DRUG-PLACEBO DIFFERENCE: IN ANTIDEPRESSANT DRUG TRIALS COULD BE 50% GREATER THAN PREVIOUSLY BELIEVED

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AZ ANTIDEPRESSZÍVUM–PLACEBO KÜLÖNBSÉG: AZ ANTIDEPRESSZÁNS VIZSGÁLATOKBAN A KORÁBBAN VÉLTNÉL 50%-KAL MAGASABB LEHET

A randomizált, placebo-kontrollált antidepresszívum-vizsgálatok összesített eredménye szerint az antidepresszívumra illetve a placebóra reagálók aránya 50, illetve 30 százalék. Az antidepresszívum–placebo különbség klasszikus számítása (50-30=20%) azon a feltevésen alapul, hogy minden placebo-responder egyben antidepresszívum-responder is. Úgy tűnik, ez nem igaz, mivel a placebo-responderek kb. egyharmada antidepresszívum-nonresponder. Mindezt figyelembe véve, a randomizált, placebo-kontrollált antidepresszívum vizsgálatokban a gyógyszer–placebo különbség a korrekt számítás alapján nem 20, hanem 30 százalék. Az összes antidepresszív gyógyszervizsgálatban az antidepresszívum– placebo különbséget újra kell számolni.

KULCSSZAVAK: antidepresszívumok, placebo, antidepresszáns–placebo különbség

SUMMARY

A pooled analysis of randomized placebo controlled antidepressant trials shows that the rate of antidepressant and placebo responders are 50% and 30% respectively. The traditional calculation of drug-placebo difference (50-30=20%) in these drug-trials is based on the assumption that all placebo responders should be antidepressant responders. However, it seems to be not the case, since about one-third of placebo responders are antidepressant nonresponders. Considering this, the fair calculation of antidepressant-placebo difference in randomized placebo controlled trials results in a 30% rather than 20% difference. The drug-placebo differences in all antidepressant drug trials should be re-calculated.

KEYWORDS: antidepressants, placebo, antidepressant–placebo difference

The role of placebos in evaluating the efficacy of antidepressants is well accepted, but frequently debated topic (Laporte and Figueras, 1994, Quitkin, 1999, Walsh et al, 2002). In randomized placebo-controlled clinical trials (RCTs) the differences in drug-placebo response rates (drug-placebo difference) are a necessary condition to establish utility of the given drug. A recent pooled-analysis of the 75 randomized controlled antidepressant studies on patients with major depression have found that in average, 50% of the drug-treated patients and 30% of the placebo-treated patients were responders (Walsh et al, 2002). The main message of this study for the clinicians and health-care policy makers is that the drug-placebo difference in antidepressant drug-trials is around 20%. Therefore to calculate the drug-placebo difference in these trials is the first and most influential step for the future of the given drug. . If the rate of drug responders is 50% and the rate of placebo responders is 30%, using the generally accepted method (postulating that 30% of the drug-responders also would be respond to placebo), the drug-placebo difference is calculated as 50%-30%= 20% (Figure 1). However, to preject all placebo responders (30%) on the column of all antidepressant-responders (50%) and to deduct the first figure from the second one (50%-30% = 20%, Figure 1) is logically seriously problematic since it implies that all placebo responders should be among

the antidepressant-responders (or no one patient in the placebo-responder subgroup would be among the antidepressant-nonresponsive patients). The traditional calculation of drug-placebo difference is based on the question „how many of drug-responders could be also placebo responders?" but neglects the other side of the problem: „how many placebo responders could be also drug-nonresponders?", or „how many of placebo patients would respond to placebo only?"

