NEWER ANTIDEPRESSANTS

26th Pharmaceutical Symposium
Department of Psychiatry
April 12, 2019
ESKETAMINE

Kiran Khalid, MBBS
PGY-4 Child and Adolescent Psychiatry Fellow
What is esketamine?

- S-enantiomer of Ketamine
Indications

- **USA:** Treatment resistant depression (Adults)
  - In conjunction with an oral antidepressant
  - Failed two or more antidepressant medications
    - For adequate duration, adequate dose, in current episode
- **Europe, South America:** Anesthetic (IM/IV formulation—submitted for approval for Treatment resistant depression)
- No off-label uses so far
Mechanism of Action

NMDA receptor antagonist (non-selective, non-competitive)

?Downstream effects – resulting increase in glutamate release

Exact mechanism of antidepressant action unknown

So the role of glutamate...

- NMDA-receptor
  - Extra-synaptic
  - Synaptic (interneurons)
- AMPA receptor
- Role of mTOR
- BDNF
- Synaptic plasticity
- Effect on dendritic spines
What happens at the synaptic level?

Source: NNCI (www.nncionline.org)
Dosing

- Intranasal delivery
- Use in conjunction with an oral antidepressant
<table>
<thead>
<tr>
<th>Table 1: Recommended Dosage for SPRAVATO</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Induction Phase</strong></td>
</tr>
<tr>
<td><strong>Weeks 1 to 4:</strong></td>
</tr>
<tr>
<td>Administer twice per week</td>
</tr>
<tr>
<td><strong>Week 9 and after:</strong></td>
</tr>
<tr>
<td>Administer every 2 weeks or once weekly*</td>
</tr>
</tbody>
</table>

* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.
Dosing

Patients must be:

• enrolled in SPRAVATO REMS prior to administration
• Receiving medication under direct observation of healthcare provider (in a certified healthcare setting)
• Monitored for at least 2 hours after administration
Adverse Effects

- Sedation
- Dissociation
- Dizziness
- Nausea/vomiting
- Vertigo
- Decreased feeling or sensitivity (hypoesthesia)
- Anxiety
- Lethargy
- Increased blood pressure
- Feeling drunk
Boxed Warning

WARNING: SEDATION; DISSOCIATION; ABUSE AND MISUSE; and SUICIDAL THOUGHTS AND BEHAVIORS

Sedation
• Patients are at risk for sedation after administration of SPRAVATO [see Warnings and Precautions (5.1)].

Dissociation
• Patients are at risk for dissociative or perceptual changes after administration of SPRAVATO [see Warnings and Precautions (5.2)].

Because of the risks of sedation and dissociation, patients must be monitored for at least 2 hours at each treatment session, followed by an assessment to determine when the patient is considered clinically stable and ready to leave the healthcare setting [see Warnings and Precautions (5.1, 5.2)].

Abuse and Misuse
• SPRAVATO has the potential to be abused and misused. Consider the risks and benefits of prescribing SPRAVATO prior to use in patients at higher risk of abuse. Monitor patients for signs and symptoms of abuse and misuse [see Warnings and Precautions (5.3)].

Because of the risks of serious adverse outcomes resulting from sedation, dissociation, and abuse and misuse, SPRAVATO is only available through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the SPRAVATO REMS [see Warnings and Precautions (5.4)].

Suicidal Thoughts and Behaviors
Antidepressants increased the risk of suicidal thoughts and behavior in pediatric and young adult patients in short-term studies. Closely monitor all antidepressant-treated patients for clinical worsening, and for emergence of suicidal thoughts and behaviors. SPRAVATO is not approved in pediatric patients [see Warnings and Precautions (5.5)].
Serious Adverse Effects

