Mood Disorders in Women of Child Bearing Age

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OUTLINE

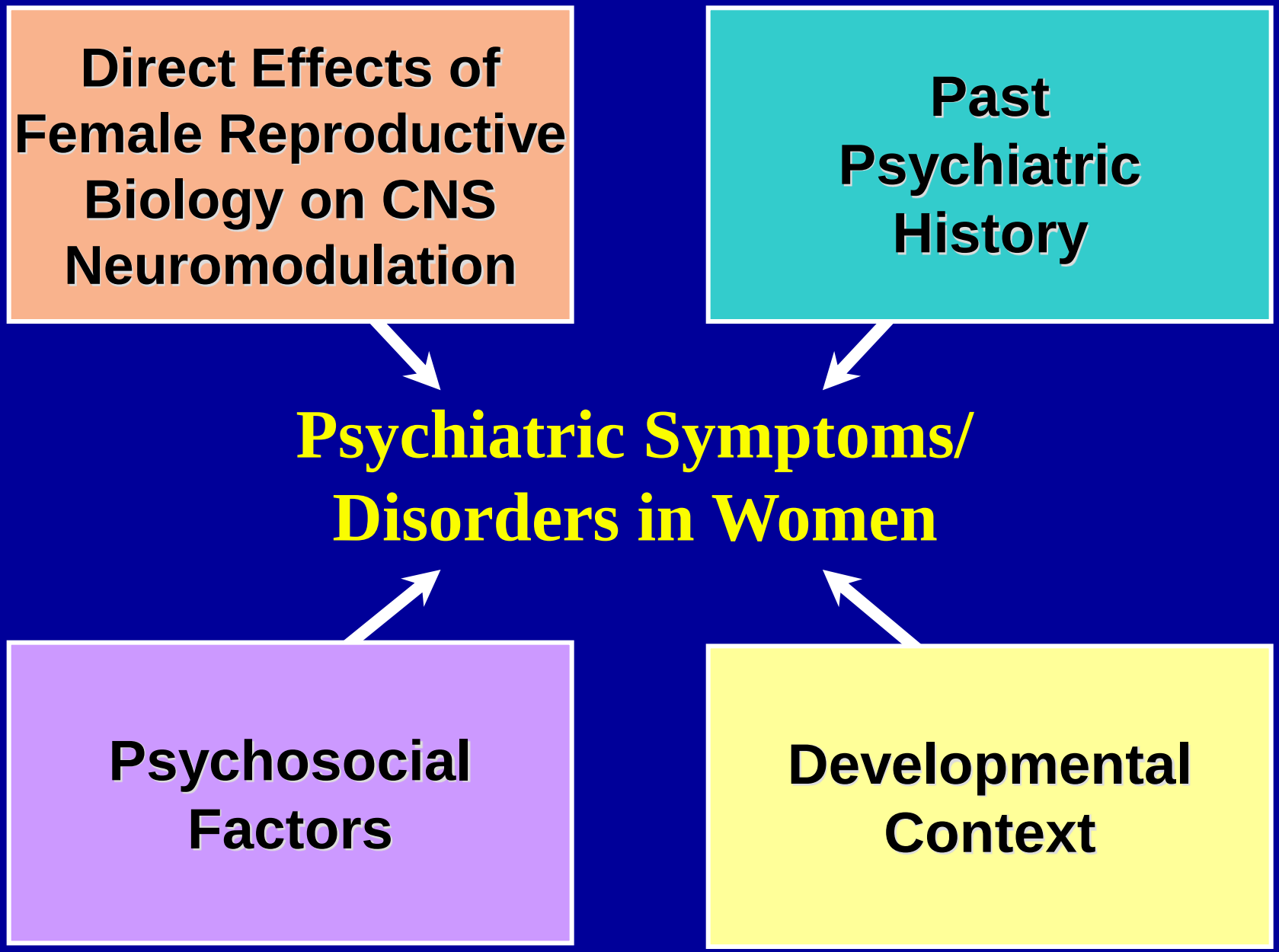
1. Premenstrual Dysphoric Disorder definition, differential diagnosis and treatment
2. Depression in Pregnancy and Postpartum
3. Psychotropic Medications use in Pregnancy and Postpartum

