Zuranolone and MCPAP for Moms Role

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UMass Chan MEDICAL SCHOOL

Lifeline for families

I have no financial disclosures to report, I have no affiliations with Sage/Biogen.

Objectives

Zuranolone

Prescribing Guidelines

MCPAP for Moms role and how we can help

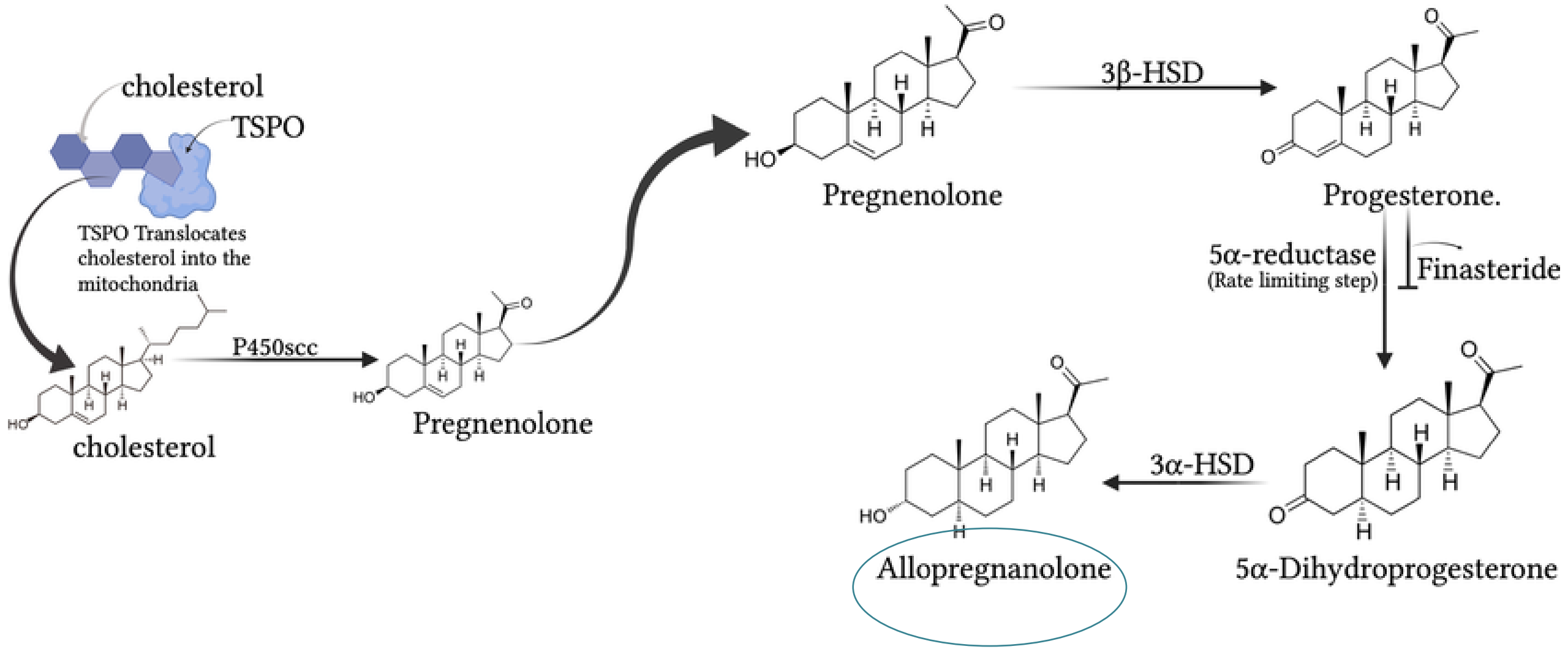
Neurosteroids in postpartum depression

PPD = postpartum reduction of neurosteroids

Neurosteroid withdrawal

Neurosteroid replacement therapy (NRT)

