Neuroactive Steroids and Perinatal Mental Health

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Weill Cornell Medicine

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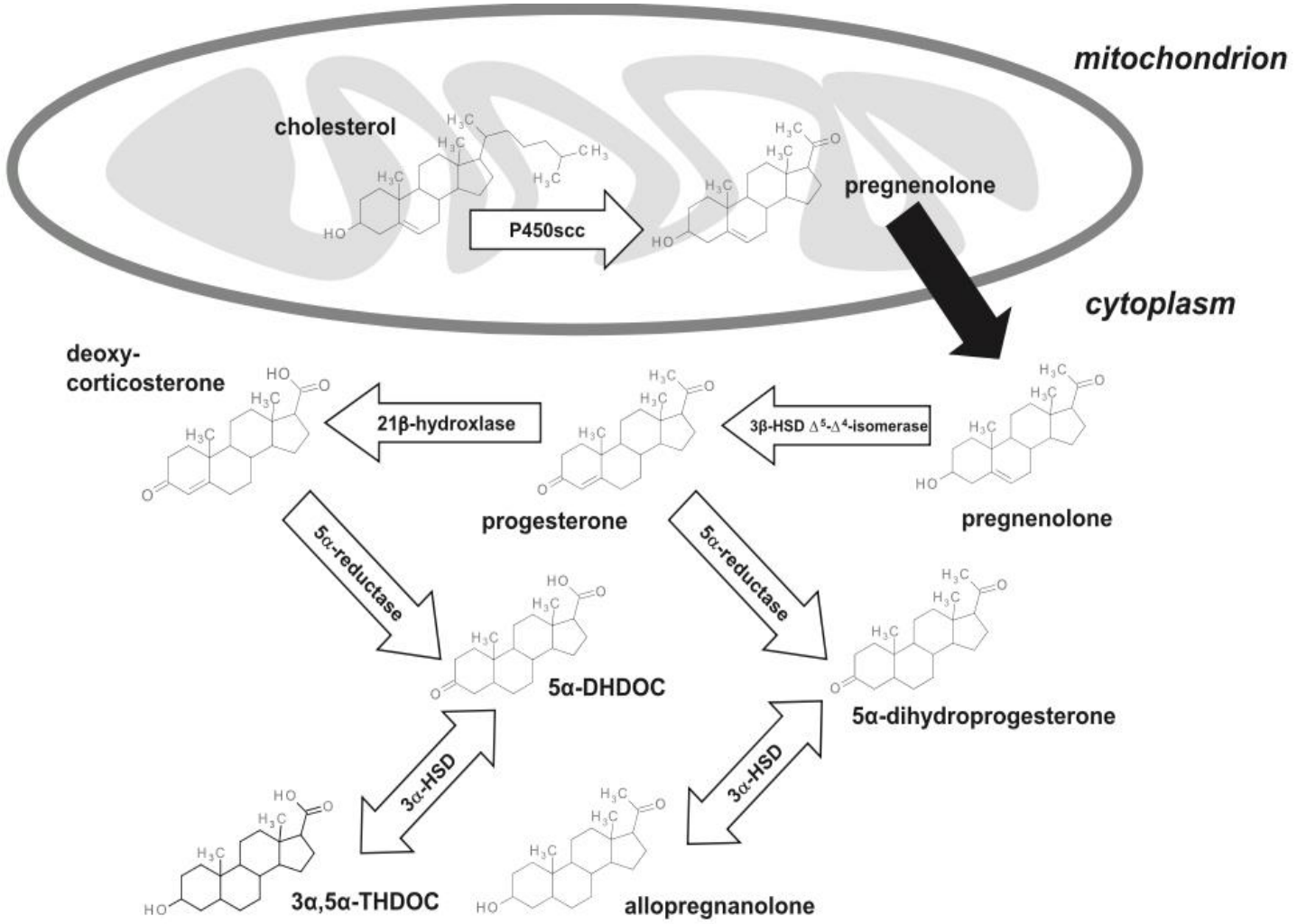
Objectives

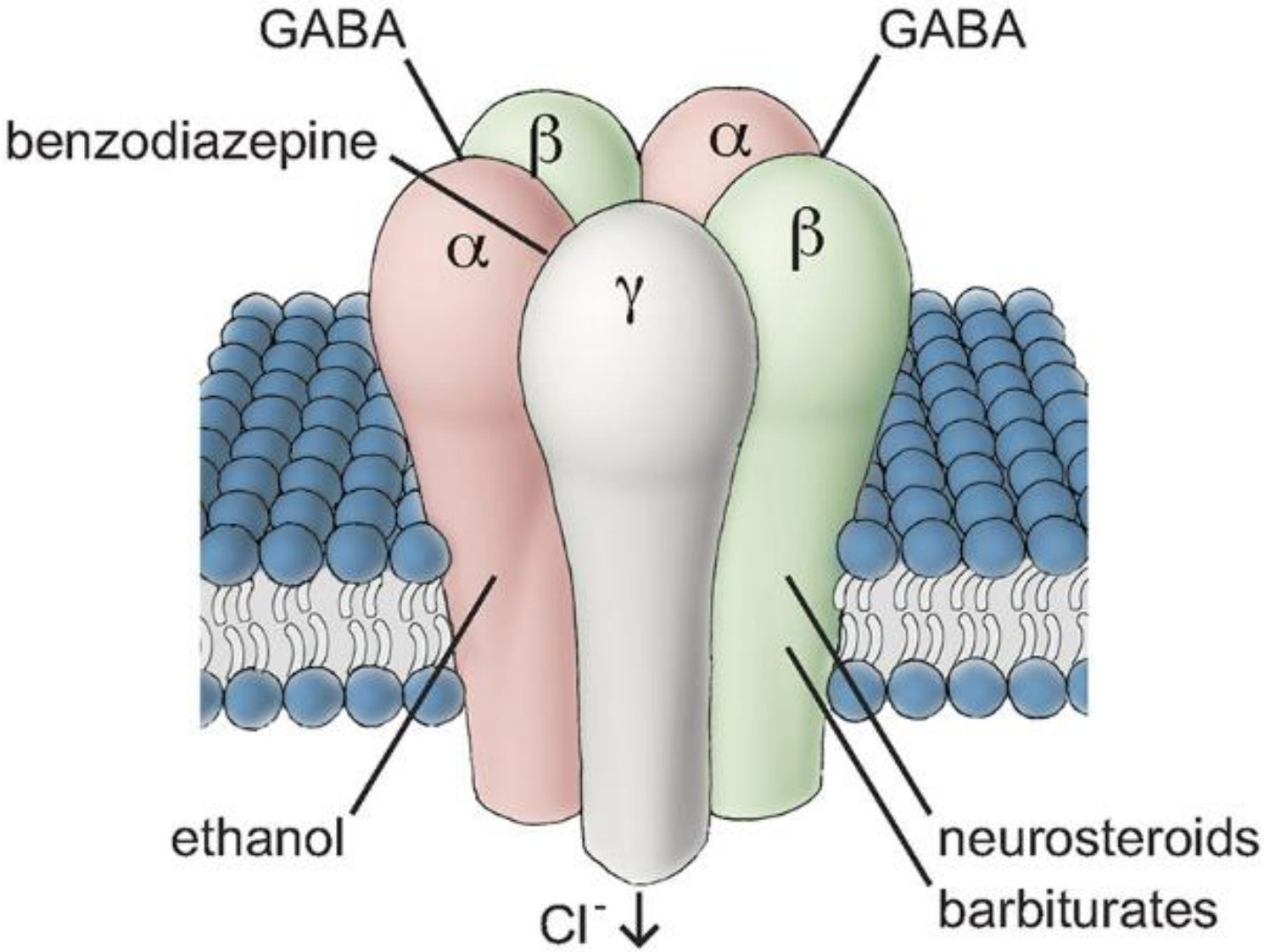
Understand

- How neuroactive steroids (NAS) act on the GABA-A receptor
- How NAS change across the peripartum and the menstrual cycle
- How mood and anxiety symptoms are related to fluctuating levels of NAS at times of reproductive transition
- How synthetic NAS can be used to treat psychiatric illness at times of reproductive transition

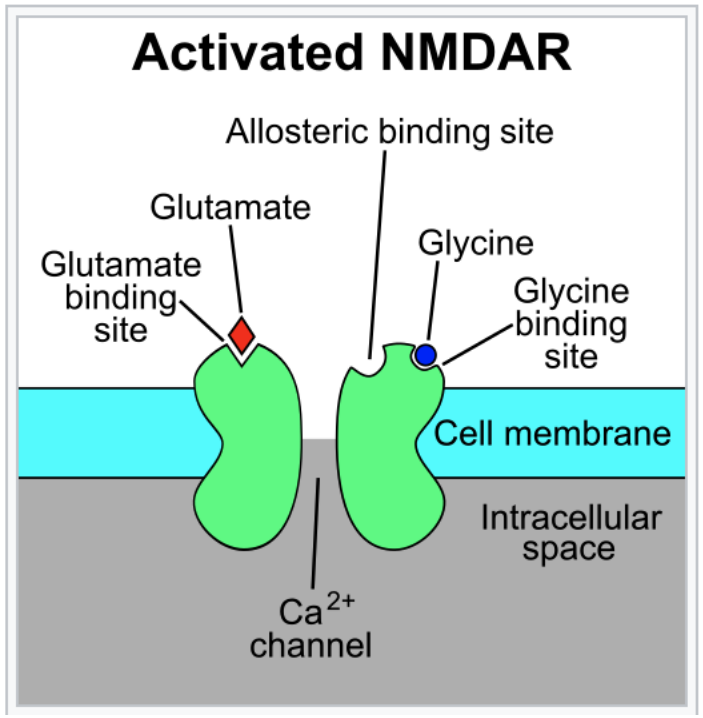


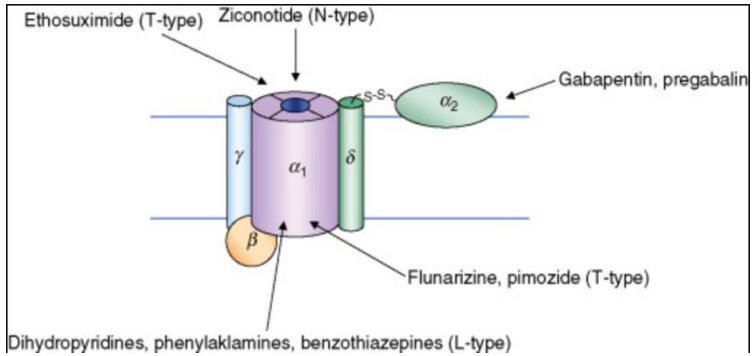
What are Neuroactive Steroids?

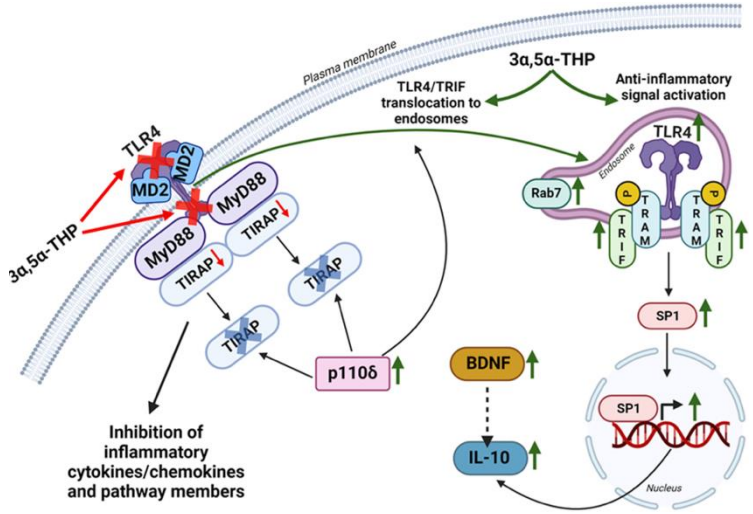
C. Schule et al. / Progress in Neurobiology 113 (2014) 79–87



http://pharmrev.aspetjournals.org/content/62/1/97





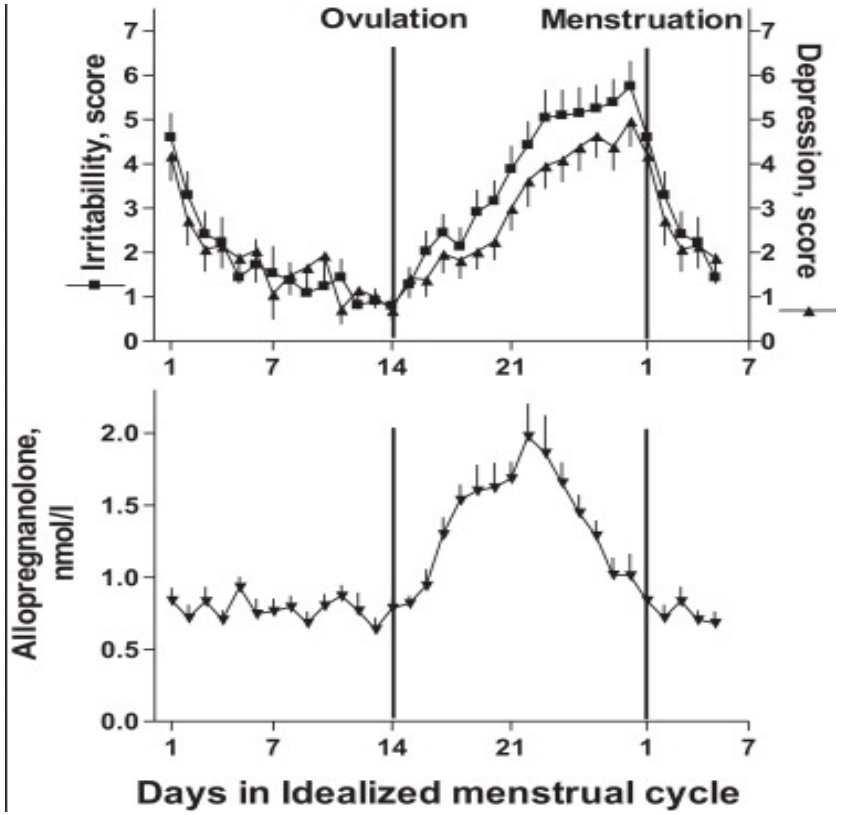


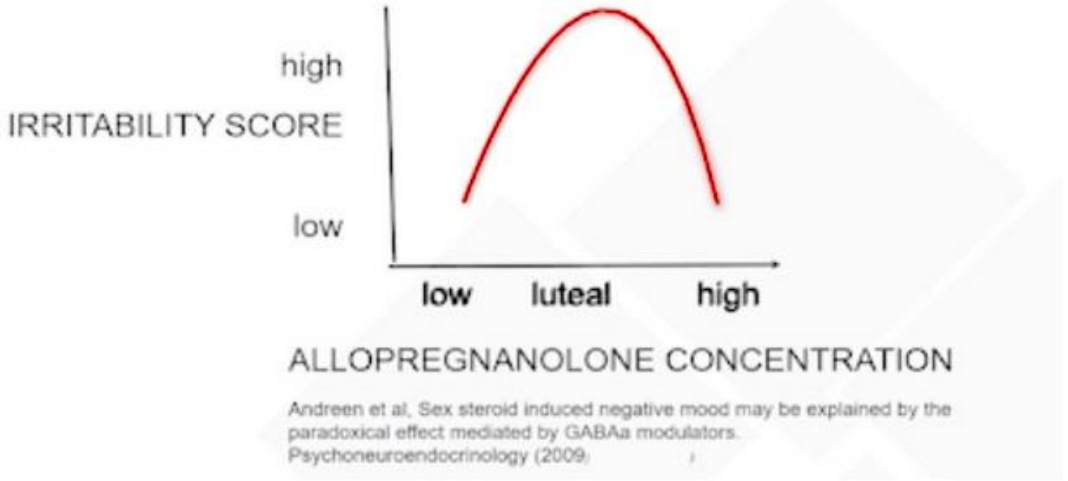
Snutch, Voltage-Gated Calcium Channels, Encyclopedia of Neuroscience 2009, pp. 427-441
Balan et al., *Life* **2024**, *14*(5), 582; https://doi.org/10.3390/life14050582

Stressful Event

Inhibitory NAS down in chronic mental illness

SSRIs reverse





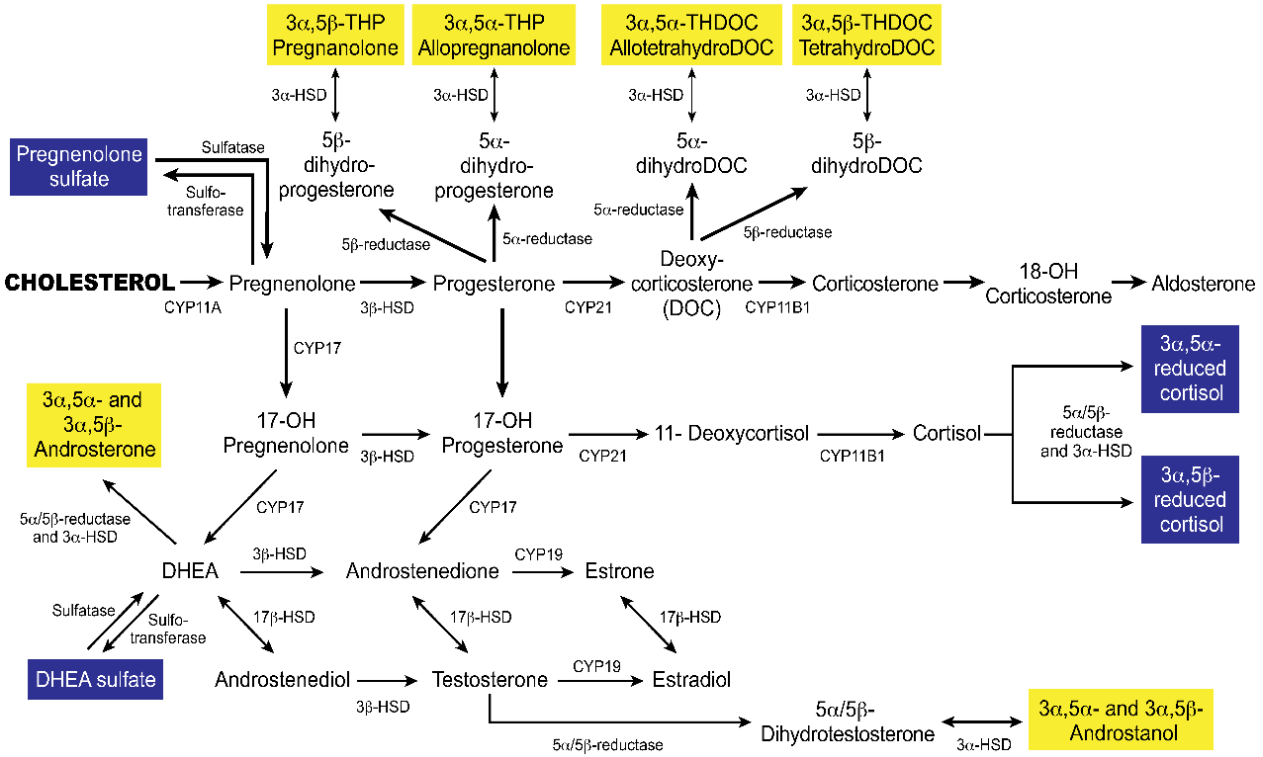
But pattern is different for PMDD!

