UBCH

Subcutaneous and Intramuscular Parenteral Ketamine for Treatment of Depression

Clinical Treatment Protocol (April 30, 2021)

Joseph Tham, MD, FRCPC, FAPA

BC Neuropsychiatry Program
VGH/UBC Neurostimulation Program

André Do, MDCM, FRCPC

Mood Disorders Program, Clinical Research Fellow

Jason Fridfinnson, MD, FRCPC

Department of Anesthesiology and Perioperative Care (VGH and UBC)

Reza Rafizadeh, BPharm

Clinical Pharmacy Specialist, Mental Health & Substance Use
Burnaby Centre for Mental Health & Addiction | BC Psychosis
Lower Mainland Pharmacy Services

Jacky TP Siu, PharmD, BCPP

Clinical Pharmacy Specialist – Tertiary MHSU
Lower Mainland Pharmacy Services

George P. Budd, PharmD, BSc (Pharm), FBCCSU, R.PEBC, R.Ph

Research Associate
Mental Health Services-Complex Pain and Addiction Services, VGH

Raymond W. Lam, MD, FRCPC, FCAHS

Mood Disorders Program
BC Leadership Chair in Depression Research

A. OVERVIEW

INTRODUCTION:

Racemic (R,S)-Ketamine has been commercially available for human use as an anesthetic agent since 1970 (1). Over the decades, the pharmacokinetic and pharmacodynamic effects of this medication have been discovered to be primarily a result of noncompetitive blockade of the glutamatergic NMDA ionotropic receptor (2).

In the last 2 decades since the report by Berman et al. (3) in the psychiatric literature, interest has been building on the use of ketamine as a novel agent in the treatment of depressive disorders including treatment resistant depression (TRD) and bipolar depression (4). While parenteral use of ketamine for mood disorders at this time remains off-label, based on the evidence accumulated, the Canadian Network for Mood and Anxiety Treatments (CANMAT) Guidelines (5) lists ketamine with Level 1 evidence as an adjunctive treatment even for a single IV dose. The intranasal, non-racemic esketamine (Spravato) has been approved for treatment resistant depression in combination with an SSRI or SNRI since 2020 in Canada (see [CADTH review](#)) but currently may be difficult to access as an outpatient due to cost, the need for close monitoring, and is unavailable in the hospital formulary.

Beyond IV therapy, ketamine can be given through other routes such as intramuscular (IM) and subcutaneous (SC). Based on pharmacokinetic research, ketamine given IM reaches maximum concentration (C_{max}) in less than 30 minutes (t_{max}) and has a half-life ($t_{1/2}$) of around 3 hours in healthy volunteers (6). Details specifically on SC administration appears to be limited. However, compared to IV treatment, clinical use of ketamine in the other conditions such as pain disorders using SC and IM modalities suggest similar levels of bioavailability, rapid onset of action (within minutes), and duration of activity (7 – see Table 1).

While there is still much research to be done, general parameters for ketamine treatment in mood disorders have been determined to be efficacious in the literature using sub-anesthetic doses ranging from 0.1-0.75mg/kg (8, 9). This is low dose compared to the typical procedural sedation amount of 0.5-9mg/kg (10). As such, while side effects may still be anticipated, generally safety has not been an issue. In fact, compared to other anesthetics, ketamine is particularly useful when cardiovascular and pulmonary monitoring is unavailable (11).

Although IV ketamine has been the primary route of administration for treatment in depression trials, pharmacokinetic data suggests that both SC and IM methods of administration will result in high amount of bioavailability (up to >90%) (2). Empirical evidence, though limited, for SC ketamine (0.1-0.5mg/kg) is promising (100% remission in a small double-blind study, 12). IM ketamine has also been shown to have similar efficacy to IV administration in a single-dose RCT protocol in 27 severely depressed patients with reduction in depression ratings by 57% within 2 hours after treatment (13).

PURPOSE:

This proposal by the authors is to develop a clinical protocol for access to parenteral (primarily SC and IM) ketamine for treatment of mood disorder for inpatients at UBC Hospital. The intent of the protocol is to evaluate:

1. **Feasibility** of providing efficient clinical care combining up to twice-a-week ketamine treatments during the electroconvulsive therapy (ECT)-scheduled times at UBC Hospital with the availability of nurses trained in parenteral anesthetic administration under the supervision of an anesthetist.
2. **Safety** of the protocol with pre-screen, treatment monitoring, and post-treatment care implemented. Monitoring for side-effects, particularly cardiovascular and pulmonary, but also mental state changes.
3. **Efficacy** of the protocol in showing evidence of relief from severe mood symptoms requiring an inpatient stay as expected based on prior research highlighted above.

