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ORIGINAL PAPER

Executive summary of the report by the WPA section on pharmacopsychiatry on general and comparative efficacy and effectiveness of antidepressants in the acute treatment of depressive disorders

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Abstract Current gold standard in the treatment of depression includes pharmacotherapeutic and psychotherapeutic strategies together with social support. Due to the actually discussed controversies concerning the differential efficacy of antidepressants, a contribution to a comprehensive clarification seems to be necessary to avert further deterioration and uncertainty from patients, relatives, and their treating psychiatrists and general practitioners. Both efficacy and clinical effectiveness of antidepressants in the treatment of depressive disorders can be confirmed. Clinically meaningful antidepressant treatment effects were confirmed in different types of studies. Methodological issues of randomized controlled studies, meta-analyses, and effectiveness studies will be discussed. Furthermore, actual data about the differential efficacy and effectiveness of antidepressants with distinct pharmacodynamic properties and about outcome differences in studies using antidepressants and/or psychotherapy are discussed. This is followed by a clinically oriented depiction—the differential clinical effectiveness of different pharmacodynamic modes of action of antidepressants in different subtypes of depressive disorders. It can be summarized that the spectrum of different antidepressant treatments has broadened during the last decades. The efficacy and clinical effectiveness of antidepressants is statistically significant and clinically relevant and proven repeatedly. For further optimizing antidepressant treatment plans, clearly structured treatment algorithms and the implementation of psychotherapy seem to be useful. A modern individualized antidepressant treatment in most cases is a well-tolerated and efficacious tool to minimize the negative impact of the otherwise devastating and life-threatening outcome of depressive disorders.

Keywords Antidepressant treatments · Depression · Pharmacological treatments · Psychotherapy

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Introduction

According to the World Health Organization (WHO), depressive disorders are of significant socio- and health-economic importance. Following the Global Burden of Disease report 2004, they were the number one cause for moderate and severe disability, independent of sociodemographic factors, with increasing importance in the projection to 2030 [125].

Treatment of depressive disorders requires a combination of proven therapies. The primary constituents of a multimodal antidepressant therapy should include pharmacotherapy, psychotherapy, and social support. Unresolved problems in the drug treatment of depression are predominantly the delay experienced by patients until symptom relief is noticed [10], a nonresponse rate of approximately 30% [26], dropout rates due to adverse side effects or ineffectiveness [19] and a fortunately at least in some countries decreasing, but still present suicide mortality rate, which reaches more than 11% [7]. The efficacy and effectiveness of antidepressants in the treatment of major depressive disorder (MDD) has been confirmed in meta-analyses [9, 80] and an ever-growing extant number of randomized controlled trials (for review see [15, 21, 103]). However, some recent meta-analyses and their conclusion that antidepressants were usually no better than placebo [55, 71] have created doubts about clinical effectiveness of antidepressants, predominantly in the minds of health care professionals, but also of concerned patients and their relatives. The aim of this review is to clarify methodological questions and provide a balanced interpretation of the objective evidence concerning the general and comparative efficacy and effectiveness of antidepressant treatments.

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Methods

The methods included consideration of divergent sources including the Medline database (up to June 2011), the Cochrane Library (www.cochrane.org), randomized controlled trials (RCTs), review articles and meta-analyses from Medline-indexed journals. In addition, several national and international treatment guidelines were considered, including the American Psychiatric Association (APA) Practice Guideline for the Treatment of Patients with Major Depressive Disorder [4], the clinical guidelines for the treatment of depressive disorders (Canadian Psychiatric Association and Canadian Network for Mood and Anxiety Treatments) [25], Guidelines of the British National Collaborating Center for Mental Health and the National Institute of Mental Health (NICE) [85, 86], the Deutsche Gesellschaft für Psychiatrie, Psychotherapie und Nervenheilkunde (DGPPN) [45], and the World Federation of Societies of Biological Psychiatry (WFSBP) Guidelines for Biological Treatment of Unipolar Depressive Disorders [15, 20, 21]. Information from all sources was used to produce a scholarly narrative review to clarify the following questions: Are antidepressants effective in the treatment of depressive disorders in RCTs and in effectiveness studies designed to represent more routine practice? Which measures, including the comparison of means, the number needed to treat (NNT) or meta-analyses, are the best to evaluate their beneficial use? Is there evidence for differences in the efficacy and effectiveness of antidepressants with different pharmacodynamic properties and in comparison with psychosocial therapies? Is there evidence for differences in effectiveness in different severity or clinical subtypes of depressive syndromes? The review considered the prediction of antidepressant efficacy, the use of treatment algorithms, and the importance of considering and preventing suicidal behavior during antidepressant treatments. The most important information was extracted to produce this executive summary, which should be supplemented by the detailed review published as a supplement of the *Eur Arch Psychiatry Clin Neurosci* [10.1007/s00406-011-0259-6, volume 261, supplement issue 3, Page range s207–s246].

