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An Evaluation on the Efficacy and Safety of Treatments for Attention Deficit Hyperactivity Disorder in Children and Adolescents: a Comparison of Multiple Treatments

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Abstract Attention deficit hyperactivity disorder (ADHD) is one of the most common neurobehavioral disorders. We carried out this comparison of multiple treatments based on sufficient data in attempt to evaluate the efficacy and safety of ADHD medication for children and adolescents. PubMed, Embase and the Cochrane Database were used to search for relevant articles. Changes in the ADHD Rating Scale (ADHD-RS) scores and the Conners' Parent Rating Scale-Revised (CPRS) scores were used as outcomes for efficacy. Withdrawals due to all-cause, adverse effects and lack of efficacy were defined as primary outcomes evaluating the safety of such medications. Both pair-wise and network meta-analyses were performed. Efficacy and safety of atomoxetine (ATX), bupropion (BUP), clonidine hydrochloride (CLON), guanfacine extended release (GXR), lisdexamfetamine dimesylate (LDX), and methylphenidate (MPH) were evaluated. LDX has the highest efficacy and a relatively lower rate of adverse effects compared to BUP, CLON and GXR. MPH has the lowest incidence rate of adverse effects and takes second place concerning ADHD-RS scores and third place concerning CPRS scores. ATX has the lowest incidence rate of all-cause withdrawals. The efficacy of ATX seems, however, to be lower than CLON, GXR, LDX and MPH. Adversely, BUP has the highest incidence rate of withdrawals and the second highest probability of causing adverse effects as well as lack of efficacy; therefore it should not be recommended as a treatment for ADHD.

Keywords ADHD · Network meta-analysis · Efficacy · Safety

Introduction

As one of the most common neurobehavioral disorders, attention deficit hyperactivity disorder (ADHD) typically begins in childhood, becomes prevalent during adolescence, and may further persist into adulthood [1]. ADHD is characterized by the development of inattention, hyperactivity and impulsivity, which leads to academic and social function impairment with an early onset [2]. It is reported there are certain habits which have a negative impact on health may increase ADHD risk, such as smoking, substance abuse and so on. ADHD patients, especially children, have great difficulty in learning how to control their own emotion and behavior [2]. According to a systematic review, ADHD prevalence in children worldwide reached 5.29 %, with an incidence rate of 5 % in Europe and 6.0 % to 6.5 % in North America [3]. A study conducted by the National Survey of Children's Health (NSCH) indicated that the percentage of children and adolescence (4–17 years) with ADHD, according to the parents, witnessed a 21.8 % increase from 2003 to 2007 in the United States [2]. In other countries, Slovenia for instance, prevalence of ADHD in 2010 is estimated to reach 1 % in children and adolescents, implying an anticipated 6.3 fold increase compared to the 1997 figures [2]. Although there may have been some bias and errors made in this estimation, it is nevertheless evident that there is an increasing trend of ADHD in children. It was also found that males were more susceptible to ADHD than females, with a

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difference in ratio of 2:1 and 9:1 [2]. Therefore, treating ADHD in children and adolescents is pivotal.

Current treatments for ADHD in children and adolescents include psychological and behavioral interventions such as training for parents, as well as medical therapy [4]. Thanks to the more recent attention brought to ADHD, as well as an early diagnosis, the rate of ADHD patients benefiting from medical treatment has increased rapidly [3]. Licensed medications for ADHD treatment of children and adolescents in the United Kingdom consist of methylphenidate (MPH) and atomoxetine (ATX). Among which ATX is most popular used. Its primary advantage over the standard stimulant treatments for ADHD is that it has little known abuse potential. While it has been shown to significantly reduce inattentive and hyperactive symptoms, the responses were lower than the response to stimulants. Additionally, 40 % of participants who were treated with Atomoxetine experienced significant residual ADHD symptoms [5]. Besides, lisdexamfetamine (LDX), guanfacine (GXR) are also drugs recently approved for ADHD treatment. For patients who do not respond to the drugs mentioned above, medications including bupropion (BUP), catecholamine, amphetamine, clonidine (CLON) are adopted as alternatives.

Multiple systematic reviews have been performed to evaluate the efficacy of ADHD treatment in children and adolescents. However, considering the limitations in trial numbers and the drawback of traditional meta-analysis that can only utilize pair-wised trials, a comprehensive evaluation and analysis is needed to compare and rank the efficacy and safety of medications for ADHD in children and adolescents. The comparison of multiple treatments, or network meta-analysis, is a credible method in calculating the effectiveness of various treatments and in ranking them by direct and indirect comparison. Several network meta-analyses have been performed to evaluate the treatments for ADHD. King et al. conducted a study to evaluate the cost-effectiveness of ADHD treatments [2], he found LDX showed significantly high efficacy than GXR, ATX and MPH [6]. Additional research also validated that LDX was an effective option over ATX and MPH, although the safety of these treatments remained inconclusive [3]. Although network meta-analyses have been performed before, there is still room for improvement in network meta-analysis. King did not measure the safety of ADHD treatments [2]. Furthermore Roskell's study results were limited by the number of trials involved and the limited outcomes, which only focus on the short-term efficacy of treatments in patients without comorbid disorders [7]. Moreover, the number of randomized clinical trials (RCTs) included in the researches mentioned above was limited, Joseph (29 RCTs) [6], Roskell (32 RCTs) [3]. Hence, we performed this comparison of multiple treatments based on a sufficient amount of data, with the objective to measure the efficacy and safety of ADHD medication for children and adolescents.

Materials and Methods

Search Strategy

The following databases were used to collect data: (1) PubMed; (2) Embase; (3) The Cochrane Central Register of Controlled Trials (CENTRAL). The search conducted included literature published up until April 2016, with no language restrictions applied. The search strategy was formed by four items: health condition (ADHD and hyperkinetic disorder), population, study type and medication (ATX, BUP, CLON, GXR, LDX, MPH). In addition, a manual search was conducted through the reference list of selected articles.

Inclusion Criteria

Two independent reviewers screened articles separately, any disagreements were openly discussed until a consensus was reached. Certain/specific criteria were included in the search terms: firstly, the patients in studies should be accurately diagnosed with ADHD; secondly, studies were conducted based on children and adolescents (4–17 years old); thirdly, studies had to be randomized, controlled clinical trials (RCTs); finally, active medications had to be involved, which compared the drugs used in combination or singly, or with placebo (PBO). An output of validated and sufficient data was also needed for credible evaluation.

Data Extraction and Outcome Measurements

Information from each enrolled study were collected in descriptive statistics, including first author, year of publication, study design, study duration, diagnostic criteria, treatments, sample size, mean age, and ADHD scores.

According to the Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria and relevant studies, the primary outcome measurements were the scores of ADHD, which contained various types such as SNAP-IV, ADHD-RS, CPRS, CPRS-RL, SWAN, IOWA-IO, CADS-T, CGI, and ASQ-T. ADHD Rating Scale-IV (ADHD-RS) [8] is an 18-item scale based on an interview conducted by an experienced clinician (nurse, psychologist, social worker, or physician) with the parent (or primary care) and child (if the child was available for the interview). Each item corresponds to one of the 18 symptoms in DSM-IV criteria, and severity for each item is scored 0 to 3(0 = never or rarely; 1 = sometimes; 2 = often; 3 = very often). The sum of the scores for 18 items was calculated to create a total score [9]. The Conners' Parent Rating Scale-Revised (CPRS) [10] includes the 39-item version of the Conners' Teacher Questionnaire and the 93-item version of the Conners' Parent Questionnaire. The symptoms were rated by the observer on a 4-score scale (not at all, just a little, pretty much, very much). Three factors were used from the Parent Form (Hyperactive-Immature, Restless-Impulsive, and

