**Supplementary material 1: Review protocol**

The Cost of Developmental Disability: Economic review of current models of care

Reviews were conducted according to the Arksey and O'Malley's scoping review methodology (1), and methodological enhancement (2). Original research was included that focused on economic evaluations based on decision analytic models for the care of children with common neurodevelopmental disorders both non-pharmaceutical and pharmaceutical.

**Data sources:** Four electronic databases - PubMed, PsycINFO, the International Network of Agencies for Health Technology Assessment (INAHTA) and Paediatric Economic Database Evaluation (PEDE) were searched.

**Search strategy:**

**Table S1: Search strategy on databases**

|  |  |  |
| --- | --- | --- |
| **Added publications after updating search terms** | | **218** |
| **After duplicate** | | **1576** |
| **All publication detected** | | **1654** |
| **PUBMED** | | **991** |
| 17 | #5 and #16 | 991 |
| 16 | #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 | 3,917,596 |
| 15 | Cognitive dysfunction [Mesh] | 23,378 |
| 14 | ADHD [Mesh] | 30,644 |
| 13 | dyscalculia [Mesh] | 252 |
| 12 | dyslexia [Mesh] | 8,783 |
| 11 | "tic disorder\*"[Mesh] | 5,559 |
| 10 | "Cerebral Palsy" [Mesh] | 21,510 |
| 9 | specific language disorder [MeSH Terms] | 45 |
| 8 | #6 and #7 | 3,914,538 |
| 7 | disorder\* or disabilit\* or impair\* or delay\* or limit\* or deficit\* or dystrophy or palsy or dysfunction | 6,727,821 |
| 6 | neuro\* or languag\* or speech\* or sound or communication\* or fluenc\* or stutter\* or "social communication" or "specific learning" or autis\* or intellectual\* or development\* or "mental retardation" or motor\* or coordination or stereotyp\* or movement\* or social\* or neurodevelopment\* or "decreased IQ" or read\* or function\* or "decreased academic achievement\*" or adhd or attention\* or hyperactivity\* or autis\* or cerebral\* or tourette\* or tic\* or dyslexia or dyscalculia or “global developmental” or “gross motor” or cognitive | 12,406,044 |
| 5 | #3 and #4 | 7,844 |
| 4 | "markov model" OR "discrete event simulation" OR "decision tree" OR "decision-analytic model" OR " decision analytic model" or “micro-simulation” or “micro simulation” or “agent based model” or “agent-based model” | 20,945 |
| 3 | #1 or #2 | 206,532 |
| 2 | "cost-benefit analysis" [Mesh] | 85,248 |
| 1 | "Cost benefit analysis" OR "cost effective\*" OR "cost-effective\*" OR "cost utility" OR "cost-utility" OR "cost benefit" OR "cost-benefit" OR "quality-adjusted life years" OR "health economic" OR "economic evaluation" | 206,532 |
| **PsychINFO** | | **294** |
| 3 | #1 and #2 | 294 |
| 2 | (((neuro\*) or (languag\*) or (speech\*) or (sound) or (communication\*) or (fluenc\*) or (stutter\*) or (social communication) or (specific learning) or (autis\*) or (intellectual\*) or (development\*) or (mental retardation) or (motor\*) or (coordination) or (stereotyp\*) or (movement\*) or (social\*) or (neurodevelopment\*) or (decreased IQ) or (read\*) or (function\*) or (decreased academic achievement\*) or (adhd) or (attention\*) or (hyperactivity\*) or (autis\*) or (cerebral\*) or (tourette\*) or (tic) or (dyslexia\*) or (dyscalculia) or (global developmental) or (gross motor) or (cognitive)) AND ((disorder\*) or (disabilit\*) or (impair\*) or (delay\*) or (limit\*) or (deficit\*) or (dystrophy) or (palsy))) or ((dyslexia\*) or (dyscalculia) or (dysfunction)) | 1,522,526 |
| 1 | ((Cost benefit analysis) OR (cost effective\*) OR (cost-effective\*) OR (cost utility) OR (cost-utility) OR (cost benefit) OR (cost-benefit) OR (quality-adjusted life years) OR (health economic) OR (economic evaluation)) AND ((markov model) OR (discrete event simulation) OR (decision tree) OR (decision-analytic model) OR (decision analytic model) OR (micro-simulation) OR (micro simulation) or (agent based model) or (agent-based model)) | 741 |
| **INAHTA** | | **88** |
| 3 | #1 and #2 | 88 |
| 2 | ((neuro\*) or (languag\*) or (speech\*) or (sound) or (communication\*) or (fluenc\*) or (stutter\*) or (social communication) or (specific learning) or (autis\*) or (intellectual\*) or (development\*) or (mental retardation) or (motor\*) or (coordination) or (stereotyp\*) or (movement\*) or (social\*) or (neurodevelopment\*) or (decreased IQ) or (read\*) or (function\*) or (decreased academic achievement\*) or (attention\*) or (hyperactivity\*) or (autis\*) or (cerebral\*) or (tourette\*) or (tic) or (dyslexia\*) or (dyscalculia) or (global developmental) or (gross motor) or (cognitive)) AND ((disorder\*) or (disabilit\*) or (impair\*) or (delay\*) or (limit\*) or (deficit\*) or (dystrophy) or (palsy) or (dysfunction)) | 3528 |
| 1 | ((Cost benefit analysis) OR (cost effective\*) OR (cost-effective\*) OR (cost utility) OR (cost-utility) OR (cost benefit) OR (cost-benefit) OR (quality-adjusted life years) OR (health economic) OR (economic evaluation)) AND ((markov model) OR (discrete event simulation) OR (decision tree) OR (decision-analytic model) OR (decision analytic model) OR (micro-simulation) OR (micro simulation) or (agent based model) or (agent-based model)) | 362 |
| **PEDE after duplicate** | | **281** |
| **PEDE before duplicate** | | **344** |
| **#3 or #4 or #5 or #6 or #6 or #7 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19** | | **344** |
| 19 | (TITLE\_ABSTRACT\_KEYWORDS " cognitive") | 58 |
| 18 | (TITLE\_ABSTRACT\_KEYWORDS " gross motor") | 5 |
| 17 | (TITLE\_ABSTRACT\_KEYWORDS " global developmental ") | 1 |
| 16 | (TITLE\_ABSTRACT\_KEYWORDS "tourette") | 0 |
| 15 | (TITLE\_ABSTRACT\_KEYWORDS "decreased academic achievement") | 0 |
| 14 | (TITLE\_ABSTRACT\_KEYWORDS "specific learning") | 0 |
| 13 | (TITLE\_ABSTRACT\_KEYWORDS "tic\*") | 0 |
| 12 | (TITLE\_ABSTRACT\_KEYWORDS "dyscalculia") | 0 |
| 11 | (TITLE\_ABSTRACT\_KEYWORDS "motor\*") | 24 |
| 10 | (TITLE\_ABSTRACT\_KEYWORDS "language disorder") | 1 |
| 9 | (TITLE\_ABSTRACT\_KEYWORDS "dyslexia") | 2 |
| 8 | (TITLE\_ABSTRACT\_KEYWORDS "communication") | 30 |
| 7 | (TITLE\_ABSTRACT\_KEYWORDS "cerebral palsy") | 21 |
| 6 | (TITLE\_ABSTRACT\_KEYWORDS "autis\*") | 38 |
| 5 | (TITLE\_ABSTRACT\_KEYWORDS "attention\*") | 62 |
| 4 | (TITLE\_ABSTRACT\_KEYWORDS "adhd") | 24 |
| 3 | #1 and #2 | 78 |
| 2 | (TITLE\_ABSTRACT\_KEYWORDS "neuro\*") | 173 |
| 1 | (TITLE\_ABSTRACT\_KEYWORDS "model\*") |  |