- Sedation
- Dissociation
- Impaired cognition/motor coordination
  (patients advised to not drive or use heavy machinery for the rest of the day)
- Abuse and misuse
- Suicidal thoughts and behaviors
- Embryo-fetal toxicity
  Not safe for use during pregnancy or lactation
- **Contraindicated** in patients with AVM, aneurysmal vascular disease, history of Intracranial hemorrhage and in those with hypersensitivity to compounds
- Risk of adverse cardiovascular or cerebrovascular effects in patients with poorly controlled hypertension
Monitoring

- Must be observed by a health care provider >2 hours after each dose (due to sedation, dissociation and elevation in blood pressure).
- Blood pressure has to be obtained prior to administration, then reassessed 40 minutes after administration, then as clinically warranted.
- Avoid food intake >2 hours before administration and liquids >30 minutes before administration.
- Use any nasal corticosteroids (if regularly using >1 hour before administration).
## Major Drug-Drug Interactions

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Examples</th>
<th>Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS Depressants</td>
<td>Benzodiazepines, Opioids, Alcohol</td>
<td>Excessive Sedation</td>
</tr>
<tr>
<td>Monoamine Oxidase Inhibitors</td>
<td>Tranylcypromine, Selegiline, Phenelzine</td>
<td>Increased blood pressure</td>
</tr>
<tr>
<td>Stimulants</td>
<td>Amphetamines, Methamphetamines, Modafanil, Armodafanil</td>
<td>Increased blood pressure</td>
</tr>
</tbody>
</table>
Cost

• $590 to $885 – cost to the clinic
• So, the cost for first month - $4,720 to $6,785
• Thereafter, weekly treatments will cost about half as much
• Not inclusive of cost of observation and administration
Pearls of Use

- Different mechanism of action, method of delivery
- Not daily dosing BUT has to be used with another antidepressant
- Must be given in certified facility, cannot be used at home
  - To consider, for patient: cost of transportation, cost of medication, possible implications for work
  - To consider, for facility: observation and monitoring, staff to monitor, certification for administration
- Abuse potential
- Only short term studies published; unclear if effect persists, if longer term side effects emerge, how generalizable to clinical population
- Cost
References

- Spravato, Full Prescribing Information, Janssen Labels (Link)
- FDA Briefing Document on Spravato (Link)
- Neurobiology of Depression: Road to Novel Therapeutics, edited by Joao Quevedo, et al., Elsevier Science & Technology, 2019
- National Neuroscience Curriculum Initiative (Link)
THANK YOU
VORTIOXETINE
(TRINTELLIX)

Amber Parden, M.D.
Child and Adolescent Psychiatry Fellow, PGY-4
Indication

- Vortioxetine is a multimodal serotonin modulator FDA approved for Major Depressive Disorder in 2013.
- Off label use for GAD
**Mechanism of Action**

1. **Synthesis**: Serotonin is produced directly in the neuron.

2. **Storage**: VMAT2 transports serotonin into vesicles.

3. **Release**: Vesicle releases serotonin into the synaptic cleft.

4. **Activation**: Serotonin binds to the receptor and initiates a signal to the cell body of the postsynaptic neuron.

5. **Reuptake pump (SERT)**: Serotonin is naturally reabsorbed through the reuptake pump (this reduces synaptic serotonin levels).
Multimodal Mechanism of Action

Based on in vitro studies.

TRINTELLIX

RECEPTOR BINDING

5-HT$_{1A}$ AGONIST
5-HT$_{3}$ ANTAGONIST
5-HT$_{1D}$ ANTAGONIST
5-HT$_{7}$ ANTAGONIST
5-HT$_{1B}$ PARTIAL AGONIST

REUPTAKE INHIBITION

SERT
Dosing

- Oral: Initial dose of 10 mg once daily; increase to 20 mg once daily as tolerated; consider 5 mg once daily for patients who do not tolerate higher doses.
- Maintenance: 5 to 20 mg once daily.
Drug Interactions

- Dosage adjustment for CYP2D6 poor metabolizers: Maximum dose: 10 mg/day.
- Dosage adjustment for concomitant therapy with strong CYP2D6 inhibitors
- Dosage adjustment for concomitant therapy with strong CYP inducers.
- Monitor for serotonin syndrome with use of other serotonergic drugs.
AE’s