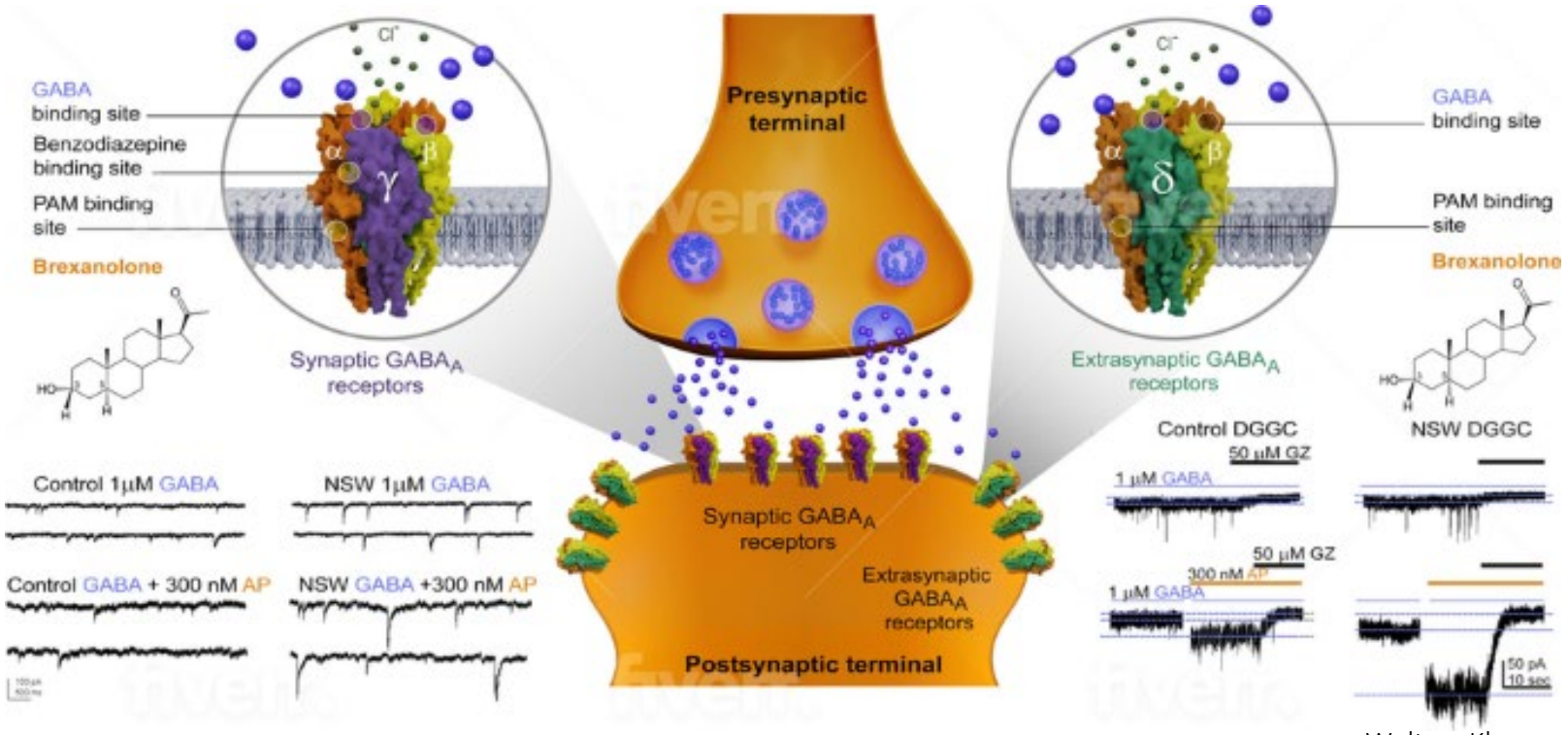
Power of neurosteroids as anxiolytic-antidepressants



