Women & Depression: Not a “Female Weakness”

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May 31, 2019

Disclosures

- I do not have any financial relationship with any of the manufacturer(s) of any commercial product(s) or provider(s) of any commercial service(s) discussed in this CE activity.
- This presentation will include discussion of off-label, experimental, and/or investigational use of drugs or devices: Ketamine, SSRIs, SNRIs

Objectives

- Describe the epidemiology, risk factors, diagnostic criteria, and clinical features of major depressive disorder, persistent depressive disorder (dysthymic disorder), premenstrual dysphoric disorder, postpartum depression, and perimenopausal depression
- Evaluate the safety and efficacy of currently-available pharmacologic treatment options for major depressive disorder
- Apply knowledge to patient cases

Depressive Disorders: Background

Background

- Depression may occur in the context of several psychiatric disorders
  - Unipolar major depressive disorder (MDD)
  - Bipolar disorder
  - Persistent depressive disorder
  - Substance/medication-induced depressive disorder
  - Premenstrual dysmorphic disorder (PMDD)
  - Peri/post-partum depression (PPD)
  - Perimenopausal depression

Major depression among adults.. National Institute of Mental Health. 2014. Available from: http://www.nimh.nih.gov

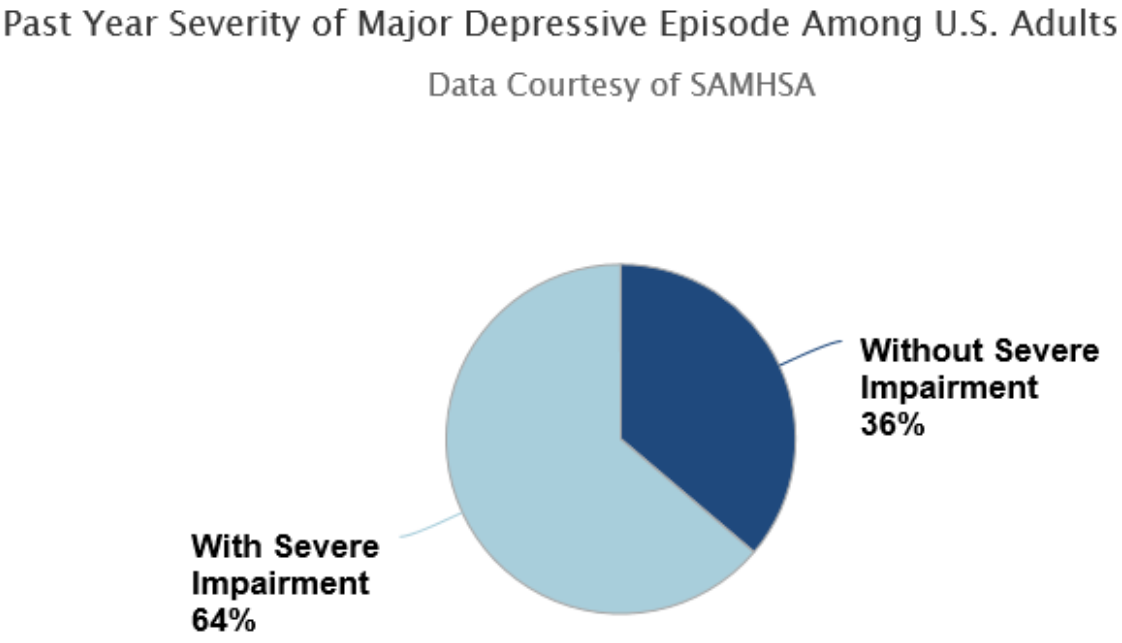
Epidemiology

- **MDD** is one of the most common psychiatric disorders in the United States
  - Affects approximately 1 out of 6 people (17.6 million Americans)
  - ~61% have a **comorbid psychiatric diagnosis**
- Prevalence of other depressive disorders less well-defined
  - PMDD: 2-5%
  - Persistent depressive disorder: ~1.5%
  - Peripartum depression: 10-15% of adult mothers per year
  - Perimenopausal depression: 10-25% in women 40-60 years of age

Major depression among adults.. National Institute of Mental Health. 2014. Available from: http://www.nimh.nih.gov; Li R, et al. *Medicine*. 2016
Gehlert S, et al. *Psychol Med*. 2009; Anokye R, et al. *Ann Gen Psychiatry*. 2018;

Morbidity and Mortality

- Higher risk of medical comorbidities:
  - Type II diabetes
  - Cardiovascular disease
  - Increased use of substances including nicotine, alcohol
- Loss of productivity, disability
- Decreased quality of life
- Risk to child (peripartum depression)
- Economic cost ~$30-44 billion per year

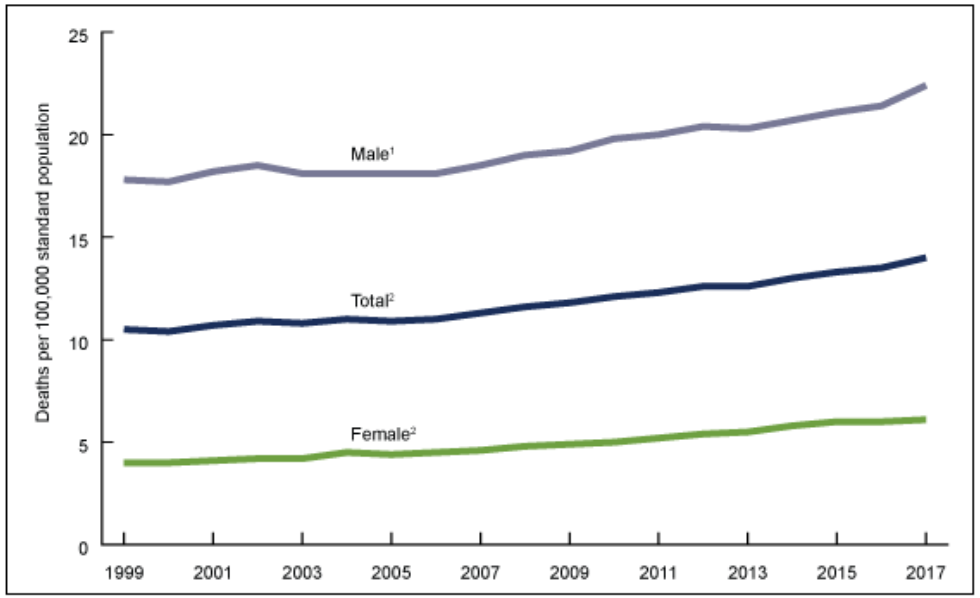


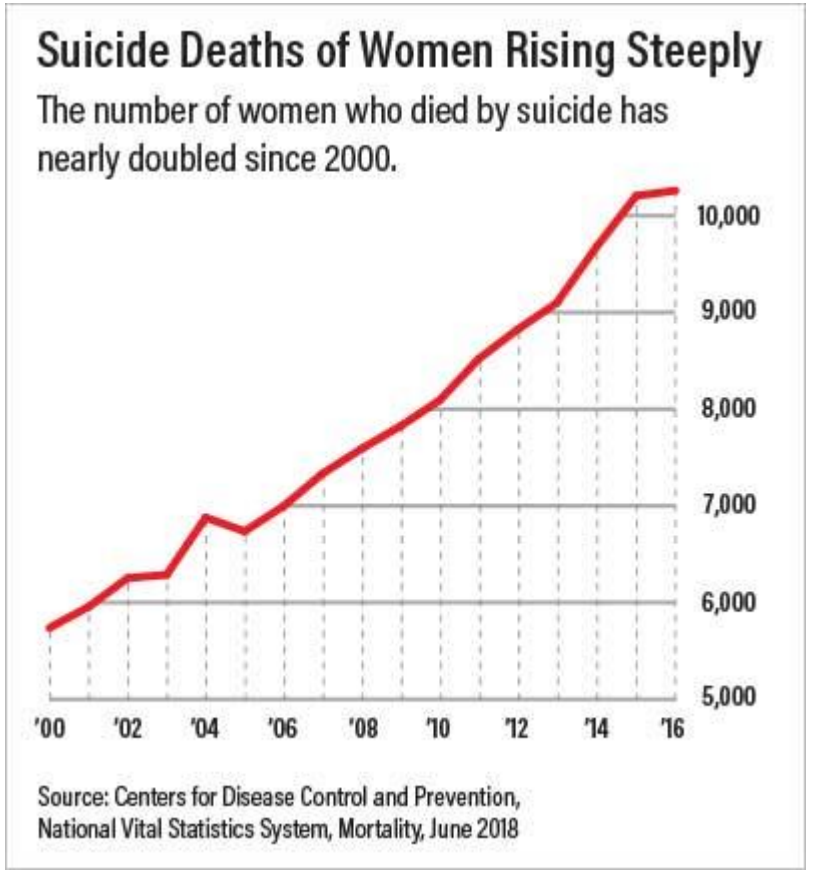
Major depression. National Institute of Mental health. Substance Abuse and Mental Health Services Administration 2017
Andrew L, et al. Depression and suicide, 2016. Available from emedicine.Medscape.com

Morbidity and Mortality

- Lifetime risk of suicide in untreated MDD: ~20%
- Suicide rate in U.S. increasing
  - 10th leading cause of death