Table 1 The main characteristics of included studies

Author	Year	Trial ID	Design	Duration (weeks)	Diagnostic criteria	Treatment	Dose	Size	Age, mean (SD)
Conners	1996	NR	RD, DB, PC	4	DSM-III	BUP	6 mg/d	72	8.5
						PBO	-	37	8.5
Michelson	2001	NR	RD, DB, PC	8	DSM-IV	ATX	0.5/1.2/1.8 mg/d	213	11.30 (2.30)
						PBO	-	84	10.9 (2.1)
Scahill	2001	NR	RD, DB, PC	8	DSM-IV	GXR	3.0 mg/d	17	10.4 (2.01)
						PBO	-	17	10.4 (2.01)
Greenhill	2002	NR	RD, DB, PC	3	DSM-IV	MPH	1.28 mg/d	155	9 (2.0)
						PBO	-	159	9 (1.8)
Michelson	2002	NR	RD, DB, PC	6	DSM-IV	ATX	1.3 mg/d	85	10.1 (2.3)
						PBO	-	85	10.5 (2.5)
Spencer	2002	NR	RD, DB, PC	12	DSM-IV	ATX	1.6 mg/d	129	9.7 (1.6)
						PBO	-	124	10.0 (1.5)
Biederman	2003	NR	RD, DB, PC	2	DSM-IV	MPH	35.7 mg/d	65	9.1 (1.7)
						PBO	-	71	8.83 (1.92)
Hazell	2003	NR	RD, DB, PC	6	DSM-IV	CLON	0.18 mg/d	38	9.9
						PBO	-	29	9.9
Kaplan	2004	NR	RD, DB, PC	9	DSM-IV	ATX	1.4 mg/d	53	9.8 (1.5)
						PBO	-	45	10.2 (1.5)
Kelsey	2004	NR	RD, DB, PC	8	DSM-IV	ATX	1.3 mg/d	133	9.5 (1.8)
						PBO	-	64	9.4 (1.8)
Allen	2005	NR	RD, DB, PC	18	DSM-IV	ATX	1.33 mg/d	74	10.9 (2.5)
						PBO	-	71	11.5 (2.4)
Findling	2011	NCT00735371	RD, DB, PC, PG	4	DSM-IV	LDX	30/50/70 mg/d	233	14.6 (1.31)
						PBO	-	79	14.6 (1.31)
Weiss	2005	NR	RD, DB, PC	7	DSM-IV	ATX	1.33 mg/d	101	9.9 (1.4)
						PBO	-	52	9.9 (1.3)
Sangal	2006	NR	RD, DB	7	DSM-IV	ATX	1.5 mg/d	44	10.1 (2.0)
						MPH	1.35 mg/d	41	10.1 (2.0)
Sumner	2006	NR	RD, DB, PG, PC	12	DSM-IV	ATX	1.42 mg/d	44	10.22 (2.02)
						PBO	-	43	9.12 (1.89)
Wilens	2006	NR	RD, DB, PC	2	DSM-IV	MPH	18 mg/d	87	14.8 (1.6)
						PBO	-	90	14.5 (1.4)
Bangs	2007	NR	RD, DB, PC	9	DSM-IV	ATX	1.51 mg/d	72	14.6 (1.8)
						PBO	-	70	14.2 (1.5)
Biederman	2007	NR	RD, DB, PC, PG	4	DSM-IV	LDX	30/50/70 mg/d	213	8.86 (1.83)
						PBO	-	72	9.4 (1.7)
Gau	2007	NR	RD, DB, PC	6	DSM-IV	ATX	1.4 mg/d	72	9.1 (2.0)
						PBO	-	34	9.5 (2.4)
Geller	2007	NR	RD, DB, PC	10	DSM-IV	ATX	1.3 mg/d	87	12.2 (2.8)
						PBO	-	89	11.8 (2.5)
Wang	2007	NR	RD, PC, DB	8	DSM-IV	ATX	1.37 mg/d	164	9.4 (2.0)
						MPH	0.52 mg/d	166	9.9 (2.3)
Bangs	2008	NR	RD, DB , PC	8	DSM-IV	ATX	1.20 mg/d	156	9.5 (1.9)
						PBO	-	70	9.7 (1.9)
Biederman	2008	NR	RD, DB, PC	8	DSM-IV	GXR	2.0/3.0/4.0 mg/d	259	10.6 (6.0–16.0)
						PBO	-	86	10.6 (6.0–17.0)
Findling	2008	NCT00444574	RD, DB, PC, PG	7	DSM-IV	MPH	18 mg/d	91	8.8 (1.94)
						PBO	-	85	8.5 (1.91)
Newcorn	2008	NR	RD, DB, PC	6	DSM-IV	ATX	1.45 mg/d	222	10.3 (2.2)
						MPH	1.16 mg/d	220	10.2 (2.5)
						PBO	-	74	10.1 (2.7)
Block	2009	NCT00486122	RD, DB, PC		DSM-IV	ATX	1.25/1.26 mg/d	201	8.8 (1.7)
						PBO	-	93	8.9 (1.7)
De Jong	2009	NCT00191906	RD, DB, PC	4	DSM-IV	ATX	1.11 mg/d	39	10 (2)
						PBO	-	37	9.3 (0.9)
Dell'Agnello	2009	NR	RD, DB, PC	8	DSM-IV	ATX	1.1 mg/d	105	9.7 (2.2)
						PBO	-	32	10.0 (2.4)
Montoya	2009	NCT00191945	DB, RD, PC	12	DSM-IV	ATX	1.2 mg/d	100	10.3 (2.5)
						PBO	-	51	10.3 (2.4)
Sallee	2009	NCT00150618		9	DSM-IV	GXR	1/2/3/4 mg/d	258	11 (3)

Table 1 (continued)