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Wolters Kluver

Neurophysiology

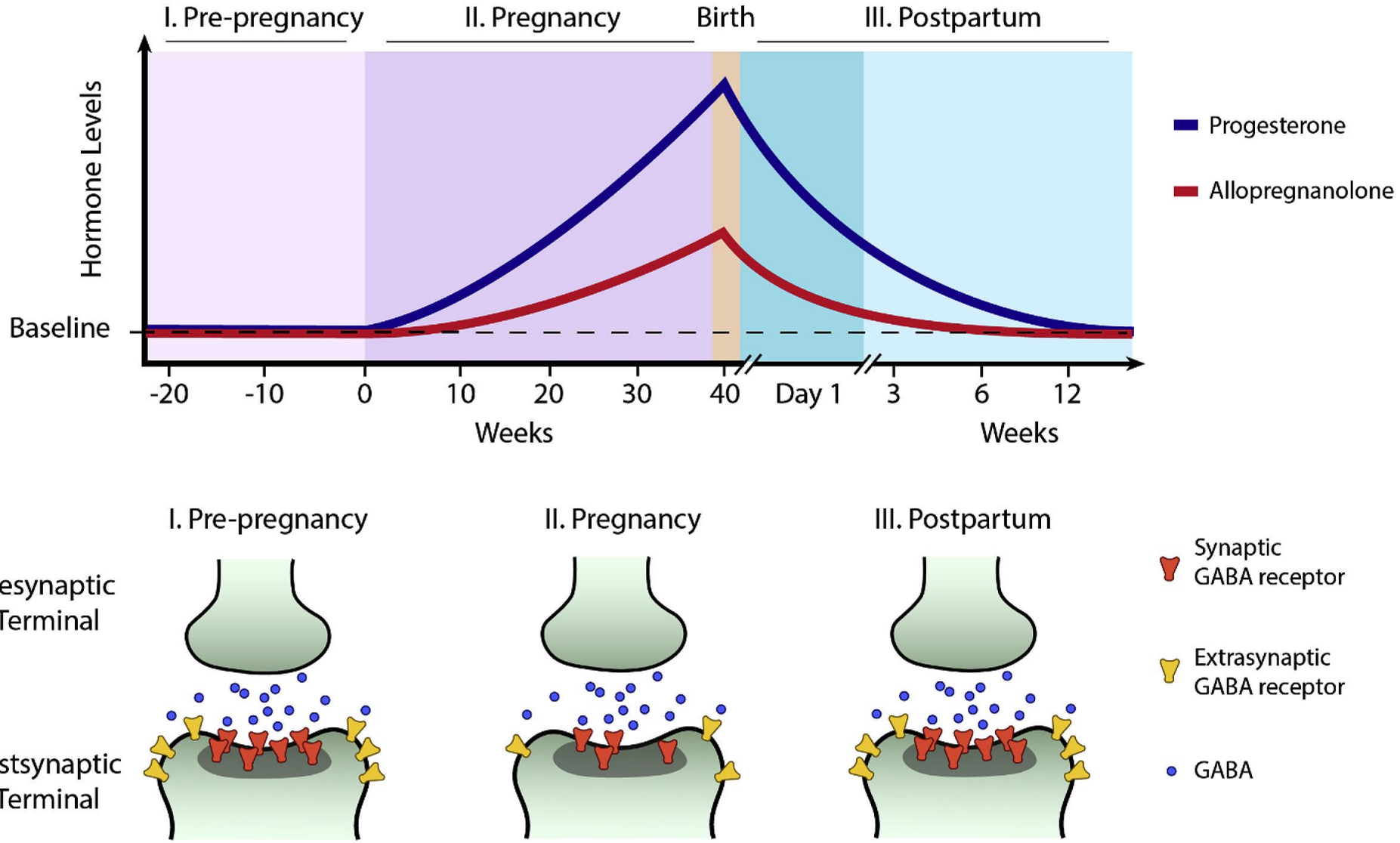


Wolters Kluver

GABA receptor = 5 subunits

Benzodiazapenes -> synaptic receptors = brief, phasic

Allopregnanolone -> extrasynaptic receptors, PAM = rapid, sustained, tonic



Meltzer-Brody, Kanes 2020

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What is Zuranolone (Zurzuvae)?

First FDA approved oral medication for the treatment of postpartum depression (PPD)

Once-daily, oral, 14-day medicine

Neuroactive steroid GABA-A receptor positive allosteric modulator

Zuranolone = synthetic form of allopregnanolone

ROBIN and SKYLARK Trials

Mirrored brexanolone studies

Hormonal triggered clinical depression

No data for Bipolar Affective Disorder, Affective Disorders with psychosis, active substance use

Only unipolar depression with peripartum onset

Good clinical application: patients had trauma, ACE's, anxiety and trauma disorders

How does it work?

Two Phase 3 clinical trials (NEST)

- Rapidly improved symptoms of PPD at Day 15 by and as early as Day 3 with sustained effect to Day 45.