Figure 1. Age-adjusted suicide rates, by sex: United States, 1999–2017



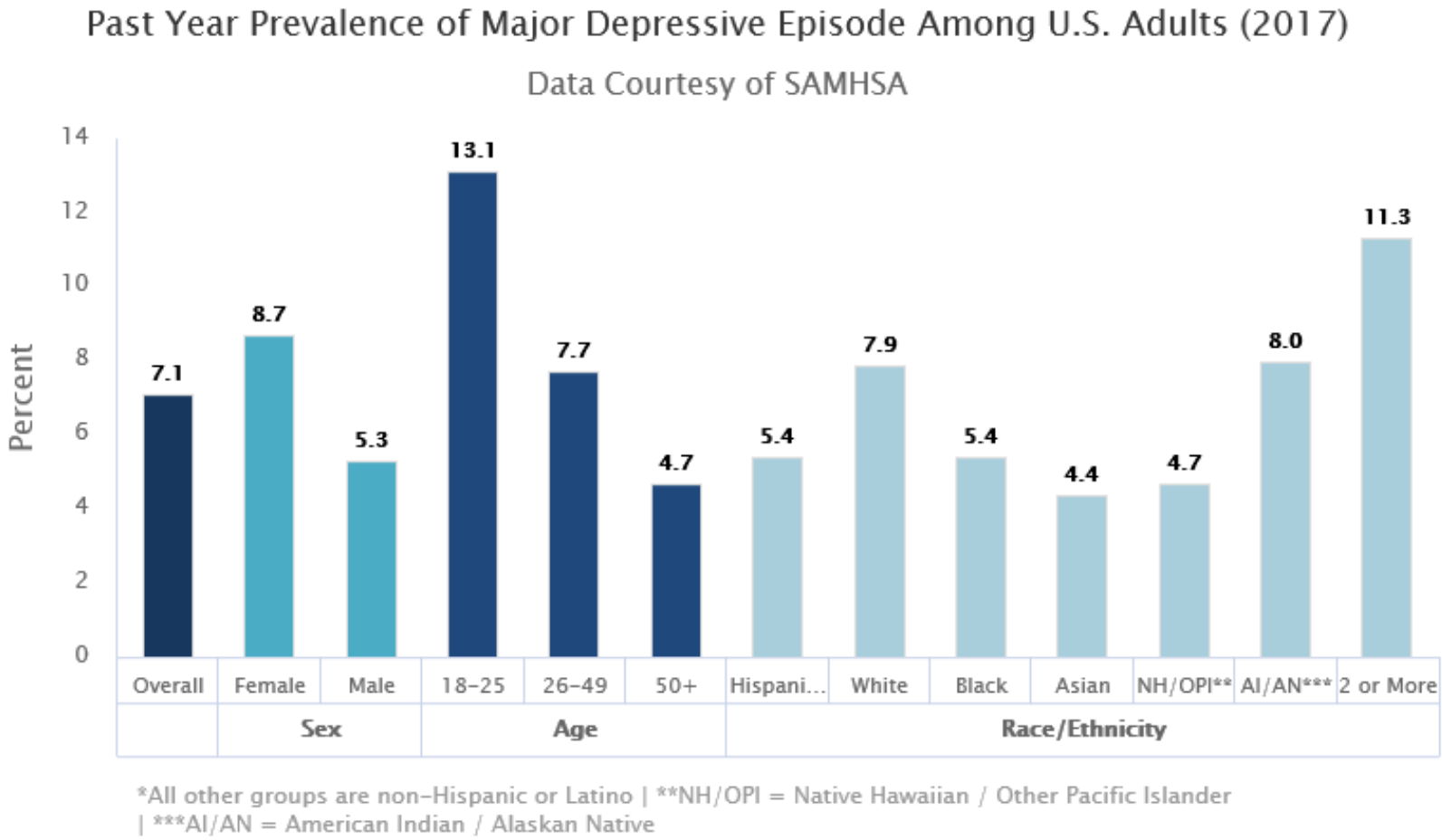


Suicide mortality in the United States, 1999-2017, CDC, 2018

Risk Factors

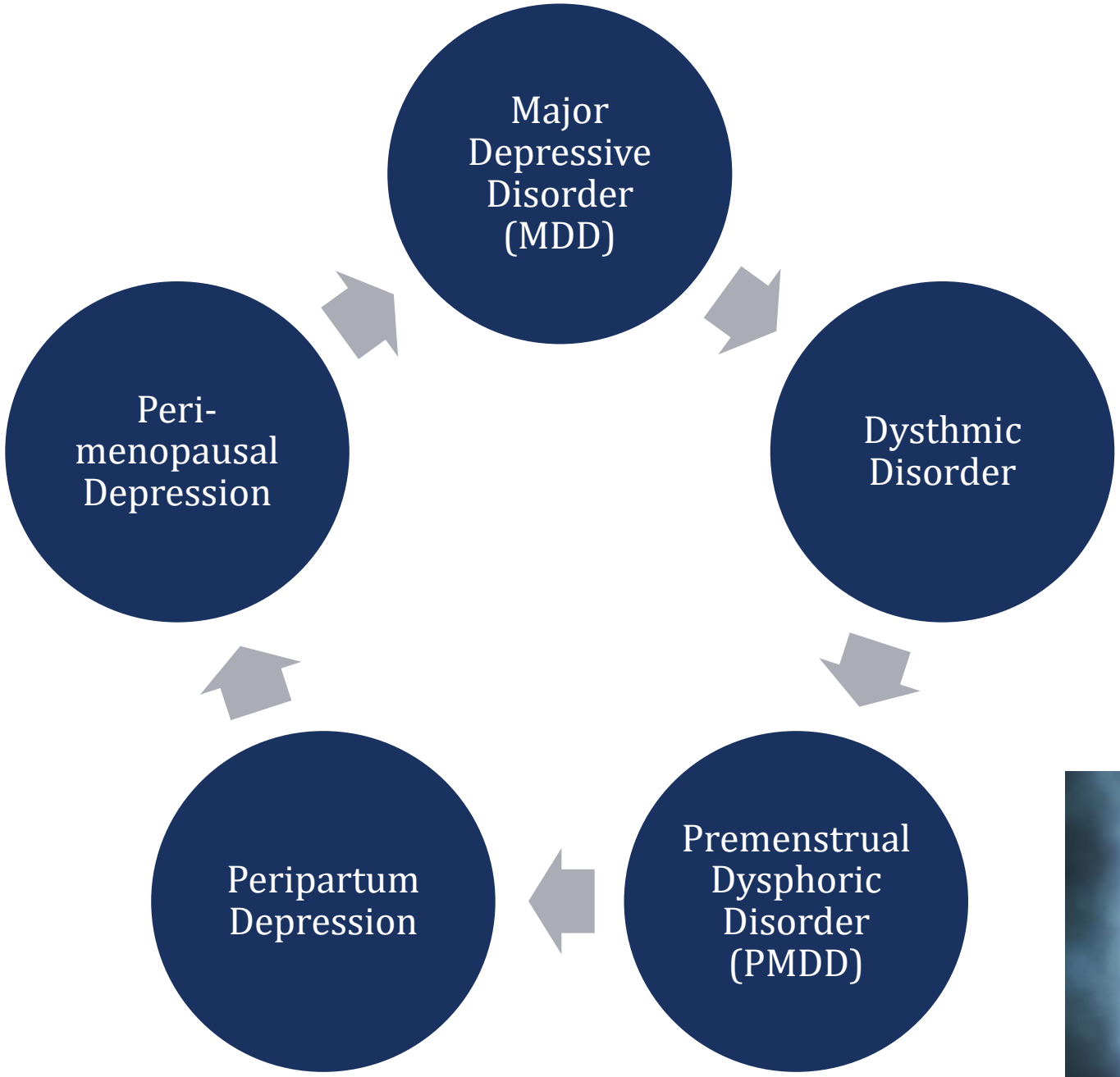
- Female (2-3x higher risk of MDD)
- Age
- Race/ethnicity
- Genetics, family history
- Low income or unemployment
- Trauma
- Parental loss or adversity
- Stressful life events
- Marital problems/divorce/widowed

Risk Factors: Race, Age, Gender



Major depression. National Institute of Mental health. Substance Abuse and Mental Health Services Administration 2017

Depressive Disorders: Diagnosis and Clinical Features



Img: canacopegdl.com; fromept.com

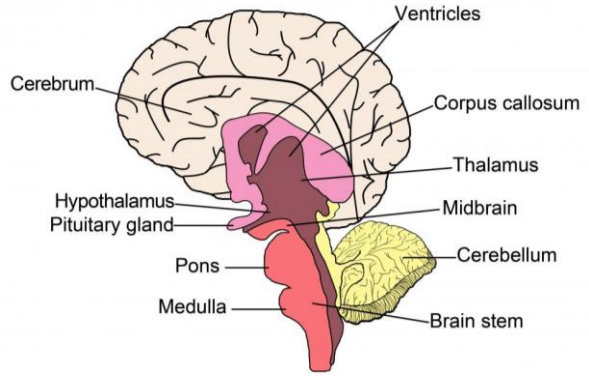
Major Depressive Disorder

Subjective Symptoms	Objective Symptoms
• **S**leep disturbance • **I**nterest (loss of) • **G**uilt (excessive) • **E**nergy changes • **C**oncentration impairment • **A**ppetite changes • **P**sychomotor agitation or slowing • **S**uicidal ideation or actions	• Poor hygiene • Weight changes • Isolation

Major depression among adults. NIMH. 2014.

Pathophysiology: MDD

- **Monoamine hypothesis**
  - Deficiency in **serotonin, norepinephrine, and dopamine**
  - **Problem:** Timing of effect on neurotransmitters is much different from time to effect on mood
- **Dysregulation hypothesis**
  - Changes in neurotransmitters leads to changes in pre- and post-synaptic receptors
- **Chronic stress**
  - Increased secretion of **glucocorticoids** and **cortisol** in response to stress → depletion in **BDNF** (brain-derived neurotrophic factor)
  - Increase in release of **substance P**
- **Anatomical structure changes:**
  - Amygdala
  - Hippocampus
  - Pituitary gland
  - Prefrontal cortex



Diagnosis (DSM-V): MDD

A. One or more major depressive episodes

- No history of manic or mixed mood episodes
- Not secondary to substance use or medical condition

B. Criteria for major depressive episode

1. **Depressed mood** most of the time on most days
2. Decreased **interest** or **pleasure** in daily activities
3. Significant change in **weight or appetite** (≥5% change)
4. Significant changes in **sleep**
5. Psychomotor agitation or retardation, observable by others
6. **Fatigue**/decreased energy
7. Feelings of worthlessness or **guilt**
8. Decreased **concentration** or difficulty making decisions
9. Recurrent thoughts of **death, suicidal ideation** with or without specific plan, or suicide attempt

American Psychiatric Association, DSM5, 2013; Img: www.acitudfem.com

Course of Disease: MDD

Onset:

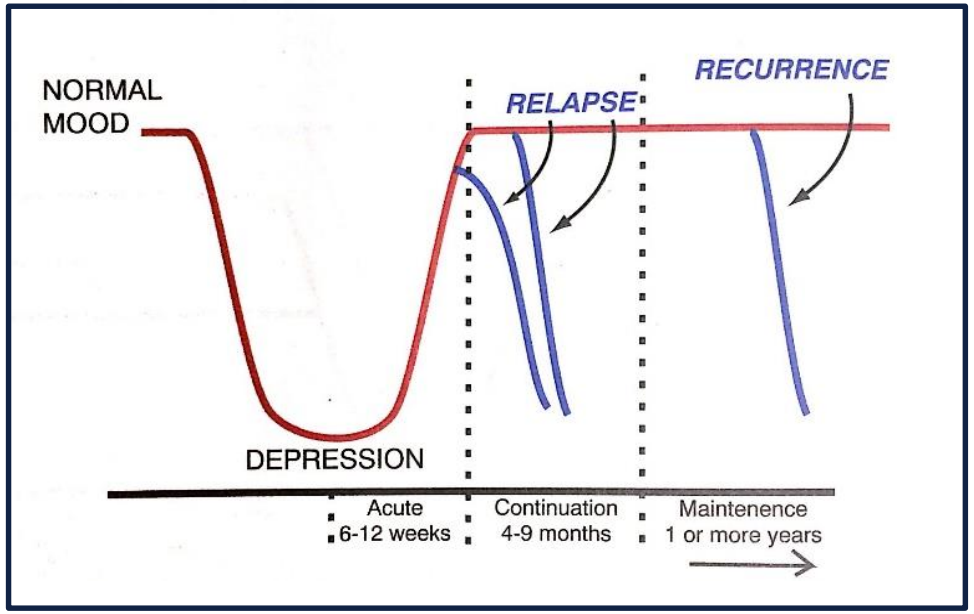
- Peak age of onset in late 20s
- Risk decreases after age 40 but may occur at any age

Duration:

- Median time to recovery: 20 weeks
- Remission periods usually longer earlier in disease course

Recurrence:

- Risk increases with each episode
  - 1 episode: 50% will have recurrence
  - 2 episodes: 70% will have recurrence
  - 3 episodes: 90% will have recurrence



Stahl SM. Essential psychopharmacology, 2000

Treatment Goals and Phases: MDD

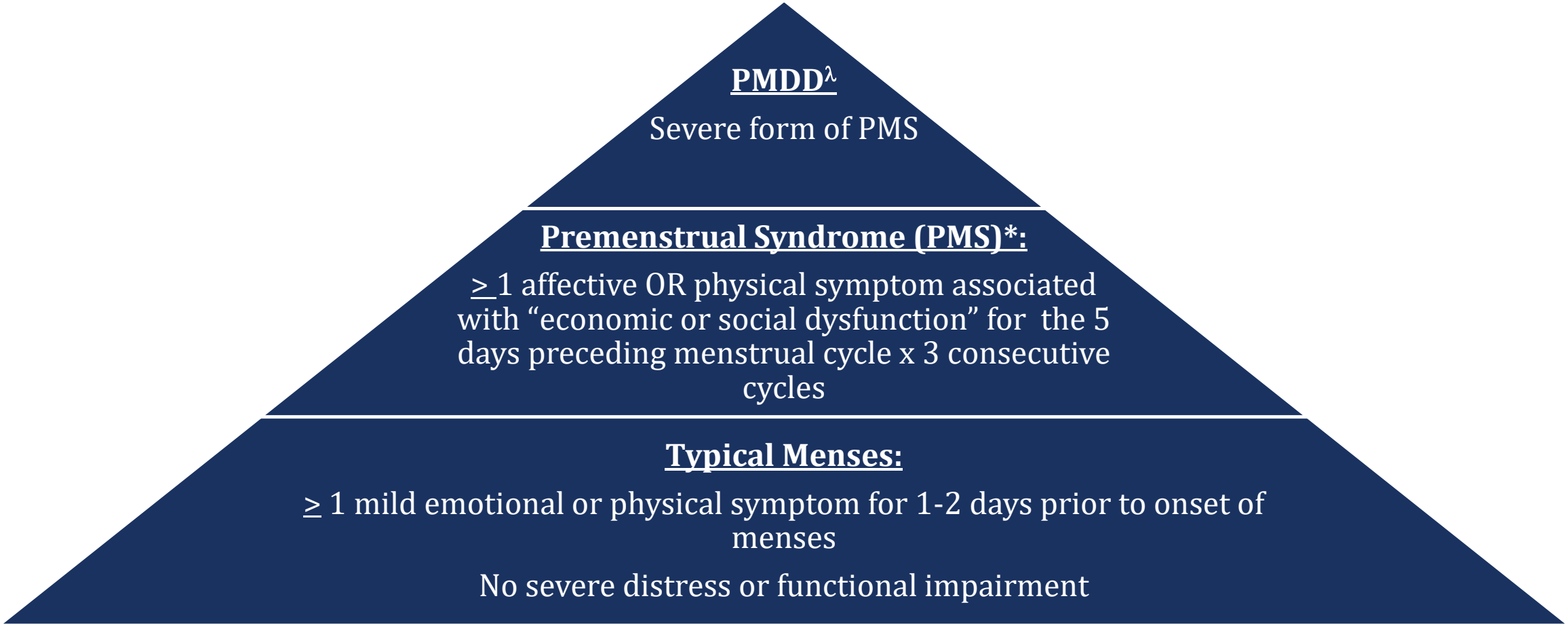
- **Goal: Achieve remission of symptoms**
  - Remission achieved in ~1/3 of patients with initial treatment
  - **Treatment resistance:** Inadequate response to ≥ 1 trial of antidepressants
- **Continuation Phase:**
  - Continue medication used successfully during acute phase for **4-9 months**
- **Maintenance Phase:**
  - Patients with chronic symptoms
  - ≥ 3 depressive episodes
  - May be **lifelong** in duration

Persistent Depressive Disorder (Dysthmic Disorder)

