Efficacy and Effectiveness of Clinical Trials Applied to the Treatment of Obesity: A Systematic Review Eficacia y Efectividad de Ensayos Clínicos Aplicados al Tratamiento de la Obesidad: Una Revisión Sistemática

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Abstract. The multidisciplinary treatment of obesity (MTO) has been recognized as the standard intervention and the basis for complementary treatments. However, it is still not clear how effective MTO programs can be and it has become more difficult to determine because normally the conditions of the intervention are not clearly stated. Therefore, it is important to make it clear if one MTO program is characterized as an efficacy trial, conducted under ideal conditions, or as an effectiveness trial developed in real-world scenarios. In this sense, this systematic review aims to explore some information from MTO studies. This systematic review made a search for potential papers using PubMed and SciELO, in which the terms efficacy or effectiveness were presented. After applying all the inclusion/exclusion criteria, four trials were included (343 participants). All the studies had characteristics of effectiveness trials. They used three different main outcomes, which made comparisons difficult. In conclusion, this review shows that a very small number of MTO studies have been published using the terminology efficacy or effectiveness. These studies do not explore the terms in a way that could make important distinctions among these distinct clinical trial models. **Keywords:** Obesity; Treatment; Efficacy; Effectiveness.

Resumen. El tratamiento multidisciplinario de la obesidad (MTO) ha sido reconocido como la intervención estándar y la base para tratamientos complementarios. Sin embargo, aún no está claro cuán efectivos pueden ser los programas MTO, y se ha vuelto más difícil determinarlo porque normalmente las condiciones de la intervención no se especifican claramente. Por lo tanto, es importante aclarar si un programa MTO se caracteriza como un ensayo de eficacia, realizado en condiciones ideales, o como un ensayo de efectividad desarrollado en escenarios del mundo real. En este sentido, esta revisión sistemática tiene como objetivo explorar cierta información de los estudios MTO. Esta revisión sistemática realizó una búsqueda de posibles documentos utilizando PubMed y SciELO, en los cuales se presentaban los términos eficacia o efectividad. Después de aplicar todos los criterios de inclusión/exclusión, se incluyeron cuatro ensayos (343 participantes). Todos los estudios tenían características de ensayos de efectividad. Utilizaron tres resultados principales diferentes, lo que dificultó las comparaciones. En conclusión, esta revisión muestra que se ha publicado un número muy pequeño de estudios MTO utilizando la terminología eficacia o efectividad. Estos estudios no exploran los términos de una manera que podría hacer distinciones importantes entre estos diferentes modelos de ensayos clínicos. **Palabras clave:** Obesidad; Tratamiento; Eficacia, Efectividad Efectividad.

Fecha recepción: 17-10-23. Fecha de aceptación: 11-01-24 Greice Westphal-Nardo

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Introduction

Obesity has been recognized as one of the main challenges to public health around the world because of all its impacts on health and well-being (Bray et al., 2017). More recently, obesity has also been recognized as a risk factor that increases the risk of complications and death from infectious diseases like COVID-19 (Madigan et al., 2022). Despite the risks associated with obesity, there are still several issues slowing down the implementation of effective responses to that critical problem (World Obesity, 2020). One of the reasons for that may be the different approaches to treating obesity with their different goals (Befort et al., 2020).

Among the variety of approaches used in the multidisciplinary treatment of obesity (MTO), we can mention the HAES (Health at every size) approach which considers behavior change as the goal and this approach has presented important results on health parameters and attendance (Bacon et al., 2002; Bacon & Aphramor, 2011). There is also the clinically significant weight loss approach which adopts a percentage of the initial body weight as a goal. This approach is based on substantial evidence that a modest weight loss like 5% is associated with significant health benefits. For that reason, this approach has been recommended by a major part of researchers in this field (Cleo et al., 2020; Wing et al., 2011). There is a more traditional approach in which the eutrophic or overweight status is the goal, and to reach that more expressive weight loss is necessary. That kind of intervention is normally characterized as efficacy trials and can be recognized in trials like the INSULA study (Do Prado et al., 2009). That kind of intervention normally requires very controlled conditions, especially related to caloric intake and energy expenditure which may require the in-patient regime during long periods and that makes it expensive and, for that reason difficult to spread out in different scenarios (Do Prado et al., 2009)

Contrasting with the condition above described the effectiveness trials take place in a less standardized and controlled situation, when there is evidence available about the efficacy of a determined model of treatment. Then the challenge is to verify if that model of intervention/treatment adapted to real-world conditions could be considered effectiveness. These studies are necessary to provide to the public health system interventions that were tested in similar conditions presented in that environment (Singal et al., 2014).

