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Ketamine for depression – evidence and proposals for practice

PERSPECTIVES

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Current treatment for serious depression is unsatisfactory, and many patients fail to achieve the desired effect. Ketamine represents a new treatment option, and randomised trials show a rapid effect of intravenous ketamine. Although knowledge about adverse effects and the duration of the effect is somewhat deficient, we believe that the time has come to start clinical treatment in Norway.

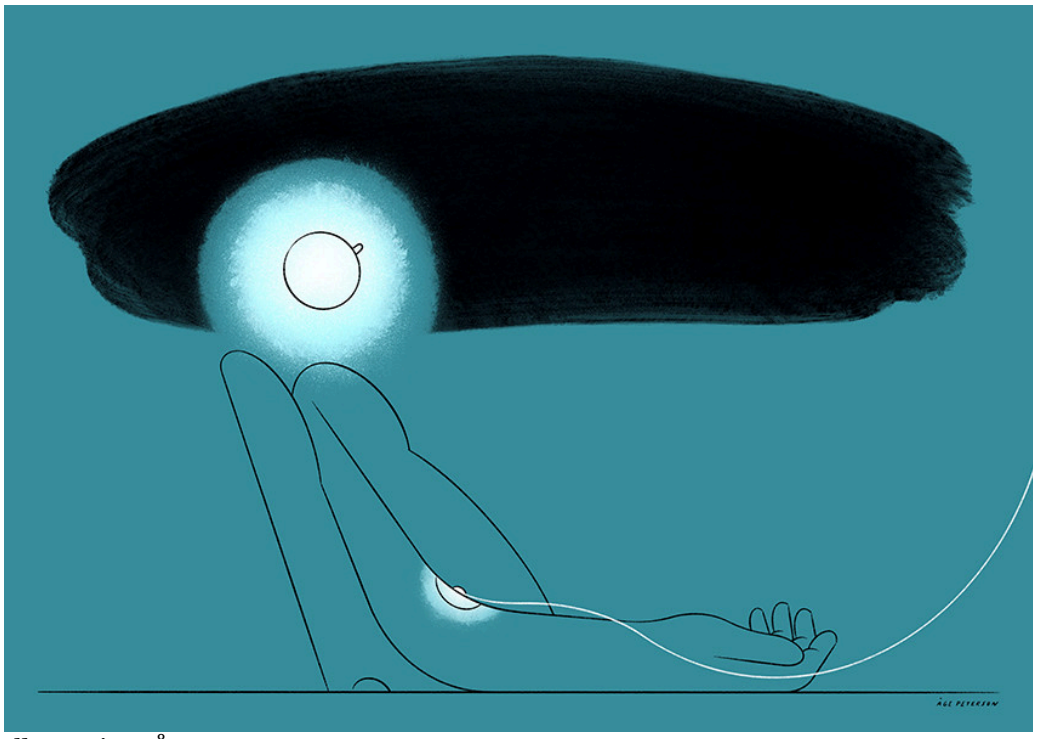

Illustration: Åge Peterson

Several treatment options for depression are currently available, both pharmacological and psychological, but severe depression is difficult to treat, and a considerable proportion of patients fail to achieve remission. New treatment options are therefore urgently needed. Ketamine is a well-known anaesthetic that in a number of studies has proven to have a fast-acting antidepressant effect with acceptable adverse effects, although its durability needs to be clarified (1). A nasal spray containing the enantiomer esketamine was recently approved for use against treatment-resistant depression. More knowledge is needed on both the duration of the effect and the adverse effects (1), but many patients with severe depression might still benefit from ketamine. A pilot project has therefore been initiated at Østfold Hospital, and we propose that coordinated clinical treatment be undertaken in Norway.

Depression and available treatment

In Norway, the lifetime prevalence of depressive disorders is approximately 17 % (2), which is consistent with the international prevalence, and depression is ranked third in the global burden of disease (3). In addition, it entails an increased risk of suicide. The effect of antidepressants, mainly selective serotonin reuptake inhibitors (SSRI), is only seen after 2–4 weeks, and the effect size is small to moderate (4). Approximately one-half of patients with depression do not respond to first-line treatment, and approximately 30 % show no response after multiple types of treatment (5). Treatment-resistant depression, defined as a lack of response to at least two types of antidepressants with adequate dosage and duration, is a serious condition (6). The existing antidepressants were developed in the 1980 s and 90 s, and few drugs have become available since then.

Ketamine

Ketamine consists of a racemic mixture of arketamine and esketamine and is a non-competitive N-methyl-D-aspartate (NMDA) glutamate receptor antagonist which produces a dosage-dependent analgesic and dissociative effect. Ketamine has been approved as an anaesthetic in Norway since 1972. How the blocking of the NMDA receptor affects depression is not fully known, but appears to include release of glutamate, neuroplasticity and synaptogenesis, as well as an effect on brain connectivity (7).

