ProjectTEACH

Treatment of Unipolar Depression and Anxiety in Perinatal Patients

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Disclosures

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Poll

- When your patient with recurrent MDD and GAD (treated with fluoxetine 40mg and mirtazapine 15mg) becomes pregnant, do you:
- a) Advise that both medications should be rapidly discontinued and not restarted until 2nd trimester.
- b) Advise that both medications should be discontinued during pregnancy and not restarted until she is done breastfeeding.
- c) Advise to stop fluoxetine and mirtazapine and switch to sertraline.
- d) Call Project TEACH for a perinatal psychiatry consultation before discussing with the patient.

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Untreated perinatal mental health disorders are associated with adverse maternal, obstetrical, infant and child developmental outcomes

- Decreased maternal functioning (Field, T, 2010)
- Psychosis, suicidal ideation, homicidal ideation and suicide attempt are psychiatric emergencies that lead to psychiatric hospitalization, maternal death (Rodriguez-Cabezas et al, 2019)
- Bidirectional relationship between depression and gestational diabetes mellitus (Fischer et al, 2023)
- Preterm labor (Bansil P et al, 2010) ,preterm birth (Grigoriadis S et al, 2013), stillbirth/neonatal death and hypertensive disorders of pregnancy (Staub et al, 2012, Thombre et al, 2015, Delanerolle et al, 2022)
- Increased requirement for surgical delivery interventions (Wang SY & Chen CH, 2010) and cesarean delivery (Bansil P et al, 2010)
- Inadequate maternal-infant bonding prenatally and post-delivery (Rossen et al, 2016; Betcher et al, 2020, Dagher et al, 2021)
- Lactation failure or unplanned weaning (Dennis CL & McQueen K, 2009; Stuebe AM et al, 2014)
- Impaired child cognitive development (Tuovinen S et al, 2018), behavioral and emotional development (Leis JA et al, 2014; Pearson RM et al, 2013)
- Impaired child brain development/antenatal stress from mental illness is associated with accelerated development of offspring neural networks via fetal (developmental) programming (Schinost D et al, 2016; Rotem-Kohavi, N et al, 2020)

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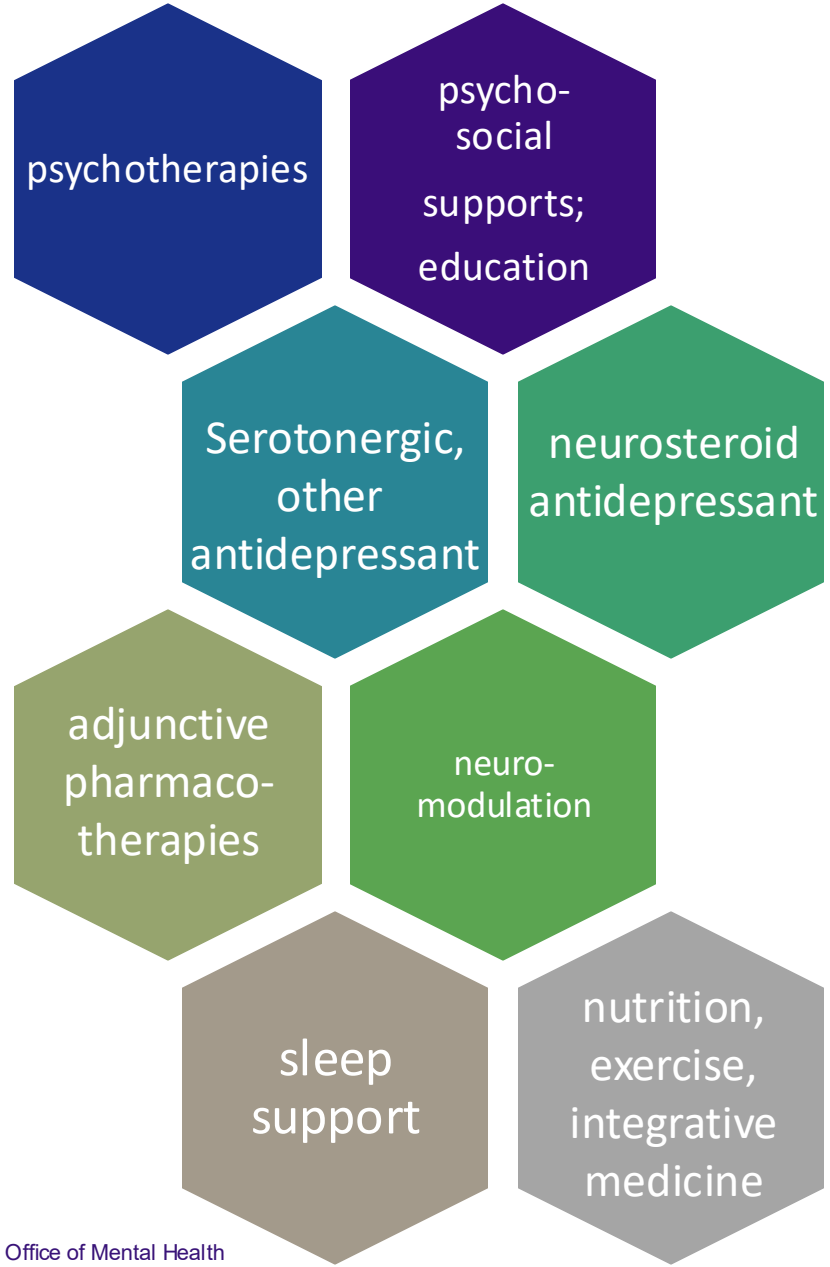
Consider all therapeutic tools in our toolbox to treat PND