These differences between efficacy and effectiveness are well explored in a paper whose main goal was to highlight that efficacy and effectiveness studies are both important ways to evaluate interventions, but they serve distinct purposes and provide different information. There are differences related to the questions and setting of research as well as in the population studied, providers, and ways of intervention. In order to assess all these characteristics, there are different tools available (Singal et al., 2014).

The challenge represented by the obesity and associated conditions requires effective interventions available to the population. Despite the research approach/intervention adopted, according to the most recognized institutions and international organizations, the model of attention applied in the treatment of obesity should be based on behavioral interventions directed to promote lifestyle changes (Westphal-Nardo et al., 2023). These programs use strategies to increase physical activity and promote better dietary habits (Westphal et al., 2023). Normally, the guidelines define a period to check the results achieved by this approach and, if it is not successful, pharmacological aids can be added after another period of follow-up, in case the results are still not obtained, only then bariatric surgery would be an option (Wharton et al., 2020).

This stepped-care approach has a practical reason, which is the well-known beneficial and safe effects of improving dietary habits and increasing physical activity on overall health. Based on the same facts, adopting a multidisciplinary approach is considered the cornerstone of obesity management (Alkhatib, 2015).

Considering the different research approaches presented many issues related to obesity management are still to be answered, such as the intensity, duration, and length of the intervention (Jensen et al., 2014). More recently it became clear that the profile of the patients is also relevant and there is a lack of evidence about the efficacy or effectiveness of MTO among underserved populations (Katzmarzyk et al., 2020). With the same importance is the model of trial to be implemented, specifically concerning efficacy or effectiveness trials (Williams et al., 2015). More than an academic debate about lexicon, the proper use of these terms might impact the results disseminated by a study, how the results may be applied to clinical practice, and finally how the results are judged by those who seek to evaluate the evidence. Thus, the understanding of the contrast between effectiveness and efficacy has important and very practical implications for those who seek to evaluate and apply research evidence to clinical practice (Fritz & Cleland, 2003).

Reinforcing the differences in the conditions characterized by these two models of trials. Efficacy trials assess the effects of the intervention in ideal and controlled conditions. In contrast, effectiveness trials (also known as pragmatic trials) assess the degree of beneficial effect under realworld conditions (Reynolds & Spruijt-Metz, 2006; Williams et al., 2015).

For example, one can imagine an intervention planned to have absolute control over the most important variables in energy balance, i.e. energy intake and expenditure. One can then compare this ideal scenario with another one in which none of these fundamental variables are controlled over time, or in other words, they are happening normally as they behave in real-world conditions. These completely different approaches are likely to lead to important differences in weight loss outcomes. Therefore, the type of trial (efficacy vs. effectiveness) should be clearly mentioned in all the studies conducted to assess the effects promoted by them. Contrary to this logic, most of the studies do not make any clear reference to these conditions (Dal-Ré et al., 2018).

Despite these definitions, it is unclear how recognized are these terms and one important evidence of that is that two recent systematic reviews with meta-analyses were published on the efficacy and effectiveness of obesity interventions and they do not make any clear definition of the specificities of these terms (Cleo et al., 2020; Madigan et al., 2022). In fact, they don't even present this definition, and that reinforces the necessity to make that distinction clear.