Given the 50% average response rate to antidepressant and the 30% average response rate to placebo in a pooled analysis of 75 placebo-controlled antidepressant drug-trials (Walsch et al, 2002), and calculating with 100-100 patients both in antidepressant and placebo groups, theoretically it is possible that antidepressant and placebo responses are absolutely independent (i.e., non-overlapping) phenomena, since all the 30 placebo responders could be among the all 50 antidepressant responders. (Fig. 2a). However, all placebo nonresponders (n=70) could not be among the all antidepressant-nonresponders (n=50), showing that a substantial part of placebo-nonresponders (20 out of the 70, that means 29% of the 70 placebo nonresponders) should be among the antidepressant-responders (Fig. 2b) In other words, at least 20 out of the 50 drug-responders (40%) are placebo non-responders. (Figure 2b). But what about the remaining 30 antidepressant-responders? Are they identical with the 30 placebo responders? Theoretically it is slightly possible (Fig 2b) but in reality it is very unlikely. Unfortunately, we could not find any study investigating directly the relationship of placebo response in relation to antidepressant response/ non-response. However, analysing the clinical response to antidepressants and placebo during a 6-week double blind clinical trial of 185 major depressives, Quitkin et al. (1984) found that 18 out of the 63 antidepressant-treated depressives (29%) who were responders at any point of the trial showed early (week 1. and 2.) but nonpersistent response, a pattern typically seen in placebo responders. The authors concluded that early and nonpersistent response to antidepressants should be primarily the consequence of placebo effect, rather than true drug effect. These results also suggest that about 30% of placebo responders could be antidepressant nonresponders. The subsequent fundamental studies of Quitkin et al (1991, 1993) also showed that placebo response and antidepressant nonresponse occur frequently in the same patient population. These facts demonstrate that antidepressant and placebo responders are greatly overlapping phenomena, and suggest that about one-third of placebo responders are also antidepressant nonresponders. Therefore to deduct all placebo responders (30%) from drug responders (50%) in calculating drug-placebo difference is unfair. In other words: about two-thirds of placebo-responders are placebo responders only, and one-third of them are both placebo respondres and antidepressant-nonresponders. According to this view the correct calculation of drug-placebo difference is 50%-(30%-10%)=30% which figure is 50% greater than the 20% calculated by traditional method (Fig. 3).

The new method, suggested here seems to be important in the interpretation of the drug-studies, particularly where both the rate of antidepressant-response and placebo-response are relativley high. If the rate of antidepressant-response is 80% and the rate of placebo-response is 60%, using our calculation the drug-placebo difference is 40% instead of 20%. On the other hand, however, if the same rates are 80% and 30% respectively, the difference is 60% rather than 50%.

The drug-placebo differences in RCTs should be re-calculated using the method suggested above. The 50% greater drug-placebo difference with this method in antidepressant RCTs (30% instead of 20%) could be serve as a resolution of the sharp contradiction between trial and real practice, i.e. we have more and more effective drugs in the clinical practice that show relatively small (and recently smaller and smaller) drug-placebo difference. (Walsh et al, 2002). In addition, as at least 50% of antidepressant nonresponders become responders after increasing the dose or switching the antidepressant (Fava et al, 1995, 2001, 2003) but it is very unlikely after the same manipulation with placebo, the drug-placebo difference in real clinical practice, where the responsibility of the doctor do not end at week 6. or 8., should be even more great.

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Figure 1
Traditional calculation of drug-placebo difference in depression

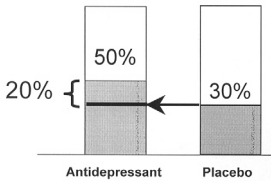


Figure 2
The relationship between placebo-responders and drug-responders (A) and placebo nonresponders and drug nonresponders (B)

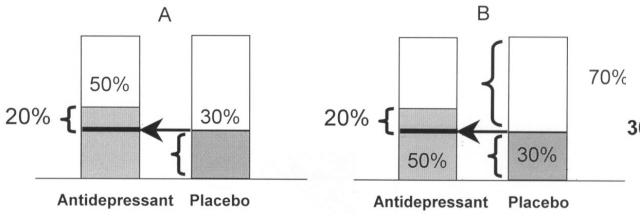
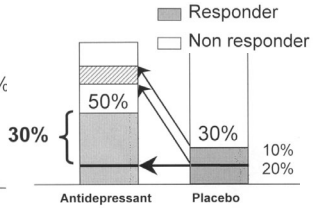


Figure 3
The proposed calculation of drug-placebo difference in depression



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