Overview

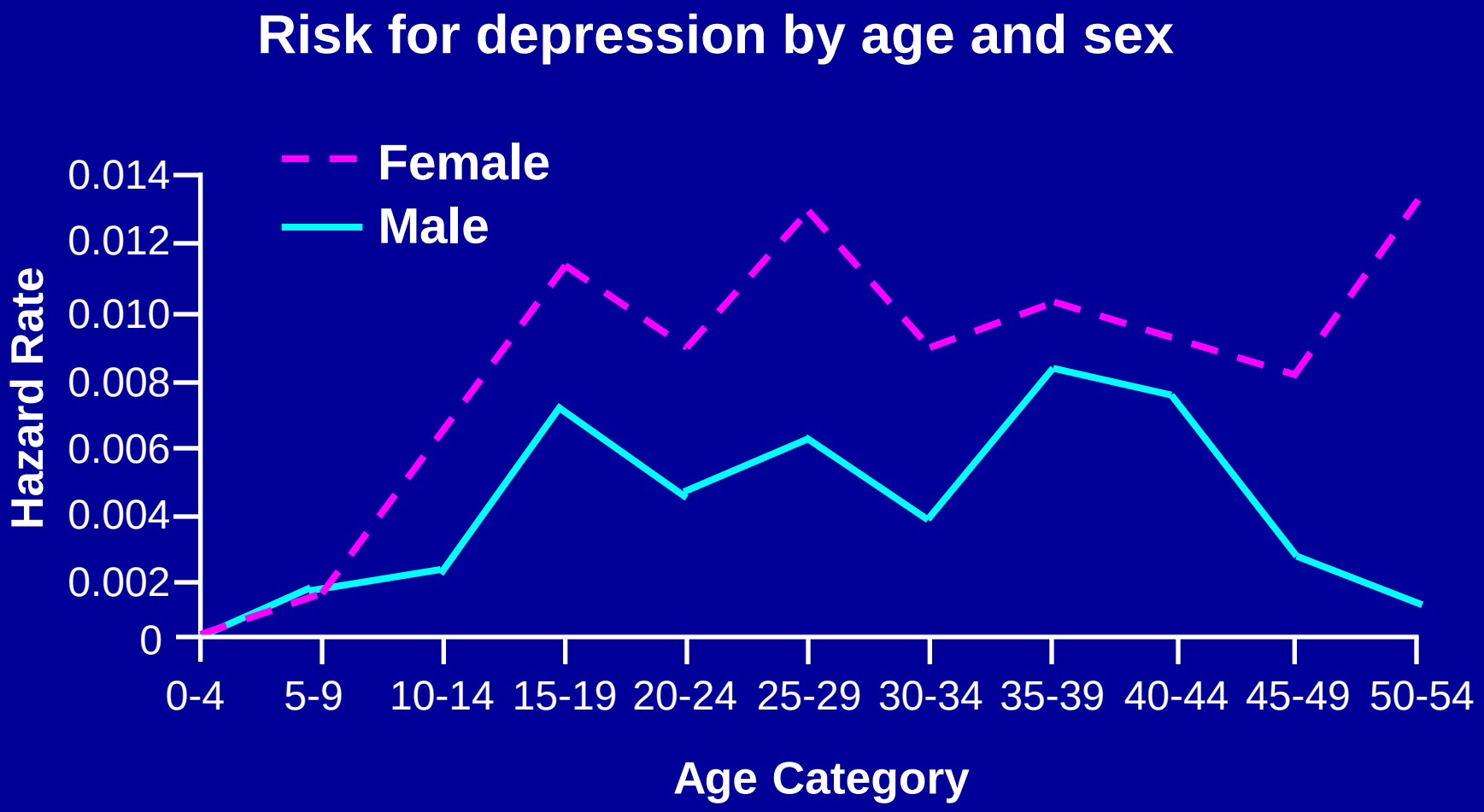
- Women are twice as likely as men to suffer from mood disorders.
- Gender differences exist in prevalence, expression, comorbidity and course of the illnesses.
- Gender differences may be due to psychosocial factors and biological factors.
- Estrogens and progestegins may play a role in psychiatric disorders.

Objectives

- To gain a better understanding of:
  - the relationship between reproductive function and mood.
  - how to effectively manage and treat depression in pregnancy and postpartum.
  - the risks associated with using psychotropic medications during pregnancy and while breastfeeding.

