Should antidepressants be used in minor depression?

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Minor/subthreshold depression is associated with functional impairment, reduced quality of life, and the risk of developing into major depression. Therefore, it should be treated. Watchful waiting should be an option only for patients who, despite adequate information, are not interested in any kind of treatment. Psychotherapy has been found to be effective, but due to methodological problems (control group, blinding), efficacy derived from randomized trials might be overestimated. Studies on the efficacy of antidepressants in the treatment of minor depression have found clinically relevant benefits over placebo, particularly the newer, better-controlled trials. One major advantage of antidepressants over psychotherapy is their immediate availability and the short period required to evaluate efficacy. Aside from the severity of depression, the patient's attitude towards psychotherapy or antidepressant treatment is of major relevance and should be explored. In a shared decision-making process, the patient should receive appropriate information on treatment options, state her or his preferences, and then receive the treatment of choice.

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Minor depression is not a minor disease

Most patients, suffering from depressive symptoms, do not reach minimum diagnostic criteria (number, severity, or duration of symptoms are insufficient) of major depression and are diagnosed as having minor or subsyndromal or subthreshold depression. For subthreshold depression, different definitions exist, based on the number of depressive symptoms, duration of symptoms, exclusion criteria, and associated functional impairments.[1] Judd et al defined subsyndromal symptomatic depression as "any two or more simultaneous symptoms of depression, present for most or all of the time, at least two weeks in duration, associated with evidence of social dysfunction, occurring in individuals who do not meet criteria for diagnosis of major depression and/or dysthymia."[2]

The major public health relevance of minor/subthreshold depression has been underlined by numerous studies, but reported rates vary dependent on the defini-

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tions used: 2.5% to 9.9% in community samples or 5% to 16% in primary care patients[2-4] with higher prevalence particularly in elderly patients.[5] In each of these settings, there are two to three times as many persons with depressive symptoms that fall short of fulfilling all criteria of major depression.[6]

The term "minor depression" is misleading, as this "minor" disease is associated with marked psychological suffering, significant decrements in health, problems with activities of daily living, and a marked reduction in quality of life.[7-11] Moreover, minor depression is also a strong risk factor for major depression.[12,13] One study found that major depression develops in 10% to 25% of patients with subthreshold depression within 1 to 3 years.[14] Minor depression/subthreshold depression is also associated with increased service utilization, suicidality, and mortality.[15-17] These findings suggest that although minor depression is milder than severe depression, it is not a mild or minor disorder, and it should be recognized, diagnosed, and treated early.

Early and effective treatment is needed

The benefit of adequate treatment has been shown in many studies,[18] particularly regarding long-term outcomes. However, there is some disagreement about the effectiveness of different treatment strategies, which include watchful waiting, herbal medicine (eg, St John's wort), psychotherapy, or psychopharmacological treatment with antidepressants.

Watchful waiting means no treatment and is associated with the dubious expectation of fast improvement and good prognosis. Watchful waiting, although suggested in some guidelines, might not be a sufficient treatment because of the risk of transition from minor to major depression, functional impairment, and the reduction of quality of life, which is observed already in minor or subthreshold depression. Candidates for watchful waiting may be only patients with good social support, lacking a family history of depression and refusing psychological or pharmacological treatment despite full information about the risks of the disease and available treatment options.

Herbal medicine, mostly St John's wort medication, is particularly popular among patients, who do not like to take "chemicals" but prefer "natural treatment." However, the efficacy of herbal medicine is controversial, as most trials have not found benefits over placebo in patients with major or minor depression.[19-21]

Efficacy of psychotherapy

The efficacy of psychological treatment of minor/subthreshold depression has been examined in a meta-analysis of randomized controlled studies.[22] Seven studies with 700 subjects were included and the mean effect size was 0.41 with very low heterogeneity. The relative risk of developing a major depressive disorder in subjects who received the psychotherapeutic intervention was 0.70. The authors conclude that psychological treatments have significant and beneficial effects on subthreshold depression and that these interventions may prevent the onset of major depression.