BACKSTROM ET AL., PROGRESS IN NEUROBIOLOGY (2014) 113, 88-94

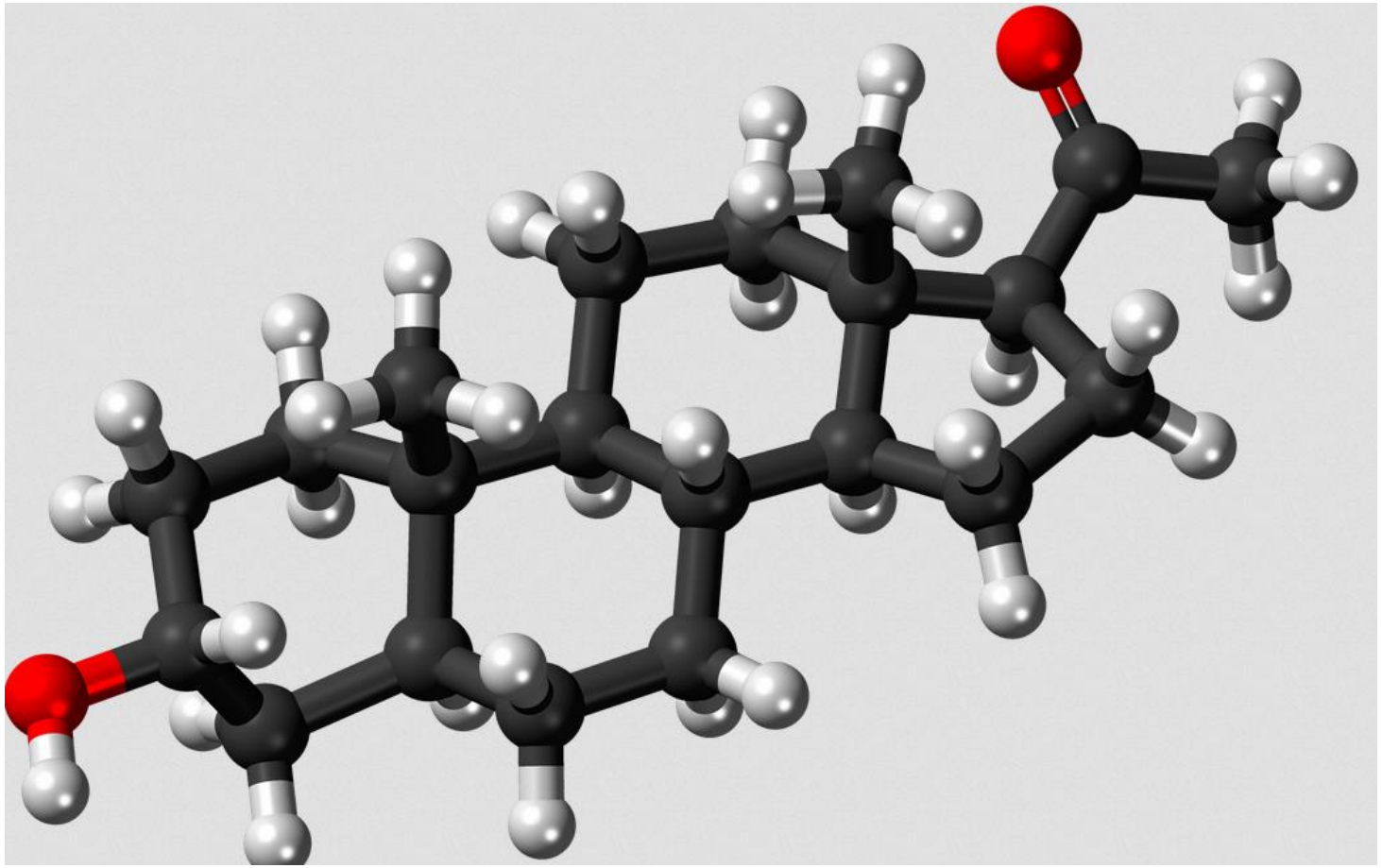
Pregnancy

Like MDD, or PMDD ?

NAS

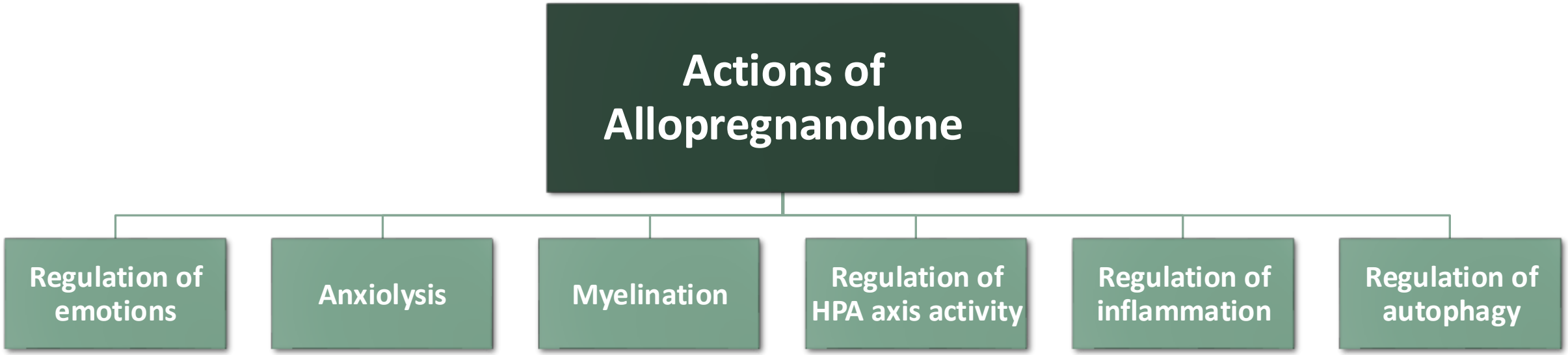


AllotetrahydroDOC	•Similar properties to ALLO •No direct perinatal evidence
Pregnanolone	•Similar properties to ALLO, •Less evidence •Deligiannidis 2013, •+ correlation depressed mood •Crowley 2016, combined w ALLO
DHEA – EXCITATORY	•Opposite to ALLO •Buckwalter 1999 found •High in pregnancy = high mood •Low in PP = low mood
DHEA-S	•Similar actions to DHEA, but •Limited evidence shows OPPOSITE correlations (Kasap 2016, Marrs 2009)



Allopregnanolone

https://commons.wikimedia.org/wiki/File:Allopregnanolone-3D-balls.png


Actions of Allopregnanolone
Regulation of emotions
Anxiolysis
Myelination
Regulation of HPA axis activity
Regulation of inflammation
Regulation of autophagy

Allopregnanolone in Healthy Pregnancy

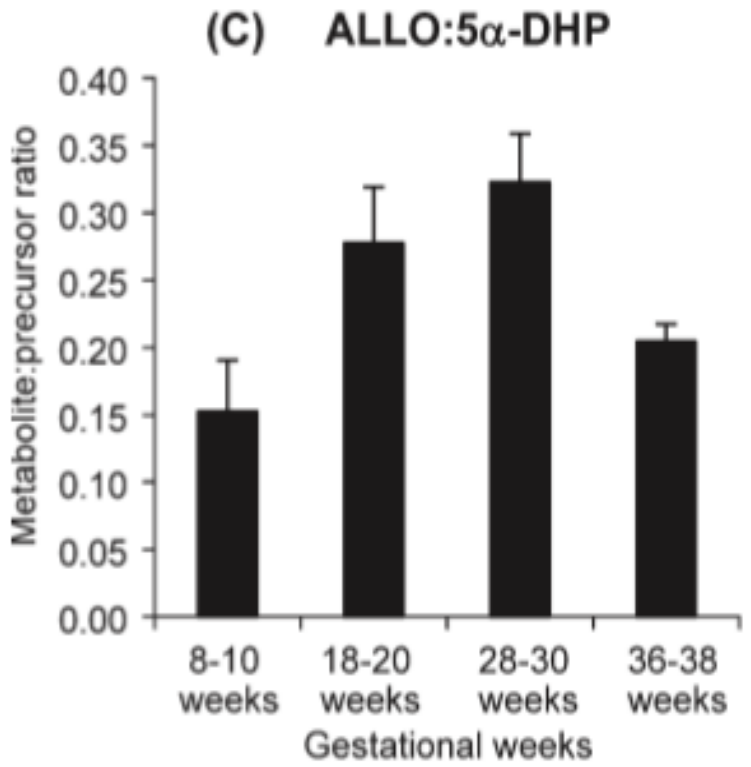
Levels 7-9x ↑

Ratio to precursor may ↓ before delivery

Return to normal by 6 weeks PP

Expression GABA-A receptor subunit & binding capacity ↓

Within 48 hours after delivery ↑



Neuropsychobiology

Neuropsychobiology 2014;69:147–153
DOI: 10.1159/000358838

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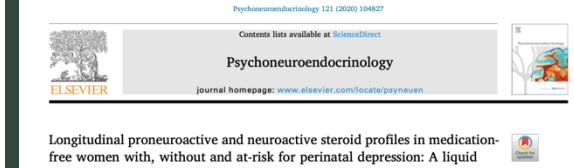
Accepted after revision: January 20, 2014
Published online: April 26, 2014

Low Serum Allopregnanolone Is Associated with Symptoms of Depression in Late Pregnancy

Charlotte Hellgren[a] Helena Åkerud[a] Alkistis Skalkidou[a] Torbjörn Bäckström[b] Inger Sundström-Poromaa[a]



Psychoneuroendocrinology 121 (2020) 104827

Contents lists available at ScienceDirect

Psychoneuroendocrinology

journal homepage: www.elsevier.com/locate/psyneuen

ELSEVIER

Longitudinal proneuroactive and neuroactive steroid profiles in medication-free women with, without and at-risk for perinatal depression: A liquid chromatography-tandem mass spectrometry analysis

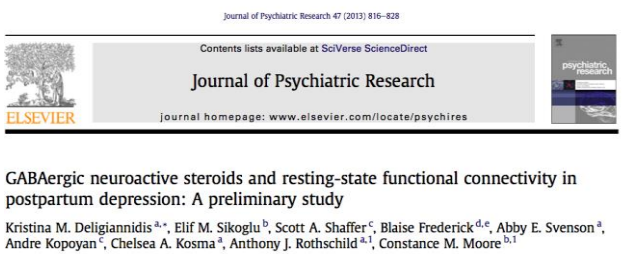
Kristina M. Deligiannidis[a,b,c,d,*], Aimee R. Kroll-Desrosiers[a,e], Yanglan Tan[a], Michelle L. Dubuke[a,f], Scott A. Shaffer[g,h]

Psychopharmacology (2016) 233:1299–1310
DOI 10.1007/s00213-016-4217-x

ORIGINAL INVESTIGATION

Blunted neuroactive steroid and HPA axis responses to stress are associated with reduced sleep quality and negative affect in pregnancy: a pilot study

Shannon K. Crowley[1] · Todd K. O'Buckley[2] · Crystal E. Schiller[1] · Alison Stuebe[3,4] · A. Leslie Morrow[1,2,5] · Susan S. Girdler[1]



Journal of Psychiatric Research 47 (2013) 816–828

Contents lists available at SciVerse ScienceDirect

Journal of Psychiatric Research

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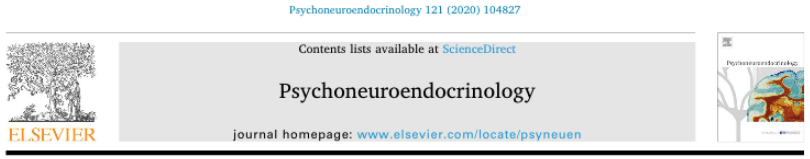
ELSEVIER

GABAergic neuroactive steroids and resting-state functional connectivity in postpartum depression: A preliminary study

Kristina M. Deligiannidis[a,*], Elif M. Sikoglu[b], Scott A. Shaffer[c], Blaise Frederick[d,e], Abby E. Svenson[a], Andre Kopoyan[c], Chelsea A. Kosma[a], Anthony J. Rothschild[a,1], Constance M. Moore[b,1]

Peripheral ALLO



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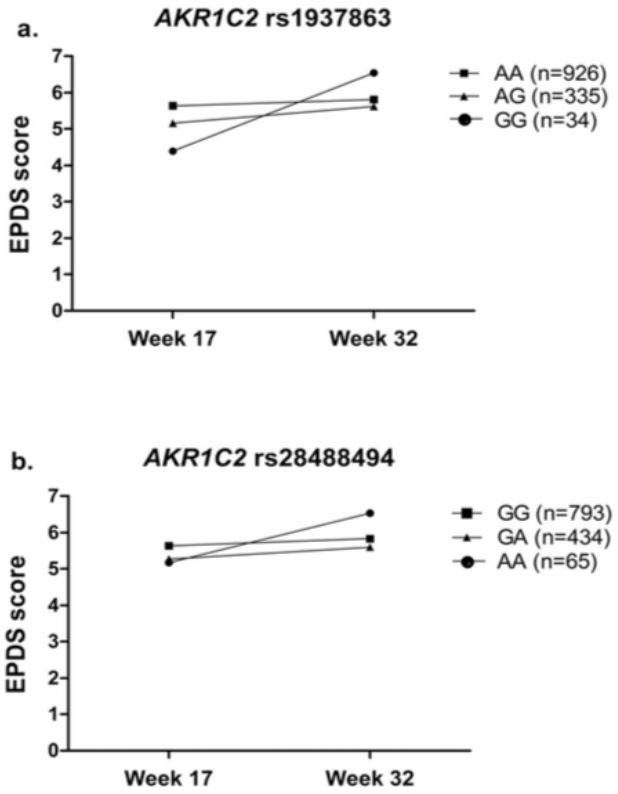
NAS across the Peripartum

- Examined multiple NAS across pregnancy and postpartum
- Strength of longitudinal measure, multiple NAS, ratios
- Strength of lab methods (LC-MS)
- Problems with group definition (at-risk)
- Problems with definition of PND
- Looked at mean levels not change across time

Allopregnanolone levels and depressive symptoms during pregnancy in relation to single nucleotide polymorphisms in the allopregnanolone synthesis pathway

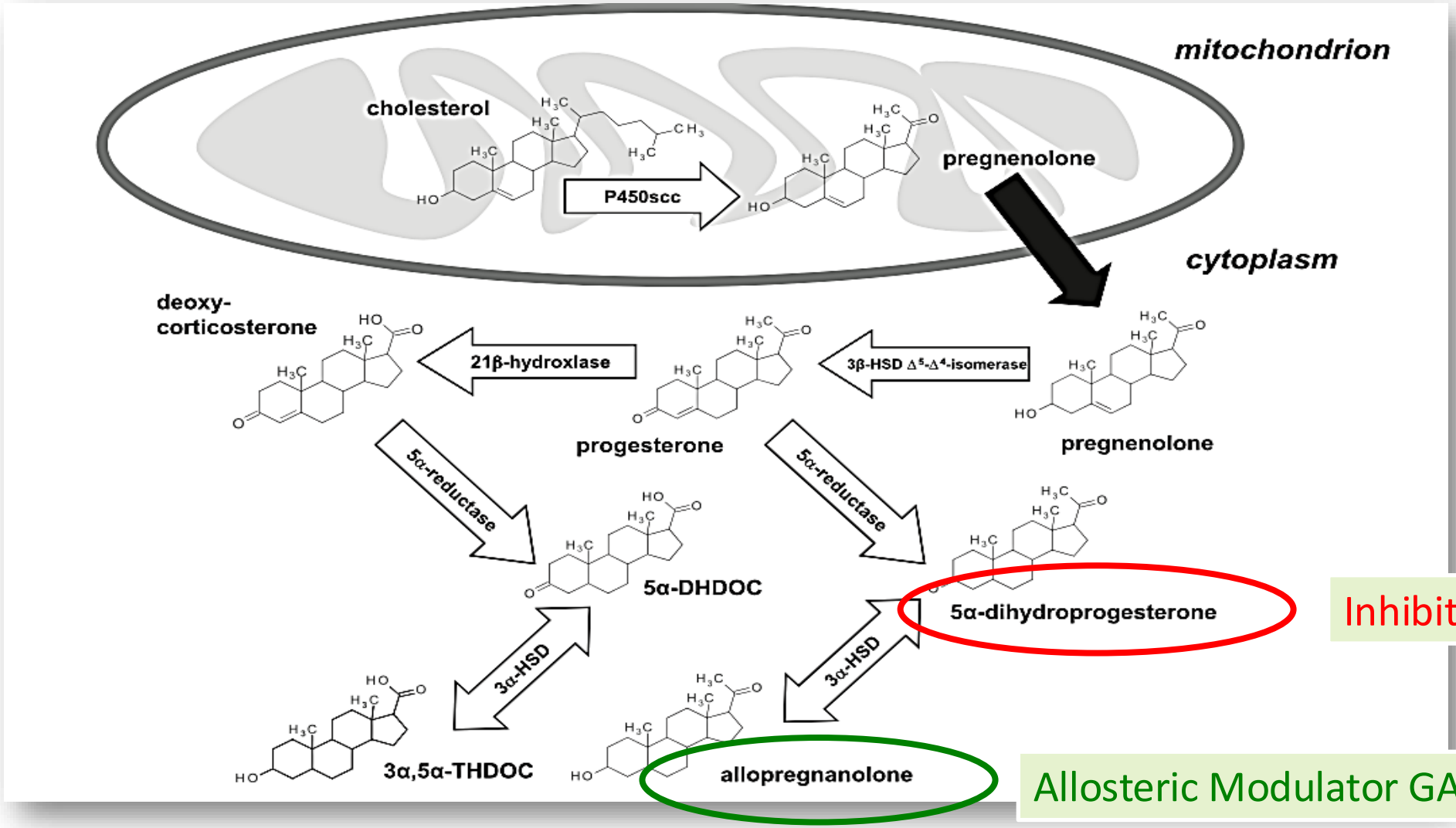
Charlotte Hellgren [a,*], Erika Comasco [b], Alkistis Skalkidou [a], Inger Sundström-Poromaa [a]

[a] Dept. of Women's and Children's Health, Uppsala University, Uppsala University Hospital, 751 85 Uppsala, Sweden
[b] Dept. of Neuroscience, Uppsala University, 751 24 Uppsala, Sweden



Genetic contribution?

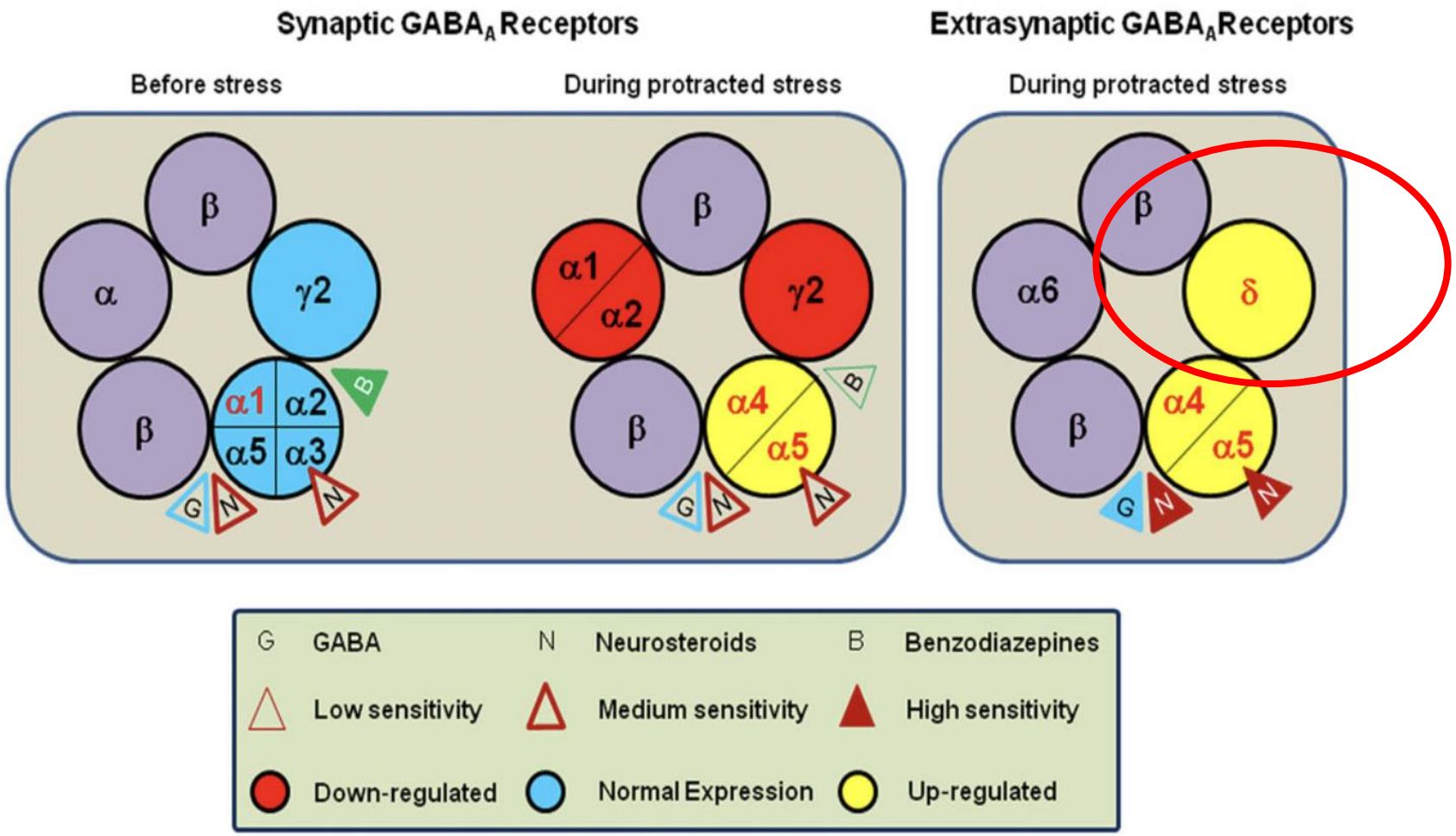
Action of Enzymes?



