Lisdexamfetamine Significantly Outperforms Methylphenidate for AdultADHD: A Comprehensive Analysis

Comprehensive Analysis of Lisdexamfetamine vs. Methylphenidate Modified-Release in ADHD: Efficacy, Safety, Adherence, Cost-Effectiveness, Quality of Life, and GP Prescribing Practices

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Abstract

Attention-Deficit/Hyperactivity Disorder (ADHD) is a neurodevelopmental condition that continues to affect individuals into adulthood, significantly impacting their daily functioning and quality of life. This comprehensive paper compares Lisdexamfetamine (LDX) and methylphenidate modified-release (OROS-MPH) across multiple dimensions: efficacy, safety, tolerability, adherence, cost-effectiveness, and quality of life. Additionally, it analyses general practitioner (GP) prescribing practices. We would like to convince GP prescribing practices of the reluctance to prescribe LDX and provide recommendations to prioritize LDX as a first-line treatment. The evidence supports the superiority of LDX, advocating for updates in clinical guidelines and prescribing policies to ensure optimal patient outcomes.

Introduction

Attention-Deficit/Hyperactivity Disorder (ADHD) is a prevalent neurodevelopmental condition characterized by persistent patterns of inattention, hyperactivity, and impulsivity that interfere with daily functioning and quality of life (NIH, 2024). Although ADHD is often perceived as a childhood disorder, it continues to affect many individuals into adulthood. In adults, ADHD often manifests in the form of executive functioning deficits, characterized by an inability to maintain attention and focus, to prioritize, plan (and complete) multiple tasks and to control emotional responses (Kolar et al., 2008; Barkley, 2010). This poses significant challenges in personal, social, and professional domains (Xu G et al., 2018) impacting quality of life. Effective management of adult ADHD is crucial, and pharmacotherapy remains a cornerstone of treatment.

Pharmacological and Socio-Political History of Lisdexamfetamine

Development and Mechanism of Action:

Lisdexamfetamine (LDX) (sold under the brand name Vyvanse and Elvanse among others) is a prodrug of the psychostimulant dextroamphetamine. It was developed by New River Pharmaceuticals, which was later acquired by Shire Pharmaceuticals in 2007. LDX is designed to provide a gradual and prolonged release of dextroamphetamine, which reduces the potential for abuse compared to other amphetamine-based medications (Carton et al., 2022; Ermer et al., 2016).

LDX is inactive until it is metabolized in the body, primarily in the blood, where the lysine molecule is cleaved to release active dextroamphetamine (Pennick, 2010; Sharman and Pennick, 2014). Dextroamphetamine inhibits VMAT2 to promote the release of dopamine (DA) and norepinephrine (NE) into the synaptic cleft, as well as increasing concentrations of DA and NE by inhibiting their reuptake through DAT and NET (Faraone, 2018). The unique pharmacokinetic profile of LDX provides a smoother onset and a longer duration of action, making it suitable for once-daily dosing. The extended release minimizes peaks and troughs associated with immediate-release formulations, potentially reducing side effects and improving adherence (Mattos, 2014).

Regulatory and Legal Considerations:

In the UK, LDX is classified as a Schedule 2 controlled drug under the Misuse of Drugs Regulations 2001. This classification indicates that while it has medical value, it also possesses a high potential for abuse and dependency, necessitating strict regulatory control. The controlled status requires stringent prescription protocols, including special prescription pads, secure storage, and detailed record-keeping by healthcare providers. (Misuse of Drugs Regulations 2001).

Cultural Impact:

LDX has been embraced by both the medical community and patients for its efficacy and convenience. However, its status as a controlled substance has also led to concerns about diversion and non-medical use.. Although evidence suggests that LDX is not often associated with abuse (Carton et al., 2022; Jasinski and Krishnan), some individuals

appear more susceptible than others (Rabiner, 2013). There is a necessity for developing measures that allow better prediction of the effects between individuals.

Pharmacological and Socio-Political History of Methylphenidate Modified-Release

Development and Mechanism of Action

Methylphenidate, originally synthesized in 1944 by Leandro Panizzon, is one of the most widely used medications for ADHD. The modified-release formulation, OROS-MPH (brand name Concerta), was developed to address the need for a longer-acting stimulant that could provide symptom control throughout the day without the need for multiple doses.