***Question of interest*:** *What model parameters and structures have informed decision-analytic models developed for economic evaluations of care for children with common neurodevelopmental disorders?*

***Common neurodevelopmental disorders:*** For the purpose of this review, the authors reviewed the published literatures and identified the most common neurodevelopmental disorders (NDDs) that include (1) ***Specific Learning Disorders*** (Dyslexia, Dyscalculia, and Impairment In Reading And Written Expression): *10%* among 5-17 years in Spain (3) and *18%* among 5-18 years in Australia (4), (2) ***Attention Deficit Hyperactivity Disorder:*** *9.9%* among 5-17 years in Spain (3), *8.2 %* among Australian children (5), and 7.2% globally (6), (3) ***Communication Disorders*** (Speech Sound Disorder, Language Disorder, Stuttering, Social Communication Disorder, and Unspecified Communication Disorder): 1.05% among 5-17 years in Spain (3) and 6.34% among 8 years old in USA (7), (4) ***Cerebral Palsy:*** 2.07% among children under 18 in China (8) and 2.7% among 2-17 years in USA (9), (5) ***Motor Disorders*** (Stereotypic Movement Disorder and Developmental Coordination Disorder): 0.76% among 5-17 years in Spain (3), (6) ***Autistic Spectrum Disorder:*** 0.70% among 5-17 years in Spain (3), 1.4% among 0-14 years in Oman (10), and 0.6% among children globally (11), (7) ***Tic Disorders*** (Tourette’s Syndrome, Persistent (Chronic) Motor or Vocal Tic Disorder, Provisional Tic Disorder, Unspecified Tic Disorder): 1.5% among 6-18 years in Iran (12) and 0.77-2.99% among children (13), and (8) ***Intellectual Disability*** (Intellectual Developmental Disorder, Global Developmental Delay, and Unspecified Intellectual Disability): 0.63% among 5-17 years (3).

***Population*:** Children with common neurodevelopmental disorders

***Intervention(s), exposure(s):***

* any pharmaceutical or non-pharmaceutical intervention / strategy for common NDDs. This may include treatment, follow up care .. etc

***Comparator(s)/control:*** Any control group or comparators assigned when comparing an intervention or strategy related to the strategy for common NDDs.

