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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

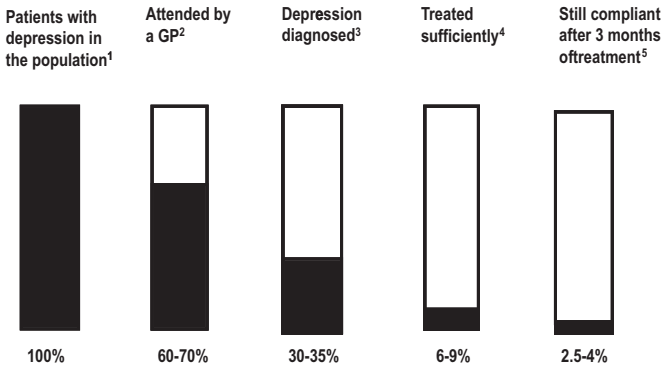
Depression is one of the most prevalent psychiatric disorders [3,206] and leads to substantial suffering of the patients, a heavy burden for the family, a high risk of suicidal behaviour (lifetime risk of suicide up to 15%) and significant socioeconomic consequences in terms of direct and indirect costs. 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