Inhibits GABA-A

Allosteric Modulator GABA-A

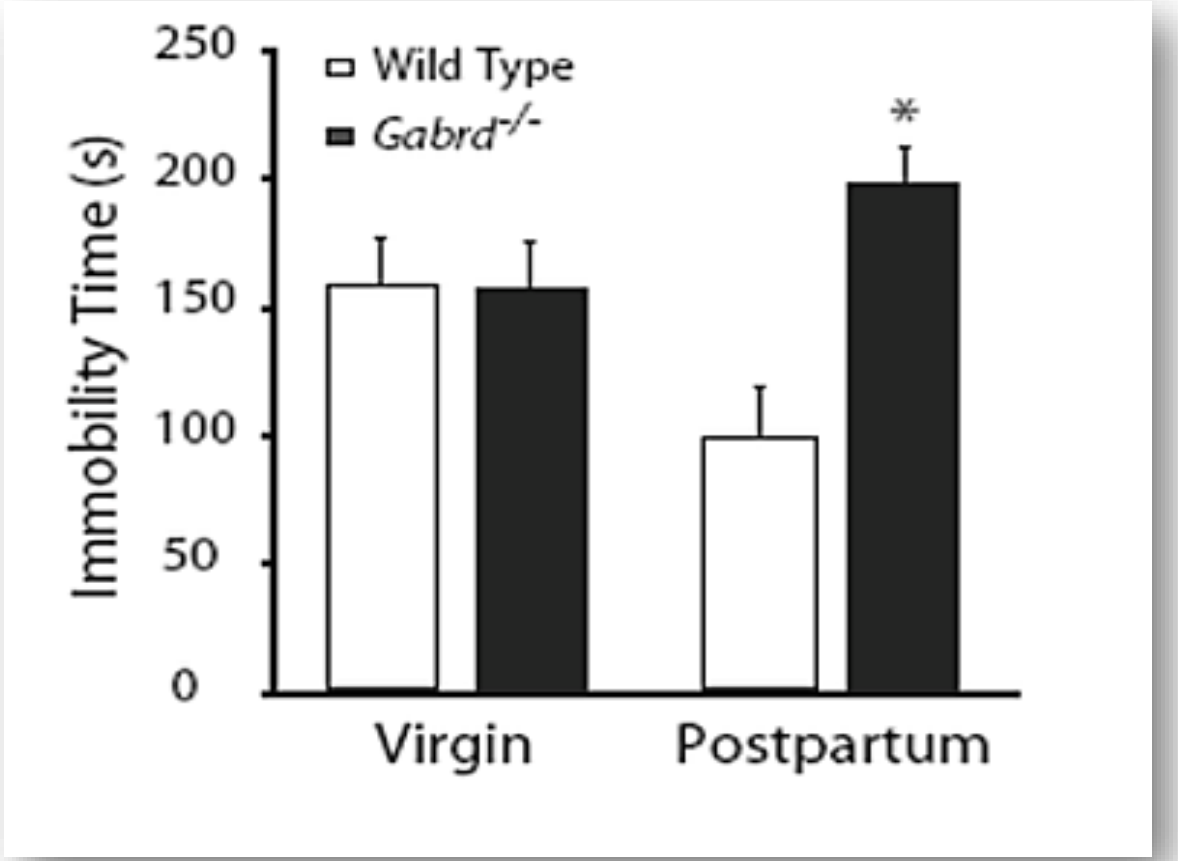
Action of Receptors?



GABA-A Receptor delta Knockout Mice

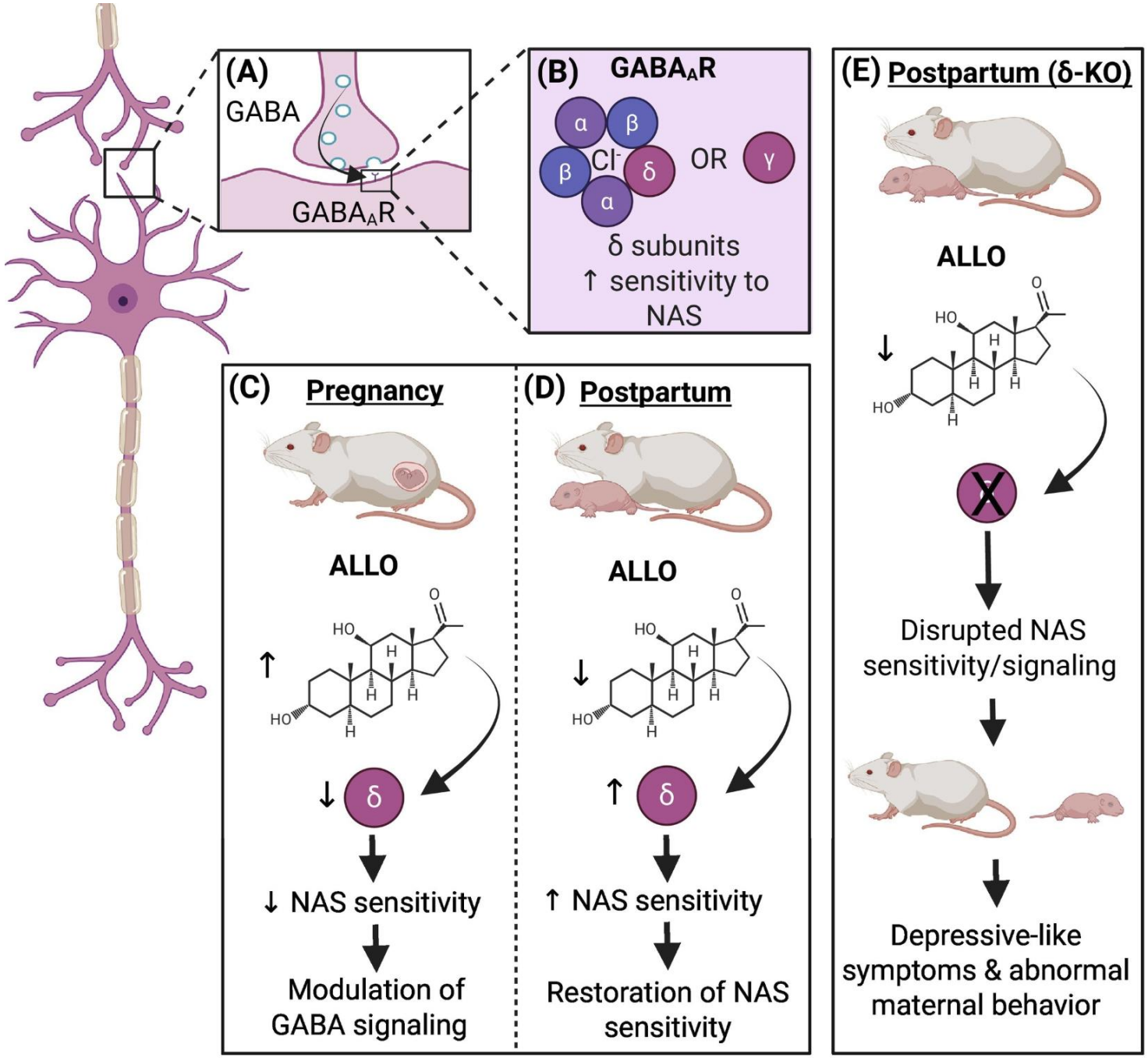
=

Increased Mood and Anxiety-like Behaviors Postpartum



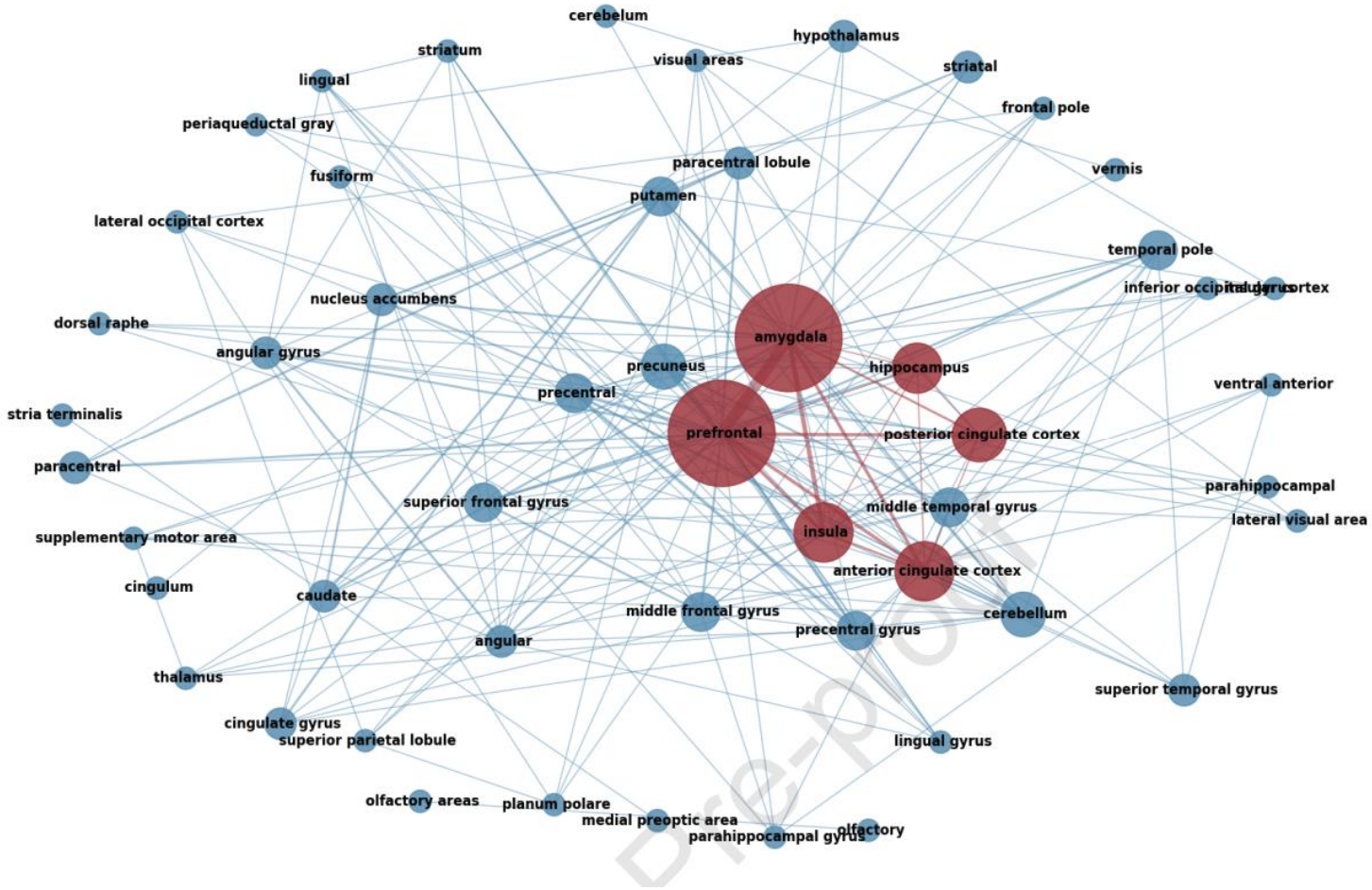
Maguire & Mody, Neuron. 2008 July 31; 59(2): 207–213.

NAS Sensitivity/GABA signaling



Wenzel et al., The neurobiology of postpartum depression, Trends in Neuroscience 2025 Jul;48(7):469-482.

Relationship of Network States



Maguire et al., GABAergic neuroactive steroids and network states: relevance to peripartum depression, Biological Psychiatry 2025 Oct 9:S0006-3223(25)01521-5.

Methods of Prospective Study

PI: PAYNE

→ 62 women, dx of mood disorder

→ Prospective through pregnancy up to 3 months PP

→ TAU, including meds

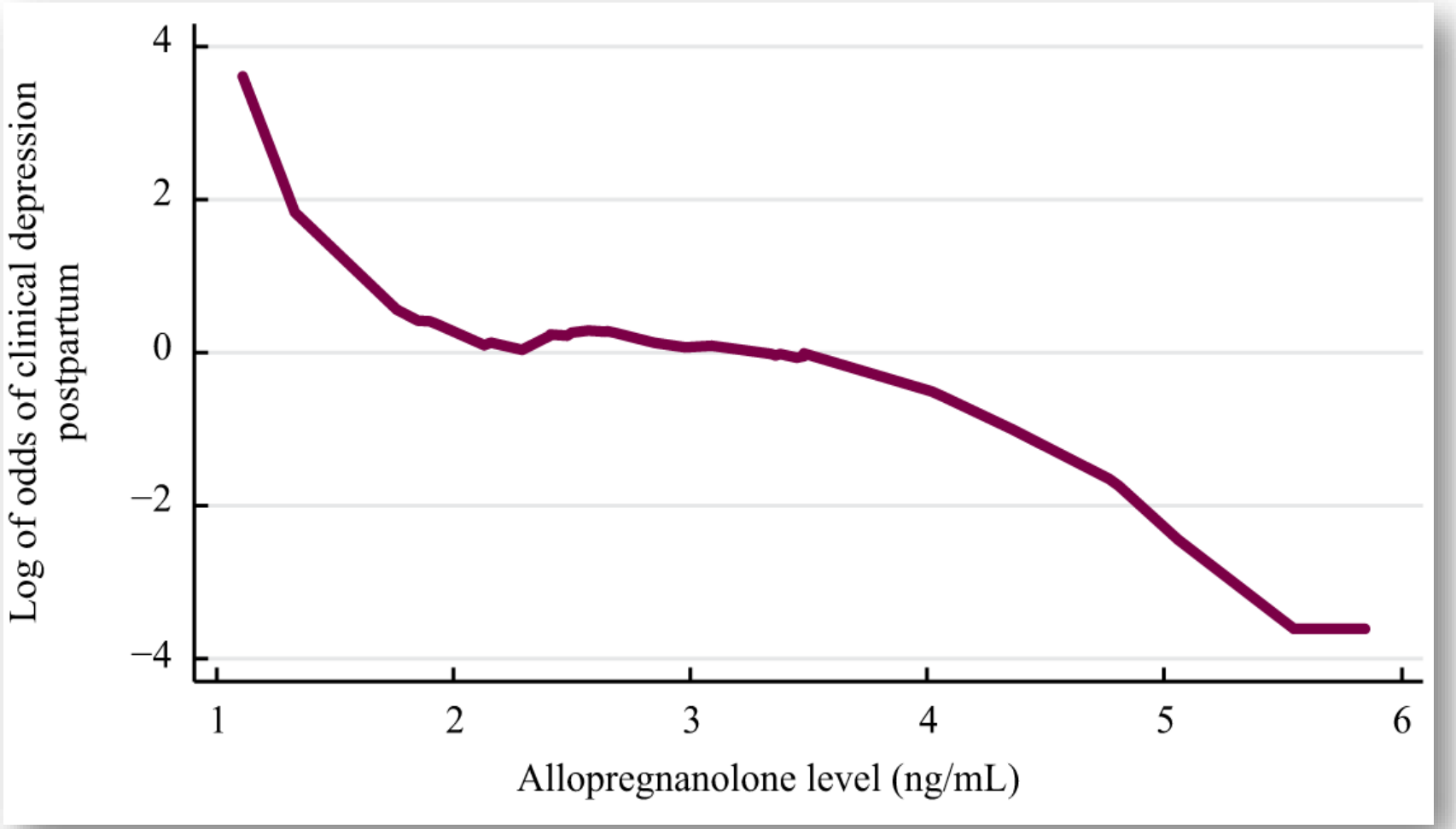
→ Scales, clinian interview, blood draw up to 6x

→ ALLO by ELISA (EIA kit from Arbor Assays LLC Cat 3 KC44-H1)

Category	Variable	Percentage
Age	<30	33%
	≥ 31	67%
Diagnosis	BPAD	30%
	MDD	70%
	Healthy	0%
Relationship	Partnered	95%
	Single	5%
Education	Some grad school & above	40%
	Some college & below	30%
Subsequent PPD*	No	47%
	Yes	43%

*Some missing data, does not add up to 100%

T2 ALLO and PPD



Osborne et al, Psychoneuroendocrinology, 2017

Methods of JHU Prospective Mood & Anxiety Studies

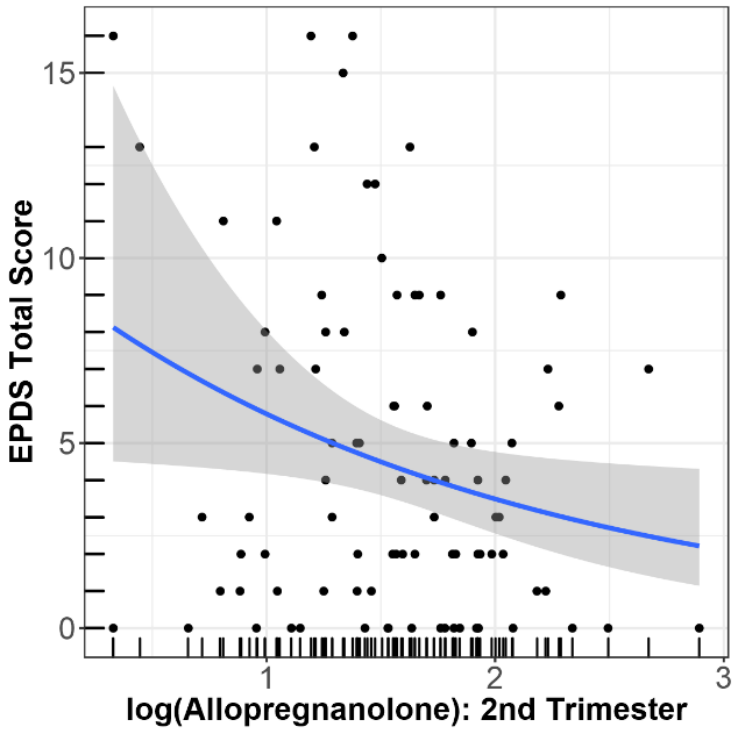
PIs: PAYNE, OSBORNE

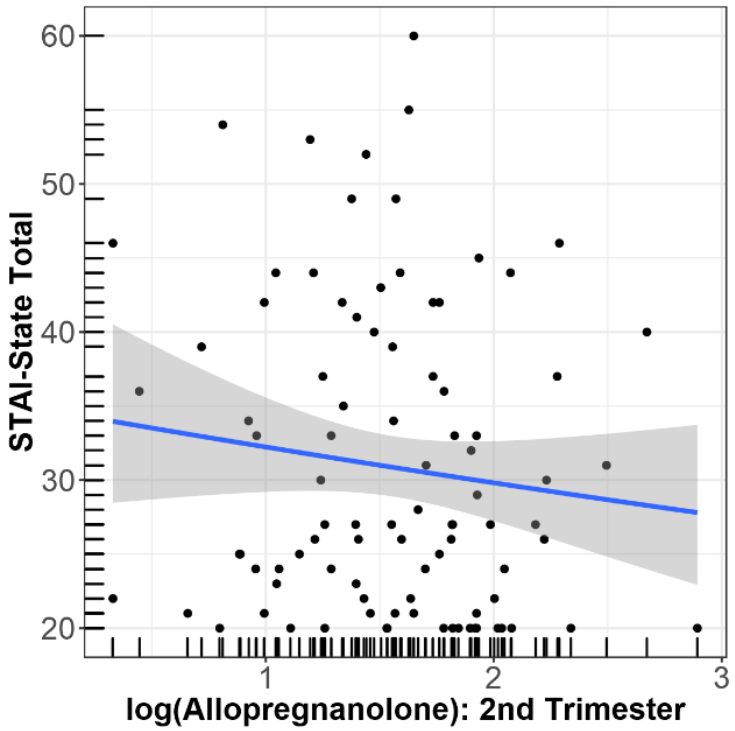
- 124 with ALLO, mood, anxiety at T2, T3, W6
- Covariates = sleep, age, visit timing
- Included if blood draw and psych scales at least once & no missing covariates
- N = 92 for predictive, N = 121 for concurrent
- Negative binomial generalized linear models

