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REVIEW

The Safety and Efficacy of Methylphenidate and Dexmethylphenidate in Adults with Attention Deficit/Hyperactivity Disorder

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Abstract

Objective: To review the literature on the safety and efficacy of methylphenidate, OROS-methylphenidate, methylphenidate ER, and dexmethylphenidate in adults with Attention-Deficit/Hyperactivity Disorder (ADHD). To analyze the effects of different doses of methylphenidate, it's various formulations, and methylphenidate on efficacy and safety in this population.

Data sources: Literature retrieval was performed through Pubmed/MEDLINE (Up to May 2010) using the terms methylphenidate, dexmethylphenidate, and attention-deficit hyperactivity disorder. In addition, reference citations from publications identified were reviewed.

Study selection and data extraction: Double-blinded, placebo-controlled clinical trials, as well as crossover and open-label trials found using the search criteria listed above were included for review. Case reports were not included in this review.

Data synthesis: Attention-deficit/hyperactivity disorder (ADHD) is a psychiatric condition that is commonly seen in children and adolescents, that persists into adulthood for about 50% of patients. Methylphenidate and dexmethylphenidate are often prescribed to treat the symptoms associated with ADHD. The literature validating the safety and efficacy of methylphenidate and dexmethylphenidate in children and adolescents with ADHD is substantial. However, the literature specifically addressing the safety and efficacy of these medications in the adult population is less extensive and prescribing is often anecdotal based on child and adolescent data. Understanding the literature regarding methylphenidate and dexmethylphenidate and its effects in adults can enhance evidence-based medicine (EBM) and improve treatment outcomes

Conclusion: Methylphenidate and dexmethylphenidate are safe and effective medications to treat the symptoms of ADHD in adults. Based on the literature, increased doses are associated with better treatment response with moderate safety concerns. The different dosage forms available enable individualization of treatment.

Keywords: methylphenidate, dexmethylphenidate, ADHD, pharmacological treatment

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Introduction

Attention-deficit hyperactivity disorder (ADHD) affects roughly 4 to 12% of children, depending on the reference, and approximately 4.7% of adults.[1] It is characterized by symptoms of hyperactivity, impulsivity, and inattention. Examples of symptoms in both children and adults can be seen in Table 1. Patients can either present with predominantly hyperactive/impulsive or inattentive symptoms, or most often a combination of both symptoms. Children, particularly boys, tend to present with predominant hyperactive symptoms that may dissipate as they get older. Meanwhile, girls tend to have more inattentive symptoms, and therefore may be under-diagnosed. While the Diagnostic and Statistical Manual-IV- Text Revision does have criteria for ADHD it is mostly geared towards children and not adults. However, about 50% of children diagnosed with ADHD continue to have symptoms into adulthood and continued treatment may be necessary.[2]

Treatment options for ADHD include pharmacological interventions, behavioral modifications, and the combination of both. Based on guidelines, first line pharmacological options are stimulant medications, methylphenidate (MPH) and amphetamine, in both children and adults.[3,4] There are also non-stimulant options, such as atomoxetine and guanfacine. This article will focus on reviewing the efficacy and safety of MPH in adults.

MPH has been approved by the Food and Drug Administration (FDA) to be used in children as young as 6 years of age and adults with ADHD since 1955. MPH exerts its effects in ADHD by blocking dopamine transport or carrier proteins, and norepinephrine to a much lesser extent. As a result, sympathomimetic activity in the CNS, including the prefrontal cortex, is increased. This leads to improved attention span, increased ability to follow directions or complete tasks, decreased distractibility, and decreased impulsivity and aggression.[5] In the periphery, the effects of MPH are minimal at therapeutic doses, but can cause tachycardia or elevated blood pressure. Other commonly observed adverse effects are anorexia and insomnia. Dexmethylphenidate, the more potent isomer of MPH, is also commercially available for the treatment of ADHD. Using dexmethylphenidate does allow for a lower dose to be used and increases the duration of action by 1–2 hours.

MPH is often prescribed anecdotally to adults with ADHD, as most of the literature validating its efficacy studied the child and adolescent population. However, numerous double-blind and open-label clinical trials have studied MPH, OROS-MPH, MPH ER, and dexmethylphenidate in adults. This article will comprehensively review the efficacy and safety of MPH at different doses and frequencies in adults with ADHD in an attempt to clarify its appropriateness in clinical practice.

Efficacy of Methylphenidate and Dexmethylphenidate in Adults

The efficacy of MPH and dexmethylphenidate in adults has been reviewed in various clinical trials

Table 1. Possible symptoms of ADHD in childhood and adulthood.[1]

	Childhood	Adulthood
Hyperactive/impulsive symptoms	- Not being able to sit still - Always on the move - Unable to wait turn - Unable to play quietly - Excessive talking - Constantly interrupts others - Blurts out inappropriately - Behavior/academic problems in school	- Not able to sit through meetings - Careless driving - May self-selects active job - Excessive talking - Interrupts others - Inappropriate comments - Inefficiencies at work
Inattentive symptoms	- Difficulty maintaining attention in school - Appears to not listen - Problems following through on tasks - Unorganized - Constantly losing homework or important items	- Difficulty maintaining attention in workplace - Extreme procrastination - Slow and inefficient - Poor time management - Unorganized - Constantly losing important items

(Table 2). The study designs, population data, dosing information, efficacy results and additional information that is pertinent to adequate analysis of these clinical trials is encompassed in Table 2. The following is a summary of the results of the various formulations, as well as any conclusions that can be drawn from this data.

Methylphenidate immediate-release formulation

Six double-blinded, placebo-controlled clinical trials were reviewed that analyzed the efficacy of MPH in adults with Attention Deficit Disorder (ADD) or Attention Deficit/Hyperactivity Disorder (ADHD).[6–11] The trial evaluating MPH's efficacy in patients with minimal brain dysfunction (MBD) was not reviewed due to differences in diagnostic criteria which could confound any useful comparisons to other trials.[12] Data revealed inconsistent response rates of 38%–78% in patients treated with MPH. However, these rates were superior to the response rates of 4%–19% with placebo, when reviewing each trial individually.[6–11] Possible reasons for the variability could be differences in diagnostic criteria of the subjects, inconsistent definitions of response rate, as well as variations of dosing titration schedules and mean doses used in each trial.