***Study designs of interest*:** Economic evaluations based on decision analytic models

***Inclusion criteria:***

1. Studies were included if they estimated the impact of either model of care, comparing it to no care, or that compared different care strategies for children with common NDDs.
2. Economic evaluations: any economic evaluation based on decision analytic models will be included if they reported both costs and benefits expected for both usual care and the comparator(s).
3. Study population – children under 18
4. Research articles published in English
5. Research limited to human studies
6. Full publication or manuscript available for review

***Exclusion criteria:***

Articles initially were excluded if they are duplicates or if the title clearly demonstrates that the intervention and outcome of interest are not the focus of the review. Articles are then excluded based on the following:

1. Economic evaluation of care for disease/condition except common NDDs (1)
2. Not full economic evaluation or non-model-based economic evaluation (6)
3. Protocols/conference abstract/review paper (1)
4. Study evaluated screening of NDDs (1)
5. Model time horizon – less than 12 months (11)

**Table S2: A list of studies that met many inclusion criteria (‘near-misses’) and were excluded due to a short analytical time horizon (less than 12 months)**

|  |  |  |
| --- | --- | --- |
| # | Study author and publication year | Time horizon |
| Attention Deficit Hyperactivity Disorder (ADHD) | | |
| 1 | Vanoverbeke et al (14) | a 1 year |
| 2 | Narayan et al (15) | a 1 year |
| 3 | King et al (16) | a 1 year |
| 4 | Cottrell et al (17) | a 1 year |
| 5 | Hong et al (18) | a 1 year |
| 6 | Prasad et al (19) | a 1 year |
| 7 | Erder et al (20) | a 1 year |
| 8 | Sikirica et al (21) | a 1 year |
| 9 | Lachaine et al (22) | a 1 year |
| 10 | Sohn et al (23) | a 1 year |
| 11 | Zimovetz et al (24) | a 1 year |

***Main outcome(s)***

* Assess economic evaluations based on decision analytic models of care for children with common neurodevelopmental disorders.
* Any reported cost-effectiveness outcome in model based economic evaluations.

***Measures of effect***

Incremental effectiveness, incremental costs and ICER (Incremental Cost Effectiveness Ratio values)

***Data extraction***

The initial search was performed by two reviewers using pre-determined search terms and strategies from chosen databases. All identified papers were imported into EndNote and were screened in accordance with PRISMA ScR guidelines (25). Review was carried out using Rayyan Software (26). After removal of duplicates, the titles and abstracts were screened for relevance and eligibility criteria by the two reviewers. The data was extracted from the studies selected for inclusion using a predesigned extraction form. The data extraction sheet was first pilot tested on five studies and then was revised accordingly to include:

***Identification of study:***

1. Record the first authors’ last name, initials
2. Record the journal name
3. Record the year of publication
4. Record the volume and page numbers

***Characteristics of study:***

1. Settings
2. Patient population (age if available)
3. Intervention
4. Comparator
5. Type of economic evaluation and model
6. Study design
7. Discount rate
8. Perspective
9. Costs included
10. Time horizon - model
11. Outcome measures
12. Baseline analysis
13. Sensitivity analysis
14. Main results
15. Additional comments (a threshold value etc…)

***Risk of bias (quality) assessment***

The full texts of all included articles were assessed for reporting quality by two independent reviewers by using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. Any discrepancies over reporting quality assessment between the two reviewers were resolved by discussion with a third reviewer. The standards of the input data for health economic analysis in decision model was ranked based on the hierarchy adapted by Cooper and colleagues.

***Strategy for data synthesis***

After screening the title abstract and full text, data were extracted from relevant articles and summarised in tables. The data fields were ‘aim of model’, ‘setting and location’, ‘perspective’, ‘time horizon’, ‘discount rate’, ‘structure of the economic model’, ‘study population’, ‘intervention and comparator’, ‘outcome measures’, ‘incremental cost-effectiveness ratio (ICER)’ and ‘sensitivity analysis method’.

The reporting quality of the selected economic evaluation was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist. This standard provides 24 items, with accompanying recommendations and examples to ensure more consistency and transparent reporting of economic evaluations.

**References:**

1. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International journal of social research methodology. 2005;8(1):19-32.

2. Levac D, Colquhoun H, O'Brien KK. Scoping studies: advancing the methodology. Implementation Science. 2010;5(1):69.

3. Bosch R, Pagerols M, Rivas C, Sixto L, Bricollé L, Español-Martín G, et al. Neurodevelopmental disorders among Spanish school-age children: prevalence and sociodemographic correlates. Psychological Medicine. 2021:1-11.

4. McLeod S, McKinnon DH. Prevalence of communication disorders compared with other learning needs in 14 500 primary and secondary school students. International Journal of Language & Communication Disorders. 2007;42(S1):37-59.

5. AIHW. The wellbeing of Aussie kids varies by family circumstances and where they live 2019 [cited 2021. Available from: https://www.aihw.gov.au/news-media/media-releases/2019/december/the-wellbeing-of-aussie-kids-varies-by-family-circ.

6. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of Attention-Deficit/Hyperactivity Disorder: A Systematic Review and Meta-analysis. Pediatrics. 2015;135(4):e994-e1001.

7. Pinborough-Zimmerman J, Satterfield R, Miller J, Bilder D, Hossain S, McMahon W. Communication disorders: prevalence and comorbid intellectual disability, autism, and emotional/behavioral disorders. American Journal of Speech-Language Pathology. 2007;16:359+.

8. Yang S, Xia J, Gao J, Wang L. Increasing prevalence of cerebral palsy among children and adolescents in China 1988-2020: A systematic review and meta-analysis. Journal of rehabilitation medicine. 2021;53(5):jrm00195-jrm.

9. Maenner MJ, Blumberg SJ, Kogan MD, Christensen D, Yeargin-Allsopp M, Schieve LA. Prevalence of cerebral palsy and intellectual disability among children identified in two U.S. National Surveys, 2011–2013. Annals of Epidemiology. 2016;26(3):222-6.