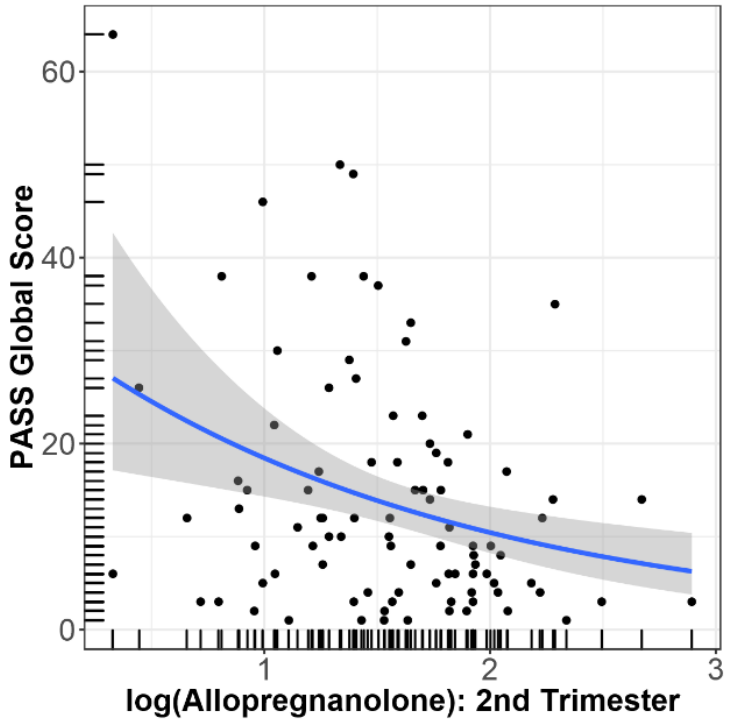
Methods of Biological Mechanisms of Anxiety

PI: OSBORNE

- 140 enrolled (115 pre-COVID)
- Anxiety alone, NO depression, at T2, T3, W6, M6
- 9 different NAS at first 3 timepoints, by GC-MS
- Moderated mediation model
- Negative binomial generalized linear models



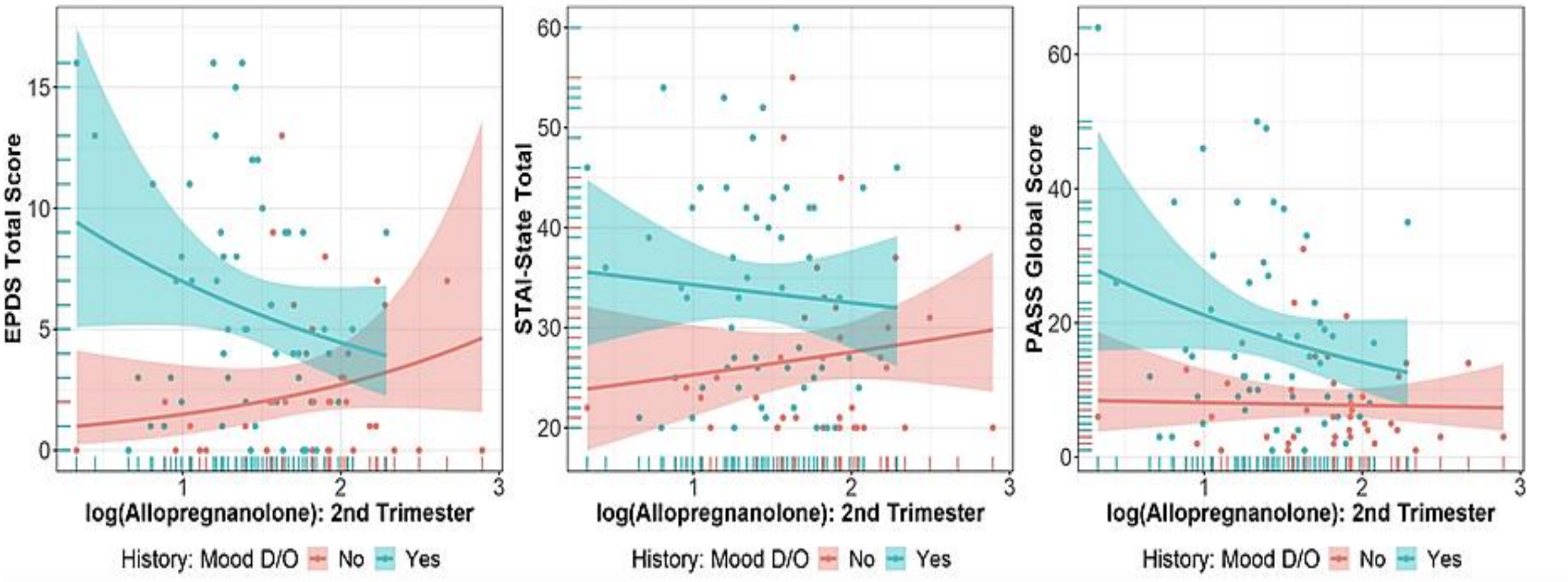




- Relationship between EPDS score at W6 and log of ALLO concentration at T2
- Relationship between STATE score at W6 and log of ALLO concentration at T2
- Relationship between PASS score at W6 and log of ALLO concentration at T2
- Smoothed averages are shown from a negative binomial generalized additive model, with 95% confidence interval.

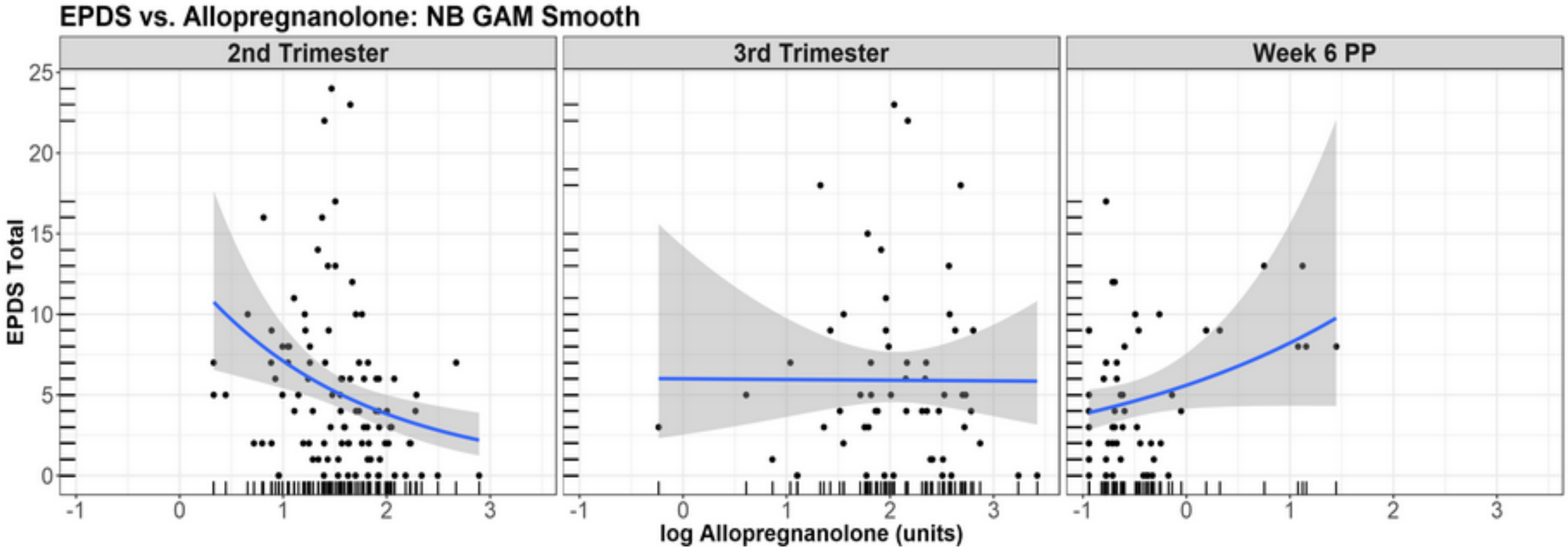
Osborne et al., *Frontiers in Psychology*, 2019

90% increase in EPDS for each unit log ALLO in those with history; 31% decrease for those without (p = 0.018)



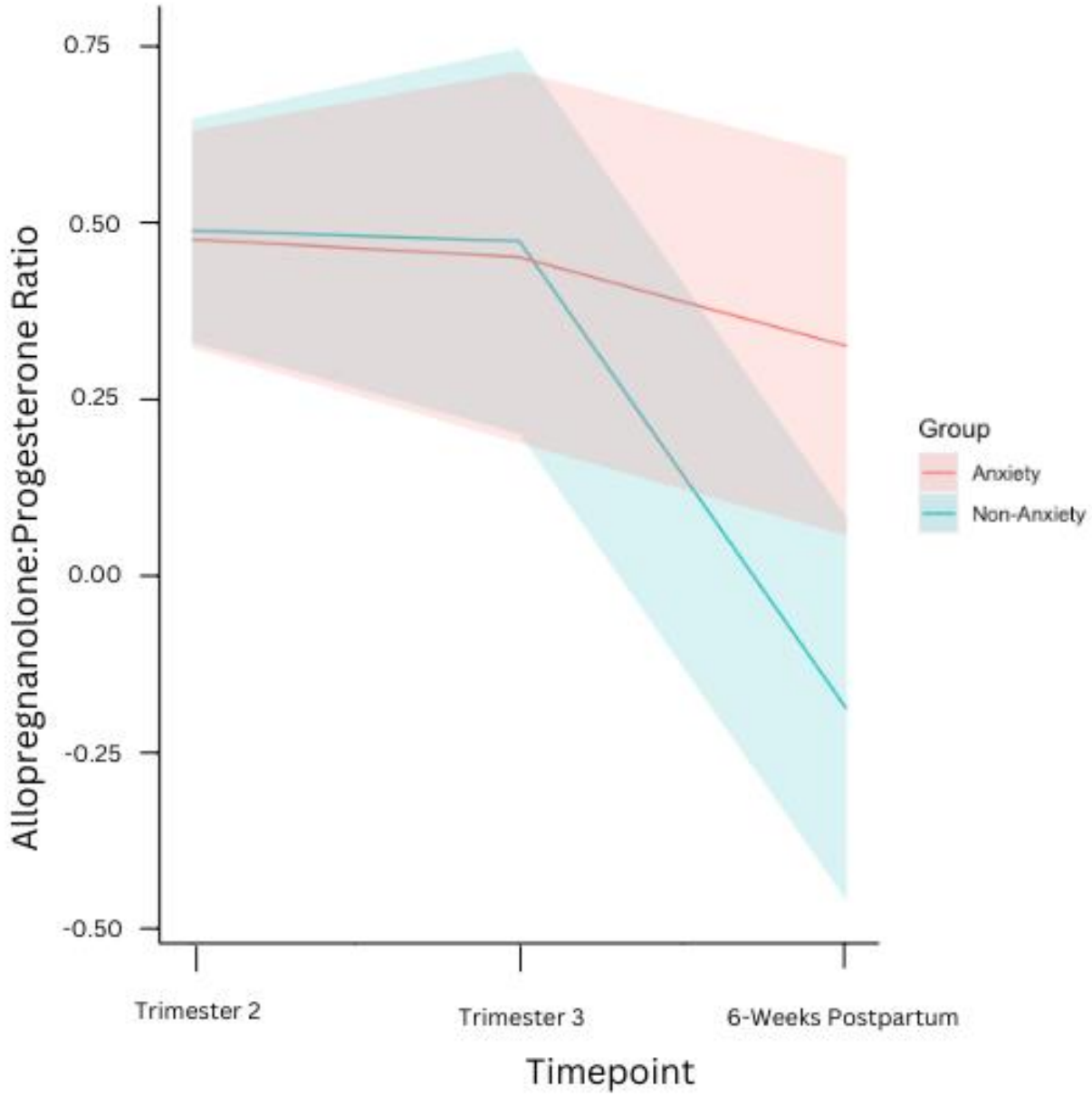
Standeven et al., Arch Women's Mental Health 2022

Sleep Matters!!



- Relationship between EPDS score and concurrent log of ALLO concentration at T2, T3, W6.
- Smoothed averages are shown from a negative binomial generalized additive model, with 95% confidence interval.

Slope change in allopregnanolone: progesterone ratio from T3 to W6



Etyemez SE, Miller KN, Voegtline KM, Ozdemir I, Standeven LR, Stantovito LS, Pinna G, Payne JL, **Osborne LM**. *Psychoneuroendocrinology* 2023,

Conclusions and Questions . . .

↓ T2 ALLO predicted ↑ W6 depression, anxiety

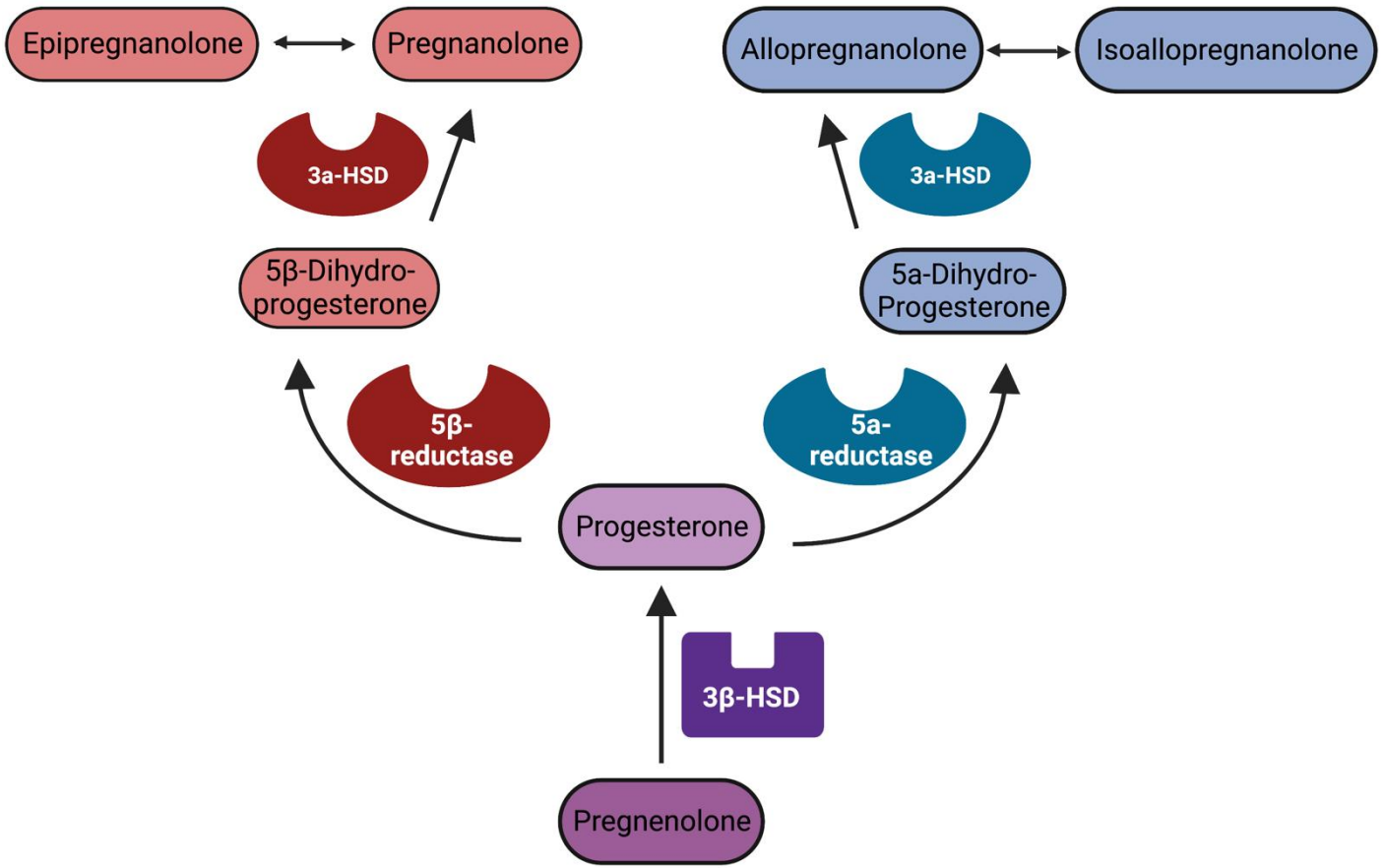
Relationship driven by those *with* mood history

Medication use did not change results, sleep an important and independent risk factor

Relationship between ALLO and mood/anx symptoms differed across peripartum

Questions

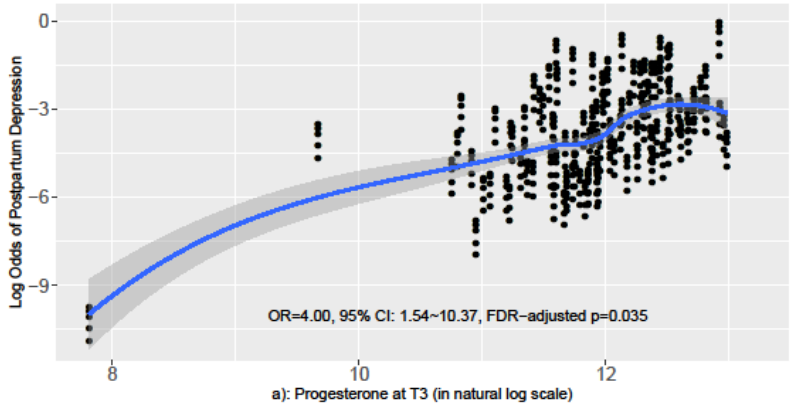
- 1. What is relationship to rest of pathway?
- 2. Does anxiety differ from depression?
- 3. Does population matter?
- 4. Do better ALLO methods matter?
- 5. How does this connect to other systems?

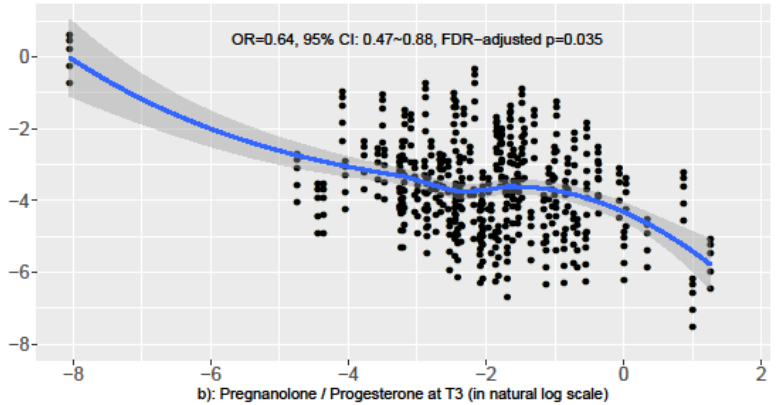


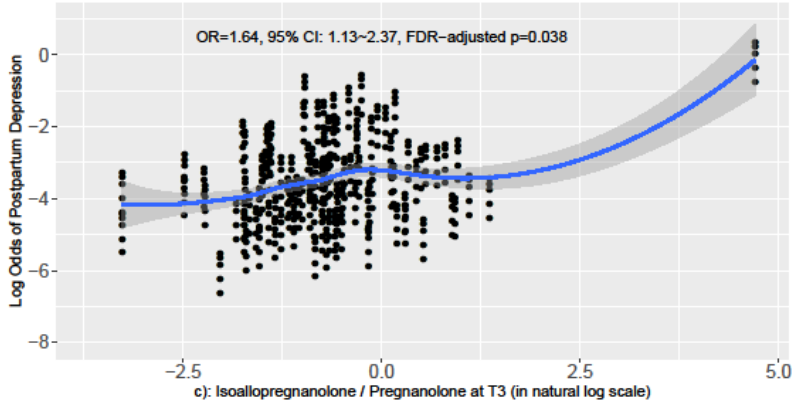
ALLO Does Not Act Alone . . .