It is difficult to determine the effect that dose had on response rate and other efficacy outcomes. Mattes, et al found no significant benefit of MPH on ADD symptomology with "low/moderate" doses.[6] Conflicting data was presented by Wender et al and Bouffard et al which reported response rates of 57% and 63%–73%, respectively, at "low-moderate" doses.[7,9] The range of response rates in the Bouffard et al trial is due to the difference in definition of response, with 63% corresponding to a more conservative designation. Robust treatment responses of 78% were seen at doses up to 1.0 mg/kg/d[8] and up to 76% with doses of up to 1.3 mg/kg/d.[11] However, Kooij et al did not show this positive dose-to-effect correlation, with only 38% of MPH subjects responding to doses of up to 1.0 mg/kg/d.[10]

Overall, MPH established statistically significant differences in most efficacy outcomes when compared with placebo. Due to the myriad of outcome measures used in these six trials, it is difficult to directly compare the results. However, these differences were more drastic with increased doses of MPH. Scores at endpoint on the Physician's Global Rating Scale (PGRS), Connors Rating Scale, Clinical Global Impression-Severity scale (CGI-S), and the Global Assessment Scale all showed statistically significant superiority for MPH compared with placebo (Table 2). However, there were differing results on the Global Assessment of Functioning (GAF), with Bouffard et al establishing positive treatment effects and Kooij, et al showing no difference between MPH and placebo.[9,10] The data from the Mattes et al trial displayed that subjects treated with MPH had less psychiatrist rated impulsivity, and MPH was more effective than placebo only in pts with a diagnosis of drug abuse. However, the authors concluded that MPH was not effective for ADD, residual type in adults.[6]

Regarding onset of treatment effect, improvement can be seen as early as week 1, at doses of 0.5 mg/kg/d.[8] Similar rapid effect starting at week 2 at doses of up to 1.3 mg/kg/d, with symptom reduction persisting until endpoint.[11] MPH subjects in the Wender, et al trial had response rates of 57% at the end of week 2 with low-moderate doses, which may indicate that the early effect is not due to quick titration.[7]

OROS-Methylphenidate (OROS-MPH)

Four double-blinded[13–16] and two open-label[17,18] clinical trials evaluated the efficacy of OROS-MPH in adults with ADHD (Table 2). The response rates for subjects taking OROS-MPH ranged from 36.9%–66%, depending on the trial.[13–18] It is important to note that in the trial reporting the response rate of 36.9%, roughly 80% of patients had ADHD, combined type and 20% had inattentive type.[14] Medori et al analyzed the effects of MPH at various doses and found that the 18 mg, 36 mg, and 54 mg doses had responses rates of 50.5%, 48.5%, and 59.6%, respectively, failing to indicate a dose-to-effect relationship.[15] It is interesting to note that in the Reimherr et al trial, researchers found that the mean daily doses of treatment responders was 57 mg, compared to a mean of 75 mg in non-responders, which also does not show a positive dose-to-effect relationship.[16] Since different trials used different outcome measurements, it is hard

Table 2. Efficacy and safety data of methylphenidate and dexmethylphenidate in adults.[6–21]

Author (drug)	Trial design	Inclusion	N (MPH/PLA)	Dosing titration
Mattes JA et al 1984 (MPH)	DB, crossover, randomized, PLA-controlled, 3 wks/med, no washout	18–45 yrs. 5 sx's of ADD (restlessness, difficulty concentrating, excitability, impulsivity, irritability) rated 0–3: Mean > 2.0. ADD, residual type	61 (29 w/childhood ADD-H, 37 w/o)	5 mg BID,↑ by 5 mg/dose every 2 days
Wender PH et al 1985 (MPH)	DB, crossover, randomized, PLA-controlled, 2 wks/med, 1 wk washout	21–45 yrs. Hx of ADD w/hyperactivity in childhood and attention deficit persisting from childhood. ≥2 of following: 1) affective lability 2) inability to complete tasks 3) hot or explosive temper 4) impulsivity 5) stress intolerance	37 (20M)	5 mg BID, ↑ by 5 mg per dose every 2–3 days
Spencer et al 1985 (MPH)	DB, crossover, randomized, PLA-controlled, 3 wks/med, 1 wk washout	18–60 yrs, DSM-III-R dx of childhood onset and current ADHD. Referred by clinicians or self-referred for life-long hx's of inattention and underachievement	23 (10M)	Titrated up to 0.5 mg/kg/d by wk 1, 0.75 mg/kg/d by wk 2, and up to 1.0 mg/kg/d by wk 3, unless AE's emerged
Bouffard et al 2003 (MPH)	DB, crossover, 2 MPH dose comparison study to PLA	17–51 yrs, referred by MD's, other professionals, family members and themselves. DSM-IV dx of ADHD w/1.5 or more on at least 1 ADHD self-report questionnaire	30 (24M)	10 mg TID for 2 wks of MPH or PLA, then increased to 15 mg TID for 2 wks, then 1 wk washout, then repeat titration process for other med (MPH or PLA)
Kooij et al 2003 (MPH)	DB, crossover, randomized, PLA-controlled 3 wks/med, 1 wk washout. ITT	20–56 yrs, met DSM-IV criteria of ADHD w/persistence into adulthood	45 (24M) (25MPH followed by PLA, 20 PLA followed by MPH)	Titrated to 0.5 mg/kg/d by wk 1, 0.75 mg/kg/d by wk 2, and up to 1.0 mg/kg/d by wk 3 unless AE's emerged. Pts given choice of QID or 5x/d dosing