• > 10% report GI s/e (nausea being most common).
  • Nausea, vomiting, constipation, diarrhea, abdominal pain, flatulence
• Less commonly:
  • Headache, sexual side effects, flushing, blurred vision, dizziness, abnormal dreams, pruritis, xerostomia
Serious AE’s

• ALERT: US Boxed Warning for suicidal thoughts and behaviors.
• Serotonin syndrome
  • Contraindication of use with MAOI’s, linezolid, methylene blue.
• Mania/ hypomania
• Seizures
Other Considerations related to A/E:

- Bleeding risk
- CNS depression
- Fractures
- Ocular effects: mild pupillary dilation
- SIADH and hyponatremia
- Vortioxetine has not been evaluated for use in pediatric patients
Monitoring

- Baseline hepatic functioning is recommended prior to initiation.
- Monitor for side effects including
  - sexual s/e
  - akathisia
- Mania
Clinical Pearls

• The brand name the medication was initially Brintellix, but was changed to Trintellix in order to avoid prescribing and dispensing errors related to the drug’s confusion with the blood thinner Brilinta.

• Procognitive effects due to 5HT-3 antagonism

• Less sexual side effects often reported - 5HT-1A receptor agonist effect may facilitate sexual performance.

• Significant GI s/e often minimized with Zofran as needed for the initiation period.
Cochrane Review

- 2016 Systematic review comparing RCT’s of vortioxetine vs SNRI’s.
- Showed that vortioxetine was more effective than placebo, but not more effective than SNRI’s.
- There was higher dropout rate and AE’s with vortioxetine compared to placebo, no difference between vortioxetine and duloxetine, and higher dropout from venlafaxine that vortioxetine.
- This data showed significant GI AE when looking at the comparison to placebo and significant Sexual AE when looking at venlafaxine.
Cost

$254 - $460.00 per month
Resources


VILAZODONE (VIIBRYD)

Chloe Leitch, MD
PGY-2
Vilazodone (Viibryd)

• Approved by the FDA for treatment of MDD in January 2011
• Combination of selective serotonin reuptake inhibition and serotonergic receptor partial agonist activity
• Therefore, termed “serotonin partial agonist reuptake inhibitor” (SPARI)
Vilazodone (Viibryd)

https://www.viibrydhcp.com/mechanism-of-action
Vilazodone (Viibryd)

- Recommended dose is 40mg once daily
- Tablets available in 10mg, 20mg, 40mg strengths
- Suggested titration: 10mg once daily for 7 days, followed by 20mg once daily for additional 7 days and then increased to 40mg once daily
- Should be taken with food
- Half – life is approximately 25 hours
Vilazodone (Viibryd)

- Adverse reactions: most common include diarrhea, nausea, vomiting
- Most common adverse effect leading to discontinuation is nausea
- Reduced sexual side effects and weight gain
- Black box warning for suicidal thoughts
- Risk of serotonin syndrome when given with other serotonergic drugs
Vilazodone (Viibryd)

- Metabolized in the liver mainly by Cytochrome P450 3A4 isoenzyme
- Should be reduced to 20mg when given concomitantly with CYP450 3A4 strong inhibitors
- No recommendations when given concomitantly with CYP450 3A4 strong inducers
- Do not give concomitantly or within 14 days of stopping MAOI
- No recommendations for dosing with hepatic impairment, renal impairment, in the elderly or when pregnant/breastfeeding
Vilazodone (Viibryd)

- There are no head to head trials with other antidepressants
- Might be useful for patients who experience/don’t want sexual side effects
- May also have a role in MDD with anxiety
- Viibryd is expected to cost $4.74 per dose for all strengths
- Approximately $142.20 per month
References