Author	Year	Trial ID	Design	Duration (weeks)	Diagnostic criteria	Treatment	Dose	Size	Age, mean (SD)
			RD, DB, PC, PG						
						PBO	-	66	11 (3)
Svanborg	2009	NR	RD, DB, PC	10	DSM-IV	ATX	1.1 mg/d	49	11.6 (2.3)
						PBO	-	50	11.3 (2.1)
Svanborg	2009	NR	RD, DB, PC	10	DSM-IV	ATX	1.2 mg/d	49	11.5 (4)
						PBO	-	50	11.5 (4)
Takahashi	2009	NR	RD, DB, PC	8	DSM-IV	ATX	0.5/1.2/1.8 mg/d	183	10.45 (2.67)
						PBO	-	62	10.76 (2.03)
Connor	2010	NCT00367835	RD, DB, PC	9	DSM-IV	GXR	3 mg/d	138	9.4 (1.73)
						PBO	-	79	9.4 (1.73)
Martenyi	2010	NCT00386581	RD, DB, PC	6	DSM-IV	ATX	1.4 mg/d	72	9.9 (2.9)
						PBO	-	33	9.6 (2.7)
Thurstone	2010	NCT00399763	RD, DB, PC	12	DSM-IV	ATX	1.19 mg/d	35	16.06 (1.35)
						PBO	-	35	16.11 (1.78)
Dittmann	2011	NR	RD, DB, PC	9	DSM-IV	ATX	1.2 mg/d	121	10.9 (3.1)
						PBO	-	59	11.1 (2.8)
Jain	2011	NCT00556959	RD, DB, PC, PG	8	DSM-IV	CLON	0.2/0.4 mg/d	158	9.5
						PBO	-	78	9.4
Kollins	2011	NR	RD, DB, PC	6	DSM-IV	GXR	2.5 mg/d	121	12.6 (2.83)
						PBO	-	57	12.8 (2.77)
Kollins	2011	NCT00641329	RD, DB, PC, PG	8	DSM-IV	CLON	0.29 mg/d	102	10.4 (2.5)
						PBO	-	96	10.5 (2.5)
Kratochvil	2011	NCT00561340	RD, DB, PC	8	DSM-IV	ATX	1.4 mg/d	44	6.1 (0.6)
						PBO	-	44	6.1 (0.5)
Wehmeier	2011	NCT00546910	RD, DB, PC	8	DSM-IV	ATX	1.2 mg/d	63	9.1 (1.93)
						PBO	-	62	8.9 (1.64)
Harfterkamp	2012	NCT00380692	RD, DB, PC	8	DSM-IV	ATX	1.2 mg/d	48	9.9 (2.7)
						PBO	-	49	10.0 (2.9)
Wilens	2012	NCT00734578	RD, DB, PC	9	DSM-IV	GXR	3.3 mg/d	302	10.80 (2.46)
						PBO	-	153	10.8 (2.3)
Coghill	2013	NCT00763971	RD, DB, PG, PC	7	DSM-IV	LDX	53.8 (15.6) mg/d	113	10.9 (2.9)
						PBO	-	111	11.0 (2.8)
						MPH	45.4 (12.7) mg/d	112	10.9 (2.6)
Newcorn	2013	NCT00997984	RD, DB, PC	8	DSM-IV	GXR	2.9 /3.0 mg/d	221	9.20 (1.76)
						PBO	-	112	8.9 (1.78)
Soutullo	2013	NCT00763971	RD, DB, PC, PG	7	DSM-IV	LDX	30, 50 or 70 mg/d	111	10.9 (2.9)
						MPH	18, 36 or 54 mg/d	111	10.9 (2.6)
						PBO	-	110	11.0 (2.8)
Coghill	2014	NCT00763971	RD, DB, PC, PG	7	DSM-IV	LDX	30, 50 or 70 mg/d	104	10.9 (2.9)
						MPH	18, 36 or 54 mg/d	107	10.9 (2.6)
						PBO	-	106	11.0 (2.8)
Cutler	2014	NCT00734578	RD, DB, PC	9	ADHD-RS-IV CGI-S	GXR	4 mg/d	302	10.8 (2.4)
						PBO	-	153	10.8 (2.4)
Findling	2014	NR	RD, DB, PC	9	DSM-IV	GXR	3.2/3.3 mg/d	179	10.8 (2.5)
						PBO	-	93	10.8 (2.3)
Hervas	2014	NCT01244490	RD, DB, PC, PG	13	NR	GXR	0.09 mg/d	115	10.9 (2.77)
						ATX	1.03 mg/d	112	10.5 (2.81)
						PBO	-	111	11.0 (2.76)
Wigal	2015	NCT01239030	RD, DB, PC, PG	1	DSM-IV	MPH	10/15/20/40 mg/d	183	10.5 (2.9)
						PBO	-	47	10.9 (3.0)
Newcorn	2016	NCT01081145	RD, DB, PC	26	DSM-IV-TR	GXR	1–7 mg/d	157	10.7 (2.64)
						PBO	-	158	11.0 (2.69)
NRgy	2016	NCT01106430	RD, DB	9	DSM-IV-TR	LDX	30 mg/d	127	10.6(2.93)
						ATX	40 mg/d or 0.5 mg/kg/d	135	10.6(2.93)

Table 1 (continued)

Author	Year	Trial ID	Design	Duration (weeks)	Diagnostic criteria	Treatment	Dose	Size	Age, mean (SD)
Wilens	2015	NCT01081132	RD, DB, PC	13	DSM-IV-TR	GXR	1–7 mg/d	157	14.5(1.35)
						PBO	-	155	14.6(1.44)
Stein	2015	NCT00997984	RD, DB, PC	8	DSM-IV-TR	GXR	1–4 mg/d	221	9.1
						PBO	-	112	9.1
Shang	2015	NCT00916786	RD	24	DSM-IV	ATX	0.5 mg/d	80	9.90 (2.78)
						MPH	18 mg/d	80	9.64 (2.42)
Handen	2015	NCT00844753	RD, DB, PC	10	DSM-IV-TR	ATX	1.38 mg/d	32	8.6 (2.3)
						PBO	-	32	8.2 (2.4)
Rugino	2014	NCT01156051	RD, DB, PC	5	NR	GXR	1–4 mg/d	12	9.15(1.76)
						PBO	-	17	8.82(1.91)
Coghill	2014	NCT00784654	RD, DB, PC	33	DSM-IV-TR	LDX	30,50,70 mg/d	78	11(2.63)
						PBO	-	79	11.3(2.58)
Garg	2014	NR	RD	8	NR	MPH	0.2–1 mg/d	33	8.47(2.22)
						ATX	0.5–1.2 mg/d	36	8.66(2.44)
Abikoff	2007	NR	RD, DB, PC	4	DSM-IV	MPH	14.22 mg/d	61	4.39 (0.72)
						PBO	-	53	4.45 (0.67)
Scahill	2001	NR	RD, DB, PC	8	DSM-IV	GXR	3.0 mg/d	17	10.4 (2.01)
						PBO	-	17	10.4 (2.01)
Buitelaar	2007	NR	RD, DB, PC	36	DSM-IV	ATX	1.2 mg/d	77	10.7 (2.4)
						PBO	-	81	11.0 (2.0)

RD: randomized; DB: double-blind; PC: placebo-controlled; PG: parallel-group; DSM: Diagnostic and Statistical Manual of Mental Disorders; PBO: placebo; ATX: atomoxetine; BUP: bupropion; CLON: clonidine hydrochloride; GXR: guanfacine extended release; LDX: lisdexamfetamine dimesylate; MPH: methylphenidate; NR: none reported

Conduct Disorder), and two factors were chosen from the Teacher Form (Hyperactivity and Conduct Disorder). In this study, we used ADHD-RS and CPRS as primary outcomes for efficacy. The changes of efficacy variables were calculated between the start and the end of treatment. Withdrawals due to all-cause, or adverse effects and lack of efficacy were also defined as primary outcomes to measure the safety of medications for ADHD.

Two reviewers scanned the full text of all identified studies, and reached a consensus through discussion if results were found to be inconsistent. All data including information regarding the studies (publication year, author), participants (sample size, age), medications (treatment duration, type of drug, dose) and outcome measurements were extracted.

Statistical Analysis

To start with, a pair-wise meta-analysis was conducted to evaluate the efficacy and safety of medications in ADHD treatment. Weighted mean differences, odd ratios and their corresponding 95 % confidence interval (CI) were calculated based on the results of a heterogeneity test. The heterogeneity was checked with Q statistics and I^2 test, with $P < 0.05$ or $I^2 > 50$ % indicating the existence of heterogeneity. We used a fixed-effects model (Mantel-Haenszel method) for studies without significant heterogeneity and a random-effects model (DerSimonian-Laird method) for studies with significant heterogeneity.

The multiple treatments comparison (MTC), under the Bayesian model, was performed on various comparator groups, which not only included direct comparisons from head-to-head trials but also indirect comparisons between two comparators. Due to the advantage of incorporating direct and indirect evidence, MTC could measure the efficacy and safety of medications for ADHD globally with the maximum statistical power by comparing these multiple treatments. We ranked the efficacy and safety of the medications based on the surface under the cumulative ranking curve (SUCRA). WinBUGS 1.4.3 and R 3.2.3 software were used to perform the MTC. Pair-wise meta-analyses were also conducted based on direct comparisons with STATA 12.1. The consistency was then assessed between direct and indirect comparisons, and the inconsistency of MTC was defined as the variability between the results of MTC analysis and the pair-wise meta-analyses.

Results

Study Characteristics

The data collected from a total of 12,930 patients from 62 studies was used in this meta-analysis [4, 11–71]. ATX, BUP, CLON, GXR, LDX, MPH were identified as widely used drugs for ADHD treatment. The main characteristics of the studies included are summarized in Table 1. A network plot of the 62 studies used is illustrated in Fig. 1 to show the comparisons in network meta-analysis. The width of the lines is proportional to the number of studies comparing treatment pairs. As can be seen from the plot, most of the trials we input

into the analysis investigated the efficacy and safety of drugs on ADHD treatment compared with placebo; not many trials had been conducted on the direct comparison between drugs. Therefore, a network meta-analysis that enables indirect comparisons based on current data is greatly needed.