Mean daily MPH/mean daily PLA (max MPH dose/d)	Efficacy results (MPH/PLA)	Safety results (MPH/PLA)	Additional notes
48.2 mg/57 mg (60 mg)	MPH subjects: Less psychiatrist rated impulsivity, more effective than PLA in pts w/dx of drug abuse.	More anorexia, late-afternoon depression, headaches w/MPH (all $P < 0.05$)	Of 16 MPH responders, 4 were not taking med at follow-up w/improvement persisting after drug d/c Authors: MPH not effective for ADD, residual type in adult
43.2 mg/50.2 mg (90 mg)	PGRS: –1.4/–0.16. Moderate-marked tx response: 21 (57%)/4 (11%) ($P < 0.005$) Of 21 MPH pts, GAS ↑ from 59 to 76. Profile of Mood States: less tensionanxiety, depressionrejection, anger-hostility, confusion and fatigue for MPH pts vs. PLA	Reported by 8/37 patients: Mild anxiety Insomnia Jaw tension and Teeth grinding Overstimulation Irritability Nose tingling	28/37 (65%) w/dysthymic disorder, 8/37 (22%) had cyclothymia and 4 (11%) had GAD. Authors: MPH as efficacious in ADD, residual type as in childhood ADD
Wk 1: 0.51 ± 0.01/0.51 ± 0.01 mg/kg Wk 2: 0.75 ± 0.03/0.81 ± 0.02 mg/kg Wk 3: 0.92 ± 0.04/1.00 ± 0.04 mg/kg (1.0 mg/kg)	MPH separated from PLA after wk 1, w/improvement ↑ w/dose ↑. RR (CGI < 2 and ⇓ of <30% in individual rating scale scores): 78%/4% ($P < 0.0001$). MPH had significantly greater reductions for all sx's of ADHD ($P < 0.01$)	Decreased appetite (26%) Insomnia (22%) Anxiety (22%) HR (80 ± 2.4/76 ± 1.5 $P < 0.05$) SBP (123 ± 2.6 vs. 117 ± 1.7, $P > 0.05$) DBP (77 ± 2 vs. 75 ± 1.5, $P > 0.05$) Wt (73.2 kg ± 3.4 vs. 74.3 kg ± 3.6, $P < 0.05$)	Pts were non-Hispanic outpatients. Comorbid psych disorders: 74% (17) had ≤1 in past, 56% (13) current
See dosing titration	ADHD sx's: 30 mg/d: 1.9–0.9 ($P < 0.0001$) 45 mg/d: 1.9–0.9 ($P < 0.0001$) PLA: 1.9 to 1.2 ($P < 0.0001$) Connors Rating Scale30 mg/d: 1.9–1.1 ($P < 0.0001$) 45 mg: 1.9–1.0 ($P < 0.0001$) PLA: 1.9–1.4 ($P < 0.0001$) MPH RR: 63%–73% GAF: ↑ 1.4 w/PLA, ↑ 6.8 w/MPH 45 mg/d ($P < 0.0001$)	Decreased appetite (41%/19%) Mild-moderate insomnia (26%/25%) HA (21%/35%) HR (+5/+1, $P > 0.05$) SBP (+5/0, $P < 0.05$) DBP (+2/+2, $P > 0.05$)	Authors: low to medium doses of MPH reduced ADHD symptoms in adults
Wk 1: 0.5 (0.31–0.55)/0.5 (0.45–0.55) mg/kg Wk 2: 0.75 (0.31–0.82)/0.76 (0.69–0.82) mg/kg Wk 3: 0.91 (0.54–1.04)/ 0.98 (0.71–1.04) mg/kg (1.0 mg/kg)	RR (Combined DSM-IV ADHD rating scale and CGI-S score): 38%/7% ($P < 0.003$). CGI-S alone: 51%/18% ($P = 0.011$). No statistically significant difference btwn MPH and PLA on GAF	Decreased appetite (22%/4%, $P = 0.039$) Sleeping problems (33%/22%, $P = 0.27$) HA (16%/4%, $P = 0.18$) Dizziness (16%/7%, $P = 0.34$) Abdominal complaints (13%/4%, $P = 0.22$) Dry mouth (24%/7%, $P = 0.06$)	All ADHD types eligible, comorbid psychiatric disorders included. Outpts. MPH associated w/higher sx levels of depression and anxiety than PLA on HAM-A and HAM-D scales ($P = 0.002$)

(*Continued*)

Table 2. (*Continued*)

Author (drug)	Trial design	Inclusion	N (MPH/PLA)	Dosing titration
Spencer et al 2005 (MPH)	DB, rando- mized to MPH or PLA at a ratio of 2.5:1, parallel, PLA-controlled, 6 wks	19–60 yrs, met DSM-IV criteria of ADHD w/persistence into adulthood, from clinical referrals or media advertisements	104/42	Titrated to 0.5 mg/kg/d by wk 1, 0.75 mg/kg/d by wk 2, 1.0 mg/kg/d by wk 3 to a max of 1.3 mg/kg/d by wks 5 and 6 unless AE's emerged. TID dosing
Biederman et al 2005 (OROSMPH)	DB, randomized, parallel, PLA-controlled, 6 wks, ITT w/LOCF	19–60 yrs, met DSM-IV criteria of ADHD w/persistence into adulthood	72/77	Initial dose of 36 mg, increasing dose by 36 mg/d only if failed to attain improvement o n CGI-I or AISRS and if didn't experience AE's. QD dosing
Fallu et al 2006 (OROS MPH *no PLA)	Uncontrolled, OL, single- center, 38 days, LOCF	18–65 yrs, Met DSM-IV TR criteria of ADHD. Retrospective childhood dx through WURS. Pts required to have baseline CAARS $>$ 24, CGI-S $\geq$ 4, and baseline MADRS $\leq$ 16	30	Initial dose of 18 mg/d for 3 days, then 36 mg/d for 7 days, then if needed dose increased to 54 for 7 days and then to a max of 72 mg/d. QD dosing

