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Original article

Position statement of the European Psychiatric Association (EPA) on the value of antidepressants in the treatment of unipolar depression

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ABSTRACT

This position statement will address in an evidence-based approach some of the important issues and controversies of current drug treatment of depression such as the efficacy of antidepressants, their effect on suicidality and their place in a complex psychiatric treatment strategy including psychotherapy. The efficacy of antidepressants is clinically relevant. The highest effect size was demonstrated for severe depression. Based on responder rates and based on double-blind placebo-controlled studies, the number needed to treat (NNT) is 5–7 for acute treatment and four for maintenance treatment. Monotherapy with one drug is often not sufficient and has to be followed by other antidepressants or by comedication/augmentation therapy approaches. Generally, antidepressants reduce suicidality, but under special conditions like young age or personality disorder, they can also increase suicidality. However, under the conditions of good clinical practice, the risk–benefit relationship of treatment with antidepressants can be judged as favourable also in this respect. The capacity of psychiatrists to individualise and optimise treatment decisions in terms of 'the right drug/treatment for the right patient' is still restricted since currently there are no sufficient powerful clinical or biological predictors which could help to achieve this goal. There is hope that in future pharmacogenetics will contribute significantly to a personalised treatment. With regard to plasma concentration, therapeutic drug monitoring (TDM) is a useful tool to optimize plasma levels therapeutic outcome. The ideal that all steps of clinical decision-making can be based on the strict rules of evidence-based medicine is far away from reality. Clinical experience so far still has a great impact.

1. Introduction

This position statement will address in an evidence-based approach [124] some of the important issues of depression treatment, which has given cause for concern and interrogation in recent years, thus inducing many uncertainties amongst doctors and patients.

This position statement does not intend to give a full review of evidence of the efficacy and safety of antidepressant treatment in general, of different groups of antidepressants, or even of single antidepressants–this is a topic for comprehensive guideline papers, and these should be referred to [4,13]–but rather focuses only on some special issues which have been discussed critically in the recent past, both in the scientific community as well as in the media. Amongst others, the issue of clinically relevant efficacy [87,147], as well as the question of whether antidepressants are safe in terms of suicidality, are addressed [34,53]. The sometimes overcritical discussion of these topics has led to uncertainties among doctors and patients and could possibly have a negative impact on the prescription of an antidepressive drug treatment as well as on compliance/adherence to treatment with antidepressants. In the context of this position statement also the fact of individual response patterns and their background factors, as well as the need for an individualised treatment approach will be discussed.

The paper is based on a careful computer-assisted systematic search (e.g. PubMed®, etc.) for all relevant publications and the expertise of the authors in the field of clinical psychopharmacology and depression treatment. The first draft has been revised several times in accordance with the critical feedback of the co-authors.

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2. Background: size and burden of unipolar depression in Europe and general problems of diagnosis and treatment

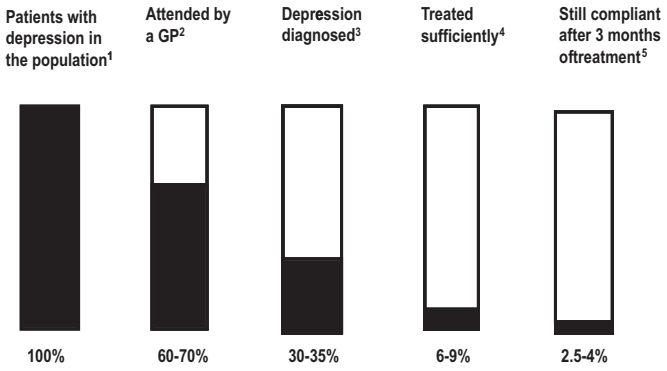
Depression is one of the most prevalent psychiatric disorders [3,206] and leads to substantial suffering of the patients, a heavy burden for the family, a high risk of suicidal behaviour (lifetime risk of suicide up to 15%) and significant socioeconomic consequences in terms of direct and indirect costs. The lifetime prevalence rate/lifetime risk amounts to about 15% if mild depressive episodes are also included [3]. According to a survey of the WHO together with the World Bank, unipolar depression ranks fourth in terms of disability-adjusted life years (DALYs), and is predicted to become second-ranking in 2020 [100]. A recent update describes the current burden of unipolar depression in terms of DALYs already as third-ranking and predicts that unipolar depression and risk of suicide (90% of people who complete suicide are suffering from depression) will become first-ranking by 2030 [208].

All these are good reasons for implementing the best care of individuals suffering from depression, in order to reduce the burden both for the individuals and society. However, apparently there are still a large number of unmet needs. For several reasons, there is a high rate of underdiagnosing, misdiagnosing and undertreatment, as can be seen in Fig. 1, and as was detected by several studies [77,95,102,106,128,195,204,205,207]. These can be explained either by lack of insight into the disease condition by the suffering individuals, lack of motivation to visit a doctor for this condition, fear of stigmatisation through a psychiatric diagnosis, insufficient training of doctors to diagnose depression, especially the not so typical types such as, for example, depression with prominent somatic symptoms as well as complexity of the symptomatology, etc.

At least some of these problems can be reduced by awareness campaigns, anti-stigma campaigns, improved education and training of doctors [57,151,155]. Screening tests applied on a general basis, especially in primary care settings, are additional useful tools [61]. The operationalised criteria of DSM-IV and ICD-10 as well as textbook descriptions are helpful guides in making the diagnosis [123]. Further short, fully standardized interviews like the Mini-International Neuropsychiatric Interview" (MINI) [169,170], or, if sufficient resources are available, major fully standardised diagnostic instruments are recommended. Above all, good psychiatric training and solid respective clinical experience are the most relevant.

As for treatment, drug treatment, primarily with antidepressants, under certain conditions with other psychotropic agents, is state-of-the-art. Also different kinds of psychotherapy, from counselling and more or less unspecific supportive therapy to different kinds of specific psychotherapy, ranging from behaviour to psychodynamic therapy, especially focussed psychotherapies like cognitive behaviour therapy (CBT), interpersonal psychotherapy (IPT) and cognitive behavioural analysis system of psychotherapy (CBASP), are gaining an increasingly important position in the treatment of depression [26,27,55,80,142,145,157,161], depending on their indication or the respective conditions of the patient. Often the combination of drug treatment and psychotherapy seems indicated, especially in partially drug-refractory patients [58].

Although there is a generally held view, especially in public opinion, that in general successful psychotherapy is of great importance for the treatment of depression, and although more and more data are becoming available underlining the efficacy of psychotherapy for mild and moderate depression, medication with antidepressants still remains currently the most widely and most frequently used treatment approach with proven efficacy, especially for severe depression, e.g. melancholia. This has to do with the fact that drug treatment is easily available everywhere without delay and that psychiatrists and many general practitioners are experienced in treating depression with antidepressants. Generally, primary care doctors are more prone towards a medication than towards a psychotherapeutic approach. Also, depressive patients who consult a primary care doctor often have a medical concept that includes expecting drug treatment. And even if they believe psychotherapy might be adequate or even better, very often they are not motivated enough to undergo the conditions of psychotherapeutic "work" [55] and there is a lack of psychotherapists.



[1]Wittchen et al. 1994; [2]Montano 1994; [3]Üstun and Sartorius 1995;[4]Lépine et al. 1997; [5]Katon et al. 1996

Fig. 1. Possibilities to optimise primary care treatment for depressive patients based on epidemiological data.
Modified from: [59].

Concerning the indication of antidepressant treatment, there are some differences in the recommendations suggested by various guidelines. While the NICE guidelines [134] do not consider mild depression as an indication for antidepressant treatment and restrict the indication for antidepressants to moderate and especially severe depression, others like the American Psychiatric Association (APA) or World Federation of Societies of Biological Psychiatry (WFSBP) guidelines [4,6,13] see antidepressants as indicated for all severity grades (depressive episode in ICD-10 and for major depression in DSM IV-TR). The FDA and EMA recommendations should also be considered with regard to this aspect.

It is important in this context to differentiate between unipolar depression and bipolar depression, because the treatment of bipolar depression (i.e. depression in the context of bipolar disorder) has to follow special rules [49]. Thus, this position statement focuses only on unipolar depression in the sense mentioned above. There is also no space here to go into the further differential diagnostics of depression–as for example, depression caused by somatic diseases–and their specific treatments.

3. The complexity of the aetiopathogenesis of depression as background for differences in the individual response and for a complex and individualised treatment of depression

Since their introduction in psychiatric treatment more than 50 years ago, antidepressants have been seen as standard treatment for patients suffering from depression. Related to current diagnostic categories of depression, especially "major depression" (DSM IV-TR) or "depressive episode" (ICD 10) respectively, are the main indications for treatment with antidepressants. These diagnostic entities, however, do not correspond to a homogenous nosological entity, if we consider different psychopathological subtypes, the contribution of different neurobiological and psychosocial aetiopathogenetic factors, the different responses to acute treatment and long-term treatment, etc. As to these different factors, there is a huge variation between individual patients, and additionally, the comorbidity with other psychiatric

or somatic disorders can increase the complexity in each individual case [116].

In current pharmacological understanding, antidepressants intervene in this multifactorial aetiopathogenesis predominantly by modulating depression-relevant transmitter systems like the noradrenalin, serotonin and dopamine systems. As a consequence, primarily the concentration of these transmitters in the synaptic cleft is increased due to reuptake inhibition or other pharmacological mechanisms [9,148,158]. This induces a complex cascade of secondary and tertiary messenger mechanisms and finally leads to a new homoeostasis on a more functional level. Beside these classical transmitter-related antidepressants, other innovative mechanisms are currently being tested and will in future hopefully bring an improved armamentarium for the drug treatment of depression [65,73,158,209], especially considering unmet needs like early onset or efficacy in drug-resistant depression or to target special symptoms or subtypes. The recent licensing of the first metatonergic antidepressant, agomelatine, offers hope that innovative mechanisms can lead to affective antidepressants with special clinical efficacy profiles.

The composition of the different possible genetic factors, probably together with relevant external factors, in each individual patient apparently determines his response pattern, whether he is an early responder or a late responder or even refractory to antidepressant treatment [8]. It does not seem astonishing that, given this diversity and complexity in the aetiopathogenesis of depression and the pharmacological mechanisms of antidepressants [19,23,41,42,76,178], there is a huge variation of different responses to treatment in general, as well as of different dispositions regarding the question as to which specific antidepressant is the most beneficial for the individual patient. This not only refers to the question of the differentiated indication of a specific drug for an individual patient but also to the differential indication of psychopharmacotherapy vs. psychotherapy. The latter is especially of interest if one goes beyond the narrow field of "major depression/depressive episode" to the broader spectrum of depressive disorders, especially regarding subtypes which were traditionally classified as belonging to the "neurotic" spectrum and now appear among others under the term dysthymia [60,98].

For several reasons, many patients do not receive optimal individualised treatment. This leads to the consequence that giving drugs or applying other therapeutic approaches cannot demonstrate the full power of psychiatric therapeutic interventions, neither on the individual level of evaluation nor on a group statistics level, because often the prescribed therapy is not the ideal one in the individual cases. In a worst-case scenario, we have to consider that the prescribed therapy could even be the therapy with the poorest outcome for the individual patient. This does not only characterise the everyday clinical situation, but is especially true for randomised clinical trials, where an individualised therapy cannot be offered. This might be one reason for the rather low verum-placebo differences, reported especially in recent decades (see sections 4 and 5). What has been explained here regarding efficacy is also applicable to safety/tolerability. As far as plasma levels are concerned, the application of TDM [93] can improve the situation. There is hope that in the near future we will be making progress in the direction of individualising the clinical decision-making process based on pharmacogenetic findings [97,125,160,181].

4. The efficacy of antidepressants is well proven and they are generally safe and well tolerated

The efficacy of antidepressants is well proven [9,13,15,18] by a huge number of double-blind randomized controlled trials (RCTs). Many of these compare the drug under investigation to placebo, which is demanded by both the American drug authority (U.S. Food and Drug Administration [FDA]) as well as by the European drug authority, Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) for principal methodological reasons [11,40,121]. Another large sample of studies are head-to-head comparisons, differentiating the clinical profile of (mostly) a new antidepressant against a standard antidepressant, such as in the old days a tricyclic antidepressant (TCA), and now a selective serotonin reuptake inhibitor (SSRI). There are also three-arm studies in which the new drug is compared against both a placebo and a standard antidepressant, a design which is regarded by the European drug authority EMA and by experts as the best design. On average the difference of the pre-post-differences between antidepressants and placebo are in the range of 2–3 points in the Hamilton Depression Rating Scale (HAM-D), and the placebo-verum responder differences are in the range of 15–20%, depending on the type of antidepressant, severity of depression, etc. [70,84,86,87,105,113,177].

There is not enough space here to describe results of individual studies. Therefore only the 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 [124] for pragmatic reasons, we follow this approach here. Several meta-analyses on published results and pooled analyses on original date 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 [9]. Most of them use the depression mean score difference of a standardised rating scale–for example, the HAM-D or the Montgomery-Åsberg Depression Rating Scale (MADRS) [119] as the outcome criterium for efficacy, some use responder or even remitter rates.