Results of Pair-Wise Meta-Analysis

In the traditional pair-wise meta-analysis, most of the results were based on comparisons between ATX, BUP, CLON, GXR, LDX, MPH and the placebo separately. As illustrated in Table 2, the efficacy of ATX, CLON, GXR, LDX, MPH was proved by changes in ADHD-RS compared to PBO (ATX vs. PBO: WMD = −0.80, 95%CI = [−1.01; −0.58] CLON vs. PBO: WMD = −0.52, 95%CI = [−0.88; −0.17]; GXR vs. PBO: WMD = −0.60, 95%CI = [−0.75; −0.44]; LDX vs. PBO: WMD = −1.39, 95%CI = [−1.80; −0.98]; MPH vs. PBO: WMD = −0.87, 95%CI = [−1.14; −0.60]). Furthermore, ATX, BUP, CLON, LDX, MPH have a better performance than the placebo in the CPRS, meanwhile only the comparison of ATX vs. MPH and BUP vs. PBO has no statistical significance (ATX vs. MPH: WMD = −0.01, 95%CI = [−0.23; 0.20]; BUP vs.

PBO: WMD = −0.13, 95%CI = [−0.52; 0.27]).

Considering the safety of the drugs involved in the analysis, in the comparisons of the all-cause withdrawals, the safety of CLON, GXR, LDX and MPH were validated compared to the placebo (CLON vs. PBO: OR =0.53, 95%CI = [0.35; 0.82]; GXR vs. PBO: OR =0.82, 95%CI = [0.70; 0.97]; LDX vs. PBO: OR =0.41, 95%CI = [0.21; 0.80]; MPH vs. PBO: OR =0.45, 95%CI = [0.30; 0.68]). It is worthy to note, in the traditional pair-wise meta-analysis, we observed that GXR had a higher likelihood of producing withdrawal symptoms due to adverse effect compared to the placebo (OR =3.09, 95%CI = [1.80; 5.28]). Regarding withdrawal due to lack of efficacy, ATX, CLON, GXR, LDX and MPH proved to have better performance than the placebo, whereas for BUP we did not obtain a significant result (OR =1.57, 95%CI: [0.16; 15.59]).

Results of Network Meta-Analysis

In this network meta-analysis, efficacy of different drugs on ADHD treatment was evaluated by ADHD-RS and CPRS. Due to the lack of sufficient clinical trials, the efficacy of
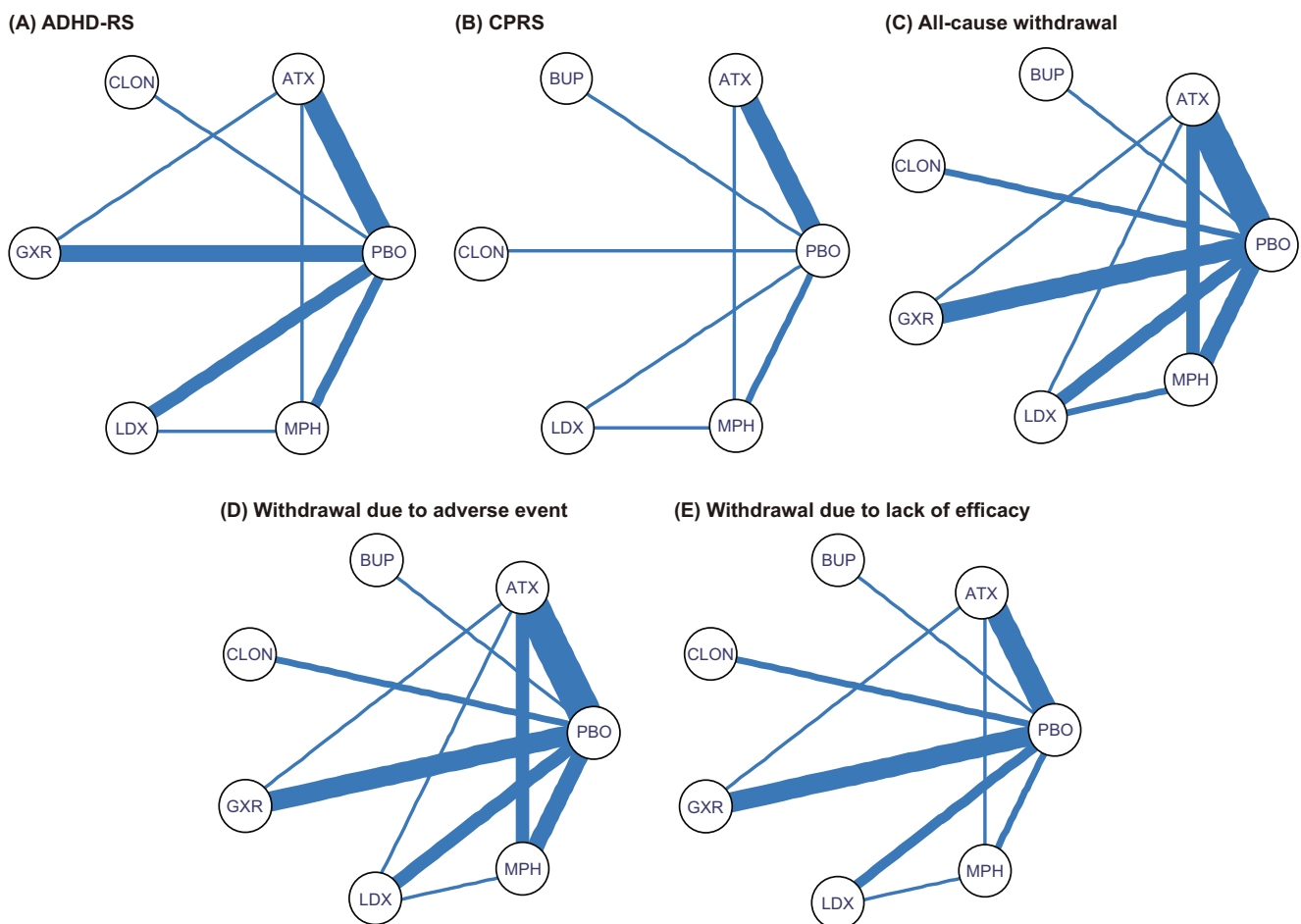

Fig. 1 Network plot of enrolled articles. The width of the lines is proportional to the number of studies comparing treatment pairs

Table 2 The results of pair-wise meta-analysis of seven drugs under five outcomes

Treatment	N	WMD (95%CI)	Q	tau^2	I^2
ADHD RS					
ATX vs. PBO	18	**-0.80 [−1.01; −0.58]**	123.99	0.18	86.30 %
ATX vs. MPH	1	0.05 [−0.17; 0.27]	–	–	–
CLON vs. PBO	2	**-0.52 [−0.88; −0.17]**	3.25	0.05	69.20 %
GXR vs. PBO	7	**-0.60 [−0.75; −0.44]**	11.30	0.02	46.90 %
LDX vs. PBO	5	**-1.39 [−1.80; −0.98]**	36.54	0.19	89.10 %
MPH vs. PBO	4	**-0.87 [−1.14; −0.60]**	11.07	0.06	72.90 %
CPRS					
ATX vs. PBO	10	**-0.88 [−1.19; −0.57]**	76.12	0.21	88.20 %
ATX vs. MPH	1	-0.01 [−0.23; 0.20]	–	–	–
BUP vs. PBO	1	-0.13 [−0.52; 0.27]	0	–	–
CLON vs. PBO	1	**-0.33 [−0.61; −0.05]**	0	–	–
LDX vs. PBO	1	**-12.65 [−13.90; −11.40]**	0	–	–
MPH vs. PBO	3	**-3.10 [−5.73; −0.46]**	295.26	5.35	99.30 %

