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Quality of evidence of anti-obesity pharmacotherapy: an overview of systematic reviews

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ABSTRACT

The safety and effectiveness of main anti-obesity drugs are controversial, and there is no consensus among regulatory agencies regarding anti-obesity drugs. We undertook an overview of systematic reviews (SR) of randomized controlled trials (RCT) to summarize the quality of evidence related to anti-obesity drugs. Data sources included Medline, Scopus, The Cochrane Library and PROSPERO. Twenty-one SR (564 RCT; average of 2,356 participants per review) satisfied the inclusion criteria. Ten SR presented a high level of heterogeneity, and only five SR included sensitivity analyses. The most important limitations reported by the SR were a high level of attrition, a small sample size, and a short follow-up. Eight different outcomes for efficacy were used, 15 different outcomes for biomarkers were used, and nine different outcomes for safety were used. Conclusions: In conclusion, the quality of SR pertaining to anti-obesity drugs is low, and these reviews have a high level of heterogeneity. Future SR should present more detailed population inclusion criteria, larger sample sizes, and focus variables reported in a predefined anti-obesity core outcome set.

Keywords: Obesity. Weight loss. Treatment Outcome. Evidence-Based Practice.

INTRODUCTION

In 2014, about 39% of adults were overweight or obese, conditions that increase their risk of experiencing associated comorbidities such as type 2 diabetes, hypertension, coronary artery disease, and a higher mortality rate (World Health Organization, 2014). Prevention effects and the initial treatment stages for overweight and obesity individuals largely focus on lifestyle modifications. If required, treatment can move to pharmacologic or even surgical options (Jensen et al., 2014).

Pharmacological treatment of obesity has been available since the 1950s. However, after 70 years of research, the role of pharmacotherapy in obesity is still under debate, not only in scientific environments but also in the political sphere. The safety and effectiveness of main anti-obesity drugs are controversial, and there is no consensus among regulatory agencies regarding anti-obesity drugs. Some drugs, widely accepted as safe in the past, have been withdrawn from the market due to increases in the incidence of psychiatric adverse events (i.e., rimonabant) and cardiac adverse events (i.e., sibutramine) (Kang & Park, 2012). More recently, evidence describing the addiction potential of some drugs such as sibutramine, fenfluramine, and anorectics agents has been reported (Li & Cheung, 2011).

The global market of anti-obesity drugs is predicted to grow between 2014 and 2019 at an annual rate of 39.45% (ReportsnReports, 2014). Considering the lack of drugs to ensure weight loss that is both safe and effective (more than 5% weight loss within six months) and also the potential market revenue, drugs with different uses, such as canaglifozin and exenatide, are being promoted as off-label alternatives for the management of obesity (Sauer et al., 2015).

When comparing the current regulatory status of anti-obesity drugs among major drug agencies, namely the U. S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA), a number of discrepancies exist. While the EMA approved only naltrexone + bupropion, orlistat, and liraglutide, the FDA authorized, in addition to these three drugs, six others: diethylpropion, benzphetamine, phendimetrazine, phentermine, phentermine + topiramate, and lorcaserin (Bray & Ryan, 2014). A plausible explanation for the different authorization practices between these two agencies may be associated with a different interpretation of the low quality of primary and secondary studies published.

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Although differences between the FDA and EMA regarding authorization process exist, both agencies are heavily dependent of the quality of randomized controlled trials (RCTs) (Eriksson et al., 2014; Tafuri et al., 2014). Attrition, small sample sizes, low methodological quality, and a high level of heterogeneity in meta-analyses are the most common limitations of regulatory drug information sources (Arterburn et al., 2004; Chilton et al., 2014; Fabricatore et al., 2009). Fabricatore et al. (Fabricatore et al., 2009), in a systematic review (SR) including 24 RCTs, identified high dropout rates (34.9%, 28.6%, 28.3%, and 35.1% in the placebo, orlistat, sibutramine, and rimonabant groups, respectively; $p < .0001$), with adverse event non-related dropout (e.g., lost to follow-up, withdrawn consent) as the greater contributor to total attrition. Arterburn et al. (2004), in an SR including 29 RCTs, identified only one trial enrolled more than 1000 patients; only one of the included trials conducted a superior form of regression imputation for missing results. Chilton et al. (2014) identified heterogeneity in most meta-analyses; the authors suggest that the high heterogeneity in the meta-analyses resulted from a wide range of methodological qualities of the studies included in the meta-analysis.

The present overview of SRs aims to summarize the quality of evidence in anti-obesity pharmacological treatments.

METHODS

We performed an SR of SRs, also called an overview of SRs, following recommendations and guidelines (Haber et al., 2015; Higgins & Green, 2011; Moher et al., 2009). Systematic reviews that included RCTs using placebo, diet, physical activity, or an active drug as a comparator and assessing the efficacy or safety of anti-obesity drugs, regardless of the follow-up time, were eligible for inclusion in this overview. In addition, the primary studies included in these SRs had to report at least one of the following outcomes: alterations associated with weight (body weight, percentage of weight loss compared with baseline weight, body mass index, waist circumference), morbidity, biomarkers (e.g., systemic arterial pressure, lipid or glycolic profile), adverse events, or tolerability. Additionally, the population should comprise overweight or obese children, adolescents, adults, or elderly individuals, with or without comorbidities.