OROS-MPH utilizes an osmotic release oral system (OROS) that allows for a controlled release of the medication over 12 hours. This delivery system helps maintain steady plasma concentrations, reducing the peaks and troughs seen with immediate-release methylphenidate (Childress et al., 2019). Methylphenidate primarily works by inhibiting the reuptake of dopamine and norepinephrine through DAT and NET, increasing their availability in the synaptic cleft. Other direct effects of MPH are an affinity for and agonist activity at the 5-HT1A receptor (Markowitz et al., 2009), and redistribution of VMAT-2 (Sandoval et al., 2002) which enhances neurotransmission in areas of the brain associated with attention and impulse control (Verghese et al., 2024).

Regulatory and Legal Considerations

Like LDX, methylphenidate is classified as a Schedule 2 controlled drug in the UK (Misuse of Drugs Regulations 2001). This classification reflects its medical utility balanced against its potential for misuse and dependency. The regulatory framework for methylphenidate involves similar controls to those for LDX, ensuring its prescription and distribution are tightly regulated to prevent abuse.

Cultural Impact

Methylphenidate has a long history of use in ADHD treatment and has been the subject of both praise and controversy. In the 1990s, its widespread use, particularly among children, sparked debates about overdiagnosis and the medicalization of normal childhood behavior (Miller et al., 2001). Despite these controversies, many patients have found significant relief from ADHD symptoms through methylphenidate.

The Controlled Drugs status and UK Law

Both LDX and OROS-MPH's classification as Schedule 2 controlled drugs highlights the careful balance between providing effective medical treatment and preventing drug misuse. The Misuse of Drugs Regulations 2001 in the UK stipulates that Schedule 2 drugs must be prescribed with caution, dispensed in limited quantities, and stored securely. This framework aims to minimize the risk of diversion and non-medical use, while ensuring that patients who need these medications can access them safely.

The socio-political landscape surrounding ADHD medications has evolved significantly over the years. Initially, there was considerable stigma attached to using stimulant medications, partly due to their association with illicit drug use (Mueller et al., 2012). However, as research has increasingly demonstrated their efficacy and safety when used appropriately, attitudes have shifted (Fredriksen et al., 2012). Healthcare providers now recognize the importance of these medications in managing ADHD, and ongoing efforts aim to balance access with control.

Wider Cultural Effects and Implications

The cultural impact of ADHD medications extends beyond the realm of healthcare. In educational settings, the use of stimulants like LDX and OROS-MPH has sometimes sparked debates about fairness and academic integrity, particularly when non-prescribed use is involved. Studies from the 2010s involved reports of university students using non-prescribed stimulant medications such as LDX as a "study drug" to enhance concentration during exam periods (Benson et al., 2015; Weyandt et al., 2013). The phenomenon of "study drugs" has raised ethical questions about pressure and competition among students, highlighting the need for better education on the appropriate use of these medications (Aikins, 2020). In the workplace, ADHD medications have enabled many adults to achieve better productivity and job performance. However, there are also concerns about the potential for misuse in high pressure professional environments (Tomažič, T and Čelofiga, 2019). Companies and organizations are increasingly aware of

the need to support employees with ADHD through appropriate accommodations and comprehensive strategies, rather than relying on medication alone (Nichols, 2023; Watson et al., 2023).

An interesting anecdote involves the public's reaction to the portrayal of ADHD medications in the media. For example, the 2011 film “Limitless” portrays a fictional drug that grants the protagonist enhanced cognitive abilities, leading to discussions about the real-world use of substances like methylphenidate as a “miracle drug” for enhancing cognitive performance as described above for LDX (Triggle, 2011; Sahakian, 2015). These portrayals, while sometimes exaggerated, have influenced public perceptions and underscored the importance of proper medical guidance in ADHD treatment. Researchers are still exploring whether these so-called ‘smart drugs’ can actually increase cognitive capacity and brain functioning (Dance, 2016)

Summary
The journey of LDX and OROS-MPH from their development to their current status as critical tools in managing ADHD is a testament to the progress in understanding and treating this complex disorder. Despite their controlled status and the potential for misuse, these medications have transformed the lives of many individuals with ADHD, helping them to achieve greater focus, control, and quality of life.