Mean daily MPH/mean daily PLA (max MPH dose/d)	Efficacy results (MPH/PLA)	Safety results (MPH/PLA)	Additional notes
At Wk 6: 82 ± 22 mg/101 ± 19 or 1.1 ± 0.24 mg/kg/1.2 ± 0.1 mg/kg (1.3 mg/kg/d)	Of completers, MPH markedly reduced ADHD symptoms (33.8 ± 8.6 to 13.1 ± 10.3 $P < 0.0001$) PLA: 35.9 ± 9.2 to 28 ± 11.2, $P < 0.0001$ Mean difference of MPH and PLA response from baseline: 44%. Using LOCF, RR: 68% (63/93)/17% (6/36). Completers analysis showed 76% responded to MPH compared w/19% on PLA	Decreased appetite (27%/7%, $P = 0.01$) Dry mouth (35%/0%, $P = 0.001$) Moody (30%/5%, $P = 0.001$) Wt (–2.4 kg, $P < 0.001$) HR (83 ± 13/76 ± 13, $P < 0.001$) ECG ventricular rate (74.3 ± 12.4/67.2 ± 9.8, $P < 0.001$) QTc interval (0.420 ± 0.02 vs. 0.413 ± 0.02, $P < 0.01$) No statistical difference in SBP or DBP	38% of pts w/lifetime prevalence of MDD, 9% had >2 lifetime prevalence of anxiety disorders. 81% (110) completed the full 6 wks. MPH progressively reduced ADHD sx's over the 6 wks, starting in the 2nd wk.
At Wk 6: 80.9 ± 31.8 mg/ 96.8 ± 25.9 or 0.99 ± 0.32 mg/kg/1.17 ± 0.18 mg/kg (1.3 mg/ kg/d)	MPH pts had greater response on AISRS compared w/PLA starting on wk 3 ($P < 0.05$). MPH had greater reduction of DSM-IV sx's of inattention and impulsivity than PLA at endpt. MPH had significant difference in # pts to have 30% reduction on AISRS ($P < 0.001$), 50% reduction on AISRS ($P < 0.001$). RR: 66%/39% ($P = 0.002$)	Decreased appetite (34%/3%, $P < 0.001$) Dry eyes, nose, mouth (34%/7%, $P < 0.001$) Tension/jitteriness (18%/0%, $P < 0.001$) Wt (–2.7 kg/+0.03 kg, $P < 0.001$) GI (28%/ 14%, $P = 0.03$ HR (+4.5 ± 10.5/–2.7 ± 12.4, $P < 0.001$) SBP (+3.5 ± 11.8/–1.1 ± 11.4, $P = 0.02$) DBP (+4 ± 8.5/–2.1 ± 8.9, $P < 0.001$)	
52.3 ± 14.0 mg/d or 0.74 ± 0.22 mg/kg/d (72 mg/d)	Total CAARS score: improvement at day 3 ($P = 0.02$) and after w/mean ↓ of 18.4 ± 10.6 at last observation ($P < 0.0001$). Inattentive subscale improvement at day 3 ($P = 0.02$) and after, w/ mean ↓ of 12 ± 7.2 at last observation ($P < 0.0001$). Hyperactivity/impulsivity subscale improvement by day 10 and after, w/mean ↓ of 6.4 ± 5.3 at last observation ($P < 0.0001$). CGI-S: 80% 'not ill', 'very mildly ill' or 'mildly ill' and 77% 'somewhat' or 'completely satisfied' w/tx at last observation	Decreased appetite (38%) HA (53%) Insomnia (31%) Dry mouth (22%) Agitation (25%) Palpitation (25%) HR (+5.9, $P = 0.003$) SBP (–2.9) and DBP (–1.4) w/$P > 0.05$ Higher doses showed higher changes in HR, not SBP, DBP, or other AE's	Single site in Canada. Known non-responders to MPH excluded. Statistical significant improvements on Stroop-Color-Word Test, WAIS-III Working Memory Index, COWAT Verbal and Object scores. 18% of pts achieved remission by day 17, and 40% at endpt

(*Continued*)

Table 2. (*Continued*)

Author (drug)	Trial design	Inclusion	N (MPH/PLA)	Dosing titration
Biederman et al 2006 (OROS MPH *no PLA)	OL, 6 wks, ITT w/LOCF	19–60 yrs, dx of ADHD NOS (met ADHD criteria w/o onset before 7 yrs)	36	Initial dose: 36 mg by wk 1, 72 mg by wk 2, 108 mg by wk 3. Dose ↑ if needed by 18 mg/wk to a max of 1.3 mg/kg (no more than 144 mg)
Reimherr et al 2007 (OROS MPH)	DB, randomized, crossover, PLA controlled, 2 4-wk arms, no washout. 3 subgroups: ADHD alone, ADHD + ED, ADHD + ED + ODD	18–65 yrs, Met DSM-IV-TR criteria of ADHD, Connors Adult ADHD Diagnostic Interview, and Utah Criteria for ADHD in adults	41	Initial dose: 18 mg. Increased by 9 mg every 2–3 days with a max of 90 mg/d
Medori et al 2008 (OROS MPH)	DB, randomized, parallel, PLA-controlled, fixed dose, 5 wk in 51 sites, LOCF	18–63 yrs, Met DSM-IV-TR criteria of ADHD, Connors Adult ADHD Diagnostic Interview	401 (218M)	18 mg group: 18 mg for 5 wks; 36 mg group: 36 mg for 5 wks; 72 mg group: initially 36 mg for 4 days, then 54 mg for 3 days, then 72 mg for 4 wks
Adler et al 2009 (OROS MPH)	DB, randomized to MPH or PLA in ratio of 1:1, parallel, PLA-controlled, dose-escalation, 7 wks in 27 sites, ITT w/ LOCF	18–65 yrs, Met DSM-IV-TR criteria for ADHD and weighed $<$100 lbs. Chronic ADHD since childhood, w/ AISRS score of $\geq$24 and GAF from 41–60	226′	Initial dose: 36 mg, ↑ by 18 mg every 7 days until pt specific dose achieved of 36 mg, 54 mg, 72 mg, 90 mg or 108 mg/d. Remain at individualized dose for 5 wks and 2 wk efficacy assessment visit

