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Problems in determining efficacy and effectiveness of antidepressants

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Antidepressants play the major role in treating depressive patients not only due to the fact that they have to undergo the most rigorous proof of efficacy but also because they are easy to apply in the everyday clinical practice. Nearly all psychiatrists and general practitioners treating depressive patients agree about the relevance of antidepressants in the treatment of depressive patients. However, a number of meta-analytic studies recently challenged this belief and it has been put up for discussion to psychiatry/clinical psychopharmacology whether the efficacy of antidepressants is clinically relevant. Despite that all medication were judged to have sufficient data to receive approval from the FDA and the EMA and other agencies worldwide, some authors went further and questioned the effectiveness of antidepressants. They even proposed that "alternative" therapies of unproven efficacy or of proven negative efficacy should be preferred to medication. These authors do not take into consideration that for methodological reasons it is not acceptable to deduce too extensive conclusions. Some assumptions they rely on, like the suggestion of NICE, which regards a mean placebo-verum difference of 3 HAM-D points as clinically relevant, is downright arbitrary on statistical grounds, and not supported by empirical findings or by expert opinion. It seems that the difference in change in HAM-D score between the active drug and placebo is somewhere between 2 and 3, with maybe some agents performing a little better than others. It is uncertain whether initial severity determines response; different interpretations exist. However, much more important for the evaluation of the clinical relevance is the result of the responder/remitter analysis, which compares the relative frequency of these categories between the placebo and verum groups. This approach results in a number needed to treat (NNT) of 5–7. In Evidence Based Medicine such a NNT is traditionally regarded as a sign of moderate to strong efficacy and corresponds to the referring values of many therapies, which e.g. are standard therapies in internal medicine. However, from many meta-analyses it is clear that when concepts of evidence-based medicine and health economy are applied, which are far away from clinical thinking, problems occur and results are very difficult to interpret in clinical terms.

Key words: depression, antidepressants, efficacy, effectiveness, tolerability

Introduction

Although pragmatic and focussed strategies of psychotherapy, such as e.g. cognitive behaviour therapy (CBT), have recently gained importance in the treatment of major depressive disorder, antidepressants still play the major role in treating depressive patients.¹⁻³ This is not only due to the fact that they have to undergo the most rigorous proof of efficacy e.g. in double-blind placebo controlled group studies, before they are licensed by the drug authorities, but also because they are easy to apply in the everyday clinical practice.^{4,5} However, like all other antidepressive treatment strategies, the efficacy is limited to a certain degree and in many cases only sequential or comedication approaches lead to sufficient therapeutic results. Although nearly all psychiatrists and general practitioners treating depressive patients agree about the relevance of antidepressants in the treatment of depressive patients, it has recently been put up for discussion to psychiatry/clinical psychopharmacology whether the efficacy of antidepressants is clinically relevant. Others went further and questioned the effectiveness of antidepressants. This is accompanied by a discussion about whether all antidepressants are similar in their clinical efficacy and effectiveness. These three important questions will be discussed in the following, taking study results and methodological issues into consideration. This paper does not claim to be a systematic review but focuses only on some selected issues and refers to the most relevant publications in this context.

Is the efficacy of antidepressants clinically relevant?

At a first glance this question will seem astonishing to most clinicians, since their clinical experience⁶ reassures them every day of the clinically relevant efficacy of antidepressants. However, in times of evidence-based medicine and pharmacoeconomics, clinicians have to adapt to a situation in which such common grounds are investigated predominantly by people from outside their own professional community – for example, by evidence-based medicine (EBM) researchers or health economists. These might reach different conclusions because they take into consideration only study results without integrating them into clinical experiences.

