Should antidepressants be used in minor depression?
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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. 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.”

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

The efficacy of psychological treatment of minor/sub-threshold depression has been examined in a meta-analysis of randomized controlled studies. 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 sub-threshold 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. 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.

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. 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. 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.30 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,31 the two methodically most stringent studies with a 12-week treatment period and sufficient sample size of 20432 and of 16233 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,31 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, i.e., the number of weeks in the follow-up period without symptoms (sertraline: 32+/−24 weeks, CBT: 28+/−24 weeks). Of clinical interest is also a 52-week pragmatic long-term trial in primary care patients with minor or mild-major depression. 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. The fundamental problem of blinding patients and therapists to treatments in trials comparing psychotherapy to control conditions has been mentioned above. 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.” This finding is in contrast to an earlier meta-analysis of studies directly comparing psychotherapy and pharmaceutical therapy in which no difference was observed.

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.” 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. 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 trials, preference did not influence treatment outcome. 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. 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.

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.

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. 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. of 1.7 points and He-
gerl et al. of 2.3 points. Williams et al. used the Hop-
kins 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, re-
ported in randomized clinical trials. This is thoroughly
discussed by Hegerl et al. who argue that the clinical
relevance or effectiveness of antidepressants cannot be
drawn from intent-to-treat and last-observation car-
ried over approaches. Moreover, in contrast to RCTs,
antidepressants in clinical practice allow individually
tailored treatment regarding the drug selected (eg, se-
dating 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 physi-
cian-patient relationship as it involves three com-
ponents: acknowledgement of the patient’s difficulties by
paying attention to his/her problem, a credible thera-
peutic ritual and the patient-perceived quality of the
relationship with the psychiatrist. Antidepressants ex-
er ait a n 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 pa-
tients with a strong positive response. Particularly pa-
tients with markedly disturbed sleep, who might be at
risk to develop a dependence on sleep medication, of-
ten strongly benefit from a sedating antidepressant.

Conclusion

The doubt about the efficacy of antidepressants in pa-
tients with minor/subthreshold depression is not jus-
tified. In contrast to the results of older and method-
ologically 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 ef-
fect, 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 an-
tidepressant treatment are limited. In contrast, psycho-
therapy 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 intro-
duced with the aim to ensure patient participation and
compliance.

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¿Se deben emplear los antidepresivos en la depresión menor?

La depresión menor / subumbral se asocia con deterioro funcional, calidad de vida reducida y riesgo de desarrollar una depresión mayor. Por lo tanto, debe ser tratada. La observación atenta de la evolución debe ser una opción sólo para los pacientes que, a pesar de la información adecuada, no están interesados en ningún tipo de tratamiento. Se ha encontrado que la psicoterapia es efectiva, pero debido a los problemas metodológicos (grupos de control, estudios ciegos) podría estar sobreestimada la eficacia derivada de los ensayos aleatorizados. Los estudios acerca de la eficacia de los antidepresivos en el tratamiento de la depresión menor han encontrado beneficios clínicamente relevantes respecto del placebo, especialmente en los ensayos más nuevos y mejor controlados. Una de las principales ventajas de los antidepresivos sobre la psicoterapia es su disponibilidad inmediata y el corto período requerido para evaluar la eficacia. La actitud del paciente hacia la psicoterapia o el tratamiento antidepresivo es de gran importancia y debe explorarse, más allá de la gravedad de la depresión. En un proceso de toma de decisiones compartido, el paciente debe recibir información apropiada sobre las opciones terapéuticas, establecer sus preferencias y luego recibir el tratamiento de elección.

Les antidépresseurs devraient-ils être utilisés dans la dépression mineure ?

Une dépression dite mineure ou infra-seuil s’associe à une déficience fonctionnelle, une détérioration de la qualité de vie et le risque de passage à une dépression majeure. Elle doit donc être traitée. Une position attentiste vigilante peut se comprendre seulement pour les patients qui ne souhaitent aucun traitement même après avoir été bien informés. La psychothérapie s’est montrée efficace mais cette efficacité a peut-être été surestimée dans les études randomisées à cause de problèmes méthodologiques (groupe témoin, aveugle). Les résultats de certaines études (surtout les plus récentes, mieux contrôlées) sur l’efficacité des antidépresseurs dans le traitement de la dépression mineure ont montré des bénéfices cliniquement pertinents par rapport au placebo. Un des principaux avantages des antidépresseurs sur la psychothérapie est leur disponibilité immédiate et la courte période nécessaire à l’évaluation de leur efficacité. Au-delà de la sévérité de la dépression, l’attitude du patient vis-à-vis de la psychothérapie ou des antidépresseurs est très importante et devrait être analysée. Dans un cadre de décision partagée, le patient devrait être correctement informé sur les choix thérapeutiques, donner ses préférences et enfin, recevoir le traitement qu’il a choisi.