Only few results of meta-analyses can be mentioned here [9]. A Cochrane Collaboration meta-analysis in 2003 identified 98 trials comparing SSRIs to other antidepressants, with a total of 5044 SSRI-treated patients, and failed to detect any clinically significant difference in efficacy between SSRIs and TCAs [44]. 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 Anderson [5], 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, but only in inpatients. Regarding tolerability, Anderson looked at 95 randomised controlled studies including a total of 10,553 patients. The SSRIs were described as being 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 [12].

Recent meta-analyses and reviews focussing on selective serotonin/noradrenalin reuptake inhibitors like venlafaxine, duloxetine and milnacipran, as well as on mirtazapine with its special mode of action involving the noradrenergic and serotonergic system gave hints towards a superior efficacy of these so-called "dual" antidepressants in comparison to SSRIs. Surprisingly, the SSRI escitalopram, the active s-enantiomer of the racemat citalopram, was found to be more effective than the racemat

citalopram in equivalent doses, hypothetically explained [129,156] by the inhibiting effect of R-citalopram at an allosteric transporter binding receptor [14,67,75,81,96,99,104,130,132,139,183,184]. Cipriani et al. [24] 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 tolerability) escitalopram is the most preferable drug, followed by sertraline. However, this metaanalysis did not include placebo-controlled studies, which makes the generalisability, together with other methodological problems, somewhat questionable [167].

Because it has been suggested that unblinding effects in placebo-controlled RCTs may influence study results, a meta-analysis of studies using so-called "active placebos" which mimic side effects of antidepressants without antidepressant efficacy, was performed [127]. Study results were very sensitive to more or less conservative predefined inclusion and exclusion criteria, but a combination of all available studies satisfying minimal inclusion criteria produced a pooled estimate of effect of 0.39 standard deviations (CI 0.24 to 0.54) in favour of the antidepressant measured by improvement in mood [127].

Besides the efficacy of antidepressants in the treatment of acute depression, the efficacy of antidepressants was also investigated in terms of relapse and recurrence prevention [9,13,15,81,94]. A respective meta-analyses performed by Geddes et al. [44] arrived at the following result: in a meta-analysis of 31 randomised, placebo-controlled studies, the placebo relapse rate resulted in 41%, the verum relapse rate in 18%. The treatment effect seems to persist for up to 36 months, although most trials were of 12 months' duration, and so the evidence on long-term treatment requires confirmation. The reduction in risk of depressive relapse seems to be largely dependent on the underlying risk of relapses, the duration of treatment before randomisation or the duration of the randomly allocated therapy. Regarding the proportion of patients withdrawing from the trial, there were 18% in the antidepressants group vs. 15% in the placebo group. Also recent placebo-controlled relapse/recurrence prevention studies published after the meta-analysis by Geddes support data on the beneficial efficacy of modern antidepressants in this respect [47,81,94].

In general, safety and tolerability of antidepressants, especially modern antidepressants, is satisfactory [13,179]. With tolerability being such an important issue when it comes to the question of whether SSRIs are preferable to TCAs, the results of the meta-analyses of Trindade et al. are mentioned here briefly: The authors compared the side-effect profile of SSRIs and TCAs meta-analytically [188]. Eighty-four comparative studies were included. This meta-analysis showed that 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, decreased libido/sexual function (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. However, the TCAs, especially due to their anticholinergic profile, are closely associated with medically more relevant adverse events like cardiac conductance disturbances, glaucoma and urinary retention, which are not reflected in this meta-analysis but which are of crucial clinical importance. 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 [9,116]. The differential indication in the individual case in terms of tolerability has to be made according to the individual predisposition towards side effects, especially medically relevant side effects.

The spectrum of tolerability issues includes other adverse events, like discontinuation symptoms, or seldom adverse events especially relevant for long-term treatment. These are not covered in the above-mentioned metaanalyses, but in individual trials or by drug surveillance systems. For special reasons they cannot be discussed here in detail. Textbook chapter and guideline papers give the respective detailed information. Only the issue of suicidality, which attracted so much awareness in the recent years and was even used as contra-argument against AD-treatment, will be addressed thoroughly in section 7.

5. The efficacy of antidepressants is clinically relevant

At first glance, the title of this subchapter will seem astonishing to most clinicians, since their clinical experience [117] reassures them every day of the clinically relevant efficacy of antidepressants. However, in times of EBM [124] 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 EBM researchers or health economists. The recently published meta-analysis by Kirsch et al. [87], which is more or less similar in its results to the results of the previous meta-analysis by Kirsch et al. in 2002 [88], despite the fact that he tried to overcome the publication bias favouring positive studies [150,191] better than the previous meta-analysis, attracted much attention in this respect, especially with the provocative conclusion that the efficacy of antidepressants cannot be judged as "clinically relevant", although the numerical results were only somewhat lower than the results of other respective meta-analyses [84–86,177]. Kirsch et al. [87] were so far the only group questioning the clinically relevant efficacy of antidepressants and recommending instead alternative approaches like cognitive therapy as a conclusion of their study, although they did not study this subject in their investigation. The argumentation of Kirsch et al. is misleading and there are good reasons to reject this position [114].

There are several arguments against the position of Kirsch. The most relevant are described in the following. The paper by Kirsch et al. [87] has apparently motivated other authors to go in the same direction, questioning the efficacy of antidepressants. Fournier et al. [36]–in this case only based on a meta-analysis of six 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 most critical paper on the efficacy of antidepressants was recently published by Pigott et al. [148], summarizing selected meta-analytical results on efficacy, predominantly the meta-analysis by Kirsch et al. [87], and the effectiveness results of the STAR*D study [154]. Apparently, the authors did not notice that the STAR*D patients do not reflect the average "real-world" patients, but more a selection of semi-chronic, partially drug refractory patients. Overemphasizing the results of the Kirsch meta-analysis and the STAR*D study, the authors come to the extreme conclusion that antidepressants ". . .. fail to result in sustained positive effects for the majority of people who receive them" [147] (page 277).

The meta-analysis by Kirsch et al. [87] involving predominantly data on SSRIs, found a mean placebo-verum pre-/post difference of 1.8 HAM-D points, which, although small, is statistically highly significant due to its huge sample size. This numerical result was heavily criticized by two recent re-analyses of the data, demonstrating methodological pitfalls and statistical errors 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 used [35] or even 2.80, when using, instead of the fixed-effects analysis the more adequately weighted random-effects model [66]. 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 [35]. In addition, the hypothesis made by Kirsch et al. 2008 that the increase in the efficacy signal in severely depressed patients compared to mildly and moderately depressed patients might be due more to a reduced placebo response in severe depression rather than to an increase was refuted by the re-analyses [35,66].

But apart from these numerical corrections which lead to a somewhat more positive estimation of the mean efficacy, it is much more important to understand that the mean score differences on a depression scale between the placebo group and the verum group gives only a global estimation of the average efficacy, and cannot show the efficacy for special patient subgroups or even for individual patients. The efficacy in different subgroups can be considerably higher [131], due to the high variance in different patient groups, e.g. with severe depression [62], than revealed by the meta-analytically shown mean score differences. This is fairly mentioned by Kirsch et al. [87] who, as in the re-analysis by Fountoulakis and Möller [35] and Horder et al. [66] found the biggest effect in severe depression at a placebo-verum difference of four HAM-D points. The traditional point of view which regarded "endogenous depression" as an indication for antidepressants–TCAs at that time–fit this data analysis well: strong verum-effect and a low placebo response [17,98]. The broader indication "depressive episode" may have caused a softening of the strength of diagnosis and consequently possibly also a thinning out of the efficacy of antidepressants, due to a higher placebo-response in mild/moderate severity degrees of depression.

For methodological reasons, it is not acceptable to deduct too extensive conclusions from only one meta-analysis [68,103,124] on general placebo-verum differences regarding the clinical relevance the way Kirsch et al. [87] did. As the two re-analyses of the data set used by Kirsch demonstrate, the results of meta-analyses can be highly variable. Additionally, 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 [13,63,136,152,187].

The principal view of Kirsch et al. [87] that a statistically significant mean score difference between placebo and verum does not automatically result in a clinical relevance of the differences found can be principally accepted. To assess the clinical relevance of the differences, Kirsch et al. referred to a suggestion of NICE [134], which regards a mean placebo-verum difference of three HAM-D points or an effect size of 0.50 as clinically relevant–criteria which are arbitrarily chosen and not based on data. Based on this, Kirsch et al. generally deny the clinical relevance of the found effects of SSRIs, except in severe depression. This can be countered by the fact that the cited NICE criterion is downright arbitrary and not supported, neither by empirical findings nor by expert opinion [114]. 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 EMA and the FDA and their efficacy was therefore obviously considered clinically relevant [177].

There is no generally accepted criterion for the clinical relevance of antidepressive effects, there are only different approaches to evaluate this [132]. For the drug approval authorities, apart from a consistent replication of positive study results, the placebo-verum difference of approved antidepressants is definitely of importance, ranging at about 2.0 HAM-D points and reaching statistical significance [71,84,105]. 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 responder/remitter analysis [132], 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 value 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 [40,105,177]. A placebo-verum difference of 15–20% amounts to an NNT of 5–7. In EBM such an NNT is regarded as a sign of moderate to strong efficacy and corresponds to the referring values of many therapies, which are standard therapies in internal medicine. This consideration equally proves the clinical relevance of SSRIs and antidepressants in general respectively. Recently, Bech [18] performed a meta-analysis on placebo-controlled AD studies focussing on those items measuring in the most consistent way the severity of clinical depression (HAM-D-6). Despite an effect size of 0.30 for the total HAM-D-17 score, he could demonstrate an effect size of > 0.40 with the HAMD-6 score, which underlines the clinically relevant antidepressive effect. Counterbalancing the position of Kirsch et al., Bech et al. [18] discussed in this context a principal methodological issue: The Hamilton 6-item scale (HAM-D-6) is a more consistent indicator for the severity grade of depression than the HAM-D-17 scale and therefore leads to a better separation in terms of effect size between verum und placebo.

Kirsch et al. [87] 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 al. [44], 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 an 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, being 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", it would already lose the "magic" effect and with this the efficacy [56].

What we need to be aware of just on the basis of the recent meta-analyses is the fact that the mean placebo-verum difference amounts to only about two HAM-D points. 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 [121,173]. In everyday clinical practice, the efficacy of antidepressants can be regarded as much more pronounced, especially in the case of patients who have not been pretreated and are not partial non-responders [56,63,163].

The fact that relatively minor differences in the placebo-verum mean score in the treatment of mild depressive disorders increase with increasing severity of the depression can be seen as a confirmation of the importance of the degree of severity for a more pronounced efficacy of AD treatment. However, there are also studies which have explicitly examined the efficacy of antidepres-

sant treatment in mild to moderate depressive disorders and which yielded positive results, whereas on the other hand, there are also studies in more severe depression with questionable efficacy [55,143,203]. In the quite classical respective study by Paykel et al. (1988), for example, amitriptyline was superior to placebo in probable and definite major depressions based on the Research Diagnostic Criteria [174] but not in minor depressions. It was also superior to placebo in patients with initial HAM-D scores of more than 12, but not within the scores of 6–12. Overall these findings, so the conclusion of Paykel et al., indicate that TCAs are of clear therapeutic benefit in a spectrum of milder depressions except for the most mild of these.

The clinical classification of degrees of severity according to e.g. the ICD-10 or HAM-D total score is of high clinical relevance for the indication of antidepressant treatment in current clinical practice. For example, the British NICE guidelines [134] recommend antidepressant treatment in outpatient settings only for moderately to severely depressed patients. For patients with a *mild* depressive disorder, "watchful waiting" or psychotherapeutic intervention was recommended as the treatment strategy of first choice. The NICE guidelines have replaced their prior recommendation of "watchful waiting" [134], now suggesting "active monitoring" strategies [133]. These strategies include discussion of present problems, information about the nature and course of depressive disorders, and arranging and assuring further contacts normally within 2 weeks. Since mild depression is associated with increased suicide risk [83,101], and the risk of chronification as well as treatment resistance of depressive disorder increases with the duration of untreated depression [82,202], this recommendation should be viewed critically. Other guidelines, such as those from the APA, recommend antidepressant treatment also in mild forms of depression [72]. Many psychiatrists share the view that the treatment of depression should start as early as possible, following the concept of early recognition and early treatment which was recently developed for good reasons in the field of schizophrenia. Also the personal suffering of patients with mild depression should not be underestimated. Nevertheless, further research is needed on this issue before final conclusions can be drawn.

Although some guidelines, e.g. the S3 depression treatment guideline of the Germany Society of Psychiatry and Psychotherapy (DGPPN) [28] even consider psychotherapy alone as an option for *moderately* depressed patients, clinical experience has shown that most moderately depressed patients require at least supplementary treatment with medication.