The meta-analysis published by Kirsch⁷ attracted much attention in this respect, even in the lay press, especially with the provocative conclusion that the efficacy of antidepressants cannot be judged as "clinically relevant". Although the numerical results were not much different from other respective meta-analyses,⁸⁻¹² this meta-analysis attracted much more public interest which is per se an interesting phenomenon. Kirsch et al⁷ were so far the only group questioning the clinically relevant efficacy of antidepressants and recommending instead alternative approaches of unproven efficacy or proven non-efficacy as a conclusion of their study, although they did not study this subject in their investigation. The paper by Kirsch et al⁷ has apparently motivated other authors to go in the same direction, questioning the efficacy of antidepressants. Fournier et al¹³ – in this case only based on a meta-analysis of 6 placebo-controlled AD trials, from which the authors were able to collect the original data sets for the individual patients – pointed out that only the very severely affected patients showed a "clinically relevant efficacy".

The meta-analysis by Kirsch et al⁷ involving predominantly data on SSRIs, found a mean between the pre-post differences score of the placebo groups and the verum groups of 1.8 HAM-D points, which, although small, is of course statistically highly significant due to its huge sample size. This numerical result was heavily criticized by two recent re-analyses of the data set, demonstrating methodological pitfalls of the Kirsch meta-analysis. Based on these two re-analyses, the correct mean placebo-verum difference amounts to 2.18 or even 2.68, depending on the weighting method used¹⁴ or, even when using, instead of the fixed-effects analysis the more adequately weighted random-effects model, to 2.80.¹⁵ In the context of these reanalyses it was also underlined that for some individual antidepressants the mean placebo-verum difference is even slightly above 3.0, e.g. for venlafaxine and paroxetine,¹⁴ thus reaching the threshold which was seen by Kirsch, following an arbitrary criterion of 3 for clinically relevant efficacy. In addition, Kirsch et al reported that the increase in the efficacy signal in severely depressed patients compared to mildly and moderately depressed patients might be more due to a reduced placebo response in severe depression rather than to an increase in the active drug response. However, these authors failed to interpret this observation

correctly and they stick to the difference between arms. A more appropriate interpretation could be that the active drug is shown to be equally effective in mild and severe depression while the response to the placebo arm seems to be restricted to the milder cases. Taking into consideration also that these observations come from trials with a duration of only a few weeks, it is obvious that the response in the placebo group is unreliable and reflects a combination of methodological problems and the natural course and fluctuation of depression.^{14,15}

In interpreting such mean score differences it has to be stated that the mean of the pre-post differences of the placebo groups and the verum groups only give a global estimation of efficacy under the artificial conditions of placebo-controlled trials, in which due to the principal characteristics of the design, the verum response is underestimated and the placebo response is overvalued.^{4,16} One cannot conclude very much from this for everyday clinical practice, especially not on the efficacy for special patient subgroups or even for individual patients. Thus, the results obtained in such RCTs should be used more as a methodologically sophisticated proof of concept in a selected group of patients (high internal validity, low external validity) than as an indicator for the size of efficacy/effectiveness under real-world conditions.¹⁷

The mean of the pre-post differences of the placebo groups and the verum groups only gives a global estimation of efficacy. The placebo vs active drug difference in efficacy in different subgroups can be considerably higher¹⁸ due to the high variance for different patient groups.^{9,19} This is fairly mentioned by Kirsch et al⁷ –supported by Fournier et al 2010–, who found the highest differential effect in severe depression at a placebo-verum mean difference of 4 HAM-D points. The traditional point of view which regarded "endogenous depression/melancholia" as the indication for treatment with antidepressants –tricyclic antidepressants (TCAs) at that time– fit this data analysis well: strong verum efficacy and a low placebo response.²⁰ The broader ICD-10 category "depressive episode" and similarly the DSM-IV-TR category "major depression" may have caused a softening of the strength of diagnosis and inflation of the indication for AD treatment, and consequently possibly also a thinning-out of the efficacy of antidepressants, due to the higher placebo-response in mild/moderate severity degrees of depression.^{2,21,22}

It should be emphasized from a clinical perspective that the effectiveness of antidepressants in clinical practice is normally optimised by sequential and combined therapy approaches.^{1,23–27}

For methodological reasons it is not acceptable to deduce too extensive conclusions from only one meta-analysis¹⁷ on general placebo-verum differences regarding the clinical relevance the way Kirsch et al⁷ do. It should also be understood that different meta-analyses on the same database can come to different results due to different methodologies applied. The meta-analytic approach is also not per se neutral or unbiased as many people might believe and meta-analysts often pretend, as demonstrated by the meta-analytic reanalysis of the dataset of the Kirsch meta-analysis (see above). Depending on the methods applied one can reach more negative or more positive results which make meta-analyses sensitive to any kind of bias.