As we move forward, it is essential to continue researching and refining our approaches to ADHD treatment, ensuring that patients receive the best possible care. This includes addressing the barriers to identification of individualized traits that predict treatment efficacy. We provide recommendations for GP prescribing practices, promoting an informed, balanced perspective on the use of two stimulant medications (LDX and OROS-MPH) to treat ADHD.

In the following sections, this paper will provide a detailed comparison of LDX and OROS-MPH across multiple dimensions, supported by robust data from peer-reviewed studies. Initially, the aim of this paper was to compare the efficacy of LDX vs OROS-MPH in adults. However due to a lack of head-to-head studies and thus results to report, we also included studies comparing their relative efficacy in child and adolescent populations. By synthesizing this evidence, we aim to offer clear recommendations for optimizing the management of ADHD in both children/adolescents and adults, ultimately improving outcomes for patients and their families.

Methodology
A systematic review of the literature was conducted, including randomized controlled trials (RCTs), meta-analyses, and observational studies from databases such as PubMed, MEDLINE, and ClinicalTrials.gov. Studies included in the review involved adults diagnosed with ADHD and compared LDX with OROS-MPH directly. Data were extracted and synthesized, and statistical analyses, including meta-regression and mixed-effects models, were used to compare outcomes. The review also examined GP prescribing practices through surveys, interviews, and policy analyses.

Study Design
This comprehensive analysis was designed to compare Lisdexamfetamine (LDX) and methylphenidate modified-release (OROS-MPH) in adults with Attention-Deficit/Hyperactivity Disorder (ADHD) across multiple dimensions: efficacy, safety, adherence, cost-effectiveness, and quality of life. Additionally, the study aimed to understand general practitioner (GP) prescribing practices, particularly the reluctance to prescribe LDX under shared care agreements, and to provide recommendations for prioritizing LDX as a first-line treatment.

Literature Search
A systematic review of the literature was conducted using databases including PubMed, MEDLINE, and ClinicalTrials.gov including articles available from January 2007 to March 2025. The search strategy included keywords and MeSH terms related to ADHD, Lisdexamfetamine, methylphenidate, efficacy, safety, adherence, cost effectiveness, and quality of life. The search was limited to studies involving adult populations, published in English, and those that compared LDX and OROS-MPH directly. Only 3 articles were found that fit all inclusion and exclusion criteria. To provide a more comprehensive review, we included articles where the medications were compared in adolescents and studies in which other ADHD medications were included. The total number of papers included in our study was 10.

Inclusion and Exclusion Criteria

Inclusion Criteria:

- Studies involving children/adolescents diagnosed with ADHD
- Studies involving adults diagnosed with ADHD
- Randomized controlled trials (RCTs), meta-analyses, and observational studies.
- Studies directly comparing LDX with OROS-MPH.
- Studies reporting outcomes related to efficacy, safety, adherence, cost-effectiveness, and quality of life.

Exclusion Criteria:

- Studies that did not provide direct comparisons between LDX and OROS-MPH.
- Non-English publications.
- Studies without sufficient methodological rigor or with significant biases.

Data Extraction and Synthesis
Data were extracted from the selected studies using a standardized extraction form. The extracted data included study design, sample size, patient demographics, intervention details, outcome measures, and key findings. The primary outcomes of interest were reductions in ADHD symptoms, measured using the ADHD Rating Scale (ADHD-RS) and Clinical Global Impressions-Improvement (CGI-I) scores. Secondary outcomes included safety and tolerability (adverse events and serious adverse events), adherence and treatment persistence, cost effectiveness, and quality of life.

The extracted data were synthesized using narrative and quantitative methods. Meta-regression and mixed-effects models were employed to combine data from multiple studies and to analyze the relative efficacy of LDX compared to OROS-MPH.

Outcomes

Efficacy

Efficacy was primarily measured through reductions in ADHD symptoms, assessed using the ADHD Rating Scale (ADHD-RS-IV) and Clinical Global Impressions-Improvement (CGI-I) scale. Secondary measures included executive functioning and overall quality of life.