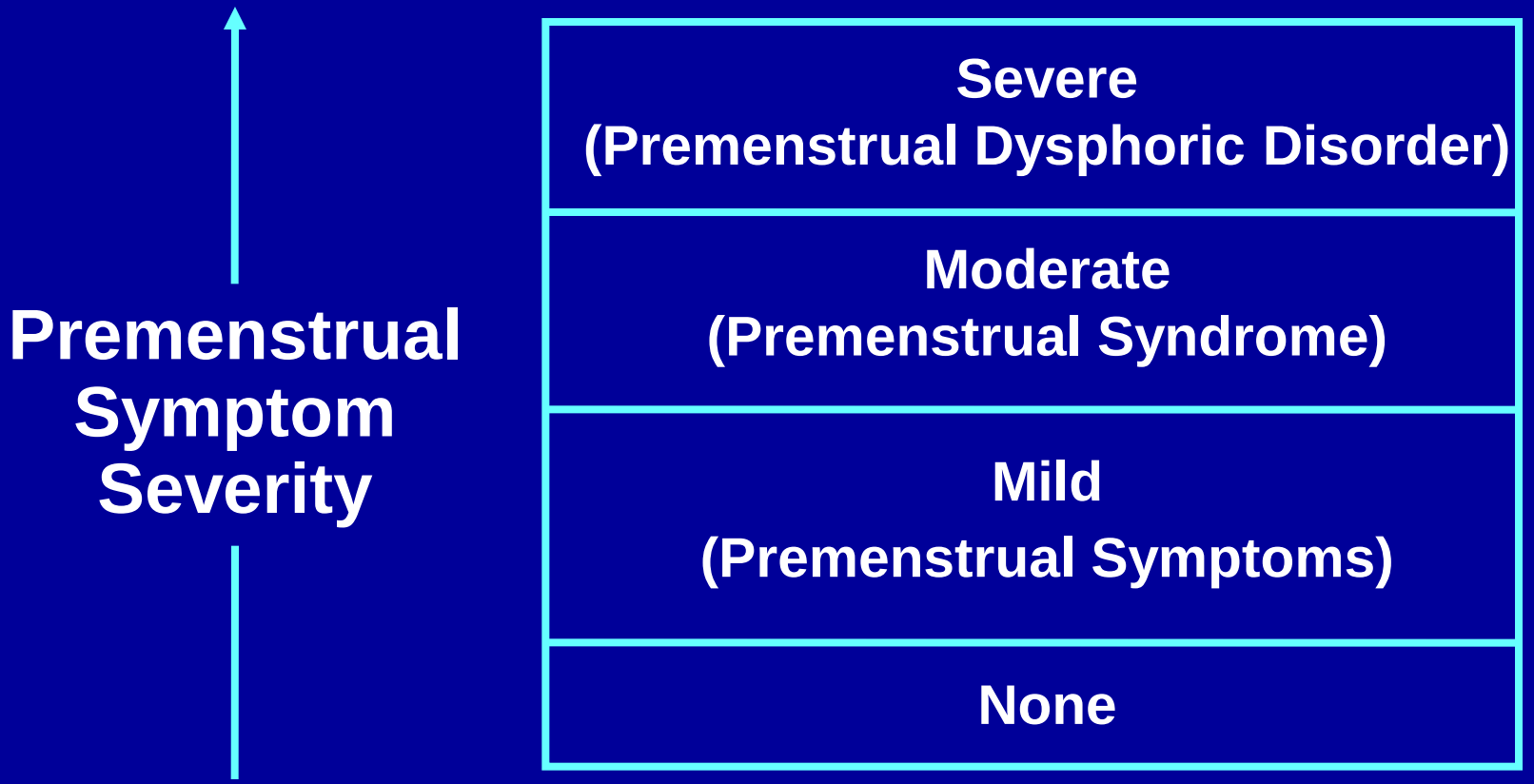

Direct Effects of Female Reproductive Biology on CNS Neuromodulation
Past Psychiatric History
Psychiatric Symptoms/ Disorders in Women
Psychosocial Factors
Developmental Context

Affective Disorders in Women



Kessler R. *J Affect Disord.* 1993;29:85-96

Spectrum of Premenstrual Symptoms[1-3]



1. Johnson S, et al. *J Reprod Med.* 1988;33(4):340-346.
2. Gise L. The premenstrual syndromes. In: Sciarra JJ, Ed. *Gynecology and Obstetrics.* Philadelphia PA: Lippincott-Raven; 1997:6:1-14.
3. ACOG Practice Bulletin. Number 15, April 2000.

PMDD, PMS, and Depression[1,2]

	Mood Symptoms	Functional Impairment	Physical Symptoms	Monthly Periodicity
Premenstrual Dysphoric Disorder (PMDD)	✓	✓ ✓	✓	✓
Premenstrual Syndrome (PMS)	✓	✓	✓	✓
Depression and Dysthymia	✓ ✓	✓ ✓	✓	—

1. Gise L. The premenstrual syndromes. In: Sciarra JJ, Ed. *Gynecology and Obstrics.* Philadelphia PA:Lippincott-Raven; 1997:6:1-14.
2. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.

Diagnostic Criteria for PMDD

Five of the following symptoms (with at least 1 of these*) must occur during the week before menses and remit within days of menses

- Irritability*
- Affective lability* (sudden mood swings)
- Decreased interest in activities
- Difficulty concentrating
- Lack of energy
- Change in appetite, eg, food cravings
- Depressed mood or hopelessness*
- Tension or anxiety*
- Change in sleep
- Feeling out of control or overwhelmed
- Other physical symptoms, eg, breast tenderness, bloating

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.

Diagnostic Criteria for PMDD (Cont'd)

- Interferes markedly with work, school, usual activities, or relationships
- Not an exacerbation of another disorder
- All criteria should be confirmed for 2 consecutive menstrual cycles

American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.

PMDD Distinct from Depression[1]

- Symptoms resolve within days of the onset of menses
- Tied to the menstrual cycle; does not occur in men
- Pregnancy resolves symptoms in PMDD
- Symptoms usually return within one to two cycles after cessation of treatment
- Unique physical symptoms (eg, breast tenderness and bloating)

1. Endicott J, et al. *J Womens Health GendBased Med.* 1999;8:663-679.

Treatment With Selective Serotonin Reuptake Inhibitors (SSRIs)

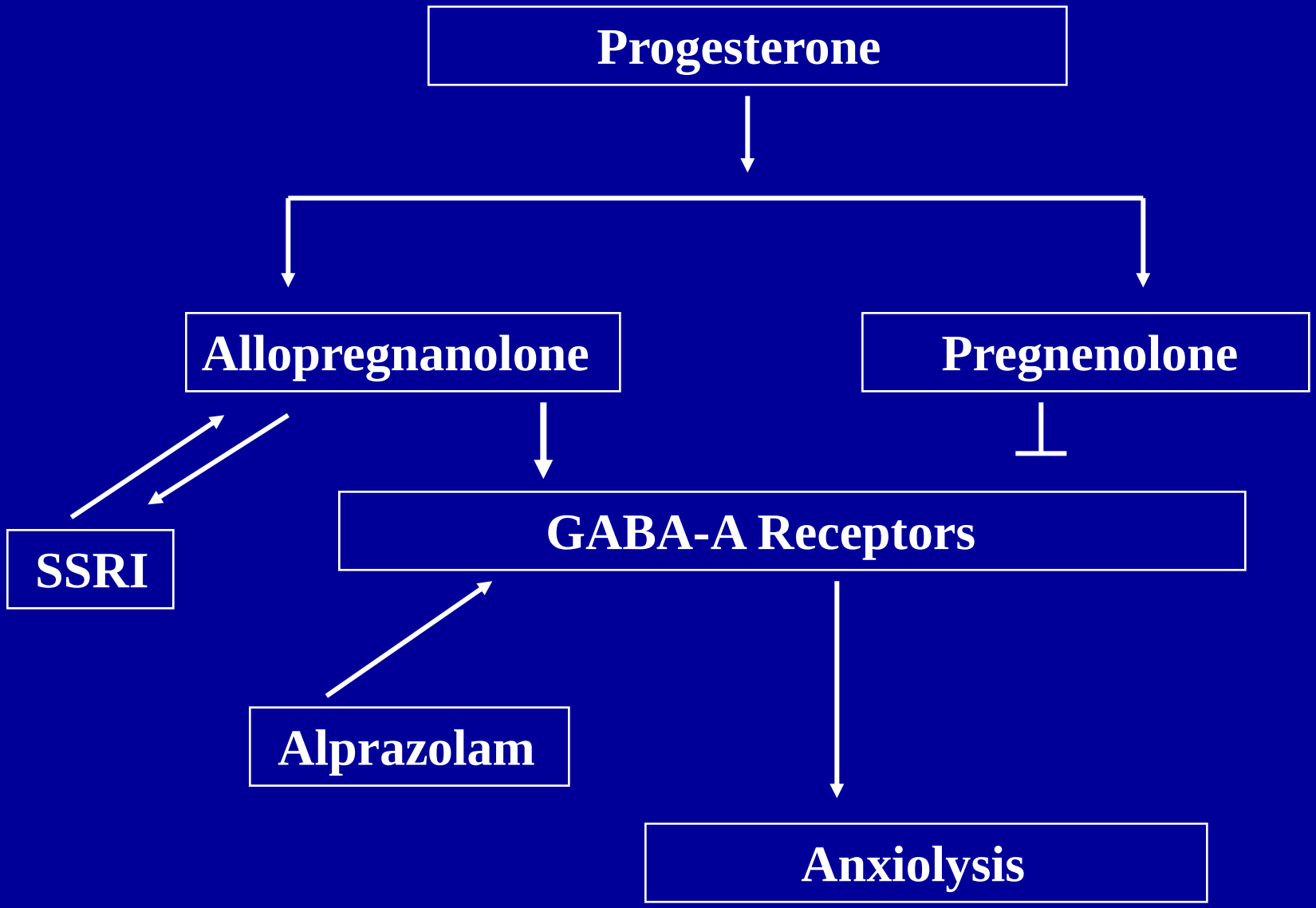
- SSRIs effective in treating depressive and anxiety symptoms of PMDD
  - Fluoxetine (20-40 mg/day) relieves fatigue, irritability, poor concentration, low appetite, and lability
- SSRIs effective in treating depressive and anxiety symptoms of PMDD and reducing premenstrual dysphoria
  - Sertraline (20-50 mg/day)
  - Citalopram (10-20 mg/day)
  - Paroxetine (20-40 mg/day)

