

*The information in this column is not intended as a definitive treatment strategy but as a suggested approach for clinicians treating patients with similar histories. Individual cases may vary and should be evaluated carefully before treatment is provided. The patient described in this column gave informed consent for its publication.*

### Medical assistance in living after failure of ECT and ketamine

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A 33-year-old single, childless man with treatment-resistant unipolar depression was referred for participation in our cross-over trial comparing electroconvulsive therapy (ECT) with ketamine in the treatment of major depression.<sup>1</sup> He had completed graduate studies, was on sick leave, and had good social support. The duration of the depression was 3 years, and this was his third lifetime episode. There was no substance misuse or personality disorder and no physical comorbidity. Bloodwork, including complete blood count, electrolytes and thyroid-stimulating hormone, as well as renal and hepatic function were normal.

The mental state examination was significant for flat affect, psychomotor retardation and decreased prosody. Although the patient did not report suicidal ideas per se, he mentioned that he would ask for medical assistance in dying (MAiD) when available in Canada on the basis of intractable mental illness.

The patient's previous pharmacological trials included sertraline, bupropion, levomilnacipran and bexiprazole, alone or in combination. Each trial was of sufficient dose and duration, following the Canadian Network for Mood and Anxiety Treatments (CANMAT) recommendations.<sup>2</sup> He was also receiving cognitive behavioural therapy.

At the time of entry in our trial, the patient's Montgomery-Åsberg Depression Rating Scale (MADRS) score was 29, indicating moderate depression.<sup>3</sup> At baseline, he was taking venlafaxine XR 300 mg and aripiprazole 5 mg daily, as well as olanzapine 5 mg, mirtazapine 60 mg, and lithium 750 mg at bedtime. He was randomized to the ketamine arm and received 9 infusions of intra-

venous ketamine 0.5 mg/kg 3 times per week. Exiting this ketamine phase, his MADRS score was 31.

The patient then crossed over to ECT, and venlafaxine XR was decreased to 225 mg. He received 6 ultra-brief pulses in the right unilateral position 3 times per week followed by 6 brief pulses bitemporally with stimulus titration. After ECT, his MADRS score was 29. He reported hopelessness and was determined to get MAiD.

Olanzapine and aripiprazole were stopped and venlafaxine XR was tapered and discontinued. Moclobemide was introduced and titrated up to 750 mg/d, and mirtazapine was decreased to 30 mg at bedtime. These interventions, performed over a few weeks, led to no improvement.

Three months after ECT, lithium was decreased to 450 mg and tranylcypromine, a nonselective and irreversible type A and B monoamine oxidase inhibitor (MAOI), was introduced. After reaching 50 mg/d of tranylcypromine, the patient became more talkative, more positive, and stopped thinking about MAiD. At 60 mg/d, he started showering every day instead of every 3 days. His mood, concentration and hedonic tone improved, and he started creative writing. His psychomotor retardation resolved. Although anxiety and low energy remained, his MADRS score dropped to 15.

The patient had repeatedly told us that he intended to ask for MAiD when it became available. Although the criteria for MAiD eligibility in Canada have not been clearly defined yet, it seems likely that he may have qualified. However, recently, when asked about MAiD, the patient said "I could not see anything working if ECT and ketamine had not worked." He then explained that he no longer wants to proceed with MAiD, as he now feels hopeful.

This patient's case illustrates the relevance of irreversible MAOIs in

modern psychopharmacology for treatment-resistant depression because, owing to their different mechanism of action, MAOIs can be very helpful when everything else fails. The case also highlights that irreversible MAOIs are worth considering even when moclobemide is ineffective.

The CANMAT guidelines for depression recommend tranylcypromine as a third-line pharmacological option.<sup>2</sup> Several trials have shown its efficacy in treatment-resistant depression (a mean responder rate of 58% has been reported).<sup>4</sup> Of note, tranylcypromine had a low remission rate of 7% in patients who had not reached remission after 3 treatment steps in the STAR\*D trial.<sup>5</sup> However, nearly half of these 58 participants were treated for less than 6 weeks, and tranylcypromine was underdosed (mean daily dose of 37 mg at exit).

A review of 66 cases of euthanasia or assisted suicide of psychiatric patients in the Netherlands found that 36 had a primary diagnosis of depression; seeing that only 7 of those individuals had been treated with an MAOI is cause for concern.<sup>6</sup> Another study found that among 2846 patients who received a first administration of ECT between 2002 and 2016 in Quebec, Canada, only 20 had been treated with an MAOI in the preceding 5 years (unpublished data, 2022).

MAOIs may be under-prescribed because of the potential for hypertensive urgency and serotonin syndrome. The risk of severe cerebrovascular events associated with hypertensive reactions has been estimated to be 1.4–7.0 per 100000 individuals treated with tranylcypromine<sup>7,8</sup>; hence, the risk is very low and may be overestimated by clinicians. It is important to note that food preparation techniques have changed over the years, and foods that contain problematic amounts of

tyramine are now uncommon.<sup>9</sup> Nevertheless, patients must follow a low-tyramine diet (e.g., avoid aged cheese, improperly stored meat, on-tap beer), and resources such as the *MAOI Diet Recipe Book* from the Sunnybrook Health Sciences Centre provide useful information for patients and clinicians.<sup>10</sup> Regarding serotonin syndrome, clinicians must keep in mind the potential for fatal interactions and must not combine irreversible MAOIs with medications that inhibit serotonin reuptake.

Perhaps most importantly, our patient's case highlights the therapeutic necessity for clinicians to remain hopeful when patients are hopeless. Otherwise, this may lead to avoidable deaths.<sup>11</sup>

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