10. Al-Farsi YM, Al-Sharbati MM, Al-Farsi OA, Al-Shafaee MS, Brooks DR, Waly MI. Brief Report: Prevalence of Autistic Spectrum Disorders in the Sultanate of Oman. Journal of autism and developmental disorders. 2011;41(6):821-5.

11. Elsabbagh M, Divan G, Koh Y-J, Kim YS, Kauchali S, Marcín C, et al. Global prevalence of autism and other pervasive developmental disorders. Autism Res. 2012;5(3):160-79.

12. Mohammadi MR, Badrfam R, Khaleghi A, Ahmadi N, Hooshyari Z, Zandifar A. Lifetime Prevalence, Predictors and Comorbidities of Tic Disorders: A Population—Based Survey of Children and Adolescents in Iran. Child Psychiatry & Human Development. 2021.

13. Knight T, Steeves T, Day L, Lowerison M, Jette N, Pringsheim T. Prevalence of Tic Disorders: A Systematic Review and Meta-Analysis. Pediatric Neurology. 2012;47(2):77-90.

14. Vanoverbeke N, Annemans L, Ingham M, Adriaenssen. A cost analysis of the management of attention-deficit/hyperactivity disorder (ADHD) in children in the UK. Journal of Medical Economics. 2003;6(79):79-94.

15. Narayan S, Hay J. Cost effectiveness of methylphenidate versus AMP/DEX mixed salts for the first-line treatment of ADHD. Expert Rev Pharmacoecon Outcomes Res. 2004;4(6):625-34.

16. King S, Griffin S, Hodges Z, Weatherly H, Asseburg C, Richardson G, et al. A systematic review and economic model of the effectiveness and cost-effectiveness of methylphenidate, dexamfetamine and atomoxetine for the treatment of attention deficit hyperactivity disorder in children and adolescents. Health Technology Assessment (Winchester, England). 2006;10(23):iii-iv.

17. Cottrell S, Tilden D, Robinson P, Bae J, Arellano J, Edgell E, et al. A modeled economic evaluation comparing atomoxetine with stimulant therapy in the treatment of children with attention-deficit/hyperactivity disorder in the United Kingdom. Value in Health. 2008;11(3):376-88.

18. Hong J, Dilla T, Arellano J, Hong J, Dilla T, Arellano. A modelled economic evaluation comparing atomoxetine with methylphenidate in the treatment of children with attention-deficit/hyperactivity disorder in Spain. BMC Psychiatry. 2009;9:15.

19. Prasad S, Arellano J, Steer C, Libretto, Se. Assessing the value of atomoxetine in treating children and adolescents with ADHD in the UK. International Journal of Clinical Practice. 2009;63(7):1031-40.

20. Erder MH, Xie J, Signorovitch JE, Chen KS, Hodgkins P, Lu M, et al. Cost effectiveness of guanfacine extended-release versus atomoxetine for the treatment of attention-deficit/hyperactivity disorder: Application of a matching-adjusted indirect comparison. Applied Health Economics and Health Policy. 2012;10(6):381-95.

21. Sikirica V, Haim Erder M, Xie J, Macaulay D, Diener M, Hodgkins P, et al. Cost effectiveness of guanfacine extended release as an adjunctive therapy to a stimulant compared with stimulant monotherapy for the treatment of attention-deficit hyperactivity disorder in children and adolescents. Pharmacoeconomics. 2012;30(8):e1-15.

22. Lachaine J, Sikirica V, Mathurin K. Is adjunctive pharmacotherapy in attention-deficit/hyperactivity disorder cost-effective in Canada: A cost-effectiveness assessment of guanfacine extended-release as an adjunctive therapy to a long-acting stimulant for the treatment of ADHD. BMC Psychiatry. 2016;16.

23. Sohn M, Talbert J, Moga DC, Blumenschein. A cost-effectiveness analysis of off-label atypical antipsychotic treatment in children and adolescents with ADHD who have failed stimulant therapy. Attention Deficit and Hyperactivity Disorders. 2016;8(3):149-58.

24. Zimovetz EA, Beard SM, Hodgkins P, Bischof M, Mauskopf JA, Setyawan J. A cost-utility analysis of lisdexamfetamine versus atomoxetine in the treatment of children and adolescents with attention-deficit/hyperactivity disorder and inadequate response to methylphenidate. CNS Drugs. 2016;30(10):985-96.

25. Peters MD, Godfrey CM, McInerney P, Munn Z, Tricco AC, Khalil H, et al. Scoping reviews. 2020. In: JBI Manual for Evidence Synthesis [Internet]. [2119-26]. Available from: https://wiki.jbi.global/display/MANUAL

https://doi.org/10.46658/JBIMES-20-12.

26. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Systematic Reviews, 5, 210. 2016.

