MOOD AND ANXIETY DISORDERS IN WOMEN

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DISCLOSURES

Relevant Financial Relationships

- None

Off-Label and/or Investigational Uses

- Will be identified in the presentation

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LEARNING OBJECTIVES

Upon completion of this activity, the learner should be able to:

- Describe epidemiology of and identify risk factors for mood and anxiety disorders in women.
- Identify female-specific presentations of depression and anxiety.

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FEMALE LIFECYCLE: DISTINCT BIO (HORMONAL) PSYCHOSOCIAL PERIODS

Childhood

- Prevalence of depression and most anxiety disorders similar for girls and boys
- Girls at higher risk for abuse, may impact development of psychiatric symptoms later in life

Puberty

- Brain remodeling
- Onset of menses for women with attendant hormone fluctuations
- Onset of sex differences in mood and anxiety disorders which persists through adulthood

Adulthood

- Most women experience PMS symptoms
- A small subset experience PMDD
- In women with depression, higher rate of suicide attempts

Perinatal

- Untreated mood and anxiety may impact the mother, fetus, or child
- Normal symptoms of pregnancy may affect assessment of mood and anxiety
- Need for specialized prescribing during pregnancy and lactation

Menopause

- Hormonal shifts over the stages of menopause
- Vasomotor symptoms may be associated with mood, and, in particular, with anxiety

Burt VK, Stein K. J Clin Psych 2002;63(suppl 7):9-15.
Hantsoo L, Epperson CN. Focus 2017;15(2): 162-172.

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PREVALENCE OF MENTAL ILLNESS

- 2020 National Survey of Drug Use and Health (NSDUH) – among U.S. adult population

Any mental illness – 21.0%

- More prevalent among females (25.8%) vs. males (15.8%)

Serious mental illness – 5.6%

- More prevalent among females (7.0%) vs. males (4.2%)

Available from: https://www.samhsa.gov/data/release/2020-national-survey-drug-use-and-health-nsduh-releases

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SEX DIFFERENCES IN PREVALENCE OF MENTAL ILLNESSES

Depression	• Consistently higher prevalence for women than for men 2:1 (Kuehner, 2017) • Odds ratio = 1.95, 95% CI [1.88, 2.03] (Salk et al. 2017)
Anxiety disorders	• Higher prevalence in women than men (McLean CP et al 2011) • Lifetime women 33.3%, men 22.0% OR=1.70 [1.48, 1.97]
Bipolar disorder	• Almost equal ratio (Diflorio & Jones 2010)
Schizophrenia	• Slightly higher incidence for men compared to women • Risk ratio ~ 1.4 (Riecher-Rössler et al. 2018)
ADHD	• Clear male predominance in childhood and adolescents (Banaschewski, 2018) • Male-to-female ratio of 4:1 in clinical setting, 2.5:1 in population setting
Autism	• Male predominance • Commonly referenced consensus ratio of ~ 4:1 (Werling & Geschwind 2013)
Substance use disorders	• Higher prevalence in men (McHugh et al. 2018) • Varies internationally and by drug of choice

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MOOD DISORDERS: MAJOR DEPRESSION

- 5 or more symptoms, 2 weeks, change from previous functioning, significant distress/impairment:
  - Depressed mood
  - Diminished interest or pleasure
  - Significant weight loss or weight gain or appetite change
  - Insomnia or hypersomnia
  - Psychomotor agitation or retardation
  - Fatigue or loss of energy
  - Feelings of worthlessness or excessive guilt
  - Decreased concentration or indecisiveness
  - Recurrent thoughts of death, recurrent suicidal ideation, specific suicide plan, or suicide attempt

Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Text Revision, APA, 2022.

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MOOD DISORDERS: BIPOLAR DISORDER

- Manic episode: BP I
  - at least 1 week or any duration if hospitalization necessary
- Hypomanic: BP II
  - at least 4 days

- Distinct period of mood change with increased activity/energy
- Inflated self-esteem or grandiosity
- Decreased need for sleep
- More talkative than usual
- Flight of ideas or subjective experience of racing thoughts
- Distractibility
- Increased in goal-directed activity
- Impulsivity (activities with potential for negative consequences)

Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Text Revision, APA, 2022.