The principal view of Kirsch et al⁷ that a statistically significant mean score difference between placebo and verum group does not automatically result in a clinically relevant efficacy can be principally accepted. To assess the clinical relevance of the differences, Kirsch et al referred to a suggestion of NICE²⁸ which regards a mean placebo-verum difference of 3 HAM-D points as clinically relevant. Based on this and on the findings of his meta-analysis, Kirsch et al⁷ generally deny the clinical relevance of the observed efficacy of SSRIs, except in severe depression. This can be countered by the fact that the cited NICE criterion is downright arbitrary on statistical grounds, but not supported by empirical findings nor by expert opinion.²⁹ As a contra-argument it should be pointed out that all antidepressants, mostly SSRIs, included in the meta-analysis were approved, among others, by the EMEA and the FDA and their efficacy was therefore obviously considered clinically relevant by the drug authorities.³⁰

This leads to the question of whether there is a generally accepted criterion for the clinical relevance of antidepressive effects. This is apparently not the case: there are only different approaches to evaluate this.³¹ For the drug approval authorities, apart from a consistent replication of positive study results, the mean of the placebo-verum pre-post score differences of approved antidepressants is definitely of importance, ranging at about 2.0 HAM-D points and reaching statistical significance.^{8,10}

Such a mean score placebo-verum difference is therefore to be considered as clinically relevant. However, much more important for the evaluation of the clinical relevance is the result of the responder/remitter analysis,³² which compares the relative frequency of these categories between the placebo and verum groups. This approach is demanded by health regulatory authorities, like EMA, as an addition to the mean score analyses by drug approval authorities, to determine the clinical benefit of the therapy with an antidepressant. Considering the responder analysis, which Kirsch et al have unfortunately not taken into account in their meta-analytical examination, and counting the patients whose depression values have been reduced by at least 50% of the baseline values, placebo-verum differences ranging at 15–20% are the average result.^{33–35} A placebo-verum difference of 15–20% amounts to a number needed to treat (NNT) of 5–7. In EBM such a NNT is traditionally regarded as a sign of moderate to strong efficacy and corresponds to the referring values of many therapies, which e.g. are standard therapies in internal medicine. This consideration equally proves the clinical relevance of SSRIs and antidepressants in general respectively.

Kirsch et al⁷ in their critical argumentation considered only short-term studies (up to 8 weeks). If the results of placebo-controlled studies regarding a maintenance therapy with antidepressants (maintenance of the response for 6–12 months after the acute therapy) are considered in the argumentation as well, the conclusion regarding the clinical relevance of antidepressants is even strengthened. Geddes et al³⁶ in their meta-analysis of 31 randomised, double-blind, placebo-controlled studies found a highly significant efficacy of continuation therapy with relapse rates of 41% under placebo versus 18% under verum. Thus, the placebo-verum difference amounts to 23%, which means a NNT of 4–5.

Kirsch, in his argumentation, seems to advise that a placebo would do as well as an antidepressant. However, it should be understood that the administration of a placebo, justified under double-blind study conditions, cannot for ethical and practical reasons be transferred to everyday clinical practice: If we were to say to the patient, "we will now offer you a placebo", the placebo would already lose its "magic" effect and with this the efficacy.³⁷

However, for all these reasons the argumentation of Kirsch et al is misleading and should be rejected.²⁹ What we need to be aware of just on the basis of the recent meta-analyses is the fact that the mean of the pre-post score differences of the placebo and the verum group amounts to only about 2 HAM-D points RCTs (mostly PIII studies). By interpreting this value it should be taken into consideration that the study conditions in phase-III studies are highly artificial and vulnerable to bias and could possibly underestimate the actual therapy effect of the antidepressant due to the blinding.^{4,16}

In everyday clinical practice the efficacy of antidepressants can be regarded as much more pronounced than in placebo-controlled RCTs, especially in the case of patients who have not been pre-treated and are not partial non-responders.^{37–40}

Do antidepressants demonstrate sufficient effectiveness?