We carried out searches in the databases Medline (via Pubmed), SCOPUS, The Cochrane Library, and PROSPERO were carried out to identify SRs published from March 2004 until July 2015. The search terms included "systematic review," "meta-analysis", "obesity", "obese", "overweight", "drug therapy", "anti-obesity agents", and "drugs" (Table 1). In addition, we performed a manual search of the references of the included studies. Two independent reviewers (BSR and RCL) conducted the search and study selection. Any disagreements were settled by a third researcher (CJC). Only studies published in English, Portuguese, or Spanish were included. To identify SRs and differentiate them from narrative reviews, the key characteristics described in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green, 2011) were used: (I) a clearly stated objective with predefined eligibility criteria; (II) an explicit, reproducible methodology; (III) a systematic search attempting to identify all the studies of interest; (IV) an assessment of the validity of the findings; and (V) data synthesis of the included studies.

Metadata extracted from each study included the SR characteristics related to the date of the search, the inclusion criteria for primary sources, the number of included studies and participants, the pharmacologic interventions assessed, and the follow-up period. In addition, results reporting efficacy, safety, and the findings of secondary outcomes related to therapy, as well as tools for assessing risk of bias, summary of quality of evidence, and reported limitations were also collected.

We evaluated the methodological quality of the included SRs using the Revised Assessment of Multiple Systematic Reviews (R-AMSTAR) (Kung et al., 2010). Meta-analyses with I^2 greater than 50% or Q (chi-square) with a p-value less than 0.05 were considered to present a high level of heterogeneity. We conducted a qualitative synthesis of the results considering characteristics and quality of the SRs.

RESULTS

Our literature search identified 1,365 articles in the databases after deleting duplicated records; 2 additional studies were collected from our manual search. We decided that a total of 1,289 articles were not relevant during the screening of title and abstracts. We accessed the full text of 78 SRs, and we excluded 55 SRs due to the various exclusion criteria (Figure 1). Three included articles, Chilton et al. (2014), Gray et al. (2012), and Ara et al. (2012), are reports of the same search. Therefore, we included 23 articles comprising 22 SRs. All of the SRs presented direct comparison meta-analyses, and two of them also carried out mixed-treatment comparisons (network meta-analyses). The majority of SRs (60.9%) were published between 2010 and 2014.

Table 1. Search strategies.

PubMed
((systematic[sb] OR meta-analysis[pt]) AND (obesity[tiab] OR obese[tiab] OR overweight[tiab]) AND ("drug therapy"[mh] OR "anti-obesity agents"[mh] OR drug[tiab])) AND ("2004/03"[Date - Publication]: "2015/06"[Date - Publication])
SCOPUS
TITLE-ABS-KEY (("systematic review" OR "meta-analysis") AND (obese OR obesity OR overweight) AND (drug OR pharmacotherapy OR "anti-obesity agent")) AND DOCTYPE (re) AND PUBYEAR > 2003
The Cochrane Library
(("systematic review" OR "meta-analysis" OR metanalysis) AND (obese OR obesity OR overweight) AND (drug OR pharmacotherapy OR "anti-obesity agent" OR "antiobesity agent")):ti,ab,kw