| Treatment	N	OR (95%CI)	Q	tau^2	I^2
All cause withdrawals					
ATX vs. PBO	26	0.89 [0.74; 1.07]	32.82	0.07	23.80 %
ATX vs. LDX	1	1.19 [0.67; 2.11]	0	–	–
ATX vs. MPH	4	1.56 [0.98; 2.48]	3.25	0.02	7.70 %
BUP vs. PBO	1	2.19 [0.44; 10.87]	0	–	–
CLON vs. PBO	3	**0.53 [0.35; 0.82]**	0.68	0	0 %
GXR vs. PBO	11	**0.82 [0.70; 0.97]**	16.38	0.05	38.90 %
LDX vs. PBO	5	**0.41 [0.21; 0.80]**	24.63	0.50	83.80 %
MPH vs. PBO	7	**0.45 [0.30; 0.68]**	15.73	0.18	61.90 %
Withdraw due to adverse event					
ATX vs. PBO	26	1.30 [0.85; 1.97]	12.82	0	0 %
ATX vs. LDX	1	1.19 [0.45; 3.12]	0	–	–
ATX vs. MPH	4	1.77 [0.88; 3.59]	3.90	0.19	23.10 %
BUP vs. PBO	1	2.72 [0.31; 24.16]	0	–	–
CLON vs. PBO	3	1.79 [0.47; 6.78]	5.78	2.7	65.40 %
GXR vs. PBO	10	**3.09 [1.80; 5.28]**	11.94	0.26	24.60 %
LDX vs. PBO	5	1.67 [0.79; 3.55]	3.87	0	0 %
MPH vs. PBO	7	1.05 [0.50; 2.22]	6.12	0.02	1.90 %
Withdraw due to lack of efficacy					
ATX vs. PBO	19	**0.45 [0.32; 0.63]**	11.35	0	0 %
ATX vs. MPH	1	0.93 [0.06; 15.39]	0	–	–
BUP vs. PBO	1	1.57 [0.16; 15.59]	0	–	–
CLON vs. PBO	3	**0.30 [0.16; 0.55]**	1.59	0	0 %
GXR vs. PBO	10	**0.38 [0.28; 0.51]**	9.09	0	1 %
LDX vs. PBO	4	**0.13 [0.08; 0.20]**	6.05	0.25	50.40 %
MPH vs. PBO	3	**0.31 [0.21; 0.45]**	3.28	0.07	39 %

N: numbers of individual studies; WMD: weighted mean difference; OR: odds ratio; CI: confidence interval; ADHD RS: Diagnostic and Statistical Manual of Mental Disorders; CPRS: Conners' Parent Rating Scale; PBO: placebo; ATX: atomoxetine; BUP: bupropion; CLON: clonidine hydrochloride; GXR: guanfacine extended release; LDX: lisdexamfetamine dimesylate; MPH: methylphenidate

Bold indicates statistic significance

BUP was only evaluated by CPRS, and the efficacy of GXR was only evaluated by ADHD-RS. Results from the network meta-analysis are plotted in Figs. 2-6 and Table 3-5 with corresponding probability of different treatment ranks. As can be observed, when compared with the placebo, the efficacy of ATX, CLON, GXR, LDX, MPH was validated if we took

Fig. 2 Network meta-analysis on change of ADHD-RS after different drug therapy compared with PBO or LDX
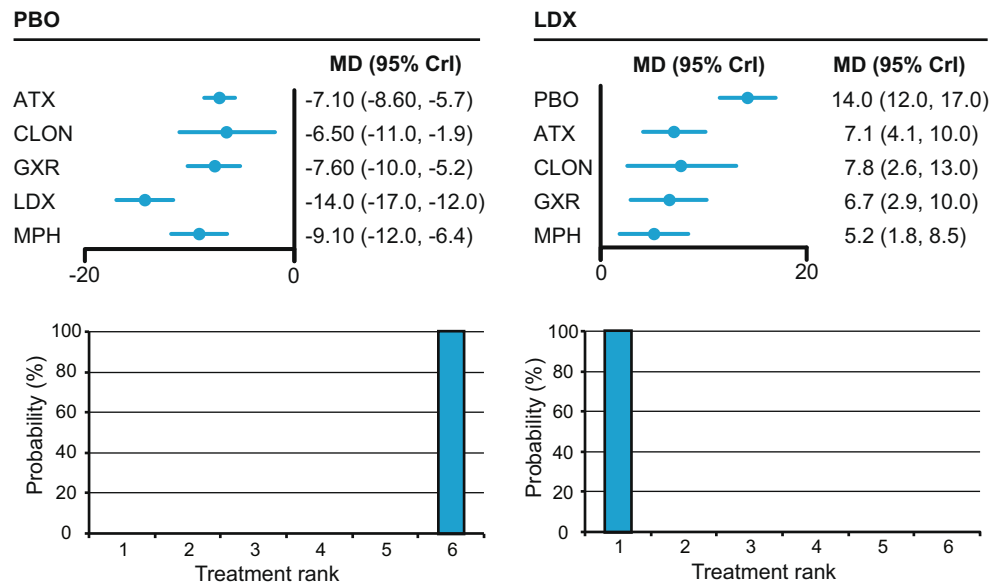
ADHD-RS as a primary outcome (ATX: MD = −7.10, 95%CI: [−8.60, −5.7]; CLON: MD = −6.50, 95%CI: [−11.0, −1.9]; GXR: MD = −7.60, 95%CI: [−10.0, −5.2]; LDX: MD = −14.0, 95%CI: [−17.0, −12.0]; MPH: MD = −9.10, 95%CI: [−12.0, −6.4], Fig. 2, Table 3). In the analysis of CPRS changes, BUP did not illustrate a significant therapeutic value compared to the placebo (MD = −0.9, 95%CI: [−7.1, 5.2], Fig. 3, Table 4).

LDX was proved to be the most efficient medication for ADHD in our results. LDX has a significantly higher efficacy than other drugs considering its change in the ADHD-RS (ATX: MD = 7.1, 95%CI: [4.1, 10.0]; CLON: MD = 7.8, 95%CI: [2.6, 13.0]; GXR: MD = 6.7, 95%CI: [2.9, 10.0];

MPH: MD = 5.2, 95%CI: [1.8, 8.5], Fig. 2, Table 3). Regarding the change of CPRS, LDX also manifested to be significantly more efficient than ATX, BUP and MPH (ATX: MD = 12.0, 95%CI: [6.4, 17.0]; BUP: MD = 17.0, 95%CI: [8.8, 25.0]; MPH: MD = 8.1, 95%CI: [3.2, 13.0], Fig. 3, Table 3). In addition to this, based on the cumulative ranking probabilities, LDX had the highest probability to rank first in terms of efficacy concerning both CPRS and ADHD-RS (Table 5).

When it came to evaluation of safety, as presented in Fig. 4, Table 4, BUP, LDX and MPH had a significantly higher incidence rate of all-cause withdrawals compared with the placebo (BUP: OR =0.05, 95%CI: [0.0012, 0.74]; LDX: OR =0.44, 95%CI: [0.29, 0.66]; MPH: OR =0.58, 95%CI: [0.41, 0.82]). Meanwhile, it was observed that BUP had a more than 90 % probability to rank highest in all-cause withdrawals, which means it ranked lowest in terms of safety compared to the
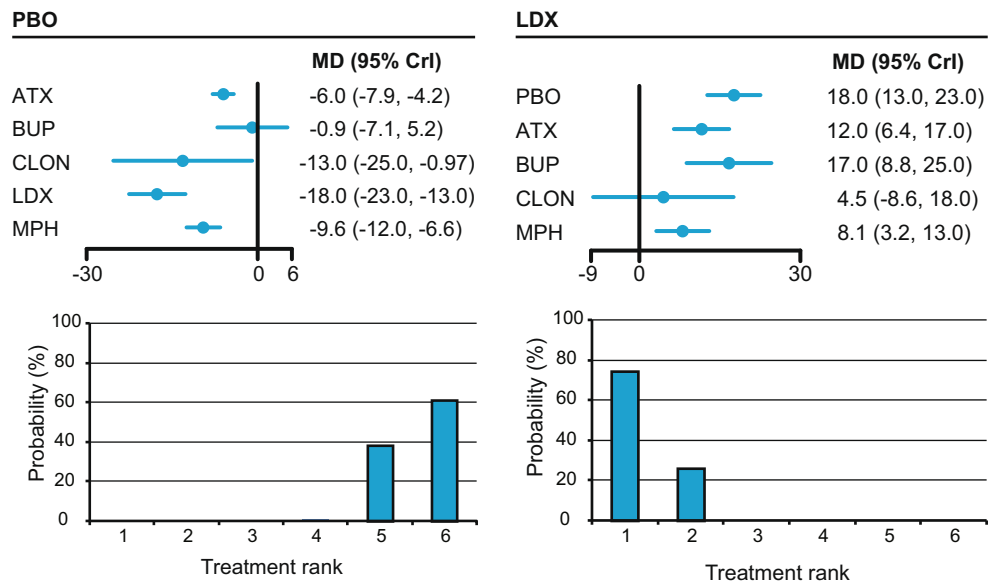
Table 3 Network meta-analysis results of seven treatments under ADHD-RS and CPRS

