BEST in Mental Health
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Best Evidence Summaries of Topics in Mental Healthcare

BEST *in* MH *clinical question-answering service*

Question

"For adults with attention deficit hyperactivity disorder (ADHD), how effective is immediate-release methylphenidate, compared to placebo or no intervention, for improving patient outcomes?"

Clarification of question using PICO structure

Patients:	Adults with ADHD
Intervention:	Immediate-release methylphenidate
Comparator:	Placebo or no intervention
Outcome:	Any patient outcomes

Email: awp.BESTinMH@nhs.net Phone: 0117 378 4232/4233/4335 @BESTinMH

Clinical and research implications

Limited evidence from one systematic review and a very small additional crossover trial indicates that immediate-release methylphenidate may be associated with improvements in the symptoms of ADHD (hyperactivity, impulsivity and inattention) and improvements in driving performance. However, evidence was derived mainly from small crossover trials and issues with the analysis methods mean that effect estimates from the systematic review may be unreliable. Further research is required to adequately assess the effects of immediate-release methylphenidate in adults with ADHD. In particular, studies with longer term follow-up and studies assessing possible adverse effects are needed.

What does the evidence say?

Number of included studies/reviews (number of participants)

We identified one systematic review,[1] and one additional randomised controlled trial (RCT) (not included in the systematic review)[2] that reported data relevant to this evidence summary. The systematic review included 11 small, placebo-controlled RCTs, nine of which were crossover trials, assessing the effects of that immediate-release methylphenidate on the symptoms of ADHD; risk of bias assessments indicated that these studies were generally poorly reported.[1] All included studies were short-term (maximum 17 weeks) and no long-term follow-up data were reported.[1] The additional study was a small (n=18), placebo-controlled crossover trial which assessed the effects of immediate-release methylphenidate on performance in a 100 km on-road driving test.[2]

Main findings

The results of meta-analyses, reported in the systematic review, indicated that immediate-release methylphenidate was associated with small but statistically significant improvements in the symptoms of ADHD: overall hyperactivity, weighted mean difference (WMD) -0.60 (95% CI -1.11 to -0.09) based on 6 studies; overall impulsivity WMD -0.62 (95% CI: -1.08 to -0.17) based on 5 studies; overall inattentiveness WMD -0.66 (95% CI: -1.02 to -0.30) based on 7 studies.[1] However, it should be noted that these meta-analyses included both parallel group and crossover study designs and there was substantial between study heterogeneity, which was not adequately explored. The results of the small additional crossover trial indicated that immediate-release methylphenidate was associated with improvements in driving performance, as indicated by a reduction in the number of attention lapses during a 100 km on-road driving test.2 The mean number of lapses in driving attention was 0.4±1.0 in the methylphenidate group and 2.4±3.1 in the placebo group, p=0.003.[2]

Authors' conclusions

The authors of the systematic review concluded that data suggest that immediate-release methylphenidate is effective for treating adults with ADHD with symptoms of hyperactivity, impulsivity, and inattentiveness, and for improving their overall clinical condition. They further noted that data suggest that adverse effects are not of serious clinical significance, but further trials, particularly on weight loss, are needed to confirm this.

The authors of the additional RCT concluded that immediate-release methylphenidate significantly improves the driving of patients with ADHD by reducing the number of lapses.

Reliability of conclusions/Strength of evidence

This evidence summary is based on one systematic review, which included mainly small crossover trials, and one additional, very small crossover trial. The evidence base is therefore weak. The

systematic review was generally well conducted, but the meta-analyses included both parallel group and crossover study designs and failed to explore possible sources of substantial between study heterogeneity. Therefore, the summary effect estimates reported in the systematic cannot be considered reliable. The additional crossover trial was small, but generally well conducted.

What do guidelines say?

NICE guidelines for the diagnosis and management of ADHD in children, young people and adults (2008, CG72) make the following recommendations regarding the use of immediate-release methylphenidate for adults with ADHD:

"10.18.7.5. Following a decision to start drug treatment in adults with ADHD, methylphenidate should normally be tried first" (pp. 308)

"1.8.1.1. Prescribers should be familiar with the pharmacokinetic profiles of all the modified-release and immediate-release preparations available for ADHD to ensure that treatment is tailored effectively to the individual needs of the child, young person or adult" (pp. 309)

No Scottish Intercollegiate Guidance Network guidelines exist for the topic.

Date question received: 04/02/2015
Date searches conducted: 10/03/2015
Date answer completed: 23/03/2015

References

Systematic reviews

1. Epstein T, Patsopoulos NA, Weiser M. (2014). Immediate-release methylphenidate for attention deficit hyperactivity disorder (ADHD) in adults. *Cochrane Database of Systematic Reviews* 2014, 9, CD005041.