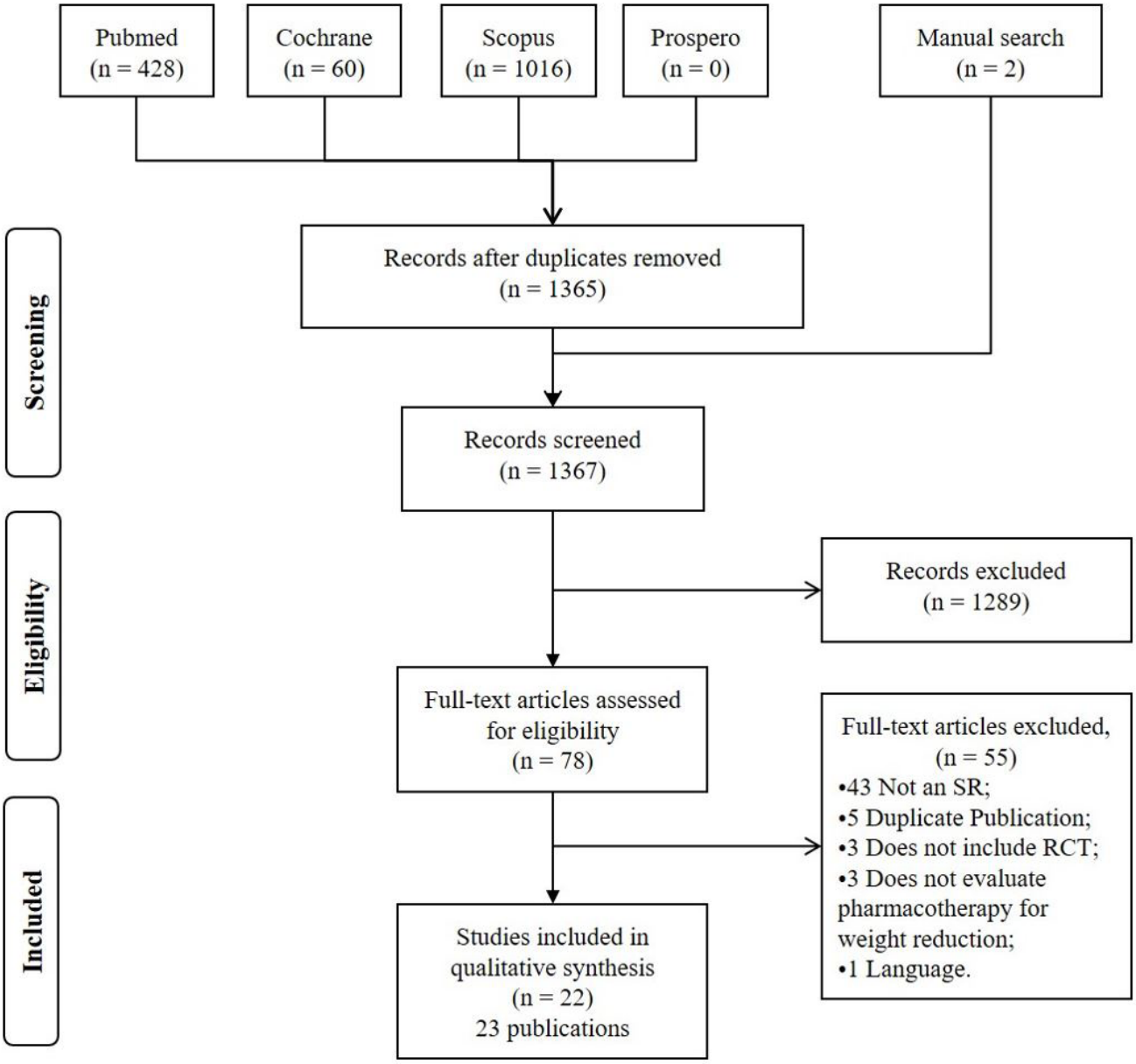

Figure 1. PRISMA flow chart.
SR: systematic review; RCT: randomized controlled trial.

The 23 included articles (22 SRs) comprised 564 RCTs (median of 14 RCTs per study; IQR = 6–37); only 14 reviews reported the total included population, with 73,229 individuals in 294 RCTs (median of 2,356 individuals per RCT; IQR = 688–1263). The follow-up period varied from 1–60 months.

Of the 21 SRs, 18 included adults, 5 included children or adolescents, and 18 included participants with other comorbidities, namely: type 2 diabetes mellitus (n=1), eating disorders (n=1), hypertension (n=1), fatty liver disorder (n=1), asthma (n=1) and comorbidities not specifically identified (n=12).

We collected data pertaining to efficacy, biomarkers, and safety for orlistat (n=13), sibutramine (n=12), rimonabant (n=7), metformin (n=3), lorcaserin (n=1), fluoxetine (n=1), exenatide (n=1), liraglutide (n=1), topiramate (n=1), and zonisamide (n=1). The quality of all of these SRs is not associated with the drug; the high R-AMSTAR scores range from 29 in a zonisamide SR to 40 in an orlistat, rimonabant, and sibutramine SR. Furthermore, no differences in publication dates existed among the SRs. The geographical origin of the SRs was mainly the United Kingdom (n=5).

All of the included SRs reported outcomes about efficacy, namely, the weight difference from baseline (n=17), the body mass index difference from baseline (n=10), waist circumference (n=9), the number of patients losing ≥ 10% of their body weight (n=5), the number of patients losing ≥ 5% of their body weight (n=4), the weight-loss percentage (n=2), the number of patients losing ≥ 5% of their body mass index (n=1), and the number of patients losing ≥10%

of their body mass index (n=1). Fourteen SRs also reported biomarkers; the most common were systolic and blood pressure (n=11), total cholesterol (n=11), LDL cholesterol (n=10), triglycerides (n=10), HDL cholesterol (n=9), fasting glucose (n=7), glycosylated hemoglobin (n=6), pulse rate (n=5), and serum insulin (n=2). Safety and tolerability were assessed in 12 SRs, including a high risk of experiencing any adverse event (n=6), the relative risk of withdrawal due to adverse events (n=4), the odds ratio of withdrawal due to adverse events (n=3), the risk difference of withdrawal due to adverse events (n=2), the odds ratio of any adverse events (n=2), the odds ratio of serious adverse events (n=2), the relative risk of serious adverse events (n=2), the risk difference of any adverse events (n=2), and the risk difference of serious adverse events (n=1).