ADHD-RS	PBO	**-7.13 (−8.64, −5.67)**	**-6.44 (−11.07, −1.81)**	**-7.58 (−10.22, −5.22)**	**-14.29 (−17.06, −11.58)**	**-9.09 (−11.74, −6.45)**
	7.13 (5.67, 8.64)	ATX	0.67 (−4.17, 5.61)	-0.46 (−3.38, 2.28)	**-7.16 (−10.27, −4.09)**	-1.96 (−4.78, 0.87)
	6.44 (1.81, 11.07)	-0.67 (−5.61, 4.17)	CLON	-1.15 (−6.47, 4.01)	**-7.83 (−13.23, −2.50)**	-2.61 (−7.88, 2.61)
	7.58 (5.22, 10.22)	0.46 (−2.28, 3.38)	1.15 (−4.01, 6.47)	GXR	**-6.71 (−10.34, −2.92)**	-1.49 (−5.01, 2.18)
	14.29 (11.58, 17.06)	7.16 (4.09, 10.27)	7.83 (2.50, 13.23)	6.71 (2.92, 10.34)	LDX	**5.21 (1.82, 8.59)**
	9.09 (6.45, 11.74)	1.96 (−0.87, 4.78)	2.61 (−2.61, 7.88)	1.49 (−2.18, 5.01)	-5.21 (−8.59, −1.82)	MPH
CPRS	PBO	**-6.03 (−7.95, −4.26)**	-0.99 (−7.22, 5.33)	**-13.04 (−25.18, −0.99)**	**-17.64 (−22.58, −12.77)**	**-9.58 (−12.55, −6.57)**
	6.03 (4.26, 7.95)	ATX	5.06 (−1.36, 11.50)	-6.99 (−19.22, 5.32)	**-11.64 (−16.66, −6.53)**	**-3.54 (−6.54, −0.37)**
	0.99 (−5.33, 7.22)	-5.06 (−11.50, 1.36)	BUP	-12.06 (−25.80, 1.78)	**-16.67 (−24.53, −8.66)**	**-8.56 (−15.32, −1.69)**
	13.04 (0.99, 25.18)	6.99 (−5.32, 19.22)	12.06 (−1.78, 25.80)	CLON	-4.68 (−17.56, 8.48)	3.46 (−9.26, 16.07)
	17.64 (12.77, 22.58)	11.64 (6.53, 16.66)	16.67 (8.66, 24.53)	4.68 (−8.48, 17.56)	LDX	**8.07 (3.12, 13.15)**
	9.58 (6.57, 12.55)	3.54 (0.37, 6.54)	8.56 (1.69, 15.32)	-3.46 (−16.07, 9.26)	-8.07 (−13.15, −3.12)	MPH

ADHD-RS: Diagnostic and Statistical Manual of Mental Disorders; CPRS: Conners' Parent Rating Scale; PBO: placebo; ATX: atomoxetine; BUP: bupropion; CLON: clonidine hydrochloride; GXR: guanfacine extended release; LDX: lisdexamfetamine dimesylate; MPH: methylphenidate

Bold indicates statistic significance

Fig. 3 Network meta-analysis on change of CPRS after different drug therapy compared with PBO or LDX

PBO

	MD (95% CrI)
ATX	-6.0 (-7.9, -4.2)
BUP	-0.9 (-7.1, 5.2)
CLON	-13.0 (-25.0, -0.97)
LDX	-18.0 (-23.0, -13.0)
MPH	-9.6 (-12.0, -6.6)

LDX

	MD (95% CrI)
PBO	18.0 (13.0, 23.0)
ATX	12.0 (6.4, 17.0)
BUP	17.0 (8.8, 25.0)
CLON	4.5 (-8.6, 18.0)
MPH	8.1 (3.2, 13.0)

other drugs. ATX and GXR are two drugs that had a relatively low probability of withdrawal (ATX: 22.83 %; GXR: 28.00 %, for the cumulative ranking probabilities see Table 5).

Considering withdrawals due to adverse effect, patients using GXR were more likely to suffer from severe adverse effects than if they were to take the other drugs (87.17 % for

Table 4 Network meta-analysis results of seven treatments under withdrawals

All-cause withdrawals	PBO	0.87 (0.69, 1.10)	**0.05 (0.00, 0.82)**	0.51 (0.25, 1.01)	0.83 (0.61, 1.12)	**0.44 (0.30, 0.66)**	**0.58 (0.41, 0.83)**
	1.15 (0.91, 1.46)	ATX	**0.06 (0.00, 0.93)**	0.59 (0.28, 1.19)	0.95 (0.66, 1.37)	**0.51 (0.33, 0.79)**	**0.67 (0.46, 0.97)**
	19.12 (1.22, 611.18)	16.73 (1.08, 526.40)	BUP	9.69 (0.56, 316.71)	15.90 (0.99, 521.07)	8.44 (0.54, 271.80)	11.02 (0.70, 352.32)
	1.96 (0.99, 3.92)	1.70 (0.84, 3.58)	0.10 (0.00, 1.77)	CLON	1.62 (0.79, 3.48)	0.86 (0.39, 1.97)	1.13 (0.53, 2.49)
	1.21 (0.89, 1.64)	1.05 (0.73, 1.52)	0.06 (0.00, 1.13)	0.62 (0.29, 1.27)	GXR	**0.53 (0.32, 0.90)**	0.70 (0.45, 1.11)
	2.27 (1.51, 3.37)	1.97 (1.27, 3.05)	0.12 (0.00, 1.85)	1.16 (0.51, 2.57)	1.89 (1.11, 3.08)	LDX	1.31 (0.83, 2.08)
	1.73 (1.21, 2.44)	1.50 (1.03, 2.16)	0.09 (0.00, 1.42)	0.88 (0.40, 1.88)	1.43 (0.90, 2.24)	0.76 (0.48, 1.20)	MPH
Withdrawals due to adverse event	PBO	**1.58 (1.03, 2.28)**	2.73 (0.35, 91.66)	2.54 (0.76, 7.73)	**3.95 (2.34, 7.30)**	**1.95 (1.05, 3.99)**	1.16 (0.67, 2.13)
	0.63 (0.44, 0.97)	ATX	1.77 (0.22, 60.17)	1.66 (0.46, 5.40)	**2.54 (1.38, 5.21)**	1.24 (0.66, 2.73)	0.74 (0.44, 1.40)
	0.37 (0.01, 2.82)	0.56 (0.02, 4.53)	BUP	0.86 (0.02, 8.62)	1.47 (0.04, 13.26)	0.73 (0.02, 6.34)	0.43 (0.01, 3.69)
	0.39 (0.13, 1.32)	0.60 (0.19, 2.15)	1.17 (0.12, 48.96)	CLON	1.60 (0.45, 6.51)	0.77 (0.22, 3.23)	0.45 (0.13, 1.80)
	0.25 (0.14, 0.43)	0.39 (0.19, 0.73)	0.68 (0.08, 24.44)	0.62 (0.15, 2.20)	GXR	0.52 (0.21, 1.16)	**0.30 (0.13, 0.64)**
	0.51 (0.25, 0.95)	0.80 (0.37, 1.52)	1.37 (0.16, 49.81)	1.30 (0.31, 4.51)	1.92 (0.86, 4.82)	LDX	0.60 (0.26, 1.28)
	0.86 (0.47, 1.50)	1.36 (0.72, 2.30)	2.35 (0.27, 78.92)	2.20 (0.56, 7.52)	3.33 (1.56, 7.82)	1.67 (0.78, 3.87)	MPH
Withdrawals due to lack of efficacy	PBO	**0.44 (0.31, 0.63)**	0.08 (0.00, 3.37)	**0.31 (0.16, 0.63)**	**0.38 (0.27, 0.52)**	**0.13 (0.08, 0.22)**	**0.32 (0.20, 0.50)**
	2.27 (1.59, 3.26)	ATX	0.19 (0.01, 7.69)	0.70 (0.32, 1.54)	0.86 (0.53, 1.35)	**0.31 (0.16, 0.55)**	0.73 (0.41, 1.30)
	12.04 (0.30, 232.07)	5.18 (0.13, 110.70)	BUP	3.73 (0.09, 76.86)	4.49 (0.11, 94.01)	1.52 (0.04, 34.67)	3.84 (0.09, 81.26)
	3.21 (1.60, 6.41)	1.42 (0.65, 3.14)	0.27 (0.01, 11.10)	CLON	1.22 (0.54, 2.60)	0.43 (0.17, 1.03)	1.03 (0.45, 2.34)
	2.63 (1.91, 3.74)	1.16 (0.74, 1.87)	0.22 (0.01, 8.93)	0.82 (0.39, 1.85)	GXR	**0.35 (0.19, 0.64)**	0.85 (0.49, 1.50)
	7.57 (4.58, 12.65)	3.28 (1.80, 6.35)	0.66 (0.03, 25.38)	2.31 (0.97, 5.83)	2.82 (1.56, 5.34)	LDX	**2.38 (1.35, 4.36)**
	3.13 (1.99, 4.92)	1.37 (0.77, 2.44)	0.26 (0.01, 11.44)	0.98 (0.43, 2.21)	1.18 (0.67, 2.06)	0.42 (0.23, 0.74)	MPH