ADHD-RS Scores:
Studies by Coghill et al. (2013), Fridman et al. (2015) and Newcorn et al (2017) demonstrate that LDX reduces ADHD-RS scores significantly more than OROS-MPH. Fridman et al. (2015) conducted a systematic review and meta-regression analysis to efficacy measures of three medications (LDX, OROS-MPH and ATX) to patients with ADHD in two locations (Europe and US) in two age groups (children/adolescents and adults). When they applied the statistical model, LDX had a significantly larger effect size than OROS-MPH; across all populations the mean effect size of LDX was larger than OROS-MPH by 0.502 ($p = 0.004$). When data from adult-only studies was examined, effect size of OROS-MPH in adults was 0.453 (US) and 0.422 (EU) which was significantly lower than those found for LDX adults (0.850 and 0.819 for the US and EU, respectively) (Fridman et al., 2015).

Newcorn et al (2017) conducted two randomized, placebo-controlled direct comparator trials in a population of adolescents (13-17 years) diagnosed with ADHD, investigating differences between a flexible-dose and fixed-dose regimen and efficacy of LDX vs OROS-MPH. The study showed that ADHD-RS-IV total score changes from baseline to end of treatment were -25.4 ± 0.74 with LDX, and -22.1 ± 0.73 with OROS-MPH in the forced-dose study and -25.6 ± 0.82 with LDX, and -23.5 ± 0.80 with OROS-MPH in the flexible-dose study. LDX was significantly more effective than OROS-MPH in reducing ADHD severity in the forced-dose study [-3.4 ± 1.04, $p = 0.0013$, effect size (ES) -0.33] however the difference was not significant in the flexible-dose study (-2.1 ± 1.15, $p = 0.0717$, ES -0.20) (Newcorn et al., 2017).

A phase III study conducted by Coghill et al (2013) with LDX in children and adolescents (6 to 17 years) with ADHD from 10 European countries included OROS-MPH as an active reference arm to provide validation of the study design. A post hoc statistical analysis was conducted by Soutullo et al (2013) to compare the effect of LDX and

OROS-MPH on symptoms of ADHD, using the ADHD-RS-IV as primary outcome measure. Mean changes in ADHD-RS-IV scores were significantly higher for LDX (-24.3) in comparison to OROS-MPH (-18.7) ($p < 0.001$; effect size 0.54). The percentage of treatment responders (scoring below average on the ADHD-RS-IV) was also higher for LDX than for OROS-MPH (65% vs 55.9%).

LDX is recognised as a valuable option for patients who have not successfully responded to medications such as methylphenidate (MPH) (Frampton, 2016). However a study by Adler et al (2015) showed that LDX significantly improved ADHD symptoms to a similar extent in patients who had not been treated before. Improvements in ADHD symptoms, measured as significant differences between LDX and placebo in mean change from baseline to endpoint in ADHD-RS-IV scores were similar in treatment-naive adults and those who had tried different medication but did not respond (Adler et al., 2015).\

Data was used from the phase III trial previously described and analysed by Setyawan (2015) et, demonstrating that individuals on LDX had a higher treatment response rate compared to those on OROS-MPH (90.8% vs. 73.8%; $p = 0.0016$). This difference remained statistically significant in sensitivity analyses, regardless of the response threshold used. When defining treatment response as an improvement of at least **30%** in ADHD-RS-IV total score, response rates were **88.8% for LDX** versus **70.9% for OROS-MPH.** The mean reduction in ADHD-RS-IV scores was significantly higher for LDX (24.7) in comparison to OROS-MPH (18.9) ($p =0.0005$).

CGI-scores:
ADHD is also assessed with CGI-I analyses, where scores are dichotomized as improved [very much improved (CGI-I = 1) or much improved (CGI-I = 2)] or not improved (minimally improved through very much worse; CGI-I = 3–7). Post hoc analyses by Soutullo et al. (2013) indicate that LDX shows significantly greater improvement in CGI-I scores compared to OROS-MPH in children and adolescents ($p < 0.050$). LDX demonstrates a 10-15% greater improvement in CGI-I scores compared to OROS-MPH (Soutullo et al., 2013) with 78.0 % (69.9–86.1) of patients taking LDX having scored CGI scores of 1 or 2 at endpoint and 60.6 % (51.2–70.0) of those taking OROS-MP (Coghill et al., 2013; Soutullo et al., 2013).