This positive positioning of psychotherapeutic approaches makes it necessary to underline some differences in the evidence level of psychotherapy and AD treatment. Psychotherapeutic approaches can reach the highest level of evidence in different evidence-grading systems [124], where there is no demand for double-blind control-group studies and no demand for a placebo control in the strict sense, but only the demand for RCTs. Due to the lack of the double-blind design and a strict placebo control in psychotherapy research also, the effect size has another meaning than in double-blind placebo-controlled trials on antidepressants, where the effect size is decreased due to this special design component. This leads to the danger of meaninglessly comparing effect sizes or respectively evidence grades based on different methodologies of therapy evaluation, given the fact that psychotherapy is for practical reasons never performed under double-blind conditions and never uses a strict placebo control group. The different methodological approaches on which the evaluation of psychotherapy and drug treatment is based implies that a direct comparison of evidence grading or effect sizes is impossible. To avoid such problems it would be advisable to develop a uniform evidence-grading system for all therapies in psychiatry which differentiates in a careful way all characteristics of study designs. With such an evidence grading system, psychotherapies could *per se* not reach the highest evidence grade due to their principal methodologically exceptional position in the evaluation since the realisation of placebo controls is difficult and the realisation of double-blind conditions is impossible. This holds true even more for other psychosocial therapies commonly used in psychiatry. This principal problem of trial methodology, of course, cannot be solved by meta-analyses, but has to be considered when interpreting the meta-analytical results of psychotherapy studies.

6. Augmentation of the efficacy of AD monotherapy by complex therapeutic strategies and its evidence

In this context it has to be underlined that in the past decades remission has increasingly been suggested as the ultimate goal of drug treatment due to the fact that remission is seen as the basis for an optimal further outcome in terms of social functioning and relapse-free outcome in the subsequent period [115]. Efforts were made to define remission in a prognostic and widely acceptable way [115]. The most generally used definition is a HAM-D score ≤ 7. However, a more complex definition of remission should in future also include social functioning.

It should be emphasised that antidepressant treatment often does not lead to a satisfactory outcome with only one antidepressant, possibly due to both general and individual factors. This is especially true if remission and not only response is seen as the goal [162]. Besides the choice of the antidepressant, even simple factors such as a suboptimal starting dose can be of relevance [137]. A sequential therapy with different antidepressants of various pharmacological modes of action should already be applied to relatively "uncomplicated" depression to achieve satisfactory therapeutic effects [78,79,91,92,153,185].

Regardless of the initial choice of antidepressant, at least 30% of depressive patients will not sufficiently respond to treatment. Various alternative treatment strategies have been proposed for these non- or partially responsive depressions [2,13,15,22,25,58,135,138,159]. The major types of strategies employed after reviewing correctness of diagnosis and sufficiency of drug dosing and compliance, are:

- switching to another antidepressant from a different pharmacologic class (e.g. from an SSRI to a dual AD or a TCA);
- combining two antidepressants from different classes (e.g. an SSRI) or a dual reuptake inhibitor with mirtazapine;
- augmenting the antidepressant with other agents (like second-generation antipsychotics, lithium or thyroid hormone) to enhance antidepressant efficacy;
- combining the antidepressant with a psychotherapeutic intervention;
- combining antidepressants with non-pharmacological biological therapies like sleep deprivation, light therapy, electroconvulsive treatment (ECT) or other types of brain stimulation.

These strategies have been examined in a variety of agents and combinations. However, most studies have not been subjected to rigorous scientific investigation or have included small study groups. Currently, no clear consensus exists on which strategy should be favoured for the non-responding patient, since to date no rigorous trial with a randomised, double blind design has been conducted to answer this question. Some authors have argued to principally favour augmentation strategies, especially in case of non-response to an antidepressant. Lithium, for example, has been repeatedly investigated in placebo-controlled trials with positive results and can possibly be seen as one of the best proven augmentation therapies. In recent years, second-generation

antipsychotics have reached a high position as augmentation therapy [197].

The efficacy of drug treatment in depression can be greatly increased through implementation of the above-mentioned strategies [1]. Hints in this direction can be taken for example from the US-American STAR*D study, which offered a complex sequential therapy program, although the study needs to be interpreted with caution due to the open nature and further methodological shortcomings such as, among others, the fact that outcome results were predominantly based on self-ratings. The percentage of remitters after the first treatment sequence with duration of 12 weeks at maximum and a treatment with citalopram was 27% (HAM-D rating). The other sequential steps increased the numbers of remitters, finally up to 67%. However, with each consecutive step of treatment sequences the chance of achieving remission was decreasing. The STAR*D was not designed in such a way that the additional steps could be proven in their efficacy because a control group condition is lacking in this study. But the Texas Algorithm Project gave some evidence that an operationalised sequential treatment strategy is superior to treatment as usual [187,189]. This was also supported by an algorithm project [1,2].

In a naturalistic multicentre study on depressive inpatients involving seven German university and five non-university psychiatric hospitals, 68.9% responders and 51.9% remitters were observed at discharge after a complex treatment program and a hospital stay of 61 days on average [162], although most of the patients could be classified already at admission as partial non-responders or difficult-to-treat patients. These patients were treated with all kinds of antidepressants, other psychotropic drugs, using among others comedication and augmentation strategies, applying drug monitoring for control of compliance and pharmacokinetic interaction, and offering other biological therapies like sleep deprivation, transcranial magnetic stimulation (TMS) and ECT, if indicated. It should be mentioned that also different kinds of psychotherapeutic interventions were offered, besides individual supportive psychotherapy, psychoeducation and focused strategies of cognitive therapy [157]**.** The complex therapeutic approach additionally involves other psychosocial therapies such as ergotherapy, physical exercise, occupational therapy, as well as music and art therapy. The therapeutic activities were offered on the basis of the individual personal needs and wishes, starting with an antidepressant monotherapy in the simpler cases, or with an antidepressant combination or even augmentation strategy for those who were admitted to the hospital in a state of partial non-response.

There are studies underlining the fact that complicated therapy approaches, e.g. comedication approaches or sequential approaches, which are common in psychiatric daily routine are meaningful from the viewpoint of the doctors and of the patients. However, it is difficult to prove their efficacy according to the demands of EBM [124]. Methodological and pragmatic problems, already arising with regard to the comparison of the evaluation of efficacy and tolerability of single drugs, are predominant in the area of complex therapies. There are mainly not enough empirical data to be able to empirically prove complex therapy procedures. For example, the data pool for switching from one antidepressant to another with a different pharmacological mechanism is not sufficient for building any evidence-based decisions, and indeed has not been shown to be very successful [136]. The complexity of studies on sequential therapies becomes apparent in recent respective research on therapy for unipolar depression. It is questionable whether it will ever be possible to prove complex therapy algorithms in methodologically stringent studies (e.g. randomised controlled studies) in a sufficient way. The necessary number is so high that the recruitment alone could only succeed if many study centres worked together. Even if the willingness were there, the financial means for a study of that kind would be very difficult to obtain [117]. From this, it follows that many procedures in daily clinical routine will be either not at all or very difficult to regulate in terms of EBM.

In recognition of the limited response of patients to therapy with antidepressants, especially monotherapy with only one antidepressant, in the recent past psychotherapy, especially the focussed and short-term approaches like CBT or IPT were suggested as alternative treatments. With the methodological limitations discussed above in mind, the general view is that the results of empirical studies seem to support the view that these psychotherapeutic approaches are on a more or less similar level of efficacy in mild and moderate depression as treatment with antidepressants [26,27,55,142]. Thus, if this therapy is available and if the patient is motivated to undergo such a psychotherapy, this might be a real alternative. This recommendation is also given by some treatment guidelines like e.g. the US American APA depression treatment guideline [4] or the recently published German depression treatment guideline [28]. Even more there might be an indication for a combination strategy. However, relatively few studies have investigated the benefits of a combination of psychotherapy with antidepressants, and study results are conflicting [37,39,58]. Under acute treatment conditions the advantage of a combination (COMBI) seems to be most obvious for patients with more severe forms of chronic depression. In the nicely designed study by Keller et al. [80] comparing the acute treatment with either nefazodone or a special short-term psychotherapy (CBASP) or both, COMBI was superior to medication alone in patients with the following diagnoses: (1) dysthymia with additional major depressive disorder (MDD), or (2) persisting MDD or (3) partially remitted MDD with poor episode recovery [80]. It cannot be excluded that the relatively low mean dose of nefazodone and the fact that nefazodone has also a weak antidepressant effect, may be the cause of the low response rate in the "medication alone" group. However, the results of some studies [31–33,144,145] support the hypothesis that patients with partial remission and/or incomplete episode recovery following medication may profit from CBT through reduced residual symptoms and relapses [142]. By contrast, in milder and more uncomplicated forms of acute MDD, a COMBI might be neither superior to psychotherapy nor to pharmacotherapy. On the other hand, the severity of depression is a clear indication for the addition of pharmacotherapy to psychotherapy [58,184]. For MDD patients suffering from more severe acute episodes, a COMBI is more effective in reducing depressive symptoms compared to psychotherapy alone. Patients also recover faster in the acute phase when treated with antidepressants and psychotherapy than if treated with psychotherapy alone.

7. Antidepressants generally have positive effects on suicidality, but under certain conditions they can also have a negative impact

Based on the clinical experience of psychiatrists, it seems obvious that antidepressant treatment of depression reduces not only depressive symptoms but–associated with these–also suicidal thoughts and intentions. There are also several randomised clinical studies indicating this [74,110]. In addition, epidemiological studies demonstrated results that e.g. a higher prescription rate of SSRIs was associated with a reduced suicide rate in several countries.

In recent years, however, the discussion has focused much more on the potentially harmful effects of antidepressants in terms of inducing/aggravating suicidality [111,120]. This debate started in child/adolescent psychiatry, but then also spread to adult

psychiatry. In this context, warnings from the U.S. FDA and the CHMP of the EMA were published [30,192,193], a position which was supported by others [21,45]. In this context the question was raised several times as to whether the use of antidepressants is safe enough to be recommended for all depressive patients, or whether antidepressive efficacy of antidepressants the prescription should be significantly restricted [88,126].

Effects of ADs on suicidality are difficult to investigate in empirical studies because of several methodological limitations [110,111]. A broad scientific approach therefore has to use complementary methods to obtain the most comprehensive evidence. One must be aware that case reports on suicidality-inducing effects of ADs which often draw much attention should be interpreted very cautiously and different kinds of bias and misperceptions inherent in case reports should be considered carefully. Case reports can function as a source of hypotheses but cannot confirm hypotheses. If only single case data are available, the extreme uncertainty of the evidence should be addressed and relevant conclusions should be tempered.

A huge number of randomised control group studies were performed to prove the efficacy of antidepressants. In this context also the effect on suicidality was evaluated. Several pooled analyses comparing industry datasets of individual ADs, mostly SSRIs, but also including serotonin-noradrenalin reuptake inhibitors (SNRIs) and mirtazepine, demonstrated a greater average reduction of the suicidal thoughts score with SSRIs, as well as comparator drugs like TCAs, compared to placebo [110]. In addition, the categories "worsening of pre-existing suicidal thoughts" or "new emergence of suicidal thoughts" were less frequent in the SSRI or TCA groups than in the placebo groups. These studies and meta-analyses generally found no increased risk of suicidal behaviour. Several meta-analyses on larger datasets of novel ADs from national drug authorities which took the suicide attempt rate or suicide rate as the outcome criterion also failed to demonstrate an increased risk of suicidal behaviour during treatment with SSRIs or ADs in general [51]. Only the meta-analysis by Fergusson et al. [34], based on a very large dataset from a Cochrane database on AD trials, found a significantly increased risk of suicide attempts for SSRIs compared to placebo–but not different from TCAs!–compared to placebo conditions [111].

A meta-analysis by the FDA of the AD studies in children or adolescents found an increase of suicidal thoughts and suicide attempts but not suicide [30,52,53,192]. The respective FDA black box warning for adolescents led to decreased antidepressant use in this age population and an increased suicide rate, however, only measured on the epidemiological level [46].

The most comprehensive and methodologically differentiated meta-analysis was performed on this topic by a special FDA task force reviewing the relationship between antidepressant drugs and suicidality in adults [175,176]. This meta-analysis included the most comprehensive database of placebo-controlled trials for various indications in this research field. The trial data were submitted by the manufacturers of the 11 antidepressant drugs studied (buproprion, citalopram, duloxetine, escitalopram, fluvoxamine, fluoxetine, mirtazapine, nefazodone, paroxetine, sertraline, venlafaxine). The primary outcome of the study was suicide-related behaviour (defined as including completed suicide, suicide attempt, preparatory acts toward imminent suicidal behaviour and suicidal ideation). Data were available from a total of 99,839 subjects in 372 trials, constituting a total of 15,505 subject years. Indications included major depressive disorder, other depression, other psychiatric disorders, other behavioural disorders and non-behavioural disorders. During the period of observation, eight subjects committed suicide, 134 attempted suicide, 10 made preparatory actions without ever attempting suicide and 378 reported suicidal ideation without taking any action. For reasons of space, it is impossible to describe in this position statement all the results of the different analyses performed, so that only the main results are reported here.

