Sun et al., 2019a) on children with ADHD and borderline intellectual functioning or intellectual disability (242 participants receiving methylphenidate, 181 participants receiving placebo) did not find a significant difference in drop-out rate [odds ratio (OR) = 1.679, p = 0.260] or rate of treatment discontinuation due to adverse events (OR = 4.815, p = 0.053) between subjects receiving methylphenidate (N=242) and those taking placebos (n=181), but due to sample size statistical power was limited.

ADHD & bipolar disorder

a. Retrospective studies have indicated a high prevalence of ADHD comorbidity among the bipolar disorder (BD) population. 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 (Wang et al., 2016). compared with ADHD patients that had never taken methylphenidate, patients with long-term use of methylphenidate (> 365 days) 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 methylphenidate has protective effects.

Summary of Available Estimates of Comparative Safety of Methylphenidate

The adverse effect profiles of methylphenidate and amphetamine-based medication are similar, with decreased appetite and sleep difficulties being most common. Stimulants and atomoxetine can be associated with slight, but in subgroups potentially clinically meaningful increases in systolic and diastolic blood pressure and heart rate, as well as weight loss and delays in expected height gains. Evidence suggests that, for most patients, differences in growth tend to attenuate after stimulant discontinuation (Faraone et al., 2008). Tic development or worsening has been linked to methylphenidate use, but meta-analyses do not support this claim on a group level. Overall, studies suggest that the frequency and severity of adverse events may be somewhat less with methylphenidate products. There is no evidence for an increased risk for serious adverse events for methylphenidate compared with other pharmacologic treatments for ADHD.

A systematic review of all literature on the nonmedical use and diversion of prescription stimulants including a total of 111 studies (most studies examined college students) found a high prevalence of nonmedical use and diversion of stimulants(Faraone et al., 2020). NMU and diversion are highly prevalent; self-reported rates among population samples range from 2.1% to 58.7% and from 0.7% to 80.0%, respectively. The majority of nonmedical use is associated with no, or minor, medical effects; however, adverse medical outcomes, including death, occur in some individuals, particularly when administered by non-oral routes. 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 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.

## 11. Summary of Available Data on Comparative Cost and Cost-Effectiveness of Methylphenidate within its Pharmacological Class/Therapeutic Group

Range of Costs

| Year Reported | Source | Package | Package Price | Unit Price |
|---|---|---|---|---|
| 2015 | OECS/PPS* | 100 Tab-cap (Tablets) | $4.68 | 0.0468/tab-cap |
| 2015 | SAFRICA | 30 Tab-cap (Tablets) | $2.01 | 0.0670/tab-cap |
| 2015 | PERU | 1 Tab-cap (Tablets) | $0.31 | 0.3112/tab-cap |
| 2014 | CRSS** | 100 Tab-cap | $5.14 | 0.0514/tab-cap |

| | | | | |
|---|---|---|---|---|
| 2013 | BDS*** | 100 Tab-cap | $ 6.29 | 0.0629/tab-cap |
| 2013 | NAMIBIA | 30 Tab-cap | $ 11.13 | 0.3710/tab-cap |
| Note: Data extracted from the International Medical Products Price Guide https://mshpriceguide.org/en/home/ *OECS/PPS Organization of Eastern Caribbean States Pharmaceutical Procurement Services **CRSS=Costa Rica Social Security ***BDS=Barbados Drug Services | | | | |

## Comparative Cost-Effectiveness

A systematic review of the cost-effectiveness literature on methylphenidate was conducted (last search, Nov 10th 2020). A PubMed search using the keywords "methylphenidate cost effectiveness" yielded 44 articles. Of these, 30 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 with other stimulant and non-stimulant medications for the treatment of ADHD in youth.

A Markov model was constructed to compare immediate release methylphenidate to no treatment from the perspective of the Brazilian Unified Health System as payer, and the time horizon was 6 years (Maia et al., 2016). Considering the immediate release methylphenidate monthly cost of I$38, the incremental cost-effectiveness ratio (ICER) of treatment was I$9,103/QALY for children and I$11,883/QALY for adolescents. In two-way sensitivity analysis, considering one Gross National Product per capita (I$11,530) as willingness-to-pay, a cost of no-treatment lower than I$45/month would render immediate release methylphenidate 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 (Catalá-López et al., 2013). 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 methylphenidate and atomoxetine 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 methylphenidate and atomoxetine presented contradictory results according to the source of funding for the study: atomoxetine was shown to be cost-effective over methylphenidate in 2 evaluations associated with the manufacturer or atomoxetine, while MPH-ER was cost-effective over atomoxetine in the evaluation associated with the manufacturer of methylphenidate.