The Progesterone Metabolic Pathway

Progesterone Metabolism in PPD…







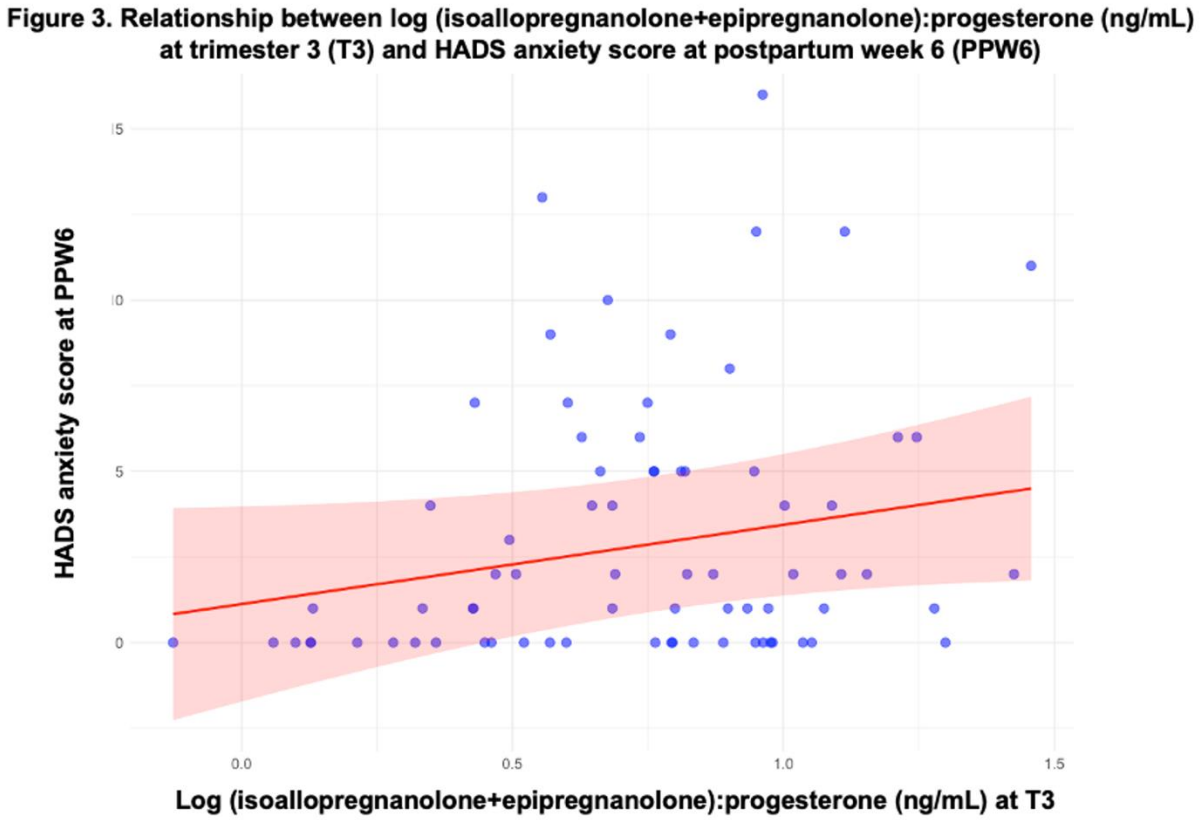
Osborne et al., *Neuropsychopharmacology* 2024, in press

Methods of Happy Mother, Healthy Baby

PI: SURKAN

- 117 enrolled in RCT for CBT intervention in Pakistan
- Anxiety alone, NO depression, at T2, T3, W6,
- 9 different NAS, by GC-MS
- Moderated mediation model
- Negative binomial generalized linear models

And in Postpartum Anxiety…



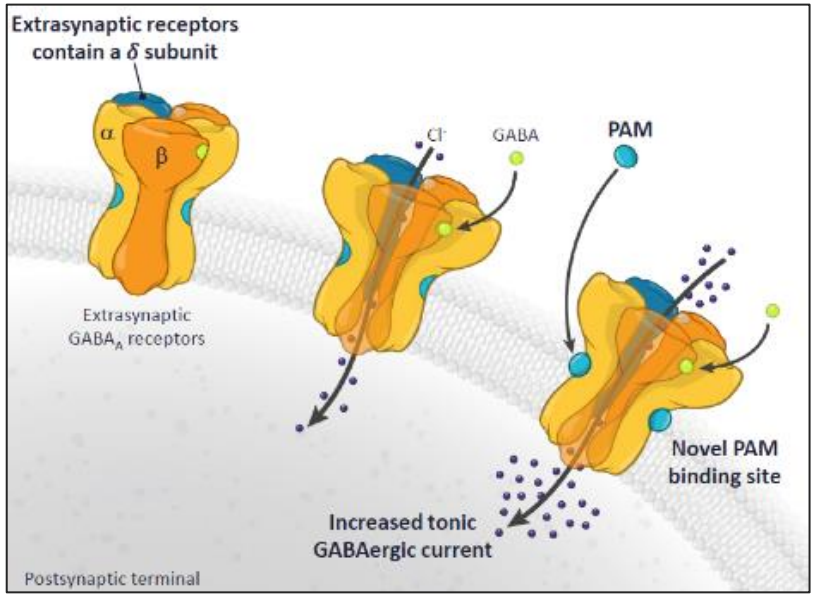
F.D.A. Approves First Drug for Postpartum Depression

The medication works quickly, within 48 hours. But it's an expensive infusion and requires a stay in a medical center.

ZULRESSO™ (Brexanolone) Injection is Hypothesized to Work in PPD by Increasing GABA Function

Brexanolone Injection

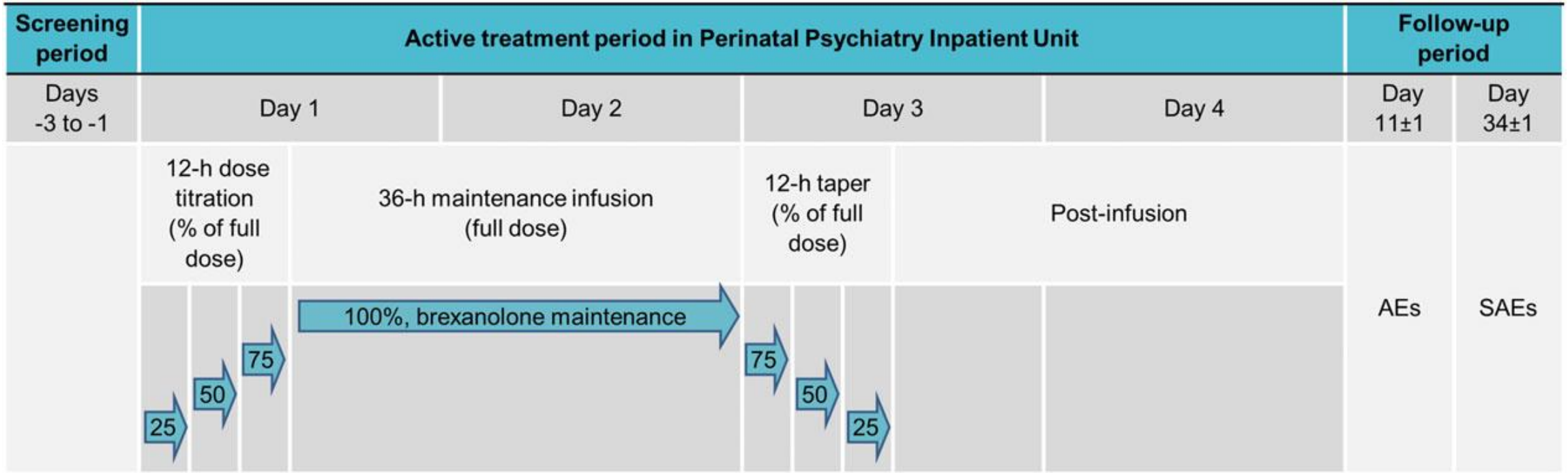
- Proprietary iv formulation of allopregnanolone
- Positive allosteric modulator of $GABA_A$ receptors



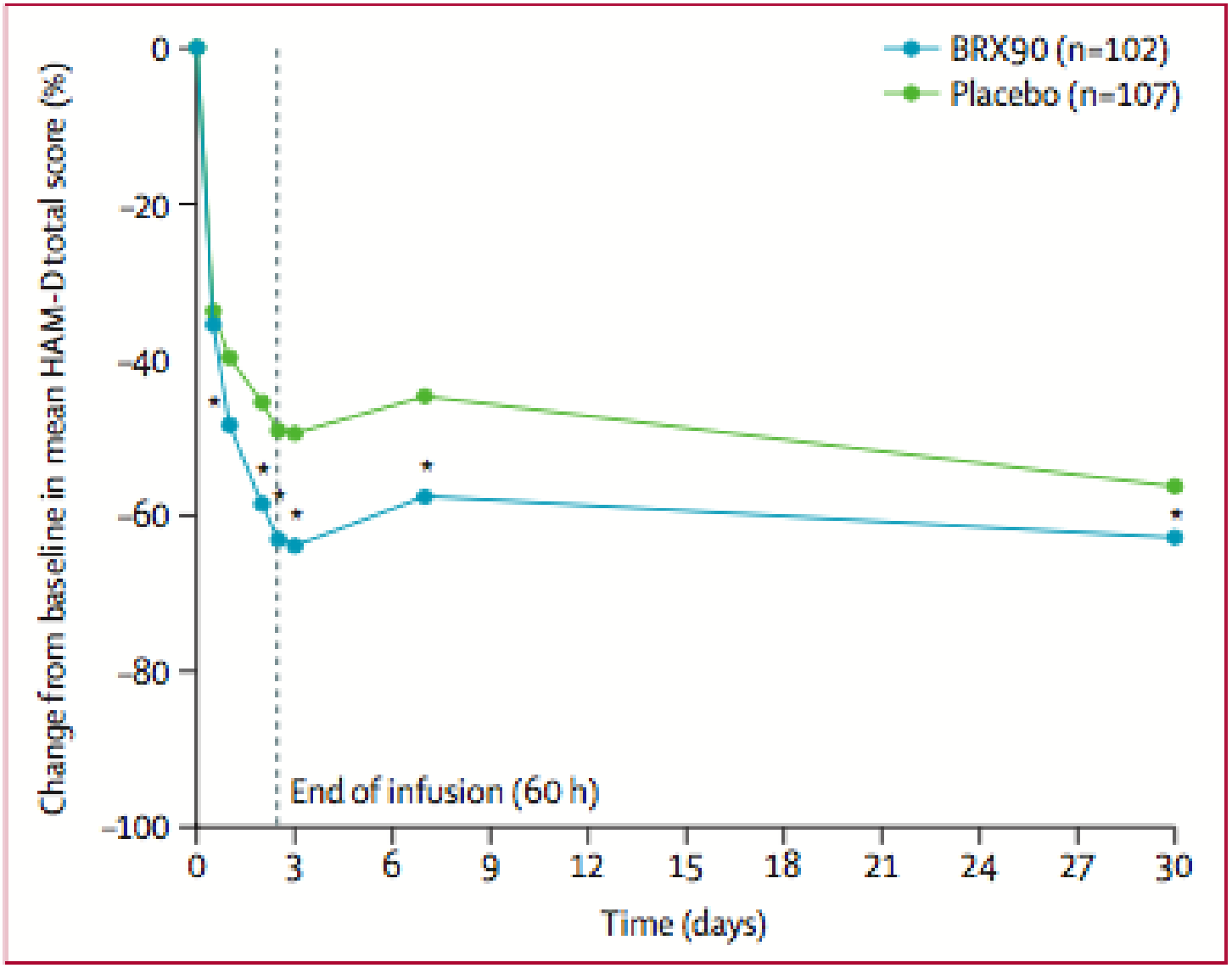
Therapeutic Rationale for Use of Brexanolone Injection

- GABAergic hypofunction has been associated with PPD[1,2,3]
- Brexanolone injection is a positive allosteric modulator of $GABA_A$ receptors[4,5]
- **Therefore, brexanolone injection may have therapeutic potential in PPD by increasing GABAergic function**

1. Luscher B, et al. *Molecular Psychiatry* 2011; 16(4): 383-406; 2. Deligiannidis KM, et al. *Psychoneuroendocrinology*. 2016;70:98-107; 3. Epperson CN et al *Psychopharmacology* 2006; 186(3): 425-433; 4. Maguire J and Mody I. *Psychoneuroendocrinology*. 2009 Dec;34 Suppl 1:S84-90; 5. Bialer M, et al. *Epilepsy Res* 2015; 11:85-141.

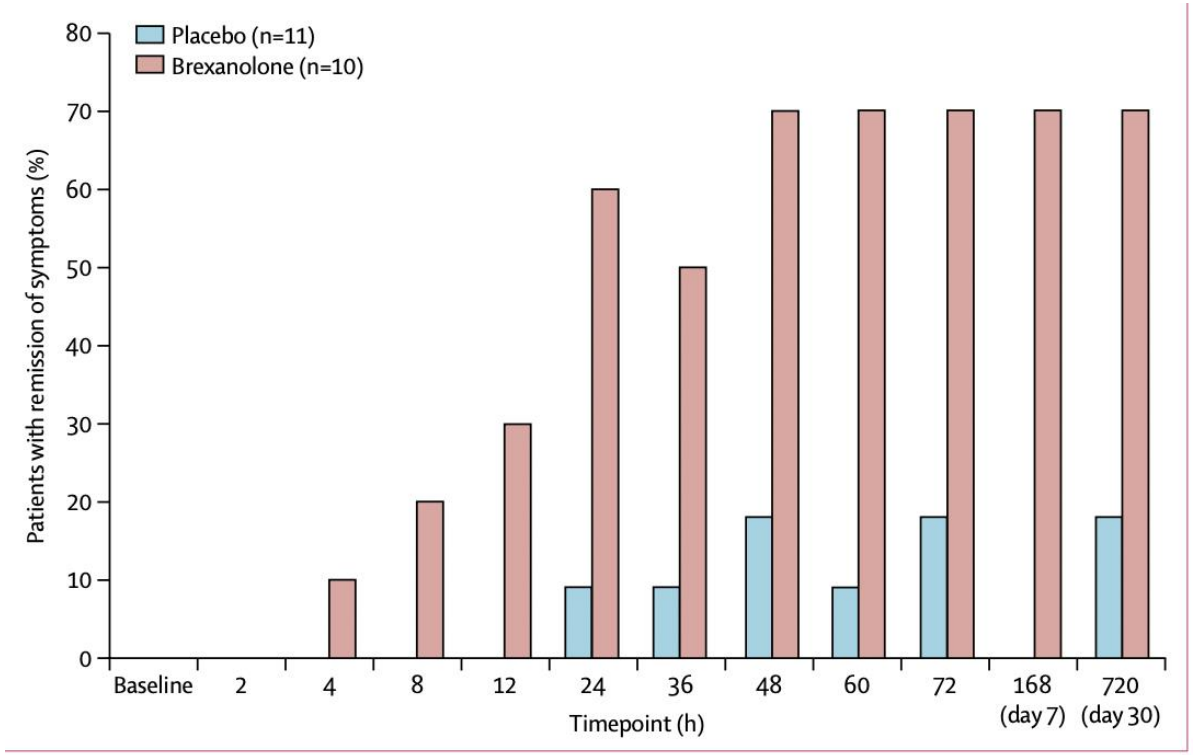


Infusion Plan – 60 HR IV INFUSION



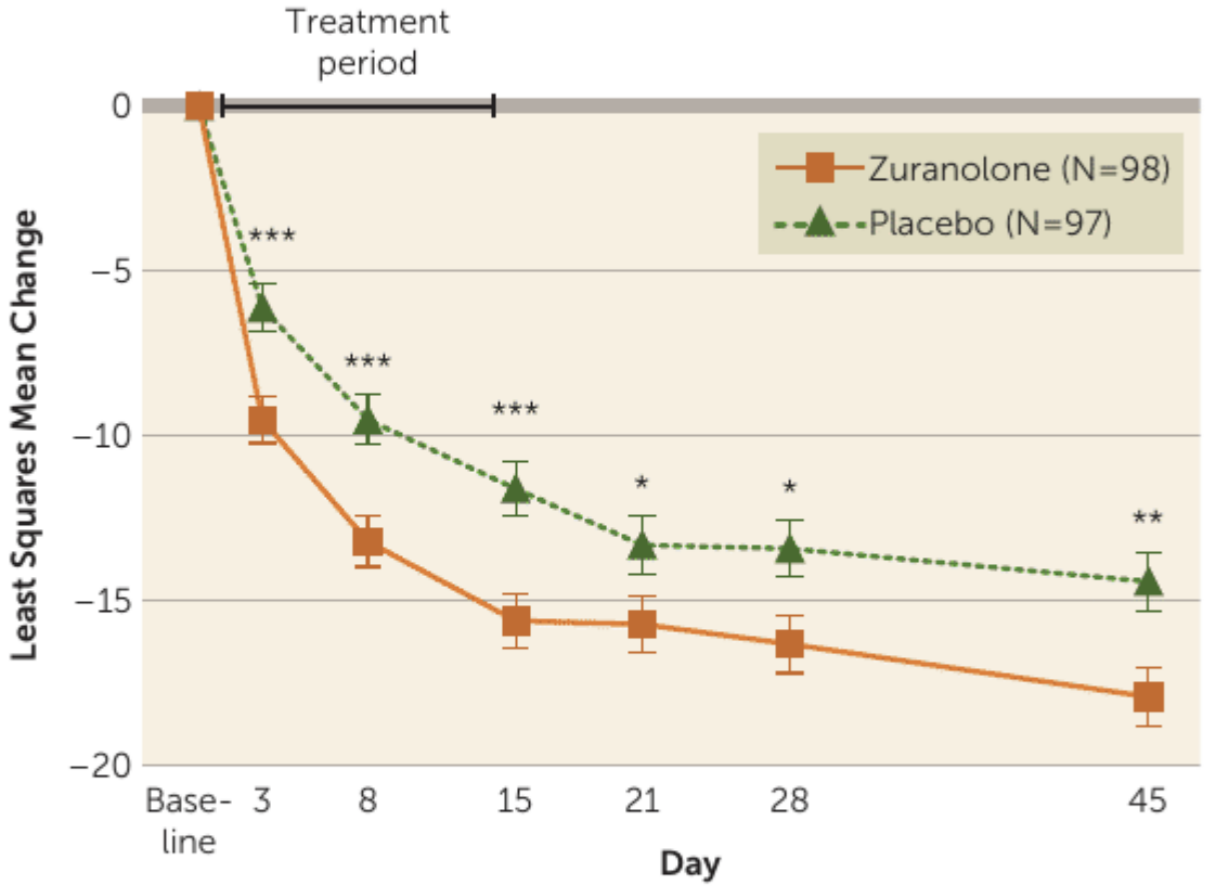
Integrated Analysis

Meltzer-Brody et al., Lancet 2018; 392: 1058–70



Remission Rates: HAM-D $\leq$ 7

FIGURE 2. Change from baseline in HAM-D score in a placebo-controlled trial of zuranolone 50 mg/day for postpartum depression (full analysis set)[a]



Zuranolone

Treatment Criteria?

Moderate to severe depression

Onset during the third trimester of pregnancy or </= 4 weeks postpartum, presenting at </= 12 months postpartum

Dosage and Administration

- Administer with fat-containing food
- Recommended dosage is 50 mg PO qhs x 14 days
- Dosage can be reduced to 40 mg if significant CNS side effects
- Hepatic or renal impairment, dosage is 30 mg PO qhs x 14 days
- Can be used alone or as an adjunct to antidepressants
- Do not drive, operate machinery, or do other dangerous activities until at least 12 hours after taking each dose

Tolerability

Incidence of adverse reactions that led to discontinuation in patients treated with 50 mg of zuranolone and placebo was 2% and 1%, respectively.

The most common adverse reaction leading to treatment discontinuation in zuranolone-treated patients was somnolence.

Dosage reduction due to an adverse reaction occurred in 14% of zuranolone-treated patients. The most common adverse reactions leading to dosage reduction in zuranolone-treated patients were somnolence (10%) and dizziness (6%).

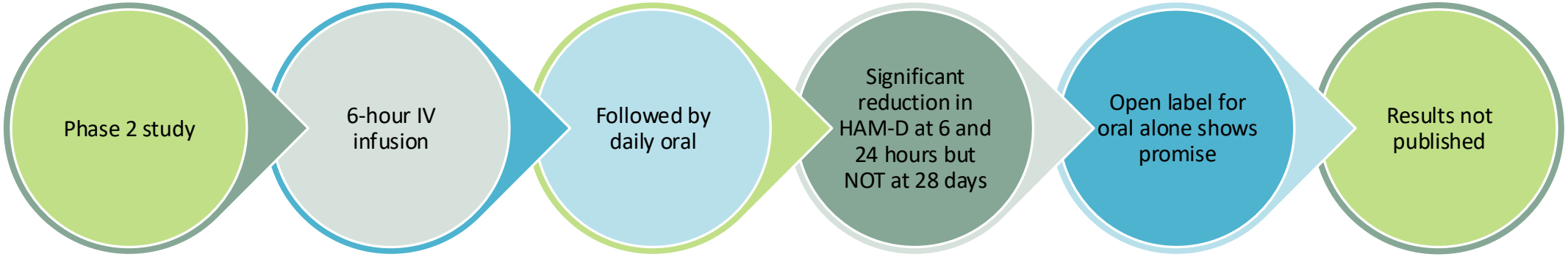
Feeding Criteria?