Divergent findings have been reported for the effectiveness of psychotherapy in the treatment of depressed patients in primary care practice. Twelve studies on the treatment of patients suffering from major depression, minor depression, or dysthymia were analyzed.[23] Since earlier studies were methodologically flawed, Schulberg et al considered only studies which employed not only efficacy, but also effectiveness designs, used standard diagnostic assessment procedures, appropriate follow-up periods, empirically evaluated treatment manuals, and adequate comparison conditions The authors' conclusion is that in the treatment of major depression, a depression-specific psychotherapy produces outcomes which are similar to those produced by pharmaceutical therapy, but better than primary care physician's usual care. Thus, regarding psychotherapy in the treatment of minor depression, the evidence is equivocal and further studies are needed to determine whether psychotherapy should be recommended as a first-line intervention.[23]

Studies on efficacy of psychotherapy and the resulting effect size have to deal with the fundamental and unresolved problem that neither the patients nor the therapists can be blinded concerning the treatment condition.[24,25] Without the possibility of blinding, patients who know to be in a control, eg, "only a waiting list" group will not profit from a placebo effect, but might often be frustrated. Therefore, randomization into the control group could even result in a negative (nocebo) effect. This hypothesis is supported by a study investigating the efficacy of sertraline, placebo, cognitive-behavioral therapy, and moderated self-help group in primary care patients.[26] The outcome in the moderated self-help group (serving as psychotherapy control group) was significantly worse than in the drug placebo group, as well as in all other groups. Due to the diffi-

culty of providing an adequate psychotherapy placebo, studies on the efficacy of psychotherapy might result in overrated treatment effects. Several studies have addressed and thoroughly analyzed factors leading to an overestimation of effects of psychotherapy in clinical studies on depression.[27,28]

Efficacy of antidepressants

Regarding the efficacy of antidepressant medication in the treatment of minor or subthreshold depression, data, and opinions are rather controversial. One meta-analysis, conducted in 2002, did not find a significant relationship between treatment-placebo difference and severity of depression.[29] However, two more recent meta-analyses reported strong associations between symptom severity at baseline and benefits of antidepressant medication over placebo.[30,31] Authors suggest that "there is little evidence to support the prescription of antidepressant medication to any but the most severely depressed patients"[30] and maintain that "the benefits of antidepressants may be minimal for patients suffering from mild or moderate depression."[31] However, these conclusions have been seriously challenged, a.o. in a re-analysis of the Kirsch data.[31] This reanalysis used a different statistical approach, detected some flaws in Kirsch's calculations and showed an effect size of antidepressants for depression of 0.34 with no role of baseline symptom severity. It was concluded that the efficacy of antidepressants is not restricted to a certain degree of symptom severity.[32]

Efficacy and tolerability of antidepressants in adult patients with minor depression have been analyzed in a meta-analysis.[33] Only double blind, randomized placebo-controlled trials were included, patients with severe organic diseases were excluded. Of 719 papers screened, a total of only six studies comprising 234 patients in the antidepressant and 234 patients in the placebo arm fulfilled the inclusion criteria for this meta-analysis. In three of these studies, the selective serotonin reuptake inhibitor (SSRI) paroxetine was compared with placebo. In the other studies, fluoxetine, amitryptiline, and isocarboxazid were the active drugs. In most studies, the number of patients participating was low (three trials included less than 50 patients), and recruitment exceeded 100 patients only in two trials.[34,35] Duration of treatment was 6 to 12 weeks, three studies were conducted in primary care and in two studies, patients older than 60 years were included. The authors rated the methodological quality of the included studies as relatively low. Their main finding was that antidepressants and placebo did not significantly differ in the non-response rate of patients with minor depression (antidepressants 59%, placebo 62%) and suggested that a clinically relevant superiority of antidepressants to placebo is unlikely. However, major methodical limitations such as small sample size as well as the short duration of treatment and of observation limit their conclusions.

