



Placebo effect in child and adolescent psychiatric trials

Mara Parellada^{a,*}, Carmen Moreno^a, Miguel Moreno^b, Ana Espliego^b, Enrique de Portugal^b, Celso Arango^a

^aHospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red de Salud Mental CIBERSAM, Spain

^bHospital General Universitario Gregorio Marañón, Spain

Received 24 June 2011; received in revised form 23 August 2011; accepted 15 September 2011

KEYWORDS

Placebo effect;
Child psychiatry;
Adolescent psychiatry;
Clinical trials

Abstract

Much literature has been written in the field of child psychiatry regarding the placebo as a tool to test drug efficacy in clinical trials, but quite little regarding the placebo effect itself or its clinical use in child psychiatry. In this article, we aim to critically review the literature regarding the placebo effect in children and adolescents with mental disorders, focusing especially on factors influencing the placebo effect and how they may influence the interpretation of clinical trials. The placebo effect seems to be more marked in children than adults, and particularly in children and adolescents with depression, although it is pervasive across ages and is present in non-psychiatric conditions as well. The use of a placebo in clinical trials as a comparator with drugs that have moderate efficacy at most makes it difficult to obtain positive results, and much effort is needed to design very high quality clinical trials that may overcome the limitations of using a placebo. In addition, the placebo effect across ages and clinical conditions must be tested directly (compared with no treatment whenever possible), in order to characterise which placebos work for what and to determine their use in clinical settings.

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1. Introduction

The term *placebo* comes from the Latin *placere* or “to please”. It is usually defined as an inert substance (Howland, 2008), or a

medicine or regime prescribed for the psychological benefit to the patient rather than for any physiological effect (Oxford English Dictionary) and the *placebo effect* as some kind of helpful or therapeutic change in response to administering a placebo (Howland, 2008). Thus, in addition to an inert substance, the term placebo has also been used to designate the nonspecific factors intrinsic to the therapeutic process (clinician-, patient- and treatment-derived) that are not homogeneous across settings and studies, but that yield robust experimental and clinical effects (Finniss et al., 2010).

*Correspondence to: Psiquiatría Infanto-Juvenil, Hospital General Universitario Gregorio Marañón, Centro de Investigación Biomédica en Red de Salud Mental CIBERSAM, Ibiza 43, Madrid 28009, Spain. Tel.: +34 91 5868133; fax: +34 91 4265004.

E-mail address: parellada@hggm.es (M. Parellada).

A placebo might be considered both an important device for monitoring research quality and also a potent clinical tool (Raz et al., 2008).

Much more literature has been written in the field of child psychiatry regarding the placebo as a tool to test drug efficacy in clinical trials than regarding the placebo effect itself (compared with no treatment) and its potential clinical use. Placebo-controlled randomised clinical trials (RCT) are the ideal standard when assessing a treatment for a condition for which there is no proven effective treatment against which to compare a new treatment, an ideal that is open to question (Fava, 1996; Goodyer et al., 2010). In contrast, the placebo effect has been rarely studied directly (compared with no treatment) in children.

We know of no meta-analytic or review studies focussing on the placebo effect in children, and there is little reason to extrapolate adult data to children (Wohlfarth et al., 2009), given the neurodevelopmental and psychological differences. Direct comparison of placebo with no treatment is particularly necessary (in disorders and situations in which placebo use is not unethical) because changes in clinical situations might occur due to treatment but also to no treatment, due to a placebo, or even to spontaneous remission, regression toward the mean, or a combination of any of those (Krogsboll et al., 2009). Therefore, although “placebo response” is defined as the change that occurs following the administration of a placebo, more precisely, the placebo effect could be considered the difference between the placebo response and the changes that occur without administration of a placebo, which is not usually measured.

Recent legislation mandating inclusion of children in clinical trials has resulted in an increase in the number of children participating in research (Fisher et al., 2011). Thus, although still less than for adults, more information than ever is appearing regarding the efficacy of psychotropic medication in children. Evidence is therefore accumulating regarding the efficacy of psychotropic drugs in children in placebo-controlled clinical trials. Based on those, the efficacy of some psychotropic drugs is increasingly being questioned.

Treatment interventions in psychiatry, particularly in children, are not solely pharmacological. Psychotherapeutic and psychosocial interventions are among the most extensive for many conditions. Although the choice of comparator and how it is implemented is one of the generally accepted quality criteria for the assessment of clinical trials (Goldbeck and Vitiello, 2011), this aspect is particularly difficult to address in psychological interventions, for the difficulty in designing placebo-like controls. Although this review will be centred on the placebo effect in pharmacological trials, due to the insights that arise from psychotherapeutic trials, a brief reference to those will be included.

Finally, there are individuals who respond better to placebos than others, and this seems to be related to both environmental and individual factors; in addition to individual characteristics, placebo response rate seems to be different depending on the disorder and also on the study characteristics, and it might differ in relation to socio-demographic characteristics such as the age of the subjects.

In this article, we aim to critically review the literature regarding how the placebo effect may influence the interpretation of clinical trials, focusing on aspects relevant to children and adolescents with mental disorders.

2. Methodology

We searched Pubmed with the following terms [“placebo effect” and (child psychiatry or adolescent psychiatry or child* or adolescent*)] and reviewed hallmark clinical trials of psychiatric drugs for child psychiatric disorders (i.e. MTA, TADS, ADAPT), clinical trials leading to FDA or EMA drug authorisation, meta-analyses of the main medications used in child and adolescent psychiatry (antidepressants, psychostimulants and antipsychotics), and looked manually at the references in English and Spanish articles regarding studies that addressed the factors that influence the placebo effect.