The most frequently evaluated anti-obesity drug for adults was orlistat; sibutramine and rimonabant, which have been withdrawn in many countries, were also very frequently studied. All of these drugs resulted in weight loss for all of the groups of patients identified, with a peak response after six months of treatment. Other anti-obesity drugs that were frequently evaluated included rimonabant and lorcaserin. No SR reported that rimonabant was withdrawn from the market due to psychiatric concerns, such as suicidal tendencies. Other drugs used as off-label were also included in the SRs (e.g., topiramate, fluoxetine, exenatide and metformin), and these drugs presented different efficacy and safety profiles. Sibutramine and metformin were reported in the SRs focusing on children and adolescents. However, the sibutramine studies were characterized by a high withdrawal rate due to adverse effects, and metformin was associated with a high incidence of gastrointestinal events that also resulted in withdrawals.

We measured the methodological quality of the SRs using R-AMSTAR (Kung et al., 2010) score, which varied from 29–40 (mean: 35) (Table 2). No association between quality score and year of publication, country, number of

Table 2. Characteristics of the systematic reviews included in overview.

Author, year	Country	Date of search	No. studies included (No. patients)	Types of participants	Interventions	Follow-up	R-AMSTAR
Adeniyi & Young (2012)	South Africa	Up to Mar 2012	4 (197)	Adults, obese or overweight, with asthma	Sibutramine and orlistat	6-months	40
Ara et al. (2012) Gray et al. (2012)	UK	Up to Jan 2009	94 (24,808)	Adults, obese or overweight, with or without co-morbidities	Orlistat (360 mg), sibutramine (10 mg and 15 mg) and rimonabant (20 mg)	3, 6 and 12-months	33
Arterburn et al. (2004)	USA	Up to Apr 2002	29 (3,913)	Adults, obese or overweight, with or without co-morbidities	Sibutramine (10-15 mg)	3 and 12-months	37
Avenell et al. (2004)	UK	Up to Apr 2003	84 (NR)	Adults, obese or overweight, with or without co-morbidities	Orlistat (360 mg) and sibutramine (10-15 mg)	12, 15, 18 and 24-months	32
Bouza et al. (2012)	Spain	Up to Jun 2011	9 (498)	Adults, obese or overweight, with or without co-morbidities	Metformin (1000-2000 mg)	2 to 6-months	39
Chan et al. (2013)	Hong Kong/ China	1946 to 2012	5 (NR)	Adults, obese or overweight, with or without co-morbidities	Lorcaserin (10 mg)	6, 8 and 12-months	32
Chilton et al. (2014)	UK	Up to Jun 2012	39 (NR)	Adults, obese or overweight, with or without co-morbidities	Orlistat (360 mg), sibutramine, rimonabant and metformin	3, 6 and 12-months	31
Christensen (2007)	Denmark	Up to Nov 2006	4 (4,105)	Adults, obese or overweight, with or without co-morbidities	Rimonabant (20 mg)	12 to 24-months	37
Curioni & André (2006)	Brazil	Up to Jun 2006	4 (NR)	Adults, obese or overweight, with or without co-morbidities	Rimonabant (5 and 20 mg)	12 and 24-months	39
Czernichow et al. (2010)	Australia	Up to Aug 2008	8 (1,391)	Adolescent or children, obese or overweight, without co-morbidities	Sibutramine (5-15 mg) and orlistat (360 mg)	5 to 15-months	33
Hiremath (2012)	India	Up to Oct 2011	3 (111)	Adults, obese or overweight, with binge eating disorder	Zonisamide (25-600 mg)	3 to 12-months	29
Hutton & Fergusson (2004)	Canada	Up to Jan 2004	28 (NR)	Adults, obese or overweight, with or without co-morbidities	Orlistat (360 mg)	12-months	30
Kramer et al. (2011)	Brazil	Up to Apr 2010	10 (3,320)	Adults, obese or overweight, with or without co-morbidities	Topiramate (96-200 mg)	16 to 60-weeks	35

NR: not reported.

Table 2. Continued...