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Perinatal depression therapeutics

- Psychotherapies: **monotherapy for mild-moderate** unipolar perinatal depression
  - Interpersonal psychotherapy (IPT) (Reay R et al, 2012; Grote NK et al, 2010; Spinelli MG & Endicott J 2003; O'Hara MW et al, 2000; Klier CM et al, 2001; Stuart S & O'Hara MW 1995)
  - Cognitive behavioral therapy (CBT) (Milgrom J et al, 2016; Milgrom J et al, 2015; Ammerman RT et al, 2013; Le HN et al, 2011)
  - Mindfulness-based CBT (Dimidijian S et al, 2016; Dimidijian S et al, 2014; Goodman JH 2014)
  - Peer support and group psychotherapies (Dennis CL et al 2009; Dennis CL 2003; Chen CH et al 2000; Honey KL 2002; Milgrom et al 2005)

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Perinatal depression and anxiety therapeutics

- Serotonergic antidepressants (SSRI, SNRI, etc.): **moderate/severe** unipolar perinatal depression, FDA approved for major depression
  - *No* randomized, placebo-controlled trials (RCT) of antidepressants for antenatal depression
  - Meta-analysis of 11 postpartum RCTs showed that there may be a benefit of SSRIs over placebo in response (55% versus 43%; pooled risk ratio (RR) 1.27, 95% CI 0.97 to 1.66) and remission (42% versus 27%; RR 1.54, 95% CI 0.99 to 2.41) at 5 to 12 weeks' follow-up. (Brown JVE et al, Cochrane Database Syst Rev, 2021)
  - Antepartum vs postpartum use is associated with different risks
  - Treatment approach: titrate until efficacy/tolerability then treat acute episode at that dose -> once reach euthymia, continue treatment (continuation phase) for 4-9 mo. to prevent relapse.
  - Often best to combine with psychotherapies

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Antidepressant dosing for perinatal depression and anxiety (see drug labels at: https://dailymed.nlm.nih.gov for full prescribing info)

Medication	Indication	Starting dose	Usual dosage range
Fluoxetine	MDD, GAD, OCD	10 mg	10 – 80 mg daily
Sertraline	MDD, GAD, OCD	25 mg	50 – 200 mg daily
Escitalopram	MDD, GAD	5 mg	5-20 mg daily
Citalopram	MDD, GAD	10 mg	10-40 mg daily
Paroxetine	MDD, GAD, OCD	10 mg	10 – 50 mg daily
Venlafaxine	MDD, GAD	37.5 mg	75-225 mg daily
Bupropion XL	MDD w/o anxious distress Nicotine dependence	150 mg	150 – 450 mg daily
Mirtazapine	MDD with nausea	7.5 mg	15 -45 mg nightly

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Pregnancy-associated changes in medication pharmacokinetics