3. Placebo response in psychiatric clinical trials with children and adolescents

The use of a placebo ideally serves to control for all non-drug-specific factors, but they may also be effective. If the drug is significantly more efficacious than the placebo, then the added benefit is generally attributed to the active component of the drug (Howland, 2008). Consequently, the greater the efficacy of non-specific factors, the more difficult it is to obtain a significant difference with an active drug (Khan et al., 2003). As an example, the degree of placebo response (and not the degree of drug response) is the single most powerful predictor of drug superiority versus placebo in children in antidepressant studies; the mean placebo response in studies positive for active drug superiority is 32.7% versus 47% in negative studies, in a review that included 23 RCT of internalising disorders in children (Cohen et al., 2010).

As shown, the placebo effect differs greatly among studies, even for equivalent conditions and populations. The heterogeneity of the placebos used may explain part of this disparity. A placebo really is a control for the beneficial effects of all the clinical management that a patient receives in such a trial, beyond the investigational medication (Preskorn, 2009). Therefore, anything different from an active drug can be considered a placebo. In the placebo arm of any given clinical trial, we may encounter any of the following: an inactive pill, regular contact with a clinician, a relationship with a caring adult, a proactive attitude on the part of the clinician seeking to recruit the patient into the trial, or even an inpatient admission. Regular contact with a clinician is indeed a very frequent part of the placebo arm; this contact might be considered therapeutic, especially with children. In fact, the intervention provided could be very powerful in the placebo arm in particular settings. The latter situation was present in one of the studies in childhood depression with the highest placebo response rate. A randomised controlled trial of amitriptyline versus placebo was conducted in adolescents with “treatment resistant” major depression admitted to a state hospital. The study concluded by questioning the efficacy of the active medication in this situation. However, both placebo and amitriptyline yielded a 70-80% improvement in the outcome measurements (although in both groups a substantial proportion of patients still had major depression or subsyndromal symptoms at the end of treatment (Birmaher et al., 1998). These results could be read as the placebo effect having great effect even in severe major depression (placebo effect defined as the change after giving placebo),

or as amitriptyline not being efficacious in severe major depression. They could also be read as inpatient admission being efficacious in severe depression, or a combination of any of the treatments (placebo and active drug) plus admission being efficacious, in this case with no comparator. The simple comparison of the selected outcome measure in the drug and placebo groups probably gives very little information about the comparative meaningful clinical effect of placebo, amitriptyline and/or admission. Many other factors in addition to the type of placebo may influence the results in RCT, such as the validity of some diagnoses in child and adolescent psychiatry and some investigator, sponsor and design-related factors.

3.1. Investigator-related factors that influence the results of placebo-controlled RCT

The quality of the assessment procedures may have an effect on the results of clinical trials. When trials include many sites, scales are not always validated in children or translated into all the languages used in the study, their implementation depending more on the raters' expertise; a reduced number of centres restrict the variability of the psychometric evaluations. In addition, the level of education and experience among raters across sites varies greatly and it is difficult to achieve proper reliability among clinicians in all assessment measures (Usala et al., 2008). Increasing numbers of recruitment sites have been used to explain the increasing placebo response rate over time (by year of publication) shown in some adult studies. Besides, a larger number of sites have been shown to result in increased enrolment of less severe cases (particularly when enrolment is competitive) and higher placebo responses, hindering the possibility of finding drug-placebo differences (Bridge et al., 2009). In fact, some authors have pointed out that the number of sites is the greatest predictor of a high placebo response in clinical trials with paediatric populations (Bridge et al., 2009).

In addition, the informants may vary between studies. Information provided by patient and parent may diverge significantly (Kahana et al., 2003; Tendal et al., 2009). Ideally, in assessing children clinically there is a need to take both pieces of information into account and pool the results with clinical judgement in order to end up with a final decision about the clinical situation. The expectations of the different informants may influence their answers. A "placebo by proxy" effect has also been described (Grelotti and Kaptchuk, 2011), in which parents identify a therapeutic effect after their child received a placebo. Parents are usually informants of their children's mental state. Significant placebo effects have been shown in adults who evaluate children with attention deficit hyperactivity disorder (ADHD), including therapists. Adults seem to evaluate children more positively when they believe they are on medication (Waschbusch et al., 2009). In a study in which an analgesic cream was given with suggestion and without suggestion, no difference was shown in the self-report of pain between the two conditions, but significant differences were detected in observers' ratings, which implies that suggestion worked more for the therapist than for the patient (Goodenough et al., 1997a).

3.1.1. Sponsor-related factors

Some of the caveats of clinical trials for children may lie in the pressures and manners of the funding industries. Since 1997 in the United States and 2006 in the European Union, the drug industry has new legal requirements to comply with, meaning that most drug trials are currently being conducted in children as a result of legislation passed in recent years. The Food and Drug Administration (FDA) Modernization Act of 1997 made it mandatory for all new compounds with potential use in the paediatric age group to be studied in children and adolescents, and it encouraged paediatric research on medications already approved for adults that were used in children and adolescents. The Paediatric Rule 1998 (Tabor, 2009) offered a 6-month patent extension to drugs studied in children irrespective of the results. The Best Pharmaceutical for Children Act of 2002 presses pharmaceutical companies to conduct trials in children in on-patent and off-patent medications. In addition, this act established a process for studying medications in paediatric populations to improve clinical trial investigations (e.g. clinical study design, weight of evidence, and ethical and labelling issues). In 2003, the Pediatric Research Equity Act authorised the FDA to require manufacturers of new drugs to conduct paediatric studies. In Europe, under the framework of the European Clinical Trials Directive (2001), Regulation No. 1901/2006 (European Parliament, 2006) sets up a system of requirements, rewards and incentives, together with horizontal measures, to ensure that medicinal products are researched, developed and authorised to meet the therapeutic needs of children. That regulation requires, for instance, that all new drugs or indications have a so-called Paediatric Investigation Plan (PIP) presenting the timing and the measures proposed to assess quality, safety and efficacy in all subsets of the paediatric population that may be affected. This PIP is then assessed by the Paediatric Committee at the European Medicines Agency, which is qualified to approve, adapt, and grant waivers or deferrals for paediatric studies (Stoyanova-Beninska et al., 2010). Such legislation has led to an increase in new information about medications used in children (Emslie, 2009; Arango et al., 2011). The increasing legal requirements come basically from three factors, two of them related to research with antidepressants. Firstly, the paucity of studies in child psychiatry before 1995, which led to the extrapolation of data from adult research, and the need to force the industry to perform research with minors; secondly, the early meta-analyses (Hazell et al., 1995) showing a very small difference between placebo and drug effect in antidepressant trials, questioning their efficacy; and thirdly, the alarm created in the nineties regarding the possible increase of suicide-related events/symptoms in relation to treatments with SSRIs (Hammad et al., 2006). Legal requirements may sometimes preclude emphasising good design with the purpose of obtaining indications in adult populations, regardless of the results in paediatric populations, as positive results are not a requirement. The potential consequence of mandatory paediatric studies is that they may be designed to gather information in a very short period of time and set up in an excessive number of sites (March et al., 2004a).