Works fast (faster than SSRIs) and with sustained effect

Most common side effects ≥ 5% with Zuranolone 50 mg were somnolence, dizziness, diarrhea, fatigue and urinary tract infection

-No loss of consciousness

Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial (ROBIN)

Phase 3, double blind, randomized, outpatient placebo controlled trial

Jan 2017-December 2018

Women 18-45 years, ≤6 months postpartum, with PPD (onset of a major depressive episode in 3rd trimester or ≤4 weeks postpartum)

Randomization 1:1 to placebo: zuranolone **30 mg** daily in evening for 14 days

Baseline 17 item Hamilton Depression Rating Scale total score≥26

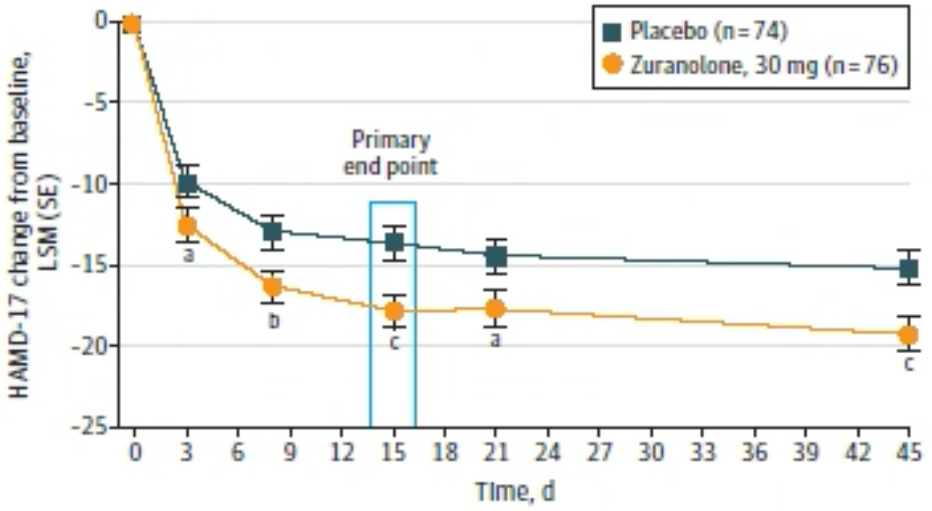
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Effect of Zuranolone vs Placebo in Postpartum Depression: A Randomized Clinical Trial (ROBIN)

Change from Baseline in HAM-D-17 Total Days 15 and 3, 8, 15, 45

-Zuranolone 30 mg vs. placebo PO once daily x14 days
-Similar baseline demographics/characteristics in Zuranolone 30 mg (n=76) and placebo (n=74) groups; ~20% on baseline ADT
-Zuranolone met the primary endpoint, CFB in depressive symptoms in the HAMD-17 total score at day 15 vs. placebo (CFB +/- SE: ZUR, -17.8 +/- 1.04; placebo, -13.6 +/- 1.07; P=0.003)
-Met secondary endpoints at Day 3, 8, 15 and 45

Figure 2. Least-Squares Mean (LSM) Change From Baseline in the 17-Item Hamilton Rating Scale for Depression (HAMD-17) Score



Treatment with zuranolone, 30 mg, achieved the primary end point of a significant change from baseline HAMD-17 total score at day 15 compared with placebo using mixed-effects model for repeated measures. HAMD-17 total score at time points other than day 15 were secondary end points, not adjusted for multiplicity and therefore reported as point estimates, which also showed sustained improvements for the zuranolone group compared with the placebo group.

[a] $P = .03$.

[b] $P = .01$.

[c] $P = .003$.

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Zuranolone for the treatment of PPD (SKYLARK)

A replication of ROBIN but at 50 mg daily

Phase 3, double blind, randomized, placebo controlled

Women with severe PPD randomized 1:1 Zuranolone **50 mg/daily** or placebo for 14 days

Women 18-45 years with PPD (onset of a major depressive episode in 3rd trimester or ≤4 weeks postpartum)

Baseline 17 item Hamilton Depression Rating Scale(HAM-D) ≥26

Zuranolone for the treatment of PPD (SKYLARK)