Mean daily MPH/mean daily PLA (max MPH dose/d)	Efficacy results (MPH/PLA)	Safety results (MPH/PLA)	Additional notes
78.2 ± 29.4 mg/d (1.3 mg/kg/d or 144 mg/d)	↓ on inattention (–9.3 ± 6.2) and hyperactivity/impulsivity (–7.2 ± 5.2) subscales.72% (26) had 30% reduction on AISRS, and 58% had 50% reduction on AISRS. RR: 67% (24)	HA (43%) Insomnia (46%) Dry eyes, nose, and mouth (37%) ↓ appetite (34%) GI (26%) HR (+8.7, $P = 0.002$) SBP (+2.8, $P = 0.2$) DBP (+2.8, $P = 0.08$) QT (–16.7, $P < 0.001$) QTc (+5.1, $P = 0.03$)	
ADHD alone: 64.8 ± 3.3 mg, ADHD + ED: 64.1 ± 24.8 mg, ADHD + ED + ODD: 60.5 ± 21.1 mg.	WRAADDS scores ↓: 42%/13% ($P < 0.001$). Mean ADHD-RS score ↓: 41%/14% ($P = 0.003$). Inattention and hyperactivity subscales significant for MPH. >50% improvement on WRAADDS 49% (20)/15% (6) CGI-I score of much or very much improved: 54%/22% ($P = 0.018$)	Decreased appetite (12%/0%, $P = 0.025$) Insomnia (22%/7%, $P = 0.05$) Anxiety (10%/0%, $P = 0.05$) HR (75.5 ± 11.7/ 73.6 ± 10.6, $P = 0.1$) SBP (121.5 ± 10.4/ 119.1 ± 8.6, $P = 0.064$ DBP (80.1 ± 8.8/ 78.2 ± 7.6, $P = 0.042$) Wt (–2.5 lb ± 3.8/ +1.3 lb ± 4.3, $P = 0.001$)	18 subjects that met criteria for ADHD + ED + ODD improved 50% on MPH and 11% on PLA ($P < 0.001$) Responders: 57 ± 20 mg, Non-responders: 75 ± 21 mg (90 mg/d)
18 mg group: 0.24 mg/kg (0.1–0.4), 36 mg group: 0.50 mg/kg (0.3–0.8), 72 mg group: 0.96 mg/kg (0.6–1.7 mg/kg)	Mean Δ from baseline to endpt in CAARS:O-SV total score, LOCF: –10.6, –11.5, –13.7 and –7.6 for the 18 mg, 36 mg, 54 mg and PLA groups, respectively ($P < 0.015$). RR: 50.5%, 48.5%, 59.6% and 27.4% in 18 mg, 36 mg, 54 mg, and PLA groups, respectively. ≥50% reduction: 22.2%, 24.8%, 31.3%, and 13.7%, respectively	Decreased appetite (25.2%, 34.3% 72 mg/7.3%) HA (21%, 25.7% 18 mg/17.7%) Insomnia (13.4%, 16.7% 72 mg/7.3%) Nausea (12.8%, 15.7% 36 mg/4.2%) Dry mouth (11.8%, 20.6% 72 mg/2.1%) Wt (–0.9 kg 18 mg, –1.1 kg 36 mg, –1.9 kg 72 mg, $P < 0.001$) HR (72 mg,+9.8; 36 mg, +5.2; 18 mg, +3.9. All $P < 0.05$) No statistically significant changes in BP	51 sites in Europe, 98% Caucasian, 71% w/ADHD combined subtype
Mean dose (SD) –67.7 (27.9)/86.9 (27.81). 36 mg was final dose for 32.7% pts, 108 mg was final dose for 20.9% pts. (108 mg/d)	Mean change on AISRS from baseline: –10.6/–6.8 ($P = 0.012$) CGI-I mean score: 3.02/3.43 ($P = 0.008$). RR: 36.9%/20.9% ($P = 0.009$) AISRS and treatment response: statistically significant difference of MPH vs. PLA at all titration visits, 2 wk efficacy assessment, and the final visit (LOCF)	Decreased appetite (25.5%/6%) HA (25.5%/13.8%) Dry mouth (20%/5.2%) Anxiety (16.4%/3.4%) Nausea (12.7%/2.6%) ↑ BP (10%/5.2%) SBP (–1.2/–0.5) DBP (+1.1/+0.4)	Most subjects white males w/mean age of ~39 yrs. Most had ADHD combined type (~80%) rather than inattentive type (~20%)

(*Continued*)

Table 2. (*Continued*)

Author (drug)	Trial design	Inclusion	N (MPH/PLA)	Dosing titration
Rösler et al 2009 (MPH ER)	DB, randomized to MPH ER or PLA in ratio of 2:1, PLA-controlled, 24 wks in 28 sites, LOCF	>18 yrs, Met DSM-IV criteria for ADHD	359 (178 M)	initial dose: 5 mg BID, titrated to a max of 60 mg by 5 wks. Minimum maintenance dose after wk 5: 20 mg/d
Spencer et al 2007 (Dex-MPH)	DB, randomized, fixed dose, PLA-controlled, 5 wks in 18 sites, ITT w/LOCF	18–60 yrs, Met DSM- IV-TR criteria for ADHD, Chronic ADHD since childhood, w/ADHD-RS score of ≥24 and GAF < 60	221 (127M) 20 mg: 58, 30 mg: 55, 40 mg: 55, PLA: 53	Initial dose: 10 mg/d titrated by 10 mg/wk to randomly assigned fixed doses and maintained at dose for <2 wks