The estimated odds ratio for suicide-related behaviour (preparatory acts, attempts and completed suicide) associated with assignment to antidepressant drug treatment compared to placebo was 1.12 (95% CI, 0.79–1.58) for the whole dataset, indicating an overall non-significant risk with antidepressant drug treatment. The estimates of suicidality risk (ideation, preparatory acts, attempts and completed suicide) associated with assignment to antidepressant drug treatment compared to placebo observed from the entire dataset showed a slightly lower but not statistically significant risk with antidepressant drug treatment. Most statistical tests for differences in effect among drugs and drug classes were negative, with the exception of an indication of differences among drugs in the SSRI category. The likelihood ratio for suicidality from older drugs relative to newer drugs was 0.84 (95% CI 0.54–1.31, $P = 0.44$), i.e. suicidality was slightly but not significantly less likely with the older than with the newer drugs. Findings were similar for suicidal behaviour of adults with psychotic disorders. The likelihood ratio for suicidal behaviour from older drugs relative to newer drugs was 0.76 (95% CI 0.38–1.50, $P = 0.43$). The odds ratios for active drug relative to placebo by different psychiatric diagnoses are not widely different from each other, but the psychiatric diagnostic categories (major depression, other depression and other psychiatric) are remarkably similar, while the non-psychiatric categories appear similar to each other but distinct from the psychiatric categories. None of these differences, however, are statistically significant [175]. This confirms the calculations of Gunnell et al. [51] that the risks in controlled trials are so low that sample sizes over 200,000 would be required to detect meaningful differences.

The age ranges within the adult and paediatric studies overlap slightly and the results can be analysed together to fully assess the interaction of age with AD treatment. For both suicidality and suicidal behaviour, the slope of the interaction between AD treatment and age did not differ among antidepressants ($P = 0.22$ for suicidality and $P = 0.81$ for suicidal behaviour), nor did it differ by antidepressant classes ($P = 0.28$ for suicidality and $P = 0.78$ for suicidal behaviour). One key observation is that suicidality is positively associated with assignment to treatment with ADs in subjects under 25 years of age (Odds Ratio 1.62, 95% CI 0.97–2.71, $P = 0.07$) but negatively associated (Odds Ratio 0.74, 95% CI 0.60–0.90, $P = 0.003$) with suicidality in subjects aged 25 and older. There also appears to be a further distinction between a modest protective effect in subjects aged 25–64 (Odds Ratio 0.79, 95% CI 0.64–0.98, $P = 0.03$) and a stronger protective effect in subjects aged 65 and older (Odds Ratio 0.37, 95% CI 0.18–0.76, $P = 0.007$). Fig. 2a shows these age categories graphically as well as displaying risk for suicidality as a continuous function of age. The results concerning the risks for suicidal behaviour associated with assignment to AD treatment for adult subjects with psychiatric disorders broken down by age also show a significant positive association with assignment to treatment with ADs in subjects less than 25 years of age but no overall association with suicidal behaviour in subjects aged 25 and older. There appears to be a significant protective effect of antidepressant treatment in subjects aged 65 and older (Fig. 2b).

Approximately 50% of subjects who received active drug and 40% of subjects who received placebo were designated as responders. Among those who were considered to have responded to treatment, 0.26% of all subjects with major depressive disorders and 0.13% of subjects with other psychiatric disorders displayed suicidal ideation or behaviour. For subjects considered non-responders, 1.18% with major depressive disorders and 0.55% with other psychiatric disorders displayed suicidal ideation or

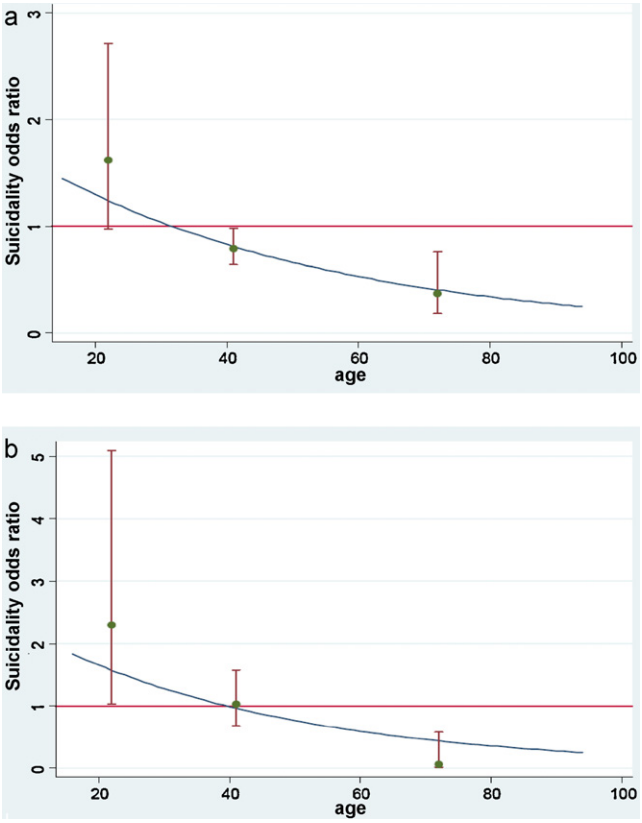


Fig. 2. a. Suicidality odds ratio for active drug relative to placebo–adults with psychiatric disorders–by age. b. Suicidal behaviour odds ratios for active drug relative to placebo–adults with psychiatric disorders–by age.

behaviour. The results for suicidal behaviour and suicidality odds ratios for active drug vs. placebo by subject response and age category are consistent with the idea that an increased risk of suicidal behaviour in young adults associated with AD treatment may be limited to subjects who do not show a clinical response to treatment, but this observation is far from statistically significant and would require a larger sample to make any conclusions. A further contributing factor to suicidality in the young age group may be the fact that bipolar depression starts at a younger age than unipolar depression [20], and bipolar depression is closely linked to suicidality best explained by the high frequency of mixed states in bipolar depression [10].

Concerning the time course of suicidality in depressed patients before and after starting pharmacotherapy or psychotherapy: In a study including more than 7000 patients, suicide attempts were "highest in the month before starting treatment, next highest in the month after starting treatment, and declining thereafter" [171].

There is a final minor but potentially important confounding point. Studies conducted in children have often been designed to establish "safety" rather than efficacy, to use the summary jargon of industry. This has had the consequence that industry-supported studies have failed to demonstrate efficacy because placebo response rates have been very high. In such studies, ascertainment bias relating to adverse event reporting may have been maximized, and might account for some or all of the differences between different age groups.

A publication by Perlis et al. [146], as part of the STAR*D study, reported an association between treatment-emergent suicidal ideation with citalopram and a polymorphism near cyclic adenosine monophosphate response element binding protein. This approach can be further substantiated for individual medications but not for all antidepressants as a group phenomenon. Currently, such a pharmacogenetic approach is far away from clinical routine application.

Additional findings come from other data sources. It is difficult to summarise the somewhat inconsistent results of the case-control and other types of clinical cohort studies. Relevant confounders like differential prescribing to patients perceived to be more ill and/or at greater risk of suicidal behaviour were not taken into account in all of these studies. When they were considered in the statistical analysis, any indications of greater risk associated with SSRIs or ADs, in general, could no longer be demonstrated or their size was reduced. Altogether, these data have to be interpreted very carefully and cannot be seen as proof in one or the other direction [111]. Of interest in this context is the study by Simon and Savarino [171] demonstrating that pharmaco-epidemiological studies that applied sophisticated statistical methods to investigate the association between the prescription risks for TCAs/SSRIs and suicide rates generally found no increased risk of suicide with ADs in general, and in particular no increase with SSRIs. The opposite is true: They generally found that a higher prescription rate of ADs, mostly SSRIs, was associated with a reduction of suicide rate [48,69,110]. Thus if SSRIs or ADs in general do have a suicidality-inducing effect, this does not appear to translate into an increased risk of suicide in the epidemiological perspective. The opposite is the case, i.e. an increased prescription of ADs, preferentially SSRIs, generally leads to a reduction of suicide risk.

The time pattern of risk under treatment either with psychotherapy or AD treatment is similar, being the highest before the start of treatment and afterwards is reduced. The case register study by Tiihonen et al. [186] is also interesting, with the following result: Among suicidal subjects who had ever used antidepressants, the current use of any antidepressant was associated with a markedly increased risk of attempted suicide and, at the same time, with a markedly decreased risk of completed suicide and death.

Differences in the fatal toxicity of ADs are of relevance for the discussions about potential harmful effects of ADs in terms of suicidality. There is clear evidence that most modern ADs, especially the SSRIs, have a lower fatal toxicity risk than the TCAs when a patient uses them to attempt suicide [38]. In everyday clinical practice, the discussion about the possible risks of SSRIs or ADs, in general, should not result in clinicians forgetting the benefits of these drugs, especially their lower fatal toxicity profile. This is a great advantage, especially in patients with severe suicidality where the choice of a less toxic AD helps to reduce the risk of fatality if the patient should misuse the AD for a suicide attempt [118].

Different mechanisms could principally lead to suicidality-enhancing effects. These might, for example, be related to the pharmacological mode of action in different transmitter systems, to pharmacogenetic dispositioning [146] to special pharmacodynamic properties like activating/drive-enhancing effects or to side effects like akathisia [163]. As for special dispositions of patients, personality disturbances such as borderline personality disorder, comorbidity, non-response, bipolarity and other factors should be considered [10,107,182]. When hypothesising possible mechanisms for a potentially higher suicide rate with ADs, the fact that determination of the suicide risk of an individual patient or the general suicide rate is very complex and involves the integration of different factors deserves consideration. For example, the hypothesised induction by of suicidal thoughts or even suicidal ideation by SSRIs may be balanced by a lower risk of a fatal outcome of a suicide attempt with an SSRI compared to a TCA. However, on the other hand, it needs to be clearly stated that no treatment might increase the suicide rate possibly threefold, as can be derived from the naturalistic study by Angst et al. [8].

Beside all these considerations, the symptoms of the acute depressive episode and the risk of relapse [16,44,149,198] require an effective drug treatment that simultaneously reduces suicidal thoughts. An overcritical position which places much more importance on the risk of inducing suicidality than on the efficacy of ADs [88,126] should be avoided [45,117,118,120]. One should remember that psychosocial interventions, which are often suggested as an alternative, might be ineffective under certain circumstances [196], and may even induce suicidality themselves [108,109]. Short-term [110] and long-term data in particular underline the beneficial effects of ADs on suicidality and suicidal behaviour [7].

Of course, particularly at the start of treatment patients are often not only emotionally labile but also have decreased motor inhibitions when still emotionally depressed, and it is theoretically possible that in single cases ADs, probably depending on their specific pharmacological and pharmacodynamic characteristics and in interaction with a patient's special predisposing characteristics such as personality traits and comorbidity, can induce or enhance suicidal thoughts or even reduce the threshold level for attempting or committing suicide. It is a question of good clinical practice to monitor every patient carefully, especially at the start of a drug treatment after one week and then every second week, and to try to avoid any kind of risk. Under these conditions, the risk of induced/increased suicidality is extremely low, as described in empirical studies [163]. In case of agitation, akathisia, sleep disturbances or other symptoms or drug side effects that may potentially induce or enhance suicidality, a sedating anxiolytic or sleep-inducing comedication should be considered. It is also of the greatest importance that the patient be offered substantial support. Finally, it should not be forgotten that depressive symptoms and suicidal thoughts can fluctuate over the course of a day or over longer time periods. It is often difficult to follow these fluctuations carefully enough on an outpatient basis. If still available, which is unfortunately not possible in all European countries (like the UK, due to financial restrictions) inpatient treatment might be a better option for patients at an especially high risk. Treatment with ADs under inpatient conditions, which allows careful monitoring in appropriate cases, seems to be quite safe in terms of emergence or worsening of suicidality [163].

8. Individualising (personalising) clinical decision making in the treatment of depression

Clinical decision-making is a very complex issue [119]. The intention to optimise clinical decision making in such a way that the aim to find the right therapy for the right patient can be achieved is full of challenges. It is possibly more an idealistic version than an achievable reality. This is true for drug treatment, and even more so for psychotherapy or the combination of both.

The compiling of a correct diagnosis is essential because specific depressive subtypes are known to have a poor response to specific antidepressants, which can imply a seeming treatment resistance [64]. What is also important is the recording of a psychiatric comorbidity, since comorbidity can be connected to a seeming treatment resistance. About three-quarters of patients with a treatment-resistant depression show comorbid psychiatric disorders such as personality and panic disorders, alcohol/substance abuse and neuroticism [168]. In these cases, the result of the treatment depends on the efficacy of the depression therapy as well as on the therapy of the comorbid disorder. A number of somatic illnesses and also medications are known to cause depression.

Subtyping of depression, e.g. in terms of psychotic depression, melancholic depression, atypical depression, etc., has a long tradition in psychiatry [63,112,113,115,198], among other approaches, in relation to treatment indication and improving outcome through the most adequate treatment. Melancholic depression, formerly also referred to as endogenous depression, is seen to be the prototype of a 'biological' depression and the type most likely to respond positively to antidepressants. This condition has been a topic of discussion for a long time, and was recently addressed by Parker et al. [140] on the basis of new research data focussing on the relevance of somatic symptoms, among others. On the basis of results of routine care documentation, Parker and colleagues came to the conclusion that TCAs and monoamine oxidase inhibitors (MAOIs) are the most effective pharmacological treatments for melancholic depression, while the newer agents (SSRIs, reversible inhibitors of non-reversible monoamine oxidase-A and antipsychotic drugs) are much less effective. In a subsequent publication, albeit of preliminary results, Parker found that TCAs and SSRIs may not differ distinctly in their effectiveness in younger patients with melancholia, but that SSRIs are differentially less effective in older melancholic patients, and this effect was unlikely to be secondary to age of disorder onset or to the length of lifetime depressive experience [141]. In Parker's view, an understanding of the impact of age on antidepressant drug response across melancholic and non-melancholic depressive subtypes may help to clarify differential drug effectiveness patterns, and to link the underlying neuropathological changes to clinical management, including the choice of an antidepressant. As another example, the subtype atypical depression can be mentioned here, which for a long time has been seen as an indication for treatment with MAO inhibitors [63,163].