Results

General efficacy and effectiveness of antidepressants

Regulatory authorities in Europe and the United States demand proof of *efficacy*—the ability to produce

antidepressant effects in RCTs—before approval of antidepressants [11, 57]. A statistically significant superiority over placebo of at least 2 points in the HAM-D17 scale [62] (or corresponding values in the Montgomery Åsberg Depression Rating Scale (MADRS) [81]) in 6- to 8-week placebo-controlled RCTs have been judged to be clinically relevant [77]; according to NICE criteria, a difference of 3 points is recommended [86].

The efficacy of antidepressants in the treatment of adults with unipolar depression is, by this criterion, well and repeatedly proven (for review see [15, 21, 103]). The evidence in bipolar depression is weaker due to the smaller number of RCTs. For atypical antipsychotics such as quetiapine and olanzapine, efficacy in both bipolar [24, 34, 42, 110, 126] and unipolar depression [18, 37] has been confirmed.

A mean reduction in the HAM-D or MADRS scale of 50% or more after 6–8 weeks of treatment with antidepressants is defined as a *response* and provides another way of expressing clinical relevance. It is seen in 32–70% of the patient groups in RCTs [120]. Responder rates have been increasing during the last decades in both verum- and placebo-treated patients [120]. The reasons are not fully understood. Even higher responder rates have been described in routine clinical practice perhaps attributable to improved treatment strategies such as individualized treatment plans and algorithm-guided treatment in case of nonresponse [65]. We have noted nonspecific therapeutic improvements in RCTs that have also occurred, associated with an increasing intensity of study-related clinical management processes [51]. We believe it is also possible that the illnesses of patients seeking help for depression have shifted in a more treatment-responsive direction, as the diagnosis has become better publicized and less stigmatized.

A useful comparative indicator confirming the efficacy of antidepressants is the *number needed to treat'* (NNT) [32], which is derived from a comparison of response and remission rates in verum- and placebo-treated patient groups in specific trials [47] after defining distinct cutoff thresholds. The NNT represents the average number of patients treated successfully in a clinical trial, in which one patient will have responded specifically to the experimental treatment. Summarizing the results of acute treatment RCTs in more than 25,000 patients using SSRI and TCA treatment, NNTs between 5 and 9 could be demonstrated [9, 76, 108, 120]. Pooled analyses of relapse prevention studies in more than 4,000 patients demonstrated a NNT of 5 [58]. An *ideal treatment* would score 1—all responses are then to the active treatment and there are none to the control—but the actual NNT compares well with many other treatments, for example, in internal medicine. This range for the NNT reflects the fact that drug treatments in medicine generally tend to have modest benefit.

Recently, a number of meta-analytic studies have questioned the clinical usefulness of antidepressants because of small effect size and publication bias [12, 55, 60, 80, 116, 118]. However, it has been suggested that these conclusions are false based on a possible misinterpretation of the data [54]. An immediate consequence is that patients suffering from mild depression could be deprived of receiving antidepressants on the basis of a false interpretation of short-term data and an over-evaluation of 'alternative therapies' while long-term observations suggest depression is, in many cases, a chronic relapsing disease.

Both *systematic narrative reviews* and *meta-analyses* provide additional useful tools for a detailed or overall evaluation of the efficacy and effectiveness of antidepressants even if a variety of systematic stumbling blocks have the potential to bias results and data interpretation [75, 79, 116]. In systematic reviews, the efficacy and effectiveness of antidepressants have been confirmed clearly for unipolar [39, 89, 103] and bipolar depression [30, 78, 90], and the same could be demonstrated in a variety of meta-analyses (e.g., [9, 80, 108]).

The above-mentioned efficacy data are often used to predict the *clinical effectiveness* of a drug, likely to be achievable during its routine clinical use [103]. There are some conflicting results in studies investigating response or remission rates of RCTs in comparison with naturalistic clinical data [104, 123], which may be potentially different due to an artificial patient selection for highly regulated clinical trials. The need for so-called *effectiveness studies*, independent from regulatory approval processes and pharmaceutical sponsoring, has been suggested [59]. One prominent example is the U.S. National Institute of Mental Health (NIMH)–funded the STAR*D ("Sequenced Treatment Alternatives to Relieve Depression") study [101], which resulted in a cumulative remission rate of 67% (36.8, 30.6, 13.7, and 13.0% after the first, second, third, and fourth acute treatment steps) attesting, despite several limitations, to the clinical effectiveness of antidepressant treatment strategies including also augmentation strategies [102]. Nevertheless, this result is not very satisfying because it could only be reached as a total remission rate over all treatment steps after a time interval of up to 48 weeks. Other prospective effectiveness studies reported remission rates of about 50% and response rates between 70 and 80% [67, 104].