Ketamine for depression

A single dose of subanaesthetic intravenous racemic ketamine has been shown to be effective against depression in more than 20 double-blind, randomised controlled trials (DB-RCT) and a number of meta-analyses (8). The effect normally appears within 1–2 days, and the response and remission rates are 70 % and 30 % respectively within 24 hours (8). After a single dose, relapse within 1–2 weeks is the rule, although in 19–34 % of patients the effect seems to last beyond 30 days (8). The evidence base for the effect of repeated doses is limited. A number of open studies have shown increasing response and remission rates during a treatment series, which indicates that some patients need repeated treatments to achieve the full effect. A double-blind, randomised controlled trial for treatment-resistant depression showed that a dose repeated two or three times per week was effective when compared to placebo (9), while another double-blind, randomised controlled trial in a patient sample with chronic suicidality and treatment-resistant depression, of which nearly one-half had tried electroconvulsive therapy (ECT), showed no effect when compared to placebo (10).

Ketamine treatment also appears to have a rapid-onset effect on suicidality. Two meta-analyses of mainly small trials with short follow-up times show a beneficial effect on suicidal thoughts that are partly independent of the antidepressant effect (11, 12).

Adverse effects and risk

The adverse effects of ketamine are mainly of a mental, cognitive, neurological, urogenital or haemodynamic nature. They are dose-dependent, mild and most often transient – serious adverse effects are rare (13). The most common adverse effects usually subside within a few hours after the treatment, and include dissociation, increased pulse rate and blood pressure, blurred vision, sedation, headache, restlessness, dizziness and nausea. The patient should be thoroughly informed in advance of the possibility of dissociation and psychotomimetic effects. Iatrogenic ketamine addiction is rarely observed in outpatient administration of ketamine for treatment of depression, but is a factor to be aware of. Ketamine has been thoroughly tested as an anaesthetic, and the risk of a cardiovascular or respiratory effects in subanaesthetic doses when used for treatment of depression is considerably lower than when used in anaesthesia.

Indications and contraindications

In light of incomplete long-term data on efficacy and adverse effects, international guidelines recommend restricting intravenous ketamine to treatment-resistant depression (8). This is the same indication as for esketamine nasal spray.

Psychiatric contraindications include psychosis and type 1 bipolar disorder in the hypomanic/manic phase. Other relative contraindications are uncontrolled hypertension, cardiovascular disease, respiratory disease and pregnancy/breastfeeding. A further relative contraindication is drug addiction, although no increased risk of addiction has so far been documented for the use of ketamine in treatment of depression (1).

Practical use

Guidelines have been drawn up for the practical use of ketamine in the United States and Canada (8, 14). Here, the treatment is provided in outpatient clinics by doctors who have training in the use of ketamine. The presence of anaesthesia personnel during the treatment is not considered necessary, but when the drug is administered outside of the hospital, equipment required for cardiopulmonary resuscitation and health professionals experienced in its use should be available. Intravenous infusion, which makes for optimal bioavailability, with doses between 0.5 mg/kg and 1.0 mg/kg given over

40 minutes, is the most common form of administration. Oxygen saturation, blood pressure and pulse rate should be monitored. The short half-life means that the patients can go home within one hour after the infusion.

Drug approval

Intravenous ketamine for treatment of depression cannot be patented, and the pharmaceutical industry has therefore no incentive to undertake costly clinical trials to obtain a marketing permit. Esketamine nasal spray on the other hand is patented, and Janssen has invested in clinical trials that gave a basis for approval for treatment-resistant depression, including in Norway (15). No trials have yet compared esketamine nasal spray with intravenous ketamine, but a meta-analysis indicates that intravenous administration has a better effect (16). In the pilot project at Østfold Hospital, the intravenous form was used in light of its efficacy, procurement cost and anti-suicidal effect.

Proposal for focus areas

Many questions remain to be answered about the long-term effects of ketamine, optimal dosage, frequency of administration, patient selection and the underlying pharmacological mechanisms (1). However, there is solid evidence that ketamine is effective for treatment-resistant depression and has an acceptable adverse effect profile (1). To prevent uncoordinated experimentation with possible unfortunate consequences, we propose a national collaboration to ensure establishment of a shared evidence-based practice in Norway. Since long-term data from clinical trials are lacking, experiences from clinical use in a naturalistic setting should be systematically collected. The professional guidelines from the North American medical communities should be revised and adapted to Norwegian conditions (8, 14).

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