In clinical research, apart from the classification of subtypes of depression also clinical/anamnestic predictors were examined regarding the response to antidepressants. The following characteristics were relatively consistently described as relevant for a rather poor response to antidepressants [89,122,164], which could mostly be confirmed in recent studies [63,168,190,199,200] (Table 1).

Especially the insufficient response in the first 14 days of therapy with antidepressants seems to be of great prognostic importance for the further therapy course as regards response and remission [63,180]. Based on such results, it was suggested [180], but not unanimously accepted, that in the case of an insufficient response after the first 14 days of treatment a switch to another AD or treatment approach (e.g. antipsychotic augmentation) should be considered.

The variance rates described by most single predictors are for the most part so minor that they hardly have any predictive value for a single patient. They can at best contribute to group statistical differentiation. The possibilities of combining predictors for the improvement of prognosis have been examined only by few authors [162]. In general, multiple variables were hardly examined regarding their prognostic meaning. The demonstrated predictors are more of a general type. On the level of clinical/anamnestic parameters, reproducible predictors for the response to specific antidepressants could not been found so far. Recently, patients' preference for a special drug or treatment approach was suggested as an important moderator of outcome in treatment of depression [90]. This might change the classical doctor–patient relationship towards the model of shared decision making.

The consideration of biological parameters has also not improved the possibilities of prediction in a way that could be employed in daily hospital routine [172]. The following are some of the possible biological predictors for the response to antidepressants which have been investigated: the metabolites from central nervous system transmitters which are relevant in depression (methoxyhydroxyphenylglycol, hydroxyindole acetic acid), the activity of enzymes involved in transmitter metabolism (MAO, DBH, COMT), neuroendocrinological parameters (dexamethasone suppression test [DST] status, growth hormone [GH] response to clonidine, thyroid stimulating hormone [TSH]

Table 1
Poor response associated with antidepressant treatment.

Poor social adaptation
Neurotic traits in the premorbid personality
Number and duration of earlier psychiatric inpatient treatments
Non-response to earlier treatments with antidepressants
Chronification of the depressive symptoms
Mild degree of depressive symptoms
Delusions
Absence of vital symptoms
Insufficient improvement in the first 10–20 days of antidepressant treatment

response to thyrotropin-releasing hormone [TRH], prolactin response to fenfluramine), neurophysiological parameters such as rapid eye movement (REM) latency, electrodermal activity, electroencephalography (EEG) resting activity, acoustically evoked potentials [54], alterations of the hippocampus measured with magnetic resonance tomography (MRT) [42]. However, so far these biological predictors have not been introduced into clinical practice, for reasons such as inconsistencies in the results, low percentage of explained variance, impracticability, costs, etc. In treatment-resistant cases, AD blood levels have to be assessed first of all.

In this context, pharmacogenetics have increasingly gained interest for the prediction of response to antidepressants in terms of individual pharmacokinetic and pharmacodynamic particularities. The initially enthusiastic statements on the possibility of making use of a "genetic fingerprint" with the help of genetic technology within a few years, to be able to show the complete picture of respective individual dispositions, has given way to the disillusion that obviously this is nothing but another process, from which the output will possibly not be reached as quickly as initially estimated [125]. Especially the polymorphisms of the serotonin transporter protein (HTT) have been examined regarding antidepressant response [29,165,166,181], but also involving other targets like a polymorphism in the drug-transporter protein ABCB1 [194].

The results are in parts often controversial and the demonstrated variance per polymorphism is relatively minor. The positive outcome of extensive further research will have to be awaited before it is possible to sufficiently determine the respective significance of pharmacogenetics. There is still hope that in the end the optimal combination of pharmacogenetic predictors in the sense of a 'genetic fingerprint' will move the field forward in the expected direction. The possibility of better prediction in single cases would be especially important: with regard to the special target group of poor responders it would be possible to make use of different treatment strategies, specific antidepressants, higher dosage, combination therapy, ECT, etc. from the very beginning instead of obtaining knowledge about the treatment process first. Similarly, also the risk of side effects could be individually predicted and the therapeutic decision could also be personalised in this respect.

9. Conclusion

Antidepressants do have a clinically relevant efficacy in acute and long-term treatment of depressive patients. Therefore they are first-choice therapy, especially in moderate to severe depression, amongst other reasons also due to their easy handling. The in part poor placebo-verum differences shown in meta-analyses on mean score values can be explained by specific baseline conditions and confounding factors of placebo-controlled studies. Differences in responder rates between antidepressants and placebo translate into clinically relevant NNTs.

Antidepressants remain first-choice therapy for most patients also because of their good tolerability, despite the issues–discussed in recent years–regarding the possible induction of suicidality by antidepressants especially through SSRIs. Extensive meta-analyses have shown that there is low risk of induction of suicidality, not only in association with SSRIs, but related to all antidepressants, especially in the age group below 25 years. Under the condition of "good clinical practice", it can be kept under control in the daily clinical care, and should not be brought up as a general argument against the treatment with antidepressants for the therapy of depression. On the contrary, the positive effect in terms of general reduction of depressive syndromes in general as well as suicidality should be emphasised in the argumentation.

The efficacy of antidepressants is increased by sequential and combination therapies in daily clinical practice. Psychosocial as well as psychotherapeutic factors also contribute to a positive therapeutic result. Therefore, it is important that therapy with antidepressants is not regarded as the only solution, but that antidepressant therapy is embedded in a complex therapeutic approach. Psychotherapeutic therapies, especially therapies from the field of cognitive behavioural therapy and other pragmatically oriented therapies such as IPT, for example, have gained importance in recent years, after the efficacy of these therapies was proven in controlled studies.

Looking at the complexity of the aetiopathogenesis of depression and the respective heterogeneity of subtypes of depression or even single patients, it is not surprising that therapy effects do have their limits regarding efficacy. An individualised indication can optimise the efficacy in single cases. However, there are only few reliable clinical and biological predictors, which could contribute to an optimal indication. High expectations in this regard are directed at pharmacogenetics, which has already generated interesting single findings. However, according to current findings, the explained variance of single gene polymorphisms seems to be minor, so that only the combination of various gene polymorphisms can realise the idea of individualising/personalising the therapy decision in individual cases. Analogous arguments and possibilities hold true for a differential indication and individualised therapy decision regarding tolerability.

Health economic analyses have not been covered in this position statement, but they play an increasingly important role in times of scarcity of resources in the healthcare sector. They can bring additional aspects into clinical decision-making processes, especially if in future the resource allocation in the healthcare system is not primarily carried out according to medical results of therapy trials, but results from healthcare economic differentiations between different therapies by respective institutions like NICE. Results will be different depending on which content and methodological criteria underlie them [24,201]. In contrast to tendencies in the healthcare economics sector, which primarily puts hard criteria such as hospitalisation or unemployability in the foreground, physicians should especially emphasise the importance of the patient's subjective well-being and quality of life in the argumentation. These thoughts demonstrate the extent to which a value-bound approach [43] is necessary when decisions on therapy are made, and that clinical decisions are by no means affected merely by empirical knowledge about efficacy and tolerability.

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References

[1] Adli M, Bauer M, Rush AJ. Algorithms and collaborative care systems for depression: are they effective and why? Biol Psychiatry 2006;59:1029–38.

[2] Adli M, Berghöfer A, Linden M, Helmchen H, Müller-Oerlinghausen B, Mackert A, et al. Effectiveness and feasibility of a standardized stepwise drug treatment regimen algorithm for inpatients with depressive disorders: results of a 2-year observational algorithm study. J Clin Psychiatry 2002;63(9):782–90.

[3] Alonso J, Angermeyer MC, Bernert S, Bruffaerts R, Brugha TS, Bryson H, et al. Prevalence of mental disorders in Europe: results from the European Study of the Epidemiology of Mental Disorders (ESEMeD) project. Acta Psychiatr Scand Suppl 2004;420:21–7.

[4] American Psychiatric Association. APA Practice Guidelines - treatment of patients with major depressive disorder, Second Edition. http://www.psychiatryonline.com/pracGuide/pracGuideChapToc_7.aspx [Second]. 2000. [Ref Type: Electronic Citation].

[5] Anderson IM. Selective serotonin reuptake inhibitors versus tricyclic antidepressants: a meta-analysis of efficacy and tolerability. J Affect Disord 2000;58(1):19–36.

[6] Anderson IM, Ferrier IN, Baldwin RC, Cowen PJ, Howard L, Lewis G, et al. Evidence-based guidelines for treating depressive disorders with antidepressants: a revision of the 2000 British Association for Psychopharmacology guidelines. J Psychopharmacol 2008;22(4):343–96.

[7] Angst J, Angst F, Gerber-Werder R, Gamma A. Suicide in 406 mood-disorder patients with and without long-term medication: a 40 to 44 years' follow-up. Arch Suicide Res 2005;9(3):279–300.

[8] Angst J, Gamma A, Sellaro R, Zhang H, Merikangas K. Toward validation of atypical depression in the community: results of the Zurich cohort study. J Affect Disord 2002;72(1):125–38.

[9] Baghai TC, Volz HP, Moller HJ. Drug treatment of depression in the 2000s: an overview of achievements in the last 10 years and future possibilities. World J Biol Psychiatry 2006;7(4):198–222.

[10] Balazs J, Benazzi F, Rihmer Z, Rihmer A, Akiskal KK, Akiskal HS. The close link between suicide attempts and mixed (bipolar) depression: implications for suicide prevention. J Affect Disord 2006;91(2–3):133–8.

[11] Baldwin D, Broich K, Fritze J, Kasper S, Westenberg H, Möller HJ. Placebo-controlled studies in depression: necessary, ethical and feasible. Eur Arch Psychiatry Clin Neurosci 2003;253:22–8.

[12] Barbui C, Campomori A, D'Avanzo B, Negri E, Garattini S. Antidepressant drug use in Italy since the introduction of SSRIs: national trends, regional differences and impact on suicide rates. Soc Psychiatry Psychiatr Epidemiol 1999;34(3):152–6.

[13] Bauer M, Bschor T, Pfennig A, Whybrow PC, Angst J, Versiani M, et al. World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders in Primary Care. World J Biol Psychiatry 2007;8(2):67–104.

[14] Bauer M, Tharmanathan P, Volz HP, Moeller HJ, Freemantle N. The effect of venlafaxine compared with other antidepressants and placebo in the treatment of major depression: a meta-analysis. Eur Arch Psychiatry Clin Neurosci 2009;259(3):172–85.

[15] Bauer M, Whybrow PC, Angst J, Versiani M, Möller HJ, WFSBP Task Force on Treatment Guidelines for Unipolar Depressive Disorders. World Federation of Societies of Biological Psychiatry (WFSBP) guidelines for biological treatment of unipolar depressive disorders, Part 1: acute and continuation treatment of major depressive disorder. World J Biol Psychiatry 2002;3:5–43 [Ref Type: Journal (Full)].

[16] Bauer MS, Wisniewski SR, Marangell LB, Chessick CA, Allen MH, Dennehy EB, et al. Are antidepressants associated with new-onset suicidality in bipolar disorder? A prospective study of participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) J Clin Psychiatry 2006;67(1):48–55.

[17] Bech P. Depressive symptomatology and drug response. Commun Psychopharmacol 1978;2(5):409–18.

[18] Bech P. Is the antidepressive effect of second-generation antidepressants a myth? Psychol Med 2009;1–6.

[19] Belmaker RH, Agam G. Major depressive disorder. N Engl J Med 2008;358(1):55–68.

[20] Benazzi F, Akiskal HS. How best identify to a bipolar-related subtype among major depressive patients without spontaneous hypomania: superiority of age at onset criterion over recurrence and polarity? J Affect Disord 2008;107(1–3):77–88.

[21] Brent DA. Antidepressants and pediatric depression - the risk of doing nothing. N Engl J Med 2004;351:1598–601.

[22] Bschor T, Berghöfer A, Ströhle A, Kunz D, Adli M, Müller-Oerlinghausen B, et al. How long should the lithium augmentation strategy be maintained? A 1-year follow-up of a placebo-controlled study in unipolar refractory major depression. J Clin Psychopharmacol 2002;22(4):427–30.

[23] Caspi A, Moffitt TE. Gene-environment interactions in psychiatry: joining forces with neuroscience. Nat Rev Neurosci 2006;7(7):583–90.

[24] Cipriani A, Furukawa TA, Salanti G, Geddes JR, Higgins JP, Churchill R, et al. Comparative efficacy and acceptability of 12 new-generation antidepressants: a multiple-treatments meta-analysis. Lancet 2009;373(9665):746–58.

[25] Crossley NA, Bauer M. Acceleration and augmentation of antidepressants with lithium for depressive disorders: two meta-analyses of randomized, placebo-controlled trials. J Clin Psychiatry 2007;68(6):935–40.

[26] Cuijpers P, van Straten A, Warmerdam L. Behavioral activation treatments of depression: a meta-analysis. Clin Psychol Rev 2007;27(3):318–26.