B. TREATMENT PROTOCOL

- Protocol for clinical use to be approved by VCH Hospital Pharmacy and Therapeutics Committee.
- Infection control protocols followed as appropriate on the inpatient units and in the Neurostimulation Program.
- All Ketamine Protocol treatment records will be maintained in the inpatient chart.
- **Indications:** achieving response as adjunctive treatment in patients with refractory depression, potential urgent reduction in suicidality.
- **Inclusion criteria:**
 - > 18 years old; able to provide informed consent.
 - Depressive episode, unipolar or bipolar inpatients.
 - Patients who have failed adequate trials of 2 or more antidepressants (e.g. SSRI, SNRI, mirtazapine, bupropion, tricyclics) AND 1 or more adjunctive treatments (e.g. 2nd generation antipsychotic, aripiprazole, lithium, thyroid hormone and if bipolar depression quetiapine, lamotrigine or lurasidone).
 - Ideally refractory to psychotherapy (e.g. cognitive-behavioural therapy, CBT) and previous ECT treatments.
 - Ketamine is considered as an augmentation strategy. Therefore, the patient will need to continue their pharmacological antidepressant regimen.
- **Exclusion criteria:**
 - Active psychosis.
 - Drug or alcohol abuse/dependence within the past 6 months, history of ketamine abuse.
 - Dementia/delirium.

- Significant personality disorder.
 - Unstable medical condition – ASA PS 1-3 (see Appendix C) patients only, uncontrolled hypertension excluded. May require anesthesia consult.
 - Recent seizures.
 - History of elevated intracranial pressure.
 - Aneurysmal vascular disease or arteriovenous malformation, and intracerebral haemorrhage.
 - Pregnancy/breast feeding.
 - Previous sensitivity to ketamine, esketamine, or related compounds.
- **Treatment parameters (see Figure 1 for summary):**
 - *Maximum 6 treatments per inpatient course:*
 - **Treatments 1 & 2:** 0.25mg/kg x 2 treatments.
 - **Treatments 3 & 4:** If patient did not experience any subjective effect from 0.25mg/kg, and no improvement in mood state as defined by <20% reduction in QIDS-SR16 or MADRS score ≥ 20), increase to 0.5mg/kg, else stay at 0.25mg/kg dose.
 - **Treatments 5 & 6:** If patient still at 0.25mg/kg and insignificant mood response, increase to 0.5mg/kg dose for last 2 treatments. If patient still not experiencing effect from 0.5mg/kg, may increase to maximum dose of 0.75mg/kg.
 - **Treatment held if response (QIDS-SR/MADRS $\leq 50\%$ of pre-treatment score) achieved.**
 - **Treatment may be held or terminated at any time by patient/inpatient physician request.**
 - *Frequency:* up to twice per week coordinated with ECT treatment schedule.
 - *Setting:* ECT suite and adjacent monitoring space on Ward 1E, Detwiller Pavilion, UBC Hospital.
 - *Monitoring:* Minimum of 60 minutes post-treatment by the UBC ward nurse, including vital signs, Modified Observer's Assessment of Alertness/Sedation (MOAS/S, Appendix D), Clinician-Administered Dissociative Symptom Scale (CADSS-6, Appendix E) and side effects immediately after SC/IM bolus. Continuation of monitoring on the inpatient ward until 4 hours post-treatment.
 - On any ECT treatment day, **maximum 2 ketamine patients on the same day**, treated concurrently.

Figure 1: Ketamine Treatment Algorithm

¹: The route of administration may be changed to IM at any treatment point at the clinician's discretion.

²: Improvement is defined as QIDS-SR16/MADRS $\leq 50\%$ of pre-treatment score.

³: No improvement is defined as a lack of subjective effect and $<20\%$ reduction in QIDS-SR16/MADRS score ≥ 20 .