- **Maternal physiologic changes affect medication pharmacokinetics** (Ke AB et al, 2014)
- Absorption slows
- Distribution expands/increases
- Excretion increases (renal)
- Metabolism changes

1st trimester: first day of LMP to 13 6/7
2nd trimester: 14 0/7 to 27 6/7
3rd trimesters: 28 0/7 to 40 7/8

- **P450 inhibition by sex hormones of pregnancy-could ↓ metabolism**
- 1A1/2 is reduced by 65-70% late preg.; 2C19 is reduced by 50% in 2nd/3rd trimester

- **P450 induction by sex hormones of pregnancy-could ↑ metabolism**
- 3A4 induced by 100% (progesterone effect); 2D6 generally induced by 20-50%; 2C9 is induced by 30-60%

- **Phase II UGT glucuronidation is increased** by rising estradiol of pregnancy; max increase seen by mid-gestation then stable until delivery (impacts lamotrigine)

(Deligiannidis KM et al 2014)

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Risk of fetal malformation with antenatal serotonergic antidepressant use

- Birth defects affect one in every 33 infants (about 3%) born in the US each year https://www.cdc.gov/ncbddd/birthdefects/data.html
- mixed results: small absolute risk increase of cardiac malformations with OR of 1.28 (CI:1.17-1.41) for any antidepressant, OR of 1.69 for SNRI and 1.25 for SSRI (De Vries C, 2021)
- possible ↑ risk of Chiari I malformation (Knickmeyer RC et al, 2014)
- small increased RR of overall major congenital malformations (RR=1.1, CI: 1.03-1.19) with SSRI use, however no significantly increased risk was observed when restricted to women with a psychiatric diagnosis (RR 1.04, 95% CI 0.95 to 1.13) (Gao SY et al 2018)
- SNRI, NRI, other AD: most studies indicate no increased risk of congenital malformations (Furu et al 2016; Cole et al. 2007; Chun-Fai-Chan et al. 2005; Djulus et al. 2006; Lennestal and Kallen 2007; Einarson et al. 2001)
- TCAs : no evidence of increased risk of cardiac malformations (De Vries C, 2021)
- Perinatal use of MAOIs have not been studied

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Risk of adverse birth outcomes with antenatal serotonergic antidepressant use

- US preterm birth rate =8.67% https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm; https://www.cdc.gov/nchs/data/nvsr/nvsr73/nvsr73-01.pdf

- Prenatal antidepressant exposure associated increased risk of moderate-to-late preterm birth (32-37 weeks, aOR=1.43) and moderately low birthweight (1500-2499 g, aOR=1.28) vs. an antidepressant discontinuation group, no difference in risk for PPHN (Rommel AS et al, 2022; Rommel AS et al, 2023)

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Risk of neonatal complications with antenatal serotonergic antidepressant use

Postnatal adaptation syndrome (PNAS): in 30% with 13.7% admitted to NICU vs. 8.2% gen pop (Norby U et al, 2016)

- infant irritability, abnormal crying, tremor, lethargy, hypoactivity, decreased feeding, tachypnea, respiratory distress, irritability, tachypnea, hypothermia, and hypoglycemia
- severity and length are impacted by multiple factors including dose, timing and duration of exposure and SSRI pharmacology including half-life, presence of active metabolites, and maternal and infant hepatic cytochrome P450 isoenzyme genotype, etc.
- most often been reported after exposure to paroxetine, fluoxetine and venlafaxine
- Symptoms can last through 1st month postnatal life; discontinuing 3rd trimester AD use does not reduce PNAS risk (Salisbury AL 2016)

Persistent pulmonary HTN of the newborn:

- reduced length of gestation and premature birth has been associated with increased risk of PPHN
- present within twelve hours of birth with cyanosis and mild respiratory distress and can develop severe respiratory failure requiring intubation and mechanical ventilation
- 1.9/1000 gen pop vs. 2.9-3.5/1000 w late gestation SSRI use (Becker M et al, 2016)
- NNH=285 for 1 infant to develop PPHN with late gestation SSRI exposure (Norby U, 2016)

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Risks to long-term child neurodevelopment with antenatal serotonergic antidepressant use

- 37% increased risk of speech/language disorders with antenatal SSRI exposure (vs. unmedicated PND) and 28% increased risk in PND-exposed infants (vs. unexposed) (Brown AS et al 2016)