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ANXIETY DISORDERS

- Specific phobia
- Social anxiety disorder
- Panic disorder
- Generalized anxiety disorder
- Historically:
  - Obsessive-compulsive disorder (OCD)
  - Posttraumatic stress disorder (PTSD)

Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Text Revision, APA, 2022.

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SEX HORMONES: MOOD AND ANXIETY COURSE

- Menstrual cycle: 2 phases
  - Follicular phase: onset of menses until ovulation
  - Luteal phase: ovulation until onset of next menses

- Anterior pituitary hormones: FSH (follicle stimulating hormone) & LH (luteinizing hormone)
- Ovarian hormones: estradiol & progesterone

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SEX HORMONES: MOOD AND ANXIETY COURSE

- Premenstrual Syndrome (PMS)
  - Cyclic recurrence of psychological and physical symptoms during the luteal phase of the menstrual cycle
  - 85% of menstruating persons experience at least 1 mild premenstrual symptom

  - 20%-25% experience moderate to severe PMS
  - Approximately 5% meet diagnostic criteria for premenstrual dysphoric disorder (PMDD)
  - When ovulation is suppressed, symptoms often improve
  - Often a strong anxiety component

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PMDD DIAGNOSTIC CRITERIA

- Symptoms, at least 5 total, present in final week before menses, start to improve within a few days after menses onset, and become minimal or absent in week postmenses:
  - 1 or more:
    - marked affective lability
    - marked irritability / anger/ increased interpersonal conflicts
    - marked depressed mood/ feelings of hopelessness/ self-deprecating thoughts
    - marked anxiety/tension /keyed up or on edge
  - 1 or more to reach a total of 5:
    - decreased interest in usual activities
    - subjective concentration problems
    - marked change in appetite / overeating /food cravings
    - hypersomnia or insomnia
    - feeling overwhelmed or out of control
    - physical symptoms (breast tenderness/swelling/joint/muscle pain/sensation of bloating)

Diagnostic and Statistical Manual of Mental Disorders, 5th edition, Text Revision, APA, 2022.

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ETIOLOGY-LANDMARK STUDY

- Women may have abnormal responses to normal hormonal fluctuations
  - 20 women with PMS (no other psychiatric illness for 2 years)
  - 15 women without PMS history
  - ALL given leuprolide (Gnrh agonist) then administration of estradiol and progesterone (in random order)
- For women with PMS – recurrence of mood and anxiety symptoms with either estradiol or progesterone added
- For women without PMS - had no change in mood issues with ovarian suppression via leuprolide or with hormonal addback
- Normal plasma concentrations of gonadal steroids can trigger abnormal response in susceptible women

Schmidt et al, NEJM 1998
Payne JL, 2003
Lanza di Scalea and Pearlstein, Med Clin N Am, 2019.

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CLINICAL CONSIDERATIONS: PMS/PMDD

- High comorbidity with other psychiatric disorders
- Highest for major depression, then anxiety disorders (most frequently panic disorder)
- Possible link between trauma exposure and PMS/PMDD
- Personality disorders do not appear to be significantly increased in persons with PMDD compared with healthy controls
- Personality traits (impulsivity, anger, affect intensity, lability) associated with PMS/PMDD in a population hospitalized after suicide attempt

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RATING SCALES

- Daily Record of Severity of Problems (DRSP)
- Premenstrual Record of Impact and Severity of Menstruation (PRISM)
- Calendar of Premenstrual Experiences (COPE)
- NIMH Mood Chart (for premenstrual exacerbation of mood or anxiety disorder)
- Premenstrual Symptoms Screening Tool (PSST)—retrospective assessment of symptoms and functional impairment over the last menstrual cycle

- **Confirm symptoms prospectively over at least 2 symptomatic cycles for formal PMDD diagnosis**

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EVALUATION FOR PMS/PMDD ROUTINELY INCLUDES THE FOLLOWING EXCEPT:

- Thyroid function testing
- Taking a detailed medical and gynecologic history
- Checking estradiol and progesterone levels
- Evaluation for anemia

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TREATMENT: FIRST LINE: SSRIS

- Response rates 60-90% compared to 30-40% with placebo
- FDA-approved: fluoxetine, sertraline, paroxetine
- Efficacy has been shown with several dosing schedules:
  - Continuous
  - Intermittent (luteal phase)
  - Semi-intermittent (“bump up” over baseline)
  - Symptom-onset
- Continuous dosing may be more effective than intermittent (particularly for somatic symptoms)

Lanza di Scalea and Pearlstein, Med Clin N Am, 2019.

