Novel Treatment Paradigms in Psychiatry

A Regulatory Perspective

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NASEM: Novel Molecular Targets in Mood Disorders and Psychosis
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Outline

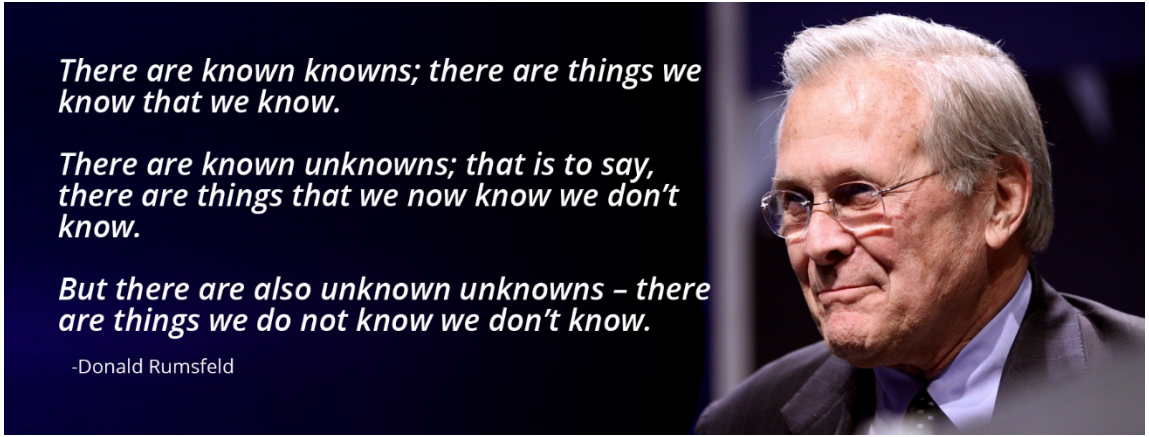
- “Traditional” antidepressant development
- Esketamine for treatment-resistant depression
- Brexanalone for postpartum depression
- Future directions

“Traditional” Antidepressants

- SSRI, SNRI, TCA, MAOI, etc.
- Daily oral administration
- Intended for chronic treatment
- Typical clinical trial length 6 to 8 weeks
- Delayed efficacy
- Maintenance treatment evaluated in post-marketing setting

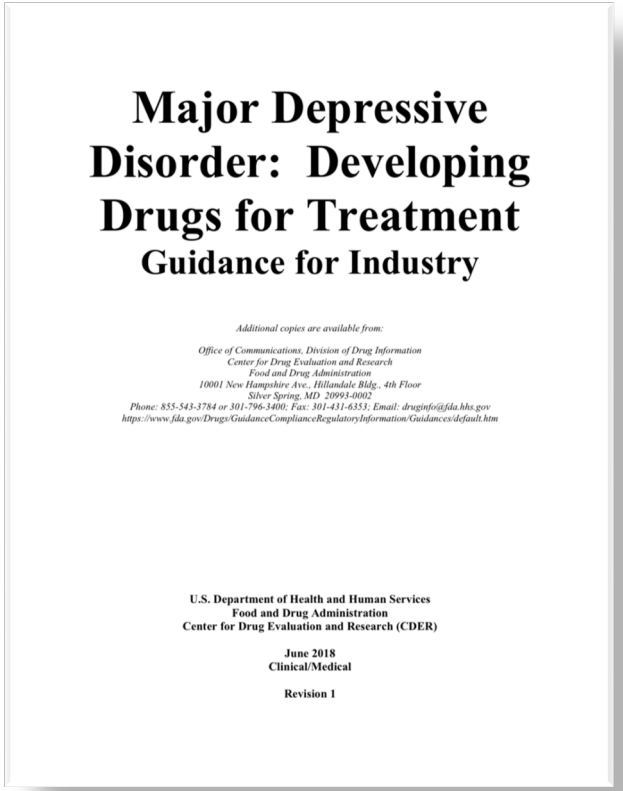
Novel Paradigms

- Single treatment
- Fixed-interval dosing
- As needed
- Induction
- Others…



Advice on Trial Design

- 2018 draft guidance includes advice for evaluating “novel” antidepressants
- Earlier primary endpoint is OK, but should characterize durability of effect
- Depression is chronic and cyclical, so need maintenance study
- Study design depends on intended use of drug
- ★ Seek advice on design early in development



Major Depressive Disorder: Developing Drugs for Treatment

Guidance for Industry

Additional copies are available from:

Office of Communications, Division of Drug Information
Center for Drug Evaluation and Research
Food and Drug Administration
10001 New Hampshire Ave., Hillandale Bldg., 4th Floor
Silver Spring, MD 20993-0002
Phone: 855-543-3784 or 301-796-3400; Fax: 301-431-6353; Email: druginfo@fda.hhs.gov
https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

June 2018
Clinical/Medical

Revision 1

Evaluating Novel Elements

- Population
- Dosage and Administration
- Duration of treatment
- Applicability of prior experience

Esketamine

- Approved March 5, 2019

npr WAMU 88.5 DONATE

Shots

TREATMENTS

FDA Approves Esketamine Nasal Spray For Hard-To-Treat Depression

March 5, 2019 · 8:46 PM ET

Heard on Morning Edition

JON HAMILTON

The New York Times

Fast-Acting Depression Drug, Newly Approved, Could Help Millions

A nasal spray version of the drug ketamine has shown promise as an antidepressant, even if its properties still aren't well understood.

The Washington Post

Democracy Dies in Darkness

Health

In biggest advance for depression in years, FDA approves novel treatment for hardest cases

The nasal spray works in a new way and is based on an old anesthetic, ketamine, that has been used as a party drug.

The U.S. Food and Drug Administration approved a nasal spray, esketamine, to treat depression. (Jacquelyn Martin/AP)

Esketamine

- NMDA receptor antagonist
- Treatment-resistant depression
- Intranasal administration
- Administered 2x/week to start
- *No a priori expectation that the dosing would remain the same throughout treatment*
  - Dosing frequency changes over time

Esketamine

1 INDICATIONS AND USAGE

SPRAVATO™ is indicated, in conjunction with an oral antidepressant, for the treatment of treatment-resistant depression (TRD) in adults *[see Clinical Studies (14.1)]*.

- TRD: Required failure of treatment of at least two different antidepressants of the same or different classes, given at an adequate dose and duration (assessed retrospectively)
- "…in conjunction with…": All patients started new oral antidepressant at the same time as double-blind intranasal treatment
- Post-marketing commitment to study monotherapy

Dosage and Administration

- Not enough to demonstrate acute treatment effect
- Required longer term data prior to initial approval
  - Under a novel paradigm, priors from traditional antidepressants not applicable
  - Needed data to inform labeling

Table 1: Recommended Dosage for SPRAVATO

		Adults
Induction Phase	**Weeks 1 to 4:**	Day 1 starting dose: 56 mg
	Administer twice per week	Subsequent doses: 56 mg or 84 mg
Maintenance Phase	**Weeks 5 to 8**:	
	Administer once weekly	56 mg or 84 mg
	Week 9 and after:	
	Administer every 2 weeks or once weekly*	56 mg or 84 mg

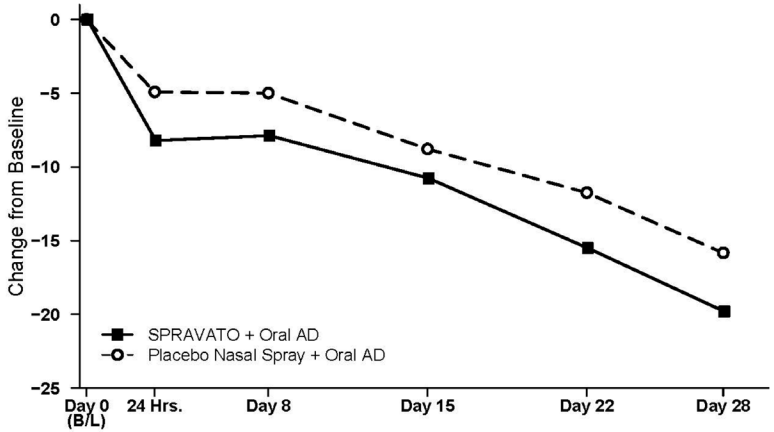
* Dosing frequency should be individualized to the least frequent dosing to maintain remission/response.

Source: Esketamine full prescribing information, initial approval, 3/5/19

Time to Onset

- Primary endpoint at 4 weeks
- Not described as “rapid acting”
  - Nonspecific terminology
  - Potential slippery slope
  - Promotional
- Change in symptoms severity over time illustrated in label

Figure 4: Least Squares Mean Change from Baseline in MADRS Total Score Over Time in Patients with TRD in Study 1* (Full Analysis Set) – MMRM Analysis



* Note: In this flexible-dose study, dosing was individualized based on efficacy and tolerability. Few subjects (<10%) had reduction in SPRAVATO dosage from 84 mg to 56 mg twice weekly.