In cases of *treatment resistance* or *nonresponse*, the absence of response to appropriate antidepressant treatment or the lack of remission [50] after at least two courses of adequate pharmacotherapy [103] is observed. *Combination treatment*, the combination of two or more antidepressants (each of which has sufficient antidepressant properties in monotherapy), is used and accepted broadly in clinical

practice despite a general paucity of evidence for its effectiveness [46]; only few RCTs have demonstrated an enhanced efficacy [38, 53]. In cases of selected patients suffering from treatment refractory depression, combination treatment resulted in remission rates of about 30% [113]. An important alternative is *augmentation*, the amplification of antidepressant treatment with a substance that does not itself necessarily exert marked antidepressant activity in monotherapy [103, 107]. *Lithium augmentation* is one of the best-documented augmentation strategies in the treatment of treatment refractory depression [13, 14, 16, 23, 33, 127] and should be considered early especially in case of psychotic depression [13, 96]. Somewhat less supported in the literature, superior efficacy and effectiveness have also been claimed for *thyroid hormone augmentation* using triiodothyronine (T_3) [8, 21]. However, the best evidence [88] is for first-generation medium potency [119] and second-generation *atypical antipsychotics* (for review see [88, 92, 93]) even in the case of nonpsychotic MDD.

Comparative efficacy and effectiveness of antidepressant treatments

Limited evidence for a general superiority of some antidepressants (serotonergic or dual-acting antidepressants) has been published [28, 82], but these results are not without controversy [105, 115]. Therefore, to date, it seems more expedient to assess the clinical relevance of specific comparisons of drugs and consider the different patient subpopulations included in RCTs or meta-analyses. For example, escitalopram was superior to citalopram and fluoxetine in acute treatment of MDD [29], venlafaxine and TCAs were more effective than SSRIs in treatment-resistant depression [19, 94] (but not in elderly patients [83]), and TCAs or newer selectively dually acting antidepressants were more effective in more severely depressed patients in comparison with SSRIs [5, 6, 27, 124] or with the RIMA moclobemide [40]. A similar result was reported for agomelatine in comparison with fluoxetine [61]. These results have to be evaluated in the light of disputed [54] meta-analyses stating that drug–placebo differences in RCTs increase with the baseline severity of depressive disorders [71]. The authors evaluated a limited section of approval studies, including predominantly patients suffering from moderate to severe depression and are therefore of limited value in addressing either mild or severe depression. In addition, the use of the terms mild, moderate, and severe depression in different ways by different authors may be a crucial factor causing or enhancing the actual controversies in the discussion about the efficacy of antidepressants. Moreover, the response of individual patients may not be predicted by RCT results, which simply compare mean responses. In addition, not only efficacy but tolerability and compliance are important determinants of successful antidepressant treatments. Therefore, an individualized therapeutic approach is always recommended in routine clinical practice.

The evidence for efficacy of psychotherapy in the treatment of MDD, especially cognitive behavioral therapy (CBT), interpersonal therapy (IPT), and cognitive behavioral analysis system of psychotherapy (CBASP), is widely accepted [22, 121, 122]. Compared with RCTs of antidepressants, however, psychotherapy trials have often been interpreted less critically although they present major problems in choice of comparator, blinding and treatment allegiance bias. IPT was apparently as efficacious as amitriptyline, imipramine, nortriptyline, and sertraline [41, 95, 122] and more efficacious than CBT [41]. A meta-analysis showed statistically significant superiority of antidepressants (predominantly SSRIs and TCAs) in dysthymia and of SSRIs in MDD, which was of questionable clinical relevance according to the authors [36]. In depression of mild to moderate severity, psychosocial interventions were as effective as antidepressants [22, 73] and CBT had sustained relapse preventive effects even after its discontinuation [44]. Conflicting results were published in severe MDD: antidepressant medication was more efficacious than cognitive therapy [48], but a pooled analysis and a recent meta-analysis found that CBT and pharmacotherapy are comparably effective even in severely depressed patients [36, 43].

Even if some studies failed to show advantages of combining antidepressants with psychotherapy [41], there is evidence from other RCTs that either a combined psychotherapeutic and pharmacological treatment [31, 35, 68, 122] or sequenced treatment strategies [56] may produce significant beneficial effects. This has been shown and is especially true for some selected subgroups of depressed patients [69] such as chronic [70] or severe [66] depression and for long-term treatment [91]. Therefore, treatment guidelines are considering this combination as a standard treatment of depression [45, 85].

