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Case 1: Usage of esketamine spray for treatment-resistant major depressive disorder (MDD)

The Question: What is the therapeutic dose and duration of treatment for esketamine (Spravato) nasal spray in depression?

The Psychopharmacological Dilemma: Finding an effective treatment regimen utilizing esketamine (Spravato) spray for treatment-resistant depression (TRD)

Sunita Singh

Pretest self-assessment question

How are the antidepressant effects of esketamine (Spravato) pharmacodynamically mediated?

A. N-methyl-D-aspartate receptor (NMDAR) antagonism
B. Increases brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) activity
C. Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid receptor (AMPAR) antagonism
D. Dopamine-2 receptor (D_2) agonism
E. A and B
F. All of the above

Patient evaluation on intake

- A 42-year-old woman with a chief complaint of being "depressed, hanging on barely"
- Chronically depressed with comorbid panic disorder (PD), uses polypharmacy and vagal nerve stimulation (VNS), all of which seem to be failing over last several weeks
- Presents for first esketamine (Spravato) spray treatment today
- Recurrent MDD now in recurrence with extensive treatment failures
- Panic disorder is remitted though
- Currently exhibits anhedonia, dysphoric mood and constricted congruent affect which are affecting her performance at work
- MDD symptoms escalating with occasional passive suicidal ideation which is worrisome
- Compliant with previous medication management
- Reports no side effects on current regimen
- No contraindications to esketamine (Spravato) nasal spray treatment, has prior authorization, and has read the patient guide regarding treatment

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Psychiatric history

- Long history of MDD with some resultant anxiety, with fear of others' judgments, and also suffers from PD with mild agoraphobic symptoms
- Previously endorsed symptoms of fatigue, hypersomnia, social isolation, low motivation, appetite disturbance, feelings of guilt and low self-worth, and negative self-thinking
- VNS implanted in 2007 with adequate response for several years, but response now fading
- Prior to today, failed 30+ medications (including electroconvulsive therapy [ECT], VNS, IV ketamine [weekly dosing], and psychotherapy)

Social and personal history

- Former smoker, quit several years ago
  - Recently restarted smoking with onset of recurrent MDD symptoms
  - Prior history of light daily cigarette-smoking
- Rare alcohol use
- No recreational drug use
- Single parent with grown son
- Works as a nurse per diem

Medical history

- Osteoarthritis
- Gastroesophageal reflux disease (GERD)
- Kidney stones
- Raynaud phenomenon

Family history

- History of depression and anxiety, but extent is unknown
- Patient's family places emphasis on appearances and impressions, which causes her to fear making mistakes and looking foolish
- Anxiety disorder in her paternal aunt and grandmother

Medication history

Previous therapeutic failures:

- SSRIs: selective serotonin reuptake inhibitors
  - Fluoxetine (Prozac)
  - Sertraline (Zoloft)
- SNRIs: serotonin–norepinephrine reuptake inhibitors
  - Venlafaxine (Effexor XR)

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- Duloxetine (Cymbalta)
- SARIs: serotonin antagonist / reuptake inhibitors
  - Trazodone (Desyrel)
  - Nefazodone (Serzone)
- NDRI: norepinephrine–dopamine reuptake inhibitor
  - Bupropion (Wellbutrin XL)
- NaSSA: norepinephrine antagonist / selective serotonin antagonist
  - Mirtazapine (Remeron)
- TCAs: tricyclic antidepressants
  - Doxepin (Adapin)
  - Desipramine (Norpramin)
  - Amitriptyline (Elavil)
  - Clomipramine (Anafranil)
- MAOIs: monoamine oxidase inhibitors
  - Selegiline (Emsam)
  - Tranylcypromine (Parnate)
- SPARIs: serotonin partial agonist / reuptake inhibitors
  - Vilazodone (Viibryd)
- Augmentations
  - Benzodiazepines (BZs)
    - Lorazepam (Ativan)
    - Diazepam (Valium)
    - Clonazepam (Klonopin)
    - Estazolam (Prosom)
    - Zolpidem (Ambien)
- Atypical antipsychotics
  - Quetiapine (Seroquel)
  - Aripiprazole (Abilify)
  - Olanzapine (Zyprexa)
- Anticonvulsant
  - Divalproex (Depakote)
  - Lamotrigine (Lamictal)
- Stimulant
  - Dextroamphetamine (Dexadrine)
  - d/l-amphetamine (Adderall)
  - Methylphenidate (Ritalin)
  - Dexmethylphenidate (Focalin)
  - Modafinil (Provigil)
  - Armodafinil (Nuvigil)
- Nutraceutical
  - N-acetylcysteine (NAC)
  - L-methylfolate (Deplin)