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TREATMENT: OVULATION SUPPRESSION

- Oral contraceptive (brand name Yaz): ethinyl estradiol 20 mcg/drospirenone 3 mg, 24/4 or continuous)*
  - Individualize assessment for risk of venous thromboembolism (2012 FDA added warning)
- Transdermal estrogen
- GnRH agonist (leuoprolide 3.75 mg IM monthly)
- Danazol 200-400 mg daily (synthetic steroid, suppresses pituitary gonadotropin output): rarely used secondary to side effects
- Hysterectomy w/BSO=last resort (confirm improvement in PMDD symptoms with medical suppression of ovulation prior to surgery)

*=FDA-approved for PMDD in persons desiring contraception

Lanza di Scalea and Pearlstein, Med Clin N Am, 2019.

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PMAD (PERINATAL MOOD AND ANXIETY DISORDER) EPIDEMIOLOGY

- Common
- Perinatal depression: 1 in 7 women, most common complication of childbearing
- Perinatal anxiety: roughly 11-21% prevalence (GAD, phobias, panic most common)
- Pregnant or postpartum women up to 2x more likely to experience OCD (Russell, 2013)
- 60% of women with perinatal depression have pre-existing comorbid psychiatric disorders
- Most significant risk factor for postpartum depression: antenatal depression

Kendig S et al. Obstet Gynecol 2017;129: 422-30.
Gavin NI et al. Obstet Gynecol 2005;106:1071-1083.
Gaynes BN et al. Evid Rep/Technol Assess (Summ) 2005:1-8.
Hantsoo L, Epperson CN. Focus 2017;15(2): 162-172.

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SCREENING

HTTPS://SAFEHEALTHCAREFOREVERYWOMAN.ORG/PATIENT-SAFETY-BUNDLES/MATERNAL-MENTAL-HEALTH-DEPRESSION-AND-ANXIETY/

Identify mental health screening tools to be made available in every clinical setting (outpatient obstetric clinics and inpatient facilities)

Without consistent screening, PMAD may go unrecognized

- Underreporting of symptoms
- Edinburgh Postnatal Depression Scale (EPDS)
- Patient Health Questionnaire 9 (PHQ-9)
- Consider screening for bipolar disorder (Mood Disorders Questionnaire—MDQ)

Whitton A et al. Br J Gen Pract 1996;46:427-428; Cox JL et al, Br J Psychiatry 1987;150:782-786;
Kroenke K et al. J Gen Intern Med 2001;16:606-613; Hirschfeld RM. Prim Care Companion J Clin Psychiatry 2002; 4:9-11;
Modified from Council on Patient Safety in Women's Health Care.
Available at: http://www.safehealthcareforeverywoman.org/.

RISK FACTORS FOR PERINATAL DEPRESSION: DEPRESSION DURING PREGNANCY

- Maternal anxiety
- Life stress
- History of depression
- Lack of social support
- Unintended pregnancy
- Medicaid insurance
- Domestic violence
- Lower income
- Lower education
- Smoking
- Single status
- Poor relationship status
- Adolescent mothers

Lancaster CA et al. Am J Obstet Gynecol 2010;202:5-14.
Robertson E et al. Gen Hosp Psychiatry 2004;26:289-95.

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RISK FACTORS FOR PERINATAL DEPRESSION: POSTPARTUM DEPRESSION

- Depression during pregnancy
- Anxiety during pregnancy
- Experiencing stressful life events during pregnancy or the early postpartum period
- Traumatic birth experience
- Preterm birth/infant admission to neonatal intensive care
- Low levels of social support
- Previous history of depression
- Breastfeeding problems

Lancaster CA et al. Am J Obstet Gynecol 2010;202:5-14.
Robertson E et al. Gen Hosp Psychiatry 2004;26:289-95.

