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Supratherapeutic Esketamine Dosing in Difficult to Treat Depression: A Case Series

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OBJECTIVES

Major depressive disorder (MDD) is a leading cause of disability, with as many as 1/3 of depressed patients failing to remit after several therapy trials.

Patients with difficult to treat depression (DTD) have higher rates of inpatient care, suicidality, comorbidities, social and occupational impairment, and all cause death. Esketamine, an NMDA antagonist, has Health Canada approval as a treatment, and has Level 1 evidence and is a second line adjunctive treatment as per CANMAT 2023 guidelines.

The labelled dose of esketamine is 56 mg to 84 mg intranasally; however, a higher dose may be considered in specific patients.

There is minimal literature on the use of supratherapeutic esketamine; this case series presents information regarding supratherapeutic esketamine in clinical practice.

METHODS

Fourteen patients administered courses of 112 mg of esketamine were identified from routine clinical practice.

Four of these patients were in early stages of supratherapeutic treatment, two prematurely discontinued (pregnancy, relocation out of country), three patients had treatments held (dysuria, logistics, payment), and five completed treatment.

Sociodemographic, clinical, and treatment variables were extracted from chart review for the patients who completed treatment.

RESULTS

Demographics: Age range was 39 to 64 yo (mean=49 y). In terms of gender, 3 patients were female and 2 male, most were divorced or single (80%). Level of education was 16 to 18 years.

Clinical: All patients had difficult to treat depression, with long durations of illness (3 to 44 years), 3 to 14 prior antidepressant trials, adjunctive trials (mean of 2), 2 had neurostimulation, and there was a mean of 2 hospitalizations related to suicidality; all had psychiatric comorbidities.

Treatment: Patients completed 26 to 38 sessions, with 50% to 71% of these sessions at supratherapeutic dosing. In all cases, partial response or tachyphylaxis and/or subjective report of limited dissociation prompted dosage increase.

All patients improved with treatment. Three of five patients had decreased QIDs scores when comparing supratherapeutic vs. regular trials (see Table 1). See Figures for individual courses of treatment.

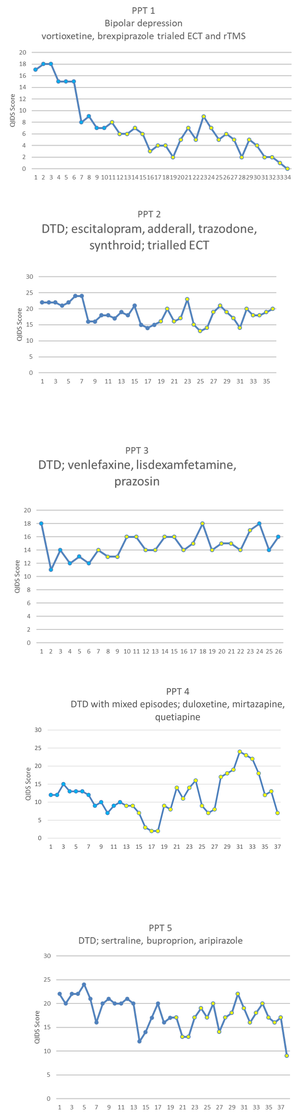
Treatments were generally well-tolerated, with the most common side effects including transient hypertension and nausea. This was managed supportively via clonidine (n=2 patients) and ondansetron (n=1 patient).

Table 1. *QIDS Difference Scores*

PPT	POST-PRE	REG-PRE	SUPRA-REG
1	-17	-10	-7
2	-2	-7	5
3	-2	-6	4
4	-5	-2	-3
5	-13	-5	-8

Table 1. QIDS difference scores, with negative scores indicating improvement in depressive symptoms with treatment course. POST-PRE=final session QIDS minus first session QIDS. REG-PRE=final session QIDS at regular dosing (84mg) minus first session QIDS. SUPRA-REG=final session QIDS at supratherapeutic dosing (112mg) minus QIDS from final session at regular dosing (84mg).

RESULTS (con't)



PPT 1
Described decreased rumination, improved energy and sleep. Improved function including achievement of advanced degree and travelling.

PPT 2
Reported decreased suicidality and rumination, improved energy and perspective. Described treatment as life-saving and the best they felt in over a decade. Anhedonia diminished, sensory experiences were improved, and they began engaging in leisure and family interactions. Ongoing chronic pain and seasonality was reported.

PPT 3
Reported decreased suicidality, decreased rumination, was able to attend outings with family and friends. Primary diagnosis PTSD, and continued to struggle with these symptoms as well as the loss of multiple first degree relatives over the course of treatment.

PPT 4
Functional improvement reported, including visiting family, starting hobbies, exercising.

PPT 5
Comorbid PTSD; More sociable, more energy, no anhedonia; family noted significant improvement.

Figure 1. *Individual Patient QIDS Scores over Treatment Course*

Session number is on the x-axis. QIDS score is on the y-axis. Yellow data points indicate sessions at supratherapeutic (112mg) dosing.

CONCLUSION

Preliminary evidence suggests supratherapeutic dosing may be beneficial for some patients with DTD. Some patients show a robust response, whereas others have a more chronic course, which may relate to other known factors for symptom persistence. Discordance between qualitative report and self-report measures was also noted.

These findings are limited by limitations inherent in case studies, including risk of bias, lack of controls, inability to establish cause and effect, as well as limited external validity.

Clinically, informed consent and discussions regarding risk: benefit should be taken collaboratively with patients prior to dose increase. As well, blood pressure and chronic health conditions should be optimized by primary care providers prior to and on an ongoing basis during treatment.

Future studies should include: measurement across domains, examination of the role of comorbid psychiatric diagnoses in treatment response, as well as prognostic factors influencing supratherapeutic response.

REFERENCES

Johnston KM, Powell LC, Anderson IM, Szabo S, Cline S. The burden of treatment-resistant depression: A systematic review of the economic and quality of life literature. *J Affect Disord*. 2019;242:195-210. doi:10.1016/j.jad.2018.06.045

Lam RW et al. Canadian Network for Mood and Anxiety Treatments (CANMAT) 2023 Update on Clinical Guidelines for Management of Major Depressive Disorder in Adults. Can J Psychiatry. 2024 Sep;69(9):641-687. doi: 10.1177/07067437241245384. Epub 2024 May 6. PMID: 38711351; PMCID: PMC11351064.

McIntyre RS, Rosenblat JD, Nemeroff CB, et al. Synthesizing the Evidence for Ketamine and Esketamine in Treatment-Resistant Depression: An International Expert Opinion on the Available Evidence and Implementation. *Am J Psychiatry*. 2021;178(5):383-399. doi:10.1176/appi.ajp.2020.20081251