N=14 healthy lactating women who were 12 or more weeks postpartum and treated with oral administration of 30 mg of zuranolone daily for 5 days.

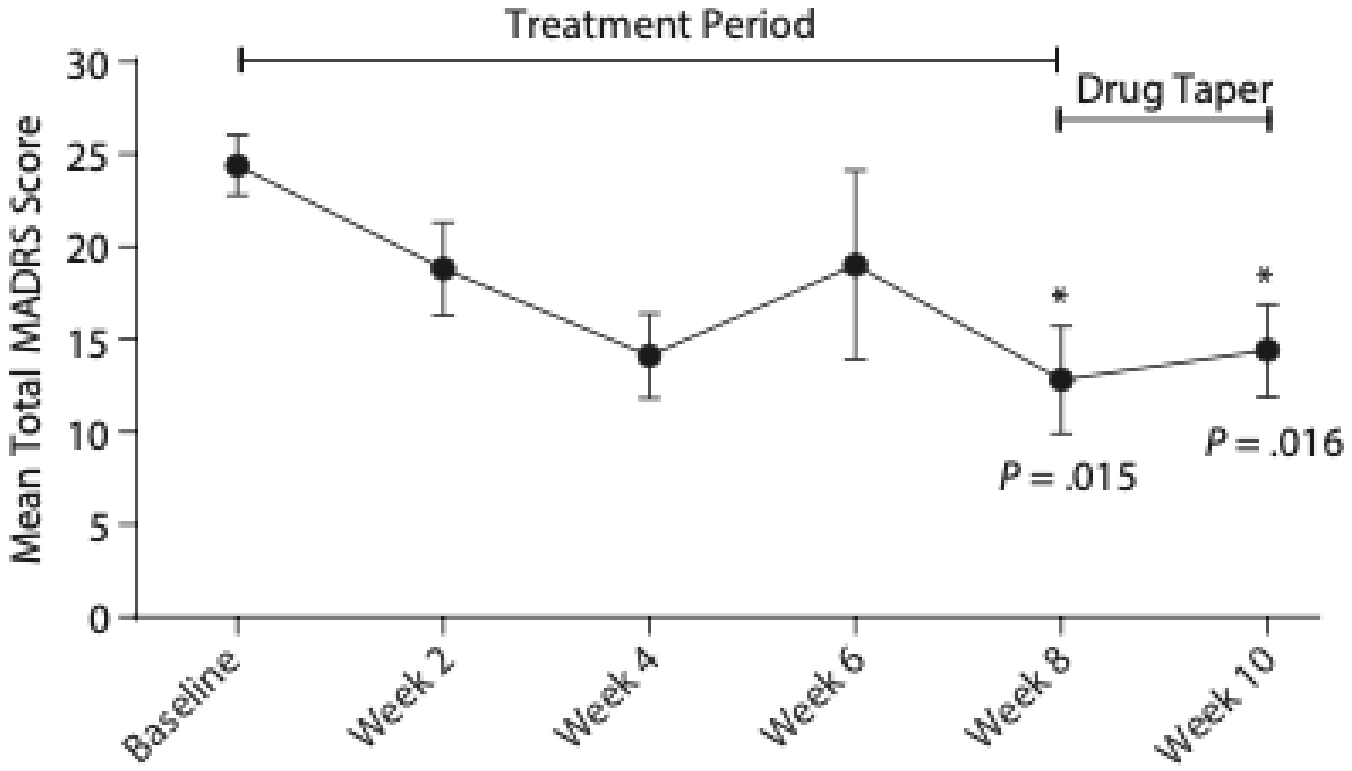
The daily infant dose via milk was estimated to be 0.00124 mg/kg, resulting in a mean weight-adjusted relative infant dose of 0.357% compared to the maternal dose.

Concentrations of zuranolone in breastmilk were below the level of quantification limit by 4 to 6 days after the last dose.

Ganaxolone for PPD

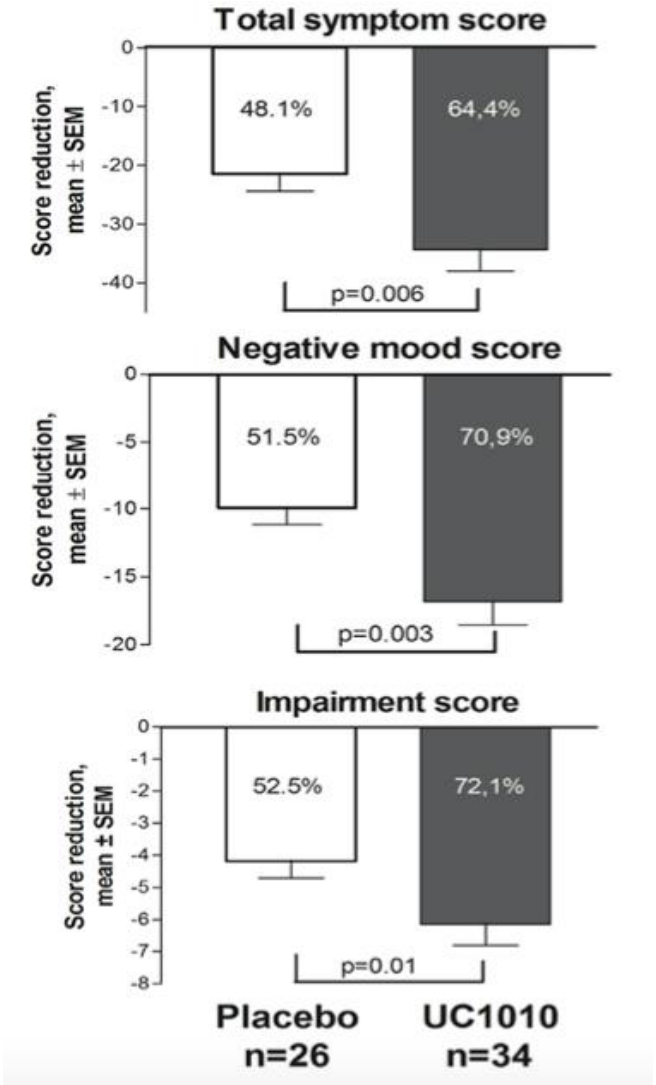


Dichtel et al., J Clin Psychiatry 81:4, July/August 2020



Ganaxolone post-menopause

Sepranolone for PMDD



PMDD symptoms arise in luteal phase – with rising ALLO

Or maybe it is slope of decline?

Proof-of-concept study with isoallopregnanolone, a GABA-A receptor ANTAGONIST

Strong effect in true PMDD, did not work in PME

Backstrom et al., Psychoneuroendocrinology 2021 Nov;133:105426

Conclusions

Substantial evidence for role of NAS dysregulation in pathophysiology

Relationship between NAS and symptoms may differ according to cycle and pregnancy state

Definition of reproductive illness crucial

Promising avenue for treatment, but early days yet

Thank You!

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- Brain and Behavior Foundation
- Doris Duke Early Clinician Investigator Award
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- Samantha Meltzer-Brody
- Laura Riley

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- Kristin Voegtline

“Untangling Anxiety: Diagnostic Pearls and Evidence-Based Treatment for Children and Adolescents”

THE UNIVERSITY OF ARIZONA
COLLEGE OF MEDICINE TUCSON
Psychiatry

Kathy W Smith MD
kwsmith@arizona.edu
January 17, 2026

No Disclosures

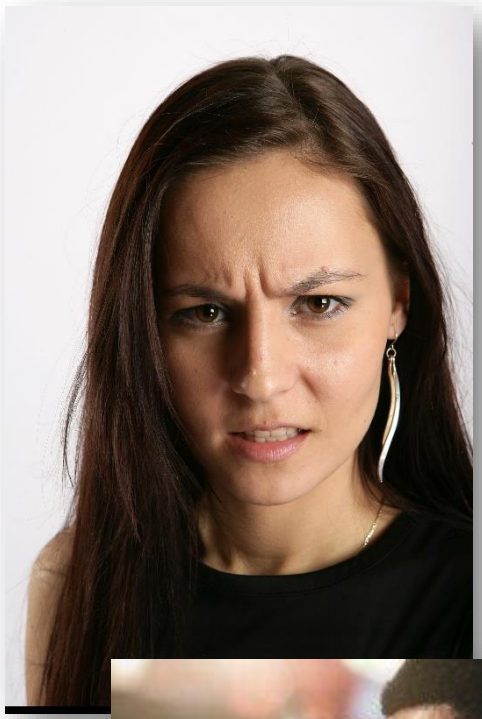
Learning Objectives

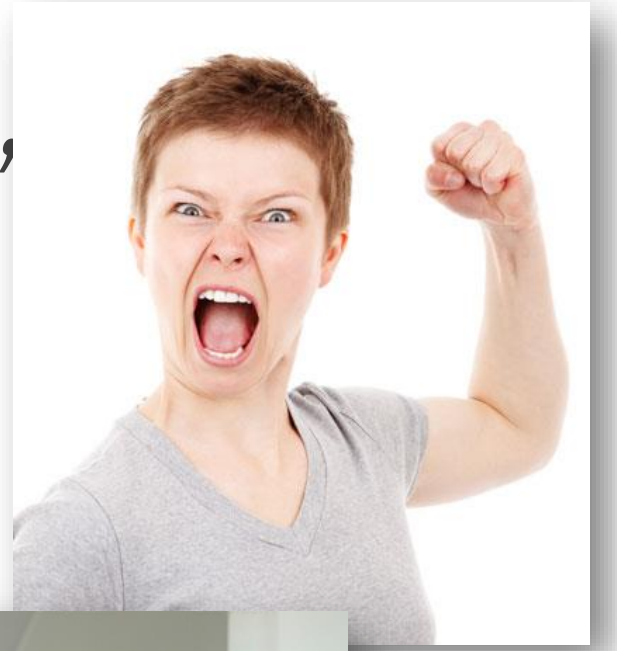
By the end of this session, participants will be able to:

1. Describe the hallmark features of common anxiety disorders in children and adolescents.
2. Explain the current evidence-based psychopharmacological treatments of common anxiety disorders in children and adolescents.
3. Recognize complex presentations of anxiety disorders in children and adolescents to develop appropriate treatment interventions in children and adolescents.

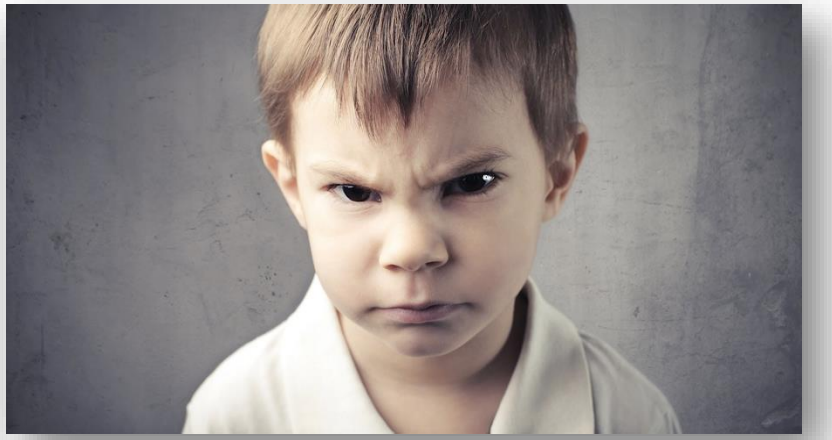
What is "Anxiety?"

“They were really upset.”





An undifferentiated term



Anxiety Disorders

Fears: Emotional response to real/perceived imminent threat

- Fight/flight
- Hyperarousal - autonomic response and escape

Worries: Anticipation of future threat(s)

- Muscle tension
- Vigilance/cautious or avoidance

Excessive Fear/Worry (+) a Hallmark Feature

Generalized Anxiety Disorder: Inability to control multiple worries; associated with physical symptoms

Separation Anxiety Disorder: Fear that harm will come to caregivers or lead to separation

Social Anxiety Disorder: Fear of scrutiny and negative judgment of others

"Other/Unspecified": When there is insufficient information

Specific Phobia

Panic Disorder

Agoraphobia

Selective Mutism

Anxiety Disorders

Severity

Must persist for > 6 months

Must have functional impairment

It isn’t something else

Assess for Opportunities for Positive Stress Response

- Brief, mild/moderate in magnitude
- Requires caring/responsive adult to bring about return to baseline
- Growth promoting for development
- Provides important opportunities to learn, observe, and practice healthy responses to adversity

Help Caregivers Create Tolerable Stress

- Non-normative exposure to stress, greater magnitude
- With buffered protection from parents
- Facilitates adaptive coping and sense of control
- Lower risk of long-term negative outcomes for health and learning

Identify and Eliminate Toxic Stress

- Prolonged exposure of severe stress
- Develops without protective buffering from caregivers
- Disrupts normal development, changes in physiologic circuitry & regulation
- Negative long-term outcomes in health, learning, behavior

To Begin - What We Need to Know

Primary Diagnosis or Target Symptoms

~~Must persist for > 6 months (separate from transient stress)~~

Assess level of functional impairment

Severity

It isn't something else

Comorbidities

Stressors

Family Hx

Family Functioning

TREATMENT
Am I going to use a medication?

CBT only:

For mild severity

Minimal functional impairment

Supportive family interactions

Minimal comorbidities

10-16 weeks

Add Medications:

When psychotherapy fails

For moderate-severe impairment

Poor school performance

School refusal

Sleep impairment

Comorbid depression

Walter HJ et al, Clinical Practice Guideline; AACAP, 2020.

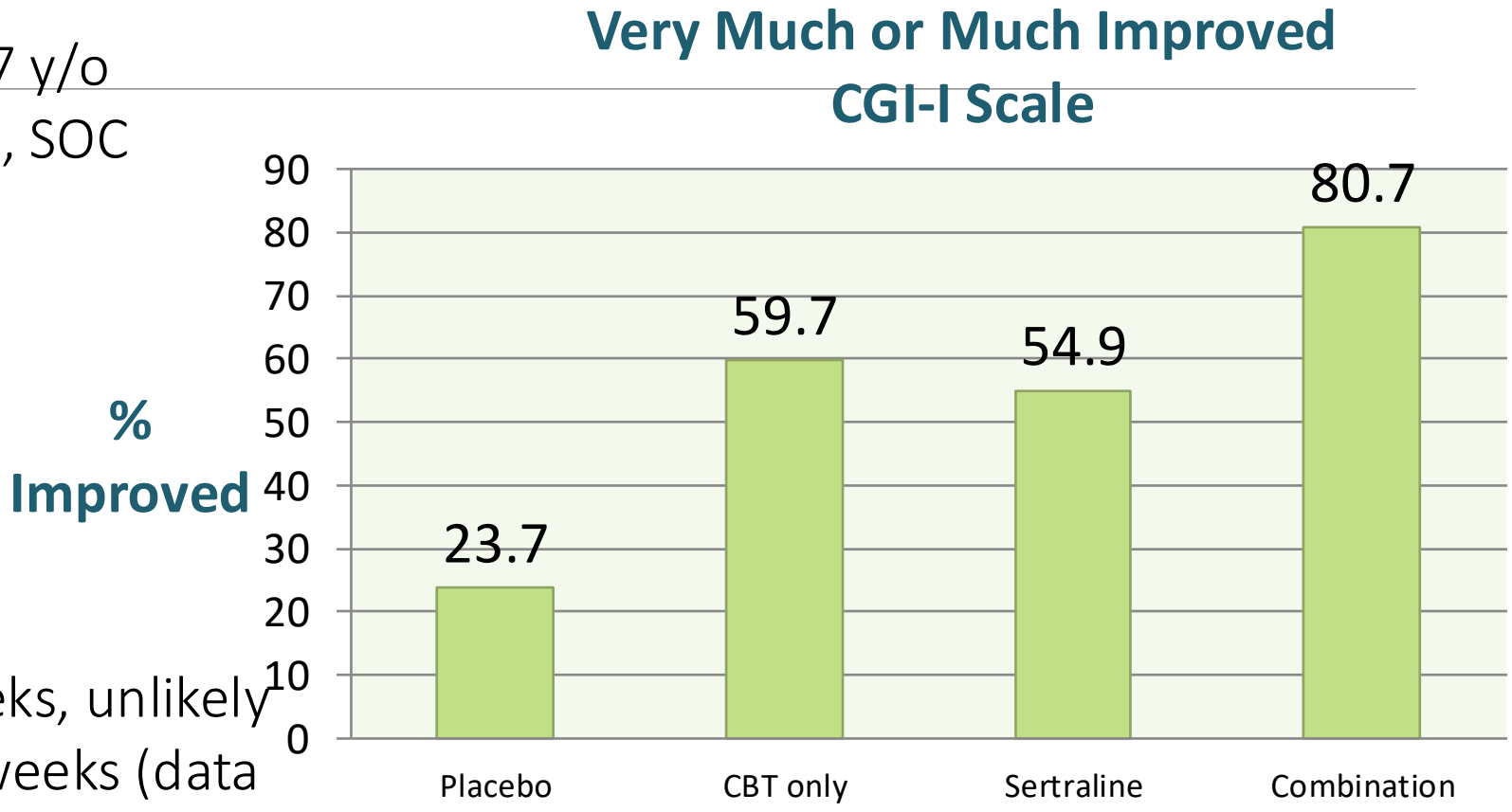
Which Medication Should I Choose?

Which drugs have FDA approval for specific anxiety disorders?

Which drugs have the most evidence for the treatment of anxiety disorders in youth?

Child/Adolescent Multimodal Anxiety Study (CAMS)

12-week study; N=488, 7-17 y/o
Moderate-Severe SAD, GAD, SOC



In SSRI group:

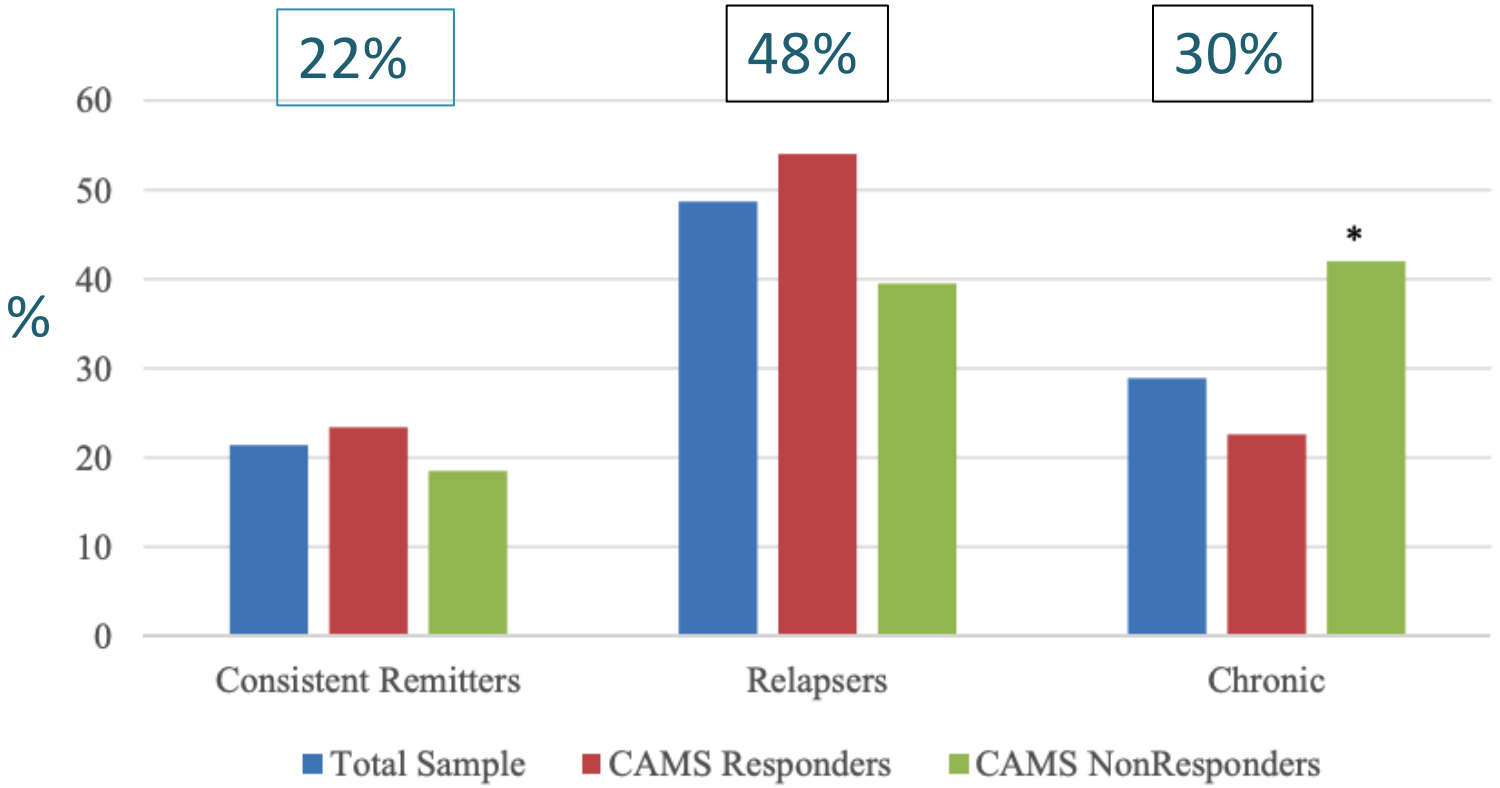
- NNT: 3
- *If no response by 8 weeks, unlikely to benefit after 4 more weeks (data not shown)

Walkup J et al. *N Engl J Med* 2008; 359:2753-2766.
*Strawn JR, Vaughn S, Ramsey LB; Focus, 2022.