PBO: placebo; ATX: atomoxetine; BUP: bupropion; CLON: clonidine hydrochloride; GXR: guanfacine extended release; LDX: lisdexamfetamine dimesylate; MPH: methylphenidate

Bold indicates statistic significance

Table 5 The cumulative ranking probabilities of seven treatments under five outcomes

Drug	ADHD-RS	CPRS	All-cause withdrawals	Withdrawals due to adverse event	Withdrawals due to lack of efficacy
PBO	0.00 %	8.00 %	433 %	**77.29 %**	3.33 %
ATX	41.20 %	41.80 %	22.83 %	**49.57 %**	33.50 %
BUP	-	14.80 %	**95.17 %**	28.00 %	**65.67 %**
CLON	37.80 %	**75.40 %**	**64.00 %**	28.29 %	**57.33 %**
GXR	**50.20 %**	-	28.00 %	11.00 %	42.83 %
LDX	**100.00 %**	**94.80 %**	76.83 %	37.57 %	**91.50 %**
MPH	**71.20 %**	**65.40 %**	58.17 %	**68.57 %**	57.33 %

ADHD-RS: Diagnostic and Statistical Manual of Mental Disorders; CPRS: Conners' Parent Rating Scale; PBO: placebo; ATX: atomoxetine; BUP: bupropion; CLON: clonidine hydrochloride; GXR: guanfacine extended release; LDX: lisdexamfetamine dimesylate; MPH: methylphenidate

Bold indicates statistic significance

cumulative ranking probabilities see Fig. 5, Table 4). Meanwhile, MPH could be considered as the drug with the least adverse effect (20.00 % in cumulative ranking probabilities). Besides, when we analyzed the results of patients' withdrawals due to lack of efficacy, we observed that LDX had the highest ranking among the drugs (91.50 % for cumulative ranking probabilities, Fig. 6, Table 4), combining LDX being confirmed as the drug with the highest efficacy.

Discussion

In this analysis, we investigated the efficacy and safety of widely used medications for ADHD, including ATX, BUP, CLON, GXR, LDX and MPH. According to our results, LDX has the highest efficacy compared to the other drugs as well as a relatively lower rate of causing adverse effects than BUP, CLON and GXR. MPH has the lowest incidence rate of withdrawals due to

adverse effects. Further in regard to MPH, it performed well in terms of efficacy and thus takes second place in correspondence with ADHD-RS and third place in CPRS. ATX is considered the safest drug for ADHD treatment based on our analysis. It has the lowest incidence rate of all-cause withdrawals as well as withdrawals due to lack to efficacy. However, the efficacy of ATX seems to be lower than CLON, GXR, LDX and MPH. Despite this, the use of CLON may be controversial considering its high efficacy but relatively low safety rate. Taking GXR into account, the high incidence rate of withdrawal due to adverse effects may also be taken into consideration when using it as an ADHD treatment. The results that LDX has the best performance and no significant difference between ATX and MPH are consistent with former NMA [72, 7]. According to previous papers, ATX is claimed by Mark E. Bangs to be statistically unrelated to suicidal behaviors in 2014 [2]. Besides, LDX has a proven long-lasting efficacy in long-term treatment among children and adolescence diagnosed with ADHD [4, 3]. In 2015, a study was carried out to
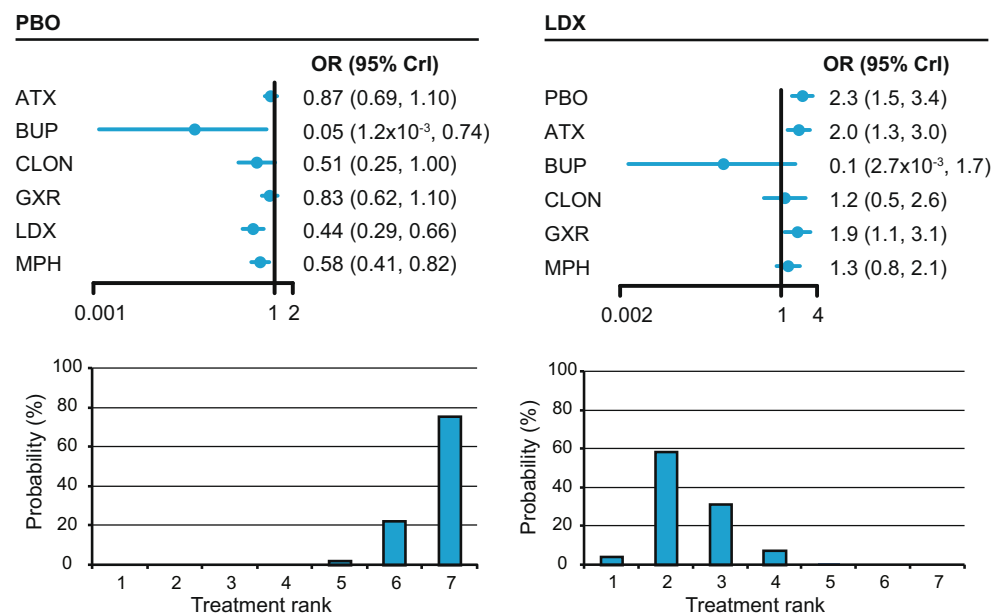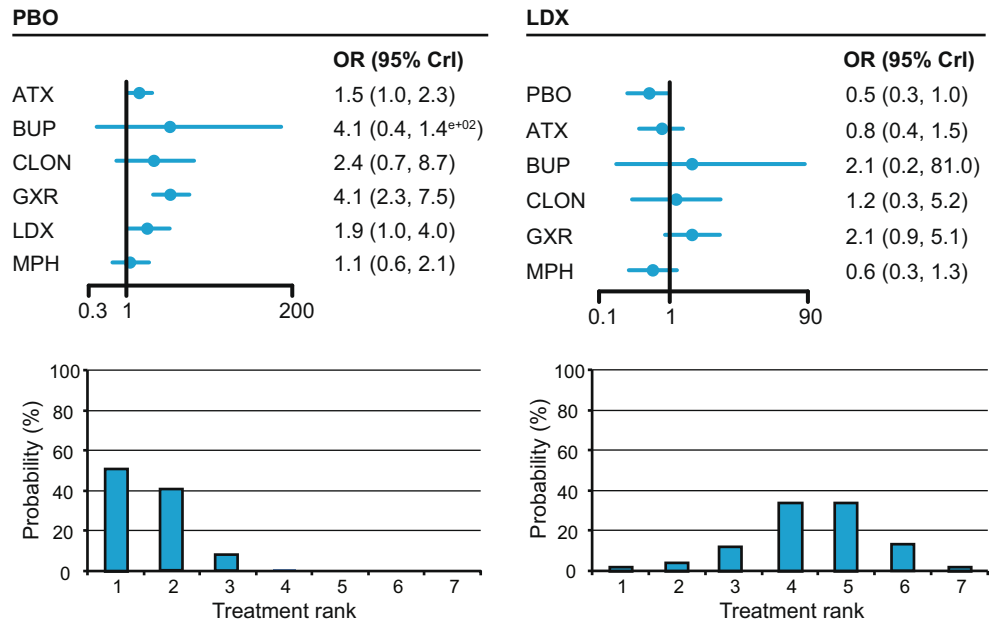
Fig. 4 Network meta-analysis on all-cause withdrawals compared with PBO or LDX