- risk for offspring to develop future depressive disorders by age 15; 8.2% with SSRI risk vs. 1.9% PND exposure alone (Malm H et al, 2016)

- no increased risk of Autism spectrum disorders or ADHD (Malm H et al, 2016; Rommel AS et al, 2020; Vega ML et al, 2020), cognition, behavior, IQ, motor development, speech, or language (Rommel AS et al, 2020)

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Postpartum depression therapeutics

First FDA-approved medication for **moderate-severe postpartum depression** (postpartum use only) was **Brexanolone,** a neuroactive steroid antidepressants, however as it was only available IV and due to success of Zulranolone, it is now discontinued.

Zuranolone is a synthetic analog of allopregnanolone and is a PAM of synaptic and extrasynaptic GABA-A receptors

- First oral FDA-approved PPD treatment in 2023
- PK/PD profile consistent with once daily oral dosing (50mg PO qPM x 14 days only)
- Rapid-acting antidepressant effects at day 15, as early as day 3, maintained through day 45 (Deligiannidis K et al 2021, and 2023)
- **Boxed warning** for impaired ability to drive or engage in other hazardous activities due to CNS depressant effects
- May be used alone or as an adjunct to oral antidepressant therapy, but avoid other CNS depressants
- Schedule IV
- Take with fat-containing food around 8pm

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Dosing for postpartum depression

(see https://dailymed.nlm.nih.gov for full prescribing info)

Medication Generic	Medication Trade	Recommended dosage
Zuranolone	Zurzuvae	50mg PO qPM x 14 days, if excessive sedation reduce dose to 40mg PO qPM; total course not to exceed 14 days treatment

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Table 2 Adverse Reactions that Occurred in ≥2% of Patients with PPD Treated with 50 mg of ZURZUVAE and Greater than in Patients Treated with Placebo (Study 1)

Adverse Reaction	Placebo (N=98) (%)	50 mg of ZURZUVAE (N=98) (%)
Somnolence[1]	6	36
Dizziness[2]	9	13
Diarrhea	2	6
Fatigue[3]	2	5
Urinary tract infection	4	5
Memory impairment	0	3
Abdominal pain[4]	0	3
Tremor	0	2
Hypoesthesia	0	2
Muscle twitching	0	2
Myalgia	0	2
COVID-19	0	2
Anxiety	1	2
Rash	1	2

[1] somnolence includes sedation and hypersomnia

[2] dizziness includes vertigo

[3] fatigue includes asthenia - all data from https://dailymed.nlm.nih.gov/dailymed/index.cfm

TABLE 2 MOST COMMON TREATMENT-EMERGENT ADVERSE EVENTS: INCIDENCE IN PLACEBO-CONTROLLED CLINICAL TRIALS

Percentage of Patients Reporting Event		
	Major Depressive Disorder/Other*	
Body System/Adverse Event	Sertraline hydrochloride	Placebo
	(N=861)	(N=853)
Autonomic Nervous System Disorders		
Ejaculation Failure(1)	7	<1
Mouth Dry	16	9
Sweating Increased	8	3
Centr. & Periph. Nerv. System Disorders		
Somnolence	13	6
Tremor	11	3
Dizziness	12	7
General		
Fatigue	11	8
Pain	1	2
Malaise	<1	1
Gastrointestinal Disorders		
Abdominal Pain	2	2
Anorexia	3	2
Constipation	8	6
Diarrhea/Loose Stools	18	9
Dyspepsia	6	3
Nausea	26	12
Psychiatric Disorders		
Agitation	6	4
Insomnia	16	9
Libido Decreased	1	<1

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Use of antidepressants during lactation

World Health Organization and The American Academy of Pediatrics recommends that children are breastfed for their first 2 years of life.

The American Academy of Family Physicians and the American Dietetic Association recommend exclusive breastfeeding for the first 6 months of life and breastfeeding with complementary food from 6 months until at least 12 months of age and as long thereafter as desired.