In the meta-analysis cited above,[33] the two methodically most stringent studies with a 12-week treatment period and sufficient sample size of 204[34] and of 162[35] patients with minor depression, both show a superiority of the antidepressant over placebo. Paroxetine (10 to 40 mg/day) showed greater symptom reduction than placebo (P=0.004), problem-solving treatment was not more effective than placebo.[34] Judd et al found that treatment with fluoxetine is more efficacious than placebo; although the placebo-treatment difference in the improvement of the Hamilton depression rating scale was only 1.7 points.[35]

Two studies were not included in the meta-analysis.[33] In a 12-week trial with three arms,[21] the effects of St John's wort, citalopram, and placebo were investigated in patients suffering from minor depression. Neither St John's wort nor citalopram differed significantly from placebo regarding depressive symptoms or quality of life. In the Hamilton Depression Rating Scale (HDRS) total score, St John's wort was less effective than placebo.

A five-arm clinical trial with a duration of 10-weeks assessed the efficacy of sertraline and cognitive-behavioral treatment in 368 patients with mild-to-moderate depression included 1099 primary care patients after screening.[26] The five arms included sertraline (flexible dose up to 200 mg/day, plasma levels were monitored), placebo, group CBT, moderated self-help groups, and free choice of sertraline or CBT. HDRS improvement in the sertraline arm was significantly larger than in the placebo arm (6.8 points vs 4.5 points), improvement in CBT (6.7 points) was significantly larger compared with the guided self-help groups (1.9 points) but not compared with placebo (4.5 points). Sertraline–placebo difference in efficacy was particularly pronounced in patients with very mild depression.

In a 1-year follow-up study, patients with sertraline treatment and those with CBT treatment did not differ

in recovery, ie, the number of weeks in the follow-up period without symptoms (sertraline: 32+/-24 weeks, CBT: 28+/-24 weeks).[36]

Of clinical interest is also a 52-week pragmatic long-term trial in primary care patients with minor or mild-major depression.[37] They were randomized into two groups, namely consultations within 3 months of usual care plus paroxetine or usual care alone. No differences in effectiveness between both treatment groups were found, patients with antidepressant medication were slightly more satisfied with their treatment.

In this context, the robust efficacy of antidepressants in the treatment of dysthymia, which is phenomenologically similar to minor depression, but different in the chronic course of illness, should be noted. Psychopharmacological therapy was found to be effective in numerous studies (for example, refs 34, 38) and a Cochrane review recommended antidepressants as first treatment in dysthymia.[39]

The fundamental problem of blinding patients and therapists to treatments in trials comparing psychotherapy to control conditions has been mentioned above.[24,25] Cuijpers et al investigated the effects of blinding on the outcomes of psychotherapy and pharmaceutical therapy for adult depression and found that studies in which both groups of patients (and therapists) are not blinded result in a "very small, but significantly higher effect for pharmaceutical therapy."[40] This finding is in contrast to an earlier meta-analysis of studies directly comparing psychotherapy and pharmaceutical therapy in which no difference was observed.[41]

Simon et al evaluated 19 751 patient records from four large US American health care systems and concluded "that prescription of antidepressant medication for minimal or mild depression is much less common than suggested by previous reports."[42] Therefore, the assumption that antidepressants are overprescribed for patient suffering from non-major depression does not appear to be justified.

In conclusion, randomized studies on the efficacy of antidepressants in minor depression indicate superiority over placebo. This result is particularly supported by newer, well-controlled trials.

Patient preferences

One issue of major relevance in clinical practice, but somewhat neglected in research, is the patient's preference regarding treatment. There is wide agreement that the majority of patients prefer psychotherapy over antidepressant medication.[43,44] Antidepressants are often regarded as addictive and psychotherapy is assumed to solve the cause of the depression. Therefore, in clinical practice, most psychiatrists try to convince only their severely depressed and suicidal patients about the efficacy of antidepressants, while patients with minor/subthreshold depression are treated according to their preference.