UNTREATED ANTENATAL DEPRESSION IMPACTS THE MOTHER

- Behaviors that occur more often in depressed women:
  - Poor prenatal care
  - Poor nutrition, weight gain during pregnancy
  - Alcohol, nicotine, and other drug use
- Pregnancy complications:
  - Nausea, vomiting, hyperemesis gravidarum, pre-eclampsia
- Impaired mother-child interaction
- Concern for postpartum worsening
- Maternal suicide

Yonkers KA et al. Obstr & Gyn 2009; 114(3):703-13.
Stewart DE. N Engl J Med 2011;365:1605-11

UNTREATED ANTENATAL DEPRESSION ASSOCIATED WITH ADVERSE REPRODUCTIVE OUTCOMES

- Miscarriage: Unknown, some with association.
- Growth effects: Unknown (delivery of low birth weight (LBW) or small for gestational age (SGA) infants). Some studies with association, others without; slower rates of fetal body and head growth
- Preterm delivery: Unknown. Inconsistent findings.
- No known studies linking maternal depression to congenital anomalies.

Yonkers KA et al. Obst & Gyn 2009; 114(3):703-13.
Marroun H et al. Arch Gen Psych 2012; 69:706-14.
Apter G et al. J Nerv Ment Dis 2011;199:575-7
Davalos DB et al. Arch Womens Ment Health 2012;14:1-14

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MATERNAL DEPRESSION IMPACTS THE OFFSPRING

- Failure to thrive
- Attachment disorders of infancy
- Developmental delay
- Impaired language development
- Lower IQ scores
- Depressive, anxiety, disruptive behavior disorders

Byatt N et al. Acta Psychiatr Scand 2013;127:94-114.

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BABY BLUES: UP TO 2 WEEKS POSTPARTUM

- Mood swings
- Anxiety
- Sadness
- Irritibility
- Feeling overwhelmed
- Crying
- Reduced concentration
- Difficulty sleeping
- Appetite problems

DSM-5 SPECIFIERS FOR DEPRESSIVE DISORDERS

- "**With peripartum onset**: This specifier can be applied to the current or, if full criteria are not currently met for a major depressive episode, most recent episode of major depression if onset of mood symptoms occurs during pregnancy or in the 4 weeks following delivery."

- Conservative interpretation, somewhat problematic for clinical care

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MANAGEMENT OF DEPRESSION DURING PREGNANCY: GENERAL PRINCIPLES

- If already utilizing psychotropic medications, plan ahead! Assume reproductive-age women will get pregnant!
- Ask about reproductive plans and contraception
- For mild to moderate illness, consider nonpharmacological interventions (psychotherapy: CBT or IPT)
- Best to do medication changes prior to pregnancy, if possible
- Consider history and diagnosis (ie, reconsider off-label use)
- Ideally, a woman should be stable psychiatrically for at least 3-6 months before attempting pregnancy

PayneJL, Meltzer-Brody S. Clin Obstet Gynecol. 2009 Sept; 52(3):469-482.
Yonkers KA et al. Ob Gyn 2009;114:703.
Yonkers KA , Wisner KL et al. Gen Hosp Psych . 2009; 31:403-413.

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GENERAL PRINCIPLES, CONTINUED

- Single medication at a higher dose favored over multiple medications
- Use lowest effective dose
- Limit changing of medication: decreases exposure to the fetus
- Consider prior exposure during pregnancy
- Available reproductive safety information

ACOG Practice Bulletin, “Use of Psychiatric Medications During Pregnancy and Lactation”, Obstr & Gyn, 110 (5), Nov 2007

PHARMACOLOGICAL TREATMENT STRONGLY CONSIDERED

- Moderate to severe depression
- Active suicidal ideation
- Psychotic symptoms
- History of highly recurrent depression
- History of depressive relapse after stopping medication
- Clinical need for faster response

Stewart DE. N Engl J Med 2011;365:1605-11
Yonkers KA et al. Gen Hosp Psychiatry 2009;31:403-13

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MEDICATIONS

- FDA Pregnancy and Lactation Labeling Rule (PLLR), 2015 update
  - Clinicians must assess risk of untreated illness as well as potential adverse effects of pharmacotherapy
  - Assess impact on mother, fetus, and infant
  - **No more letter categories for medication safety during pregnancy**
    - Overly simplistic
    - Could lead to false assumptions