- **PATIENT REFERRAL:**

- Inpatients identified by treating clinicians as potentially able to benefit from parenteral ketamine as per inclusion and exclusion criteria above.
- Baseline medical investigations: physical examination documented, weight documented, blood work (CBC, electrolytes, liver function tests, renal functions, urine drug screen, pregnancy test as appropriate, TSH, ECG within 30 days)
- **Referral form** completed and submitted to Ketamine Protocol Coordinator for review / consultation by Coordinator and cleared with anesthesia (possible anesthesia consultation requested). MOST form reviewed for level of care. Medications reviewed for potential interactions and on ketamine antidepressant efficacy (Appendix A).
- **Written, informed consent** obtained from patient.
- Initiate **PSYCHIATRIC EFFICACY MONITORING PROTOCOL** for documentation of psychiatric state prior to starting treatments.

- **TREATMENT PROCESS:**

- Patient enters treatment area with **UBC ward nurse**, preferably nurse familiar with patient already.
- Anesthesiologist available during procedure. Resuscitation equipment arrived in ECT treatment room prior to medication administration. Automatic BP machine and pulse oximeter available if needed.
- Patient seated comfortably – they will remain seated for minimum 60 minutes monitoring. Capture pre-treatment blood pressure, heart rate, respiratory rate, and Modified Observer's Assessment of Alertness/Sedation Score (MOAA/S, see Appendix D).
- **Trained Neurostimulation nurse**, anesthesiologist available if needed – Make sure that pre-treatment blood pressure $\leq 140/90$ mm Hg. **Subcutaneous (default)** or

intramuscular injection of 0.25mg/kg, 0.5mg/kg, or maximum 0.75mg/kg ketamine (see Treatment Parameters above for scheduling), rotating injection site as appropriate, administered as bolus to patient. 25G 5/8" needle and 1cc syringe would generally be adequate for subcutaneous, preferred abdominal site, posterolateral forearm alternate site. For IM, 22-25G 1-1.5" needle and syringe, deltoid site.

- **UBC ward nurse monitors patient for the next 60 minutes minimum in the ECT suite (1 nurse up to 2 ketamine patients).** *** Ward-specific logistics and additional nursing resources that may be required to be determined.*
 - Blood pressure, heart rate, respiratory rate, MOAA/S at 15 minutes, 30 minutes, and 60 minutes recorded. Side effects documented including CADSS-6 (see Appendix B for most common side effects). Inform Neurostimulation team if at any point systolic BP rises >140 mm Hg or diastolic BP >90mm Hg. Use pulse oximeter if there are any concerns around respiratory rate.
 - **Nurse should take opportunity to interact with patients to provide emotional support as appropriate depending on familiarity.**

- **POST-TREATMENT:**

- If no significant concerns arise in the TREATMENT PROCESS above, sign off with Neurostimulation nurse and make sure the anesthesiologist and ECT psychiatrist are aware when patient(s) ready to return to ward with UBC ward nurse after 60 minutes. Appropriate handover of patient back to ward if the UBC ward nurse present during the TREATMENT PROCESS is not directly assigned to patient.
- Vital signs and MOAA/S documented at 2 hours post-treatment and 4 hours post-treatment. Make sure to include this information in the Ketamine Protocol Treatment Record for review before the next ketamine administration.

C. PSYCHIATRIC EFFICACY MONITORING PROTOCOL

A comprehensive **Psychiatric Monitoring Form** will be created to capture admission and discharge dates, medication regimen, rationale for ketamine treatment, discontinuation date, number of total treatments, side-effects/issues for the clinical record.

The following data will also be captured for the clinical record to be used to assess treatment efficacy and for quality assurance of the clinical treatment:

- **Pre-Treatment (within 7 days before first treatment):**
 - Montgomery-Åsberg Depression Rating Scale (MADRS)
 - Columbia Suicide Severity Rating Scale (C-SSRS)
 - CADSS-6
 - Clinical Global Impression – Severity (CGI-S)
 - Quick Inventory of Depressive Symptomatology (QIDS-SR) (self-report)
 - Generalized Anxiety Disorder scale (GAD-7) (self-report)
 - CNS-VS Cognitive Screen
- **Day 1 post treatment (“immediate” effects):**

