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PALLIATIVE CARE PHARMACY PHAST PHACT

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If you have a topic you would like the pharmacy team to answer, please send your suggestions to: pruskowskija@upmc.edu

TODAY'S TOPIC:

What's New in Palliative Care Medications

Drug #3: Esketamine (Spravato®)

Background:

Esketamine (Spravato®) is a non-competitive N-methyl D-aspartate (NMDA) receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults

- Initial US approval: 2019
- Available as: 28mg device – each nasal spray device delivers two sprays containing a total of 28 mg of esketamine

Importance:

Major depressive disorder affects more than 16 million adults each year in the US. Depression is a common and often severe symptom palliative care patients suffer from. Palliative care providers should be aware of options for treatment-refractory depression.

Pharmacology:

MoA:	Esketamine, the S-enantiomer of racemic ketamine, is a non-selective, noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor, an ionotropic glutamate receptor. The mechanism by which esketamine exerts its antidepressant effect is unknown. The major circulating metabolite of esketamine (noresketamine) demonstrated activity at the same receptor with less affinity.
ADME:	- A: Absolute bioavailability is approximately 48% following administration, Tmax: 20-40 minutes - M: Primarily metabolized to noresketamine metabolite via cytochrome P450 (CYP) enzymes CYP2B6 and CYP3A4 and to a lesser extent CYP2C9 and CYP2C19 - E: T ½: 7-12 hours

DIs:	Concomitant use of CNS depressants, psychostimulants, and monoamine oxidase inhibitors

Key: MoA: Mechanism of Action; ADME: Absorption, Distribution, Metabolism, and Excretion; DI: Drug Interaction; Tmax: time until max concentration; T ½: terminal half-life; Cmax: max concentration; AUC: area under the curve

Other Clinical Points:

CIs:	- Hypersensitivity - Aneurysmal vascular disease (including thoracic and abdominal aorta, intracranial and peripheral arterial vessels) or arteriovenous malformation - Intracerebral hemorrhage
Warnings and Precautions:	- Increases in Blood Pressure: Patients with cardiovascular and cerebrovascular conditions and risk factors may be at an increased risk of associated adverse effects - Cognitive Impairment: may impair attention, judgment, thinking, reaction speed and motor skills - Impaired Ability to Drive and Operate Machinery: Do not drive or operate machinery until the next day after a restful sleep - Embryo-fetal Toxicity: May cause fetal harm. Consider pregnancy planning and prevention in females of reproductive potential.
Dosing:	Administer intranasally under the supervision of a healthcare provider; assess blood pressure prior and after administration
ADRs:	The most commonly observed adverse reactions (incidence ≥5% and at least twice that of placebo plus oral antidepressant) were dissociation, dizziness, nausea, sedation, vertigo, hypoesthesia, anxiety, lethargy, blood pressure increased, vomiting, and feeling drunk.

Key: CI: contraindications; ADRs: adverse drug reactions

The Literature:

- JAMA Psychiatry. 2018 Feb 1;75(2):139-148.
  Efficacy and Safety of Intranasal Esketamine Adjunctive to Oral Antidepressant Therapy in Treatment-Resistant Depression: A Randomized Clinical Trial.
  - Methods: Phase 2, double-blind, doubly randomized, delayed-start, placebo-controlled study was conducted in multiple outpatient referral centers from January 28, 2014, to September 25, 2015. The study consisted of 4 phases: (1) screening, (2) double-blind treatment (days 1-15), composed of two 1-week periods, (3) optional open-label treatment (days 15-74), and (4) posttreatment follow-up (8 weeks). One hundred twenty-six adults with a DSM-IV-TR diagnosis of MDD and history of inadequate response to 2

or more antidepressants (ie, TRD) were screened, 67 were randomized, and 60 completed both double-blind periods. Intent-to-treat analysis was used in evaluation of the findings.

- Results: Change (least squares mean [SE] difference vs placebo) in MADRS total score (both periods combined) in all 3 esketamine groups was superior to placebo (esketamine 28 mg: -4.2 [2.09], P=.02; 56 mg: -6.3 [2.07], P=.001; 84 mg: -9.0 [2.13], P<.001), with a significant ascending dose-response relationship (P<.001). Improvement in depressive symptoms appeared to be sustained (-7.2 [1.84]) despite reduced dosing frequency in the open-label phase. Three of 56 (5%) esketamine-treated participants during the double-blind phase vs none receiving placebo and 1 of 57 participants (2%) during the open-label phase had adverse events that led to study discontinuation (1 event each of syncope, headache, dissociative syndrome, and ectopic pregnancy).
- Conclusion: "In this first clinical study to date of intranasal esketamine for TRD, antidepressant effect was rapid in onset and dose related. Response appeared to persist for more than 2 months with a lower dosing frequency. Results support further investigation in larger trials."

So… What does this all mean Jenn?

- There is promising data for esketamine – see here for a well written review
- There are some complications with dosing: patients must be enrolled in the Spravato REMS program prior to administration. They should self-administer IN esketamine under the direct supervision of a health care provider.
- Long-term efficacy beyond one year has not yet been established however a majority of patients responded to treatment doses of 84 mg and approximately one-third of patients responded to 56 mg, with doses administered either weekly or every other week
- The adverse effects of esketamine may be the less appetizing for palliative care patients – while some appreciate ketamine's psychomimetic effects – some do not
- Cost of esketamine could range from $5,664 to $8,142 in the first month of induction-phase treatment, $2,832 to $4,248 in the second month, and possibly $1,416 to $4,248 each month thereafter, depending on whether dosing is weekly or bi-weekly
- The UPMC review of esketamine is here: it is currently formulary restricted to psychiatry for outpatient administration for new-starts and continuation of therapy with a psychiatry consult

CLINICAL PEARL:
Esketamine is a non-competitive NMDA receptor antagonist indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression in adults, was approved in 2019.