EDITORIALS

Ketamine and ECT in Depression — Risks and Rewards

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Investigators from five referral clinics for electroconvulsive therapy (ECT) report in the *Journal* the results of an open-label, randomized, noninferiority trial of ECT or ketamine infusion in patients with moderately severe depression.[1] After randomization, 365 patients (170 in the ECT group and 195 in the ketamine group) were included in the primary analysis. At the conclusion of the 3-week, randomized, active-treatment phase, 41% of the patients in the ECT group and 55% of those in the ketamine group reported a 50% or greater reduction in symptoms, findings that are consistent with moderate-to-excellent responses to treatment.[2] Patients who had a response were followed for an additional 6 months. By the end of the 6-month follow-up period, relapse had occurred in 56% of the patients in the ECT group and in 34% of those in the ketamine group. The incidence of expected adverse effects of memory loss from ECT and dissociative symptoms from ketamine had decreased by the 6-month mark, and patient-reported quality of life was similar in the two treatment groups. The investigators concluded that ketamine was noninferior to ECT in the treatment of moderately severe depression in this trial.

When thinking about this trial, one should note that these patients represent a severely affected, chronically ill group of men and women with depression in midlife. All had had multiple episodes of depression with onset in adolescence or early adulthood. Most had family histories of depression, and many had made suicide attempts. Most patients had coexisting severe anxiety or post-traumatic stress disorder, and some had coexisting alcohol use disorder. All the patients had been treated with a wide range of psychotropic medicines. Some had received previous treatment with either ECT or ketamine. Patients with psychotic symptoms were excluded because ketamine can induce psychotic symptoms. Menopause, cerebrovascular illness, loss of parental and occupational roles, and other concomitant issues of midlife may have contributed to their depression.

Proponents of ECT will note that, as pointed out by the authors of the trial, unilateral delivery of electricity to the nondominant hemisphere, in an effort to minimize memory loss, resulted in inadequate induced-seizure duration in many patients. These patients were switched to bilateral treatment (electrode placement on both sides of the head), but the duration of seizures during the first 3 weeks of the trial may not have been sufficient and may have led to the slightly lower response in the ECT group. It is noteworthy that all the patients who were considered for trial entry were initially referred for ECT because they and their clinicians thought that ECT was their best option.

The positive response to ketamine is not without precedent.[2] Ketamine has mixed pharmacologic properties as an anesthetic, an opiate, and a sympathomimetic. The agent thus combines properties that many persons — not only those with severe depression — find rewarding. Accordingly, ketamine is also widely used recreationally.[3] The question raised by this trial and others is how clinicians and regulatory agencies should regard its use and abuse.[4] For someone

who is chronically ill with depression, 3 weeks of lightened mood is undoubtedly a gift. Many patients have reported ketamine therapy to be life-changing,[5] and many clinicians are enthusiastic about bringing this gift to patients who otherwise seem unreachable. However, the results of this current trial suggest that the 3-week treatment was not life-changing. Ketamine treatment was effective, but by 6 months, a brief period in a lifetime of depression, the quality of life was no better with the agent than with ECT.

Patients who have received oxycodone or other opiates from physicians for pain have reported initial highly positive responses similar to those reported by patients who received ketamine in the current trial, but prescription use was associated with a subsequent epidemic of addiction to both oxycodone and heroin.[6,7] The follow-up period of the current trial was not long, nor did it assess future drug-seeking behavior among those who did or did not have a response to ketamine. The experience with oxycodone is that a highly pleasurable release from pain, including the pain of depression, can indelibly change behavior. Prescription drug–monitoring programs include ketamine as a Schedule III narcotic medication, but there are no barriers to stop a patient who has received ketamine in a referral clinic for severe depression from going to another provider who uses less stringent criteria to provide treatment.[8] We need to remember that only a minority of physicians were responsible for the oxycodone epidemic.

Patients in an ECT-referral clinic may seem to be an unlikely nidus for a wave of drug addiction, but even in this trial, treatment with ketamine was continued during the 6-month follow-up period in 41% of the participants who had been assigned to receive ketamine in the initial 3-week treatment phase. A longer duration of treatment increases the likelihood of both drug dependence and cognitive adverse effects, including dissociation, paranoia, and other psychotic symptoms.[9] ECT clinics have informed consent documents that list the various cognitive and other adverse effects of that treatment. A similar informed consent document for ketamine should caution patients and clinicians that temporary relief may come with longer-term costs.

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