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PREGNANCY AND ANTIDEPRESSANTS: PRACTICAL

- Data is reassuring for use during pregnancy (SSRIs, SNRIs, tricyclic agents, bupropion, mirtazapine)
- No one ‘right’ choice
- Treat to euthymia
- May need to increase dose later in pregnancy given physiologic changes of pregnancy
- Recommendation to taper and discontinue use around labor and delivery problematic given high risk for recurrence in the postpartum period

NEW AGENT: BREXANOLONE MARCH 2019

- Proprietary formulation of the neuroactive steroid allopregnanolone, an allosteric modulator of GABA type A receptor
- 1st agent specifically FDA-approved for treatment of postpartum depression
- FDA granted the application Priority Review and Breakthrough Therapy designation
- 60 hour continuous IV infusion with continuous pulse oximetry monitoring
- Administered through a REMS program at a certified facility by a healthcare provider (concern for sudden loss of consciousness)
- On the horizon: zuranolone (oral agent, similar mechanism of action)

https://www.fda.gov/news-events/press-announcements/fda-approves-first-treatment-post-partum-depression
Meltzer-Brody S et al. Lancet. 2018 Sep 22;392(10152):1058-1070.

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DEPRESSION AND PERIMENOPAUSE

- Perimenopause = window of vulnerability for the development of both depressive symptoms and major depressive episodes (MDE)
- Risk of depressive symptoms ↑ even in women with no history of MDD
- 1st episode of MDD during this period is less common
- Most MDE will represent recurrent illness
- Data mixed regarding whether women who undergo surgical menopause are at ↑ or ↓ risk for developing depression compared with those who transition through menopause naturally
- Data suggest an ↑ risk of depression in women following hysterectomy with and without oophorectomy

Maki PM et al. Menopause 2018;25:1069-1085;
Maki PM et al. J Womens Health 2018; [Epub ahead of print]

RISK FACTORS FOR PERIMENOPAUSAL DEPRESSIVE SYMPTOMS OR MDE

- **Demographic**
  - Lower SES
  - Younger age at menopause onset
- **Clinical**
  - History of major depression or anxiety disorder
  - More severe/persisting vasomotor symptoms
  - History of postpartum depression/PMDD
  - High BMI
  - Smoking
  - Nulliparity
  - Chronic medical conditions
- **Psychosocial**
  - Stressful life events, marital stress
  - Sleep problems (with or without hot flashes)
  - Negative attitudes towards aging/menopause
  - Lower physical functioning

Vivian-Taylor J & Hickey M. *Maturitas*. 2014;79:142-146.