The concept of effectiveness is difficult to define. It tries to cover the aspect of "real world" performance of a treatment opposite to the results in selected study populations, especially Phase III study populations.^{41,42} Apart from the fact that the STAR-D results⁴³ were interpreted in the sense of effectiveness of antidepressants⁴⁴ the concept of effectiveness was so far primarily and predominantly used in clinical psychopharmacology in the field of schizophrenia treatment. There the concept led to several difficulties, when problematic effectiveness measures such as non-discontinuation were used.⁴⁵ It can be generally questioned whether "non discontinuation" really reflects only efficacy and tolerability aspects or whether also other parameters beyond drug effects are involved, e.g. the confidence in the therapeutic concept. For example, therapeutic concepts like psychotherapy, herbal drug therapy, etc. might be more acceptable to certain subgroups of patients who highly appreciate these kinds of treatment, although these treatments may have a lower efficacy. Different aspects of tolerability can have different effects on discontinuation, depending on the specific tolerability problems and on the time patterns of side effects. For example, frequent subjectively disturbing side effects (e.g. dry mouth) can have a much higher impact on discontinuation than less frequent but medically more relevant side effects (e.g. metabolic syndromes).

Barbui and co-workers⁴⁶ applied the concept of effectiveness to question the relevance of antidepressants in the treatment of depression, using the meta-analyses of placebo-controlled paroxetine studies. They calculated the proportion of patients who left a study earlier for any reasons (drop outs) as the primary outcome measure, because it represents in their view a hard measure of treatment effectiveness and acceptability (or to be more precise than these authors: as a measure of treatment non-effectiveness). They included in the meta-analysis 29 published and 11 unpublished clinical trials, with a total of 3704 patients who received paroxetine and 2687 who received placebo. There was no difference between paroxetine and placebo in terms of the proportion of patients who left the study early for any reason [random effect relative risk (RR) 0.99, 99% confidence interval (CI) 0.88–1.11]. Paroxetine was more effective than placebo, with fewer patients who did not experience improvement in symptoms of at least 50% (random effect RR 0.83, 99% CI 0.77–0.90). Significantly more patients in the paroxetine group than in the placebo group left their respective studies because of side effects (random effect RR 1.77, 95% CI 1.44–2.18) or experienced suicidal tendencies (odds ratio 2.55, 95% CI 1.17–5.54). Based on these results they came to the conclusion that among adults with moderate to severe major depression in the clinical trials reviewed, paroxetine was not superior to placebo in terms of overall treatment effectiveness and acceptability, but on efficacy.

This conclusion, primarily putting efficacy secondary to non-discontinuation as an effectiveness parameter will be seen by most clinical psychiatrists. It clearly indicates that if concepts of evidence-based medicine and health economy are applied, which are far away from clinical thinking, problems occur: Here we encounter the situation that an antidepressant, which in the Kirsch meta-analysis⁷ came out as a superior one in terms of efficacy, although it included the non-published studies in the same way Barbui did, is now described as one with lacking effectiveness, simply based on a problematic definition of effectiveness and over interpreting effectiveness in a one-sided way.

The most critical paper on the efficacy and effectiveness of antidepressants was recently published by Pigott et al⁴⁴ summarizing selected meta-analytical results on efficacy, predominantly the meta-analysis

by Kirsch et al,⁷ and the results of the STAR*D study, a so-called "real-world study".⁴³ The efficacy results of the STAR-D study were interpreted as effectiveness results because they included "real world", not Phase III patients. Apparently, the authors did not notice that the STAR*D patients do not reflect the average "real-world" patients, but preferably a selection of semi-chronic, partially drug refractory patients, thus leading to interesting results primarily for this subgroup of patients.⁴⁷ Overemphasizing the results of the Kirsch meta-analysis and the STAR*D study, the authors come to the overcritical conclusion that antidepressants "fail to result in sustained positive effects for the majority of people who receive them"⁴⁴.