- MADRS
- C-SSRS
- CGI-S, Clinical Global Impression – Improvement (CGI-I)
- QIDS-SR16 (self-report)
- GAD-7 (self-report)
- **After 2 treatments (approx. Day 7):**
 - MADRS
 - C-SSRS
 - CGI-S, CGI-I
 - QIDS-SR16 (self-report)
 - GAD-7 (self-report)
- **After 4 treatments (approx. Day 14):**
 - MADRS
 - C-SSRS
 - CGI-S, CGI-I
 - QIDS-SR16 (self-report)
 - GAD-7 (self-report)
- **After 6 treatments or at Termination (maximum, approx. Day 21):**
 - MADRS
 - C-SSRS
 - CADSS-6
 - CGI-S, CGI-I
 - QIDS-SR16 (self-report)
 - GAD-7 (self-report)
 - CNS-VS Cognitive Screen
- **Discharge timeframe (if >7 days after Day 21) (assess sustained response/remission):**
 - MADRS
 - C-SSRS
 - CGI-S, CGI-I
 - QIDS-SR16 (self-report)
 - GAD-7 (self-report)

D. PILOT PROJECT ESTIMATES

- Aim initially for **30 patients** to obtain adequate data to report on feasibility, safety, and evidence of efficacy to determine value of continuing clinical protocol.
- Given proposal limits of 2 patients each time at most, assuming maximum 6 treatments each, maximum ~30 patients per year assuming constant demand. A realistic expectation would be approximately 24 months for 30 cases.

Appendix A: Ketamine Interactions / Antidepressant Efficacy

Drug Interactions: Decreased Ketamine Antidepressant Effect		
Class of Drug	Example	Interaction effects
<i>Benzodiazepines</i>	clonazepam, lorazepam, diazepam	Benzodiazepines (specifically at higher doses) may attenuate ketamine's antidepressant effects. ¹ Consideration should be given to holding/reducing benzodiazepine for a duration based on the half-life prior to ketamine administration.
<i>Opioid Antagonists</i>	Naltrexone	Preliminary evidence suggests ketamine's acute antidepressant effect appears to require opioid system activation, and effect may be reduced by opioid antagonists. ² Consideration should be given to holding opioid antagonists for a duration based on the half-life prior to ketamine administration.
Drug Interactions: Potential Increased Ketamine Toxicity		
Class of Drug	Example	Interaction effects
<i>CNS depressant</i> (opioid agonists, alcohol, benzodiazepines)	Morphine, buprenorphine, hydromorphone clonazepam, lorazepam, diazepam	Possible additive CNS depression and increased risk of respiratory depression. ³
<i>Monoamine oxidase inhibitors (MAO-I) & Reversible inhibitor of monoamine oxidase (RIMA)</i>	Tranylcypromine, phenelzine, isocarboxazid Moclobemide	Theoretical risk of potentiating sympathomimetic activity resulting in severe hypertension. Preliminary evidence suggests the combination may be safe in some cases ⁴ , but data is limited.
<i>Strong CYP3A4 inhibitors</i>	Antibiotics (e.g. clarithromycin), anti-fungals (e.g. itraconazole, ketoconazole), anti-retrovirals (e.g. darunavir) ritonavir)	May decrease metabolism of Ketamine and resulting in adverse effects ⁴ (especially if higher doses of ketamine is used).

References:

- 1- Andrashko V, Novak T, Brunovsky M, et al. (2020) The Antidepressant Effect of Ketamine Is Dampened by Concomitant Benzodiazepine Medication. *Front Psychiatry* 2020;11:844.
- 2- Williams NR, Heifets BD, Blasey C, et al. Attenuation of Antidepressant Effects of Ketamine by Opioid Receptor Antagonism. *Am J Psychiatry*. 2018;175(12):1205-1215.
- 3- World Health Organization. Ketamine (INN) update review report agenda item 6.1. Expert committee on drug dependence 37th meeting. Geneva, Switzerland. 2015 November 16–20.

- 4- Katz RB, Toprak M, Wilkinson ST, et al. Concurrent use of ketamine and monoamine oxidase inhibitors in the treatment of depression: a letter to the editor. *Gen Hosp Psych* 2018;54:62-64
- 5- Andrade C. Ketamine for Depression, 5: Potential Pharmacokinetic and Pharmacodynamic Drug Interactions. *J Clin Psychiatry*. 2017; 78:e858-e861.
- 6- 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 in advance* (17 Mar 2021)

Appendix B: Ketamine Potential Side Effects

(Based on ketamine hydrochloride injection monograph and publicly available information) *

Common:

- Tachycardia
- Hypertension
- Tremors
- Fatigue/tiredness
- Spontaneous vocalizations
- Injection site discomfort
- Dream-like / dissociative experience