Mean daily MPH/mean daily PLA (max MPH dose/d)	Efficacy results (MPH/PLA)	Safety results (MPH/PLA)	Additional notes
		HR (+3.6/–1.6) Wt (–2.2 kg/+0.2 kg) Adverse events reported (63.6% at 36 mg, 39.7% at 54 mg, 50% at 72 mg, 35.6% at 90 mg, 31% at 108 mg) Pts requiring ↓ dose (3.8% of 54 mg, 5% of 72 mg, 13.3% of 90 mg, 17.2% of 108 mg)	
41.2 ± 18.2/40.8 ± 19.6 or 0.55 ± 0.27 mg/kg/0.55 ± 0.29 mg/kg (60 mg/d)	MPH statistically significant d ifference w/PLA at all assessments after titration phase on WRAADDS total score. Significant treatment effects of MPH compared w/PLA in all 7 domains of WRAADDS. CAARS-DATS score significantly superior in MPH group compared w/the PLA group at wk 24 ($P = 0.016$) RR: 61%/42% ($P = 0.001$)	Decreased appetite (38%/13%) Dry mouth (30%/16%) Palpitation (23%/9%) Excessive thirst (24%/12%) Insomnia (25%/18%) HR, wk 4 (77 ± 11/72.9 ± 9, $P < 0.0001$) HR, wk 24 (76 ± 11/74 ± 11, $P = 0.1169$) SBP (124 ± 13/123 ± 15, $P = 0.1243$) DBP (78 ± 9/78 ± 10, $P = 0.2688$)	28 sites across Germany. 110 subjects dropped out of study (24% MPH/43% PLA)
Fixed dose: see dosing titration	ADHD-RS change from baseline: –7.9 PLA, –13.7 20 mg, –13.4 30 mg, –16.9 40 mg (all $P < 0.05$) All dosages combined were superior to placebo on ADHD-RS inattentive and hyperactive- impulsive subscales. RR: PLA: 26.4%, 20 mg: 47.4%, 30 mg: 37%, 40 mg: 55.6%. ⇓ on CGI-S: PLA: 41.5%, 20 mg: 68.4%, 30 mg: 61.1%, 40 mg: 64.8%.d-MPH superior to PLA on CAARS-S:S and CAARS-O:S total scores ($P < 0.05$)	Dry mouth (15.8%, 20.4% >30 mg/3.8%, $P < 0.05$) HA (31.5%, 38.9% 40 mg/18.9%) Jitteriness (12.1%, 18.5% 30 mg/1.9%, $P < 0.05$) ↓ appetite (18.2%, 19.3% 20 mg/11.3%) Insomnia (16.4%, 18.5% 40 mg/11.3%) Wt (–1.4 kg/–0.1 kg) HR (+4.4 ± 11, $P = 0.0007$) SBP (–0.5 ± 11.5/–1.7 ± 11.3) DBP (+1 ± 8.4/+0.3 ± 7.8) Higher doses showed higher changes in HR, not SBP or DBP	

(*Continued*)

Table 2. (*Continued*)

Author (drug)	Trial design	Inclusion	N (MPH/PLA)	Dosing titration
Adler et al 2009 (Dex-MPX *no PLA results given)	6 months OLE of Spencer et al 2007 study	For pts that completed DB phase of Spencer study.	170 (20 mg: 46, 30 mg: 43, 40 mg: 42, PLA: 39)	All initiated at 10 mg/d for 1st wk. Then flexible dosages of 20–40 mg/d according to response and AE's.

to determine if the different dosing titration strategies had an effect on symptom reduction.

Biederman et al and Adler et al showed statistically significant decreases on the Adult ADHD Investigator System Report Scale (AISRS) when compared with placebo, with differences at all titration visits in the Adler et al trial.[13,14] When isolating the inattention and impulsivity subscales, MPH subjects had greater reduction of these symptoms than PLA patients (Table 2).[13,16–18] OROS-MPH showed statistically significant differences with placebo on all of the following scales: Connors Adult ADHD Rating Scale (CAARS),[15,17] the CGI-S[17], the CGI-I,[14,16] and the Wender-Reimherr Adult Attention Deficit Disorder Scale (WRAADDS).[16] See Table 2 for numerical results and clinical trial information.

Methylphenidate Extended-Release (MPH-ER)

Literature review only yielded one clinical trial that analyzed the effect of MPH-ER in adults.[19] This study was conducted in 28 sites across Germany, with 359 subjects. The mean dose of MPH-ER was 41.2 mg/d, or 0.55 mg/kg/d, which indicates a moderate dose. The response rates in this group were 61%, compared with 42% in the placebo group ($P = 0.001$).[19] MPH-ER subjects also had a statistically significant difference compared with placebo on the WRAADDS total score and on the Connors Adult ADHD Rating Scale-DSM-IV ADHD symptoms total subscale (CAARS-DATS). Of note, subjects treated with MPH-ER had statistical significant improvement on all 7 domains (inattention, hyperactivity, hot temper, affective lability, emotional hyperactivity,

Mean daily MPH/mean daily PLA (max MPH dose/d)	Efficacy results (MPH/PLA)	Safety results (MPH/PLA)	Additional notes
0.32 mg/kg/d (0.42 mg/kg/d)	ADHD-RS from end of DB phase to end of OLE: PLA:−10.2 (24.9 to 14.7). Combined d-MPH groups: −8.4 (19.0 to 10.6). Similar results on Inattentive and Hyperactive-Impulsive subscales. At end of OLE, 95.1% (78/82) of pts maintained on d-MPH pts had improvement and 95% (19/20) had improvement of those switched from PLA to d-MPH. GAF Mean scores at end of OLE: Pts maintained on d-MPH: 75.7. Switched from PLA: 74.7.	HA (27.6%, 37.5% 20–30 mg) Insomnia (20%, 32.8% 20–30 mg) ↓ appetite (17.6%, 25% 20–30 mg) Jitteriness (13.5%, 29.3% <20 mg) URI (12.9%, 16.9% >30 mg) Anxiety (12.4%, 14.1% 20–30 mg) Dry mouth (12.4%, 16.9% >30 mg) HR (+3.7 ± 11.3) SBP (+2.3 ± 12.6) DBP (+1.6 ± 9.8) Clinical weight loss ≥7% from baseline ≤20 mg/day: 7.3% 20–30 mg/day: 17.2% >30 mg/day: 29.2%	85% white w/combined inattention/Hyperactivity form. 103 pts completed OLE (~50% due to AE's). Mean exposure was 4.5 months. Pts on PLA in DB phase had marked improvement w/d-MPH in OLE and those on d-MPH in DB had sustained improvement for 6 months.