Fig. 5 Network meta-analysis on withdrawals due to adverse effect compared with PBO or LDX

further confirm the relatively high performance of MPH in treating ADHD [3]. All in all, results from our study are greatly consistent with those concluded before.

As demonstrated in the results, traditional meta-analysis, which only facilitates direct comparisons based on clinical trials, has huge limitations. In our results, limited by sample size, we did not acquire significant results on the efficacy and safety variables of BUP in treating ADHD in pair-wise meta-analysis; whereas in network meta-analysis, which combined direct evidence and indirect evidence, we observed that BUP had a higher rank than the placebo using CPRS, all-cause withdrawals, as well as withdrawals due to lack of efficacy.

Moreover, using network meta-analysis, we were able to make comparisons between different drugs via indirect evidence.

In previous guidelines for ADHD [1], stimulant medications, selective norepinephrine-reuptake inhibitor and selective α_2-adrenergic agonists were shown to have high efficacy in reducing symptoms. In this study, drugs from all the three categories were covered in the analysis concerning efficacy and safety. Of the six drugs involved in this study, ATX and BUP are a selective norepinephrine-reuptake inhibitor; CLON and GXR are selective α_2-adrenergic agonists; LDX and MPH are stimulants.

From the results, we observed that the efficacy of selective norepinephrine-reuptake inhibitors ATX and BUP might not be

Fig. 6 Network meta-analysis on withdrawals due to lack of efficacy compared with PBO or LDX
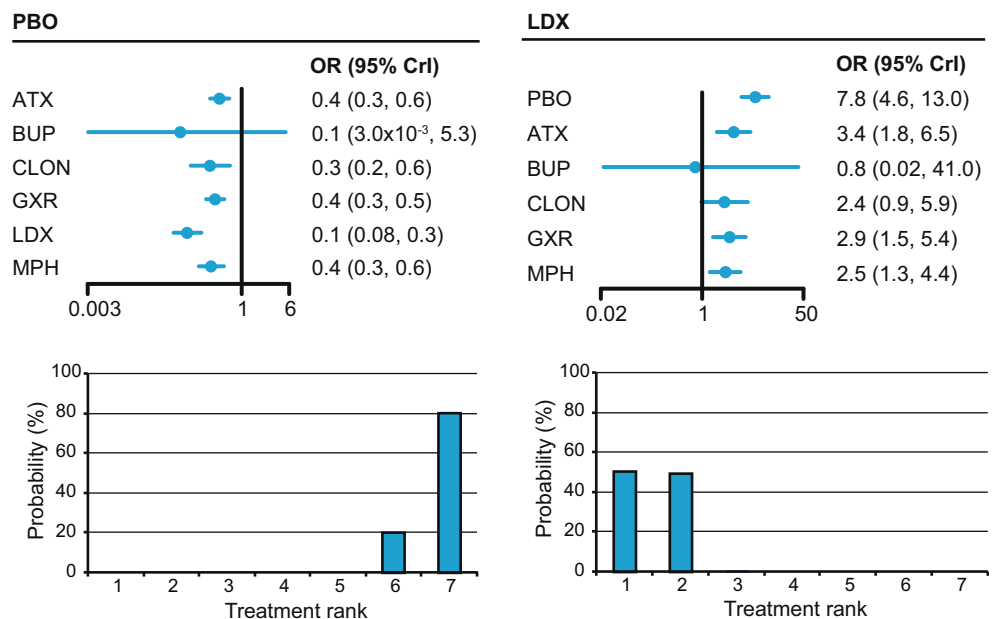
as high as other medications. As reported previously by the Texas Children's Medication Algorithm Project, BUP was listed as a fourth-line medication for ADHD after initial attempts to use two stimulants and then ATX [73]. Concerning the adverse effects, the application of BUP was found to be related to increased risk of epileptic seizures [74]. In regards to ATX, the most common adverse effects were nausea, xerostomia, appetite loss, insomnia, fatigue, headache and coughs. Due to its strong effect on the cardiovascular system, the application of ATX is not allowed on patients with symptomatic cardiovascular disease. Conversely, a significant advantage of ATX over α_2-adrenergic agonists is that the use of ATX can be stopped abruptly without causing significant withdrawal effects. CLON and GXR were primarily used as medications for hypertension. Although they were also proven to be effective for ADHD patients, being used for such treatment gave rise to common adverse effects such as hypotension, dizziness, somnolence, xerostomia and fatigue. Stimulant medications, including LDX and MPH were observed to have the highest efficacy and safety in our analysis. The most common adverse effects of these stimulant medications are appetite loss, abdominal pain, headaches, and sleep disturbance. Despite the positive outcomes for LDX and MPH, it is nonetheless important to note their potential to cause drug dependence and withdrawal symptoms. It is reported that 87.6 % of chronic, high-dose users had withdrawal symptoms including anxiety, drug craving, depressed mood, fatigue, increased appetite and dizziness during the first week of drug withdrawal [75].Some drawbacks in our NMA should be mentioned. Although our NMA included 62 publications and studies, not all outcomes in this NMA can form a network, which decreases the credibility of these comparisons. Besides, although several reviews reviewed the RS application, studies related to sensitivity, specificity and diagnose OR analysis are limited. Therefore, ongoing researches are encouraged to overcome these limitations.

Admittedly, there are still some notable flaws lying in our study. For example, the criteria to measure the severity of ADHD: ADHD-RS is reported to be bias in some cases because the parents or teachers may sometimes go subjective and ignore the concrete context of the symptoms when giving rates. Still, the amount of the data concerning ATX unexpectedly outnumbered others and thus may have a chance to cause inaccuracy in our study. Moreover, the dose of MPH involved in our study ranged significantly from 0.52 mg/d to 54 mg/d, the effect of which is believed to be related with the reliability of our results.

In summary, in this NMA we investigated the efficacy and safety of drugs used for ADHD treatment. According to the results, LDX, MPH, CLON and GXR have a high efficacy when ADHD-RS and CPRS were applied as variables, among which LDX has the highest efficacy together with safety ranking the fourth place and MPH is the second safest treatment with efficacy ranking the forth. Still, the high incidence of withdrawals should be taken in to consideration when BUP, CLON, GXR and LDX are used on ADHD patients.

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