3.1.2. Design-related factors

Poor patient screening is often a factor underlying the high placebo response that is frequently observed in failed clinical trials in children and adolescents (Emslie, 2009). One possible cause is that, as more and more studies are performed, competition for patients increases and clinicians loosen criteria, admitting people who are more likely to respond to a placebo. Because a high placebo response rate can make a drug seem less effective, the FDA now recommends that drug companies add a third “arm” to every trial—a group of patients that gets a drug whose effectiveness has been demonstrated in previous trials. This is not possible in the case of clinical conditions in children and adolescents in which no drug is approved as yet.

The selection of the principal outcome variable(s) is of great importance. Results of RCT are commonly interpreted as differences between the active-drug and placebo arms of the study in one predefined principal outcome measure. This widely accepted approach does not capture the complexity and heterogeneity of the clinical changes over time. The patterns (and timing) of the change may differ with the placebo and the drug, or a complex outcome measure addressing internal changes or a combination of symptom change and subjective well-being may differ between interventions, but this is not commonly measured and it is not the common way in which the results of the RCT are interpreted.

As an example, secondary analyses of outcomes at week 12 in the TADS study (a multi-site clinical research study examining the short- and long-term effectiveness of an antidepressant medication and psychotherapy alone and in combination for treating depression in adolescents) showed that the combination of Cognitive Behaviour Therapy (CBT) and fluoxetine but not fluoxetine alone proved superior to CBT alone and placebo with respect to function and quality of life, remission, acceptability, tolerability and safety. Reflecting the order of effect sizes at week 12 (combined fluoxetine plus CBT [effect size=0.98] > fluoxetine [effect size=0.68] > CBT [effect size=0.03]), combined fluoxetine plus CBT proved superior to CBT and placebo for >90% of the 16 possible week-12 endpoints and to fluoxetine for one-half of the 16 possible week-12 endpoints (March and Vitiello, 2009).

Another example of analysing the results of clinical trials in a complex and more clinically relevant way than just taking into account primary outcome variables is the case of the Multimodal Treatment Study of Children with ADHD (MTA). Although this study did not include a placebo arm, the information is relevant to this point. In this landmark study, lack of medication advantage results from the 36-month assessment have been reanalysed, leading to the finding that different clusters (latent classes) of groups have different trajectories and responses to medication (Swanson et al., 2007). In many clinical conditions, it would be very informative to have week-by-week data on the timing of response so as to examine whether placebo response tends to occur earlier (or later) than true drug response (Quitkin et al., 1984) and whether it is sustained over time. In fact, knowledge of treatment trajectories of the interventions studied (active drug and placebo) has been considered necessary to handle the protocol deviations and missingness

occurring in trials in a sensible manner and to decide the most appropriate type of analysis (intent-to-treat, per-protocol or hybrid analysis) to provide reliable results in clinical trials (Matilde Sanchez and Chen, 2006).

On the contrary, it has been shown that using simple and general outcome measures such as the CGI-I may yield different results than using more depression-specific scales. Although the general results of studies that used the CGI were comparable to those that used different outcome variables in the Cohen meta-analysis (Cohen et al., 2010), some specific results may not be the same. For instance, a higher baseline severity of depression correlates with a lower placebo effect when CGI is used but not if a depression scale such as CDRS-R is considered (Bridge et al., 2009). The different scales probably measure different aspects of the illness that must be examined when analysing individual trials.

4. Placebo response by diagnosis and other clinical specifiers

Although the essence of a clinical condition (meaning its nuclear characteristics, such as for instance being influenced in its origin and solution by interpersonal issues) may influence the placebo effect, a placebo effect has been described for most clinical conditions and drugs, within and outside of psychiatry. Even in persons with developmental disabilities (who could be thought of as less suggestible, as their problems are basically biological in origin), a placebo effect has been shown (Sandler, 2005). Changes in environment, care-giving situation, care-giver characteristics, expectancy and many other individual attributes associated with the providing of a putative treatment may influence placebo response.

4.1. Placebo response in children and adolescents with disorders other than depression

Despite the frequent negative response rates to antidepressants in paediatric depression clinical trials, the establishment of SSRI efficacy has been easier in child and adolescent obsessive-compulsive disorder (OCD) (Geller et al., 2003) and anxiety disorders other than obsessive-compulsive disorder (AD-non-OCD) (Bridge et al., 2007), supporting a greater drug effect or a lesser placebo effect specific to these disorders. In a systematic review conducted to assess the placebo effect in studies of different internalising disorders, placebo response rates were 49.6% (range: 17-90%) for studies of major depressive disorder, 31% (range: 4-41%) for OCD and 39.6% (range: 9-53%) for AD-non-OCD, with 1528, 371 and 634 children and adolescents included in placebo arms, respectively (Cohen et al., 2008).