MILNACIPRAN & LEVOMILNACIPRAN

Asuma Tanaka
PGY2
• Milnacipran. No generic.
• FDA approved for treatment of Fibromyalgia (FM) in adults in 2009
• Levomilnacipran (Fetzima and generic): FDA MDD adults
• SNRI
- Off label uses: Depression, Anxiety, panic disorders, neuropathic pain, OCD, ADHD and stress incontinence
- Works similar to Duloxetine (Cymbalta), Venlafaxine (Effexor), and Desvenlafaxine (Pristiq)
- According to 2 phase 3 studies (2084 patients); Milnacipran at dosages of 100 and 200 mg/day for the management of fibromyalgia was associated with reduction in pain by 30% and improvements in patient global assessment and physical function.
- Treatment with milnacipran was safe and generally well tolerated, with nausea being the most often reported adverse effect.
Tx of Depression?

• Approved for treatment of MDD in France in 1996
• 45 countries worldwide (Russia, Japan, Portugal, Austria and more) marketed for treatment of depression
• Meta-analysis of a total of 16 randomized controlled trials with 2200 patients showed no statistically significant differences when compared to other antidepressants in efficacy, acceptability (drop out rate) and tolerability (adverse effect).
• Dosing:
  • 12.5 mg once a day for one day
  • then 12.5 mg PO BID for days 2 and 3,
  • then 25 mg PO BID days 4 to 7
  • then 50 mg PO BID
  • maximum dose is 200 mg per day.

• May be administered with or without food, but food improves the ability to tolerate this medication.

• Not studied in the pediatric population (under age 18).
Adverse effects

- **Common adverse effects**: Nausea, Vomiting, headaches, constipation, insomnia, dizziness, palpitations, flushing, blurred vision
- **Serious AE**: Serotonin syndromes, seizures, urinary retention, HTN, tachycardia, abnl bleeding, hepatotoxicity, hyponatremia
- **Blackbox warning**: Increased suicidal thoughts or actions, especially in children, teenagers and young adults within the first few months of tx or when the dose is changed.
• Lab monitoring: No serum level monitoring. However, baseline creatinine, BP, HR should be obtained before starting.
• Renal excretion.. (don’t give it to pts with CKD)
• Predominantly metabolized through phase 2 conjugation, minimally (8%) metabolized via p450(CYP3A4)
• Half life 6-8 hrs
Drug –drug interactions

- Drug interactions: Should not be used with Monoamine oxidase inhibitor (MAOI). Milnacipran → (5 days) → MAOI.
- MAOI-> (14days) ->Milnacipran
- Combination of MAOI and SNRI … Increased risk for Serotonin syndrome.
- Similar reaction might occur with any medications that affect serotonin level in the brain.
- Combining Milnacipran with aspirin, NSAIDs, warfarin might increase the risk of bleeding.
Levomilnacipran (Fetzima)

• Enantiomer of Milnacipran
• More potent NE and 5HT reuptake inhibition than Milnacipran
• 5HT:NE ratios of reuptake inhibition; Milnacipran=1.6 :1, Levomilnacipran=1:2
• FDA approval MDD
• 3 placebo-controlled trials showed significant improvement in motivation, energy level, alertness, and attention
• Similar adverse effects profiles, most common= nausea
• Generic available
Levomilnacipran

• **Dose**
  - start 20mg QD x2d
  - Then 40 mg QD
  - Max 120mg daily

• With/without food; don’t open capsule

• Renal excretion, max dose for severe renal failure is 40mg daily

• Minimally metabolized via P450 3A4 (not significant inducer or inhibitor)– less likely to have drug-drug interaction

• Half life:12hr
Cost

- 1 titration pack (4 weeks) which includes 12.5 mg, 25mg, and 50mg tabs: $395.42
- 12.5 mg (60 count, a month supply BID dosing): $430.99
- Compared to Levomilnaciprain (Fetzima) 20mg (#30): $389.99
- Cymbalta: 20mg (#30): $236
- Pristiq: 50mg (#30): $489.71
- Effexor: 37.5mg (#30): $408.99
- Generic of all of these are fraction of the cost
- No Generic of Milnacipran is available