Randomised controlled trials

2. Verster, J. C., & Roth, T. (2014). Methylphenidate significantly reduces lapses of attention during on-road highway driving in patients with ADHD. *Journal of clinical psychopharmacology*, *34*(5), 633-636.

Guidelines

3. National Institute for Health & Clinical Excellence (2008). *Attention deficit hyperactivity disorder: Diagnosis and management of ADHD in children, young people and adults. CG72.* National Institute for Health & Clinical Excellence. http://www.nice.org.uk/guidance/cg72/evidence/cg72-attention-deficit-hyperactivity-disorder-adhd-full-guideline-2

Results

Systematic reviews

Author (year)	Search date	Inclusion criteria	Number of included studies	Summary of results	Risk of bias
Epstein et al. (2014)	02/2015	*Participants*: Adults diagnosed with ADHD. Exclusion: Specific sub-populations of adults with ADHD (e.g. comorbidity of substance abuse or brain injury) *Intervention*: Immediate-release methylphenidate administered at any dosage as part of any treatment regimen. *Comparator*: Placebo or no intervention. *Outcomes*: Primary outcome: Symptoms of ADHD Secondary outcomes: Overall change (The number of people per treatment group who showed an overall change in condition.); General mental state changes (Changes in measures of depression, anxiety, or other psychiatric symptoms. Assessments of functioning.); Adverse effects	11 studies (n=474 participants)	This systematic review aimed to assess the efficacy and tolerability of immediate-release methylphenidate versus placebo in the treatment of adults with ADHD. The review included 11 randomised, placebo-controlled trials, of which ten trails (n=466 participants) were included I the meta-analyses. Two studies used a parallel group design and the remainder were crossover trials. Six of the nine crossover trials reported washout periods of 68 hours to one week, however, three crossover trials reported no washout period. Sample sizes were generally small (8 to 146), with eight of the 11 studies in the range 25 to 45. Study durations were short (range 1 to 17 weeks). All but one of the included studies were rated as high or unclear risk of bias on at least three criteria;. Studies included participants with similar	The research objective was clearly stated and appropriate inclusion criteria were defined. Literature searches included an appropriate range of sources and were not limited by date, language, or publication status. Search strategies were reported in full and appeared adequate. All stages of the review process were undertaken

		(Any adverse effects, including worsening of symptoms (defined as any deleterious changes in the symptoms of ADHD on any scale). *Study design*: Randomised controlled trials (RCTs)		age ranges; the overall age range of included participants was 17 to 60 years. All participants had a diagnosis of ADHD, but the method of diagnosis varied. The results of meta-analyses indicated that methylphenidate was associated with small, statistically significant, improvements for all symptom outcomes assessed: overall hyperactivity, weighted mean difference (WMD) -0.60 (95% CI -1.11 to -0.09) based on 6 studies; overall impulsivity WMD -0.62 (95% CI: -1.08 to -0.17) based on 5 studies; overall inattentiveness WMD -0.66 (95% CI: -1.02 to -0.30) based on 7 studies. When sub-group analyses were performed for low (0 to 0.9 mg/kg/day) and high (>0.9 mg/kg/day) dose methylphenidate, the direction of effect remained the same in both sub-groups, but statistical significance was lost for most outcomes. Only the two parallel group trials reported the number of participants in each group showing an overall change in condition. One study found that methylphenidate was associated with a significant increase in the number of participants with overall change	independently by two reviewers, minimising the potential for error and/or bias. Risk of bias in the included studies was assessed using the Cochrane risk of bias tool. Meta-analyses combined parallel group with crossover trials. There was a high level of between study statistical heterogeneity, which was not adequately explored.

				and the other found no significant difference between treatment groups; the summary estimate from the two studies showed no significant difference. No numerical data were reported for mental state change outcomes. The review authors stated that the limited available data suggest that adverse effects from immediate-release methylphenidate for adults with ADHD are not of serious clinical significance.	