A moderate to high placebo response has been documented with most drugs across different psychiatric disorders in children and adolescents. Studies on ADHD have shown that around 30% of children with ADHD are clinical responders to placebo (Sandler et al., 2008). In schizophrenia trials supporting the efficacy of antipsychotics, placebo response ranged between 26% and 36% (Haas et al., 2009). In autism, a trial with citalopram showed a placebo response (34%) very similar to that of the active drug (33%) (King et al., 2009).

A high placebo response has been shown also in inpatient youths with severe mood dysregulation (Dickstein et al., 2009).

However, many examples show that in the case of ADHD, psychosis or OCD, the difference between the active drug and placebo is higher than in the case of depression. In clinical conditions such as irritability in autism (Munarriz et al., 2002) or hyperactive symptoms in ADHD (Peterson et al., 2008), there are studies with a low placebo response. In some cases, as with psychostimulants in ADHD or antipsychotics for psychotic conditions, the active drug has a very high response rate, with high effect size. Although there are significant differences between different stimulants, effect sizes for stimulants in children and adolescents with ADHD are around 1.2 and the number needed to treat (NNT) range between 2 and 2.6, figures hardly ever seen in adult neuropsychopharmacology (Faraone and Buitelaar, 2010). In the case of antipsychotics, although the information is very limited and conclusions premature, NNT have been shown to be around 3-10 for schizophrenia (Zuddas et al., 2011) and 2.5-4 in bipolar disorder (Fonseca et al., 2007; Haas et al., 2009), respectively, effects similar to those in adults; in these cases there is a clear separation from placebo.

4.2. Placebo response in children in antidepressant trials for depression

The efficacy of antidepressants for children has lately been a subject of particular discussion; much of the available information leads to a conclusion of no efficacy of antidepressants when compared with a placebo. Due to its relevance and the controversies generated in both the scientific and lay press, this aspect will be more deeply examined.

On average, in trials testing antidepressants in depressed children and adolescents, about 60-65% of patients on a new drug commonly get better while 24-60% of the patients in the placebo group typically also improve (Keller et al., 2001; Emslie et al., 2002; Wagner et al., 2003; March et al., 2004b; Berard et al., 2006; von Knorring et al., 2006; Usala et al., 2008; Bridge et al., 2009). As previously mentioned, frequently, the differences between the two groups are so small as to be statistically insignificant. Indeed, placebo-controlled trials have rarely demonstrated the superiority of both tricyclic and non-tricyclic antidepressants over the placebo in childhood depression; however, in general, doses have been low and sample sizes small in these studies (Moreno et al., 2007). Bridge et al., 2009 report on a meta-analysis of 12 antidepressant trials conducted since 1995, all using "second-generation" antidepressants, involving a total of 2862 children and adolescents with major depression (an average of 238 subjects per trial). In this meta-analysis, the mean response to placebo was 48% and to active medications 59%, and the majority of the variability between positive and negative trials was in the variability of the placebo response rate.

Another meta-analysis of the short-term efficacy of antidepressants in juvenile depression (with 29 studies that involved 3069 participants) that included both selective serotonin reuptake inhibitors (SSRI) and tricyclic antidepressants

also showed that the difference between active drug and placebo was modest, around 10%, with a placebo response rate as high as 49.2%. There was no difference by drug class, although the number needed to treat was greater for tricyclic antidepressants (TCA) (8.85 versus 14.49) (Tsapakis et al., 2008).

In addition, very little data are available regarding the placebo effect in the maintenance phase of the treatment of depression; results are convergent in showing greater efficacy in preventing relapses while on the active drug in fluoxetine responders (relapse rate 34-42%) as compared with the placebo (60-69%) (Emslie et al., 2004; Emslie et al., 2008).

For comparison purposes, antidepressants have been shown to be efficacious in adult depression, with no differences between SSRI and TCA (Geddes et al., 2005) except for depressed inpatients (Anderson, 1998). Mean placebo response of 29.7% (range 12.1-51.8%) and response to antidepressants of around 50% (31.6-70.4%) (Geller et al., 1989) were reported in the eighties, although later meta-analyses have reported mean placebo effects in antidepressant trials as high as 68% (Walsh et al., 2002; Kirsch et al., 2008; Rief et al., 2009). However, although the response rate to antidepressants in adult studies is not impressive and the placebo effect in some studies is very high, the results are positive probably due to the difference in the placebo and the drug effect in trials that include severely ill patients (Kirsch, 2008; Kirsch et al., 2008).

The validity of the diagnosis of depression in children and adolescents was questioned for many years, but this disorder has been recognised as a valid condition in the last 25 years, particularly in adolescence (Moreno et al., 2007). However, the biology underlying adult and children depression is not necessarily exactly the same, which may influence both drug and placebo effects. In fact, there are metabolic, neurophysiological and immunological data suggesting different biological correlates for adult and child depression (Moreno et al., 2007). Although considered a valid condition, depression may be more difficult to diagnose in children for evaluators with little experience, as the symptoms may be more nonspecific than in adult depression and comprise psychomotor, sensory-perceptual and psychosomatic psychopathology (Ryan et al., 1987); this, together with the frequent comorbidity present in childhood depression (Ryan et al., 1987; Kovacs et al., 1988; Goodyer et al., 2008; Usala et al., 2008), might make individuals included in trials more heterogeneous than in the case of other disorders.

The heterogeneity of the inclusion criteria used in trials with antidepressants in aspects such as severity, suicidality and comorbidity, together with the fact that most studies are industry-funded, limit the ability to draw definite conclusions from antidepressant trials (Cohen et al., 2008), and is probably partly behind the wide range of placebo response rates across studies (17-90%). In addition, patients in depression clinical trials may not be representative of all depressed youths from a therapeutic alliance care perspective. It is likely that recruited patients and families have some basic level of therapeutic alliance and therefore a better prognosis could be expected.