Rickels K, et al. *Cur Thes Res.* 1990;48:161-166.
Stone AB, et al. *J Clin Psychiatry.* 1991;52:290-293.
Menkes DB, et al. *BMJ.* 1992;305:346-347.
Woods SH, et al. *Obstet Gynecol.*1992;80:339-344.

Relationship Between PMDD and Sex Steroids

- Recent studies on the TX of PMDD lend strong support to serotonin being key in modulation of sex-steroid-related behavior
- Major argument for involvement of serotonin in PMDD is that SSRIs are very effective in reducing symptoms
- SSRIs' onset of action is shorter (1-2 days) than when used to treat other indications

Eriksson E, et al. *CNS Spectrums.* 2001; 6(2):141-149.


Progesterone
Allopregnanolone
Pregnenolone
SSRI
GABA-A Receptors
Alprazolam
Anxiolysis

Physiologic Responses to Neurosteroid Challenge in Women With PMDD

- Patients with severe PMDD had a reduced sensitivity to GABAergic substances (Sundstrom I, et al, 1997)
- Similarly, panic disorder patients exhibit reduced sensitivity to benzodiazepines (Roy-Byrne PP, et al, 1990)
- Both disorders are treated with SSRIs

SSRIs and Neurosteroids

- Fluoxetine and paroxetine selectively change rat brain steady-state levels of ALLO and 5alpha-DHP (Guidotti A, et al, 1996; Uzunov DP, et al, 1996)
- Fluoxetine and fluvoxamine treatment of major depression for 8-10 weeks increased ALLO content in CSF (Uzunova A, et al, 1998)

Menstrual Cycle Effects on Neurosteroid-Serotonergic Interaction Conclusions

- Baseline ALLO levels significantly increased in women with PMDD in the ovulatory and luteal phases of the menstrual cycle
- Controls did not manifest expected ovulatory and luteal phase increase in ALLO

Rasgon NL, et al. *Eur J Endocrinol*, 2001.

Conclusions (Cont'd)

- Increased levels of ALLO in response to 5-HT challenge support the postulate that SSRIs exert their anxiolytic effects through modulation of neuroactive steroids
- PMDD is a model of interactions between reproductive and serotonergic systems in humans

Rasgon NL, et al. *Eur J Endocrinol* 2001.

Pregnancy and PMDD

- 50% of pregnancies are unplanned[1]
- Treatment of PMDD should take into account planning for and the possibility of pregnancy[2]

1. Henshaw S. *Family Plann Perspect.* 1998;30(1):24-29, 46.
2. Cohen L. *Depression and Anxiety.* 1998;8:18-26.

Major Depression During Pregnancy

- Are pregnant women protected against relapse
  or new onset of major depression?

Relapse of Major Depression During Pregnancy* (N=32)

Medication condition	Trimester relapsed I	II	III	Total relapsed	Total not relapsed
Discontinued (n=25)	60% (n=15)	8% (n=2)	0% (n=0)	68% (n=17)	32% (n=8)
Discontinuation Attempt/Change (n=7)	57% (n=4)	29% (n=2)	14% (n=1)	100% (n=7)	0% (n=0)
Total (N=32)	59% (n=19)	13% (n=4)	3% (n=1)	**75% (n=24)**	25% (n=8)

*Euthymic pregnant patients with histories of depression who discontinued or attempted antidepressant discontinuation or modification.

Cohen LS, et al, 2000 (submitted).