- Chronic depressed mood for ≥ 2 years
- No symptom-free period lasting > 2 months
- ≥ 2 additional depressive symptoms must be present → but with **no** episodes of MDD

Diagnostic and Statistical Manual, Fifth Edition. 2013

Menstrual Cycle-Related Syndromes



*Defined by American College of Obstetricians and Gynecologists

λ Defined by DSM-5

Premenstrual Dysphoric Disorder

- **≥ 5 symptoms present during the week prior to menses (luteal phase), resolve a few days after start of menses**

Core Symptoms (>1 for diagnosis)

1. **Mood swings**, sudden **sadness**, increased **sensitivity** to rejection
2. Anger, irritability
3. Sense of **hopelessness**, depressed mood, **self-critical** thoughts
4. Tension, **anxiety**, feeling on edge

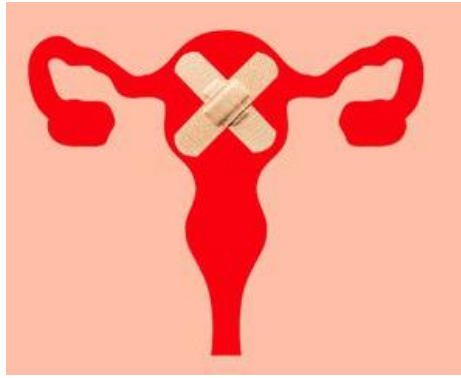
Other Symptoms (to make up >5 symptoms)

- Difficulty **concentrating**
- Change in **appetite** (cravings, overeating)
- Decreased **interest** in usual activities
- Feeling **overwhelmed**, out of control
- **Breast tenderness, bloating, weight gain, joint/muscle aches**
- **Sleeping** too much or too little

Diagnostic and statistical manual, fifth edition, 2013
Eisenlohr-Moul TA. Treatment of premenstrual dysphoria with continuous versus intermittent dosing of oral contraceptives. *Depress Anxiety*. 2017

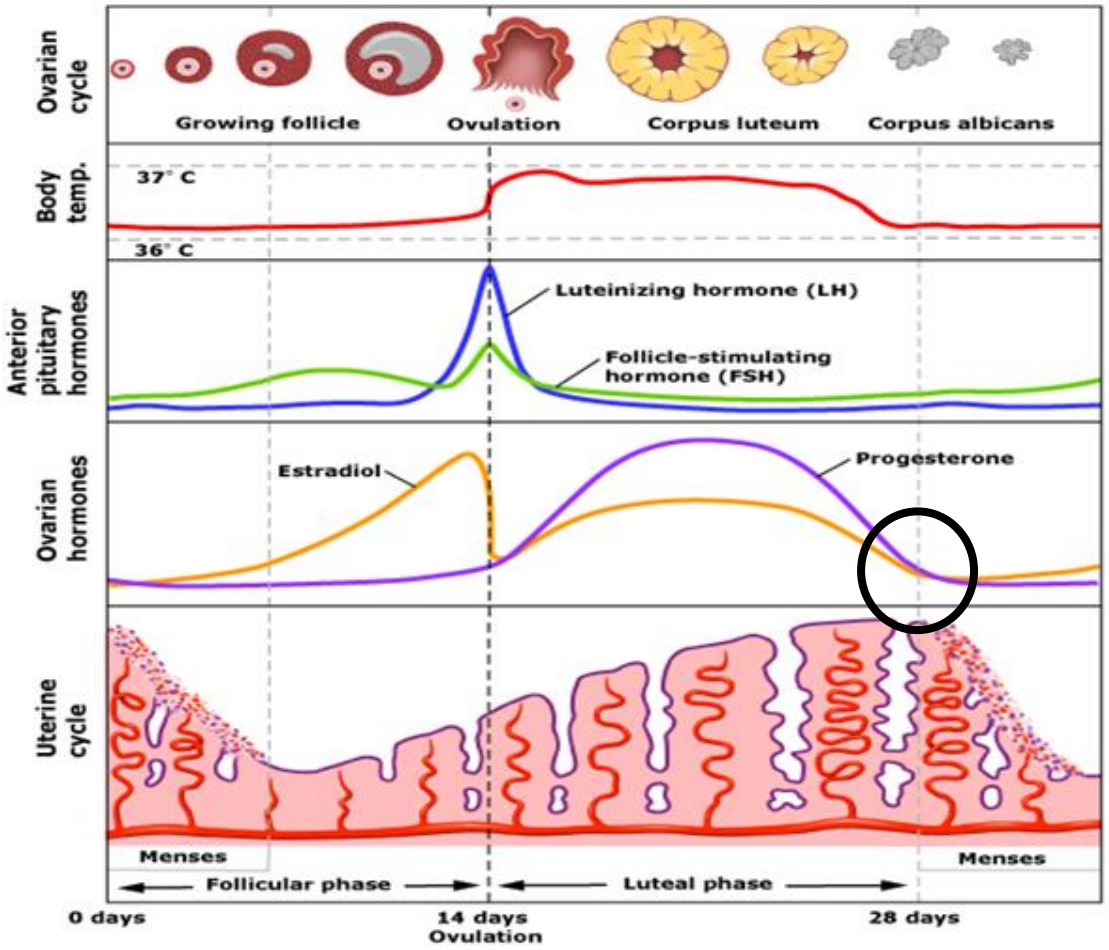
Impact of PMDD

- Problems with relation-ships
- ↓ Quality of Life
- ↓ Work produc-tivity
- ↓ Work, school attendance
- ↑ Risk of suicide or attempts
- ↑ Amb care visits



Pathophysiology of PMDD

- Potentially due to **altered sensitivity** to normal hormonal fluctuations
- **Progesterone, allopregnanolone (ALLO)**
  - Levels drop rapidly around menses
- **Estrogen**
  - May impact serotonergic function especially in luteal phase



Hantsoo L, Premenstrual dysphoric disorder: epidemiology and treatment. *Curr Psychiatry Rep*, 2016

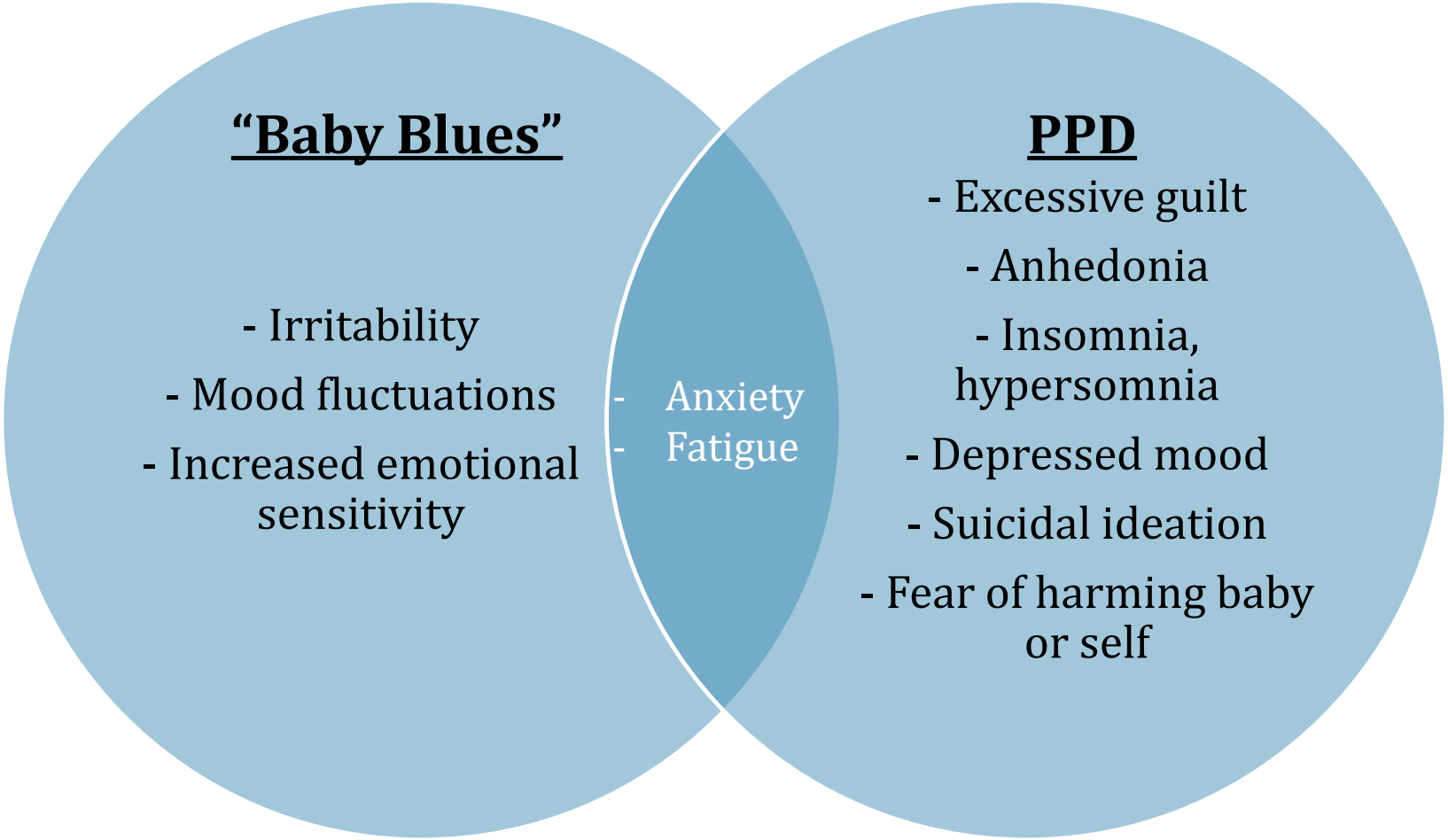
Peripartum/Postpartum Depression (PPD)

- Onset of MDD symptoms **during pregnancy or within 4 weeks** after childbirth
  - 14-23% of pregnant women experience a depressive episode
  - +/- psychotic features
- Associated with adverse pregnancy outcomes:

Child	Mother
•Premature birth/low birth weight •Lower APGAR scores •Difficulty with emotional regulation •Impaired social behaviors •Decreased academic performance •Increased risk of depression •Malnutrition	• Preeclampsia • Suicide • Poor recognition of infant cues • Poor attachment and withdrawal • Loss of work days

Diagnostic and Statistical Manual, Fifth Edition. 2013

PPD vs. “Baby Blue”



Postpartum Depression FAQ, American College of Obstetricians and Gynecologists. Available at: https://www.acog.org/Patients/FAQs/Postpartum-Depression

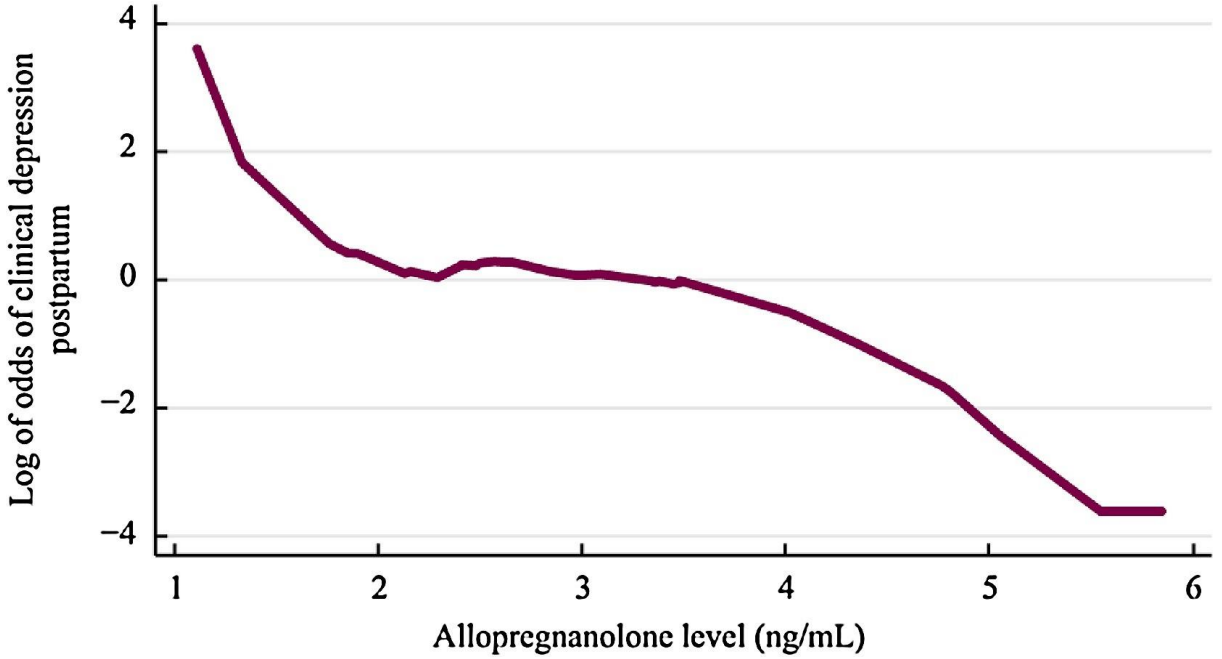
PPD Risk Factors

- Depression during pregnancy
- Anxiety during pregnancy
- Stressful life events during pregnancy
- Traumatic birth experience
- Preterm infant/infant admission to neonatal intensive care
- Low levels of social support
- Previous history of depression
- Problems with breastfeeding

Gen Hosp Psychiatry. 2004;36:289-95.