A high placebo response in paediatric depression may not be exclusive of antidepressants. Interestingly, in an RCT

assessing efficacy of quetiapine for bipolar depression in adolescents, the placebo response was as high as 67%, with remission rates of 40% (DelBello et al., 2009). Although there is no other study to compare with, from this study, it can be concluded that major depression in youth with bipolar disorder is also amenable to the placebo effect, independent of the use of antidepressants.

Moreover, it is well established that some specific (Harrington et al., 1998a; Weisz et al., 2006) and nonspecific psychotherapies provide effective treatment for child and adolescent depression (Harrington et al., 1998b; Birmaher et al., 2000; Goodyer et al., 2007). The same nature of depressive disorders may lead to a better response to nonspecific clinical care than other disorders. Psychological explanations have been put forward to explain why depressive children may be more amenable to the placebo effect (or nonspecific treatment effect); for instance, depression is more likely in subjects with past loss experiences; in these, nonspecific caring and recognition (which form part of all nonspecific supportive therapy) may be particularly helpful (Cohen et al., 2008).

4.3. Placebo response in non-psychiatric conditions

Outside the field of psychiatry, placebo response has also been shown to be high in children with other disorders, such as migraine, both in prophylaxis and treatment (Fernandes et al., 2008; Termine et al., 2008), partial epilepsy (Rheims et al., 2008), pain (Goodenough et al., 1997b; Rheims et al., 2008) and functional gastrointestinal disorders (Saps et al., 2009). The subject of the influence of the placebo effect on the results of clinical trials, the effect of age, design and the condition treated have also been discussed in these fields. For example, a negative clinical trial of the antimigraine drug zolmitriptan in adolescents showed an active drug response of 53-57% at three different doses versus a placebo response of 58%. However, placebo response varies depending on migraine trial design: a cross-over design has shown a lower placebo response than a parallel design in the acute treatment of migraine (27.1% versus 56.9% for pain relief), in a review of 19 studies (Evers et al., 2009). In drug-resistant partial epilepsy, the placebo effect has been shown to be age-dependent, with a two-fold higher placebo response in children than in adults (Rheims et al., 2008). In this meta-analysis, the interpretation of the authors is that the result partially depends on the higher placebo response in a particular type of epilepsy (idiopathic) rarely included in adult trials; they also suggest other factors influencing the higher placebo response in children, such as a placebo effect by proxy, a regression to the mean effect or the reluctance of parents to enrol their children in placebo-controlled trials. Moreover, a 4-week study comparing amitriptyline and placebo for the treatment of functional gastrointestinal disorders in children showed a 63% clear improvement in the verum drug group versus 57.5% in the placebo arm (with a fail, good or excellent placebo beneficial effect of 68% in the intent-to-treat (ITT) analysis and a 75% in the per protocol analysis). This was read as both interventions being effective (Saps and Di Lorenzo, 2009).

4.4. Other clinical specifiers

Duration of illness, severity of illness, age, race and comorbidity also influence placebo response. The longer the duration of illness, the lower the placebo response in child studies (Cohen et al., 2010). The greater the baseline severity, the lower the placebo response in adults and probably in children (Khan et al., 2002; Kirsch, 2008; Bridge et al., 2009; Fournier et al., 2010), although these data are only consistent for depression (Cohen et al., 2010). Direct data from child studies are not available, as very few studies have included moderate or severe cases of childhood depression. The TADS study is an exception to those. In that study, severity was reported as a moderator of efficacy. At lower levels of severity, fluoxetine treatment was no better than cognitive-behavioural therapy (CBT), while at the severe end, fluoxetine was better than CBT (Curry et al., 2006). In the acute phase - the only one with a placebo arm - the differences between treatments were clearer. After 12 weeks of TADS treatment, CBT alone was far less effective than the combination of fluoxetine with CBT or fluoxetine alone, with response rates of 71% for combined fluoxetine plus CBT, 61% for fluoxetine alone, 43% for CBT alone and 34% for the placebo. CBT "caught up" with fluoxetine at 18 months (response rates: fluoxetine, 69%; CBT, 65%), while combined fluoxetine plus CBT reached maximum medical benefit at week 18 (response rate 85%), 3 months earlier than fluoxetine alone or CBT alone, with all treatments converging by week 36 (response rates: combined fluoxetine plus CBT, 86%; fluoxetine, 81%; CBT, 81%) (March et al., 2004b; March et al., 2007). In the meta-analysis by Tsapakis (Tsapakis et al., 2008), of all 29 studies included, the one the greatest size effect of response is the TADS study, considered the sole clinical trial in adolescents with moderate-severe depression and a placebo arm (Tsapakis et al., 2008).

Results from meta-analyses show that the higher the age, the lower the placebo response and the higher the drug effect (Tsapakis et al., 2008; Bridge et al., 2009; Cohen et al., 2010), at least in antidepressant studies, probably excluding fluoxetine. This has not been shown to be the case in studies with psychostimulants or antipsychotics (Findling et al., 2001; Correll et al., 2010).

Comorbidity is very common in childhood depression (Ryan et al., 1987; Kovacs et al., 1988; Usala et al., 2008); although many of the trials conducted so far allow for some comorbidities, most studies exclude many of those. The differential response to placebo of factors such as conduct problems, anxiety, sexual abuse and others should be clarified in order to disentangle the effects of drug and placebo, particularly in studies with very general outcome measures such as the CGI. Regarding sociodemographic characteristics in paediatric trials, at least in internalising disorders, male gender and Caucasian race are both associated with lower placebo response (Cohen et al., 2010).