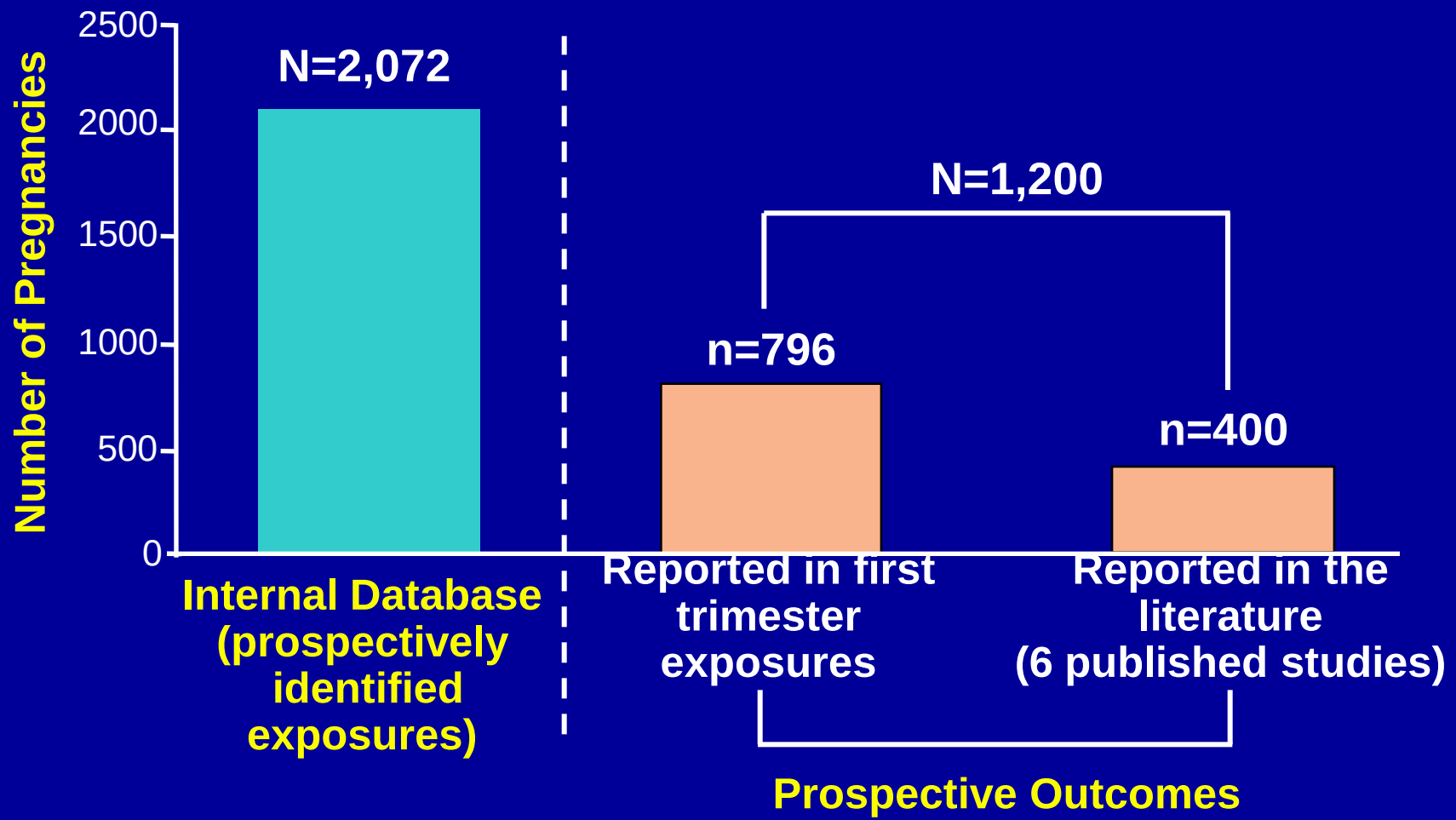
Psychotropic Drug Use in Pregnancy

- Drugs used when risk to mother and fetus from disorder outweighs risks of pharmacotherapy
- Optimum risk/benefit decision for psychiatrically-ill pregnant women
- Patients with similar illness histories make different decisions regarding treatment during pregnancy
- No decision is risk-free

Goal of Risk/Benefit Assessment

- To limit exposure to **either** illness or treatment, and help patient decide which exposure path poses the **least risk**

Pregnancy Databases with Fluoxetine HCl*



*Goldstein D, et al. *Hum Psychopharmacol Clin Exp.* 1999;14:319-324.

New Antidepressants During Pregnancy (Cont'd)

- SSRIs
  - Sertraline (n=147), paroxetine (n=97), fluvoxamine (n=26)
  - N=270 total
- No higher rates of major malformations compared to nonexposed controls
- Medications in same family may have different reproductive safety profiles

Kulin NA, et al. *JAMA*. 1998;279:609-610.

Depression During Pregnancy: Treatment Implications

- To discontinue or maintain antidepressant treatment: consider maternal illness history, patient wishes, and available reproductive safety data
- Consider risk of relapse and risk of untreated disorder

Steer, Orr, and Miller, *Epidemiologic Reviews.* 1995.
Cohen LS, et al. *APA.* 2000.

Depression During Pregnancy: Treatment Implications

- To switch antidepressant before or during pregnancy
  - Pregravid: switch to safest treatment that affords efficacy
  - During pregnancy: avoid switching compounds without previous history of response
- Maintain treatment across labor and delivery

Breastfeeding and Psychotropic Drug Use

- All psychotropic medications found in breast milk
- Concentrations of medications in breast milk vary: milk/plasma ratio poor indicator of exposure
- Majority of clinical practice guided by case reports and clinical impression vs systematic data