[27] de Maat S, Dekker J, Schoevers R, van Aalst G, Gijsbers-van Wijk C, Hendriksen M, et al. Short psychodynamic supportive psychotherapy, antidepressants, and their combination in the treatment of major depression: a mega-analysis based on three randomized clinical trials. Depress Anxiety 2008;25(7):565–74.

[28] Deutsche Gesellschaft für Psychiatrie PuN. S3-Leitlinien/Nationale VersorgungsLeitlinie Unipolare Depression. In: DGPPN, BÄK, KBV, AWMF, AkdÄ B, BApK et al., editors. 2009. Berlin, Düsseldorf, Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde.

[29] Drago A, De Ronchi D, Serretti A. Pharmacogenetics of antidepressant response: an update. Hum Genomics 2009;3(3):257–74.

[30] European Medicines Agency Press Office. European Medicines Agency finalises review of antidepressants in children and adolescents. http://www.ema.europa.eu/pdfs/human/press/pr/12891805en.pdf. 2005 Ref Type: Internet Communication.

[31] Fava GA, Grandi S, Zielezny M, Canestrari R, Morphy MA. Cognitive behavioural treatment of residual symptoms in primary major depressive disorder. Am J Psychiatry 1994;151:1295–9.

[32] Fava GA, Grandi S, Zielezny M, Rafanelli C, Canestrari R. Four-year outcome for cognitive behavioural treatment of residual symptoms in major depression. Am J Psychiatry 1996;153:945–7.

[33] Fava GA, Rafanelli C, Grandi S, Canestrari R, Morphy MA. Six year outcome for cognitive behavioural treatment of residual symptoms in major depression. Am J Psychiatry 1998;155:1443–5.

[34] Fergusson D, Doucette S, Glass KC, Shapiro S, Healy D, Hebert P, et al. Association between suicide attempts and selective serotonin reuptake inhibitors: systematic review of randomised controlled trials. BMJ 2005;330(7488):396.

[35] Fountoulakis KN, Möller HJ. Efficacy of antidepressants: a re-analysis and re-interpretation of the Kirsch data. Int J Neuropsychopharmacol 2011;14(3):405–12.

[36] Fournier JC, DeRubeis RJ, Hollon SD, Dimidjian S, Amsterdam JD, Shelton RC, et al. Antidepressant drug effects and depression severity. A patient-level meta-analysis. JAMA 2010;303(1):47–53.

[37] Frank E, Kupfer D, Perel J, Cornes C, Jarrett D, Mallinger A. Three-year outcomes for maintenance therapies in recurrent depression. Arch Gen Psychiatry 1990;47:1093–9.

[38] Frey R, Schreinzer D, Stimpfl T, Vycudilik W, Berzlanovich A, Kasper S. Suicide by antidepressant intoxication identified at autopsy in Vienna from 1991–1997: the favourable consequences of the increasing use of SSRIs. Eur Neuropsychopharmacol 2000;10:133–42.

[39] Friedman MA, Detweiler-Bedell JB, Leventhal HW, Horne R, Keitner GI, Miller IW. Combined psychotherapy and pharmacotherapy for the treatment of depression disorder. Clin Psychol Sci Pract 2004;11:47–68.
[40] Fritze J, Möller HJ. Design of clinical trials of antidepressants. Should a placebo control arm be included? CNS Drugs 2001;15(10):755–64 [Ref Type: Journal (Full)].
[41] Frodl T, Meisenzahl EM, Zill P, Baghai T, Rujescu D, Leinsinger G, et al. Reduced hippocampal volumes associated with the long variant of the serotonin transporter polymorphism in major depression. Arch Gen Psychiatry 2004;61(2):177–83.
[42] Frodl T, Moller HJ, Meisenzahl E. Neuroimaging genetics: new perspectives in research on major depression? Acta Psychiatr Scand 2008;118(5):363–72.
[43] Fulford KWM. Facts/values: ten principles of value-based medicine. In: Radden J, editor. The philosophy of psychiatry: a companion. New York: Oxford University Press; 2004.
[44] Geddes JR, Carney SM, Davies C, Furukawa TA, Kupfer DJ, Frank E, et al. Relapse prevention with antidepressant drug treatment in depressive disorders: a systematic review. Lancet 2003;361(9358):653–61.
[45] Geddes JR, Cipriani A. Selective serotonin reuptake inhibitors. BMJ 2004;329(7470):809–10.
[46] Gibbons RD, Brown CH, Hur K, Marcus SM, Bhaumik DK, Erkens JA, et al. Early evidence on the effects of regulators' suicidality warnings on SSRI prescriptions and suicide in children and adolescents. Am J Psychiatry 2007;164(9):1356–63.
[47] Goodwin GM, Emsley R, Rembry S, Rouillon F. Agomelatine prevents relapse in patients with major depressive disorder without evidence of a discontinuation syndrome: a 24-week randomized, double-blind, placebo-controlled trial. J Clin Psychiatry 2009;70(8):1128–37.
[48] Grunebaum MF, Ellis SP, Li S, Oquendo MA, Mann JJ. Antidepressants and sucide risk in the United States, 1985–1999. J Clin Psychiatry 2004;65(1):1456–62.
[49] Grunze H, Vieta E, Goodwin GM, Bowden C, Licht RW, Möller HJ, et al. The World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for the Biological Treatment of Bipolar Disorders: update 2010 on the treatment of acute bipolar depression. World J Biol Psychiatry 2010;11(2):81–109.
[50] Guaiana G, Andretta M, Corbari L, Mirandola M, Sorio A, D'Avanzo B, et al. Antidepressant drug consumption and public health indicators in Italy, 1955 to 2000. J Clin Psychiatry 2005;66(6):750–5.
[51] Gunnell D, Saperia J, Ashby D. Selective serotonin reuptake inhibitors (SSRIs) and suicide in adults: meta-analysis of drug company data from placebo controlled, randomised controlled trials submitted to the MHRA's safety review. BMJ 2005;330:385–9.
[52] Hammad T. Review and evaluation of clinical data: relationship between psychotropic drugs and pediatric suicidality.www.fda.gov/OHRMS/DOCKETS/AC/04/briefing/2004-4065b1-10-TAB08-Hammads-Review.pdf. 16-8-2004. Ref Type: Electronic Citation.
[53] Hammad TA, Laughren T, Racoosin J. Suicidality in pediatric patients treated with antidepressant drugs. Arch Gen Psychiatry 2006;63(3):332–9.
[54] Hegerl U, Gallinat J, Juckel G. Event-related potentials. Do they reflect central serotonergic neurotransmission and do they predict clinical response to serotonin agonists? J Affect Disord 2001;62(1–2):93–100.
[55] Hegerl U, Hautzinger M, Mergl R, Kohnen R, Schütze M, Scheunemann W, et al. Effects of pharmacotherapy and psychotherapy in depressed primary care patients: a randomised, controlled trial including a patient choice arm. Int J Neuropsychopharmacol 2010;13(1):31–44.
[56] Hegerl U, Mergl R. The clinical significance of antidepressant treatment effects cannot be derived from placebo-verum response differences. J Psychopharmacol 2010;24(4):445–8.
[57] Hegerl U, Mergl R, Havers I, Schmidtke A, Lehfeld H, Niklewski G, et al. Sustainable effects on suicidality were found for the Nuremberg alliance against depression. Eur Arch Psychiatry Clin Neurosci 2010;(5):401–6.
[58] Hegerl U, Plattner A, Moller HJ. Should combined pharmaco- and psychotherapy be offered to depressed patients? A qualitative review of randomized clinical trials from the 1990s. Eur Arch Psychiatry Clin Neurosci 2004;254(2):99–107.
[59] Hegerl U, Seemann O, Müller-Siecheneder F. Depression and suicidal behavior more effectively controlled by a team approach. Pilot project to optimize diagnosis and therapy. MMW Fortschr Med 1999;141(48):43–5 [Article in German].
[60] Henkel V, Mergl R, Allgaier AK, Kohnen R, Möller HJ, Hegerl U. Treatment of depression with atypical features: a meta-analytic approach. Psychiatry Res 2006;141(1):89–101.
[61] Henkel V, Mergl R, Kohnen R, Maier W, Möller HJ, Hegerl U. Identifying depression in primary care: a comparison of different methods in a prospective cohort study. BMJ 2003;326(7382):200–1.
[62] Henkel V, Seemüller F, Obermeier M, Adli M, Bauer M, Kronmüller K et al. Relationship between baseline severity of depression and antidepressant treatment outcome. Pharmacopsychiatry 2011;44(1):27–32.
[63] Henkel V, Seemuller F, Obermeier M, Adli M, Bauer M, Mundt C, et al. Does early improvement triggered by antidepressants predict response/remission? Analysis of data from a naturalistic study on a large sample of inpatients with major depression. J Affect Disord 2009;115(3):439–49.
[64] Hirschfeld RM, Montgomery SA, Aguglia E, Amore M, Delgado PL, Gastpar M, et al. Partial response and nonresponse to antidepressant therapy: current approaches and treatment options. J Clin Psychiatry 2002;63(9):826–37.
[65] Holsboer F, Ising M. Central CRH system in depression and anxiety - evidence from clinical studies with CRH1 receptor antagonists. Eur J Pharmacol 2008;583:350–7.
[66] Horder J, Matthews P, Waldmann R. Placebo, Prozac and PLoS: significant lessons for psychopharmacology. J Psychopharmacol 2010, [Epub ahead of print].
[67] Höschl C, Svestka J. Escitalopram for the treatment of major depression and anxiety disorders. Expert Rev Neurother 2008;8(4):537–52.
[68] Huf W, Kalcher K, Pail G, Friedrich ME, Filzmoser P, Kasper S. Meta-Analysis: fact or fiction? How to interpret meta-analyses. World J Biol Psychiatry 2011;12(3):188–200.
[69] Isacsson G. Suicide prevention - a medical breakthrough? Acta Psychiatr Scand 2000;102:113–7.
[70] Kahn A, Khan S. Placebo response in depression: a perspective for clinical practice. Psychopharmacol Bull 2008;41(3):91–8.
[71] Kahn RS, Fleischhacker WW, Boter H, Davidson M, Vergouwe Y, Keet IP, et al. Effectiveness of antipsychotic drugs in first-episode schizophrenia and schizophreniform disorder: an open randomised clinical trial. Lancet 2008;371(9618):1085–97.
[72] Karasu TB, Gelenberg A, Merriam A, Wang P, American Psychiatric Association. Practice guideline for the treatment of patients with major depressive disorder (revision). Am J Psychiatry 2000;157:1–45.
[73] Kasper S, Hamon M. Agomelatine, a new antidepressant with an innovative mechanism of action - an overview on its preclinical and clinical development program. World J Biol Psychiatry 2009;10:117–26.
[74] Kasper S, Montgomery SA, Möller HJ, van Oers HJJ, Schutte AJ, Vrijland P, et al. Longitudinal analysis of the suicidal behavior risk in placebo-controlled studies of mirtazapine in major depressive disorder. World J Biol Psychiatry 2010;11:36–44.
[75] Kasper S, Sacher J, Klein N, Mossaheb N, Attarbaschi-Steiner T, Lanzenberger R, et al. Differences in the dynamics of serotonin reuptake transporter occupancy may explain superior clinical efficacy of escitalopram versus citalopram. Int Clin Psychopharmacol 2009;24(3):119–25.
[76] Kato T. Molecular genetics of bipolar disorder and depression. Psychiatry Clin Neurosci 2007;61(1):3–19.
[77] Katon W, Robinson P, von Korff M, Lin E, Bush T, Ludman E, et al. A mutlifaceted intervention to improve treatment of depression in primary care. Arch Gen Psychiatry 1996;53(10):924–32.
[78] Keller MB. Rationale and options for the long-term treatment of depression. Hum Psychopharmacol 2002;17Suppl1:S43–6.
[79] Keller MB, Gelenberg AJ, Hirschfeld RM, Rush AJ, Thase ME, Kocsis JH, et al. The treatment of chronic depression, part 2: a double-blind, randomized trial of sertraline and imipramine. J Clin Psychiatry 1998;59(11):598–607.
[80] Keller MB, McCullough JP, Klein DN, Arnow B, Dunner DL, Gelenberg AJ, et al. A comparison of nefazodone, the cognitive behavioral-analysis system of psychotherapy, and their combination for the treatment of chronic depression. N Engl J Med 2000;342(20):1462–70.
[81] Keller MB, Trivedi MH, Thase ME, Shelton RC, Kornstein SG, Nemeroff CB, et al. The Prevention of Recurrent Episodes of Depression with Venlafaxine for Two Years (PREVENT) Study: outcomes from the 2-year and combined maintenance phases. J Clin Psychiatry 2007;68(8):1246–56.
[82] Kelsey JE, Entsuah R. Abstract P. 4. W. 031. Neuropsychopharmacol 2002;5(Suppl. 1):S207 [Ref Type: Abstract].
[83] Kessing LV. Severity of depressive episodes according to ICD-10: prediction of risk of relapse and suicide. Br J Psychiatry 2004;184:153–6.
[84] Khan A, Detke M, Khan SR, Mallinckrodt C. Placebo response and antidepressant clinical trial outcome. J Psychiatr Res 2003;191(4):211–8.
[85] Khan A, Khan S. Placebo response in depression: a perspective for clinical practice. Psychopharmacol Bull 2008;41(3):91–8.
[86] Khan A, Leventhal RM, Khan SR, Brown WA. Severity of depression and response to antidepressants and placebo: an analysis of the Food and Drug Administration database. J Clin Psychopharmacol 2002;22(1):40–5.
[87] Kirsch I, Deacon BJ, Huedo-Medina TB, Scoboria A, Moore TJ, Johnson BT. Initial severity and antidepressant benefits: a meta-analysis of data submitted to the Food and Drug Administration. PLoS Med 2008;5(2):e45.
[88] Kirsch I, Moore TJ, Scoboria A, Nicholls S. The emperor's new drugs: an analyses of antidepressant medication data submitted to the U.S. Food and Drug Administration. Prev Treat 2002;23:5.
[89] Klein DF. Listening to meta-analysis but hearing bias. Prev Treat 1, Article 0006c, posted June 26, 1998. http://journals.apa.org/prevention/volume1/pre0010006c.html. 1998. [Ref Type: Electronic Citation].
[90] Kocsis JH, Leon AC, Markowitz JC, Manber R, Arnow B, Klein DN, et al. Patient preference as a moderator of outcome for chronic forms of major depressive disorder treated with nefazodone, cognitive behavioral analysis system of psychotherapy, or their combination. J Clin Psychiatry 2009;70(3):354–61.
[91] Koran LM, Gelenberg AJ, Kornstein SG, Howland RH, Friedman RA, DeBattista C, et al. Sertraline versus imipramine to prevent relapse in chronic depression. J Affect Disord 2001;65(1):27–36.
[92] Lam RW, Hossie H, Solomons K, Yatham LN. Citalopram and Bupropion-SR: combining versus switching in patients with treatment-resistant depression. J Clin Psychiatry 2004;65(3):337–40.
[93] Laux G, Baumann P, Hiemke C. TDM group of the Arbeitsgemeinschaft Neuropsychopharmakologie und Pharmakopsychiatrie. Therapeutic drug monitoring of antidepressants - clinical aspects. J Neural Transm Suppl 2007;72:261–7.