5. Placebo effect in psychotherapy studies

A recent meta-analysis of trials of controlled cognitive-behavioural therapy (CBT), including adolescents with a

diagnosis of depression, has reported that effects of CBT have declined steadily from the large effects reported in early trials, and confidence intervals have become progressively narrower (Klein et al., 2007). Smaller treatment effects have been associated with several methodological characteristics that, in general, distinguish recent from early trials. These characteristics include the use of ITT analyses, comparison of effects of CBT to active treatment control conditions, administration of treatment in clinical settings, and the application of greater methodological rigour. Klein's meta-analysis included placebo-controlled trials under the active-control condition, due to the large placebo effect in prior antidepressant trials. The difference between studies that used waiting list as a control or other "inactive" treatments and those using a placebo or other "active" treatments was highly significant ($p < 0.005$; effect size 0.72) (Klein et al., 2007).

In a meta-analysis of different kinds of psychotherapy in child anxiety disorders, the mean overall treatment versus control effect sizes across all active treatments was 0.66 (95% CI=0.36-0.96) (In-Albon and Schneider, 2007). In total, 69% of patients who completed therapy recovered versus 13% for waiting list. Interestingly, this meta-analysis also showed quite a high effect of the attention-placebo control condition (provision of information about anxiety, but no encouragement or instruction to confront the problematic situations), which suggests that psychoeducation could be an effective intervention in anxiety disorders in this population.

One unresolved problem with the study of the efficacy of psychotherapies is the need to further develop methods of assessing them appropriately, given the difficulties of comparing them with a placebo or assessing them blindly. Manualised psychotherapies are easier to assess with the methods of regular clinical trials. Very little information is available regarding the efficacy of psychotherapies other than CBT, interpersonal therapy or some family therapies.

6. Direct assessment of placebo effect in child psychiatry

Very little direct assessment of placebo effect has been conducted hitherto. Only a few studies have shown that nonspecific short-term psychotherapeutic interventions are effective for depressive disorders in children (Harrington et al., 1998b; Birmaher et al., 2000; Goodyer et al., 2008).

The difference in placebo effect using different outcome measures has also been tested in a pilot trial with ADHD children, which compared the response to placebo obtained using both the ADHD-RS (subjective way of assessing attention deficit/hyperactivity symptoms) and the Quotient Global Score (an objective measure of the same symptoms). The percentage of participants who responded to placebo was higher when the outcome measure was the ADHD-RS than when the Quotient Global Score was used, and the difference in placebo responders between both measures was statistically significant. This suggests that choice of the outcome measure has an impact on trial results, and that objective measures are more likely to yield statistically significant differences between active treatments and placebos (Sumner et al., 2010).

The use of placebos incorporated into drug treatment of ADHD has also started to be evaluated. In a study including 99 children (6-12 years old) with ADHD, after finding the optimal stimulant dose, participants were randomly assigned to 50% reduced stimulant dose plus pill placebo, 50% reduced stimulant dose alone or full stimulant dose. Participants were aware of the use of a placebo, although defined as having dose-extender effects. After 8 weeks, both the full dose and the 50% reduced dose plus placebo arms showed better symptom control than the 50% reduced dose alone, with lower adverse events in the reduced dose plus placebo arm (Sandler et al., 2010). An effective stimulant dose reduction was previously documented in the maintenance phase of the MTA study when combining medication and behavioural treatment (Vitiello et al., 2001). This could be a clinically relevant finding, with an alternative that is easy to implement in clinical practice and that could allow responders to medication who develop dose-related adverse events to continue to benefit from treatment. The use of placebos in clinical practice is however still under discussion (Miller and Colloca, 2009).

7. Neurodevelopmental considerations

There seems to be a differential response to psychotropic drugs and/or placebo in children and adolescents, at least in certain conditions. The differential course of the maturation of the different neurotransmitter systems may explain the differences. Some neurotransmitter receptors that are substrates for certain antidepressants mature throughout adolescence, and that may explain the low or absent response to the active drug in young individuals and the difficulty of showing differences versus placebo. Although the density of most monoaminergic receptors increases over childhood to peak to levels superior to those of adults, and then decline up until puberty, the magnitude of the physiological overproduction and subsequent reduction in receptor density varies across cortical areas in a manner that is specific for each receptor site (Lidow and Rakic, 1992).

Pharmacokinetic and pharmacodynamic differences between children and adults may account also for the differential response to active drugs. For instance, most drugs have shorter half-lives in children, due to a more efficient liver metabolism and a greater volume of distribution. Moreover, gender differences may mark specific responses in adolescence; i.e. body fat increase in adolescent girls may also affect distribution and half-life and subsequently drug response. In fact, the male/female depression ratio changes around puberty (Dekker et al., 2007), suggesting an influence of female hormones on the development of depression.

7.1. Suggestibility

Among the multiple factors that influence the placebo effect, there is a psychological one based on the personal capacity to respond to suggestions. The meaning of suggestibility as well as its influence on the response to clinical interventions, especially those consisting of an interpersonal relationship, has been studied for decades (Dixon et al., 1996; Cardena et al., 1998; De Pascalis et al., 2002).

Studies up to the eighties showed that suggestibility is different in each person and constitutes a personal trait as stable as IQ (Piccione et al., 1989). It also changes over the course of development (Page and Green, 2007) and is validly measured; it has been shown that approximately 15% of the adult population could be considered highly suggestible, while in the case of children around 12 years old, the rate would raise to almost 80% (Morgan, 1973; Bauman and Bul, 1981). Generally, children are easily influenced by authority figures like clinicians. Their belief system is not shaped by experience as it is in adults, and children are usually open to whatever comes from someone who inspires security and confidence in them, such as a clinician. They are usually motivated to learn and to experience new sensations; they usually exhibit fewer prejudices and show a less developed ability for inhibition in general, since their frontal lobes are less mature. The possibility that children are more suggestible than adults and physiologically predisposed to a higher placebo response has to be taken into account when analysing the effects of any potential therapy (e.g. placebo) in this particular population (Enserink, 1999; Kaptchuk et al., 2008; Whalley et al., 2008).