Author, year	Country	Date of search	No. studies included (No. patients)	Types of participants	Interventions	Follow-up	R-AMSTAR
Oude Luttikhuis et al. (2009)	Netherlands	Up to May 2008	64 (5,230)	Adolescent or children, obese or overweight, without co-morbidities	Orlistat (360 mg), metformin, sibutramine and rimonabant	6 and 12-months	36
Norris et al. (2005)	USA	Up to May 2004	64 (NR)	Adults, obese or overweight, with T2DM	Fluoxetine (60 mg), orlistat (360 mg) and sibutramine (5-15 mg)	8 to 57-weeks	37
Osei-Assibey (2011)	UK	Up to Jun 2010	18 (1,275)	Adults, obese or overweight, with or without co-morbidities	Sibutramine (15-20 mg) and orlistat (360 mg)	≥ 6-months	33
Padwal et al. (2009)	Canada	Up to Dec 2006	30 (19,619)	Adults, obese or overweight, with or without co-morbidities	Orlistat (360 mg), rimonabant (5-20 mg) and sibutramine (10-20 mg)	12 to 48-months	40
Peirson et al. (2014)	Canada	2005 to Apr 2013	68 (NR)	Adults, obese or overweight, with or without co-morbidities	Metformin (500-1500 mg) and orlistat (360 mg)	12 to 52-weeks	30
Peng et al. (2011)	China	Up to Feb 2011	7 (373)	Adults, adolescents and children, obese or overweight with fatty liver disease	Orlistat (360 mg)	1 to 12-months	39
Siebenhofer et al. (2013)	Germany	Up to Aug 2012	8 (3,751)	Adults, obese, or overweight, with hypertension	Orlistat (360 mg) and sibutramine (10-20 mg)	6 to 48-months	37
Vilsboll et al. (2012)	Denmark	Up to May 2011	25 (NR)	Adults, obese or overweight, with T2DM/ Adults, obese or overweight, without T2DM	Exenatide: 10-20 μg/day; Liraglutide: 1.2-1.8 mg/day)	≥ 20-weeks	37
Viner et al. (2010)	UK	Up to Jul 2008	6 (1,259)	Adolescent or children, obese or overweight, without co-morbidities	Orlistat, sibutramine and rimonabant	6 to 15-months	34

NR: not reported.

included studies and participants, risk of bias assessment method, drug evaluated, follow-up duration, or outcomes was identified.

The Cochrane tool for risk of bias (n=7) and Jadad (n=8) were the most commonly used instruments in the SRs, followed by the Verhagen Delphi list (n=2), GRADE (n=2), and several *ad hoc* adaptations of these tools (n=6). Three SRs (Adeniyi & Young, 2012; Norris et al., 2005; Peirson et al., 2014) used two different tools concomitantly (Table 3). In those SRs using the Cochrane risk of bias instrument, the domains that were more poorly reported were 'professional blinding' (n=5) and 'investigator blinding' (n=4); while 'blinding of participants' was reported by all of the SRs. Blinding of outcome assessment (detection bias), incomplete outcome data (attrition bias), and selective reporting of outcomes (report bias) were the domains more frequently associated with a low risk of bias. Domains of generation of the allocation sequence and concealment of the allocation sequence (selection bias) were more frequently considered to be unclear in terms of risk of bias. Domains of blinding of participants (performance bias), blinding of health professionals (performance bias), and other sources of bias appeared more frequently to be associated with a high risk of bias (Table 3).

Among the studies using the Jadad assessment tool, three did not report individual results of each primary study. Of the five SRs reporting individual scores, the majority of primary studies presented randomization, participant blinding, and flow of participants; however, the methodology of randomization and/ or blinding was poorly described or nonexistent (Table 3). GRADE was used in parallel with the Cochrane risk of bias assessment tool in two studies, indicating a low-to-moderate strength of evidence, substantiating the findings of the Cochrane instrument (Table 3). The two SRs that used the Verhagen Delphi list reported high methodological quality for the majority of primary studies included.

Two SRs did not conduct any meta-analysis (Adeniyi & Young, 2012; Peng et al., 2011). Ten SRs presented a high level of heterogeneity (Ara et al., 2012; Arterburn et al., 2004; Avenell et al., 2004; Bouza et al., 2012; Czernichow et al., 2010; Kramer et al., 2011; Oude Luttikhuis et al., 2009; Norris et al., 2004; Peirson et al., 2014; Siebenhofer et al., 2013), one SR stated that it assessed the heterogeneity without reporting it (Hutton & Fergusson, 2004) and two other SRs described the presence of heterogeneity without providing any I^2 statistics (Chilton et al., 2014; Vilsboll et al., 2012). Only seven SRs performed sensitivity analyses to identify potential causes of heterogeneity (Ara et al., 2012; Chan et al., 2013; Chilton et al., 2014; Curioni & André, 2006; Czernichow et al., 2010; Gray et al., 2012; Padwal et al., 2009).

The most relevant limitations reported by the SRs included a lack of long-term follow-up (n=12), a lack of studies assessing specific populations such as children,

Table 3. Quality assessment of randomized controlled trials included in the systematic reviews.