[94] Lépine JP, Caillard V, Bisserbe JC, Troy S, Hotton JM, Boyer P. A randomized, placebo-controlled trial of sertraline for prophylactic treatment of highly recurrent major depressive disorder. Am J Psychiatry 2004;161(5):836–42.
[95] Lépine JP, Gastpar M, Mendlewicz J, Tylee A. Depression in the community: the first pan-European study DEPRES (Depression Research in European Society). Int Clin Psychopharmacol 1997;12(1):19–29.
[96] Lepola U, Wade A, Andersen HF. Do equivalent doses of escitalopram and citalopram have similar efficacy? A pooled analysis of two positive placebo-controlled studies in major depressive disorder. Int Clin Psychopharmacol 2004;19(3):149–55.
[97] Lerer B, Macciardi F. Pharmacogenetics of antidepressant and mood-stabilizing drugs: a review of candidate-gene studies and future research directions. Int J Neuropsychopharmacol 2002;5(3):255–75.
[98] Lichtenberg P, Belmaker RH. Subtyping major depressive disorder. Psychother Psychosom 2010;79:131–5.
[99] Llorca PM, Azorin JM, Despiegel N, Verpillat P. Efficacy of escitalopram in patients with severe depression: a pooled analysis. Int J Clin Pract 2005;59(3):268–75.
[100] Lopez AD, Murray CJL. The global burden of disease, 1990–2020. Nat Med 1998;4(11):1241–3.
[101] Lyness JM, Heo M, Datto CJ, Ten Have TR, Katz IR, Drayer R, et al. Outcomes of minor and subsyndromal depression among elderly patients in primary care settings. Ann Int Med 2006;144(7):496–504.
[102] Maginn S, Boardman AP, Craig TK, Haddad M, Heath G, Stott J. The detection of psychological problems by General Practitioners - influence of ethnicity and other demographic variables. Soc Psychiatry Psychiatr Epidemiol 2004;39(6):464–71.
[103] Maier W, Möller HJ. Meta-analyses: a method to maximise the evidence from clinical studies? Eur Arch Psychiatry Clin Neurosci 2010;260(1):17–23.
[104] Mallinckrodt CH, Prakash A, Houston JP, Swindle R, Detke MJ, Fava M. Differential antidepressant symptom efficacy: placebo-controlled comparisons of duloxetine and SSRIs (fluoxetine, paroxetine, escitalopram). Neuropsychobiology 2007;56(2–3):73–85.
[105] Melander H, Salmonson T, Abadie E, Zwieten-Boot B. A regulatory Apologia - a review of placebo-controlled studies in regulatory submissions of new-generation antidepressants. Eur Neuropsychopharmacol 2008;18(9):623–7.
[106] Mitchell AJ, Vaze A, Rao S. Clinical diagnosis of depression in primary care: a meta-analysis. Lancet 2009;374(9690):609–19.
[107] Möller HJ. Antidepressants - do they decrease or increase suicidality? Pharmacopsychiatry 1992;25:249–53.
[108] Möller HJ. Attempted suicide: efficacy of different aftercare strategies. Int Clin Psychopharmacol 1992;6Suppl6:58–69.
[109] Möller HJ, Suicide. suicidality and suicide prevention in affective disorders. Acta Psychiatrica Scandinavica Supplementum 2003;(418):73–80.
[110] Möller HJ. Evidence for beneficial effects of antidepressants on suicidality in depressive patients: A systematic review. Eur Arch Psychiatry Clin Neurosci 2006;256(6):329–43 [Ref Type: Journal (Full)].
[111] Möller HJ. Is there evidence for negative effects of antidepressants on suicidality in depressive patients? A systematic review. Eur Arch Psychiatry Clin Neurosci 2006;256(8):476–96.
[112] Möller HJ. Is the identification of the core symptoms of depression clinically relevant? Medicographia 2008;30(1):3–8.
[113] Möller HJ. Is there a need for a new psychiatric classification at the current state of knowledge? World J Biol Psychiatry 2008;9(2):82–5.
[114] Möller HJ. Isn't the efficacy of antidepressants clinically relevant?. A critical comment on the results of the metaanalysis by Kirsch et al. Eur Arch Psychiatry Clin Neurosci 2008;258(8):451–5.
[115] Möller HJ. Outcomes in major depressive disorder: the evolving concept of remission and its implications for treatment. World J Biol Psychiatry 2008;9(2):102–14.
[116] Möller HJ. Antidepressants: controversies about their efficacy in depression, their effect on suicidality and their place in a complex psychiatric treatment approach. World J Biol Psychiatry 2009;10(3):180–95.
[117] Möller HJ. Is evidence sufficient for evidence-based medicine? Eur Arch Psychiatry Clin Neurosci 2009;259(Suppl. 2):S167–72.
[118] Möller HJ. Pharmacological and biological treatment of suicidal individuals. In: Wasserman D, Wasserman C, editors. Oxford Textbook of Suicidology and Suicide Prevention. A Global Perspective. New York: Oxford University; 2009 p. 395–405 [Press].
[119] Möller HJ. Standardised rating scales in psychiatry: methodological basis, their possibilities and limitations and descriptions of important rating scales. World J Biol Psychiatry 2009;10(1):6–26.
[120] Möller HJ, Baldwin DS, Goodwin G, Kasper S, Okasha A, Stein DJ, et al. Do SSRIs or antidepressants in general increase suicidality? WPA Section on Pharmacopsychiatry: consensus statement. Eur Arch Psychiatry Clin Neurosci 2008;258(Suppl. 3):3–23.
[121] Möller HJ, Broich K. Principle standards and problems regarding proof of efficacy in clinical psychopharmacology. Eur Arch Psychiatry Clin Neurosci 2010;260(1):3–16.
[122] Möller HJ, Fischer G, von Zerssen D. Prediction of therapeutic response in acute treatment with antidepressants. Results of an empirical study involving 159 endogenous depressive inpatients. Eur Arch Psychiatry Neurol Sci 1987;236:349–57.
[123] Möller HJ, Henkel V. What are the most effective diagnostic and therapeutic strategies for the management of depression in specialist care? World Health Organisation http://www.who.dk/Document/E86602.pdf. 2005 [Ref Type: Electronic Citation].
[124] Möller HJ, Maier W. Evidence-based medicine in psychopharmacotherpy: possibilities, problems and limitations. Eur Arch Psychiatry Clin Neurosci 2010;260(1):25–39.
[125] Möller HJ, Rujescu D. Pharmacogenetics - genomics and personalized psychiatry. Eur Psychiatry 2010;25:291–3.
[126] Moncrieff J, Kirsch I. Efficacy of antidepressants in adults. BMJ 2005;331(7509):155–7.
[127] Moncrieff J, Wessely S, Hardy R. Active placebos versus antidepressants for depression. Cochrane Database Syst Rev CD003012 2004;(1).
[128] Montano CB. Recognition and treatment of depression in a primary care setting. J Clin Psychiatry 1994;55 (Suppl):18–37.
[129] Montgomery SA, Andersen HF. Escitalopram versus venlafaxine XR in the treatment of depression. Int Clin Psychopharmacol 2006;21(5):297–309.
[130] Montgomery SA, Baldwin DS, Blier P, Fineberg NA, Kasper S, Lader M, et al. Which antidepressants have demonstrated superior efficacy? A review of the evidence. Int Clin Psychopharmacol 2007;22(6):323–9.
[131] Montgomery SA, Kasper S. Severe depression and antidepressants: focus on a pooled analysis of placebo-controlled studies on agomelatine. Int Clin Psychopharmacol 2007;22(5):283–91.
[132] Montgomery SA, Möller HJ. Is the significant superiority of escitalopram compared with other antidepressants clinically relevant? Int Clin Psychopharmacol 2009;24(3):111–8.
[133] National Collaborating Centre for Mental Health. Depression in adults (update); depression: the treatment and management of depression in adults. London: National Institute for Health and Clinical Excellence; 2009.
[134] National Institute for Clinical Excellence (NICE). Depression: management of depression in primary and secondary care. Clinical practice guideline No 23. London: National Institute for Clinical Excellence; 2004.
[135] Nelson JC, Papakostas GI. Atypical antipsychotic augmentation in major depressive disorder: a meta-analysis of placebo-controlled randomized trials. Am J Psychiatry 2009;166(9):980–91.
[136] Papakostas GI. Managing partial response or nonresponse: switching, augmentation, and combination strategies for major depressive disorder. J Clin Psychiatry 2009;70(Suppl. 6):16–25.
[137] Papakostas GI, Charles D, Fava M. Are typical starting doses of the selective serotonin reuptake inhibitors sub-optimal? A meta-analysis of randomized, double-blind, placebo-controlled, dose-finding studies in major depressive disorder. World J Biol Psychiatry 2010;11(2):300–7.
[138] Papakostas GI, Shelton RC, Smith J, Fava M. Augmentation of antidepressants with atypical antipsychotic medications for treatment-resistant major depressive disorder: a meta-analysis. J Clin Psychiatry 2007;68:826–31.
[139] Papakostas GI, Thase ME, Fava M, Nelson JC, Shelton RC. Are antidepressant drugs that combine serotonergic and noradrenergic mechanisms of action more effective than the selective serotonin reuptake inhibitors in treating major depressive disorder? A meta-analysis of studies of newer agents. Biol Psychiatry 2007;62(11):1217–27.
[140] Parker G. Classifying depression: should paradigms lost be regained? Am J Psychiatry 2000;157(8):1195–203.
[141] Parker G. Differential effectiveness of newer and older antidepressants appears mediated by an age effect on the phenotypic expression of depression. Acta Psychiatr Scand 2002;106(3):168–70.
[142] Paykel ES. Cognitive therapy in relapse prevention in depression. Int J Neuropsychopharmacol 2007;10(1):131–6.
[143] Paykel ES, Freeling P, Hollyman JA. Are tricyclic depressants useful for mild depression? A placebo-controlled trial. Pharmacopsychiatry 1988;21(1):15–8.
[144] Paykel ES, Scott J, Cornwall PL, Abbott R, Crane C, Pope M, et al. Duration of relapse prevention after cognitive therapy in residual depression: a follow-up of controlled trial. Psychol Med 2005;35:59–68.
[145] Paykel ES, Scott J, Teasdale JD, Johnson AL, Garland A, Moore R, et al. Prevention of relapse in residual depression by cognitive therapy: a controlled trial. Arch Gen Psychiatry 1999;56(9):829–35.
[146] Perlis RH, Purcell S, Fava M, Fagerness J, Rush AJ, Trivedi MH, et al. Association between treatment-emergent suicidal ideation with citalopram and polymorphisms near cyclic adenosine monophosphate response element binding protein in the STAR*D study. Arch Gen Psychiatry 2007;64:689–97.
[147] Pigott HE, Leventhal AM, Alter GS, Boren JJ. Efficacy and effectiveness of antidepressants: current status of research. Psychother Psychosom 2010;79:267–79.
[148] Racagni G, Popoli M. Cellular and molecular mechanisms in the long-term action of antidepressants. Dialogues Clin Neurosci 2008;10(4):385–400.
[149] Reynolds III CF, Dew MA, Pollock BG, Mulsant BH, Frank E, Miller MD, et al. Maintenance treatment of major depression in old age. N Engl J Med 2006;354(11):1130–8.
[150] Rising K, Bacchetti P, Bero L. Reporting bias in drug trials submitted to the Food and Drug Administration: a review of publication and presentation. PLoS Med 2008;5(11):e217.
[151] Rix S, Paykel ES, Lelliott P, Tylee A, Freeling P, Gask L, et al. Impact of a national campaign on GP education: an evaluation of the Defeat Depression Campaign. Br J Gen Pract 1999;49(439):99–102.
[152] Rush AJ. STAR*D: what have we learned? Am J Psychiatry 2007;164(2):201–4.
[153] Rush AJ, Koran LM, Keller MB, Markowitz JC, Harrison WM, Miceli RJ, et al. The treatment of chronic depression, part 1: study design and rationale for