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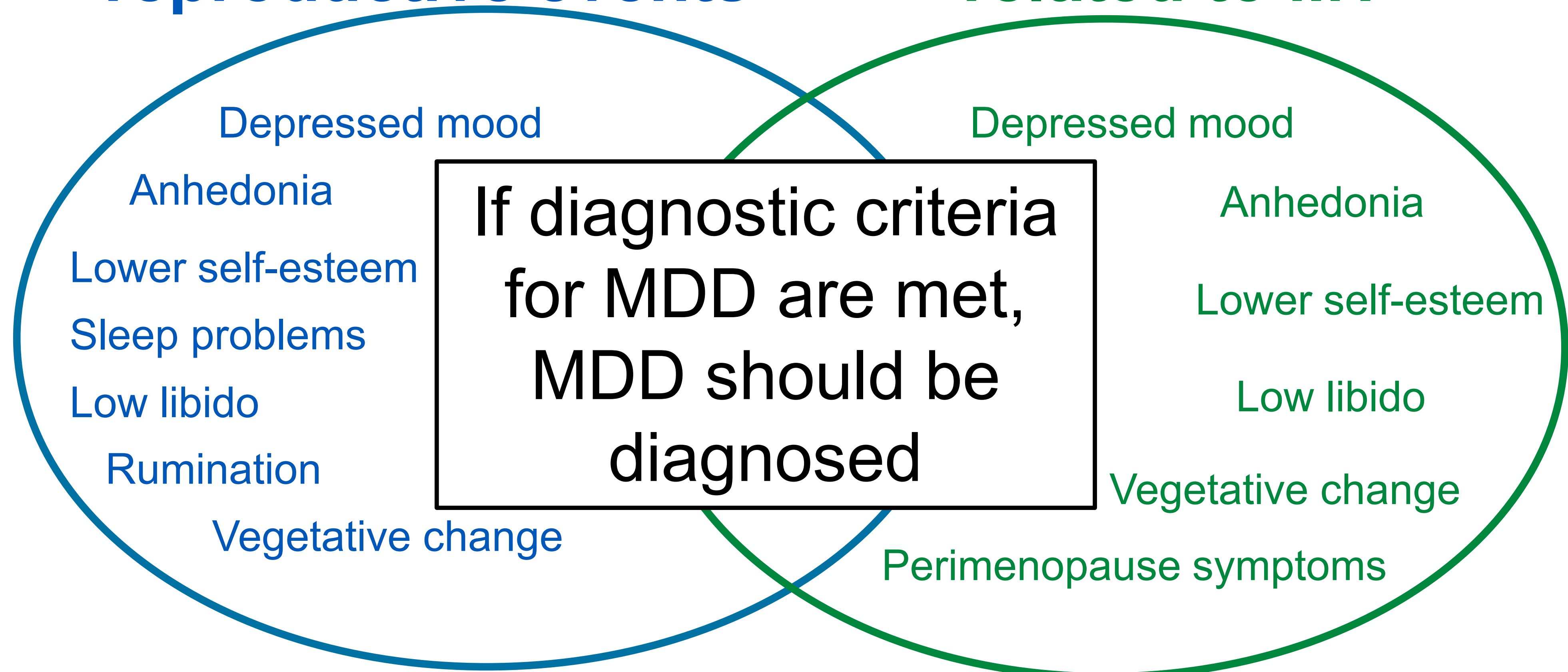
DEPRESSIVE SYMPTOMS DURING MT



Gordon JL & Girdler SS. *Curr Psychiatry Rep*. 2014;16:517.

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ASSESSMENT AND DIAGNOSIS

- Assessment of co-occurring and overlapping menopause and psychiatric symptoms
- Consideration of psychosocial risk factors
- Evaluate for past history of mood disorder
- Evaluate suicidal ideation/safety concerns
- Differential diagnosis during perimenopause:
  - MDD
  - Subsyndromal depression
  - Adjustment disorder
  - Psychological distress
  - Bereavement
  - Depressive disorders associated with bipolar disorder
  - General medical causes of depression

Maki PM et al. Menopause. 2018; 25: 1069-1085.

ASSESSMENT AND DIAGNOSIS

- Identification of menopause stage
- Scales
  - PHQ-9, no menopause-specific mood disorder scale available
- Validated menopause symptom and health-related QOL
  - Menopause Rating Scale (MRS)
  - Menopause-Specific Quality-of-Life Scale (MENQOL)
  - Greene Climacteric Scale
  - Utian Quality-of-Life Scale

MAJOR DEPRESSION ASSOCIATED WITH MT: TREATMENT

- **Antidepressants**
  - First line for moderate and severe depression
- **Psychotherapy**
  - First line when symptoms are less-severe
  - Established adjunct (moderate and severe depression)
- **Alternative/complementary therapies trialed**
- **Role of estrogen replacement is controversial**

Hickey M, Bryant C & Judd F. *Climacteric*. 2012;15:3-9.
Rubinow DR et al. *Depress Anx*. 2015;32:539-549.

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SUMMARY

- Consider the distinct hormonal periods of the female lifecycle and how they may affect presentation
- Tailor evaluation and assessment to these
- Consider and discuss a woman’s conception plans as medications are considered
- Know that there are safe and effective treatments for mood and anxiety disorders across the lifespan

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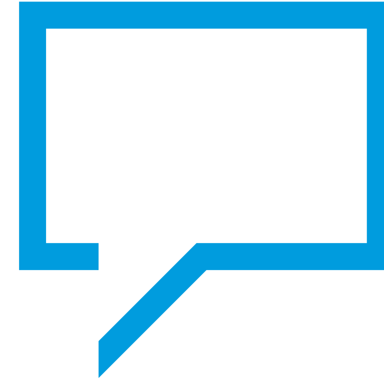

QUESTIONS & ANSWERS

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