Author, year	Tool	Quality assessment of randomized controlled trials
Adeniyi & Young (2012)	Cochrane 2011 (Higgins & Green, 2011)	- Allocation sequence generation: 4 unclear risk; - Concealment of allocation: 4 unclear risk; - Blinding of participants and investigators: 4 high risk; - Incomplete outcome data: 2 unclear risk; 1 low risk; 1 high risk; - Selective outcome reporting: 2 low risk; 2 unclear risk; - Other sources of bias: 2 low risk; 2 unclear risk.
Ara et al. (2012), Gray et al. (2012)	Jadad (1996)	- Randomization: 0 = none, 1 = mentioned (56), 2 = described and adequate (38) - Allocation concealment: 0 = none (72), 1 = yes (22) - Double blinding: 0 = none (28), 1 = mentioned (47), 2 = described and adequate (19) - Flow of participants: 0 = none (18), 1 = mentioned (36), 2 = described and adequate (40)
Arterburn et al. (2004)	Jadad (1996)	- High score: 23; low score: 6.
Avenell et al. (2004)	Self-made	- Quality of random allocation concealment: 12 A; 68 B(I); 3 B(II); 1 C. - Description of withdrawals and dropouts: 43 A; 39 B(I); 1 B(II); 1 C. - Intention to treat: 24 A; 18 B; 42 C; - Participants blinded to treatment status? 5 A(II); 62 C. - Healthcare providers blinded to treatment status? 7 A(I); 4 A(II); 10 B(II); 63 C; - Outcome assessors blinded to treatment status? 8 A(I); 2 A(II); 27 B(I); 47 C.
Bouza et al. (2012)	Cochrane 2009 (Higgins & Green, 2009)	- Concealment in allocation to treatment: 2 NR; 7 adequate; - Adequate randomization: 2 NR; 6 yes; 1 not clear; - Blinding: 8 yes; 1 doubtful; - Reasons for withdrawal: 3 NR; 6 reported; - Incomplete data: 3 yes; 6 no; - Free of other biases: 8 yes; 1 doubtful. Risk of bias: 4 low; 5 moderate.
Chan et al. (2013)	Jadad (1996)	- Randomization: 0 = none (0), 1 = mentioned (4), 2 = described and adequate (1); - Blinding: 0 = none (0), 1 = mentioned (2), 2 = described and adequate (3); - Fate of all patients: 1 = mentioned (5); - ITT analysis: yes (4); no (1).
Chilton et al. (2014)	Jadad (1996)	- Randomization: 0 = none, 1 = mentioned (21), 2 = described and adequate (18); - Allocation concealment: 0 = none (26), 1 = yes (13); - Double blinding: 0 = none (17), 1 = mentioned (13), 2 = described and adequate (9); - Flow of participants: 0 = none (4), 1 = mentioned (9), 2 = described and adequate (26).
Christensen (2007)	Jadad (1996)	- All the four, score 5 (high quality).
Curioni & André (2006)	Self-made	- Randomized controlled clinical trial: 4 yes; - Method of randomization: 2 unclear; 2 yes; - Concealment of allocation: 4 double blind; - Stated blinding: 4 unclear; - Drop-outs described: 4 yes; - Withdrawals described: 4 yes.
Czernichow et al. (2010)	Self-made	- Randomization: 8 yes; - Double-blinding: 6 yes; 2 not recorded in the paper; - ITT analysis: 5 yes; 2 not recorded in the paper; 1 no.
Hiremath (2012)	Self-made	- Randomization: none (2); mentioned (1); - Blinding: none (1), mentioned (2); - Follow-up: mentioned (3)
Hutton & Fergusson (2004)	Jadad (1996)	- High quality (x±SD: 3.25±0.70). 2 studies low quality; 26 studies high quality.
Kramer et al. (2011)	Self-made	- Concealment of randomization: all the 10 yes; - Stopped early: 2 yes; 8 no; - Patients blinded: 10 yes; - Health care providers blinded: 10 yes; - Data collectors blinded: 10 yes; - Outcome assessors blinded: 10 yes.
Oude Luttikhuis et al. (2009)	Cochrane (2008) (version 5.0.0)	- Allocation: 22 concealed; 39 unclear; 3 not concealed; - Blinding: 7 not blinded; 50 unclear; 7 blinded; - Incomplete outcome data: no participants were lost to follow-up (1); drop-out rates: 0 to 42% (6 and 9-m) and 12 to 52% (12-m); ITT analysis: 24 yes; 40 no; - Other potential sources of bias: Power calculation, sample size, baseline differences study arms, contamination, studies before 2005, without registration number, conflict of interest.
Norris et al. (2005)	Cochrane 2003 (Anderson, Green & Higgins, 2004)	- Blinding: 49 double-blind; 10 NA; 5 NR; 1 no; 1 open-label; - Blinding patient: 2 no; 2 yes; 60 NA or NR; - Blinding assess: 53 unclear; 8 no; 3 yes; - Blinding provider: 1 not reported; 2 unclear; 1 no; 60 NA or NR; - Baseline comparable: 28 not reported; 23 yes; 10 NA; 3 unclear; 1 similar; 1 no; ***Jadad*** (16 de 64 não foram avaliados segundo Jadad) - Randomization: 0 = none (2), 1 = mentioned (42), 2 = described and adequate (4) - Blinding: 0 = none (3), 1 = mentioned (43), 2 = described and adequate (2). - Fate of all patients: 0 = none (23); 1 = mentioned (25).

Table 3. Continued...