Are all antidepressants the same in their clinical efficacy and effectiveness?

It has already been mentioned before that even in the data set of the Kirsch meta-analysis there were some differences between the investigated antidepressants, among others in the sense that e.g. venlafaxine and paroxetine demonstrated a mean difference of the pre-post changes between verum and placebo above 3.

There is not enough space here to describe results of individual studies. Therefore, only a condensation of the results of individual studies in meta-analyses, which are seen in evidence-based medicine (EBM) as the best approach to prove efficacy, are discussed. Although this view has to be critically reflected (17) for pragmatic reasons, we follow this approach here. Several meta-analyses on published results and pooled analyses on original data were performed in the recent past, especially focusing on the question of whether SSRIs are equivalent to TCAs in efficacy, whether SSRIs are better tolerable than TCAs, whether certain modern antidepressants like the selective noradrenalin/serotonin reuptake inhibitors or the allosteric serotonin reuptake inhibitor escitalopram have superior efficacy to SSRIs.⁴⁸ Most of them use the depression mean score difference of a standardised rating scale – for example, the HAM-D or the MADRS⁴⁹ as the outcome criterion for efficacy, some use responder or remitter rates.

Only few results of meta-analyses can be mentioned here.⁴⁸ A Cochrane Collaboration meta-analysis in 2003 identified 98 trials comparing SSRIs to other anti-

depressants, with a total of 5044 SSRI-treated patients, and failed to detect any clinically significant difference in efficacy between SSRIs and TCAs (Geddes et al 2003). Another Cochrane Collaboration meta-analysis investigated the tolerability and efficacy of the TCA amitriptyline in comparison with other antidepressants and SSRIs, and found no difference in overall efficacy between amitriptyline and either other TCAs or the SSRI comparators, but tolerability and acceptability measures favoured SSRIs.⁵⁰ An almost classical example is the meta-analysis by Anderso.⁵¹ which comprised 102 randomised controlled trials including 10,706 patients. Overall, no difference in efficacy was found between SSRIs and TCAs; however, TCAs seemed to be more efficacious than SSRIs in inpatients. Regarding tolerability, Anderson looked at 95 randomised controlled studies including a total of 10,553 patients. The SSRIs were described to be better tolerated than the TCAs, with a significantly lower overall rate of treatment discontinuations and of treatment discontinuations due to side-effects, although this did not apply to fluvoxamine. A Cochrane Collaboration review identified 136 randomised trials in which SSRIs and TCAs were compared among depressed patients, and found a modest but significant difference favouring SSRIs in terms of discontinuation of treatment.⁵²

Recent meta-analyses and reviews focussing on selective serotonin/noradrenalin reuptake inhibitors like venlafaxine, duloxetine and milnacipran, as well as on the noradrenergic and specific serotonergic antidepressant mirtazapine, gave hints towards a superior efficacy of these so-called "dual" antidepressants in comparison to SSRIs. But the results were inconsistent.^{53,54} Surprisingly, also the SSRI escitalopram, the active *s*-enantiomer of the racemat citalopram, was found to be more effective than the racemat in equivalent doses, hypothetically explained⁵⁵ by the inhibiting effect of *R*-citalopram at an allosteric transporter binding sector.⁵⁶⁻⁶⁵