evaluating the comparative efficacy of sertraline and imipramine as acute, crossover, continuation, and maintenance phase therapies. J Clin Psychiatry 1998;59(11):589–97.
[154] Rush AJ, Trivedi MH, Wisniewski SR, Nierenberg AA, Stewart JW, Warden D, et al. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am J Psychiatry 2006;163:1905–17.
[155] Rutz W, Von Knorring L, Walinder J, Wistedt B. Effect of an educational program for general practitioners on Gotland on the pattern of prescription of psychotropic drugs. Acta Psychiatr Scand 1990;82:399–403.
[156] Sanchez C, Bogeso KP, Ebert B, Reines EH, Braestrup C. Escitalopram versus citalopram: the surprising role of the R-enantiomer. Psychopharmacology (Berl) 2004;174(2):163–76.
[157] Schaub A, Roth E, Goldmann U. Kognitiv-Psychoedukative Therapie zur Bewältigung von Depressionen: Ein Therapiemanual. Göttingen: Hogrefe; 2006.
[158] Schechter LE, Ring RH, Beyer CE, Hughes ZA, Khawaja X, Malberg JE, et al. Innovative approaches for the development of antidepressant drugs: current and future strategies. NeuroRx 2005;2(4):590–611.
[159] Schlaepfer TE, George MS, Mayberg G, Mayberg H, on behalf of the WFSBP Task Force on Brain Stimulation. WFSBP Guidelines on Brain Stimulation Treatments in Psychiatry. World J Biol Psychiatry 2010;11:2–18.
[160] Schosser A, Kasper S. The role of pharmacogenetics in the treatment of depression and anxiety disorders. Int Clin Psychopharmacol 2009;24:277–88.
[161] Schramm E, Schneider D, Zobel I, van Calker D, Dykierek P, Kech S, et al. Efficacy of interpersonal psychotherapy plus pharmacotherapy in chronically depressed inpatients. J Affect Disord 2008;109(1–2):65–73.
[162] Seemüller F, Möller HJ, Obermeier M, Bauer M, Adli M, Mundt C, et al. Prediction of response and remission in inpatients with depressive symptoms. J Affect Disord 2011;133(1-2):137–49.
[163] Seemüller F, Riedel M, Obermeier M, Bauer M, Adli M, Mundt C, et al. The controversial link between antidepressants and suicidality risks in adults: data from a naturalistic study on a large sample of in-patients with a major depressive episode. Int J Neuropsychopharmacol 2009;12(2):181–9.
[164] Seemüller F, Riedel M, Wickelmaier F, Adli M, Mundt C, Marneros A, et al. Atypical symptoms in hospitalised patients with major depressive episode: frequency, clinical characteristics, and internal validity. J Affect Disord 2008;108(3):271–8.
[165] Serretti A, Cusin C, Rausch JL, Bondy B, Smeraldi E. Pooling pharmacogenetic studies on the serotonin transporter: a mega-analysis. Psychiatry Res 2006;145(1):61–5.
[166] Serretti A, Kato M, De Ronchi D, Kinoshita T. Meta-analysis of serotonin transporter gene promotor polymorphism (5-HTTLPR) association with selective serotonin reuptake inhibitor efficacy in depressed patients. Mol Psychiatry 2007;12(3):247–57.
[167] Seyringer ME, Kasper S. Ranking antidepressants. Lancet 2009;373:1760–1.
[168] Sharan P, Saxena S. Treatment-resistant depression: clinical significance, concept and management. Natl Med J India 1998;11(2):69–79.
[169] Sheehan DV, Lecrubier Y. Mini International Neuropsychiatric Interview (M.I.N.I.). Medical Outcome Systems, Inc. 2005 [Ref Type: Electronic Citation].
[170] Sheehan DV, Lecrubier Y, Sheehan KH, Amorin P, Janavs J, Weiller E, et al. The Mini-International Neuropsychiatric Interview (M.I.N.I.): the development and validation of a structured diagnostic psychiatric interview for DSM-IV and ICD-10. J Clin Psychiatry 1998;59(Suppl. 20):22–57.
[171] Simon GE, Savarino J. Suicide attempts among patients starting depression treatment with medications or psychotherapy. Am J Psychiatry 2007;164(7):1029–34.
[172] Singh I, Rose N. Biomarkers in psychiatry. Nature 2009;460:202–7.
[173] Sinyor M, Levitt AJ, Cheung AH, Schaffer A, Kiss A, Dowlati Y, et al. Does inclusion of a placebo arm influence response to active antidepressant treatment in randomized controlled trials? Results from pooled and meta-analyses. J Clin Psychiatry 2010;71(3):270–9.
[174] Spitzer RL, Endicott J, Robins E. Research Diagnostic Criteria (RDC). Biometrics Research. New York: New York State Psychiatric Institute; 1975.
[175] Stone M, Jones ML, Levenson M, Holland PC, Hughes A, Hammad TA, et al. Risk of suicidality in clinical trials of antidepressants in adults: analysis of proprietary data submitted to US Food and Drug Administration. BMJ 2009;339:b2880.
[176] Stone MB, Jones ML. Clinical review: Relationship between antidepressant drugs and suicidality in adults. www.fda.gov/OHRMS/DOCKETS/AC/06/briefing/2006-4272b1-01-FDA.pdf 17-11-2006 [Ref Type: Electronic Citation].
[177] Storosum JG, Elferink AJ, van Zwieten BJ, van den BW, Gersons BP, van Strik R, et al. Short-term efficacy of tricyclic antidepressants revisited: a meta-analytic study. Eur Neuropsychopharmacol 2001;11(2):173–80.
[178] Sullivan PF, Neale MC, Kendler KS. Genetic epidemiology of major depression: review and meta-analysis. Am J Psychiatry 2000;157(10):1552–62.
[179] Swinkels JA, de Jonghe F. Safety of antidepressants. Int Clin Psychopharmacol 1995;9(Suppl. 4):19–25.
[180] Szegedi A, Jansen WT, van Willigenburg AP, van der ME, Stassen HH, Thase ME. Early improvement in the first 2 weeks as a predictor of treatment outcome in patients with major depressive disorder: a meta-analysis including 6562 patients. J Clin Psychiatry 2009;70(3):344–53.
[181] Tadic A, Muller MJ, Rujescu D, Kohnen R, Stassen HH, Dahmen N, et al. The MAOA T941G polymorphism and short-term treatment response to mirtazapine and paroxetine in major depression. Am J Med Genet B Neuropsychiatr Genet 2007;144B(3):325–31.
[182] Teicher MH, Glod CA, Cole JO. Antidepressant drugs and the emergence of suicidal tendencies. Drug Safety 1993;8(3):186–212.
[183] Thase ME, Entsuah AR, Rudolph RL. Remission rates during treatment with venlafaxine or selective serotonin reuptake inhibitors. Br J Psychiatry 2001;178:234–41.
[184] Thase ME, Pritchett YL, Ossanna MJ, Swindle RW, Xu J, Detke MJ. Efficacy of duloxetine and selective serotonin reuptake inhibitors: comparisons as assessed by remission rates in patients with major depressive disorder. J Clin Psychopharmacol 2007;27(6):672–6.
[185] Thase ME, Rush AJ, Howland RH, Kornstein SG, Kocsis JH, Gelenberg AJ, et al. Double-blind switch study of imipramine or sertraline treatment of antidepressant-resistant chronic depression. Arch Gen Psychiatry 2002;59(3):233–9.
[186] Tiihonen J, Lönnqvist J, Wahlbeck K, Klaukka T, Tanskanen A, Haukka J. Antidepressants and risk of suicide, attempted suicide, and overall mortality in a nationwide cohort. Arch Gen Psychiatry 2006;63:1353–67.
[187] Toprac MG, Dennehy EB, Carmody TJ, Crismon ML, Miller AL, Trivedi MH, et al. Implementation of the Texas Medication Algorithm Project patient and family education program. J Clin Psychiatry 2006;67(9):1362–72.
[188] Trindade E, Menon D, Topfer LA, Coloma C. Adverse effects associated with selective serotonin reuptake inhibitors and tricyclic antidepressants: a meta-analysis. CMAJ 1998;159(10):1245–52.
[189] Trivedi MH, Rush AJ, Crismon ML, Kashner TM, Toprac MG, Carmody TJ, et al. Clinical results for patients with major depressive disorder in the Texas Medication Algorithm Project. Arch Gen Psychiatry 2004;61(7):669–80.
[190] Trivedi MH, Rush AJ, Wisniewski SR, Nierenberg AA, Warden D, Ritz L, et al. Evaluation of outcomes with citalopram for depression using measurement-based care in STAR*D: implications for clinical practice. Am J Psychiatry 2006;163(1):28–40.
[191] Turner EH, Matthews AM, Linardatos E, Tell RA, Rosenthal R. Selective publication of antidepressant trials and its influence on apparent efficacy. N Engl J Med 2008;358(3):252–60.
[192] U.S. Food and Drug Administration (FDA). Suicidality in children and adolescents being treated with antidepressant medications. http://www.fda.gov/cder/drug/antidepressants/SSRIPHA200410.htm. 2004 [Ref Type: Internet Communication].
[193] U.S. Food and Drug Administration (FDA). Suicidality in children and adolescents being treated with antidepressant medications. http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm096273.htm. 2007 [Ref Type: Internet Communication].
[194] Uhr M, Tontsch A, Namendorf C, Ripke S, Lucae S, Ising M, et al. Polymorphisms in the drug transporter gene ABCB1 predict antidepressant treatment response in depression. Neuron 2008;57(2):203–9.
[195] Ustün TB, Sartorius N. Mental illness - General Health Care: an international study. Chichester: Wiley; 1995.
[196] Vaiva G, Vaiva G, Ducrocq F, Meyer P, Mathieu D, Philippe A, et al. Effect of telephone contact on further suicide attempts in patients discharged from an emergency department: randomised controlled study. BMJ 2006;332(7552):1241–5.
[197] Valenstein M, McCarthy JF, Austin KL, Greden JF, Young EA, Blow FC. What happened to lithium? Antidepressant augmentation in clinical settings. Am J Psychiatry 2006;163(7):1219–25.
[198] Volz HP, Baghai TC, Möller HJ. Drug treatment of depression in the 2000s - an overview of achievements in the last ten years and future possibilities. World J Biol Psychiatry 2006;7(4):198–222.
[199] Wade A, Andersen HF. The onset of effect for escitalopram and its relevance for the clinical management of depression. Curr Med Res Opin 2006;22(11):2101–10.
[200] Wade AG, Schlaepfer TE, Andersen HF, Kilts CD. Clinical milestones predict symptom remission over 6-month and choice of treatment of patients with major depressive disorder (MDD). J Psychiatr Res 2009;43:568–75.
[201] Wade AG, Toumi I, Hemels MEH. A probabilistic cost-effectiveness analysis of escitalopram, generic citalopram and venlafaxine as a first-line treatment of major depressive disorder in the UK. Curr Med Res Opin 2005;21(4):631–41.
[202] Weinberger MI, Sirey JA, Bruce ML, Heo M, Papademetriou E, Meyers BS. Predictors of major depression six months after admission for outpatient treatment. Psychiatr Serv 2008;59(10):1211–5.
[203] Williams WJr, Barrett J, Oxman T, Frank E, Katon W, Sullivan M, et al. Treatment of dysthymia and minor depression in primary care: a randomized controlled trial in older adults. JAMA 2000;284:1519–26.
[204] Wittchen HU, Höfler M, Meister W. Prevalence and recognition of depressive syndromes in German primary care settings: poorly recognized and treated? Int Clin Psychopharmacol 2001;16(3):121–35.
[205] Wittchen HU, Holsboer F, Jacobi F. Met and unmet needs in the management of depressive disorder in the community and primary care: the size and breadth of the problem. J Clin Psychiatry 2001;62(Suppl. 26):23–8.
[206] Wittchen HU, Jacobi F. Size and burden of mental disorders in Europe - a critical review and appraisal of 27 studies. Eur Neuropsychopharmacol 2005;15:357–76.
[207] Wittchen HU, Knäuper B, Kessler RC. Lifetime risk of depression. Br J Psychiatry 1994;Suppl. 26:16–22.
[208] World Health Organization. The global burden of disease: 2004 update. World Health Organisation. 2008. 5-12-2010 [Ref Type: Electronic Citation].
[209] Zobel AW, Nickel T, Kunzel HE, Ackl N, Sonntag A, Ising M, et al. Effects of the high-affinity corticotropin-releasing hormone receptor 1 antagonist R121919 in major depression: the first 20 patients treated. J Psychiatr Res 2000;34(3):171–81.