8. Discussion

There is some evidence to support that children have a higher placebo response than adults. As children are in general more suggestible than adults and since suggestibility may correlate with placebo response, children should potentially be considered better responders to placebo than adults, but this needs further investigation.

For some disorders and for some drugs, efficacy is not questionable in child psychiatry. However, efficacy of antidepressants (other than fluoxetine) is still controversial; this may be partly due to the likely efficacy of a placebo in depressive disorders. One of the main problems regarding the high placebo effect in children is the small effect size of some treatments for paediatric mental disorders, which may be partially real and partially derived from the low quality of the studies, with issues such as validity of diagnoses and instruments, reliability of raters, doses, posology and duration of treatments or selection of outcome variables. Nevertheless, the problem of high placebo response does not arise in the case of treatments with psychostimulants, one of the drug families with the highest effect size in psychiatry.

The lack of difference between placebo and active drug could mean that both drugs and placebo are ineffective or that both are equally effective. This latter possibility should be studied by designing trials that directly compare the effect of nonspecific interventions (regular contact with clinician with no active drug involved) versus the effect of waiting lists or doing nothing. Another possibility is that “placebo”, meaning a nonspecific therapeutic intervention (be it a placebo-drug or placebo-psychotherapy), enter clinical trials as an active arm, at least in conditions with known high placebo effects. In these, it would be useful to consider placebo-controlled studies as real active-control studies, analysing their effects against the active drug not only as potential superiority studies but also as non-inferiority studies. By this means, a deeper exploration

of the efficacy of a placebo in some psychiatric conditions could result. This type of design involves specific statistical analyses that differ from those for superiority studies in order to avoid biases and over-estimations of equivalence. For instance, what in a superiority study may yield less conservative results (a per-protocol analysis) may be the contrary in a non-inferiority study (Matilde Sanchez and Chen, 2006). In fact, drop-out rates are higher in placebo-controlled studies than in active-control studies (Kemmler et al., 2005), and that influences the interpretation of the results and the biases of analysing studies on a per-protocol or intent-to-treat basis (Matilde Sanchez and Chen, 2006). Negative studies should not necessarily be interpreted as demonstrative of lack of efficacy, particularly if the comparator is efficacious. Rather, they should inform better designs and more sophisticated scientific questions.

8.1. Implications for clinical trials

The use of structured interviews, age-appropriate and validated instruments, proper training and inter-rater reliability process, use of certified child psychiatrists (and not trained lay persons), and close monitoring of sites are some of the possible remedies for investigator-related factors associated with high placebo effect in clinical trials.

Careful selection of enrolment sites, proper monitoring of the study, a decrease in the number of sites per study, and elimination of competitive enrolment would help to overcome sponsor-related problems, but of course this is not always feasible. To partially avoid the inflation effect of including patients with a mild disorder, inclusion criteria could be based on a different scale than is used as the primary outcome variable that assesses efficacy during the study, a strategy already used in clinical trials in children and adolescents (Birmaher et al., 2003; Walkup et al., 2008).

Possible remedies for design-related factors precluding finding differences between active drug and placebo (efficacy trials) would be to establish narrow inclusion criteria, starting with a placebo washout-screening period, and then re-randomising placebo non-responders. The first studies with any given drug should be very clear and simple trials with clear-cut inclusion criteria (i.e. “the efficacy of a certain antidepressant for moderate symptoms of depression, within a major depressive disorder and no comorbid conditions”). Selecting homogeneous groups of patients, adequately characterising the included cases, avoiding comorbidities; powering trials to use both ITT and PP analyses; selecting appropriate drug doses and posologies, etc., should overcome difficulties showing the potential efficacy of drugs. The screening phase should be long enough and include psychological counselling offered to all patients. This will make it possible not to include patients who respond and are in no need of psychopharmacological treatment. A washout-screening period with placebo has been used in clinical trials to exclude patients with a placebo response (shown to be up to 49% in two positive fluoxetine studies and 53% in one negative paroxetine study, Emslie et al., 1997; Emslie et al., 2002; Berard et al., 2006). However, this manoeuvre has served its purpose only moderately in child studies (as in adults), but questions

about methodology (such as too short a washout periods) have arisen (Cohen et al., 2010).

Once efficacy is proved in specific subsets of patients, subsequent designs of trials for those drugs should be sophisticated in order to get real answers to real clinical problems, such as those of complex, comorbid, multiple risk patients. In order to get answers to complex problems, the need is there to establish clinically meaningful outcome variables, study subpopulations, trajectories of improvement, etc. Well powered complex trials, with clinical samples with broader inclusion criteria (allowing for some comorbid conditions and for suicidal intention), from one or very few sites (to reduce the heterogeneity added by investigators and sites) would serve this purpose. This purposed and simple sequential approach (efficacy and then effectiveness trials) has not been taken for many drugs in child psychiatry; some drugs have been dismissed after early studies with designs inadequate to answer the initial efficacy questions appropriately (such as, for example, venlafaxine for adolescent depression) (Mandoki et al., 1997).

The selection of a placebo is particularly important in clinical trials. In order to test the active drug most appropriately, patients in the placebo arm should be exposed to the same situation (treatment, management, etc.) as patients in the active treatment arm, except for the tested condition. The use of three arms (active drug, active comparator and placebo) has also been proposed.

If placebo efficacy is proven in certain conditions, the drug should be considered adjunctive treatment and not the only treatment, or the study should be considered a non-inferiority one. Considering it proven that nonspecific interventions are efficacious, some authors have suggested combined treatment designs as the most appropriate way to focus treatment trials for depressed children (Harrington et al., 1998b; Goodyer et al., 2007).