With tolerability as such an important issue (especially in relation to effectiveness), when it comes to the question of whether SSRIs are preferable to TCAs, also the results of the meta-analyses of Trindade et al⁶⁶ shall be mentioned in short. Trindade et al compared the side-effect profile of SSRIs and TCAs meta-analytically. Eighty-four comparative studies were included. In this meta-analysis many adverse events occurred statistically more often with at least one of

the included SSRIs than with TCAs, namely nausea, "anorexia", diarrhoea, insomnia, nervousness, anxiety and agitation (which indicate the typical SSRI side effect profile). The SSRI-associated adverse effects seem to be related to drug dose, since they may reflect a functional increase in central 5-HT activity or 5-HT sensitivity. The TCAs are closely associated with medically more relevant adverse events like postural hypotension, cardiac conductance disturbances, glaucoma and urinary retention. These are not reflected in this and other meta-analyses because they refer primarily/only to rating scale data which do not include these kinds of side effects. It should be considered that the latter described side effects are of much greater clinical importance and medical relevance than the SSRI-associated symptoms described above.⁴⁸ Taking into consideration the recently approved antidepressant agomelatine it has to be stated that this AD is apparently the one with the lowest rate of any side effects.⁶⁷ Differences related to suicidality can not be discussed here due to space reasons; the reader will find respective papers in the literature.⁶⁸⁻⁷⁰

Cipriani et al⁷¹ recently performed a so-called "multiple-treatment" meta-analysis (indirect meta-analysis) which enabled them to describe a full picture of the different efficacy/tolerability profiles of single antidepressants, even if, for example, drug B was never directly tested against drug C, but both only against drug A. Based on a comparison of 12 new-generation antidepressants, the authors came to the conclusion that, considering both efficacy and non-discontinuation (as proxy for acceptability) escitalopram is the most preferable drug, followed by sertraline. Taking price issues into account sertraline was eventually placed first rank because this medication costs less than escitalopram. However, this meta-analysis did not include placebo arms of controlled studies which, together with other methodological issues, are considered problematic⁷² (table 1).

Apart from differences based on clinical evaluations and respective meta-analyses brain imaging can help us to gain additional insight into the different effects of antidepressants in terms of brain functioning and networks involved.⁷³ This might be a future way for a better understanding of the differences in efficacy and effectiveness of antidepressants.

Table 1. Efficacy and acceptability using fluoxetine as reference compound⁷¹

	<i>Efficacy (response rate) OR (95% CI)</i>	<i>Acceptability (dropout rate) OR (95% CI)</i>
Bupropion	0.93 (0.77–1.11)	1.12 (0.92–1.36)
Citalopram	0.91 (0.76–1.08)	1.11 (0.91–1.37)
Duloxetine	1.01 (0.81–1.27)	0.84 (0.64–1.10)
Escitalopram	0.76 (0.65–0.89)*	1.19 (0.99–1.44)
Fluvoxamine	1.02 (0.81–1.30)	0.82 (0.62–1.07)
Milnacipran	0.99 (0.74–1.31)	0.97 (0.69–1.32)
Mirtazapine	0.73 (0.60–0.88)	0.97 (0.77–1.21)
Paroxetine	0.98 (0.86–1.12)	0.91 (0.79–1.05)
Reboxetine	1.48 (1.16–1.90)*	0.70 (0.53–0.92)*
Sertraline	0.80 (0.69–0.93)*	1.14 (0.96–1.36)
Venlafaxine	0.78 (0.68–0.90)	0.94 (0.81–1.09)

OR=odds ratio, CI=credibility interval, *P<0.05. For efficacy, OR higher than 1 favours fluoxetine. For acceptability, OR lower than 1 favours fluoxetine

Προβλήματα σχετικά με τον καθορισμό της αποτελεσματικότητας και της δραστηριότητας των αντικαταθλιπτικών φαρμάκων