Infrequent:

- Hallucinations / vivid imagery
- Anxiety / panic / excitement
- Decreased lung function
- Hypotension
- Bradycardia
- Hypertonia
- Drowsiness
- Erythema
- Memory issues, confusion
- Nausea/vomiting
- Unpleasant dreams

Rare:

- Anaphylaxis
- Laryngospasm
- Arrhythmia
- Skin rash
- Diplopia
- Muscle spasms
- Nystagmus

* [Sandoz Canada, May 6, 2015 Revision, UpToDate Ketamine Drug Information.](#)

Appendix C: ASA Physical Status Classification

American Society of Anesthesiologists Physical Status (ASA PS) Classification System

ASA Physical Status (PS) Classification System*:		
ASA PS Category	Preoperative Health Status	Comments, Examples
ASA PS 1	Normal healthy patient	No organic, physiologic, or psychiatric disturbance; excludes the very young and very old; healthy with good exercise tolerance
ASA PS 2	Patients with mild systemic disease	No functional limitations; has a well-controlled disease of one body system; controlled hypertension or diabetes without systemic effects, cigarette smoking without chronic obstructive pulmonary disease (COPD); mild obesity, pregnancy
ASA PS 3	Patients with severe systemic disease	Some functional limitation; has a controlled disease of more than one body system or one major system; no immediate danger of death; controlled congestive heart failure (CHF), stable angina, old heart attack, poorly controlled hypertension, morbid obesity, chronic renal failure; bronchospastic disease with intermittent symptoms
ASA PS 4	Patients with severe systemic disease that is a constant threat to life	Has at least one severe disease that is poorly controlled or at end stage; possible risk of death; unstable angina, symptomatic COPD, symptomatic CHF, hepatorenal failure
ASA PS 5	Moribund patients who are not expected to survive without the operation	Not expected to survive > 24 hours without surgery; imminent risk of death; multiorgan failure, sepsis syndrome with hemodynamic instability, hypothermia, poorly controlled coagulopathy
ASA PS 6	A declared brain-dead patient who organs are being removed for donor purposes	
*ASA PS classifications from the American Society of Anesthesiologists		

Appendix D: Modified Observer's Assessment of Alertness/Sedation (MOAA/S) Scale

Modified Observer's Assessment of Alertness/Sedation (MOAA/S)

MOAA/S Score	Description	ASA continuum
5	Responds readily to name spoken in normal tone (awake)	Minimal sedation
4	Lethargic response to name spoken in normal tone	Moderate sedation
3	Responds after name called loudly or repeatedly	Moderate sedation
2	Purposeful response to mild prodding or mild shaking	Moderate sedation
1	Responds to trapezius squeeze (includes purposeful and reflexive withdrawal)	Deep sedation
0	No response to painful stimulus (trapezius squeeze)	General anaesthesia

MOAA/S, Modified Observer's Assessment of Alertness/Sedation; ASA, American Society of Anesthesiologists.

Appendix E: Clinician-Administered Dissociative Symptom Scale (CADSS-6)

Clinician-Administered Dissociative Symptom Scale (CADSS-6)

1. Do things seem to be moving in slow motion?

0 = Not at all.

1 = Mild, things seem slightly slowed down, but not very noticeable.

2 = Moderate, things are moving about twice as slow as normally.

3 = Severe, things are moving so slowly that they are barely moving.

4 = Extreme, things are moving so slowly, I have the perception that everything has come to a stop, as if time is standing still.

2. Do things seem to be unreal to you, as if you are in a dream?

0 = Not at all.

1 = Mild, things seem a little unreal, but I'm well aware of where I'm at.

2 = Moderate, things seem dreamlike, although I know I am awake.

3 = Severe, things seem very dreamlike, although I know that I am here, I have the feeling like I might be asleep.

4 = Extreme, I feel like nothing is real, like I should pinch myself to wake up, or ask someone if this is a dream.

3. Do you feel disconnected from your own body?

0 = Not at all.

1 = Mild, I feel a little bit disconnected from myself, but I am basically all here.

2 = Moderate, I feel somewhat detached from my own body, but I am basically all together.

3 = Severe, I feel detached from my own body, but not far removed from my body, and I feel as if it is me there.

4 = Extreme, I feel like I am completely out of my body, as if I am looking at my own body from a long way off, as if there is another person there.