Long-term efficacy trials in which the natural history of the condition is compared with the efficacy of a placebo, and relapse prevention trials to study the continuity of the response, are necessary to complement the evidence provided by short-term RCT with respect to the efficacy of drugs. Designs must also become large enough and be creative, with post-hoc analyses that can be stated in advance in order to account for clinical specificities that may influence the response to treatments. Very sound individual clinical trials (with some replication) could be the most informative design for clinical practice.

Poorly designed studies have a negative effect on the field. It is likely that they yield negative results, which precludes further studies from being conducted with the same active principle.

8.2. Clinical implications

There is a special risk in translating data from meta-analyses to clinical practice. Meta-analyses are the best tool to inform the design of subsequent research, but not necessarily to inform the treatment of real patients in clinical practice, who differ greatly from patients in clinical trials. These studies in general suffer from great heterogeneity and large confidence intervals among individual studies, leading to very conservative results (favouring no

difference between interventions). Meta-analyses are not scientific studies per se, but statistical examinations of scientific studies (Thompson and Pocock, 1991; Slavin, 1995). The difference is important, as they have sometimes been given maximum credit to support classification of the levels of evidence attributed to interventions for any given disorder. However, the level of the data that are available from meta-analysis is limited in order to lead individual treatments. Most of the studies on any given topic are not included in meta-analyses and most of the data from the individual studies included are lost when they are combined (on the grounds of comparability, a lot of power for many scientific questions is lost). In fact, recent levels of evidence do not mention meta-analyses as a source of evidence for clinical advice. Systematic reviews of RCT (with homogeneity of trials included) are now being credited as the maximum level of evidence for that purpose (Center for Evidence Based Medicine, 2009). However, interpretation of the differences between placebo and active treatment in clinical trials requires careful consideration, particularly if there is not an arm with no treatment (Krogsboll et al., 2009). Placebo response/non-response in relation to antidepressant response/non-response could be a better way to show the difference between drug and placebo than the standard placebo/drug response (Goodyer et al., 2010).

Guidelines should also be clearly attuned to the real resources existing in different settings; therefore, the inclusion of treatment-as-usual as a third arm in clinical trials would be particularly useful in this regard. A systematic study of the placebo effect across conditions and situations would very positively inform routine clinical practice and service provision.

The use of a placebo in clinical situations is controversial. Inert pills are frequently used in clinical settings for the treatment of pain or anxiety/agitation, and there may be a basis for that (Vitiello et al., 1991; Fernandes et al., 2008; Hrobjartsson and Gotzsche, 2010), although there is little specific evidence of this in children. In fact, there is preliminary evidence suggesting that for some paediatric neuropsychiatric conditions deception might not be necessary for a placebo to work (Sandler et al., 2010), thus overcoming the ethical issues inherent in the use of this intervention in clinical settings (Miller and Colloca, 2009). There is also some basis for the use of brief nonspecific supportive psychotherapeutic interventions (called a placebo in some trials) in children with depression (Harrington et al., 1998b; Goodyer et al., 2008) and for the use of a placebo in the continuation treatment of ADHD (Sandler et al., 2008). However, there is a need for replication of the little evidence available because, for the majority of situations and for most nonspecific interventions, there is no literature supporting how to proceed.

9. Conclusions

Non-specific therapeutic effects of interventions in psychiatry are probably greater for children than for adults in some clinical conditions (particularly in depression), but there is still little strong evidence to support this. In addition, children probably have lower response to antidepressants than adults. These factors may explain the amount of negative trials of

antidepressants in child/adolescent depression despite the likely efficacy of some of the drugs. Available data should inform the design of clinical trials to minimise the placebo effect in order to try and assess the real efficacy of the drugs. Children and adolescents should probably be studied separately, inclusion and exclusion criteria should be carefully selected, a combination of measures (including self-reported and observer-based) should be used. Selection of sites is a crucial step in order to ensure good selection and clinical characterisation of patients and allow recruitment of an adequate number of patients without involving too many centres. The efficacy of a placebo should be assessed directly in specifically designed studies; not only against interventions that are assumed to be potentially more effective (drugs or psychotherapies) but also against no intervention (waiting lists for example), as it is clear that a placebo is not similar to doing nothing. Robust clinical trials should inform clinical guidelines more than meta-analyses and placebo interventions should also be considered a potentially effective basis on which to take clinical decisions.

Role of funding source

Authors did not get any specific funding for this study; Dr. Mara Parellada is under a partial research contract with the CIBERSAM, which had no further role in study design; in the collection, analysis and interpretation of data; in the writing of the report; and in the decision to submit the paper for publication.

Contributors

Authors M. Parellada, C. Moreno, M. Moreno and C. Arango discussed the main topics to be included in this review and organised the manuscript. M. Parellada, C. Moreno and M. Moreno managed the literature searches. M. Parellada wrote the first draft of the manuscript. All authors contributed to and have approved the final manuscript. All authors contributed to make the appropriate changes in the first manuscript after the reviewers corrections and suggestions.

Conflict of interest

Dr. Parellada serves as an expert consultant for the European Medicines Agency.

Dr. Arango has served as a consultant for AstraZeneca, Bristol-Myers Squibb, Janssen-Cilag, Lundbeck, Otsuka, Pfizer, Roche, Servier and Schering-Plough.

Dr. Moreno has served as a consultant for Otsuka and Bristol Myers Squibb and as an expert consultant for the European Medicines Agency.

Dr. M. Moreno, Dr. de Portugal and Dr. A. Espliego report no conflict of interest.

Acknowledgements

Funding from centro de Investigación Biomédica en Red de Salud Mental CIBERSAM is acknowledged.

We want to thank Jose de Arriba, who helped with the literature research.

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