

Antidepressant drugs – clinical practices must change

Antidepressant drugs are less effective than the extent of their use would indicate. These drugs are fraught with side effects that call for more caution in prescribing them.

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Antidepressants can reduce the symptoms of depression, but their effect may also be unsatisfactory or lead to serious deterioration in the patient's condition (1). Knowledge of effects and serious side effects of the drugs should have consequences for prescription practices.

Antidepressants are among the world's most frequently prescribed drugs. Their extensive use may partly be regarded as an expression of the increasing medicalisation of modern society (2). In Norway too, consumption is high and rising (3).

Antidepressants come in a number of main forms. What we set out in this article applies in principle to all the main forms, although most references concern so-called selective serotonin reuptake inhibitors (SSRI) and serotonin-noradrenalin reuptake inhibitors (SNRI). These are largely equivalent in terms of the extent and type of their side effects (4–6).

Effects

Hundreds of clinically randomised studies have been published to show statistically significant results in favour of antidepressant drugs (7). The studies have a varying degree of weakness in, for example, their design, inclusion criteria, measurement of effects, study populations, follow-up time, recording of data and use of statistics (7, 8).

Recent meta-analyses indicate that antidepressants are less effective than has previously been assumed and than their extensive consumption would indicate (7, 9–11). Turner and collaborators have documented a considerable selection bias in favour of studies where antidepressants have scored positively when compared to placebo. Studies with unfavourable results have a tendency to remain unpublished (9).

When compared to placebo, Kirsch and collaborators found effects in favour of antidepressants only for the most afflicted patients. In this population, the main difference consisted in a lesser effect of placebo

(10). Fournier and collaborators found that compared to placebo, antidepressants had little effect for patients suffering from mild or moderate depression, while the effect was considerable for patients with very severe depression (11). The various comparisons of antidepressants and placebo that have been published show a clear tendency indicating that the positive effects of the drugs, when compared to placebo, were greater in older studies than in more recent ones (12). The causes for this are unclear, although a lower threshold value in measurement of depression at baseline may provide a partial explanation (12).

Side effects

Randomised clinical studies of antidepressants have been governed by the pharmaceutical companies and designed to demonstrate short-term effects rather than long-

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term safety of use (13). Little attention has been devoted to revealing side effects and harmful effects of these drugs (7). There is an imbalance between the emphasis placed on positive and negative effects (14). A number of serious side effects in clinical studies have not been reported or have been reported incorrectly (15). This notwithstanding, we now have data that call for an increased degree of caution in prescription practices.

Since 2004, the American Food and Drug Administration (FDA) has published numerous safety warnings concerning potentially increased suicidal intent following from the use of antidepressants among children, adolescents and young

adults (13). Since 2007, all these drugs must carry a so-called «black box warning» that provides information on an increased risk of suicidal symptoms. This issue was raised as early as in 1958 (15). SSRI-induced suicidal intent as a class effect of antidepressants has been known since the early 1990s (16). A recently published Norwegian study among patients with bipolar disorder showed that attempted suicide in the case history is associated with previous use of antidepressants (17).

Whether such drugs overall serve to increase the number of suicides among adolescents and adults must be deemed unclear (18). In their review article, Healy and Aldred found that the risk of suicide during treatment with antidepressants is 2–3 times higher compared to placebo (15). The cause of this increase in suicidal intent during the use of antidepressants has not been conclusively determined, but several authors indicate a relationship to specific sub-groups and an association between drug-induced psychomotor agitation, «racing thoughts» and suicidal behaviour (1, 19).

Like antipsychotics, antidepressants may cause akathisia, i.e. inability to sit still, severe restlessness and an urge to wander around (16, 20). Several studies show that intense affective states characterised by desperation, anxiety, agitation and anger, even those of a passing nature, result in crises with a high risk of suicidal behaviour (21). Many highly suicidal patients tend to deny any suicidal intentions in their sessions with the therapist. Presence of severe anxiety and agitation are currently the only secure predictors of suicide during hospitalisation and immediately after discharge (22).

Antidepressants have a number of psychoactive effects and side effects, especially during the first days following the start of the treatment or after a change of dosage (6). Some patients develop paradoxical effects, including an exacerbation of their depressive symptoms (23). An American study showed that approximately 8% of the admissions to psychiatric hospitals were due to mania or psychosis that had been induced by antidepressants (24).