Pathophysiology of PPD

- Levels of ALLO increase during pregnancy and then drop off → depression, anxiety
- ALLO = allosteric modulator of GABA
  - Depressed subjects display reduced GABA concentration in CNS
  - Stress modulation



Mol Psychiatry. 2011 Apr;16(4):383-406.; Prog Neurobiol. 2014 Feb;113:79-87
Osborne L. Lower allopregnanolone during pregnancy predicts postpartum depression: an exploratory study. *Psychoneuroendocrinology*, 2017

Menopause and Perimenopausal Depression

- **Menopause:** Defined by the Stages of Reproductive Aging Workshop (STRAW)
  - First major variations in menstrual cycle length → 12 consecutive months without menses
- Menopausal transition includes significant changes in sex hormones, reproductive function
- **Common menopausal symptoms:**
  - Vasomotor symptoms
  - Sleep disturbances
  - Vaginal dryness
  - Breast pain
  - Joint pain
  - **Mood disturbances**

Willi J. Assessment of perimenopausal depression: a review. *J Affect Disord*. 2019

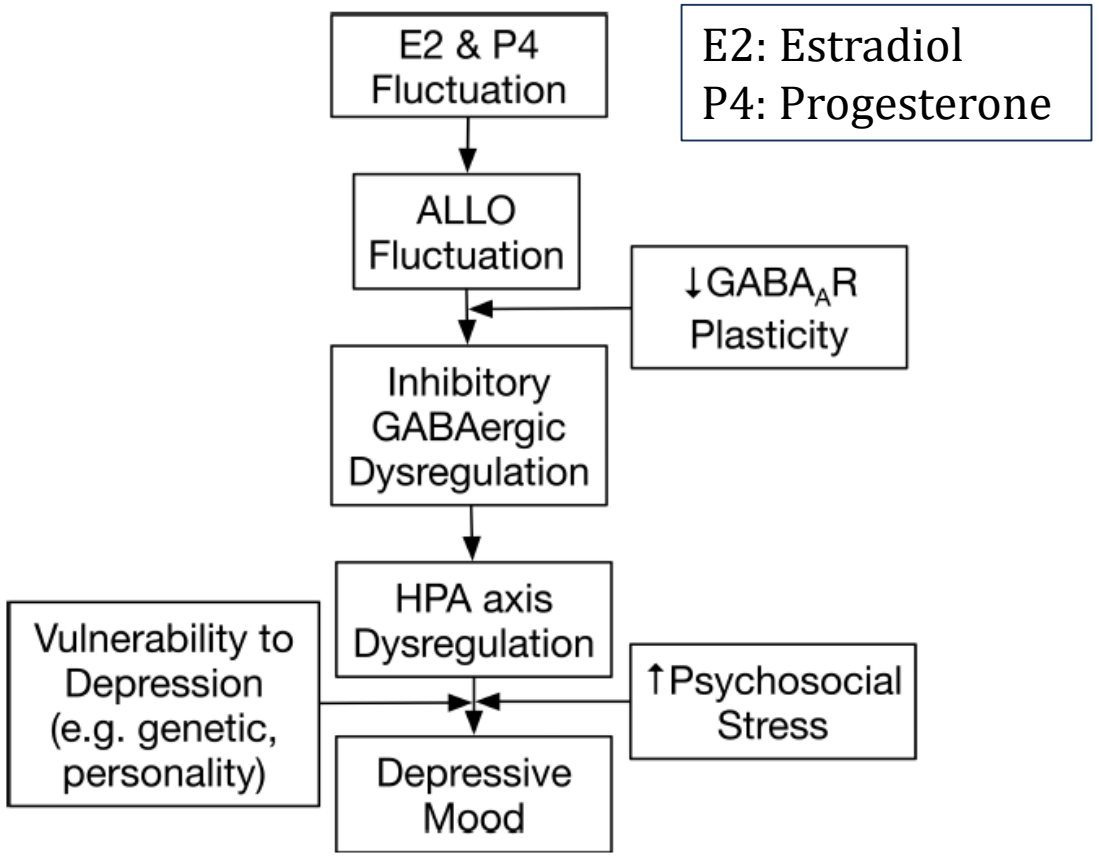
Perimenopausal Depression

- Up to **20%** of women develop mood disorders during **menopausal transition**
- Higher risk of depression compared to pre- or postmenopausal years
- New-onset or recurrence in women with previous history of depression
- Often occur with vasomotor symptoms of perimenopause

Willi J. Assessment of perimenopausal depression: a review. *J Affect Disord*. 2019

Pathophysiology of Perimenopausal Depression

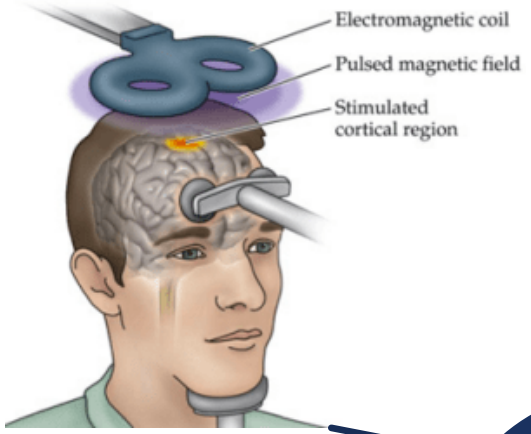
- Not thoroughly understood
- Fluctuation in ovarian hormones trigger mood disturbances
  - Estradiol, progesterone, ALLO
- ALLO = potent allosteroic modulator of $GABA_A$ receptors → GABA regulates HPA axis to limit stress response
  - Fluctuations in ALLO may contribute to dysregulation of HPA axis → depression



Gordon JL. Ovarian hormone fluctuation, neurosteroids, and HPA axis dysregulation in perimenopausal depression: a novel heuristic model. *Am J Psychiatry*. 2015

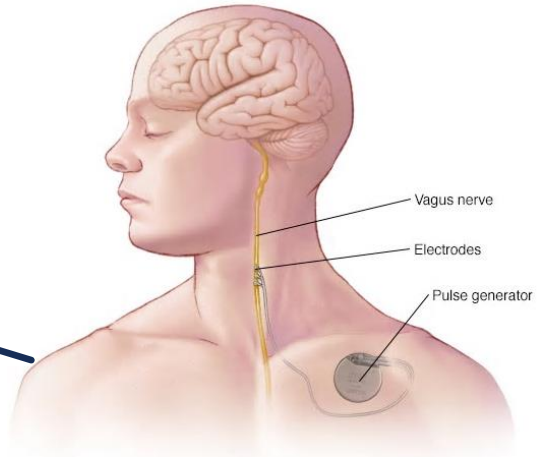
Treatment of Depressive Disorders

CBT: Cognitive behavioral therapy
DBT: Dialectical behavioral therapy
IPT: Intrapersonal therapy



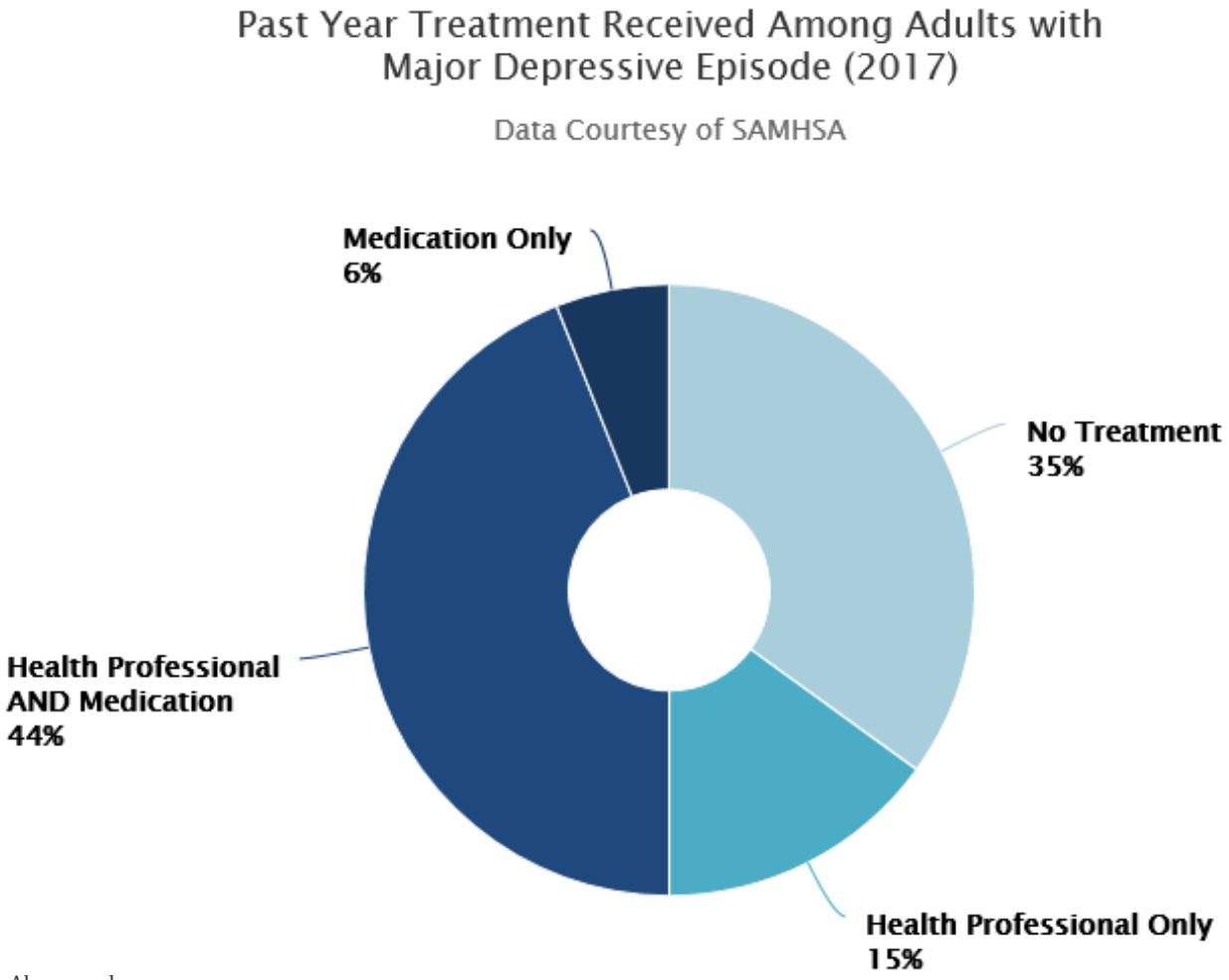
Non-pharmacologic treatment of MDD

- Psychotherapy (CBT, DBT, IPT)
- Bright light therapy
- Vagal nerve stimulation (VNS)
- Electro-convulsive therapy (ECT)
- Transcranial magnetic stimulation (TMS)



Imgs: mayoclinic.org, morningsidemaryland.com

Treatment of MDD in the U.S.



Major depression. National Institute of Mental health. Substance Abuse and Mental Health Services Administration 2017

Pharmacologic Treatment: MDD, Persistent Depressive Disorder

First-Line Treatment Options:

- Selective serotonin reuptake inhibitors (SSRIs)
- Serotonin norepinephrine reuptake inhibitors (SNRIs)
- Bupropion (Wellbutrin®)
- Mirtazapine (Remeron®)

Second-Line Treatment Options:

- Augmentation: Second-generation antipsychotic, lithium, liothyronine (T3)
- Tricyclic antidepressants (TCAs)
- Monoamine oxidase inhibitors (MAOIs)
- Ketamine/Esketamine?