Therefore, this systematic review has the purpose of exploring the characteristics of the trials that have been implemented in the treatment of obesity in which the terms "efficacy" or "effectiveness" were used in their descriptors, abstracts, or text. We sought to verify if they were considering the translational approach when they used these terms in their articles and highlighted potential ways to make that subject clearer. Our hypothesis is that efficacy trials are going to be in a smaller number but are going to show more expressive results compared to effectiveness trials, due to the conditions of the intervention.

Materials and methods

Protocol and Registration

This systematic literature review was registered in the International Prospective Register of Systematic Reviews— PROSPERO (CRD42022308530) (Westphal et al., 2022) and described according to the items suggested by the Preferred Reporting Items for Systematic Reviews and Meta-Analyses—PRISMA (Page et al., 2021).

Eligibility Criteria

Eligible studies for this review included: (i) original articles published in English, Spanish, or Portuguese; (ii) clinical trials and intervention studies; and (iii) studies with data from multidisciplinary or interdisciplinary treatment of obesity. The selection of descriptors in interdisciplinary obesity treatment studies was based on the scarcity of clinical trials of efficacy or effectiveness presented in the literature. Based on this information, studies that investigated the efficacy or effectiveness in the multidisciplinary treatment of obesity, which obtained primary outcome, intervention, and pre-and post-intervention data were included in this review. Published peer-reviewed original manuscripts were eligible for inclusion. Gray literature and conference abstracts were not included. Among the exclusion criteria, the most common reasons for it were: not presenting the terms efficacy or effectiveness in the paper, not presenting the primary outcome, missing data regarding the condition pre and post-intervention, or just presenting qualitative data gathered by questionnaires.

Information Sources

The systematic search for potential articles for this review occurred during the months of March until May 2022 using two electronic databases: PubMed and SciELO.

Search

Systematic searches were adjusted and applied to all databases based on the method developed for PubMed, combining different terms for efficacy and effectiveness in the treatment of obesity. A variety of descriptors related to each of these terms were entered into each database. The descriptors used were "Efficacy"; "Effectivity"; "Effectiveness"; "Obesity"; "Treatment". They were used in combinations and with the Boolean operators "AND" and/or "OR". Thus, these terms should be present and associated in order to be included in the research. There was no restriction on the period of publication of original articles. Manual searches were performed on the reference lists of included studies and in review articles in which the topics were similar to the one investigated in this review were analyzed.

Data Extraction and Synthesis

The procedures for searching and evaluating titles, abstracts, and full-text articles, as well as methodological quality, were completed independently by three researchers (G.W.N, B.H.M.B, and N.N.J), with guidance from a senior researcher (J.P.C), who in addition to supervising the information-gathering process, established consensus and assisted in resolving any disputes. There were selected as the more relevant variables the following information: the authors of each study, year of publication, country where the study was developed, type of study (Efficacy or Effectiveness), sample size, primary outcome, secondary outcomes, the duration of Intervention, and if they have a follow up after the intervention period.

Data Collection Process and Data Items

Descriptive and methodological information and results on the efficacy or effectiveness of obesity treatment and outcomes investigated in each study were extracted. As it was mentioned above the data collected include information about the group who conducted the research, the country where the research was conducted among other data about the main outcome and secondary outcomes.

A decision not to perform a meta-analysis was taken after the searches revealed substantial methodological and clinical heterogeneity between studies, including the different primary outcomes presented.

Quality assessment of selected studies

The methodological quality of the included studies was

independently assessed by three researchers (G.W.N, B.H.M.B, and N.N.J). For cases of disagreement between researchers, a four-researcher with experience (J.P.C) in systematic reviews was consulted through consensus meetings.

To assess the methodological quality/risk of bias, a tool proposed by the National Heart, Lung, and Blood Institute (NIH) was used for Quality Assessment of Controlled Intervention Studies. The tool's criteria include questions that could indicate a possible risk of bias regarding the description of the study, method of randomization, allocation concealed, the blindness of participants and providers, similarities between the groups on important characteristics that could affect outcomes, drop-out rates, etc (National Heart and Institute, 2014).