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- D_2/D_3 partial agonist
  - Pramipexole (Mirapex)
- Others
  - Buspirone (Buspar), a serotonin 1A ($5\text{-}HT_{1A}$) partial receptor agonist
  - Lithium (Eskalith), a calcium modulating mood stabilizer
  - Liothyronine (Cytomel), a thyroid augmentation
  - Atomoxetine (Strattera), a norepinephrine reuptake inhibitor (NRI)
- Interventional
  - VNS
  - ECT
  - Ketamine (Ketalar) IV failed (6 sessions, 0.5 mg/kg once weekly)

Psychotherapy history

- Limited success in weekly psychotherapy
- Admits that she has given up quickly with psychotherapy when she feels uncomfortable
- Not currently in psychotherapy

Current medications

- Vortioxetine (Trintellix) 20 mg/d (SPARI)
- Alprazolam (Xanax) 0.75 mg/d, a BZ
- Cariprazine (Vraylar) 0.75 mg/d, an atypical antipsychotic
- Lisdexamfetamine (Vyvanse) 70 mg/d, a stimulant
- L-methylfolate (Deplin) 15 mg/d, a nutraceutical one carbon cycle enhancer
- Vagus nerve stimulator

Question

Considering the patient's multiple failed treatments, including previous failure of ketamine IV, do you think it is likely that the esketamine (Spravato) intranasal spray treatment will be effective?

- Yes: as the ketamine (Ketalar) IV was given weekly, and esketamine (Spravato) will use a loading dose with multiple sessions within the first few weeks
- No: as ketamine (Ketalar) IV is absorbed more efficiently than intranasal esketamine (Spravato), it is unlikely that intranasal esketamine (Spravato) will be effective at this time

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Attending physician's mental notes: initial psychiatric evaluation

- Although intranasal absorption of a drug is much less compared to IV administration, esketamine has four-fold more potency for NMDAR antagonism compared to racemic ketamine
- Given the ease of intranasal administration compared to IV treatments, it is worth evaluating intranasal esketamine spray as a treatment option for TRD even if ketamine (Ketalar) IV failed
- Additionally, her ketamine (Ketalar) IV treatments did not use a loading dose. Therefore, it was possibly subtherapeutic. A loading dose will be used for the esketamine (Spravato) treatments
- Patient with chronic MDD and anxiety is on polypharmacy and VNS, but now has recurrence of a new MDD episode without many new options or new treatments available in the current pipeline
- Esketamine (Spravato) is newly available and likely worth a trial, even if palliative

Case outcome: first esketamine (Spravato) treatment

- Patient was prepped and dosed with the usual starting 56 mg esketamine (Spravato) spray over several minutes and tolerated administration well with initial blood pressure of 126/78
- 40 minutes after administration, patient reported mild sedation and some "loopy" feelings for several minutes but was not sedated nor dissociative, with a blood pressure of 110/70
  - Interestingly, blood pressure lowered here when there are regulatory warnings for likely increases during treatment sessions
- 2 hours after administration, patient reported no side effects and was ready to go home, with a final blood pressure of 112/68
  - Patients are obligated to have someone else drive them home after sessions

Question

What adverse effects are common and should be monitored for after esketamine (Spravato) spray administration?

Blood pressure elevation?
Bradycardia?
Wheezing?
Sedation?
Dissociation?
Nausea?
Respiratory suppression?