Abbreviations: MPH, Methylphenidate; PLA, Placebo; d, day; DB, double-blind; wks, weeks; yrs, years; sx's, symptoms; DSM, Diagnostic and Statistical Manual of Mental Disorders; dx, diagnosis; ADD-H, Attention Deficit Disorder with Hyperactivity; BID, twice a day; mg, milligram; pts, patients; d/c, discontinued; hx, history; M, male; PGRS, Physician's Global Rating Scale; tx, treatment; pts, patients; GAS, Global Assessment Score; vs., versus; ADHD, Attention-Deficit Hyperactivity Disorder; kg, kilogram; AE's, adverse effects; CGI, Clinical Global Impression; HR, heart rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; Wt, Weight; TID, Three times a day; GAF, Global Assessment of Functioning; RR, Response rate; HA, headache; ITT, Intent-to-treat; QID, Four times a day; CGI-S, Clinical Global Impression-Severity; HAM-A, Hamilton Anxiety Scale; HAM-D, Hamilton Depression Scale; GI, gastrointestinal OROS-MPH, oral-release osmotic system methylphenidate; AISRS, Adult ADHD Investigator System Report Scale; OL, open-label; WURS, Wender Utah Rating Scale; CAARS, Connors Adult ADHD Rating Scale; MADRS, Montgomery-Asberg Depression Rating Scale; WAIS-III, Wechsler Adult Intelligence Scale 3rd Edition; COWAT, Controlled Oral Word Association Test; NOS, Not otherwise specified; ED, emotional dysregulation; ODD, oppositional impairment; WRAADDS, Wender-Reimherr Adult Attention Deficit Disorder Scale; Δ, change; SD, standard deviation; CAARS-DATS, CAARS DSM-IV ADHD Symptoms total subscale; MPH ER, Methylphenidate Extended-release; d-MPH, dexmethylphenidate; OLE, Open-label extension phase; URI, Upper Respiratory infection.

disorganization, and impulsivity) of the WRAADDS compared with placebo. Regarding the high placebo response rates in this study, the authors offered several possible explanations: the use of a disease management program to reduce ADHD symptoms for all patients; prolonged and flexible titration schedule over 5 weeks; the use of the WRAADDS instead of the DSM-IV criteria to determine response; and 30% of participants did not complete follow-up.

Dexmethylphenidate

The efficacy data in adults with ADHD treated with dexmethylphenidate is confined to one double-blinded, fixed-dose, placebo-controlled, 5 week trial[20] and a 6-month, open label extension phase.[21] The double-blinded trial started all patients at 10 mg/d and then patients were assigned to fixed-dose treatment groups of 20 mg/d, 30 mg/d, 40 mg/d, and placebo. Response rates for these groups are as follows: 47.4%, 37%, 55.6% and 26.4%, respectively. Dexmethylphenidate treated subjects also had statistically significant reductions ($P < 0.05$) compared with placebo subjects on the ADHD-Rating Scale; −13.7, −13.4, −16.9, and −7.9. On the CGI-S scale, dexmethylphenidate subjects also had greater decreases than placebo: 68.4%, 61.1%, 64.8%, and 41.5%. When looking at the CAARS total scores and ADHD-RS inattentive and hyperactive-impulsive subscales, dexmethylphenidate proved to be superior to placebo as well.

The 6-month, open-label follow-up trial primarily evaluated the safety effects of patients taking dexmethylphenidate for an extended period of time.[21] However, the researchers did perform various effectiveness measures to determine persistent effect.

All patients were initiated on 10 mg/d for the first week, and then flexible dosages of 20 to 40 mg/d were given according to treatment response and tolerability. Specific numerical values are given in Table 2. In summary, the positive treatment effect of dexmethylphenidate from the double-blinded phase was maintained throughout the 6 months. Worth mentioning, about half of subjects discontinued the open-label phase due to adverse effects.

Safety of Methylphenidate

Following an in-depth review of all clinical data relevant to MPH and its derivatives, a few key adverse effects have shown up repeatedly among these trials. The most common side effects noted were loss of appetite (anorexia), headache, insomnia, and dry mouth. In addition to these, there was a notable degree of weight loss. The cardiovascular implications will also be reviewed and summarized below.

The rates of appetite loss varied greatly among the different trials; as low as 12%,[16] to a high of 41%.[9] Both MPH (22%–41%) and OROS MPH (12%–38%) showed higher occurrences of this side effect when compared to dexmethylphenidate (17.6%–18.2%). The most plausible explanation for this discrepancy is that dexmethylphenidate is the active enantiomer of MPH, making it a more effective drug with less side effects. OROS MPH is merely a reformulation of MPH, so it contains the same active ingredient (MPH), and therefore has a similar rate of appetite loss. An additional formulation of MPH ER showed a similar rate to MPH (38%). It should be noted that only two trials have been done with dexmethylphenidate, as opposed to six each for MPH and OROS MPH.

Headaches appeared in multiple trials with contradictory results. An older trial conducted by Wender et al[7] found a statistically significant higher rate of headache in MPH over placebo. On the other hand, Kooij et al[10] found a higher rate, but no statistical significance (16% vs. 4%, $P = 0.18$). In addition, Bouffard et al[9] found a lower rate in MPH than in placebo (21% vs. 35%). Trials conducted with OROS MPH showed slightly higher rates. Although not compared to placebo, trials showed results as high as 43%[13] and 53%.[17] Trials with OROS MPH and placebo showed lower rates (21% vs. 17.7%[15] and 25.5% vs. 13.8%[14]), but no statistical comparison was done with this information to evaluate significance. It is clear that an increased incidence of headache does exist, but it would be difficult to extrapolate an all-encompassing summary.