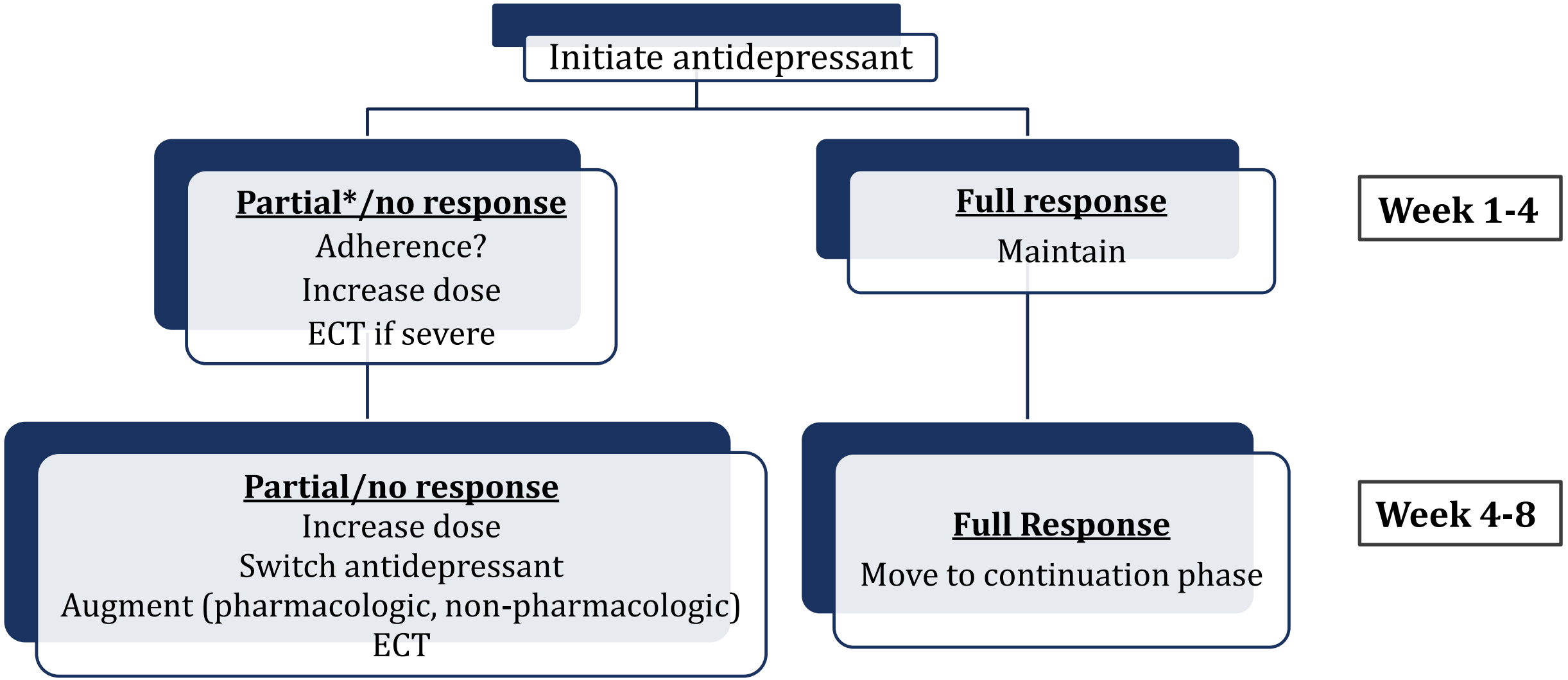
Pharmacotherapy of MDD

Effectiveness generally comparable among antidepressant classes

- **Treatment decisions guided by:**
  - Comorbid medical and psychiatric conditions
  - Anticipated side effects
  - Pharmacologic properties of the medications
    - Half-life, CYP450 activity, drug interactions, metabolites
  - Previous response to antidepressants
  - Cost
  - Patient preference

Maximum effect of any antidepressant will not be seen for **4-6 weeks!**

Treatment: Acute Phase

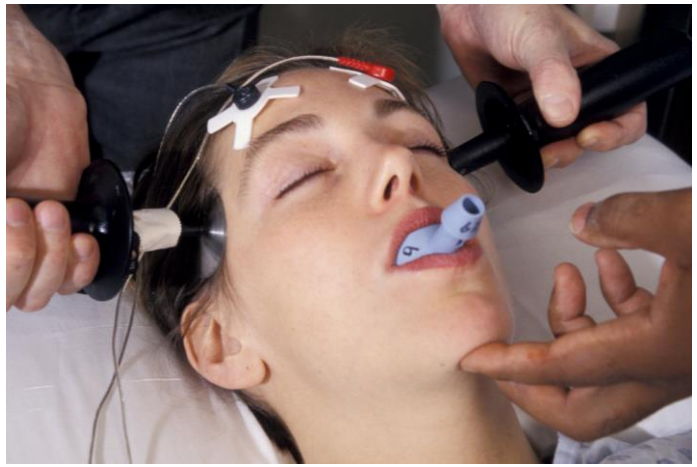


*<50% reduction in symptoms

American Psychiatric Association, 2010; Canadian Network for Mood and Anxiety Treatments, 2016

Electroconvulsive Therapy

- 80-90% effective for MDD
- **Time to response: 10-14 days**
  - Typically require 6-12 treatments → may require maintenance ECT
- Recommended for:
  - Severe depression
  - Depression with psychotic features
  - Depression with catatonic features
  - Severe suicidal ideation or food refusal
- Potential adverse effects:
  - Post-ictal confusion
  - Memory impairment after procedure
  - Headache/muscle ache



Gutierrez C. Depression. *College of Psychiatric and Neurologic Pharmacists.* 2018; Img: psychintegrity.org

Ketamine

- High-affinity, noncompetitive, N-methyl-D-aspartate (NMDA) glutamate receptor antagonist
  - FDA-approved as a dissociative anesthetic for procedural sedation
- Studied and used as a subanesthetic infusion for treatment resistant depression and acute suicidality in MDD

Common Adverse Effects	Serious Adverse Effects

• Hypertension
• Tachycardia
• Psychiatric symptom (12-50%)
  ▪ Vivid dreams
  ▪ Dissociative experience (out-of-body)
  ▪ Floating sensations
  ▪ Hallucinations
  ▪ Confusion
	• Bradyarrhythmia
	• Hypotension
	• Apnea, laryngeal spasm, respiratory depression

Murrough JW, et al. *Neuropsychopharmacology*, 2015

Initial Ketamine Studies

- Initial studies generally assessed efficacy of a single ketamine infusion (0.5 mg/kg)
- Rapid improvement in depressive symptoms within 2 to 72 hours post-infusion
  - Variety of scales used to assess efficacy including:
    - Montgomery-Åsberg Depression Rating Scale
    - Hamilton Depression Rating Scale
    - Beck Depression Inventory
    - Scale for Suicide Ideations
- ~70% response rate across studies
- Duration of effect estimated to be ~5 days

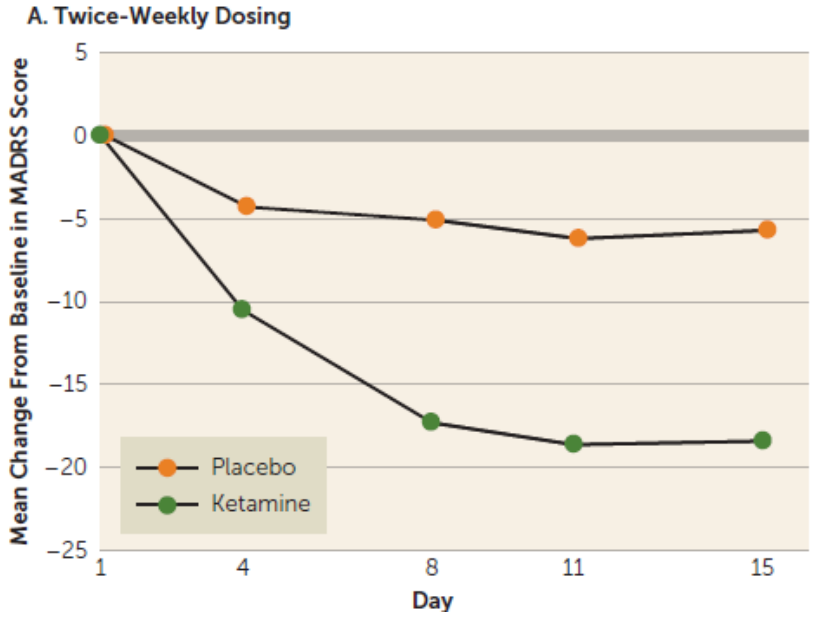
DiazGranados N, *J Clin Psychiatry*, 2010; Zarate CA Jr, et al, *Arch Gen Psychiatry*, 2006; Murrough JW, et al. *Am J Psychiatry*, 2013

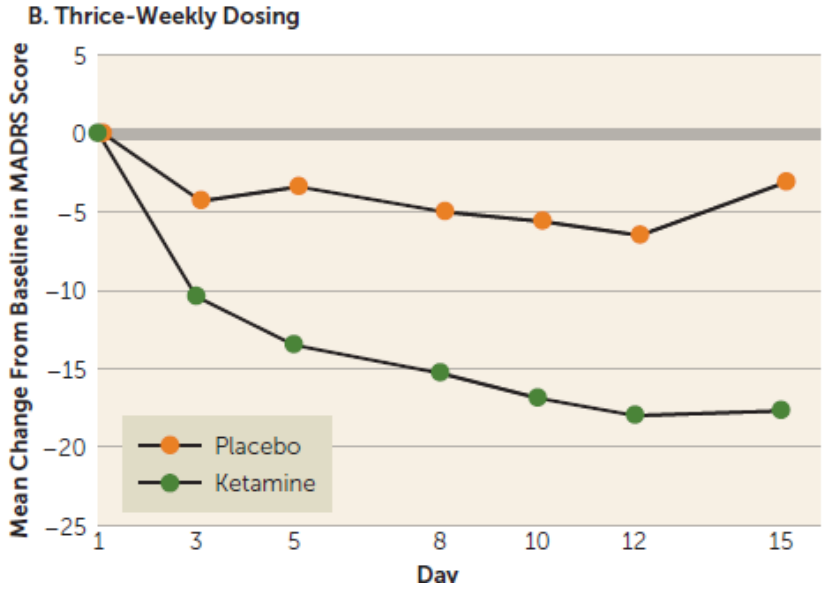
Placebo-controlled, Multi-infusion Study

Singh JB, et al. *Am J Psychiatry*, 2016		
Objective	Evaluate efficacy of two dosing regimens: twice weekly or three times weekly	
Design	Randomized, double-blind, placebo-controlled, parallel-group, phase 2 study at 14 sites in the U.S.	
Inclusion/ Exclusion Criteria	**Inclusion:** • Age 18-64 years with TRD • Inadequate response to ≥ 2 antidepressants (≥1 antidepressant failure in current episode)	**Exclusion:** • Other psychiatric diagnoses • "Clinically significant" suicidal ideation (SI) • Substance use disorder within ≤ 1 year
Methods	**Phase I (screening):** Up to 4 weeks **Phase II (double-blind treatment):** Randomized 1:1:1:1 for 4-week duration • IV ketamine 0.5 mg/kg IV twice weekly OR IV placebo twice weekly • IV ketamine 0.5 mg/kg IV three times weekly or IV placebo three times weekly **Phase III (open-label treatment):** 2-weeks (optional) **Phase IV (follow-up):** Ketamine-free follow-up for up to 3 weeks	

Results: Primary Outcome

Group (N=68)		Mean Change in MADRS from Baseline to Day 15	p-value
Twice Weekly	Ketamine	-18.4 [SD 12.0]	p<0.001
	Placebo	-5.7 [SD 7.3]	
Three Times Weekly	Ketamine	-17.7 [SD 10.2]	p<0.001
	Placebo	-3.1 [SD 5.7]	





- **Conclusion:** Ketamine showed statistically and clinically significant improvement in treatment-resistant depression compared to placebo (2x weekly = 3x weekly)

Assessment Question

- Intranasal esketamine (Spravato™) has been classified as a _____ by the FDA.

A. C II Medication
B. C III Medication
C. C IV Medication
D. C V Medication

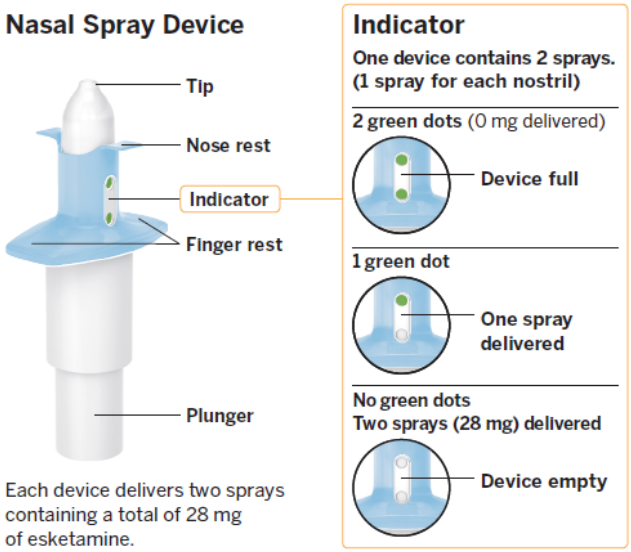
Intranasal Esketamine (Spravato™)

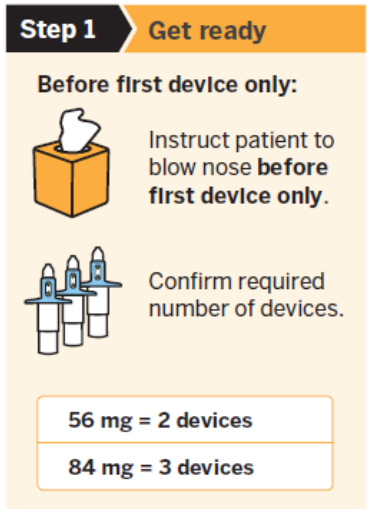
- Approved by the FDA in March 2019
  - S-enantiomer of ketamine
- **Indication:** Refractory major depressive disorder, adjunct
- **Dose:**