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Attending physician's mental notes: first psychiatric follow-up visit

- Effects of esketamine (Spravato) and ketamine (Ketalar) are primarily mediated by its antagonistic NMDAR activity, causing its anesthetic and analgesic effects
- Esketamine/ketamine also can have antagonistic activity at monoaminergic, muscarinic, and nicotinic receptors, causing a range of adverse effects that should be monitored for after administration
- Patient tolerated first esketamine (Spravato) spray well and had minimal issues with the usual side effects of sedation, nausea, hypertension, and dissociation
- Due to recurrent MDD, we agreed to continue current medications and increase dosing of esketamine (Spravato) sprays to the higher available 84 mg/d dose and continue them twice weekly
- Reported feelings of anxiety are stable and only situational; panic has not worsened due to nasal sprays

Case outcome: weeks 2 through 8

- Over the next 4 weeks, patient received seven more esketamine (Spravato) 84 mg spray treatments, where the usual is to receive twice a week for the first month and then once weekly for the second month
- For the following 4 weeks, patient received four esketamine (Spravato) spray treatments of 84 mg each, completing the US Food and Drug Administration (FDA) approved protocol
- During this course, patient continued her previous oral medication regimen as well:
  - Vortioxetine (Trintellix) 20 mg/d
  - Cariprazine (Vraylar) 0.75 mg/d
  - Lisdexamfetamine (Vyvanse) 70 mg/d
  - L-methylfolate (Deplin) 15 mg/d
- Patient MDD symptoms went into full remission
- However, once esketamine (Spravato) spray was discontinued at the end of 8 weeks, patient had return of MDD symptoms at 12 days without ongoing nasal sprays

Question

What options exist for patients who relapse when esketamine (Spravato) sessions end?

- Start new 12-dose course of esketamine (Spravato)
- Start maintenance treatments with esketamine (Spravato) every 7–10 days
- Increase dose of esketamine (Spravato) above regulatory limits

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Attending physician's mental notes (weeks 2 through 8)

- The approved dosing guidelines for esketamine (Spravato) spray are an induction spray twice weekly for 4 weeks
- Based on patient's response and tolerability, this dose can be increased from 56 mg to 84 mg
- After evaluating its therapeutic benefit for 4 weeks, the established dose (56 mg or 84 mg) can be continued weekly as maintenance therapy up to 8 weeks
- Maintenance therapy for MDD with IV ketamine (Ketalar) is well established, providing support to the use of esketamine (Spravato) spray off label for maintenance therapy, which has not been well delineated or FDA approved
- Since our patient had remission of MDD symptoms with esketamine (Spravato) spray, likely is best to continue ongoing maintenance treatments every 7–10 days

Case outcome: follow-up visit at 2 months

- Patient re-started weekly 84 mg dosing of esketamine (Spravato) spray and MDD symptoms remitted again
- Patient reported that esketamine (Spravato) spray would alleviate depressive symptoms for 7–10 days, but then would lose effectiveness and depressive symptoms would return before next scheduled dose
  - Reports sadness, amotivation, fatigue, and inability to get out of bed when the esketamine (Spravato) spray effect diminishes
- Otherwise tolerating esketamine (Spravato) spray treatment well with no side effects

Attending physician's mental notes: second interim follow-up visit (month 2)

- Because of her intermittent return of symptoms, her current oral medication regimen seems to be inadequate despite ongoing esketamine (Spravato) use
- Need to consider novel treatments of off-label therapies with a similar mechanism of action to esketamine (Spravato) spray, which may help ultimately to taper off esketamine (Spravato) spray

Question

How would you alter her medication regimen to alleviate her return of MDD symptoms between esketamine (Spravato) doses?

- Decrease length of time between esketamine (Spravato) spray treatments and continue its use indefinitely

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- Add dextromethorphan / quinidine sulfate (Nuedexta) as it manipulates glutamate activity as well
- Recommend new trial of psychotherapy
- Recommend new trial of ketamine IV (Ketalar)
- Recommend new series of ECT

Attending physician's mental notes: second interim follow-up visit (month 2) (continued)

- Patient likely cannot afford indefinite weekly treatments of esketamine (Spravato) spray and declines psychotherapy. She also declines ECT as it would interfere with her work
- As esketamine (Spravato) spray is helping to decrease her MDD symptoms, another glutamate medication may mimic the effects of esketamine (Spravato) spray and allow increased time between nasal spray sessions
- Decided to add dextromethorphan / quinidine sulfate (Nuedexta) as it will weakly antagonize NMDA receptors (NMDARs), somewhat similar to the effect of esketamine (Spravato) spray
  - This agent is approved for use in treating pseudobulbar affect
- Will keep esketamine (Spravato) spray weekly, but patient will take dextromethorphan / quinidine sulfate (Nuedexta) only on days 5/6 when depressive symptoms start appearing again, hopefully avoiding MDD relapse