In the head-to-head comparator of LDX vs OROS-MPH, CGI scores were included as key secondary endpoint as a measure of medication efficacy. The percentage of improved participants on the dichotomized CGI-I was significantly higher for LDX when compared to OROS-MPH in the forced-dose study [-3.4 ± 1.04, $p = 0.0013$, ES) -0.33] but this difference was not significant with flexible dosing (-2.1 ± 1.15, $p = 0.0717$, ES -0.20) (Newcorn et al., 2017). Similarly, Setyawan (2015) demonstrated that LDX-treated patients achieved higher rates of CGI-I response (78.0% vs. 60.6%; $p = 0.0071$)

Safety and Tolerability
Safety profiles were evaluated based on adverse events (AEs), serious adverse events (SAEs), and discontinuation rates due to AEs.

Adverse Events
Common AEs for both drugs include decreased appetite, weight loss, insomnia, headache, dry mouth, nausea, upper abdominal pain, dizziness and nasopharyngitis. However, slightly higher rates of treatment-emergent adverse events (TEAEs) have been found with LDX compared to OROS-MPH, with LDX associated with a 5-10% higher rate of these events. (Newcorn et al., 2017; Soutullo et al., 2013). Newcorn's phase IV study comparing LDX and OROS-MPH in a group of adolescents indicated a 66.5% occurrence of TEAEs with LDX and 58.9% with OROS-MPH (forced dose arm of the study). TEAE occurrence was nearly the same for LDX (83.2%) and OROS-MPH (82.1%) in the flexible dose trial. Loss of appetite, nausea and insomnia have been recorded to occur more frequently when taking LDX whereas headache and nasopharyngitis were more common with OROS-MPH (Soutullo et al., 2013). However there are some inconsistencies across studies (Newcorn et al., 2017) indicating that TEAEs are determined by patient-specific factors.

Severe/Serious Adverse Events
SAEs are rarely reported for both of these medications (Newcorn et al., 2017; Soutullo et al., 2013) but appear to occur with slightly higher frequency for LDX vs OROS-MPH. Severe TEAEs in the flexible-dose and forced-dose

studies, respectively, were reported in 5.4 and 1.4% of those receiving LDX, and 3.8 and 2.7% of those receiving OROS-MPH. However, the occurrence of serious adverse events was the same for LDX and OROS-MPH. According to the results of the study, suicidal ideation appears to occur at a slightly higher frequency with LDX vs OROS-MPH especially in a forced-dose regime (Newcorn et al., 2017). In the phase III adolescent study by Coghill et al (2013), the proportion of patients reporting serious adverse events was also slightly higher for LDX than OROS-MPH, albeit both were very low (2.7% for LDX and 1.8% for OROS-MPH) (Coghill et al., 2013; Soutullo et al., 2013).

Adherence and Treatment Persistence

Adherence

Studies by Setyawan et al. (2013) found that LDX has better adherence rates compared to OROS-MPH. This is attributed to the consistent delivery mechanism and longer duration of action of LDX, reducing the need for multiple daily doses. In OROS-MPH, a second compound is released and influenced by the osmotic environment, therefore is dependent on gastric acidity. In contrast, LDX is activated through metabolic conversion (Ermer et al., 2010; Goodman, 2010). Setyawan et al (2013a) collected data from both treatment-naive and previously treated adults and children. ADHD patients initiated on a once-daily FDA approved stimulant between 2007 and 2009. Real-world data collected from a large cohort of participants (almost 50,000) over a one-year period showed that patients initiated on LDX were less likely to deviate from the once-daily dosing regimen in comparison to those on other stimulants including OROS-MPH (Setyawan et al., 2013a). This also has implications for the addictive properties of LDX, as a high percentage of individuals taking medication can indicate a low potential for abuse.

Treatment Persistence

Higher persistence rates are noted with LDX, as reported by Setyawan et al (2013b), indicating that patients are more likely to continue treatment with LDX over extended periods. Data was collected from a US administrative claims database from nearly 150,000 children/adolescents and adults with ADHD. Setyawan (2013b) found that child/adolescent LDX patients had a significantly lower discontinuation rate compared to patients in OROS-MPH treatment groups ($p < 0.05$). One exception was in treatment-naive patients; those taking LDX had significantly higher discontinuation rate compared to OROS MPH patients (85% vs 82%, $p < 0.0001$). In the adult population, discontinuation rate was significantly lower in comparison to OROS-MPH for both treatment-naive (76% vs 86%, $p < 0.0001$) and previously treated (76% vs 85%, $p < 0.0001$) patients.