Author, year	Tool	Quality assessment of randomized controlled trials
Osei-Assibey (2011)	Verhagen Delphi list	- Randomization adequate: 1 unreported; 3 no; 14 yes; - Allocation concealment: 4 no; 14 yes; - Baseline similarity: 4 no; 2 unreported; 12 yes; - Eligibility criteria specified: all yes; - Patient blinded: 4 no; 14 yes; - Care provider blinded: 4 no; 14 yes; - Outcome assessor blinded: 3 no; 15 yes; - Point and measures of variability for the primary outcome: 1 no; 17 yes; - ITT analysis: 2 no; 3 unreported; 13 yes.
Padwal et al. (2009)	Verhagen Delphi list	- Randomization adequate: 17 unreported; 1 no; 12 yes; - Allocation concealment: 19 unreported; 1 no; 10 yes; - Baseline similarity: 5 unreported; 25 yes; - Eligibility criteria specified: all yes; - Patient blinded: all yes; - Care provider blinded: all yes; - Outcome assessor blinded: all unreported; - Primary outcome reported: 2 no; 28 yes; - ITT analysis: 27 no; 3 yes.
Peirson et al. (2014)	Cochrane 2011 (Higgins & Green, 2011)	- Sequence generation: unclear (35); low risk (30); high risk (1); - Allocation concealment: unclear (50); low risk (15); high risk (1); - Blinding of participants/ personnel: unclear (26); low risk (4); high risk (36); - Blinding of outcome assessors (objective): unclear (0); low risk (49); high risk (0); NA (17); - Blinding of outcome assessor (subjective): unclear (41); low risk (15); high risk (3); NA (7); - Blinding of outcome assessor (self-reported): unclear (21); low risk (9); high risk (6); NA (30); - Incomplete reporting (objective): unclear (1); low risk (35); high risk (13); NA (17); - Incomplete reporting (subjective): unclear (2); low risk (39); high risk (18); NA (7); - Incomplete reporting (self-reported): unclear (1); low risk (22); high risk (13); NA (30); - Selective reporting: unclear (5); low risk (56); high risk (5); - Other bias: unclear (4); low risk (29); high risk (33).
Peng et al. (2011)	Cochrane 2011 (Higgins & Green, 2011)	- Sequence generation: 5 unclear; 2 low; - Allocation concealment:6 unclear; 1 low; - Blinding: 5 unclear; 2 low; - Incomplete outcome data: 1 high; 3 low; 3 unclear; - Selective outcome reporting: 2 unclear; 5 low - Other bias: 1 high, 1 low, 5 unclear.
Siebenhofer et al. (2013)	Cochrane 2011 (Higgins & Green, 2011)	- Random sequence generation: 4 unclear; 4 low; - Allocation concealment: 4 unclear; 4 low; - Blinding: 5 unclear; 3 low; - Incomplete outcome data: 1 unclear, 2 low, 5 high; - Selective reporting: 3 unclear; 5 high; - Other biases: 2 low, 6 high.
Vilsboll et al. (2012)	Self-made	- Randomization methods: Adequate in all trials; - Blinding: 13 double blind, with masking of both patients and investigators; none of the included trials reported the success of blinding; - Whether the primary outcome measure was defined and reported: all trials reported clinically relevant outcome measures; - Whether sample size calculations were done: all trials provided a clear description of losses to follow-up, accounted for patients with missing data in the analyses, and undertook sample size calculations - For trials terminated prematurely, whether this termination was based on predefined criteria: None of the trials were terminated prematurely.
Viner et al. (2010)	Self-made	- All studies included an ITT analysis, reported eligibility criteria, and cointerventions were similar in intervention and control arms. - High attrition rates, averaging 19% for sibutramine studies and 25% for orlistat studies; - Most studies did not describe the randomization process nor comment on allocation concealment or blinding of outcome assessors.

adolescents, participants with psychiatric disorders or metabolic or cardiac conditions (n=7), a high attrition rate (n=5), a poor description of patients' characteristics (n=4), and risk of bias (allocation, concealment, randomization, blinding, recruiting, and participant selection) (n=3), a small sample size (n=3), the absence of intention to treat analysis in primary studies (n=3), and a lack of studies assessing biomarkers (n=4), mortality (n=2), and quality of life (n=2).

DISCUSSION

Among the included SRs, we observed an overall good level of methodological quality assessed using the R-AMSTAR score. The most relevant methodological aspects missed in the SRs were a predefined protocol and a list of excluded studies fully assessed. The most common reported outcome of efficacy was the mean weight-loss difference between the intervention and control groups. We note that 5 and 10% losses of body weight were not frequently reported. It is important to highlight the clinical relevance of these cut-offs in practice, since the reduction of 5-10% relative to a baseline weight over six months of treatment is commonly accepted as a major goal of drug therapy (Jensen et al., 2014). Additionally, several studies reported the impact of drugs on systolic and diastolic blood pressure, pulse rate, fasting glucose, and LDL cholesterol. These biomarkers are extremely important for guiding the selection of drugs for patients diagnosed with comorbidities or a high likelihood of experiencing comorbidities.