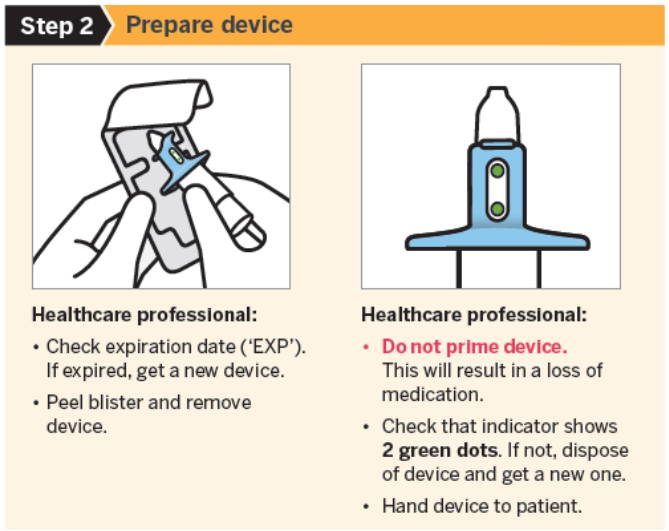
Initiation Week 1-4	Maintenance Week 5-8	Continuation Weeks > 8
• **Day 1:** 56 mg intranasally (IN) • 56 mg or 84 mg IN **twice a week**	• 56 mg or 84 mg IN **once a week**	• 56 mg or 84 mg IN **every 1 to 2 weeks** • If indicated

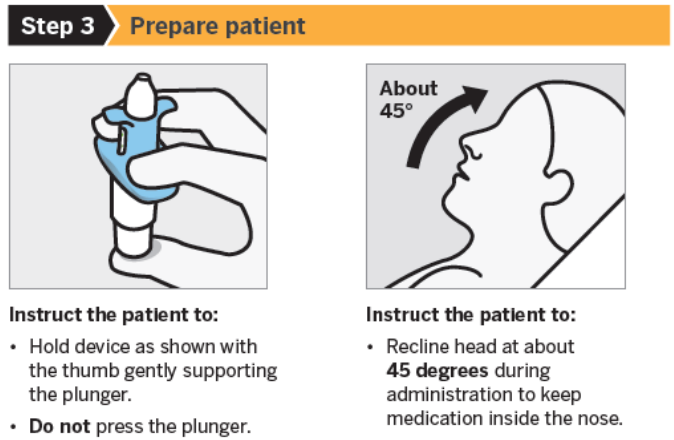
Esketamine Administration

- Patients must be monitored for 2 hours after full dose is administered
  - Each device contains 28 mg of esketmaine → if multiple devices required, patient must rest for ≥ 5 minutes between administrations

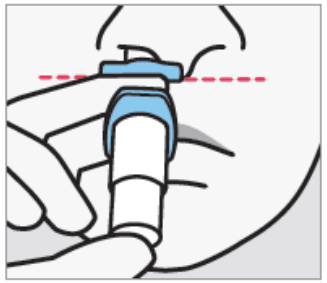






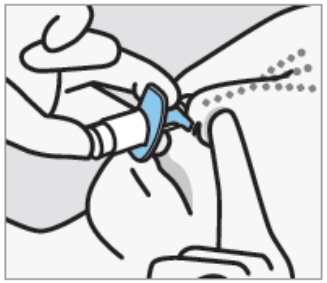


Step 4 Patient sprays once into each nostril



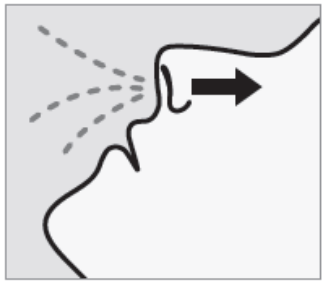
Instruct the patient to:

- Insert tip straight into the **first nostril**.
- Nose rest should touch the **skin between the nostrils**.



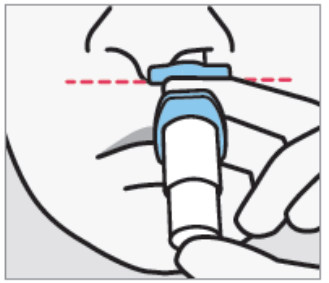
Instruct the patient to:

- Close opposite nostril.
- **Breathe in through nose** while pushing plunger all the way up until it stops.



Instruct the patient to:

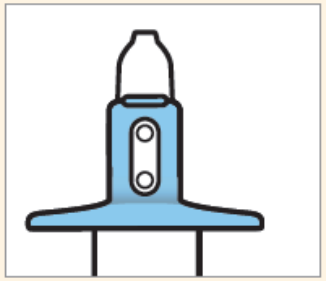
- **Sniff gently** after spraying to keep medication inside nose.



Instruct the patient to:

- Switch hands to insert tip into the **second nostril**.
- Repeat Step 4 to deliver second spray.

Step 5 Confirm delivery and rest



Healthcare professional:

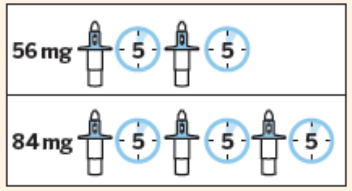
- Take device from patient.
- **Check that indicator shows no green dots**. If you see a green dot, have patient spray again into the second nostril.
- Check indicator again to confirm device is empty.

Instruct the patient to:

- Rest in a comfortable position (preferably, semi-reclined) for **5 minutes after each device.**
- If liquid drips out, dab nose with a tissue.

⚠ **Do not** blow nose.

Next device



Healthcare professional:

- **Repeat Steps 2-5** for the next device.

IMPORTANT: Ensure that patient **waits 5 minutes after each device** to allow medication to absorb.

Disposal

Dispose of used device(s) per facility procedure for a Schedule III drug product and per applicable federal, state, and local regulations.

Esketamine: Adverse Effects

Common Adverse Effects	Serious Adverse Effects
• **GI:** Nausea (28%), vomiting (9%) • **Neurologic:** Dizziness (29%), hypesthesia (18%), lethargy (11%), vertigo (23%) • **Psychiatric:** Anxiety (13%)	• **Cardiovascular:** Increased blood pressure (10%) • **Neurologic:** Sedation (23%)
Boxed Warnings: • Sedation and dissociation after administration • Potential for abuse and misuse • ↑ risk of suicidal thoughts/behaviors in pediatric and young adult patients taking antidepressants	

- **Spravato™ REMS Program:**
  - **Healthcare settings** must be certified in the program and ensure that Spravato™ is:
    - Only dispensed in healthcare settings and administered to patients enrolled in the program
    - Administered by patients under direct observation of healthcare provider and monitored for ≥ 2 hours
  - **Pharmacies** must be certified and only dispense to healthcare settings that are certified

Esketamine: Evidence for Use

	TRANSFORM-1	TRANSFORM-2
Design	• Randomized, double-blind, active-controlled, multicenter • TRD in adults 18-64 years old (failed ≥ 1 antidepressant in current episode)	
Methods	**Phase I:** Current antidepressant continued **Phase II (Double-Blind Induction): Week 1-4** New antidepressant* + **Fixed dosing**λ intranasal esketamine or placebo **Primary Outcome:** Change in MADRS at week 4	**Phase I:** Current antidepressant continued **Phase II (Double-Blind Induction): Week 1-4** New antidepressant* + **Flexible dosing**ϕ intranasal esketamine or placebo **Primary Outcome:** Change in MADRS at week 4
Results	N=331 Clinically meaningful but statistically insignificant change in MADRS for esketamine 56 mg and 84 mg and placebo (-19.0 vs. -18.8 vs. -14.8, p=0.059)	N= 286 Clinically and statistically significant improvement of MADRS score in ketamine group (-21.4 vs -17.0, CI: -7.31 to -0.64, p =0.002) Onset was rapid and increased over time

*Escitalopram, sertraline, duloxetine or venlafaxine XR

λ 56 mg or 84 mg intransally twice weekly

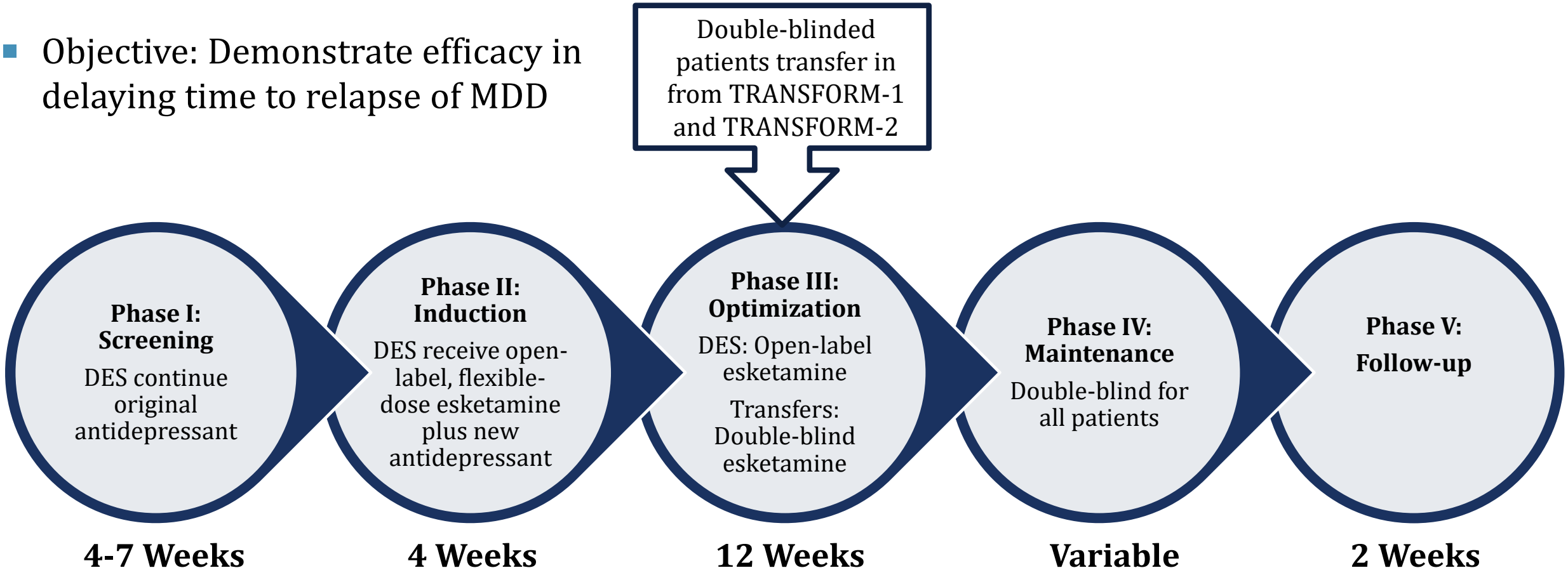
ϕ Patients started with 56 mg intranasally twice weekly and could be increased to 84 mg twice weekly. Doses could be changed until day 15

TRANSFORM-3

- Same design and methods as TRANSFORM-2
  - Flexible-dose esketamine
  - **28 mg**, 56 mg, 84 mg or placebo twice weekly
- Included only patients ≥ 65 years of age
- **Results:** No statistically significant different in MADRS score

SUSTAIN-1

- Objective: Demonstrate efficacy in delaying time to relapse of MDD



DES: Direct entry subjects

SUSTAIN-1

- **Primary endpoint:** Time to relapse **among stable remitters** during the maintenance phase
  - **Stable remitters:** Achieved remission before entry to maintenance phase (16 weeks of treatment)
- **Results:**
  - N=703
  - **Esketamine reduced the risk of relapse in stable remitters by 51%** (HR: 0.49; 95% CI: 0.29, 0.84)
  - Stable remitters in esketamine group did not have an estimable median time to relapse compared to median of 273 days in placebo group
  - Reduced time to relapse in treatment *responders* who received esketamine (635 days) compared to placebo (88 days) → risk reduced by 70%

Approximate Cost

Drug	Cost Per Unit (AWP)	Cost per 28 days (Induction phase)	Cost per 28 days (Maintenance phase)	Annualized cost (Maintenance phase)
SPRAVATO™ 56 mg (28 mg nasal spray devices x 2)	$590	$4720	$2360	$30764
SPRAVATO™ 84 mg (28 mg nasal spray devices x 3)	$885	N/A	$3540	$46020

Note: IV ketamine relatively inexpensive, however may cost patient ~$1500/infusion → not covered by insurance

Pharmacologic Treatment: PMDD

- Few clinical trials available
- **First-line:** SSRIs (60-90% response rate) or venlafaxine
  - Consider avoiding paroxetine → congenital abnormalities
  - Intermittent vs. continuous: Mixed results
    - Continuous possibly > intermittent
    - May be difficult for patients to anticipate onset of symptoms and when to initiate monthly dosing (i.e. 1-2 weeks/month)
- **Second-line:** Oral contraceptives
- **Alternatives:** Supplementation with calcium, vitamin B_6

Box 2
Treatments for premenstrual dysphoric disorder

A. Antidepressant medications
- Fluoxetine 20 mg daily[a]
- Sertraline 50 to 150 mg daily[a]
- Paroxetine CR 12.5 to 25 mg daily[a]
- Citalopram 5 to 20 mg daily
- Escitalopram 10 to 20 mg daily
- Venlafaxine 75 mg daily
- Clomipramine 25 to 75 mg daily

B. Ovulation suppression
- Yaz (oral contraceptive containing ethinyl estradiol 20 μg/drospirenone 3 mg)[b]
- Transdermal estrogen
- GnRH agonist (eg, leuprolide 3.75–7.5 mg intramuscularly monthly)
- Danazol 200 to 400 mg daily

C. Other treatments
- Alprazolam 0.25 mg twice a day during luteal phase
- Bromocriptine for mastalgia
- Spironolactone for bloating
- Calcium 600 mg twice a day
- Chasteberry
- Cognitive-behavioral therapy

[a]Approved by the FDA for full cycle and luteal phase dosing.