Antidepressant use should not discourage women from breastfeeding; overwhelming benefits of breastfeeding usually outweigh risks of medication use in women with unipolar depression +/- anxiety

- PND is associated with ↓ breastfeeding duration and ↑ breastfeeding difficulties (Dennis CL 2009)
- Relative infant doses (RID) less than 10% of maternal dosage are generally acceptable per FDA
- Side effects to watch for: sedation, irritability, poor feeding, GI upset

- The National Library of Medicine at the NIH maintains the Drugs and Lactation Database (LactMed) found at: https://www.ncbi.nlm.nih.gov/books/NBK501922/
  - This useful database is maintained by a peer review panel who reviews scientific data to assure validity and currency. It includes information on levels of drugs in breastmilk and infant blood and the possible adverse effects in the nursing infant.

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Infant exposure to antidepressants via breastmilk

Relative infant doses less than 10% of maternal dosage are acceptable per FDA and AAP

Antidepressant	RID %
Fluoxetine	<14
Fluxovamine	<2
Citalopram	3-10
Escitalopram	3-6
Paroxetine	0.5 -3
Sertraline	0.5 -3
Duloxetine	<1
Venlafaxine	6-9
Desvenlafaxine	5.5 -8.1
Bupropion	2
Mirtazapine	0.5-3
Amitriptyline	1.9-2.8
Imipramine	0.1 – 4.4

Zuranolone: <1

Adapted from Chad et al., 2013

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MDE with peripartum onset treatment considerations

- **Psychotherapies:** consider use in all patients

Consider SSRI/SNRI

- Current **moderate/severe** symptoms, patient preference
- Patient presents to treatment in pregnancy
- Previous response/remission with acceptable tolerability
- Mild/moderate functional impairment
- Engaged in psychotherapy; past response/remission with psychotherapy
- Low risk for suicide/infanticide/homicide
- Active alcohol, opioid, sedative, hypnotic or anxiolytic use disorder
- Patient prefers not to use effective contraception required of zuranolone treatment (for 21d)

Consider Zuranolone

- Current **moderate/severe** symptoms
- Failed AD during gestation or prior MDEs
- Patient is postpartum and not trying to conceive
- Partial response to maximally dosed AD→ use as adjunct
- Moderate/severe functional impairment
- Challenges to engage in psychotherapy or failed psychotherapy
- Intolerability to other ADs
- Elevated risk for suicide/infanticide/homicide

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Perinatal benzodiazepine use

Benzodiazepines are indicated for short-term use only. Longer term use should be avoided.

- increased risk of congenital malformations with combo antenatal benzo/SSRI use (OR=1.40 (CI:1.09-1.80) (Oberlander TF et al, 2008; Grigoriadis S et al 2019)
  - Prenatal benzo use *not* associated with increased risk congenital malformations (OR: 1.13; CI:0.99-1.3) including first trimester specifically (OR=1.08; CI:0.93-1.25) (Grigoriadis S et al 2019)
  - Prenatal benzo use *not* associated with cardiac malformations (OR: 1.27; CI:0.98-1.65) (Grigoriadis S et al 2019)
- single study noted potential increased OR for Dandy-walker malformation (any benzo), anophthalmia or microphthalmia and esophageal stenosis (alprazolam) and pulmonary valve stenosis (lorazepam) (Tinker SC et al 2019)
- **neonatal withdrawal syndrome: floppy baby syndrome**: poor tone, lethargy, hypothermia, low APGAR (Yonkers KA et al 2017); also hypertonia, hyperreflexia and tremors (Iqbal MM et al, 2002); worse neurobehavioral outcomes in SSRI + benzo than SSRI alone or depressed alone (Salisbury AL, 2016)
- increased rates of ventilator support, cesarean section and low birth weight (Yonkers KA et al 2017)
- symptoms of floppy baby syndrome can appear shortly after delivery to 3 weeks after delivery and last for several months

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Perinatal benzodiazepine use

- Benzodiazepines with shorter half-lives and no/few active metabolites preferred over mid to long-acting (e.g. lorazepam, not clonazepam, not diazepam).
- In term neonates (>37 weeks GA), elimination is extended due to poor hepatic function (immature Phase II metabolism). Neonates born prematurely can have prolonged plasma elimination (and thus increased side effects).
- Alprazolam: 13hr half-life; RID=3%- I do not prescribe due to increased risk of tolerance
- Lorazepam: 14hr half-life (is 85% bound to plasma proteins; RID=2.5%, often a benzodiazepine of choice
- Clonazepam: 20-50hr half-life; RID=2.8, LactMed recommends use of shorter half-life benzo over clonazepam
- Diazepam: 30-60hr half-life for parent drug plus 30-100 hours major active metabolite dimethyldiazepam; RID = 7.1% , LactMed recommends use of shorter half-life benzo

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Clinical pearls

- First and foremost, consider how you would treat the patient's unipolar depression/anxiety if the patient was not pregnant.