**Supplementary material 2**

**Table S3: PRISMA 2020 item checklist**

|  |  |  |  |
| --- | --- | --- | --- |
| **Section and Topic** | **Item #** | **Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | 1 |
| **ABSTRACT** | | |  |
| Abstract | 2 | See the PRISMA 2020 for Abstract’s checklist (Table 2). | 2 |
| **INTRODUCTION** | | |  |
| Rationale | 3 | Describe the rationale for the review in the context of existing knowledge. | 4 |
| Objectives | 4 | Provide an explicit statement of the objective(s) or question(s) the review addresses. | 4 |
| **METHODS** | | |  |
| Eligibility criteria | 5 | Specify the inclusion and exclusion criteria for the review and how studies were grouped for the syntheses. | 6 |
| Information sources | 6 | Specify all databases, registers, websites, organisations, reference lists and other sources searched or consulted to identify studies. Specify the date when each source was last searched or consulted. | 5 |
| Search strategy | 7 | Present the full search strategies for all databases, registers and websites, including any filters and limits used. | 5, Supplementary Material 1 |
| Selection process | 8 | Specify the methods used to decide whether a study met the inclusion criteria of the review, including how many reviewers screened each record and each report retrieved, whether they worked independently, and if applicable, details of automation tools used in the process. | 5, Supplementary Material 1 |
| Data collection process | 9 | Specify the methods used to collect data from reports, including how many reviewers collected data from each report, whether they worked independently, any processes for obtaining or confirming data from study investigators, and if applicable, details of automation tools used in the process. | 5, Supplementary Material 1 |
| Data items | 10a | List and define all outcomes for which data were sought. Specify whether all results that were compatible with each outcome domain in each study were sought (e.g. for all measures, time points, analyses), and if not, the methods used to decide which results to collect. | 5, Supplementary Materials 1 and 3 |
| 10b | List and define all other variables for which data were sought (e.g. participant and intervention characteristics, funding sources). Describe any assumptions made about any missing or unclear information. | 5, Supplementary Materials 1 and 3 |
| Study risk of bias assessment | 11 | Specify the methods used to assess risk of bias in the included studies, including details of the tool(s) used, how many reviewers assessed each study and whether they worked independently, and if applicable, details of automation tools used in the process. | 7, Supplementary Material 4 |
| Effect measures | 12 | Specify for each outcome the effect measure(s) (e.g. risk ratio, mean difference) used in the synthesis or presentation of results. | NA |
| Synthesis methods | 13a | Describe the processes used to decide which studies were eligible for each synthesis. | 5-6 |
| 13b | Describe any methods required to prepare the data for presentation or synthesis, such as handling of missing summary statistics, or data conversions. | 5-6,  Supplementary Material 3 |
| 13c | Describe any methods used to tabulate or visually display results of individual studies and syntheses. | 5-7,  Supplementary Material 3 |
| 13d | Describe any methods used to synthesize results and provide a rationale for the choice(s). If meta-analysis was performed, describe the model(s), method(s) to identify the presence and extent of statistical heterogeneity, and software package(s) used. | 5-7 |
| 13e | Describe any methods used to explore possible causes of heterogeneity among study results. | NA |
| 13f | Describe any sensitivity analyses conducted to assess robustness of the synthesized results. | NA |
| Reporting bias assessment | 14 | Describe any methods used to assess risk of bias due to missing results in a synthesis (arising from reporting biases). | 5, Supplementary Material 4 |
| Certainty assessment | 15 | Describe any methods used to assess certainty (or confidence) in the body of evidence for an outcome. | NA |
| **RESULTS** | | |  |
| Study selection | 16a | Describe the results of the search and selection process, from the number of records identified in the search to the number of studies included in the review, ideally using a flow diagram (see Figure 1). | 7-11,  Supplementary Materials 3 and 4 |
| 16b | Cite studies that met many but not all inclusion criteria (‘near-misses’) and explain why they were excluded. | Supplementary Material 1 |
| Study characteristics | 17 | Cite each included study and present its characteristics. | 7-11,  Supplementary Materials 3 and 4 |
| Risk of bias in studies | 18 | Present assessments of risk of bias for each included study. | Appendix 4 |
| Results of individual studies | 19 | For all outcomes, present, for each study: (a) summary statistics for each group (where appropriate) and (b) an effect estimate and its precision (e.g. confidence/credible interval), ideally using structured tables or plots. | 7-11,  Supplementary Material 3 |
| Results of syntheses | 20a | For each synthesis, briefly summarise the characteristics and risk of bias among contributing studies. | 7-11 |
| 20b | Present results of all statistical syntheses conducted. If meta-analysis was done, present for each the summary estimate and its precision (e.g. confidence/credible interval) and measures of statistical heterogeneity. If comparing groups, describe the direction of the effect. | 7-11 |
| 20c | Present results of all investigations of possible causes of heterogeneity among study results. | Supplementary Materials 3 and 4 |
| 20d | Present results of all sensitivity analyses conducted to assess the robustness of the synthesized results. | 9-11; Appendices 3 and 4 |
| Reporting biases | 21 | Present assessments of risk of bias due to missing results (arising from reporting biases) for each synthesis assessed. | Supplementary Material 4 |
| Certainty of evidence | 22 | Present assessments of certainty (or confidence) in the body of evidence for each outcome assessed. | Supplementary Material 4 |
| **DISCUSSION** | | |  |
| Discussion | 23a | Provide a general interpretation of the results in the context of other evidence. | 11-14 |
| 23b | Discuss any limitations of the evidence included in the review. | 11-14 |
| 23c | Discuss any limitations of the review processes used. | 11-14 |
| 23d | Discuss implications of the results for practice, policy, and future research. | 11-14 |
| **OTHER INFORMATION** | | |  |
| Registration and protocol | 24a | Provide registration information for the review, including register name and registration number, or state that the review was not registered. | NA |
| 24b | Indicate where the review protocol can be accessed, or state that a protocol was not prepared. | 4 |
| 24c | Describe and explain any amendments to information provided at registration or in the protocol. | 4 |
| Support | 25 | Describe sources of financial or non-financial support for the review, and the role of the funders or sponsors in the review. | NA |
| Competing interests | 26 | Declare any competing interests of review authors. | 14 |
| Availability of data, code and other materials | 27 | Report which of the following are publicly available and where they can be found: template data collection forms; data extracted from included studies; data used for all analyses; analytic code; any other materials used in the review. | Supplementary Materials 1-4 |