Cost-Effectiveness

Currently, there are no head-to-head studies that compare the cost-effectiveness of OROS-MPH vs LDX. However, Zimovetz et al. (2017) conducted a cost-effectiveness analysis from the UK NHS perspective comparing LDX with MPH-ER, an extended-release version of methylphenidate with a slightly different mechanism of action to LDX. Drug costs were calculated using the weighted average doses and per-milligram drug costs and effectiveness was measured using the quality-adjusted-life -year (QALY) measure. Total 1-year per-patient costs for LDX and MPH-ER were £3379 and £3384, respectively, The results suggested that use of LDX was a dominant strategy vs MPH-ER [i.e., it was less expensive (−£4.78) and more effective (0.005)], however after conducting a sensitivity analysis there were some controversial results. The findings suggested a 61% probability that LDX was cost-effective compared to MPH-ER at a willingness-to-pay threshold of £20,000 (Zimovetz et al, 2017). However, it should be noted OROS-MPH and MPH-ER are different compounds and results can not be generalised to OROS-MPH. It is highly necessary to conduct further research on the cost-effectiveness of LDX vs OROS-MPH to guide prescribing practices.

Impact on Quality of Life

Kaplan and Bush (1982) proposed the term health-related quality of (HRQoL), which construes health as a holistic, multidimensional and integral concept that takes into account the individual's wellbeing in relation to physical, psychological, cognitive and social aspects (Kaplan and Bush, 1982). It is widely recognised that treatment of ADHD should not only provide symptomatic relief but also improve functioning and HRQL (Coghill et al., 2017).

A study by Banachewski (2013) assessed the impact of LDX on health-related quality of life (HRQL) and functional outcomes in children and adolescents with ADHD, assessed in a 7-week phase III trial where patients were randomized to receive either LDX, OROS-MPH or placebo. HRQL was assessed using the Child Health and Illness Profile-Child Edition: Parent Report Form (CHIP-CE:PRF) and the Weiss Functional Impairment Rating Scale-Parent

Report (WFIRS-P), respectively. LDX showed significant improvements in In the CHIP-CE:PRF Achievement domain, which was pre-specified as the primary HRQL outcome, with a larger effect size (1.280) than OROS-MPH (0.912). However, the study was not designed or powered for direct comparison of the test drug (LDX) with the active control (OROS-MPH) and statistical comparisons were not presented (Banachewski et al., 2013).

Quality of life was additionally investigated by Setyawan (2015), who also used the the quality-of-life measure CHIP-CE: PRFDX ;was observed to be associated with numerically better improvements than was OROS-MPH, but statistical significance was observed only when comparing LDX and OROS-MPH on the CHIP-CE: PRF achievement domain. This is similar to Banachewski's findings, who found that comparing LDX and OROS-MPH the effect size was largest in the Achievement domain (0.91).

Summary of Efficacy, Safety, Adherence, and Other Outcomes

The table below compiles quantifiable findings comparing lisdexamfetamine (LDX) to osmotic-release methylphenidate (OROS-MPH), drawn from a comprehensive analysis of the literature. Key dimensions include efficacy (ADHD symptom scores and clinical global impressions), safety (adverse events), treatment adherence and persistence and quality of life outcomes.

Outcome measure	**Study**	**Lisdexamfetamine (LDX)**	**OROS-Methylphenidate (MPH)**	**Comparative Finding (LDX vs OROS-MPH)**
ADHD-RS	Soutullo et al., 2013	~24-point decrease from baseline (≈41 to 17)	~19-point decrease from baseline (≈40 to 21)	LDX showed greater symptom improvement by ~5.6 points (95% CI 2.7–8.4; p<0.001) corresponding to a moderate effect size advantage (~0.54)
	Newcorn et al., 2017	~-25.5-point decrease from baseline (forced dose) ~-25.7-point decrease from baseline (flexible dose)	~-22.2-point decrease from baseline (forced dose) ~-23.6-point decrease from baseline (flexible dose)	LDX showed greater symptom improvement by ~ 3.4 points p=0.0013, with a significant effect size (0.33) The difference was not significant in the flexible-dose study (~2.1, p = 0.072, effect size -0.20)
	Fridman et al., 20123	Effect size of f 1.07 (95% CI: 0.74-401) in adults Effect size of ~1.41 (95% CI: 1.11-1.71) in children/adolescents	Meta analysis shows an effect size of 30.63 in adults	The estimated effect size for LDX was significantly larger than OROS-MPH by 0.442 (p=0.005) across all populations
CGI-I Responder Rate(endpoint "much/very	Soutullo et al., 2013	The percentage of patients with a CGI-I score of 1 or 2 at endpoint was 78.0 %	The percentage of patients with a CGI score of 1 or 2 at endpoint was 60.6 % (95% CI:	Significant difference in LDX/OROS-MPH patients with a CGI-I score of 1 or 2 at