Research on the relevance of patients' preference in the treatment of depression is scarce and controversial. A review conducted in 2004 reported that in two patient-preference trial, preference did not influence treatment outcome.[43] However, in two more recent trials, the findings were different: patients who were assigned to their preferred treatment were found to be more often compliant and had better clinical outcomes.[37] The other trial showed that depressed patients receiving their preferred treatment (n=36), whether sertraline or CBT, responded better than those who did not receive their preferred therapy (n=54, P=0.001); effect size of the differences between matched and mismatched patients was 0.42.[44]

The controversy regarding the importance of preference, as reported in two positive and two negative trials, might be explained by methodological problems. The majority of patients with a strong preference for psychotherapy might not enter a clinical trial in which they have any "risk" of being treated with an antidepressant. This problem is particularly relevant for patients with minor/subthreshold depression who may be particularly opposed to pharmaceutical treatment.

In clinical practice, patient preferences should be taken into account in a shared decision-making process. A recent review indicates its benefits in terms of adherence, satisfaction with care, and outcome.[45]

Is the efficacy of antidepressants in the treatment of minor depression clinically relevant?

The NICE guidelines proposed a drug-placebo difference of at least 3 points regarding the improvement in the Hamilton-Depression rating scale-17 total score as the threshold for clinical significance.[46] As mentioned before, this difference has not been reached in any clinical trial. However, of the three methodologically most

stringent investigations, all found a significant difference: using the HDRS, Judd et al[35] of 1.7 points and Hegerl et al[26] of 2.3 points. Williams et al[34] used the Hopkins Symptom Checklist Depression scale and found a difference of 0.21 points, which after transformation is equivalent to about 2.5 HDRS points.

The question arises whether it is justified to assess the threshold of clinically relevant efficacy on the basis of an arbitrary antidepressant-placebo difference, reported in randomized clinical trials. This is thoroughly discussed by Hegerl et al[25] who argue that the clinical relevance or effectiveness of antidepressants cannot be drawn from intent-to-treat and last-observation carried over approaches. Moreover, in contrast to RCTs, antidepressants in clinical practice allow individually tailored treatment regarding the drug selected (eg, sedating vs non-sedating), dosage in case of tolerability problems or insufficient efficacy, and administration of augmentation or combination strategies.

The argument that antidepressants' efficacy is similar or not much stronger than "only placebo" is based on weak evidence only and also misleading. It is wellknown that a placebo has pronounced effects on symptoms due to expectation and conditioning. The placebo effect may be enhanced by a positive physician-patient relationship as it involves three components: acknowledgement of the patient's difficulties by paying attention to his/her problem, a credible therapeutic ritual and the patient-perceived quality of the relationship with the psychiatrist. Antidepressants exert an effect not only because of their pharmacology, but because a prescription can be expected to provide these components.

A small overall difference between antidepressant and placebo does not exclude that there are single patients with a strong positive response. Particularly patients with markedly disturbed sleep, who might be at risk to develop a dependence on sleep medication, often strongly benefit from a sedating antidepressant.

Conclusion

The doubt about the efficacy of antidepressants in patients with minor/subthreshold depression is not justified. In contrast to the results of older and methodologically less solid reviews and meta-analyses, newer studies found a significant advantage over placebo. Studies also show that antidepressants are at least equal to psychotherapy in reducing depressive symptoms and both treatments are better than usual care.

In order to define a clinically relevant treatment effect, more effectiveness rather than efficacy studies are needed, which include effects sizes and after treatment an observation period of 6 to 12 months. Moreover, outcomes are still defined in terms of classical expert-rated symptoms only, rather than by patient-reported outcomes such as health-related quality of life.

One major advantage of antidepressant treatment is its immediate availability (together with rather low costs) and the short time span (within 2 to 3 weeks) in which knowledge about the effects of the treatment is available. Risks or disadvantages of a probationary antidepressant treatment are limited. In contrast, psychotherapy is often not readily accessible, time -intensive and frequently associated with a long waiting period.

In order to identify an appropriate treatment for the individual patient, patients should be well informed about treatment options, their preferences should be explored, and shared decision-making should be introduced with the aim to ensure patient participation and compliance. ❑

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