**Table S4. PRISMA 2020 for Abstracts checklist\***

|  |  |  |  |
| --- | --- | --- | --- |
| **Section and Topic** | **Item #** | **Checklist item** | **Reported on page #** |
| **TITLE** | | |  |
| Title | 1 | Identify the report as a systematic review. | 1 |
| **BACKGROUND** | | |  |
| Objectives | 2 | Provide an explicit statement of the main objective(s) or question(s) the review addresses. | 2 |
| **METHODS** | | |  |
| Eligibility criteria | 3 | Specify the inclusion and exclusion criteria for the review. | 2 |
| Information sources | 4 | Specify the information sources (e.g. databases, registers) used to identify studies and the date when each was last searched. | 2 |
| Risk of bias | 5 | Specify the methods used to assess risk of bias in the included studies. | 2 |
| Synthesis of results | 6 | Specify the methods used to present and synthesize results. | 2 |
| **RESULTS** | | |  |
| Included studies | 7 | Give the total number of included studies and participants and summarise relevant characteristics of studies. | 2 |
| Synthesis of results | 8 | Present results for main outcomes, preferably indicating the number of included studies and participants for each. If meta-analysis was done, report the summary estimate and confidence/credible interval. If comparing groups, indicate the direction of the effect (i.e. which group is favoured). | 2 |
| **DISCUSSION** | | |  |
| Limitations of evidence | 9 | Provide a brief summary of the limitations of the evidence included in the review (e.g. study risk of bias, inconsistency and imprecision). | 2 |
| Interpretation | 10 | Provide a general interpretation of the results and important implications. | 2 |
| **OTHER** | | |  |
| Funding | 11 | Specify the primary source of funding for the review. | NA |
| Registration | 12 | Provide the register name and registration number. | NA |

\*This abstract checklist retains the same items as those included in the PRISMA for Abstracts statement published in 2013 but has been revised to make the wording consistent with the PRISMA 2020 statement and includes a new item recommending authors specify the methods used to present and synthesize results (item #6).