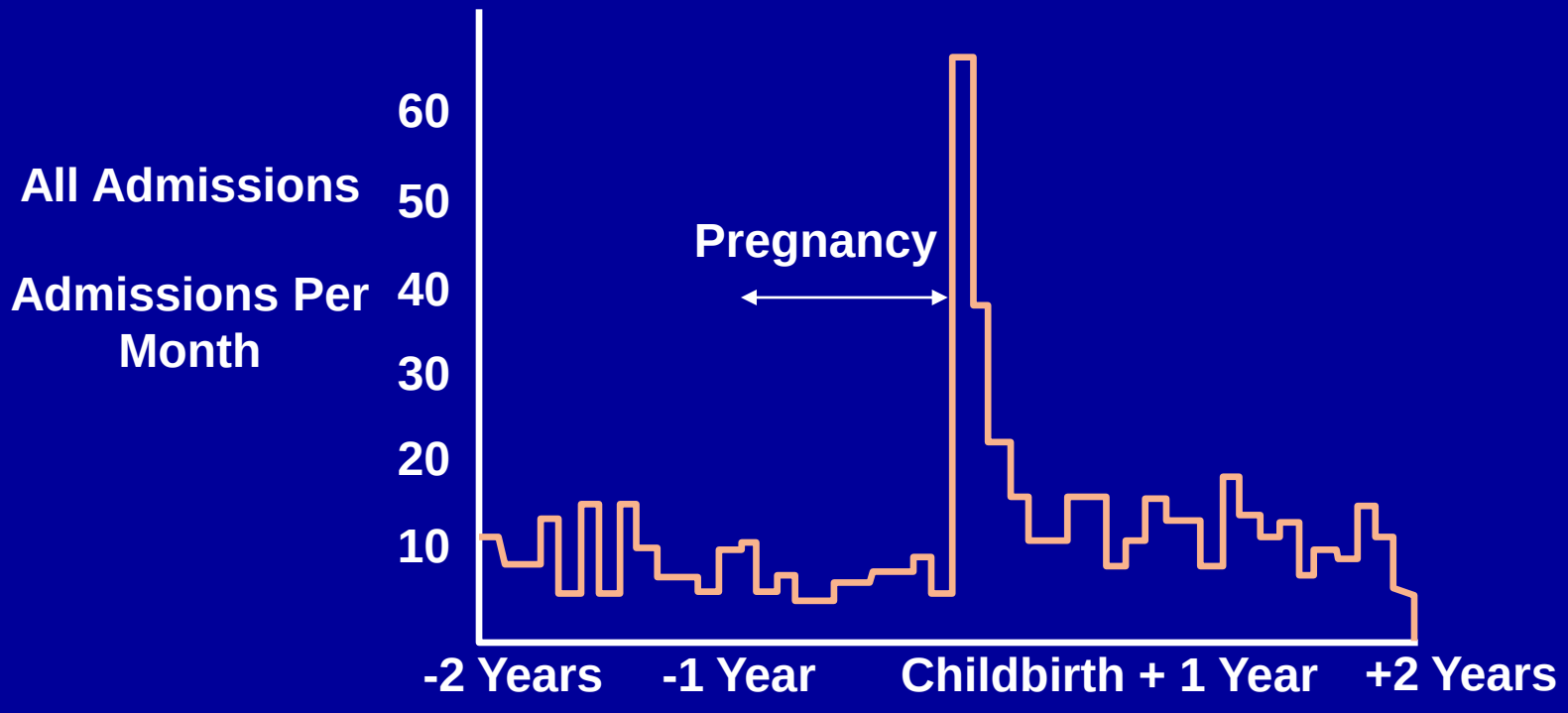
Wisner KL. *Am J Psychiatry*. 1996;153:1132-1137.

Llewellyn A, Stowe ZN. *J Clin Psychiatry*. 1998;59:41.

Breastfeeding and Psychotropics Conclusions

- Limited role for routine infant-serum monitoring
- Long-term impact of trace levels of medication unknown
- No antidepressant safer than another

Postpartum Psychiatric Hospitalizations



Kendell RE, et al. *Br J Psychiatry*. 1987;150:662.

Postpartum Mood Disorders

Disorder	Incidence (%)	Treatment	Presentation
Postpartum blues	26 to 85	Support/reassurance	80% resolve by week 2; 20% evolve to PPD
Postpartum depression	10 to 20	Antidepressant & psychotherapy	Major depression often with obsessions
Postpartum psychosis	0.2	Hospitalization; antipsychotics; mood stabilizers; benzodiazepines; antidepressants; ECT	Early onset usually by day 3; mixed/rapid cycling; risk of infanticide

PPD = postpartum depression.