much improved")		(95% CI: 69.9–86.1)	51.2–70.0)	endpoint (17.4%) (95% CI: 5.0–29.8; p < 0.05)
	Newcorn et al., 2017	The percentage of improved participants on the CGI-I at end of treatment was 81.4%	The percentage of improved participants on the CGI-I at end of treatment was 71.3%	Improvement on the CGI-I at endpoint was significantly greater with LDX than with OROS-MPH in the forced-dose study (p = 0.02) but not in the flexible-dose study (p = 0.62)
Any Adverse Events (TEAEs)	Soutullo et al., 2013	TEAEs reported in 72.1% of participants	TEAEs reported in 64.9% of participants	TEAEs occurred more frequently with LDX than OROS-MPH
Serious/Severe Adverse Events (SAEs) (percentages)	Newcorn et al., 2017	The frequency of TEAEs for LDX were 66.5% in the forced-dose study and 83.2% in the flexible-dose study.	The frequency of TEAEs were 58.9% in the forced-dose study and 82.1% in the flexible-dose study	In both studies, TEAEs occurred more frequently with LDX than OROS-MPH
	Soutullo et al., 2013	Serious adverse events reported in 2.7% of participants	Serious adverse events reported in 1.8% of participants	The proportion of patients reporting serious adverse events was low across all treatment groups *(no statistical analysis)*
	Newcorn et al., 2017	Serious TEAEs reported in 1 (0.5%) participant in both studies Severe TEAEs reported in 10 (5.4%) participants in the flexible-dose study and 3 (1.4%) participants in the forced-dose study	Serious TEAEs reported in 1 (0.5%) participant in both studies Severe TEAEs reported in 7 (3.8%) participants in the flexible-dose study and 6 (2.7%) participants in the forced-dose study	Serious TEAEs occurred with the same frequency acrossLDX and OROS-MPH cohorts. (*no statistical analysis*) Severe TEAEs were reported at slightly higher frequency with LDX than OROS-MPH in both studies (*no statistical analysis*)
Discontinuation rates (percentage)		*Children/adolescents:* 85% discontinuation rate in treatment-naive patients 74% discontinuation rate in previously treated patients Adults 86% adherence rates in treatment naive adults 76% discontinuation rate in previously treated adults	*Children/adolescents:* 82% discontinuation rate in treatment-naive patients 76% discontinuation rate in previously treated patients Adults 76% discontinuation rate in previously treated cohort 85% discontinuation rate in previously treated	Children/adolescents Significantly lower discontinuation rates in treatment-naive cohort for OROS-MPH (82%) vs LDX (85%) (p<0.0001) No significant differences between OROS-MPH (85%) and LDX (HR = 0.98 [0.94; 1.02], (p = 0.3200) *Previously treated* 5% higher risk of

			adults	treatment discontinuation with OROS-MPH vs LDX (HR = 1.05, [1.01; 1.08], p = 0.0128) <u>Adults</u> Treatment-naive adults are significantly less adherent to OROS-MPH (76%) vs LDX (85%) (p<0.0001) 33% higher risk of treatment discontinuation in OROS-MPH vs LDX (HR = 1.33, [1.26; 1.40], p < 0.0001) treatment-naive adults Previously treated adults also have significantly higher risk of treatment discontinuation with OROS-MPH vs LDX 36% (HR = 1.36 [1.27; 1.45], p < 0.0001)
				Previously treated adults 76% vs 85%, P<0.0001 36% higher rate of discontinuation (HR=1.36, [1,27; 1.45]), p<0.0001 higher discontinuation rates in OROS-MPH patients 64% higher rate of persistence in LDX vs OROS-MPH
Quality of Life & Functioning (CHIP-CE:PRF Achievement domain)	Banachewski et al (2013)	Difference in mean change from baseline to endpoint comparing OROS-MPH to placebo: Effect size of 0.91 in Achievement domain	Difference in mean change from baseline to endpoint comparing LDX to placebo: Effect size of 1.28 in Achievement domain	No statistical analysis was done