[b]Approved by the FDA for women desiring contraception.

Biggs W. Premenstrual syndrome and premenstrual dysphoric disorder. *Am Family Phys*. 2015; Lanza di Scalea T. Premenstrual dysphoric disorder. *Psychiatr Clin North Am.* 2017

PMDD and Oral Contraceptives

- Mixed results in trials:
  - Traditionally-dosed combined oral contraceptives (21 days active, 7 days inactive) not superior to placebo
  - Oral contraceptives with shortened or eliminated hormone-free interval superior to placebo

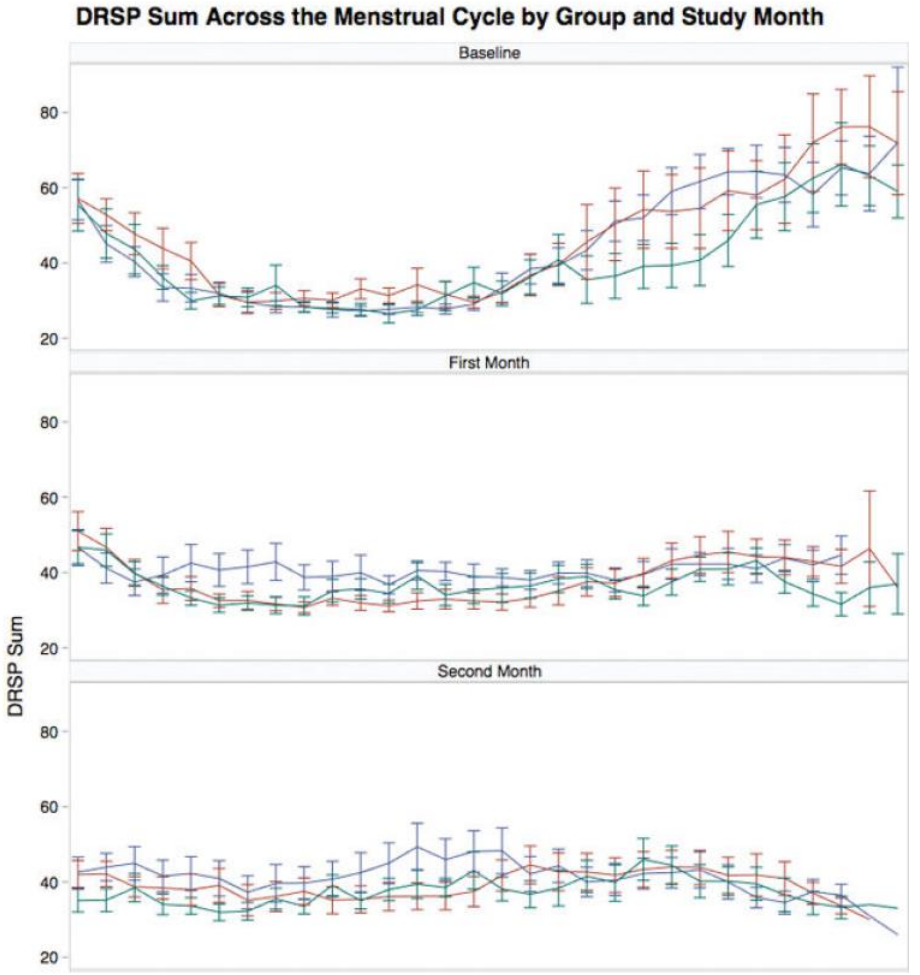
Intermittent OC vs. Continuous OC vs. placebo	
Design	Double-blind, randomized (1:1:1), placebo-controlled
Inclusion Criteria	• Emotional symptoms of **PMD** for 2-4 menstrual cycles with ≥ 1 emotional symptom in luteal phase • Age 18-40 years with regular menstrual cycles • No medication use or hormonal preparations except stable thyroid supplementation • No current psychiatric treatment with medication or psychotherapy
Methods	1. Drospirenone/ethinyl estradiol 3 mg/20 µg **(21day/7day)** 2. Drospirenone/ethinyl estradiol 3 mg/20 µg **(continuous)** 3. Placebo } x 3 months **Primary Outcome:** Daily Record of Severity of Problems (DRSP) parameters (worst baseline emotional symptom, physical symptoms, depression, anxiety, mood swings, anger/irritability, functional impairment)

Eisenlohr-Moul TA. Treatment of premenstrual dysphoria with continuous versus intermittent dosing of oral contraceptives. *Depress Anxiety*. 2017

PMDD and Oral Contraceptives

- **Results (N=55)**
  - Placebo=22
  - Intermittent = 17
  - Continuous = 16

- PMD symptoms declined significantly in all groups (high placebo response)
  - ↓ mean symptoms
  - ↓ variance of symptoms across cycle improved (less robust response in intermittent OC group)



Eisenlohr-Moul TA. Treatment of premenstrual dysphoria with continuous versus intermittent dosing of oral contraceptives. *Depress Anxiety*. 2017

Pharmacologic Treatment: PPD

- **Mild to moderate symptoms:** Psychotherapy
- **Moderate to severe symptoms:** Pharmacologic + psychotherapy, ECT
- **First-line:** SSRIs/SNRIs
  - Consider breastfeeding status: Most antidepressants result in > 10% concentration in breast milk
    - Long-term effects not known
    - Massachusetts General Hospital Pregnancy Registry for Antidepressants
  - Patients not previously treated with antidepressants usually treated with **sertraline** or **paroxetine**
- May consider alternative antidepressants such as tricyclics, mirtazapine, bupropion

Stuart-Parrigan K. Perinatal depression: an update and overview. *Curr Psychiatry Rep*, 2014.
Guille C. Management of postpartum depression. *J Midwifery Womens' Health*. 2013
Sachs HC. The transfer of drugs and therapeutics into human breast milk: an update on selected topics. *Pediatrics*. 2013

Brexanolone (Zulresso™) and PPD

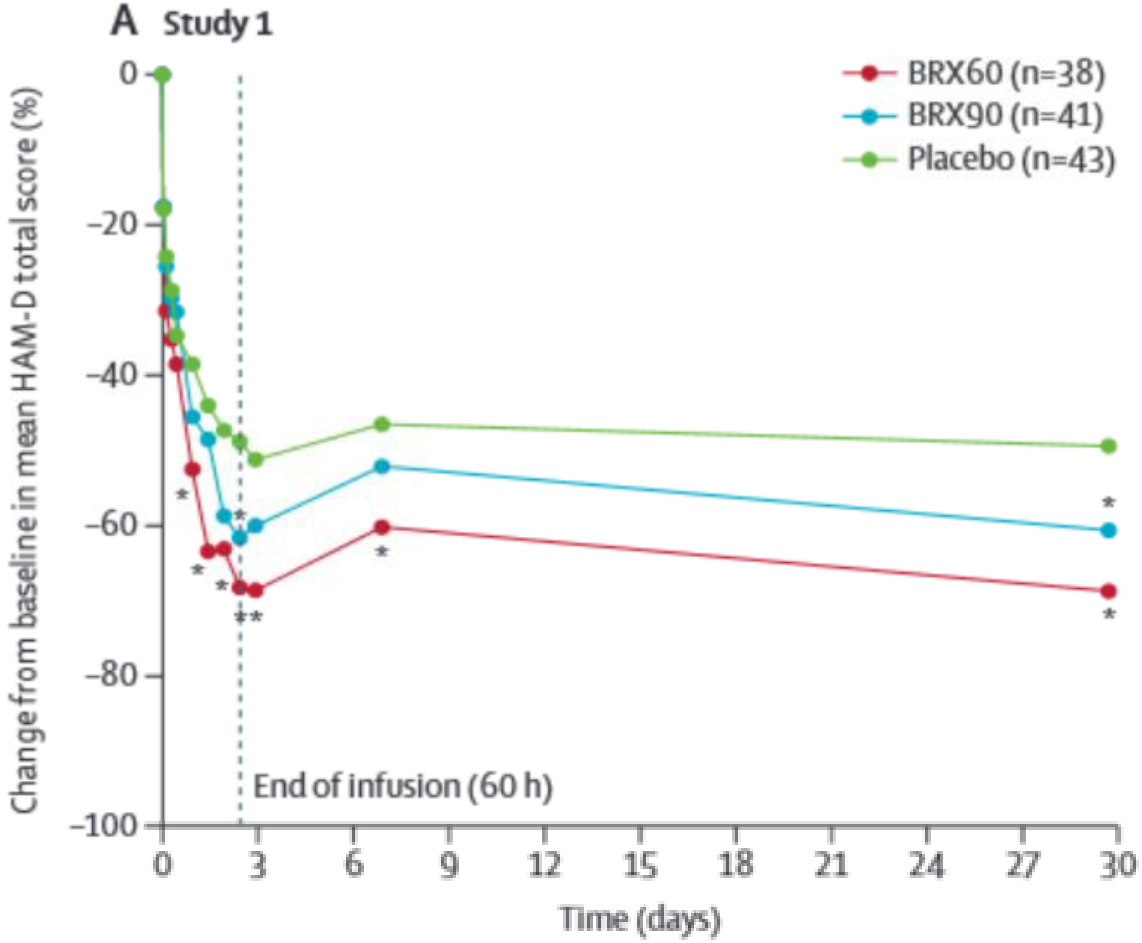
- Approved March 2019
- **MOA:** Neuroactive steroid identical to endogenous allopregnanolone→ modulator of $GABA_A$ receptors
- Single, 60-hour infusion with continuous monitoring

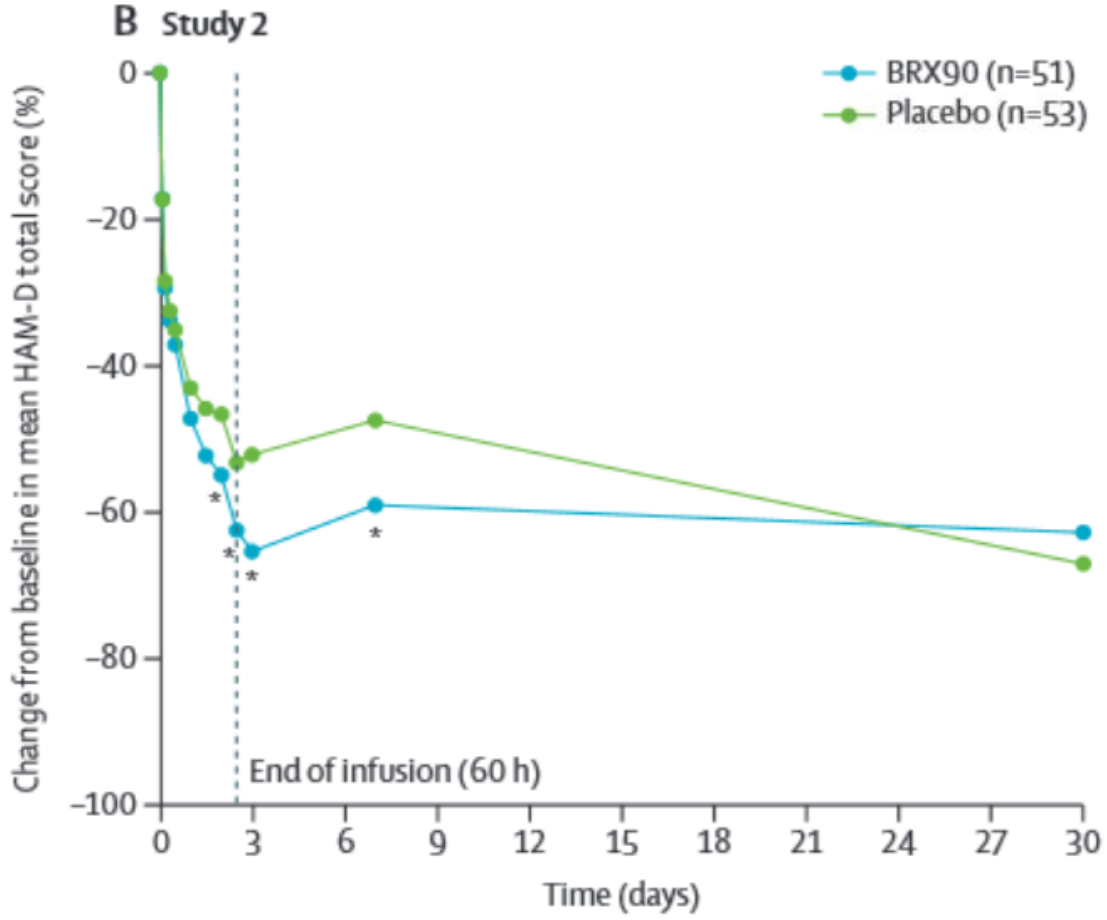
Brexanolone (BRX) injection in post-partum depression

Study Design	Two multicenter, double-blind, randomized, placebo-controlled, phase 3 trials	
Methods	**Study 1**: 138 patients with mod-severe PPD • 90 mcg/kg/h BRX 60 h infusion • 60 mcg/kg/h BRX 60 h infusion • Placebo 60 h infusion	**Study 2**: 106 patients with mod-severe PPD • 90 mcg/kg/h BRX 60 h infusion • Placebo 60 h infusion
Outcomes, Results	Change from baseline HAM-D score at 60 hr • -19.5 points for BRX60 (p=0.0013) • -17.7 points for BRX90 (p=0.052) • -14.0 points for placebo	Change from baseline HAM-D score at 60 hr • -14.6 points for BRX90 (p=0.0160) • -12.1 points for placebo
Treatment-Emergent Adverse Events (TEAEs)	Adverse events • 19 events for BRX60 • 22 events for BRX90 • 22 events for placebo	Adverse events • 25 events for BRX90 • 24 events for placebo
	Most common AE: headache, dizziness, sedation/somnolence (~30% of patients), dry mouth, flushing; Some instance of serious AE: SI, SA, syncope	
Conclusion	Administration of brexanolone injection for post-partum depression resulted in significant and clinically meaningful reductions in HAM-D total score at 60 h compared with placebo, with rapid onset of action and durable treatment response during the study period.	