Each question was scored with "N", "Y", and "NA", in which "N" was applied to questions answered as this information was not provided and "Y" for those answered as yes, this information was provided. The option "NA", as not applicable, was being used when it was not possible to evaluate one of the criteria of the instrument due to the type of study. The total score was obtained by adding the score of each question answered as "Y" and "NA" (Table 1).

Table 1.		
Quality assessment	of the included	studies

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	Score Total	8	8	10	12		

Note. Y, yes; N, no; NA, not applicable 1.Gomes et al. (2018), 2. Ferrari et. al. (2017), 3. Miguel-Etayo et. al. (2015), 4. López-Padrós, et. al. (2020).

Results

Literature identification

The systematic search of the database yielded a total of 62 records. After excluding duplicates, a first screening based on titles and abstracts resulted in the selection of 29 eligible articles. Full-text articles were later obtained and evaluated according to eligibility criteria, leaving 4 articles included for full review and synthesis. Among these four studies, all of them were considered effectiveness trials assessing the effectiveness of a multidisciplinary obesity treatment. For an overview of the screening process, see Figure 1. This section may be divided by subheadings. It should provide a concise and precise description of the experimental results, their interpretation, as well as the experimental conclusions that can be drawn.





Table 2.

Year of publication, origin and sample size of selected studies 2012-2022.

Authors	Year of Publication	Countries	Efficacy or Effectiveness	Sample (n)	Primary Outcome	Secondary Outcomes	Duration of Intervention	Follow Up
Gomes et al (Gomes et al., 2018)	2018	Brazil	Effectiveness	107 adolescents (63 Girls and 44 Boys)	Body composition	Effect of Aerobic Training	12 weeks	N/A
Ferrari et al (Ferrari et al., 2017)	2017	Brazil	Effectiveness	46 adults CG (46.7 ±11.5 years) IG (46.2 ±14.1 years) 39 women 7 men	Body mass index	Waist circumference	12 weeks	N/A
Miguel-Etayo et al (De Miguel-Etayo et al., 2015)	2015	Spain	Effectiveness	156 adolescents 85 Girls (14.68 ±1.32 years) 71 Boys (14.51 ±1.07 years)	Body composition	Body mass index	2 Months and Follow Up 13 months	Yes
López-Padrós et al (López-Padrós et al., 2020)	2020	Spain	Effectiveness	34 adults (18 y 65 years) 4 women 30 men	Reduction in the apnea-hypopnea index (AHI)	Body composition	3 a 12 months	Yes

CG means Control Group and IG intervention Group.

This systematic review resulted in four studies after applying all the exclusion criteria. Among them, two were from Brazil and the other 2 were from Spain. None of these studies was classified as a pragmatic clinical trial or used a tool to classify their level of pragmatism like the PRECIS-2 developed to help the researchers to assess how pragmatic are their trials. According to these authors, the degree of pragmatism should be evaluated by the trial investigators themselves using that tool, which comprises 9 domains, each scored from 1 (very explanatory) to 5 (very pragmatic) (Dal-Ré et al., 2018). Only one of these studies has the term effectiveness in its title (López-Padrós et al., 2020) and only one study had no control group (De Miguel-Etayo et al., 2015).

The studies were published between 2015 and 2020. The number of participants ranged from 34 to 156. The two studies with adolescents had larger samples (107 and 156). While the studies with adults had the number of participants ranged from 34 and 46. The duration of the interventions ranged from 8 weeks to 24 weeks. Related to the setting where the intervention took place, only the De Miguel-Etayo et al., (De Miguel-Etayo et al., 2015), study was not conducted in a public university. The dropout rates ranged from 11.9% and 38.6%, but one study did not report the dropout rate Gomes et al., (Gomes et al., 2018). The analysis of the results was based on the per-protocol model. The only exception was the study of Lópes-Padrós et al., (López-Padrós et al., 2020), in which they used both the per protocol and intent-to-treat analyses.

With regards to the main outcomes, the two studies with adolescents have body composition as their main outcome. The studies with adults had as main outcomes the weight loss by Ferrari et al., (Ferrari et al., 2017), and the reduction in the apnea-hypopnea index (AHI) in the Lópes-Padrós et al., (López-Padrós et al., 2020) study. Regarding the follow-up of participants after the intervention, only the studies conducted in Spain have reported it.