Insomnia, in itself, is a possible implication of adult ADHD. Out of all the trials reviewed, Reimherr et al[16] was the only trial to show a statistically significant higher rate of OROS MPH over placebo: 22% vs. 7%, $P = 0.05$. Bouffard et al[9] showed an almost identical rate with MPH and placebo (26% vs. 25%), while other trials showed higher rates with no statistical significance.[10,11] Some of the other trials showed slightly higher rates when compared to placebo, but no statistical comparison was done to evaluate how significant they were.[15,20]

Due to its properties as a CNS stimulant, it was not surprising that dry mouth (eyes and nose) was a common complaint among study participants. Statistical significance over placebo was demonstrated by Spencer et al,[11] Biederman et al[13] and Spencer et al.[20] Higher rates with no statistical comparison were also demonstrated by Medori et al,[15] Adler et al[14] and Rösler et al.[19] Please note the corresponding incidence rates of dry mouth in the various trials in Table 2. Regardless of formulation, a clearly evident pattern of dry mouth occurred across most trials.

Weight loss has shown to be another side effect of stimulant use, even over short periods of time. Spencer et al[8] showed a statistically significant change in weight between MPH and placebo in three weeks of medication use. Spencer et al[11] showed a decrease of 2.4 kg in 6 weeks ($P < 0.001$), and Biederman et al[13] showed a 2.7 kg decrease in 6 weeks ($P < 0.001$) with MPH. Reimherr et al[16] demonstrated a decrease of 2.5 kg vs. a 1.3 kg increase in placebo in 4 weeks ($P = 0.001$) with OROS MPH. Adler et al (2009) showed similar results in 7 weeks with OROS MPH (–2.2 kg vs. + 0.2 kg).[14] Adler et al demonstrated a dose dependant increase in clinical weight loss as doses of dexmethylphenidate increased. It should be noted that no follow-up was done following these trials over a sustained period of time to verify how much weight loss was possible, or if the weight loss was sustained following discontinuation of therapy.

Cardiovascular implications

Much controversy has arisen regarding the cardiovascular implications of stimulant therapy in adults.

Enough data had been shown to warrant the FDA ordering an amendment to MPH information to include a warning for adults regarding the risk of sudden death, stroke, and myocardial infarction. In addition, warnings of hypertension and tachycardia are also included in the package insert.

In general, many of the trials trended towards slightly increased heart rates, with some showing statistical significance. It should be noted that there was very little clinical significance in this data. Trials from Spencer et al,[8] Spencer et al[11] and Rösler et al[19] all showed a significantly higher final heart rate at the end of MPH treatment versus placebo. Trials with OROS MPH showed mean increases in heart rate ranging from 3.6 bpm to 9.8 bpm. It should be noted that Medori et al 2008 showed a dose dependant relationship between higher doses of OROS MPH and heart rate. Dexmethylphenidate showed slightly lower rates of increased heart rate (4.4 bpm and 3.7 bpm).

In contrast, clinical information regarding systolic and diastolic pressures varied significantly amongst trials. Most trials showed no statistically significant increases in systolic pressure; some even showed decreases.[14,17,20] Changes in systolic pressure ranged from −2.9 mmHg[17] to +5 mmHg.[9] Diastolic pressures followed similar trends (−1.4 mmHg[17] to +4 mmHg[13]), with very little statistical significance. As with the heart rate, these subtle changes in blood pressure were of no clinical significance. Nonetheless, it would behoove prescribers to educate patients of these possible cardiovascular effects.

Abuse potential

Due to its structural similarity to amphetamine, there is an abuse potential associated with MPH similar to that of cocaine. By acting on dopamine transporters, MPH can show similar effects to cocaine and other stimulants. Kollins et al summarized the possible abuse potential for MPH in both animals and humans.[22] In studies of reinforcement or self-administration, 13/15 trials reported increased rates of abuse with MPH or dexmethylphenidate over placebo. It should be noted that, for the two trials not showing increased reinforcement, the route of administration was oral. Since oral medications take longer to act, it was hypothesized that this may account for the discrepancy. In trials comparing subjective ranking systems, (Profile of Mood States, Addiction Research Center Inventory, Visual Analog Scales, etc.) MPH and dexmethylphenidate showed increased rates as well.[22]

Discussion

The efficacy of MPH, OROS-MPH, MPH-ER, and dexmethylphenidate is firmly established based on our review. All efficacy measures proved that these medications significantly improve ADHD symptoms in adults when compared with placebo. There is conflicting evidence regarding whether increasing doses yield greater symptom improvement. Therefore, in clinical practice, each patient should be given individualized care. MPH and dexmethylphenidate have proven to be effective on all ADHD symptoms, including inattentive and hyperactive/impulsive symptoms. It is important for clinicians to understand that treatment effects with MPH and dexmethylphenidate can be seen as early as the first week of treatment. Also, the different formulations of MPH enhance patient care through the capability for individualized dosing regimens.

After a thorough review of all adverse events, a few key side effects reoccur throughout the data. These side effects include headache, insomnia, loss of appetite, weight loss, and dry mouth. It should be noted that no true dose-dependant relationship has been noted for any of these aside from weight loss. Adler et al[21] demonstrated dose-related increases in weight loss with dexmethylphenidate. In addition, Medori et al[15] showed similar results with OROS-MPH at dosages ranging from 18–72 mg. Of primary concern are the cardiovascular implications of MPH use in adults. Although no statistical comparisons were done, a dose-relationship can still be noted between MPH and heart rate.[15] Slight increases in blood pressure, although of little clinical significance, should still be taken into consideration when prescribing. Patients with borderline cardiovascular conditions (hypertension, palpitations, family history, etc.) should be monitored carefully when starting a stimulant medication, such as methylphenidate. As a schedule II substance, it should be noted that a potential risk for abuse does exist. Patients should be educated on this before beginning treatment and should be monitored accordingly. As with many medications, frequency of these adverse

events increase as dosages increase; it should be noted that many of these events occur within the first few weeks of use.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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