- Consider…
  - the risk to the patient and the fetus/infant of stopping or reducing current pharmacotherapies
    - Risk of untreated illness to patient and fetus/infant
  - the risk to the patient and the fetus/infant of continuing those pharmacotherapies
    - Consider antenatal vs. postnatal (lactational) risks
  - the risk of switching to an alternative pharmacotherapy
    - Is the alternative really safer? Consider the absolute risk reduction between the current medication and the alternative medication.
    - Will the alternative control depressive/anxiety symptoms as well as the current regimen?

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Clinical pearls: serotonergic antidepressants

- When possible, any changes to a medication regimen should be made prior to conception to ensure symptom stability and to minimize exposure to the fetus. Abrupt discontinuation of antidepressants in pregnant women with a history of depression is associated with high risk of relapse without known benefit (L.S. Cohen et al., 2006).

- Women with history of recurrent unipolar MDD or history of symptom recurrence associated with past reduction or discontinuation of pharmacotherapy **should not discontinue their antidepressant during pregnancy.**

- If SSRI/SNRI dose increased in pregnancy, monitor for side effects after delivery, can decide when to reduce SSRI/SNRI dose (if at all) once reassured of continued euthymia; don't immediately resume pre-pregnancy dose as could precipitate MDD relapse.

- TCA dose often must slowly be decreased towards the preconception dose during the two to six weeks after delivery to reduce risk of TCA toxicity, check levels whenever side effects and check no later than 6 weeks postpartum

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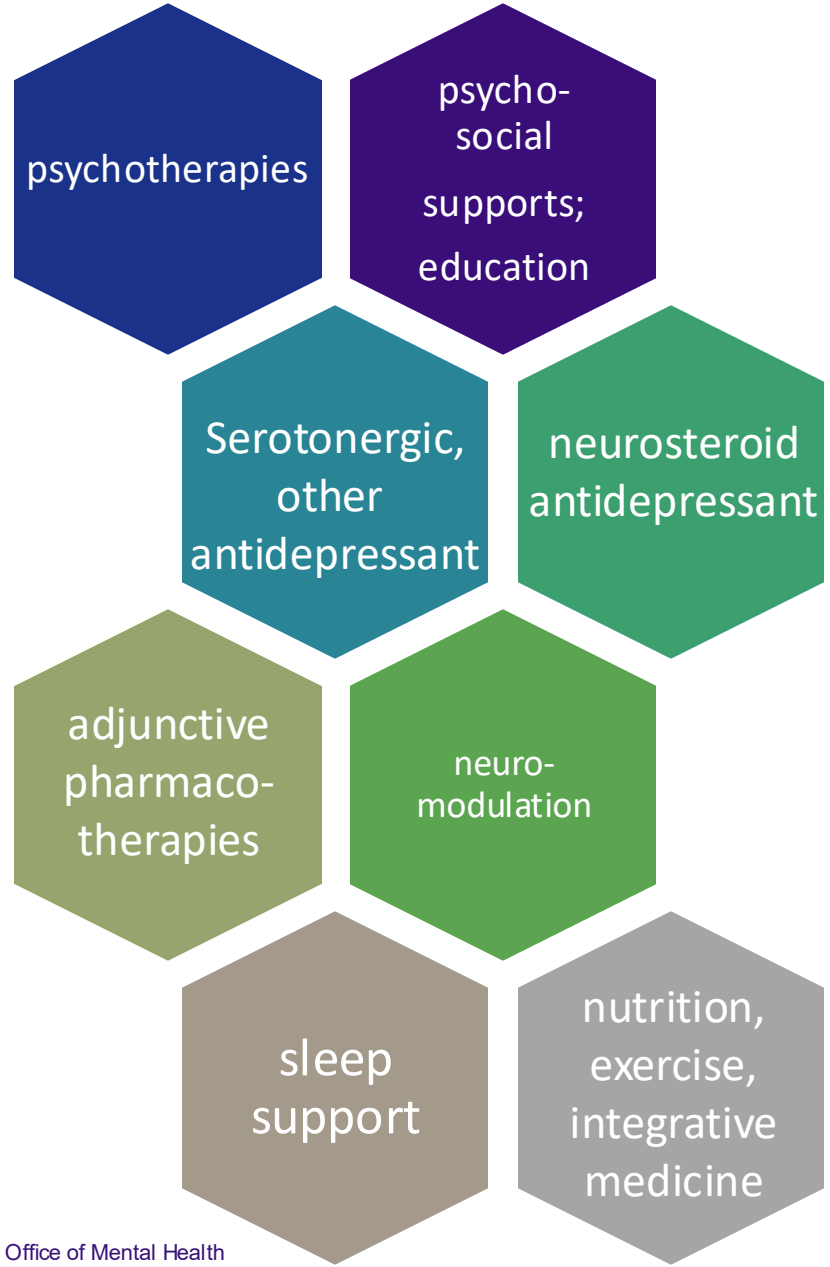
Consider all therapeutic tools in our toolbox to treat PND