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Τα αντικαταθλιπτικά φάρμακα παίζουν τον κύριο ρόλο στη θεραπεία των ασθενών με κατάθλιψη όχι μόνο λόγω του γεγονότος ότι υποβάλλονται στις πλέον εκτεταμένες δοκιμασίες για την απόδειξη της δραστηριότητάς τους αλλά και στο γεγονός ότι είναι εύκολη η χρήση τους στην καθημερινή κλινική πράξη. Σχεδόν όλοι οι ψυχίατροι και οι γενικοί ιατροί που θεραπεύουν καταθλιπτικούς ασθενείς συμφωνούν πάνω στη χρησιμότητα των αντικαταθλιπτικών για τη θεραπεία των ασθενών αυτών. Ωστόσο, πρόσφατα μια σειρά από μετα-αναλύσεις αμφισβήτησε την πεποίθηση αυτή και πρόσφατα τέθηκε προς συζήτηση στον χώρο της ψυχιατρικής και της κλινικής ψυχοφαρμακολογίας το κατά πόσον η δραστηριότητα των αντικαταθλιπτικών έχει κλινική αξία. Παρά το γεγονός ότι για όλα τα φάρμακα έχει κριθεί ότι διαθέτουν επαρκή δεδομένα ώστε να τους δοθεί έγκριση από το FDA και EMEA καθώς και από άλλους οργανισμούς παγκοσμίως, μερικοί συγγραφείς προχώρησαν παραπέρα και αμφισβήτησαν την αποτελεσματικότητα των αντικαταθλιπτικών φαρμάκων. Ακόμα περισσότερο, πρότειναν ότι «εναλλακτικές» θεραπείες με αναπόδεικτη αποτελεσματικότητα ή και με αποδεδειγμένη έλλειψη αποτελεσματικότητας θα πρέπει να προτιμούνται σε σχέση με τα αντικαταθλιπτικά. Αυτοί οι συγγραφείς δεν έλαβαν υπόψη τους ότι για μεθοδολογικούς λόγους δεν είναι αποδεκτό να εξάγει κανείς υπερβολικά εκτενή συμπεράσματα. Μερικές υποθέσεις στις οποίες βασίζονται, όπως η πρόταση του NICE, το οποίο θεωρεί ότι μία μέση διαφορά 3 βαθμών HAM-D μεταξύ placebo-δραστικής ουσίας έχει κλινική αξία, και είναι σαφώς αυθαίρετη με βάση τη στατιστική και δεν βασίζεται ούτε σε εμπειρικά δεδομένα ούτε στην άποψη ειδικών. Φαίνεται ότι η διαφορά στη βαθμολογία HAM-D μεταξύ της δραστικής ουσίας και του placebo είναι μεταξύ 2 και 3, και ενδεχομένως κάποιες ουσίες να εμφανίζουν ελαφρά καλύτερη απόδοση σε σχέση με άλλες. Είναι ασαφές το κατά πόσον η αρχική βαρύτητα καθορίζει την απάντηση. Υπάρχουν διαφορετικές προσεγγίσεις. Ωστόσο, πολύ σημαντικότερα για την εκτίμηση της κλινικής αξίας είναι τα αποτελέσματα που αφορούν την ανάλυση απάντησης/ύφεσης, η οποία συγκρίνει τη σχετική συχνότητα των κατηγοριών αυτών μεταξύ placebo και δραστικής ουσίας. Η προσέγγιση αυτή έχει ως αποτέλεσμα έναν Αναγκαίο Αριθμό προς Θεραπεία (number needed to treat, NNT) ίσο με 5–7. Στη Βασισμένη σε Δεδομένα Ιατρική (Evidence Based Medicine) ένας παρόμοιος NNT παραδοσιακά θεωρείται ως σημείο μέτριας προς ισχυρής δραστηριότητας και αντιστοιχεί στην ισχύ που έχουν πολλές θεραπείες αναφοράς της εσωτερικής παθολογίας. Ωστόσο, από αρκετές μετα-αναλύσεις είναι σαφές ότι όταν χρησιμοποιούνται έννοιες της Βασισμένης σε Δεδομένα Ιατρικής και των οικονομικών της υγείας που είναι μακριά από την κλινική σκέψη, εμφανίζονται προβλήματα και τα αποτελέσματα είναι πολύ δύσκολο να ερμηνευτούν με κλινικούς όρους.

Λέξεις ευρητηρίου: Κατάθλιψη, αντικαταθλιπτικά φάρμακα, αποτελεσματικότητα, δραστηριότητα, ανοχή

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