**Supplementary material 3**

**Table S5: Reporting of cost effectiveness analysis, findings, and policy suggestions (n=12)**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **#** | **Authors, Year** | **Country** | **Type of economic evaluation** | **Incremental cost** | **Incremental utility/incremental effect** | **ICER** | **Cost (Currency base year)** | **Conclusion/Policy suggestions** |
| **Attention Deficit Hyperactivity Disorder (ADHD)** | | | | | | | | |
| 1 | Faber et al (1) | The Netherlands | CUA | €276 | QALY differed by 0.13 per youth | €2004 per QALY | Euro/2005 | MPH OROS may be considered to be a cost-effective treatment. |
| 2 | Denchev et al (2) | The US | CUA | Cost per person: Strategy 2=$52 and Strategy 3=$38 | QALY gained per person: Strategy 2=0.001269, Strategy 3=0.001387 | Strategy 2=$39300/QALY; Strategy 3=$27200/QALY | US$/? | These models suggest that adding ECG screening to current practice has borderline cost-effectiveness for identifying children at risk of SCD before initiating stimulant medication for ADHD. |
| 3 | Schawo et al (5) | The Netherlands | CUA | -€5815 (95 % CI -5661 to -5969) | 0.22 (95 % CI -0.206, 0.228) | dominant | Euro/? | For children responding sub optimally to treatment with IR, the beneficial effect of OROS on compliance may be worth the additional costs of medication. |
| 4 | van der Schans et al (6) | The Netherlands | CUA | MPH OROS vs IR MPH: -€4,235 (-2,904 to -5,335); Medikinit CR/ Equasym vs IR MPH XL: -€5,477 (-4,394 to -6,268) | MPH ORIS vs IR MPH: 0.318(0.053 to 1.285); Medikinit CR/ Equasym XL vs IR MPH: 0.18 (0.061 to 1.313) | dominant | Euro/2013 | Despite the higher costs, the longer-term economic analysis suggests that switching sub-optimally treated patients from IR-MPH to ER-MPH is very likely to be cost-saving and more effective. |
| 5 | Maia et al (7) | Brazil | CUA | Children: I$138.08; Adolescents: I$133.28 | Children: 0.01; Adolescents: 0.01 | Children: I$9,103/QALY; Adolescents: I$ 11,883/QALY | I$/2014 | MPH-IR treatment of children and adolescents is cost-effective for ADHD patients from the Brazilian public health system perspective. Both patients and the healthcare system might benefit from such a strategy. |
| 6 | Freriks et al (8) | The US | CEA | medication management was US$242, behavioural treatment US$7,633, and the combined treatment US$8,990 | -0.24 for medication management, -0.20 for behavioural treatment, 0.07 for the combined treatment. | MNB: Routine community care US$98,660, medication management US$95,449 , behavioural treatment US$88,553, and the combined treatment US$90,536. | US$/? | Results of the economic evaluation revealed that the combined treatment was the only active treatment mode that further decreases serious delinquent behavior compared with routine community care. However, the substantial difference in treatment cost renders the routine community care to be the optimal treatment strategy in terms of NMB. |
| **Autistic spectrum disorder (ASD)** | | | | | | | | |
| 7 | Penner et al (9) | Canada | CEA | ESDM-PD: saved $9,000 per person over the lifetime compared to EIBI; ESDM-I: additional cost of $12,237 per person to age 65 compared to EIBI | ESDM-PD: additional 0.17 DFLYs per person; ESDM-I: additional 0.53 DFLYs per person | ICERs were calculated for the ESDM-I. Compared to  the SQ, an ICER of approximately $23,000/DFLY. Compared with the ESDM-PD, an ICER of approximately $58,000/DFLY. | Can$/2015 | Our CEA shows that pre-diagnosis intervention with a parent-delivered ESDM (ESDM-PD) dominated the Ontario Status Quo (SQ) from a provincial perspective, with an intensive ESDM (ESDM-I) becoming the preferred strategy at a willingness-to-pay of approximately $58,000 per additional dependency-free life year (DFLY). From a societal perspective, the ESDM-I was the most effective and cost the least of all comparators. |
| 8 | Piccininni et al (4) | Canada | CEA | **Provincial:** IBI-RWT: -Can$29,306; IBI-EWT: -Can$52,976; **Societal:** IBI-RWT: -Can$146,800; IBI-EWT: -Can$267,300 | IBI-RWT: 1.28.  IBI-EWT:2.52 | **Provincial perspective:** IBI-RWT: dominant; IBI-EWT: dominant; **Societal perspective:** IBI-RWT: dominant IBI EWT: dominant | Can$/2013 | The study revealed that eliminating wait times for IBI was the dominant strategy over the CWT and halving the wait time from both provincial and societal perspectives. |
| 9 | Mark et al (10) | UK | CUA | Pessimistic: £57,879  Optimistic: £57,233 | Pessimistic: 0.24 additional QALYs.  Optimistic: 0.84 additional QALYs | Pessimistic: £236,837/QALY  Optimistic: £68,362/QALY | Pound/? | Assuming an NHS and social services perspective, the results of cost-effectiveness analysis suggest an ICER of £240,868 per QALY when pessimistic assumptions are made about long-term effects and an ICER of £69,386 per QALY when optimistic assumptions are made. When a broader public sector perspective was adopted, the ICER in respective scenarios was £189,122 per QALY and £46,768 per QALY |
| **Cerebral palsy** | | | | | | | | |
| 10 | Vallejo-Torres et al (11) | Spain | CUA | €956(394-1708) | 0.0778(0.028-0.131) | €12,282/QALY (3,013-60,707) | Euro/? | The results of this study suggest that a surveillance program to prevent hip dislocation in children with cerebral palsy is likely to be a cost-effective use of health care resources of the Spanish National Health System. |
| 11 | Kazarian et al (3) | The US | CUA | -$56,306.64 | 1.34 | Dominant | US/? | Surgery is associated with lower direct, indirect, and total costs, as well as a greater number of accumulated quality-adjusted life-years. Surgery provides a greater benefit at a lower cost, which suggests that botulinum injections should be used sparingly in this population. Treatment with surgery could represent savings of $5.6 to $11.3 billion annually in the United States. |
| **Dyslexia** | | | | | | | | |
| 12 | Hakkaart-van Roijen et al (12) | The Netherlands | CUA | €44,537,030 | 759 QALY gained | €58,647 per QALY at 6 years;  €26,386 per QALY at 12 years;  €17,663 per QALY at 18 years | Euro/2006 | The long-term cost-effectiveness would generally be considered favourable when compared with current guidelines for use of cost-effectiveness in funding decisions (RVZ, 2006) and with cost-effectiveness of treatments currently included in the Dutch benefit package. |

Applied Behavior Analysis=**ABA**; Intensive Behavioral Intervention with Reduced Wait Time=**IBI With RWT**; Intensive Behavioral Intervention with Eliminated Wait Time=**IBI With EWT**; Intensive Behavioral Intervention with Current Wait Time=**IBI With CWT**; Intensive Early Start Denver Model =**ESDM-I**; Parent Delivered Early Start Denver Model =**ESDM-PD**; Early Intensive Behavioral Intervention =**EIBI**; Electrocardiogram= **ECG**; Dependency Free Life Years=**DFLY**; History and Physical Examination=**H&P**; Cost-Utility Analysis= **CUA**; Cost-Effectiveness Analysis=**CEA**; Cost-Benefit Analysis =**CBA**; Cost Consequences Analysis= **CCA**; Methylphenidate Osmotic Release Oral System=**MPH OROS**; Immediate Release Methylphenidate=**IR MPH**; Extended-Release Methylphenidate=**ER MPH**; History and Physical examination= **H&P**;

Quality -Adjusted Life-Years=**QALY;** Life Years**=LY**; One-Way= **OW**; Two-Way**=TW**; Treatment as Usual=**TAU**; Multi-Way= **MW**; Scenario Analysis= **SA**; Probabilistic Sensitivity Analysis**=PSA**; Threshold Analysis= **TA**; Not Applicable= **NA**; Willingness To Pay= **WTP**. The intervention is cost saving and improves health compared to the comparator=**Dominant**

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**Supplementary material 4:**