HAMD-17 Total Score on Day 15 and Days 3, 28, and 45: CFB

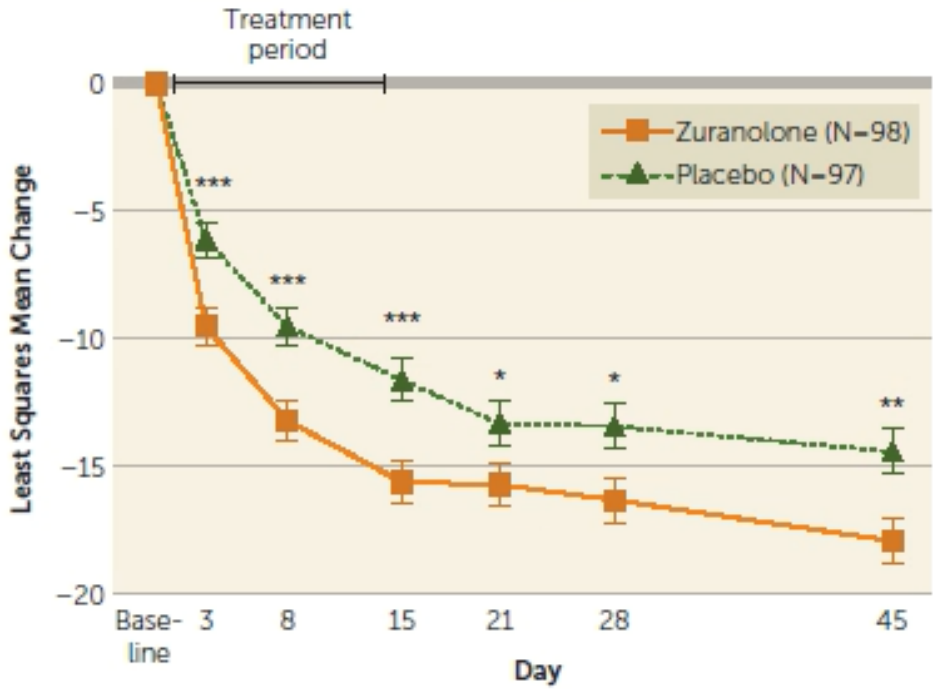
-The SKYLARK study met its primary endpoint (Day 15) and all key secondary endpoints (Days 3, 28, 45)

-Statistically significant improvements in depressive symptoms were seen as early as Day 3 and sustained to Day 45

-HAMD-17 at Baseline, Mean (SD):

Zuranolone 50 mg	28.6 (2.49)
Placebo	28.8 (2.34)

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]



[a] The primary endpoint was change from baseline in score on the 17-item Hamilton Depression Rating Scale (HAM-D) at day 15, and the key secondary endpoints included change from baseline in HAM-D score at days 3, 28, and 45. Multiplicity was accounted for when analyzing primary and key secondary endpoints. All other secondary endpoints were not adjusted for multiplicity and are to be interpreted with nominal p values. Error bars indicate standard error. *p<0.05. **p<0.01. ***p<0.001.

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Conclusions from NEST studies

Zurnaolone improved the core symptoms of depression as measured by HAMD-17 scores in women with PPD and was generally well tolerated

Clear evidence supporting the potential of zuranolone as a novel, rapid acting oral treatment for PPD

Limitations: not globally generalizable, sustainability of treatment response beyond day 45 is unclear, safety in breastfeeding needs to continue to be evaluated

How do I prescribe Zuranolone?

Monotherapy: 50 mg x 14 days is the evidence based FDA recommended treatment course

If hepatic/renal impairment, use of other sedating meds, drug-drug interactions then consider 30-40 mg daily

Tapering not studied and not necessary – no withdrawal symptoms in SKYLARK trial

If on an antidepressant already, continue the antidepressant and then prescribe Zuranolone.

Prescribing antidepressants after Zuranolone treatment depends on the patient

Ask your patients: do you remember when you started to feel differently or unwell? Follow evidence based guidelines for perinatal onset.