RCTs

Author (year)	**Inclusion criteria**	**Number of participants**	**Summary of results**	**Risk of bias**
Verster et al. (2014)	*Participants*: Adults diagnosed with ADHD *Intervention*: Immediate-release methylphenidate administered orally *Comparator*: Placebo *Outcome*: Number of lapses in attention during a 100 km, on-road driving test; patient-rated subjective assessments of driving style and quality.	18	This re-analysis of data from a double-blind, placebo-controlled, randomised, crossover trial aimed to determine lapses in patients with ADHD after treatment with methylphenidate and placebo. The trial included adults with a diagnosis of ADHD who were on a stable daily dose of methylphenidate, did not experience adverse effects from the treatment, and were considered to be a clinical responder by the treating physician. Treatment or placebo were administered orally with 240 mL	Randomisation was performed independently, using a random number sequence without blocking or

			tap water, 1.5 hours before performing the on-the-road driving test. For the standard driving test, patients were instructed to drive with a steady lateral position in the slower traffic lane, maintaining a constant speed of 95 km/h. Patients were allowed to deviate from the instructions to overtake a slower moving vehicle in the same traffic lane. Lapses in driving attention were defined as a change in lateral position > 100 cm, lasting for at least 8 seconds. The mean number of lapses in driving attention was 0.4±1.0 in the methylphenidate group and 2.4±3.1 in the placebo group, *p*=0.003. The mean total lapse time was 8.1±18.0 seconds in the methylphenidate group and 35.9±47.6 seconds in the placebo group, *p*=0.017. Patient-rated subjective assessments of driving quality were significantly improved in the methylphenidate group (mean rating 13.1±4.2) compared to the placebo group (mean rating 9.9±5.1), *p*=0.026. Five out of six dimensions of patient-rated driving style (unpredictable-predictable, dangerous-safe, tense-relaxed, foolish-wise, responsible-irresponsible) also showed significant improvements for the methylphenidate group compared to placebo; there was no significant difference between the groups for inconsiderate-considerate driving style.	stratification. Randomisation codes were stored at the pharmacy. The trial was described as 'double blind' and the majority of outcomes were patient-reported. All participants were included in the analyses and data were reported for all listed outcomes.

Risk of bias:

Systematic reviews

Author (year)	RISK OF BIAS				
	Inclusion criteria	Searches	Review process	Quality assessment	Synthesis
Epstein 2014	☺	☺	☺	☺	☹

Randomised controlled trials

Study	RISK OF BIAS					
	Random allocation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective Reporting
Verster 2014	☺	☺	☺	☺	☺	☺

☺Low risk ☹High risk ? Unclear risk

Search details

Source	Search Strategy	Number of hits	Relevant evidence identified
SRs and Guidelines			
NICE	ADHD	1	1
Primary studies			
CENTRAL	#1 MeSH descriptor: [Methylphenidate] explode all trees 1072 #2 methylphenidate 1762 #3 ritalin 141 #4 #1 or #2 or #3 1788 #5 MeSH descriptor: [Attention Deficit Disorder with Hyperactivity] this term only 1633 #6 adhd 1891 #7 addh 49 #8 hyperactiv* 3465 #9 hyperkin* 514 #10 attention next deficit* 2724 #11 brain next dysfunction 167 #12 #5 or #6 or #7 or #8 or #9 or #10 or #11 4380 #13 #4 and #12 1291 Central only 2013 – 2015 113	113	1
PsycINFO	13. PsycINFO; ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY/; 14939 results. 14. PsycINFO; adhd.ti,ab; 18758 results. 15. PsycINFO; addh.ti,ab; 129 results. 16. PsycINFO; hyperactiv*.ti,ab; 29587 results. 17. PsycINFO; hyperkin*.ti,ab; 1677 results. 18. PsycINFO; "Attention deficit*".tw; 24031 results. 19. PsycINFO; "brain dysfunction".tw; 1993 results. 20. PsycINFO; 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19; 39380 results. 21. PsycINFO; METHYLPHENIDATE/; 3036 results. 22. PsycINFO; methylphenidate.tw; 4015 results.	41	0

	23. PsycINFO; ritalin.tw; 510 results. 24. PsycINFO; 21 OR 22 OR 23; 4292 results. 25. PsycINFO; CLINICAL TRIALS/; 8407 results. 26. PsycINFO; random*.ti,ab; 138812 results. 27. PsycINFO; groups.ti,ab; 384814 results. 28. PsycINFO; (double adj3 blind).ti,ab; 18590 results. 29. PsycINFO; (single adj3 blind).ti,ab; 1508 results. 30. PsycINFO; EXPERIMENTAL DESIGN/; 9497 results. 31. PsycINFO; controlled.ti,ab; 85992 results. 32. PsycINFO; (clinical adj3 study).ti,ab; 8394 results. 33. PsycINFO; trial.ti,ab; 73086 results. 34. PsycINFO; "treatment outcome clinical trial".md; 29146 results. 35. PsycINFO; 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34; 597845 results. 36. PsycINFO; 20 AND 24 AND 35; 1222 results. 37. PsycINFO; ANIMALS/; 5995 results. 38. PsycINFO; (mice OR rat*).ti,ab; 753218 results. 39. PsycINFO; 37 OR 38; 758112 results. 40. PsycINFO; 36 not 39; 588 results. 41. PsycINFO; 40 [Limit to: Publication Year 2013-2015]; 73 results. Nov 2013 - 2015		
Embase	30. EMBASE; ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY/; 34749 results. 31. EMBASE; adhd.ti,ab; 20273 results. 32. EMBASE; addh.ti,ab; 133 results. 33. EMBASE; hyperactiv*.ti,ab; 49090 results. 34. EMBASE; hyperkin*.ti,ab; 4655 results. 35. EMBASE; "Attention deficit*".tw; 23592 results. 36. EMBASE; "brain dysfunction".tw; 2901 results. 37. EMBASE; 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36; 74998 results.	76	1