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General Recommendations

- Encourage patient to have psychiatric care during and after pregnancy
- If there are medications that the patient is taking that do not clearly contribute to euthymia, consider simplifying the regimen, monotherapy in adequate dose is preferred over polypharmacy
- Frequently the best option is a medication that the patient found helpful in the past, due to known efficacy and tolerability

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General Recommendations

- Ideally, all medication changes should be done before pregnancy, and the patient should be psychiatrically stable and regimen remains consistent throughout
- The goal of treatment is full symptom remission, and medications should be adjusted to the lowest efficacious and fully therapeutic dose
- Consider breastfeeding when discussing possible medications during pregnancy

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Case: contemplating pregnancy

- 30 y.o. F G2P2 with PPH recurrent MDD and GAD currently taking venlafaxine 150mg daily with mild depression/anxiety symptoms. Contemplating 3rd pregnancy and wants to know what to do with her med since she saw an ad on TV from a lawyer that venlafaxine causes birth defects if taken in pregnancy.
- In the chat: what do you advise her do?
- In the chat: Is there other info you would like to know?

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Case: contemplating pregnancy

- PPH: 4 episodes of MDD including severe PPD with 2nd child (stopped her antidepressant proximate to conception)
- failed to respond with full dose and adequate duration trials of sertraline, fluoxetine, citalopram and could not tolerate bupropion in past
- 2 prior hospitalizations for suicide attempts
- no hx. mania or psychosis

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Poll

- How would advise your patient?
- a) Transfer patient care to a reproductive psychiatrist.
- b) Discontinue venlafaxine proximate to conception, restart venlafaxine after delivery
- c) Reduce venlafaxine to 75mg proximate to conception and increase dose back to 150mg after delivery.
- d) Continue venlafaxine 150mg and monitor for potential need for dose increase due to changes in P450 metabolism in late gestation.
- e) Call Project TEACH to consult with a perinatal psychiatrist before advising your patient.

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Post-test question #1

1) Which of the following is true about postnatal (poor neonatal) adaptation syndrome (PNAS)?
   a) Occurs in approximately 30% of neonates with antenatal antidepressant exposure
   b) Can be prevented by discontinuing antidepressant use in third trimester
   c) Is less severe in neonates with antenatal polypharmacy exposure
   d) On average symptoms last approximately six months post-delivery

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Post-test question #2

2) Which of the following about neonatal benzodiazepine withdrawal syndrome is true?

a) Symptoms can include changes in muscular tone, lethargy, hypothermia, low APGAR scores, tremor

b) Symptoms are less common with antenatal diazepam exposure as compared to lorazepam exposure

c) Symptoms appear most commonly at one month post-delivery

d) Combined antenatal antidepressant with benzodiazepine exposure is associated with less severe symptoms as compared to benzodiazepine exposure alone

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Post-test questions #3

3) Which of the following regarding antenatal physiologic changes affecting medication pharmacokinetics?

a) Absorption accelerates

b) Distribution decreases

c) Urinary excretion decreases

d) Phase I and phase II metabolism change

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