Dosing adjustments

Dose adjustments necessary if patients are taking medications that are strong CYP3A4 inhibitors

- Clarithromycin, erythromycin, diltiazem, itraconazole, ketoconazole, ritonavir, goldenseal, grapefruit

Concomitant use with CYP3A4 inducers should be avoided

- Phenobarbital, phenytoin, rifampicin, St. John's wort, glucocorticoids

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Zuranolone and fatty foods

To maximize benefit of the medication, consume with a fatty snack, qhs

-Discuss overall caloric intake, high fat diet if breastfeeding

Take with 25-50% fat in a 400-1000 calorie meal

In a 1500 calorie diet that's equivalent to 50 grams of fat daily (equivalent to 1-2 tablespoons of peanut butter, avocados, eggs, whole milk yogurt)

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Zuranolone and SUD

Would start at 50 mg unless there are other CNS depressant medications
Then consider decreasing to 40 mg daily, 30 mg daily

Less of drug-drug interaction concern, more of a concern with oversedation

Somnolence was a side effect in these trials

No loss of consciousness in clinical trials to date (unlike brexanolone)

Alcohol use: psychoeducation, consider reduction in dosage, monitor somnolence closely, this is a short course pill, reduce any potential for cognitive impairment

Legalized substances: no data on for ex. marijuana since patient's were drug tested
-Its patient specific, and always *ask are they using any substances or taking any medications that are CNS depressants?*

Intentional overdose? No antidote but closely and cautiously monitor somnolence

Zuranolone: Other precautionaries

FDA recommends that patients of reproductive potential use effective contraception for 14 day treatment period and one additional week.

Missed doses: don't double it, resume the next day

Shouldn't drive or engage in hazardous activities due to potential CNS depressant effects

Shouldn't operate machinery for at least 12 hours

Not evidence based for mild illness

Not FDA approved for MDD; follow evidence based guidelines for perinatal onset

Zuranolone and Lactation Data

The amount of zuranolone found in breast milk following daily administration of zuranolone 30 mg over 5 days was low compared with maternal dose

The estimated mean RID was 0.3% and daily infant dose was 0.00124 mg/kg/day on day 5

The estimated mean RID was consistent with a low fraction of unboundzuranolone ($\leq$0.52%) in plasma

Zuranolone 30 mg was generally well tolerated when administered to healthy lactating participants for 5 days

Pharmacokinetic modeling techniques are intended to be used to further determine the time course of zuranolone in milk and examine the possible role of covariates, such as the amount of milk expressed, and other individual participant characteristics

The above information is unpublished data from a poster presentation by KristinaDeligiannidis MD, summarized by Uruj Haider MD*

Zuranolone and Lactation Data: Study Limitations

Limited Generalizability: sample size was small, therefore effect ofzuranolone on milk production based on the small sample size may not be generalizable to broader populations

Variability of Milk Production at Baseline: Interpretation of the effect ofzuranolone on milk production is limited due to variability in inter-patient milk production at baseline

No Comparator Arm: No placebo arm; limited interpretation

Not Designed to Assess Safety in Infants: Infants were not intended to receivezuranolone, therefore safety of zuranolone in infants was not evaluated during study

The above information is unpublished data from a poster presentation by KristinaDeligiannidis MD, summarized by Uruj Haider MD*

Access

Six Largest U.S. Insurance Companies Zurzuvae™ Coverage Policies*

**by Market Share (12-15-2023)*

Insurer	Has a Published Coverage Policy?
Kaiser Permanente	No
Elevance Health (Anthem)	No
HCSC (including BCBS plans)	No
UnitedHealth Group	No
Centene Corporation	Yes
CVS Health Corp. (Aetna)	No

Access

Insurance Companies with Zurzuvae™ Coverage Policies

Chart Detailing Coverage Policies and any Restrictions

Insurers with Coverage Policies	Requires Use of Another Drug First	Requires Severe PPD Diagnosis	Requires Full SCID Eval	Restricts Ob/Gyn Prescribing
Blue Cross Blue Shield Arizona	No	No	No	No
Blue Cross Blue Shield Illinois	No	No	No	No
Blue Cross Blue Shield Montana	No	No	No	No
Blue Cross Blue Shield New Mexico	No	No	No	No
Blue Cross Blue Shield North Dakota	No	No	No	No
Blue Cross Blue Shield Oklahoma	No	No	No	No
Blue Cross Blue Shield Texas	No	No	No	No
Blue Cross Blue Shield Wyoming	No	No	No	No
Blue Shield California	No	No	No	No
Centene Corporation	Yes	No	Yes	Yes
Horizon BCBS New Jersey	Yes	No	No	No
LifeWise Health Plans	No	No	No	No
Nebraska Total Care	Yes	No	Yes	Yes
Oscar Health Insurance	No	No	No	No
Premera	No	No	No	No
Prime Therapuetics (BCBS PBM)	No	No	No	No
Superior Health Plan of Texas	Yes	No	Yes	Yes
Uniform Medical Plan	Yes	Yes	No	No