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 (Wu et al., 2012). 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. $US35 in 2010, and a 2.7- point decrease in CTRS) (Miller et al., 1998). Finally, a Marchetti et al. study found that branded methylphenidate had the lowest annual expected cost per patient among all medications considered ($US1487/patient in 2001) and branded SA amphetamine/dexamphetamine salts had the highest expected cost ($US2232/patient in 2001) (Marchetti et al., 2001).

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 (Cottrell et al., 2008). For stimulant-naïve 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 methylphenidate).

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, dexamfetamine and atomoxetine in children and adolescents diagnosed with ADHD (King et al., 2006). 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 dexamphetamine first-line, followed by IR-MPH for treatment failures followed by atomoxetine for repeat treatment failures. If dexamphetamine is considered not suitable as a first-line therapy, the optimal strategy is IR-MPH first-line, followed by dexamphetamine as second-line and atomoxetine 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 (Jensen et al., 2005). 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 (Matza et al., 2005). 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 methylphenidate 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 methylphenidate.

A comprehensive literature review was conducted using HEALTHSTAR and MEDLINE regarding the use of amphetamine/dexamphetamine mixed salts, methylphenidate and dexamphetamine in the treatment of ADHD, as well as relevant ADHD studies on cost-effectiveness and quality of life (Narayan and Hay, 2004). 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 amphetamine/dexamphetamine 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 trials was performed from a health sector perspective in Australia to determine cost-effectiveness of dexamphetamine and methylphenidate interventions to treated childhood ADHD (Donnelly et al., 2004). 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 methylphenidate and dexamphetamine are cost-effective interventions for childhood ADHD. The ICER For dexamphetamine is A$4100/DALY saved and for methylphenidate is A$15,000/DALY saved. dexamphetamine is more costly than methylphenidate for the government but much less costly for the patient. Therefore, dexamphetamine is more cost-effective than methylphenidate, although if methylphenidate 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 (Gilmore and Milne, 2001). 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 all but one paper favor methylphenidate or is at least cost-neutral relative to both stimulant and non-stimulant treatments among treatments for ADHD.

## 12.Summary of the Regulatory Status and Availability of Methylphenidate

Methylphenidate is approved for use in various jurisdictions as follows:

### US Food and Drug Administration (FDA)

#### Methylphenidate Immediate Release

*Liquid Preparation*

- Methylin Solution

*Chewable*

- Methylin Chewable

*Tablets*

- Ritalin
- Focalin

#### Methylphenidate Intermediate and long acting

*Oral*

*Liquid Preparation*

- Quillivant XR liquid)

*Disintegrating tablets*

- Cotempla-XR-ODT

*Chewable*

- Quilichew ER

*Caplet*

- Concerta

*Sprinkles*

- Metadate CD/ER
- Ritalin LA
- Focalin XR
- Aptensio XR
- Adhansia XR
- Jornay PM

*Transdermal Patch*

- Daytrana

European Medicines Agency (EMA) (Agency, 2018)

The availability of methylphenidate in European Union countries is given in Appendix B.

United Kingdom Medicines and Healthcare Products Regulatory Agency https://tinyurl.com/owt629g

Methylphenidate hydrochloride – generic immediate release 10mg and several brand name counterparts are licensed in Australia for the treatment of ADHD. These are IR methylphenidate 10mg; Medikinet tablets 5, 10, 20 mgs Ritalin tablets 10mg; Generic methylphenidate 10, 20mgs; Concerta XL 18, 27, 36, 54mgs; Xaggitin XL 18, 27, 36, 54mgs; Matoride XL 18, 27, 36, 54mgs; Delmosart 18, 27, 36, 54mgs; Xenidata XL 18, 27, 36, 54mgs.

Australian Government, Department of Health, Therapeutic Goods Administration (Australian Government Department of Health, 2018)

Methylphenidate hydrochloride – generic immediate release 10mg and several brand name counterparts are licensed in Australia for the treatment of ADHD. These are Ritalin 10mg; Ritalin LA 10, 20, 30, &40 mgs, OROS methylphenidate 18, 27, 36, & 54mgs.

Japanese Pharmaceuticals and Medical Devices Agency (Pharmaceuticals and Medical Devices Agency, 2018)

Methylphenidate hydrochloride, immediate release 10mg and brand name counterparts are licensed in Japan for the treatment of ADHD.

Health Canada (Government of Canada Indigenous Services, 2017)

Methylphenidate hydrochloride, immediate release 5mg, 10mg, 20mg and brand name counterparts are licensed in Canada for the treatment of ADHD.

Chinese National Medical Products Administration http://english.nmpa.gov.cn/

Immediate release methylphenidate (10mg) and OROS methylphenidate (18mg, 36mg) are licensed in China for the treatment of ADHD.