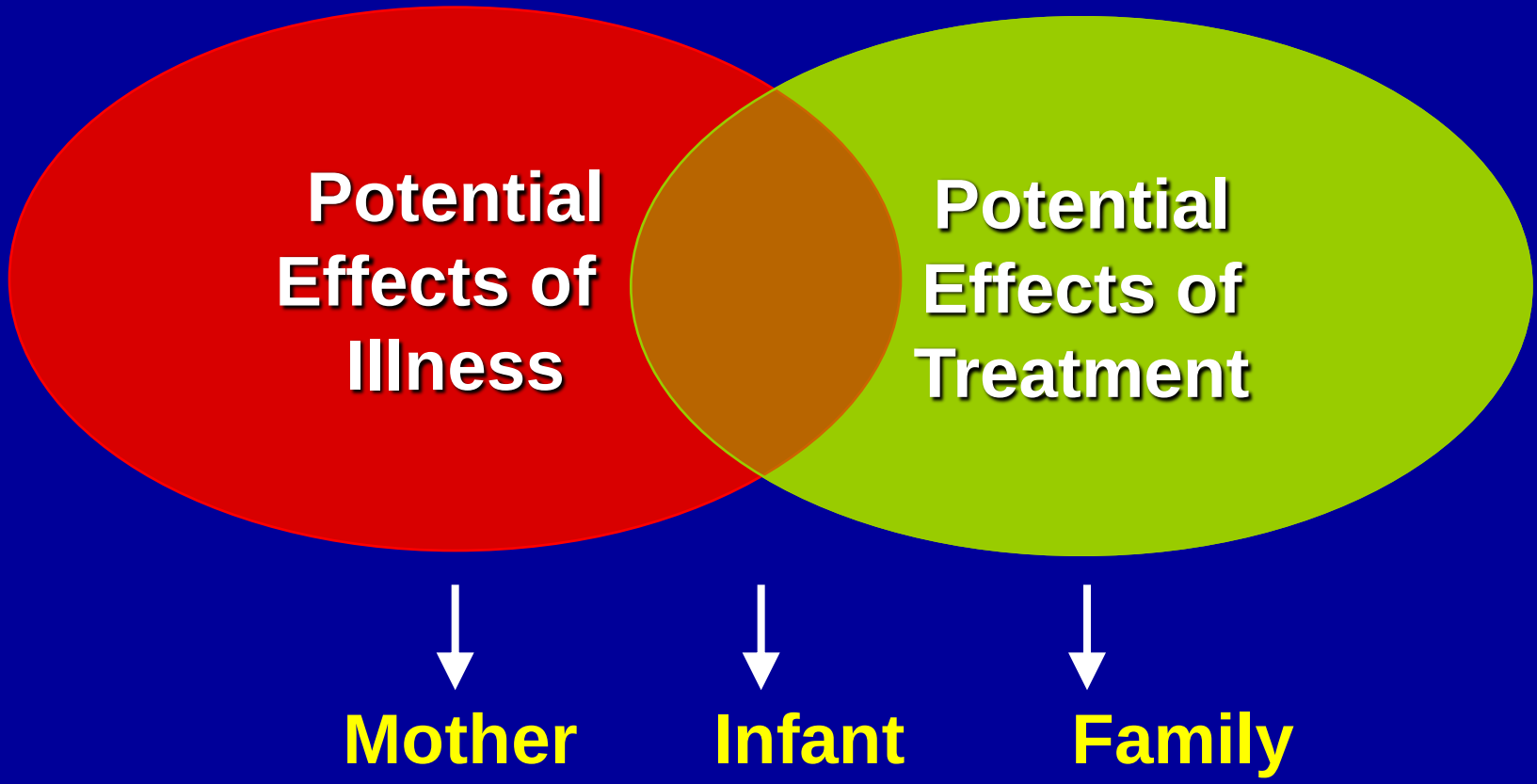
Bright DA. *Am Fam Physician*. 1994;50:595.
Suri RA, Burt VK. *J Pract Psychiatry Behav Health*. 1997;3:67.

Postpartum Depression

- Onset 1st month postpartum
- Often identified after 1st postpartum month
- ↑ Depression risk:
  - Past mood disorder
  - Past postpartum disorder
  - Depression during pregnancy
  - Poor support system

Cox JL, et al. *Br J Psychiatry*. 1993;163:27.
Suri RA, Burt VK. *J Pract Psychiatry Behav Health*. 1997;3:67.

Treatment of Depression During Lactation: Risk-Benefit Assessment



Treatment Strategies for Breast-feeding Women

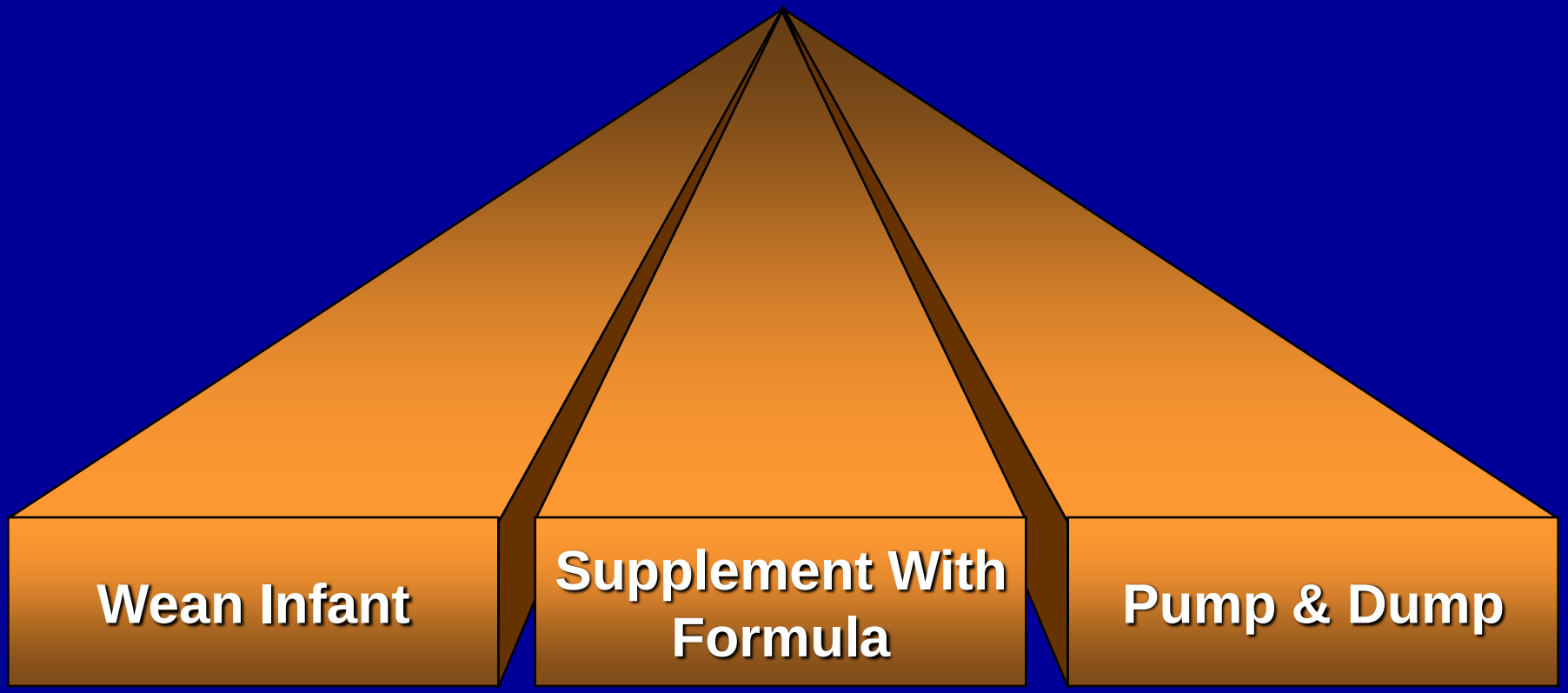
- Nonpharmacological interventions
  - Psychotherapy (interpersonal, CBT)
  - Stress reduction modalities
- Psychopharmacological treatment