Discussion

There is consistent evidence of one unequal distribution of obesity, diabetes, and cardiovascular disease with a higher proportion of these diseases affecting the population with the lowest socioeconomic status (Lindahl et al., 2009). That could be more clearly observed by the constatation that the greatest rise and highest numbers of obesity are now seen in low- and middle-income countries. This brings important consequences like the highest GDP loss as a result of obesity are now affecting Mexico and Brazil, with 5.3 and 5% of their GDP, respectively (World Obesity, 2020). Considering that, it is evident that real-world interventions or pragmatic clinical trials must be tested and scaled up at the population level, as they are the ones more likely to have an impact in reducing the comorbidities associated with obesity (Reynolds & Spruijt-Metz, 2006; Sussman et al., 2006).

As one piece of evidence of that, two large randomized clinical trials conducted in developed countries such as Finland and the USA, the Finnish Diabetes Prevention Study (DPS) and the American Diabetes Prevention Program (DPP), respectively, have clearly demonstrated that lifestyle intervention can reduce the progression of impaired glucose tolerance and type 2 diabetes in people with overweight or obesity (Jensen et al., 2014).

However, there is a lack of robust studies that examine the multicomponent program outcomes in the treatment of obesity. This systematic review made it clear that efficacy clinical trials are clearly missing and that represents a very important limitation when trying to understand the impact of this specific approach. On the other hand, studies addressing the effectiveness of those programs are still very limited regarding the number of participants, duration, and intensity of the intervention.

The variety of main outcomes in MTO has also made it difficult to compare studies and to present targets to be reached in ideal conditions trials, like efficacy trials, or even in the effectiveness or real-world clinical trials. That is fundamental to translating the findings from the labs to the public health programs.

Some more information about the translation of findings to the health professionals is necessary to better understand the low progress in the fight against obesity. As Sussman et al., (Sussman et al., 2006), affirmed, currently, it may take as long as one or two decades for original research to be translated into routine medical practice. Normally, the evidence found in basic research is translated to other applications until it is implemented in real-world scenarios when the effectiveness trials will confirm their utility. Before that level, there are the interventions conducted under ideal conditions, or efficacy clinical trials, to assess if the intervention works. And only when the efficacy is confirmed, the effectiveness is tested and then the dissemination trials can be done, as the final phase of investigation in a 5 phases model employed to improve the translational process in health sciences.

Health policies should be based on evidence from both efficacy and effectiveness clinical trials. However, it is not the norm. Instead of that, there are so many different intervention programs that assess different primary outcomes, which makes it difficult to establish their efficacy or effectiveness.

If the model of 5 phases of research mentioned by Sussman et al., (Sussman et al., 2006), and also by Reynold &

Spruijt-Metz (Reynolds & Spruijt-Metz, 2006), was used tar-gets could be selected for different phases with cut-off points or targets for the primary outcomes for different populations. This would allow the healthcare system to evolve with a logic that would result in more effective intervention programs. Every aspect of the intervention would be considered, thus, comparations would be more equitable.

Within this logic, the results promoted by a program directed to soccer or hockey fans on their weight loss and lifestyle improvements could be interesting and relevant for the healthcare system and could be compared to more traditional intervention programs delivered by the healthcare system (Blunt et al., 2017; Bunn et al., 2018). These are some examples of pragmatic clinical trials delivered in very real-life conditions where they can reach out to people who are more difficult to get in traditional randomized clinical trials as the Finnish Diabetes Prevention Study (DPS) and the American Diabetes Prevention Pro-gram developed in Finland and USA, respectively (Jensen et al., 2014).

Without falling into the tendency to consider one research approach better than another, Ford and Norrie (Ford & Norrie, 2016) stated that there is a pragmatic—explanatory continuum that should be considered depending on the goals and the public of interest (Ford & Norrie, 2016).