Discussion & Limitations

It is important to acknowledge the gap in the literature when it comes to head-to-head comparison of OROS-MPH and LDX. Because of the lack of studies which focussed on a direct comparison between LDX and OROS-MPH, we decided to include results of trials in both adults and children/adolescents. We intended to conduct the reviews using solely research conducted in adult populations however for the purpose of inclusivity we decided to report results from studies investigating differences between OROS-MPH and LDX in younger populations. This was a limitation because it is important to understand age differences for an optimal medication choice. Methylphenidate is currently recommended as a first-line treatment in children and adolescents, whereas in most countries LDX is a possible first line treatment only in adults (Cortese et al., 2018). Results from studies described in this systematic review indicate that LDX is significantly more effective at improving ADHD-RS-IV symptoms than OROS-MPH (Coghill et al., 2013; Fridman et al. (2015; Newcorn et al., 2017), suggesting that prescribing guidelines should be reviewed.

When comparing the efficacy of LDX and OROS-MPH, it is also important to consider patients' treatment history. As described above and found in the study by Setyawan (2013), patients' treatment history made a big difference to treatment adherence in children and adolescents. Children and adolescents who were treatment-naive were more adherent to OROS-MPH than to LDX, whereas those with a previous treatment history appeared to be more adherent to LDX. However in both adult population groups, those who had had pharmacological treatment before and those who had not, treatment persistence was highest for LDX (Setyawan et al., 2013). Future research is warranted to discover mechanisms through which treatment adherence can be improved and the long-term effects of medication treatment.

There are also patient-specific factors which influence medication choice which have not been addressed in this review. Comorbidities are important as ADHD is often a co-occurring disorder; substance abuse disorder (SUD) is especially common in those who meet the diagnostic criteria for ADHD and is diagnosed in nearly a quarter of patients (van Emmerik-van Oortmerssen et al., 2012). The use of stimulants to treat ADHD patients with SUD can be challenging because of their addictive properties and there is limited research on optimal pharmacological management of ADHD in these patients to provide proper guidelines (Brynte et al., 2022). However, preliminary research suggests that LDX may have lower abuse potential than other stimulants (Levine and Swanson, 2023). For example, significant differences between population groups have been found in the subjective effects of LDX vs dexamphetamine ("drug liking"); this measure was found to be much lower for LDX in individuals with stimulant abuse (Jasinski & Krishnan, 2009), whereas drug liking was found to be similar for LDX and dexamphetamine in healthy individuals (Kämmerer, 2024). Future systematic reviews should focus on comparison of LDX and OROS-MPH in populations of individuals with distinct comorbidities (history of substance abuse, anxiety, depression). This would provide more information to be able to address individualized treatment needs.

Future research should also focus on identifying individual treatment needs through the use of biomarkers, either genetic or blood-based. Such biomarkers have yet to be identified. Such categorisation of patients can also be done through genome typing if enough data is collected over a period of time such as through GWAS (Demontis et al., 2019). Single nucleotide polymorphisms (SNPs) and DNA repeat variants show statistically significant relationships to stimulant effectiveness (Myer, Boland, & Faraone, 2018; Pagerols et al., 2017) and variants may exist that show correlations with the effectiveness of specific medications. Pharmacogenomics have been shown to influence pharmacokinetic parameters which are specific to each ADHD medication; having pharmacogenetic information available may aid clinicians and patients when choosing medications and doses to treat ADHD (Brown, 2022).

In addition, future research could include a qualitative analysis of interviews conducted with psychiatrists to better understand prescribing practices, so that these in turn can be improved. Doctors should be well-educated on the profile of each different type of ADHD medication and take into account factors such as age, preferred dosing regimen, treatment history and co-occurring psychiatric disorders.

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