Lancet. 2018 Sep 22;392(10152):1058-1070.

Results: Mean Change in HAM-D





Lancet. 2018 Sep 22;392(10152):1058-1070.

Brexanolone REMS Requirements

- **Monitoring:**
- Excessive sedation
- Sudden loss of consciousness
- Must have caregiver or family member to care for children while receiving brexanolone

- **Registration:**
- Healthcare facility
- Pharmacy
- Patient
- Wholesaler/distributor

Pharmacologic Treatment: Perimenopausal

- Treatment guidelines released in 2019 by North American Menopause Society
- **First-line treatment** = proven therapeutic options for MDD
  - Antidepressants → good efficacy and tolerability established in trials at usual doses
    - May also help with other menopause-related symptoms (hot flashes, sweating, pain)
  - Psychotherapy (CBT)
- **Estrogen therapy** has some evidence to support use during perimenopause but is ineffective in postmenopausal women

Maki PM. Guidelines for the evaluation and treatment of perimenopausal depression: summary and recommendations. *J Womens' Health*, 2019

Conclusions

- A variety of factors may contribute to depressive disorders in women, including hormonal fluctuations associated with life transitions (menstruation, pregnancy, menopause)
- In general, antidepressants and psychotherapy are first-line options for all depressive disorders
- New treatments, including ketamine, esketamine, and brexanolone, may be used more commonly in the future to treat depression and postpartum depression

Patient Case 1

LA is a 24 y/o AA female with no previous psychiatric history who gave birth to a healthy baby 6 days ago. Since then she has felt fatigued, irritable, and has struggled to fall asleep at night. She has also been tearful several times over the past 6 days.

What is the likely cause of LA's symptoms?

A. Baby blues
B. Postpartum depression
C. PMDD
D. Not able to make a diagnosis

Patient Case 1

LA is a 24 y/o AA female with no previous psychiatric history who gave birth to a healthy baby 6 days ago. Since then she has felt fatigued, irritable, and has struggled to fall asleep at night. She has also been tearful several times over the past 6 days. **A week later, LA returns and reports that she feels excessively guilty with thoughts to end her life because she "is the worst mother in the world" and does not feel any attachment to her child.**

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Patient Case 1

LA is a 24 y/o AA female with no previous psychiatric history who gave birth to a healthy baby 6 days ago. Since then she has felt fatigued, irritable, and has struggled to fall asleep at night. She has also been tearful several times over the past 6 days. **A week later, LA returns and reports that she feels excessively guilty with thoughts to end her life because she "is the worst mother in the world" and does not feel any attachment to her child.**

LA agrees that she requires treatment but is adamant that she wants to stay at home with her child to do so and she is able to contract for safety (will not attempt suicide). Which of the following is the best treatment option?

A. Paroxetine

B. ECT

C. Brexanolone

Patient Case 2

Patient KU is a 62 y/o female with a history of major depression for the past 40 years. She has had a partial response to **escitalopram, her current antidepressant**. She has been treated with the following antidepressants at adequate doses for an adequate length of time:

- Bupropion
- Duloxetine
- Paroxetine

KU is assessed to be severely depressed by her outpatient psychiatrist. Which of the following is the best pharmacologic treatment option at this time?

A. Switch escitalopram to citalopram

B. Switch escitalopram to duloxetine

C. Add lithium to escitalopram

D. Add selegiline to escitalopram

Patient Case 2

Pt KU returns 1 month later with worsening symptoms of depression and with new-onset suicidal ideation with a plan to overdose on medications. The outpatient psychiatrist recommends inpatient hospitalization to stabilize patient. Which of the following is a reasonable treatment approach?

A. Optimize dosing of lithium
B. Initiate treatment with ECT
C. Initiate treatment with ketamine or esketamine
D. All of the above

Questions?

Kristin Waters, PharmD, BCPS, BCPP
Clinical Pharmacy Specialist in Psychiatry
Yale New Haven Hospital
May 31, 2019

Placebo-controlled, Multi-infusion Study 2

Ionescu DF, et al. *J Affect Disord,* 2019		
Objective	Examine short-term and long-term antidepressant efficacy of repeated-dose ketamine augmentation compared to placebo in TRD outpatients with chronic suicidal ideation (SI)	
Design	Randomized, double-blind, placebo-controlled	
Inclusion/ Exclusion Criteria	**Inclusion:** Adults 18-65 years with TRD Failed ≥ 3 antidepressant treatments SI for ≥ 3 months HDRS suicide item score ≥ 2 in current episode	**Exclusion:** Bipolar disorder Psychotic illness Substance use disorder within past year SI requiring hospitalization
Methods	Patients randomized to ketamine 0.5 mg/kg or saline placebo twice a week for 3 weeks (6 treatments) **Primary outcome:** HDRS total score • Response: ≥ 50% improvement • Remission: Score ≤ 7 **Secondary outcome:** Suicidal ideation measured on Columbia-Suicide Severity Rating Scale (C-SSRS)	

Placebo-controlled, Multi-infusion 2: Results

- N=26

Table 1.
Demographic and illness characteristics.

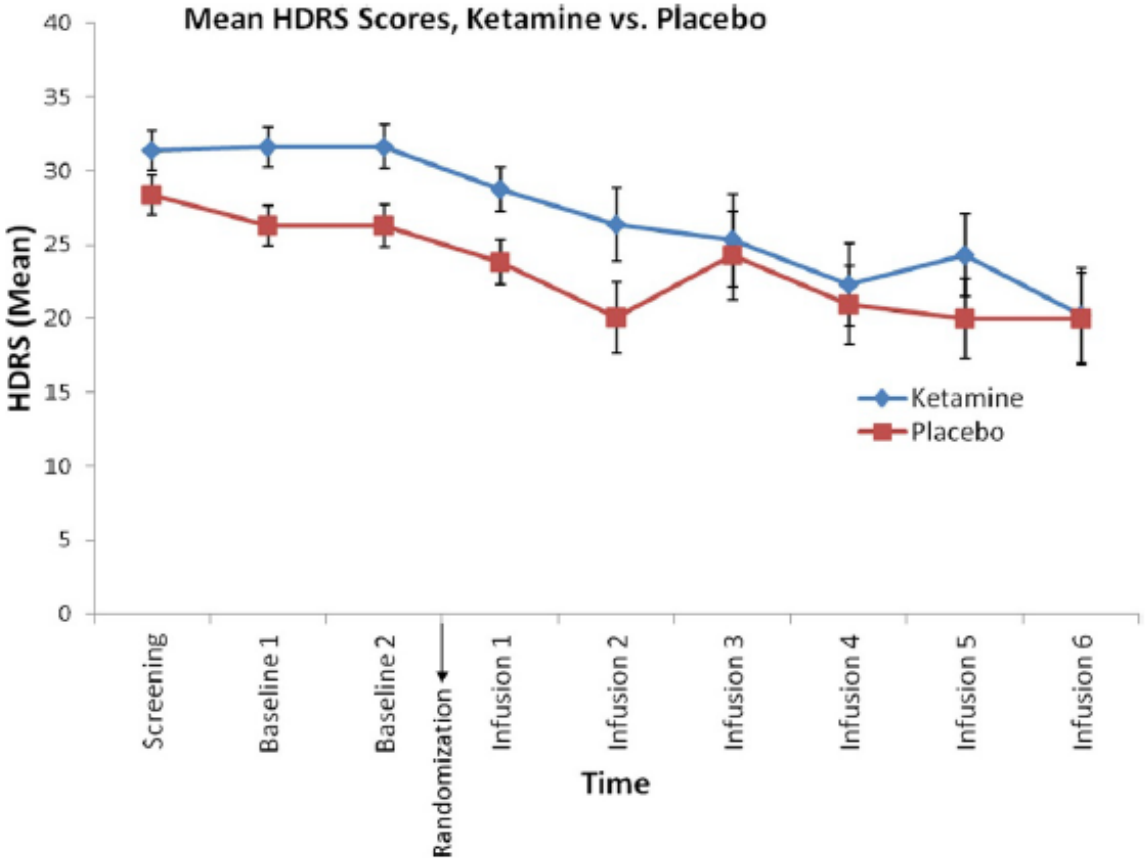
	Total Sample (n = 26)	Ketamine (n = 13)	Placebo (n = 13)	Range	p-value
Age	45.4 ± 12.4	45.5 ± 13.6	45.3 ± 11.7	21–65	0.52
Age of first depressive episode	19.3 ± 12.6	23.7 ± 15.4	14.6 ± 6.2	4–55	0.07
Number of past suicide attempts	1.6 ± 3.4	2.2 ± 4.6	1 ± 1.6	0–17	0.35
Number of failed medication trials	7.2 ± 3	6.6 ± 2.9	8.2 ± 3.1	3–13	0.63
Length of current episode of depression (Months)	115 ± 141.3 Median: 60	132.5 ± 154.6 Median: 66	91.6 ± 126.4 Median: 48	1.5–504	0.63
Number of lifetime depressive episodes	5.3 ± 6.7	5.2 ± 8.2	5.4 ± 5.2	1–25	0.26
Drug dose, based on weight (mg)	45.7 ± 11.7	44.9 ± 12.8	46.6 ± 10.8	26–70	0.52
	Total Sample (n = 26)	**Ketamine (n = 13)**	**Placebo (n = 13)**	**p-value**	
Sex (Female)	10 (38%)	7 (54%)	3 (23%)	0.11	
Race (Caucasian)	21 (81%)	11 (85%)	10 (77%)	0.28	
History of self harm	8 (31%)	4 (31%)	4 (31%)	1.0	
History of trauma or abuse	10 (38%)	6 (46%)	4 (31%)	0.42	
Family history of suicide (n = 23)[a]	8 (35%)	5 (22%)	3 (13%)	0.30	
Failed ECT (n = 25)[a]	11 (44%)	6 (46%)	5 (38%)	0.83	

Abbreviation: ECT = Electroconvulsive Therapy.
[a] Percentages were calculated based on the number of patients with available data, not based on total sample size.

Ionescu DF, et al. J Affect Disord, 2019

Primary Outcome: Depression

- **Primary Outcome: HDRS**
  - **HDRS scores improved significantly** in ketamine group ($p<0.01$) however **no statistical difference between ketamine and placebo groups** ($p=0.47$)
  - Mean HDRS score remained >20 for both groups after infusion 6 (moderately depressed)
  - No difference in proportion of responders/remitters between groups



Ionescu DF, et al. J Affect Disord, 2019

Secondary Outcomes

- **Secondary Outcomes: Presence** of suicidality and **intensity** of suicidality
  - **C-SSRS scores improved significantly** in both groups → no statistical difference
  - No significant effect on **intensity** of suicidal ideation between groups
  - No statistical difference in patients with no suicidal ideation (C-SSRS = 0) at end of study
- 3-month naturalistic follow-up phase:
  - No significant difference in number of responders/remitters between groups at month 3
- Significantly more dissociative symptoms in ketamine group

- **Conclusions:** Ketamine was not superior to placebo in short-term or long-term effects on MDD symptoms or suicidality
- Patients in this study a higher level of treatment resistance than previous studies
  - Most patients failed ≥ 5 previous antidepressant trials
  - 44% of patients had failed previous ECT treatment

Ionescu DF, et al. J Affect Disord, 2019