	38. EMBASE; METHYLPHENIDATE/; 16136 results. 39. EMBASE; methylphenidate.tw; 6494 results. 40. EMBASE; ritalin.tw; 2598 results. 41. EMBASE; 38 OR 39 OR 40; 16543 results. 42. EMBASE; random*.ti,ab; 939745 results. 43. EMBASE; factorial*.ti,ab; 24204 results. 44. EMBASE; (crossover* OR cross-over*).ti,ab; 71944 results. 45. EMBASE; placebo*.ti,ab; 209029 results. 46. EMBASE; (doubl* ADJ blind*).ti,ab; 147652 results. 47. EMBASE; (singl* ADJ blind*).ti,ab; 15298 results. 48. EMBASE; assign*.ti,ab; 251551 results. 49. EMBASE; allocat*.ti,ab; 89115 results. 50. EMBASE; volunteer*.ti,ab; 183278 results. 51. EMBASE; CROSSOVER PROCEDURE/; 41657 results. 52. EMBASE; DOUBLE BLIND PROCEDURE/; 118089 results. 53. EMBASE; RANDOMIZED CONTROLLED TRIAL/; 361087 results. 54. EMBASE; SINGLE BLIND PROCEDURE/; 19568 results. 55. EMBASE; 42 OR 43 OR 44 OR 45 OR 46 OR 47 OR 48 OR 49 OR 50 OR 51 OR 52 OR 53 OR 54; 1488307 results. 56. EMBASE; 37 AND 41 AND 55; 1696 results. 57. EMBASE; ANIMALS/; 1600512 results. 58. EMBASE; (mice OR rat*).ti,ab; 5406150 results. 59. EMBASE; 57 OR 58; 6620702 results. 60. EMBASE; 56 not 59; 865 results. 61. EMBASE; 60 [Limit to: Publication Year 2013-2015]; 119 results Nov 2013 – 2015 76		
Medline	1. MEDLINE; ATTENTION DEFICIT DISORDER WITH HYPERACTIVITY/; 20818 results. 2. MEDLINE; adhd.ti,ab; 15109 results. 3. MEDLINE; addh.ti,ab; 112 results.	97	0

	4. MEDLINE; hyperactiv*.ti,ab; 40022 results. 5. MEDLINE; hyperkin*.ti,ab; 4040 results. 6. MEDLINE; "Attention deficit*".tw; 19031 results. 7. MEDLINE; "brain dysfunction".tw; 2486 results. 8. MEDLINE; 1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7; 54879 results. 9. MEDLINE; METHYLPHENIDATE/; 5843 results. 10. MEDLINE; methylphenidate.tw; 5294 results. 11. MEDLINE; ritalin.tw; 589 results. 12. MEDLINE; 9 OR 10 OR 11; 7255 results. 13. MEDLINE; "randomized controlled trial".pt; 387168 results. 14. MEDLINE; "controlled clinical trial".pt; 88869 results. 15. MEDLINE; randomized.ab; 311641 results. 16. MEDLINE; placebo.ab; 158989 results. 17. MEDLINE; "drug therapy".fs; 1745898 results. 18. MEDLINE; randomly.ab; 225410 results. 19. MEDLINE; trial.ab; 322049 results. 20. MEDLINE; groups.ab; 1422665 results. 21. MEDLINE; 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20; 3468540 results. 22. MEDLINE; 8 AND 12 AND 21; 3363 results. 23. MEDLINE; ANIMALS/; 5405055 results. 24. MEDLINE; (mice OR rat*).ti,ab; 4645054 results. 25. MEDLINE; 23 OR 24; 7944666 results. 26. MEDLINE; 22 not 25; 2045 results. 27. MEDLINE; 26 [Limit to: Publication Year 2013-2015]; 179 results. Nov 2013 – 2015 97		

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