CAMELS Study Anxiety Outcomes

Predictors of Remission:

-CAMS responder to ANY treatment arm
-Male
-Younger
-No social phobia
-Better global function
-Better family functioning
-Fewer interim (-) life events



Naturalistic study, 6 sites; 4-yrs
N=319 (65.3% CAMS sample)

Ginsburg GS, et al.. JAACAP, 2018.

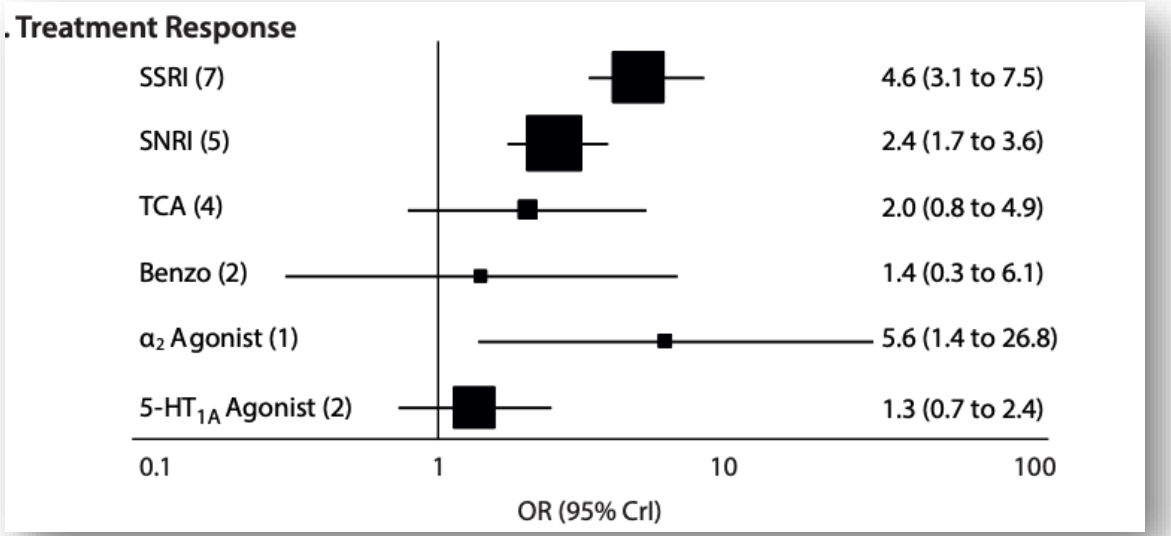
Network Meta-Analysis of Medications for Pediatric Anxiety Disorders

For treatment response and reduced anxiety symptoms:

- SSRIs were superior to SNRIs
- Sertraline most tolerated and efficacious

For treatment response:

- SNRIs and alpha-2 agonists also superior to placebo
- SSRIs had more discontinuation due to AEs than SNRIs



Dobson et al, J Clinical Psychiatry, 2019.

Other Medications

Not enough data:

TCAs

Benzodiazepines

Buspirone - 1 (+) open label

Mirtazapine

Alpha-2 agonists - 1 (+) open label PTSD

Atomoxetine - 1 (+) with comorbid ADHD

5-HT agonists

Stahl and Strawn; Prescriber's Guide – Children and Adolescents; 2nd Ed, 2024.

Which Medication to Choose?

Which drugs have FDA approval for specific anxiety disorders in youth?

General Anxiety Disorder

Duloxetine, 7 – 17 y/o

Escitalopram, 7 -17 y/o

Which drugs have the most evidence for the treatment of anxiety disorders in youth?

SSRIs

Starting Medication

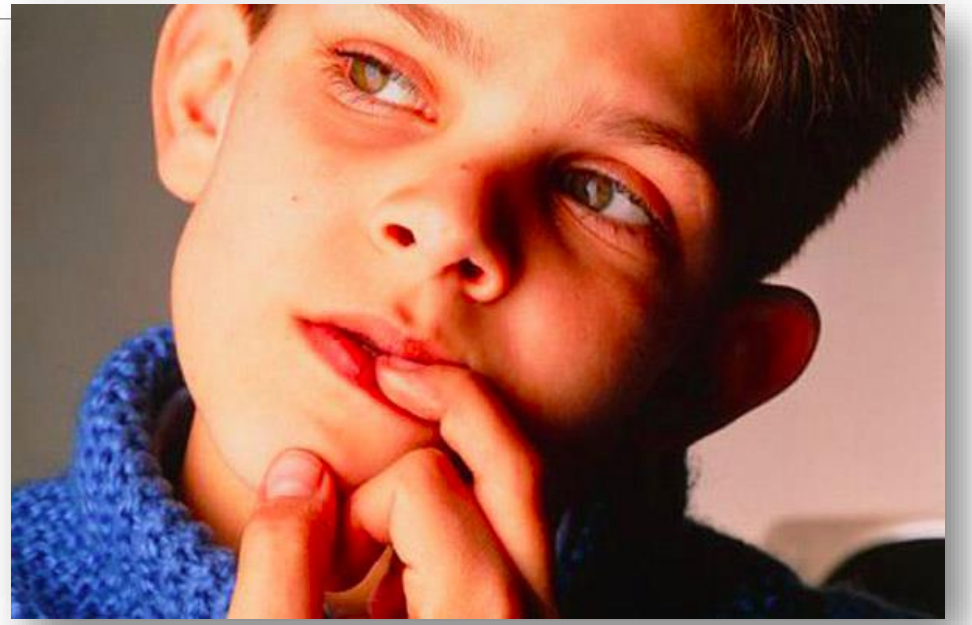
1. **CONSIDER:**

Drugs:

- FDA indications for specific diagnoses
- Clinical guidelines
- Best data
- Drug SE profile, interactions

Patient:

- Pharmacokinetics/Pharmacodynamics
- What worked for patient before
- What worked for family member
- Assess for baseline somatic symptoms
- Screen for bipolar disorder



Strawn JR, Vaughn S, Ramsey LB; Pediatiric Psychopharmacology for Depressive and Anxiety Disorders; Focus, 2022.
Walter HJ et al. Clinical Practice Guideline, AACAP, 2020

Antidepressants - Pediatric Anxiety

Class	Medication	FDA Approval	Drug Attributes
SSRIs			**SSRIs more discontinuation syndrome and activation**
	Escitalopram	**≥ 7 y/o**	
	Fluoxetine		Long half-life, can dose QD
	Sertraline		Lower doses BID
	Fluvoxamine		Short half-life, higher risk discontinuation, dose BID, may have greater risk drug interactions
	Paroxetine		Short half-life, higher risk discontinuation, dose BID
	Citalopram		Concern for QTc prolongation above 40mg
SNRIs			**Less discontinuation, less activation than SSRIs**
	Duloxetine	**≥ 7 y/o**	GI SEs oropharyngeal pain, monitor HR/BP
	Venlafaxine		Some data, monitor HR/BP

Strawn et al; Focus, 2022. Rynn MA, Yanes-Lukin P, Goldberg P. Anxiety Disorders,; Clinical Manual of Child and Adolescent Psychopharmacology; 4th ed.; 2024

2. DOSING: Start Low

Starting Medication

Developmental Differences in Psychopharmacology

PHARMACOKINETICS

Absorption: Faster

Higher peak drug levels

Distribution: V_D smaller and less protein binding

More bioactive drug in plasma

Metabolism: Faster

Increased metabolite:parent blood levels

Shorter half-life

Larger dose/kg than adults

Excretion: Higher renal clearance

PHARMACODYNAMICS

Differences in pathways and receptor densities

More activation

Different side effect profiles

Stahl and Strawn; Prescriber's Guide – Children and Adolescents; 2nd Ed, 2024.

Pharmacogenetics – A Supportive Role

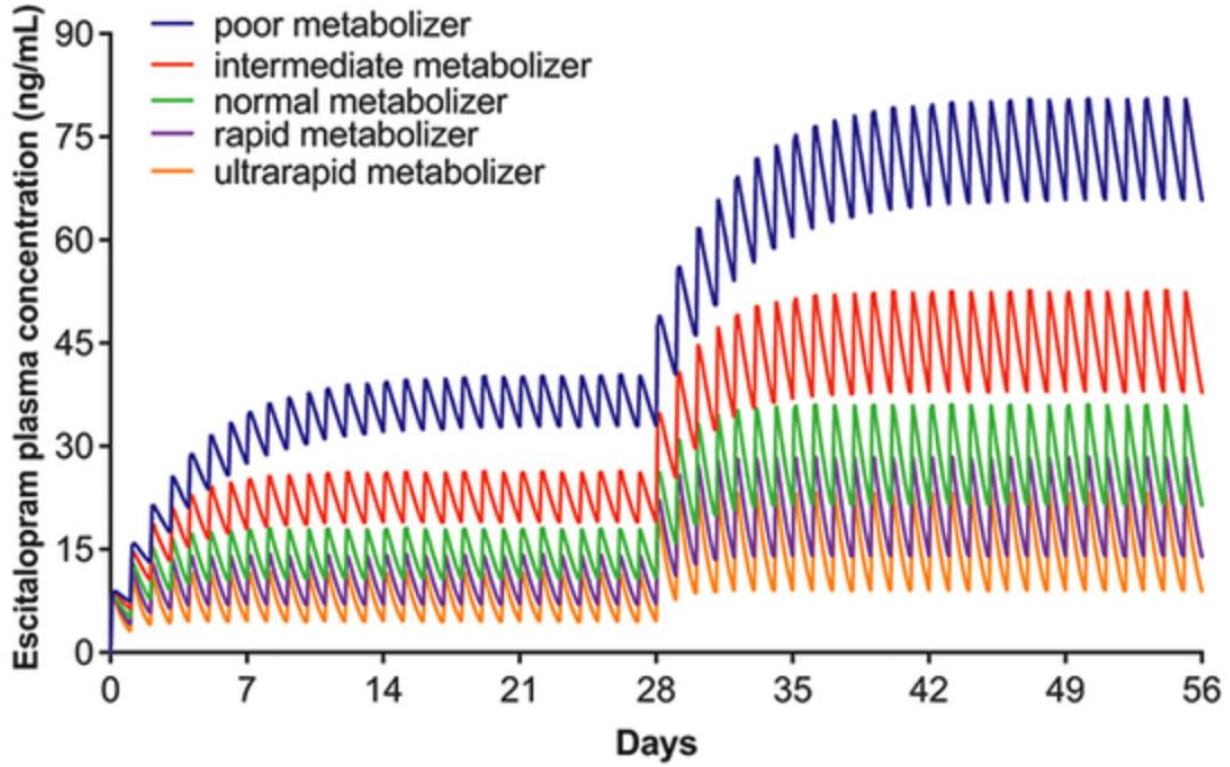


Figure 1 Escitalopram plasma concentrations in adolescents with different CYP2C19 phenotypes. Treatment was initiated at 10 mg daily and increased to 20 mg daily at week 4. There is considerable variation in blood concentrations of escitalopram among the CYP2C19 phenotypes, as demonstrated in this series of adolescent patients.

- Higher plasma concentration levels for poor or intermediate metabolizers
- Can consider dose adjustments for metabolizer phenotypes

Strawn JR & Stahl SM; Prescriber's Guide: Children and Adolescents, 2024.

Starting Medication

3. Informed Consent/Assent

Target symptoms, prioritize

Proposed medication plan

Specific rationale and risks

Alternatives to medication

FDA-approved versus off-label

Cost

Monitoring plan

Concurrent treatment/interventions

Stahl and Strawn; Prescriber's Guide – Children and Adolescents; 2nd Ed, 2024.

Starting Medication

4. Titrate:
   - Increase slowly q1-2 weeks with short half-life
   - ~~Increase q3-4 weeks with longer half-life~~
   - Faster if severe impairment

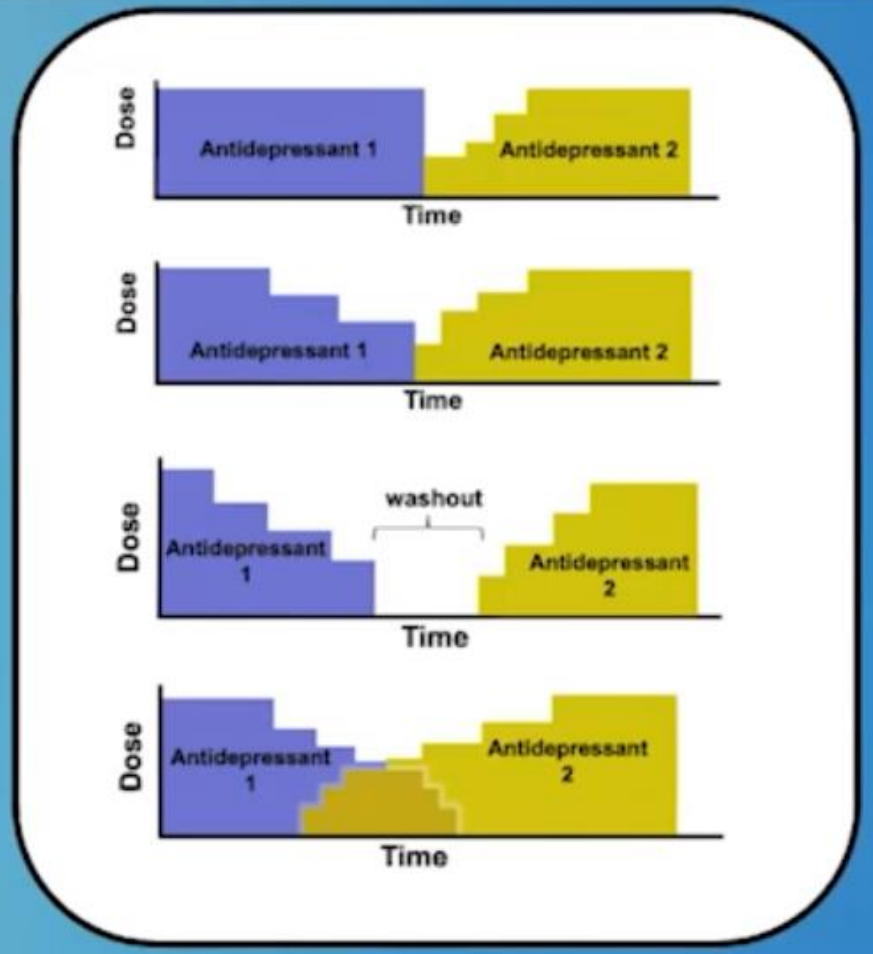
5. Optimize for at least 8 weeks
   - Until remission or intolerable side effects
   - May need higher doses, may take longer

6. If no response after 8 weeks: SWITCH
   - Another SSRI or SNRI

Strawn JR, Vaughn S, Ramsey LB; Pediatric Psychopharmacology for Depressive and Anxiety Disorders; Focus, 2022.
Walter HJ et al. Clinical Practice Guideline, AACAP, 2020

Switching Medications

- **Direct switch:** stop first antidepressant and start new antidepressant
- **Taper and switch immediately:** gradually taper the first antidepressant and start the new antidepressant immediately after discontinuation
- **Taper and switch after a washout:** gradually withdraw the first antidepressant then start the new antidepressant after a wash out period
- **Cross-tapering:** taper or maintain the first antidepressant while beginning the new antidepressant



Keks N et al. Aust Prescr 2016;39(3):76-83;
Stahl. Stahl's Essential Psychopharmacology: The Prescriber's Guide. 4th Edition.

Continuation Phase:

- Monitor for SEs to improve adherence
- Optimized treatment for 9-12 months

What if there is a relapse?

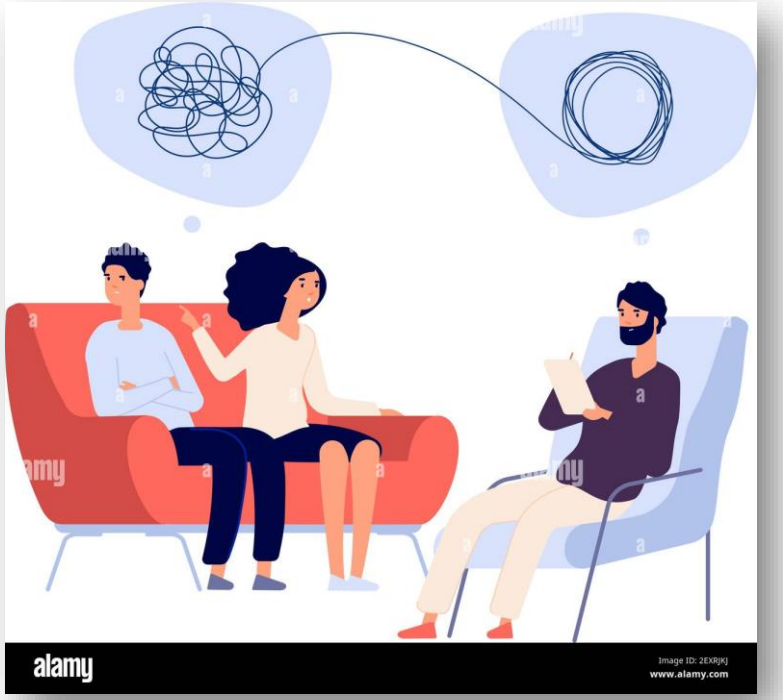
….Start Over…

Goal is remission,

not a shorter duration of treatment

Maintenance Phase:

- Monitor for risk factors recurrence
- What is there is a recurrence?
  - …Start Over…



Monitoring

Common:

SSRIs

- Nausea, diarrhea, GI distress
- Dry mouth
- Restlessness
- Bruxism, tremor
- Diaphoresis
- Headache, dizziness, vivid dreams
- Sleep changes
- Weight loss/gain

SNRIs - HR and BP changes

Side Effects

Serious:

~~Behavioral activation~~

Suicidal Ideation

Serotonin syndrome

Discontinuation syndrome

Seizures

Abnormal bleeding

Duloxetine – liver failure

Walter HJ et al; Ciinical Practice Guideline for the Assessment and Treatment of Children and Adolescents With Anxiety Disorders; JAACAP, 2020.

Behavioral Activation

Activation

10-15% clinical trials

Increased impulsivity, agitation, silliness, motor activity or irritability

No mood changes

Pharmacokinetics

- Occurs early with initiation or increase in dose
- gets worse with higher dose

Remits with decreased dose or discontinuation

“More of the same”

Does not lead to suicidality

Hypomania/Mania

<1.0%

Increased motor activity or irritability

Euphoria, grandiosity, hypersexuality, decreased need for sleep

Pharmacodynamics

- Occurs later (4-6 weeks)

May not remit with decreasing dose

Family Hx bipolar disorder

“He has never been like this before” or “…and then one day…”

Luftt et al; Curr Probl Pediatr Adolesc Health Care, 2018.
Walter HJ et al; Practice Guideline; JAACAP, 2020.