**Table S6: CHEERS checklist- items to include when reporting economic evaluation of health interventions**

|  |  |  |
| --- | --- | --- |
| **Number of ITEM** | **Description of ITEM** | **Summary of criterion** |
| Item 1 | Identify the study as an economic evaluation or use more specific terms such as “cost-effectiveness analysis”, and describe the interventions compared. | Title identifies an economic evaluation |
| Item 2 | Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions. | Structured summary was presented in abstract |
| Item 3 | Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions. | Background and objectives were provided |
| Item 4 | Describe characteristics of the base case population and subgroups analysed, including why they were chosen. | Target population and subgroups were reported |
| Item 5 | State relevant aspects of the system(s) in which the decision(s) need(s) to be made. | Setting and location were reported |
| Item 6 | Describe the perspective of the study and relate this to the costs being evaluated. | Study perspective was reported |
| Item 7 | Describe the interventions or strategies being compared and state why they were chosen. | Comparators was/were reported |
| Item 8 | State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate. | Time horizon was reported |
| Item 9 | Report the choice of discount rate(s) used for costs and outcomes and say why appropriate. | Discount rate was used |
| Item 10 | Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed. | Choice of health outcomes was reported |
| Item 11 | a. Single study-based estimates: Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.  b. Synthesis-based estimates: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data. | a. Measurement of effectiveness (single study based)  b. Measurement of effectiveness (synthesis based) was/were reported |
| Item 12 | If applicable, describe the population and methods used to elicit preferences for outcomes. | Measurement and valuation of preference-based outcomes |
| Item 13 | a. Single study-based economic evaluation: Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.  b. Model-based economic evaluation: Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs. | a. Estimating resource and costs – single study based  b. Estimating resource and costs – model based |
| Item 14 | Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate. | Currency, price date and conversion were reported |
| Item 15 | Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended. | Choice of model was reported |
| Item 16 | Describe all structural or other assumptions underpinning the decision-analytical model. | Assumptions were described |
| Item 17 | Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty. | Analytic methods were described |
| Item 18 | Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended. | Study parameters were reported |
| Item 19 | For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios. | Incremental cost and outcomes were reported |
| Item 20 | a. Single study-based economic evaluation: Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as  discount rate, study perspective).  b. Model-based economic evaluation: Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions. | a. Characterizing uncertainty (single study based)  b. Characterizing uncertainty (model based) were reported |
| Item 21 | If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information. | Characterizing heterogeneity was reported |
| Item 22 | Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge. | Study findings, limitations, generalizability, and current knowledge were mentioned |
| Item 23 | Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other nonmonetary sources of support. | Source of funding was mentioned |
| Item 24 | Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors  comply with International Committee of Medical Journal Editors recommendations. | Conflicts of interest was presented |

The reporting quality of selected papers was assessed using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), consisting of a 24 item checklist, with accompanying recommendations to ensure consistent and transparent reporting in economic evaluations (1).

**Table S7 Quality assessment using the CHEERS criteria**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  | Item 1 | Item 2 | Item 3 | Item 4 | Item 5 | Item 6 | Item 7 | Item 8 | Item 9 | Item 10 | Item 11 | Item 12 | Item 13 | Item 14 | Item 15 | Item 16 | Item 17 | Item 18 | Item 19 | Item 20 | Item 21 | Item 22 | Item 23 | Item 24 |
|  | Summary of criterion | Title identifies an economic evaluation | Structured summary was presented in abstract | Background and objectives were provided | Target population and subgroups were reported | Setting and location were reported | Study perspective was reported | Comparators was/were reported | Time horizon was reported | Discount rate was used | Choice of health outcomes was reported | a. Measurement of effectiveness (single study based)  b. Measurement of effectiveness (synthesis based) was/were reported | Measurement and valuation of preference-based outcomes | a. Estimating resource and costs (single study based)  b. Estimating resource and costs (model based) | Currency, price date and conversion were reported | Choice of model was reported | Assumptions were described | Analytic methods were described | Study parameters were reported | Incremental cost and outcomes were reported | a. Characterizing uncertainty (single study based)  b. Characterizing uncertainty (model based) were reported | Characterizing heterogeneity was reported | Study findings, limitations, generalizability, and current knowledge were mentioned | Source of funding was mentioned | No Conflicts of interest was presented |
| **Attention Deficit Hyperactivity Disorder (ADHD)** | | | | | | | | | | | | | | | | | | | | | | | | | |
| 1 | Faber et al (2) | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ |
| 2 | Denchev et al (3) | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | \_ | ✔ |
| 3 | Schawo et al (4) | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | \_ |
| 4 | van der Schans et al (5) | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ |
| 5 | Maia et al (6) | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ |
| 6 | Freriks et al (7) | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | \_ | \_ |
| **Autistic spectrum disorder (ASD)** | | | | | | | | | | | | | | | | | | | | | | | | | |
| 7 | Penner et al (8) | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | \_ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | 0 |
| 8 | Piccininni et al (9) | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ |
| 9 | Mark et al (10) | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ |
| **Cerebral palsy** | | | | | | | | | | | | | | | | | | | | | | | | | |
| 10 | Vallejo-Torres et al (11) | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ |
| 11 | Kazarian et al (12) | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | \_ | \_ |
| **Dyslexia** | | | | | | | | | | | | | | | | | | | | | | | | | |
| 12 | Hakkaart-van Roijen et al (13) | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | ✔ | ✔ | ✔ | ✔ | \_ | ✔ | \_ | \_ |

NOTE: ✔ criterion met; blank: criterion partially met or criterion not met or criterion not applicable - due to their nature, not all CHEERS items were relevant to all studies.

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