4. Does your sense of your own body feel changed: for instance, does your own body feel unusually large or unusually small?

0 = Not at all.

1 = Mild, I have a vague feeling that something about my body has changed, but I can't say exactly what it is.

2 = Moderate, I feel like my body has increased or decreased in size slightly, or that it feels somewhat as if it is not my body.

3 = Severe, I feel as if my body has increased to twice its normal size, or decreased to twice its normal size, or I very much feel as if this is not my body.

4 = Extreme, I feel as if my body has swelled up to at least ten times its normal size, or as if it is ten times as small, or as if my arms have become like toothpicks.

5. Have you spaced out, or in some other way lost track of what was going on during this experience?

0 = Not at all.

1 = Mild, I have had some episodes of losing track of what is going on, but I have followed everything for the most part.

2 = Moderate, I have lost at least a minute of time, or have completely lost track of what is going on now.

3 = Severe, I have lost several segments of time of one minute or more.

4 = Extreme, I have lost large segments of time of at least 15 minutes or more.

6. Do you have gaps in your memory?

0 = Not at all.

1 = Mild, there are some recent things which I cannot remember.

2 = Moderate, there have been a few gaps in my memory which lasted a few minutes.

3 = Severe, there have been large gaps in my memory which lasted for more than a few minutes.

4 = Extreme, I cannot piece together what is happening from one moment to the next due to large gaps in my memory.

REFERENCES:

1. Dundee JW, Knox JW, Black GW, et al. Ketamine as an induction agent in anaesthetics. *Lancet*. 1970;1:1370–1371.
2. Zanos P, Moaddel R, Morris PJ, et al. Ketamine and Ketamine Metabolite Pharmacology: Insights into Therapeutic Mechanisms. *Pharmacol Rev*. 2018;70:621-660.
3. Berman RM, Cappiello A, Anand A, et al. Antidepressant effects of ketamine in depressed patients. *Biol Psychiatry*. 2000;47(4):351-354.
4. Lara DR, Bisol LW, Munari LR. Antidepressant, mood stabilizing and precognitive effects of very low dose sublingual ketamine in refractory unipolar and bipolar depression. *Int J Neuropsychopharmacol*. 2013;16(9):2111-2117.
5. Lam RW, Kennedy SH, Parikh SV, et al. Canadian Network for Mood and Anxiety Treatment (CANMAT) 2016 clinical guidelines for the management of adults with major depressive disorder: Section 3. Pharmacological Treatments. *Can J Psychiatry*. 2016;61(9):540-560.
6. Peltoniemi M, Hagelberg NM, Olkkola KT, Saari TI. Ketamine: A Review of Clinical Pharmacokinetics and Pharmacodynamics in Anesthesia and Pain Therapy. *Clin Pharmacokinet*. 2016;55:1059-1077.
7. Cohen SP, Bhatia A, Buvanendran A, et al. Consensus guidelines on the use of intravenous ketamine infusions for chronic pain from the American Society of Regional Anesthesia and Pain Medicine. *Reg Anesth Pain Med*. 2018;43:521-546.
8. Swainson J, McGirr A, Blier P, et al. The Canadian Network for Mood and Anxiety Treatments (CANMAT) Task Force Recommendations for the Use of Racemic Ketamine in Adults with Major Depressive Disorder. *Can J Psychiatry*. 2020;Nov:1-13.
9. Andrade C. Ketamine for Depression, 4: In what dose, at what rate, by what route, for how long, and at what frequency? *J Clin Psychiatry*. 2017;78(7):e852-e857.
10. Kurdi MS, Theerth KA, Deva RS. Ketamine: Current applications in anesthesia, pain, and critical care. *Anes, Essays, Res*. 2014;8(3):283-290.
11. Blier P, Zigman D, Blier J. On the safety and benefits of repeated intravenous injections of ketamine for depression. *Biol Psychiatry*. 2012;72(4):e11-e12.
12. Loo CK, Galvez V, O'Keefe E, et al. Placebo-controlled pilot trial testing dose titration and intravenous, intramuscular and subcutaneous routes for ketamine in depression. *Acta Psychiatr Scand*. 2016;134(1):48-56.
13. Chilukuri H, Reddy NP, Pathapati RM, et al. Acute antidepressant effects of intramuscular versus intravenous ketamine. *Indian J Psychol Med*. 2014;36(1):71-76.