Bryant et al. (Bryant et al., 2014) identified 145 different outcomes in 200 RCTs that assessed weight-management interventions in children. The vast majority of these studies presented inconsistencies and inaccuracies in the use and reporting of outcomes, which led the authors to suggest that researchers should use consensus as Core Outcome Measures in Effectiveness Trials guidelines (COMET), Consolidated Standards of Reporting Trials (CONSORT) (87), and the National Obesity Observatory Standard Evaluation Framework (NOO SEF) (88). The NOO SEF recommends that studies at least report measures of height and weight to enable body mass index calculations; studies should also evaluate the impact of interventions, with a minimum of three follow-up points within one year (88). In addition to this poor reporting in primary studies, SRs add some other limitations to the evidence-gathering process. Although many studies reported their results using the three-month follow-up, some SRs merged results from different treatment time-points into only one result (Czernichow et al., 2010; Oude Luttikhuis et al., 2009; Siebenhofer et al., 2013; Viner et al., 2010), which contradicts NOO SEF recommendations.

Despite systematic searches being well conducted in terms of methodological quality, their results should be interpreted with caution. A notable fraction of the included RCTs presented crucial limitations such as small sample sizes, and high levels of attrition. Attrition rate has being described as a major concern in primary studies of anti-obesity drugs (Fabricatore et al., 2009). Moreover, the most common method to calculate results in primary studies was the last observation carried forward, instead of intention to treat. Jorgensen et al. compared different methodologies for handling missing data in a 60-week, placebo-controlled, anti-obesity drug trial on topiramate and reported that different methods led to significant differences in weight loss: 9.5 kg in the complete case analysis (n=86), 6.8 kg using the last observation carried forward (n=561), 6.4 kg through multiple imputation (n=561), and 1.5 kg by means of the baseline carried forward (n=561) (Jørgensen et al., 2014). The authors also concluded that compared with the intention to treat, the last observation carried forward overestimated weight loss and, consequently, the baseline carried forward approach was preferable.

There are SRs with limitations not included into R-AMSTAR criteria. Although the PICOS acronym was appropriately described in all of the included studies, we observed that populations must be carefully identified to avoid high levels of heterogeneity. Unspecific data resulting from evidence gathered in from diverse populations will be of limited use to decision makers and clinicians (Jensen et al., 2014). Future SRs of studies assessing pharmacotherapy for overweight and obese patients should define a minimum sample size as an inclusion criterion and, even more importantly, clearly define the characteristics of the intervention and the control patients included. These SRs should also assess more recent drugs such as exenatide, lorcaserin, phentermine/topiramate, and older drugs still in use such as diethylpropion when considering specific types of patients. If head-to-head RCTs are not available, a mixed-treatment comparison should be considered (Kim et al., 2014).

It is important to highlight that although we included only published SRs in our analysis. Although our overview was limited to three languages, we only excluded one SR (published in Danish) on the basis of language.

Although we identified SRs about pharmacological management of overweight and obese patients with high methodological quality, we found that the results of these SRs were characterized by high levels of heterogeneity and uncertainty, which limits their use in decision-making and clinical practice. The potential causes of this heterogeneity include the low quality of the primary studies (including small sample sizes, heterogeneous populations, and high attrition rates), the lack of an obesity management core outcome set, and the use of different cut-offs and follow-up periods.

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RESUMO

Qualidade de evidência de farmacoterapia anti-obesidade: uma overview de revisões sistemáticas

A segurança e a efetividade dos principais medicamentos anti-obesidade são controversas e não há consenso entre as agências reguladoras em relação aos medicamentos

anti-obesidade. Conduzimos uma *overview* de revisões sistemáticas (RS) de ensaios clínicos randomizados (ECR) para sumarizar a qualidade da evidência relacionada aos medicamentos antiobesidade. Fontes de dados incluíram Medline, Scopus, The Cochrane Library e PROSPERO. Vinte e um RS (564 ECR, média de 2.356 participantes por revisão) preencheram os critérios de inclusão. Dez RS apresentaram alto nível de heterogeneidade, e apenas cinco RS incluíram análises de sensibilidade. As limitações mais importantes relatadas pelas RS foram alto nível de atrito, pequeno tamanho amostral e curto tempo de acompanhamento. Utilizaram-se oito resultados diferentes para eficácia, 15 resultados diferentes para biomarcadores e nove resultados diferentes para segurança. Em conclusão, a qualidade das RS é baixa e estas revisões têm um elevado nível de heterogeneidade. RS futuras devem apresentar critérios de inclusão populacionais mais detalhados, tamanhos amostrais maiores e foco em variáveis pré-definidas em *core outcome set*, ou seja, um conjunto mínimo acordado de desfechos que devem ser reportados por todos os ECR de medicamentos antiobesidade.

Palavras-chave: Obesidade. Perda de Peso. Resultado do Tratamento. Prática Clínica Baseada em Evidências.

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