In that context, one challenging aspect is the fact that the articles do not make it clear if they were conducted in ideal conditions or in real-world conditions. That can be observed since the publication of the book Managing Overweight and Obesity in Adults, by Jensen et al., (Jensen et al., 2014), in which no distinction is made between the term's efficacy and effectiveness. In this important reference for the field, those terms were simply mentioned as they have no different meanings (Jensen et al., 2014). This is not unusual as Burches and Burches (Enrique & Marta, 2020) have described that in real life, the terms efficacy and effectiveness are used interchangeably and the words efficiency and effectiveness are often considered synonyms (Enrique & Marta, 2020).

The same lack of accuracy related to those terms (efficacy and effectiveness) was observed in two recent systematic review articles that mentioned the terms but didn't define them in any part of their papers which just reinforces the importance of making that clear to avoid misinterpretation about the effects of these different kinds of interventions (Cleo et al., 2020; Madigan et al., 2022). By the effects of these intervention programs, we may consider the amount of weight loss or the proportion of the studied participants who reached the clinically significant weight loss of five percent.

When we consider the four studies included in this systematic review, the way that they described their intervention was not different. They also did not present the definitions or make considerations regarding the possible impacts of those scenarios. It is noteworthy that only one of those studies used the term effectiveness in its title (López-Padrós et al., 2020). The others just mentioned it in the text and did not give more importance to that definition or the specificity of the approach and environment where they were developed.

One of the issues that need to be better addressed is related to the design and settings where the research is developed (Shaw et al., 2018). Efficacy trials or exploratory trials are better represented by the randomized clinical trial (RCT) in which the conditions to conduct the intervention are considered ideal. Those interventions are rare in the treatment of obesity. But they might produce very important results like those made public by the IN-SULA project in Germany where they offered an inpatient multidisciplinary therapy for adolescents with severe obesity and have shown reductions of around 10 kg/m2 in the BMI among boys and girls after a period of that inpatient treatment close to 6 months (Do Prado et al., 2009).

On the other end, the translational approach to treat obesity lies in the pragmatic clinical trials (PCT), which seek to answer important questions that are applicable to everyday clinical practice (Ahern et al., 2016; Befort et al., 2020). This approach is much more likely to be applied in the health care systems around the world but it seems still not well explored as a research approach as that systematic review has revealed.

Given these findings, several study protocols from developed countries whose results are not yet available, and therefore, are not included in this review, have emphasized that programs of this nature (focusing on promoting lifestyle changes) are urgently needed (Berk et al., 2018; Looijmans et al., 2017; Shaw et al., 2018). Additionally, because the efficacy of on-site (face-to-face), comprehensive, high-intensity lifestyle intervention has been established in academic settings, translational studies are needed to confirm that when adjusted to real-world scenarios they can be effective as well (Jensen et al., 2014).

In this way, Ritzwoller et al., (Ritzwoller et al., 2013), reinforced that there are few studies of weight loss in the real world, nonacademic primary care, and even fewer in largely racial/ethnic minority, low-income samples. Patients who receive care in community health centers are particularly impacted by the limited availability of practical, evidence-based obesity treatments (Katzmarzyk et al., 2020). These patients have high rates of obesity and obesityassociated conditions, particularly hypertension and cardiovascular disease, and have been underrepresented in obesity trials (Ritzwoller et al., 2013). This systematic review has some limitations that must be recognized. Only SciELO and PubMed were searched and it is possible that searching other databases would have led to more studies to be included. The small number of studies included can impair the interpretation and discussion of results. We think, however, that these limitations can be balanced by the relevance of bringing this topic to the reflection with all the potential that this field of investigation has for the public health system. In other words, this can bring more attention to the theoretical and practical limits of each research approach. This can also highlight the necessity of a clearer definition of the structure and goals that could be used in the implementation of multidisciplinary programs for obesity.

Conclusions

In conclusion, very few intervention studies have been published using the terminology efficacy or effectiveness of multidisciplinary treatment programs for obesity. These few studies don't use the terms in a way that could make important distinctions among these models of clinical trials. Therefore, more studies are necessary to make clear the potential of these kinds of interventions in different settings.

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