Suicide Risk:

FDA sponsored meta-analysis of 24 RCTs (2004)

- Reported an increase in *spontaneous* reporting of suicidal thinking/behavior in treatment group (4%) compared to placebo (2%)

Has never been replicated

Monitor for disinhibition, interpersonal conflicts, substance abuse or activation

Discontinuation (Withdrawal) Syndrome:

Can mimic relapse or recurrence or worsening of anxiety

More likely with shorter acting drugs, and QD dosing

Change to BID if needed

Taper slowly

Birmaher B & Re M; Major Depressive Disorder; Clinical Manual of Child and Adolescent Psychiatry; 4th Ed.; 2024
Strawn JR, Vaughn S, Ramsey LB; Pediatiric Psychopharmacology for Depressive and Anxiety Disorders; Focus, 2022..

Continuation Phase:

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- Monitor for risk factors recurrence
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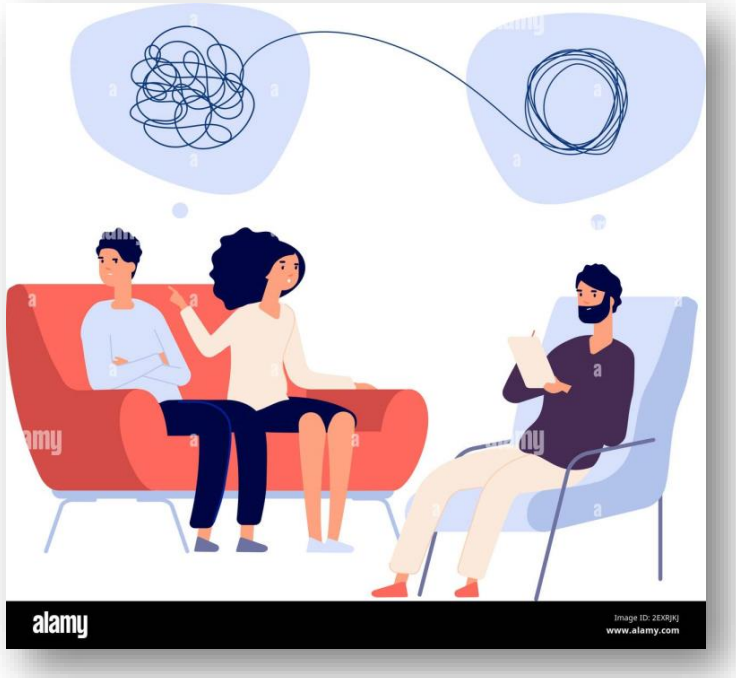


TREATMENT RESISTANCE… REMEMBER THE NNT

Reassess for:

Correct diagnosis

Psychiatric/medical comorbidities complicating clinical picture or contributing factor to anxiety

Adherence issues/Intolerable SEs

Contributing stressors that need to be addressed

- Family stressors, sleep, trauma

Cytochrome P450 polymorphisms

Appropriate length of drug trial/early discontinuation

Evidence-based practices

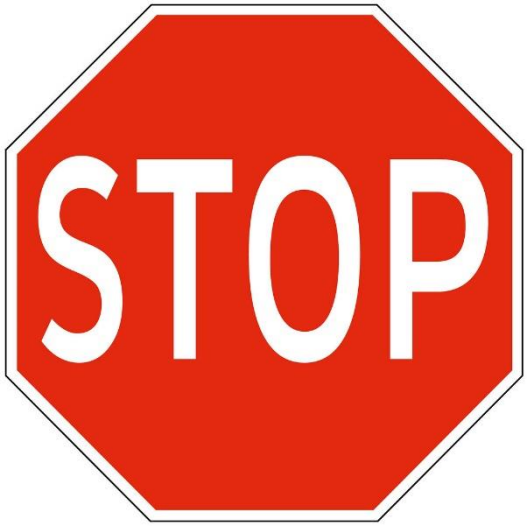
Strawn, J. AACAP Psychopharm Update, 2024.

IF no response with evidence-based strategies
STOP and START OVER

If diagnosis correct, retrial of SSRI at higher dose

Address specific comorbidities and stressors with evidence-based interventions

There is no data for polypharmacy



If you are feeling the need for polypharmacy, refer or seek consultation for diagnostic clarification

Strawn JR, Vaughn S, Ramsey LB; Pediatric Psychopharmacology for Depressive and Anxiety Disorders; Focus, 2022.
Walter HJ et al. Clinical Practice Guideline, AACAP, 2020
Stahl & Strawn. The Prescriber's Guide: Children and Adolescents, 2024.

Discontinuation

After remission

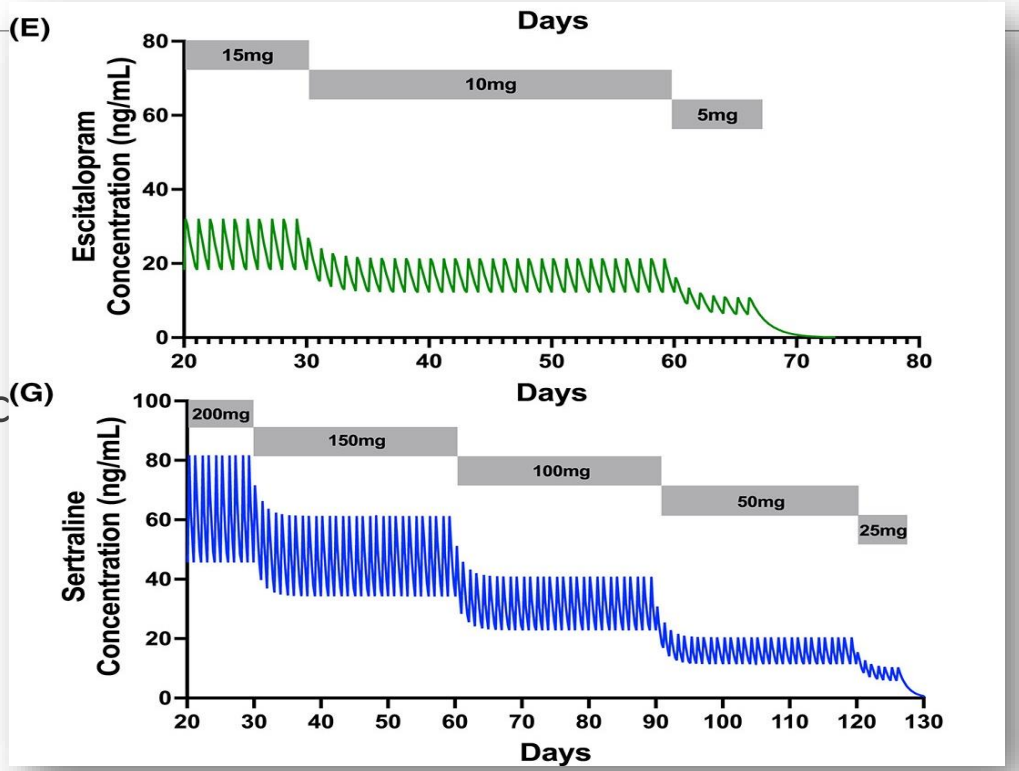
Timing: low stress

“Hyperbolic” discontinuation

Slow taper at least 6 weeks

Avoids withdrawal symptoms which confuses clinic picture

Rapid discontinuation can precipitate relapse



Strawn et al, Pharmacotherapy, Volume: 43, Issue: 7, January 2023.

CASEY *is a 16-year-old with a history of ADHD treated with a long-acting stimulant for the last 6 years, presents for evaluation of worsening anxiety and "always feeling stressed" for the last five months. The patient lives at home with two younger siblings and their parents who are both professionals and work outside the home.*

Constant worry about grades and recently received a "lower than expected" score on the PSAT.

Increased muscle tension, more trouble concentrating, poor appetite with a 5 lb wt loss, and poor sleep secondary to ruminations at night (though parents report poor sleep related to excessive phone use in the evenings.)

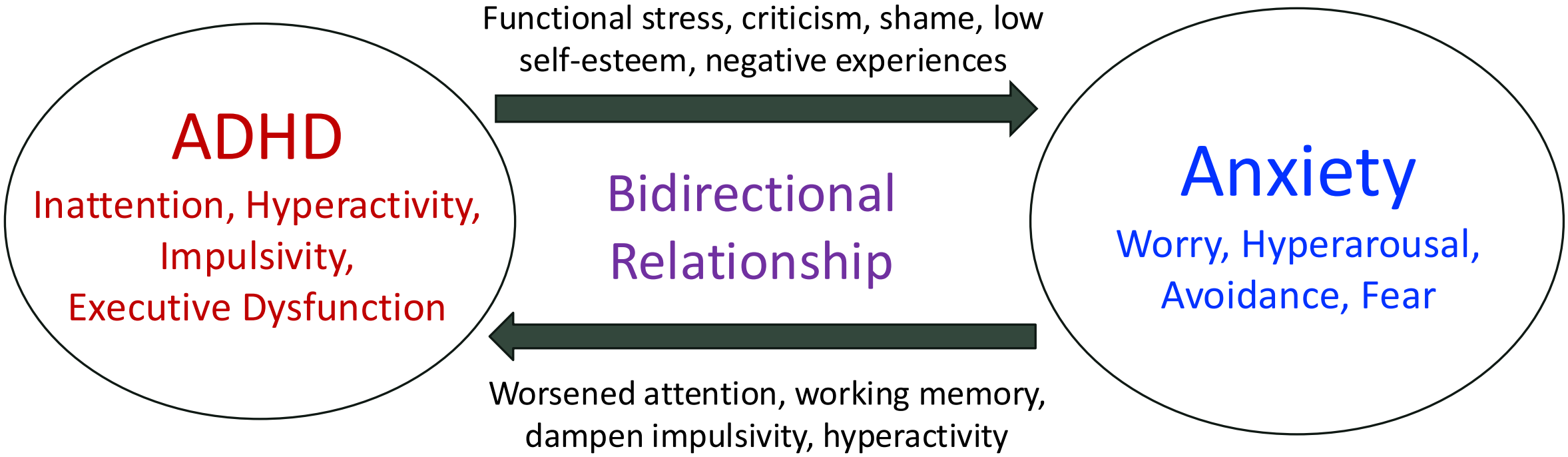
Denies depression, suicidal thoughts or illicit substance use.

Sophomore in an academically accelerated high school, with increasing difficulties keeping up with schoolwork and spends several hours on homework most school nights, and on weekends.

Has done well academically in the past, has a 504 plan for extra time for examinations but is worrying will no longer be competitive for a top tier university.

Plays the trombone in a community orchestra with practice two afternoons/wk and performances 2x/yr and participates in an extramural lacrosse team which practices 3x/wk.

Has good friends but is avoiding social events feeling too overwhelmed to attend, and embarrassed by the PSAT score stating, "EVERYONE did better than me."



Recommend:

- Evaluate and treat separately
- Treat most impairing first
- If equal, treat ADHD first
- Add CBT/SSRIs when ADHD optimized

Koyuncu et al, Current Psychiatry Reports, 2022.

Final Thoughts:

Medications have an important role, but should be driven by accurate diagnosis with evidence-based treatment interventions

Define a therapeutic goal and track to determine response

SSRIs/SNRIs are effective for anxiety disorders

- SSRIs have greater and faster improvement, but more activation and discontinuation symptoms

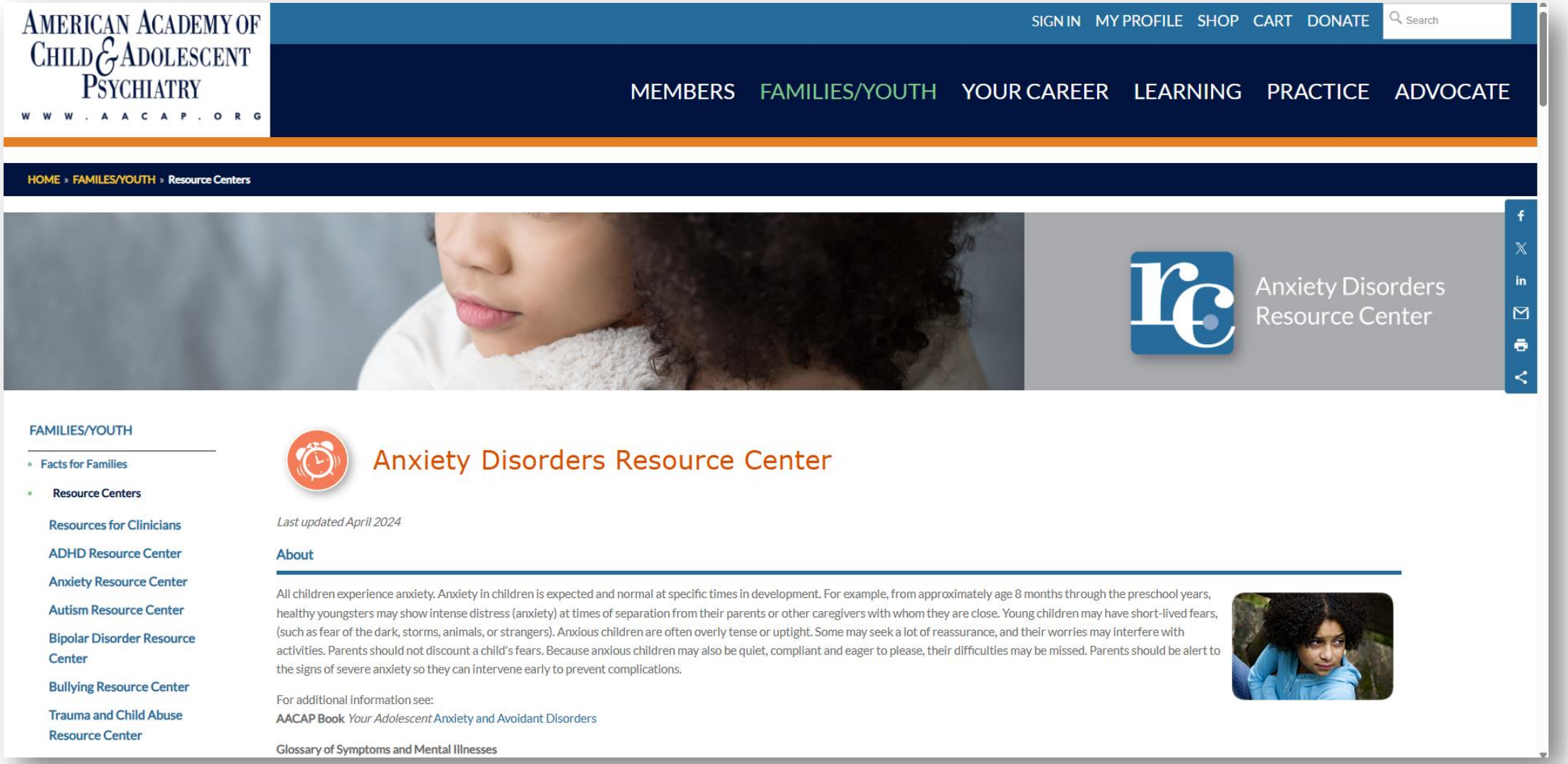
CBT only for “mild” anxiety

CBT/SSRIs is best

Psychoeducation is key to maintain adherence and prevent early termination and misdiagnosis

Watch for comorbidities and stressors, particularly if “treatment resistant” and manage

Resources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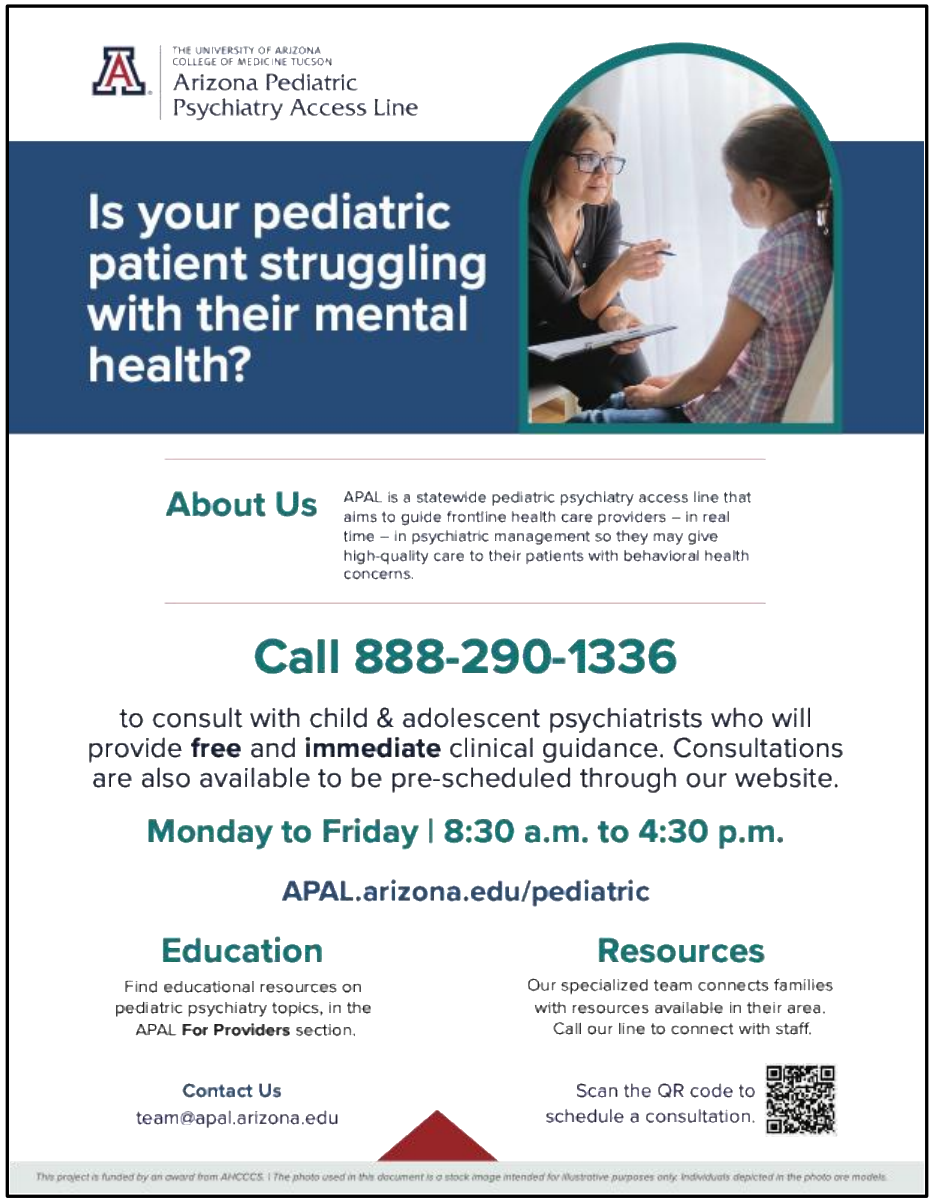
Resources for Clinicians
ADHD Resource Center
Anxiety Resource Center
Autism Resource Center
Bipolar Disorder Resource Center
Bullying Resource Center
Trauma and Child Abuse Resource Center
Anxiety Disorders Resource Center
Last updated April 2024
About
All children experience anxiety. Anxiety in children is expected and normal at specific times in development. For example, from approximately age 8 months through the preschool years, healthy youngsters may show intense distress (anxiety) at times of separation from their parents or other caregivers with whom they are close. Young children may have short-lived fears, (such as fear of the dark, storms, animals, or strangers). Anxious children are often overly tense or uptight. Some may seek a lot of reassurance, and their worries may interfere with activities. Parents should not discount a child's fears. Because anxious children may also be quiet, compliant and eager to please, their difficulties may be missed. Parents should be alert to the signs of severe anxiety so they can intervene early to prevent complications.
For additional information see:
AACAP Book Your Adolescent Anxiety and Avoidant Disorders
Glossary of Symptoms and Mental Illnesses

Resources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Psychiatry Access Line
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About Us
APAL is a statewide pediatric psychiatry access line that aims to guide frontline health care providers – in real time – in psychiatric management so they may give high-quality care to their patients with behavioral health concerns.
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Find educational resources on pediatric psychiatry topics, in the APAL For Providers section.
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team@apal.arizona.edu
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This project is funded by an award from AHCCCS. | The photo used in this document is a stock image intended for illustrative purposes only. Individuals depicted in the photo are models.

Thank You!!

Kathy W Smith, MD

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