Enhancement of antidepressant effectiveness using treatment algorithms

Treatment algorithms (e.g., [1–3, 17, 49, 63, 72, 74, 99, 114]) in most cases derived from locally (e.g., [4, 25, 45, 85, 86]) or internationally (e.g., [15, 20, 21]) accepted guidelines help to provide a structured approach to patient management and increase cumulative response rates potentially to more than 90% [100, 111]. Algorithms may address different subtypes of MDD [87] and support the use of sometimes underused treatment strategies such as lithium augmentation [72] or electroconvulsive therapy

(ECT) [63] especially in case of severe and psychotic depression. Due to their superiority over unstructured antidepressant treatment strategies, their regular use in clinical practice has been strongly advocated [112].

Suicide prevention during antidepressant treatments

Long-term naturalistic studies suggest that the suicide mortality rate in severe mood disorder (of more than 10%) may be substantially decreased by long-term pharmacological treatments [7, 98]. Especially for lithium, long-term treatment seems to reduce suicide mortality in patients suffering from severe affective disorders [84]. Somewhat paradoxically, for adults, an association of suicidal acts with SSRI treatments compared with placebo has been reported in meta-analyses [52, 64]. More convincingly, after SSRI treatment in children and adolescents, an increase of suicidal ideations without increased rates of suicide attempts or completed suicides was demonstrated in meta-analyses [117, 118]. In the wake of intense media pressure, the U.S. FDA published a warning valid especially during the first 2 months after treatment initiation. The warning is still current, even if in other studies antidepressant-induced suicidality appears to be an uncommon phenomenon [97] and a prospective drug surveillance program detected low rates of suicidality and very low rates of suicides in adult patients taking antidepressant medication in the community [109]. Nevertheless, during the first month after treatment initiation with antidepressants or psychotherapy, even if reduced in comparison with the time before, suicide attempts are more probable than during later times [106]. Thus, the use of antidepressants in the treatment of depressive disorders requires caution and early monitoring visits especially during the first weeks of antidepressant treatments. Even if some studies and meta-analyses do not support a reduction in suicides due to the use of SSRIs (e.g., [52]) because of divergent methodological problems, the closely monitored use of antidepressants may, by reducing depression, contribute more to the decline rather than the increase of suicides.

Conclusion

Modern strategies for the clinical management of depression, which include pharmacotherapy, should consider structured treatment plans and algorithm-guided treatments, especially in cases of primary treatment failures. Psychotherapies with sufficient evidence for efficacy in the treatment of depression should also be considered along with psychosocial support and providing healthy life style information to the patient and any caregivers. This is simply good clinical practice.

Up to now, new pharmacodynamic treatment principles have not increased the response rate to an initial antidepressant treatment strategy, but have broadened the spectrum of available treatment options, especially in cases of nonresponders and may increase the overall response rate after the use of sequenced treatment strategies. In addition, antidepressant psychotherapies show evidence of clinical effectiveness, not only confirmed by clinical experience, but in well-designed studies as well. In general, both the efficacy under idealized conditions in RCTs and the clinical effectiveness of antidepressant drugs and antidepressant psychotherapy can be supported. Moreover, synergistic effects of both have been suggested in a variety of studies.

For antidepressants, statistically significant verum–placebo differences including calculation of the number needed to treat (NNT) are a clear confirmation of the efficacy of antidepressants and an indicator of the likelihood of clinically relevant effectiveness. Meta-analyses and systematic reviews endorse this conclusion for antidepressants in the treatment of depressive disorders. The more clinically oriented effectiveness studies, albeit at a lower methodological level, confirm these results. The inherent character of psychotherapy studies makes the design of valid control procedures challenging. They cannot reach the methodological quality of pharmacotherapy RCTs, but, nevertheless, they contribute sufficiently to the pool of effectiveness data.

The individual response of depressed patients to individualized antidepressant treatment algorithms, including augmentation or combination strategies, may greatly exceed mean differences between verum and placebo in RCTs. Nevertheless, further research is warranted to investigate how to achieve higher remission rates and shorter time to remission intervals. It is necessary to find the optimal antidepressant, psychotherapeutic approach, and social support to provide a maximum of improvement in an individual patient. This may include nonpharmacological treatments, such as different psychotherapeutic methods, but also older somatic treatments such as wakefulness therapy, light therapy, and ECT.

Novel treatment strategies and the progress in depression research will hopefully lead to a more efficacious, better-tolerated and therefore better-accepted treatment for depression in the future. Although not discussed in this review, the role of cultural sensitivity of the provider, general physical health of the patient, and a healthy life style are potentially important factors to consider in the bio-psycho-social evaluation and treatment of mood disorders.

Conflict of interest T.C. Baghai accepted paid speaking engagements and acted as a consultant for Astra-Zeneca, Glaxo-Smith-Kline, Janssen-Cilag, Organon, Pfizer and Servier. M. Bauer has received

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