Case outcome: follow-up visit at 3 months

- Reports depressive symptoms are recurrent between sessions, but mild and possibly improving with esketamine (Spravato) spray plus dextromethorphan / quinidine sulfate (Nuedexta) treatment augmentation
- Patient expressed concern about affording esketamine (Spravato) spray treatment long term and is worried about having to stop treatment abruptly
- Chooses to increase length between sessions to 2 weeks as she feels she can only afford 20 more sessions

Attending physician's mental notes: follow-up visit (month 3)

- Esketamine (Spravato) spray every 2 weeks still allows MDD relapses to occur
- Dextromethorphan / quinidine sulfate (Nuedexta) now increased to daily use without side effects
- Still difficult to wean off esketamine (Spravato) spray without MDD relapse

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Question

What would you do next?

- Stop dextromethorphan / quinidine sulfate (Nuedexta) and try to find another novel glutamate-based treatment
- Review chart and remove current non-effective medications and restart medications that seemed to help in the past

Case outcome: follow-up at 3 months

- Dextromethorphan / quinidine sulfate (Nuedexta) has not been able to replace esketamine (Spravato) and was discontinued as it was ineffective
- Cariprazine (Vraylar) removed as it was ineffective
- L-methylfolate (Deplin) removed as it was ineffective
- Confirmed alprazolam (Xanax) was not being taken, as some accounts suggest benzodiazepine use may lower ketamine/esketamine effectiveness
- Main residual MDD symptoms are increased fatigue and amotivation and she has failed multiple stimulant treatments; will try medications that will increase norepinephrine activity perhaps instead of dopamine
- She has never taken the more highly noradrenergic SNRI levomilnacipran (Fetzima), so will titrate that next

Case outcome: follow-up at 6 months

- With levomilnacipran (Fetzima) 120 mg/d treatment, she only requires esketamine (Spravato) spray now every 30–45 days
- Maintenance began with nasal sprays every 7 days, then 10 days, then 15 days, and so on until 45+ days was achieved
- Nasal sprays continue to be spaced farther apart in this manner
- Lisdexamfetamine (Vyvanse) effectively lowered from 70 mg/d down to 20 mg/d
- Vortioxetine (Trintellix) lowered to 10 mg/d to avoid serotonin toxicity when combining with newer levomilnacipran (Fetzima)
- Current medications now include:
  - Vortioxetine (Trintellix) 10 mg/d
  - Lisdexamfetamine (Vyvanse) 20 mg/d
  - Levomilnacipran (Fetzima) 120 mg/d
  - Esketamine (Spravato) 84 mg every 2 months
- Vagal nerve stimulator battery depleted and not replaced due to its ineffectiveness

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Case debrief

- This patient has clear TRD and had failed practically every treatment available, including psychotherapy, polypharmacy, and intervention with ECT, VNS, and ketamine (Ketalar) IV
- Interestingly, nasal esketamine (Spravato) helped to gain temporary remission from MDD when the IV racemic ketamine treatment failed previously
  - Assume this is due to the fact that the nasal spray used an induction or loading strategy with multiple treatments per week, whereas the IV used an older once-weekly protocol
- Patients often do not remit in a sustained or durable fashion from their depression symptoms after acute IV treatment, nor do they from the nasal sprays
- In this case, ineffective medications were streamlined and taken away (l-methylfolate [Deplin], cariprazine [Vraylar]) or lowered (vortioxetine [Trintellix], lisdexamfetamine [Vyvanse]), and new medications (dextromethorphan/quinidine [Nuedexta] and levomilnacipran [Fetzima]) were tried to gain a more durable response to allow a tapering off of esketamine (Spravato) nasal sprays, seemingly with good effectiveness
- This approach allowed for minimizing esketamine (Spravato) nasal spray treatments, to occur every 3 months instead of every week

Take-home points

- Incidence of TRD is common, 30% or greater prevalence
- Some definitions suggest this is a failure to respond to two different antidepressants from different classes
- Many patients are actually more treatment resistant than this, as this case illustrates
- It is unclear when patients become truly refractory, but the goal of treatment regardless should be to keep trying for symptom remission prior to assuming a more palliative psychiatric approach
- Interestingly, nasal esketamine (Spravato) can work even if IV ketamine has previously failed
- Finally, many patients who use esketamine (Spravato) will likely need maintenance treatment, whereas the most recent 4-year data suggests that about 70% of patients who respond will durably maintain their responses