Managing Postpartum Depression in Breast-Feeding Women

- Baseline assessment of infant
- Monitor infant clinical status
- Use lowest effective dose
- SSRIs appear to be safe and effective
- Consider infant serum levels

Burt VK, et al. *Am J Psychiatry.* 2001. In press.

Breast-Feeding: Minimizing Infant Exposure



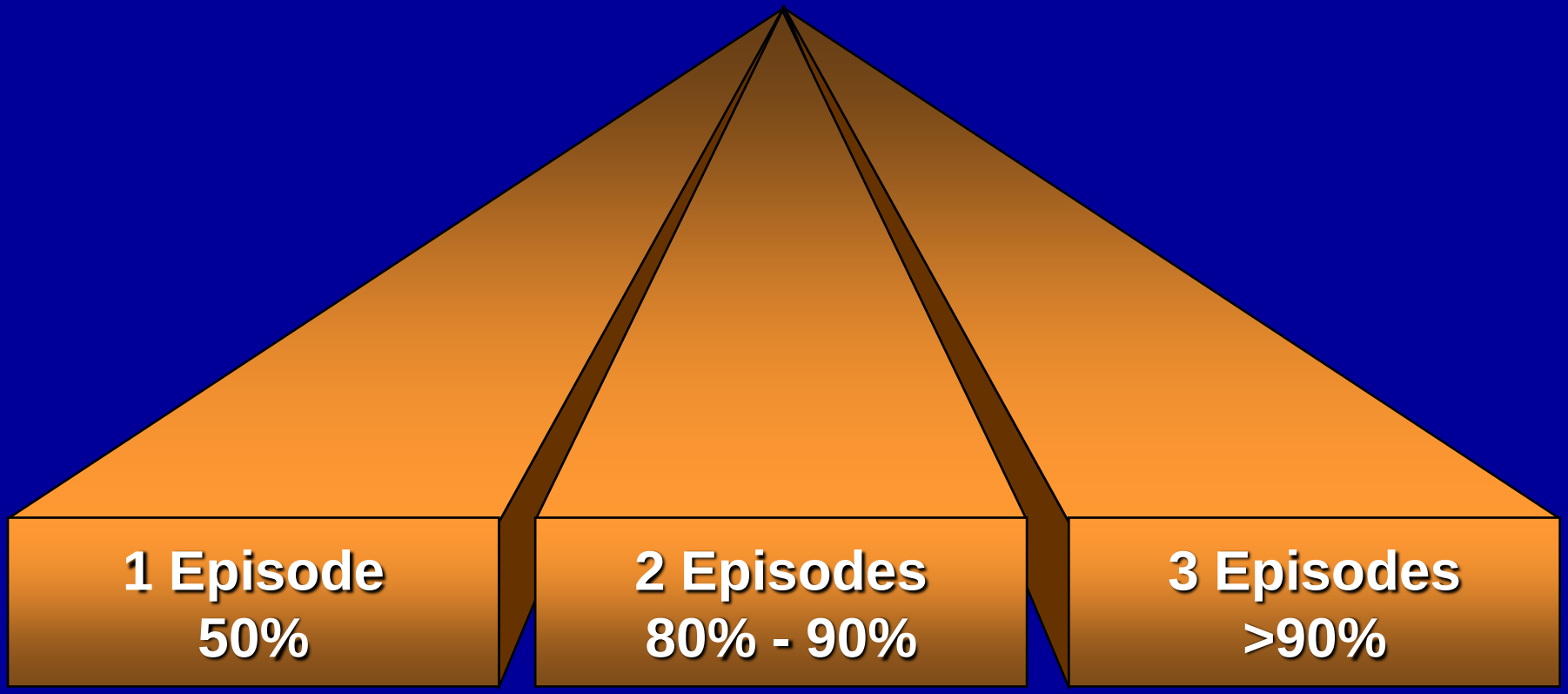
Recurrent Depression: Treatment Implications

- Continue antidepressant for first 4-9 months
- Continue antidepressant indefinitely after ≥3 episodes or 2 episodes in patients with risk factors

Depression Guideline Panel. *Depression in Primary Care, Volume 2: Treatment of Major Depression*. Clinical Practice Guidelines, Number 5. 1993.

Schulberg HC, et al. *Arch Gen Psychiatry*. 1998;55:1121.

Depression: Recurrence Risks



Angst J. *Psychopathology*. 1986;19(suppl 2):47.
Kupfer DJ. *J Clin Psychiatry*. 1991;52(suppl 5):28.

5 Questions

1. Do gender differences exist in prevalence, expression, comorbidity and course of the illnesses?
2. What is the differential diagnosis and treatment of premenstrual dysphoric disorder?
3. What are some of the risks associated with using psychotropic medications during pregnancy and while breastfeeding?
4. Are pregnant women protected against relapse or new onset of major depression?
5. What are the risk factors for postpartum depression?