South African Medicines Control Council https://www.sahpra.org.za/

Ritalin 10mg; Methylphenidate Douglas 10mg (generic); Ritalin LA 10mg, 20g, 30mg, 40mg; OROS methylphenidate (branded): 18mg, 27mg, 36mg, 54mg (Lilly); OROS methylphenidate (generic): 18mg, 27mg, 36mg, 54mg (clone - Sanofi); MUPS technology: Contramyl 18mg, 27mg, 36mg, 54mg

Israeli Ministry of Health Pharmacology Department https://www.gov.il/en/service/israeli-drug-inde

Ritalin IR. Ritalin LA (8 hours) and OROS methylphenidate are approved for doses up to 90 mg (no matter which formula) for all prescribers. Specialists can be authorized to prescribe up to 120mg..

Central Drugs Standard Control Organization (CDSCO)—Directorate General of Health Services Ministry of Health & Family Welfare, Government of India

https://cdscoonline.gov.in/CDSCO/Drugs

Methylphenidate hydrochloride Extended release tablet- each extended release contains: methylphenidate HCL USP-18mg, 36 mg, 54 mg

National Administration on of Drugs, Foods, and Medical Devices (ANMAT)-Argentina

http://www.anmat.gov.ar/webanmat/EspecMed/febrero/especmed_monodrogas06.asp

Methylphenidate hydrochloride-20 mg

Ministry of Food and Drug Safety- South Korea

https://synapse.koreamed.org/articles/1111906

Methylphenidate Instant release (Penid, Perospin) 10-60 mg; Extended Release (Metadate CD, Medikinet retard, Bisphentin controlled release) 20- 60 mg; OROS (Concerta OROS) 18-72

Ministry of Health-Singapore https://www.moh.gov.sg/cost-financing/healthcare-schemes-subsidies/drug-subsidies-schemes

Methylphenidate Hydrochloride Extended Release tablet 18 mg, 27mg, 36 mg, 54 mg; Long acting tablet 20 mg; Modified-release capsule (Medikinet) 5 mg, 10 mg, 20 mg, 30 mg, 40 mg; Sustained-release tablet 20 mg; Tablet 10 mg.

National Agency for Food and Drug Administration and Control, Nigeria

https://www.nafdac.gov.ng/wp-content/uploads/Publications/Narcotics/1-NATIONAL-GUIDELINES-ON-ESTIMATION-OF-PSYCHOTROPIC-SUBSTANCES-AND-PRECURSORS.pdf

Methylphenidate tablet 10 mg, 18 mg, 36 mg

The Norwegian Medical Agency

https://legemiddelverket.no/nyheter/tilbakekalling-av-batch-med-methylphenidate-teva-10-mg-kapsler

Methylphenidate tablet 10 mg

Methylphenidate is also available in the following countries under different brand names

| Brand Name | Country |
|---|---|
| Adaphen | South Africa |
| Addwize | India |
| Artige | Australia |
| Attenta | Australia |
| Cognil | Paraguay |
| Concentra | Bangladesh |
| Equasym | Belgium, Switzerland, Spain, Ireland |
| Inspiral | India |
| Medikinet | Belgium, Switzerland, Germany, Denmark, Estonia, Great Britain, Ireland, Norway, Poland, Sweden |
| Methylin | Argentina |
| Nebapul | Chile |
| Penid | Republic of Korea |
| Phenida | Pakistan |
| Prohiper | Indonesia |
| Ritaline | Luxembourg |
| Ritalin | 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 |
| Ritalina | Argentina, Brazil, Paraguay, Uruguay |
| Ritaline | Belgium, France, Greece |
| Rubifen | Argentina, Spain, Sri Lanka, Malaysia, New Zealand, Portugal, Singapore, Thailand, Uruguay |
| Tradea | Costa Rica, Dominican Republic, Guatemala, Honduras, Mexico, Nicaragua, Panama, El Salvador |

## 13.Availability of Pharmacopeial Standards for Methylphenidate

British Pharmacopoeia: Yes, https://www.pharmacopoeia.com

European Pharmacopoeia: Yes, https://www.edqm.eu/en/european-pharmacopoeia-ph-eur-9th-edition

Indian Pharmacopeia: Yes, https://www.indianpharmacopoeia.in

International Pharmacopeia: No, http://apps.who.int/phint/en/p/docf/

United States Pharmacopeia: Yes, http://www.usp.org

Australian Pharmacopeia: Yes, https://www.tga.gov.au/pharmacopoeias

Japanese Pharmacopeia: Yes, https://www.pmda.go.jp/english/index.html

South Africa (observer, European Pharmacopoeia)

China: Yes, see Appendix C

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# APPENDICES

Appendix A: Letters of Support

Appendix B: Methylphenidate Formulations Approved in European Union Countries

Appendix C: Chinese Pharmacopeia