The information folders for various drugs

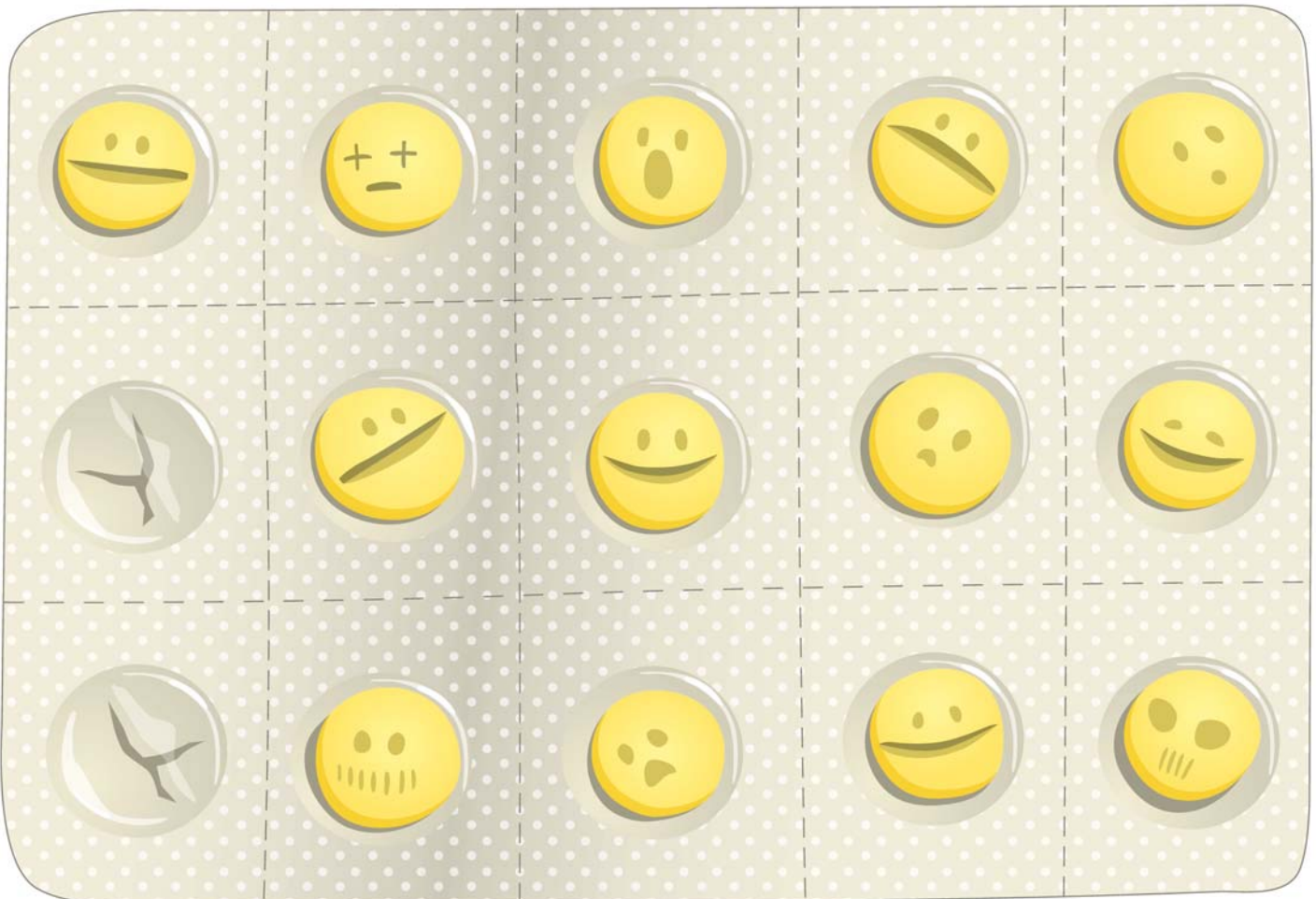


Illustration: Stein Løken

quite often contain warnings of behavioural change involving a potential for violence towards others. Most antidepressants are supplied with such information. In a recent study, Moore and collaborators analysed data from the American reporting system for side effects of drugs (25). They found that violence towards others is overall associated with few drugs. Antidepressants with serotonergic effects had the strongest association with such violent events.

Development of tolerance

Antidepressants may cause development of tolerance. This manifests itself primarily during discontinuation of the medication (26). Most symptoms are of relatively short duration. Chronic, tardive dysphoria has also been described after long-term use of antidepressants, in the same manner as

tardive dyskinesia after dopamine blockade (27). Patients will often have an initially positive effect from the drug. This effect is gradually lost and chronic, therapy-resistant conditions may develop (28).

In a clinical context it is essential to be aware of development of tolerance when antidepressants are discontinued, since a number of patients will then experience an increased symptom pressure. This can easily be misinterpreted as recidivation.

Discussion

There is ample evidence to assume that antidepressants are used to excess in Norwegian practice. One key reason could in part be uncritical marketing by the pharmaceutical industry. Most studies are designed to detect effects in favour of the drugs, small results of doubtful clinical signifi-

cance are often inflated while side effects are played down, and critical arguments are scarcely heeded. This situation has much in common with Chomsky's descriptions of propaganda and its instruments (18, 29).

We need independent clinical research. It is essential that research activities and practices are undertaken without any ties to the pharmaceutical industry. Most of all, we need drug information from independent sources. Access to such information could have the potential to change prescription practices.

Antidepressants may provide good relief for certain types of depression. The question is: which ones. We have no reliable data. It is easier to have an opinion as to who should not use such drugs. Patients with bipolar depression should not use antidepressants, at least not without the simul-

taneous use of mood stabilisers. In patients suffering from depression accompanied by agitation, severe anxiety or desperation, treatment with antidepressants should be undertaken with great caution (22), especially as a monotherapy. If such symptoms should occur during treatment with antidepressants, the treatment must be reconsidered immediately.

Dosage and serum concentrations of antidepressants receive remarkably little attention. High dosages are frequent (30). There are indications that some drugs produce anti-convulsive effects at low dosages and pro-convulsive effects at higher dosages (31). Other data indicate that some antidepressants have a therapeutic window, implying that the drugs have no effect or only undesirable effects below and above a certain dosage interval (32).

A discontinuation of antidepressant drugs should be considered in patients who have used such drugs over a long period. The patients should be informed in detail about the development of tolerance and withdrawal reactions. Symptoms that occur after discontinuation are rarely an effect of recidivation. The effect of such drugs after more than six months' use are not scientifically documented (27). In patients who have used the drugs over a long period, the dosage should be gradually reduced. There is some documentation showing that mood-stabilising antiepileptic drugs may have an effect on withdrawal reactions, as a monotherapy and in combination with antidepressants during discontinuation (26).

Patients who are being treated with antidepressants should be followed up closely after the start of treatment, since most serious events occur during the first 12 weeks of the treatment sequence (33). Continuous, individual and frequent follow-up and monitoring is absolutely necessary.

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