Source: Esketamine full prescribing information, initial approval, 3/5/19

Brexanolone

- Approved March 19, 2019

CNN.COM

FDA approves first postpartum depression drug

Brexanolone

- Neuroactive steroid
- Post-partum depression
- 60-hour intravenous infusion
- Single administration

Brexanolone

1 INDICATIONS AND USAGE

ZULRESSO is indicated for the treatment of postpartum depression (PPD) in adults *[see Clinical Studies (14)]*.

- By definition, limited to episodes of depression that occur in the postpartum period (study participants ≤ 6m postpartum)
- Important to assess durability of effect to determine need for additional treatments
- Balance assessment of durability with potential for dropouts
- Primary endpoint at Hour 60; secondary endpoint at Day 30

Dosage and Administration

- IV infusion with initial titration, taper prior to discontinuation
- Continuous monitoring required due to risk of excessive sedation or sudden loss of consciousness
- Post-marketing commitment to evaluate outpatient dosing in a non-24hr facility

2.2 Recommended Dosage

Administer ZULRESSO as a continuous intravenous (IV) infusion over a total of 60 hours (2.5 days) as follows:

- 0 to 4 hours: Initiate with a dosage of 30 mcg/kg/hour
- 4 to 24 hours: Increase dosage to 60 mcg/kg/hour
- 24 to 52 hours: Increase dosage to 90 mcg/kg/hour (a reduction in dosage to 60 mcg/kg/hour may be considered during this time period for patients who do not tolerate 90 mcg/kg/hour)
- 52 to 56 hours: Decrease dosage to 60 mcg/kg/hour
- 56 to 60 hours: Decrease dosage to 30 mcg/kg/hour

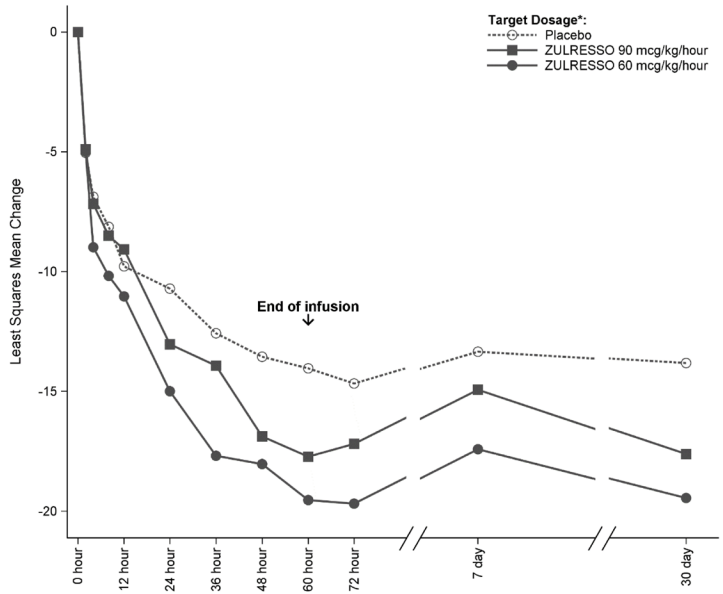
If excessive sedation occurs at any time during the infusion, stop the infusion until the symptoms resolve. The infusion may be resumed at the same or lower dose as clinically appropriate.

Source: Brexanolone full prescribing information, initial approval, 3/19/19

Time to Onset

- Statistically significant improvement at hour 60
- Persistent effect at Day 30
- In a second study, no difference at Day 30
  - Effect in brexanolone group persisted
  - Placebo group improved

Figure 1: Change from Baseline in HAM-D Total Score Over Time (Days) in Study 1



*ZULRESSO was administered via a 60-hour intravenous infusion as follows:
90 mcg/kg/hour-target dosage: 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 20 hours, 90 mcg/kg/hour for 28 hours, 60 mcg/kg/hour for 4 hours, 30 mcg/kg/hour for 4 hours
60 mcg/kg/hour-target dosage: 30 mcg/kg/hour for 4 hours, 60 mcg/kg/hour for 52 hours, 30 mcg/kg/hour for 4 hours

Source: Brexanolone full prescribing information, initial approval, 3/19/19

Future Directions: Re-evaluating Endpoints

- MADRS, HAM-D not fit for purpose for assessing early efficacy signal
- Accepted Letters of Intent:

  Symptoms of Major Depressive Disorder Diary (SMDDD)

  – Concept of Interest: Depression symptom severity
  – Context of Use: Adults with MDD with a 24-hour recall period

  Symptoms of Major Depressive Disorder Momentary Assessment (SMDDMA)

  – Concept of Interest: Depression symptom severity
  – Context of Use: Adults with MDD “at this moment”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