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Specialty Pharmacies

Provide medications used to treat rare or complex health problems

Handle high priced drugs, infusable drugs, special handling or administration, scheduled products

Offer clinical services that are above what retail pharmacies can provide

Zuranolone is a federal controlled substance (C-IV)

Not a retail pharmacy = no footprint

Mailed to patients

Access

Payors so far seem interested, but there is heterogeneity in approval

Coverage policies and prior authorization policies are still being worked out

Prior authorization varies per insurer and per plan
- -Learning about coverage through prior authorization requests
- -Are there limitations for the plan?

No specific FDA approved medication other than brexanolone for patients with PPD

Aiming for fair and equitable access

Legwork: Engage insurance company and specialty pharmacy in this process

Access: What are the steps?

Clinicians should run a benefits investigation first (Sage/Biogen can assist with that):

1) Clinician/patient calls patient's insurance company and finds out patient's specialty pharmacy.

2) Clinician calls patient's insurance companies and inquires about appropriate documentation, prior authorization, etc. Completes all paperwork.

2) Clinician sends zuranolone prescription to specialty pharmacy

3) Clinician should alert patient they will be receiving a phone call from the specialty pharmacy trying to process the benefits investigation with their clinician, and to confirm patient's address for shipping medication

4) Specialty pharmacy calls payor and finalizes documentation, prior authorization process, etc.

5) Payor finalization complete, medication shipped from specialty pharmacy to patient's home

844-987-9882 (Zurzuvae for you, for both HCP's and consumers)

MCPAP for Moms can help at any point during this process

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Zuranolone: 5 Specialty Pharmacies

CVS Caremark 866-993-4779

Walmart 877-453-4566

Accredo 901-385-3600

Alto 800-874-5881

Specialty Care Pharmacy for Puerto Rico only (unlisted at this time)

Health Care Provider: zurzuvaehcp.com
Consumer: zurzuvae.com

Patient Support Program: **844-987-9882**
M-F 8am-6 pm EST (Zurzuvae for you, for both HCP's and consumers)

Clinicians should run a benefits investigation first

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Masshealth and Zuranolone

Zurzuvae is currently Under Review (UR) and is scheduled to be added to the MassHealth Drug List on March 4, 2024 and will require prior authorization (PA). While UR, DUR will be reviewing PAs for medical necessity (and approving when criteria is met)

PA criteria includes:

- specialist provider (obstetrician-gynecologist/family medicine or psychiatrist) or having consult notes from a specialist
- member is ≤ 12 months postpartum and not currently pregnant;
- inadequate response (defined as ≥ 4 weeks of therapy) or adverse reaction to ONE antidepressant (i.e., citalopram, bupropion, duloxetine, escitalopram, fluoxetine, mirtazapine, sertraline, venlafaxine).

Cost, other limitations

$16,000 for a 14 day course

>45 days and bridging to treatment

Long term?

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How can MCPAP for Moms help?

SSRI's

Individual therapy

Support groups

Resource and referral

If insurers require consultation with a psychiatrist

If patient experiences side effects to the medication

If patient experiences lack of symptom remission

Any questions about the prescribing or titration process

Any questions about patient eligibility

MCPAP for Moms can help with any of the above

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M4M Collaboration

Can notice improvement as early as 3 days – can a social worker check in with patient around that time?

Consider contacting MCPAP for Moms at any point during 2 week period

Phone consultations or FTF may be clinically indicated or beneficial for the patient during this time period

Connection to care in community: psychotherapy, peer support, dyadic intervention, psychiatric prescriber

In summary, our aim is to promote maternal and child health by building the capacity of front line providers to address perinatal mental health and substance use disorders.





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How can MCPAP for Moms Help?

Call MCPAP for Moms at 855- 666-6272, Monday – Friday 9:00 a.m. – 5:00 p.m. to request the following services:



Trainings and Toolkits
https://www.mcpapformoms.org/Toolkits/Toolkit.aspx



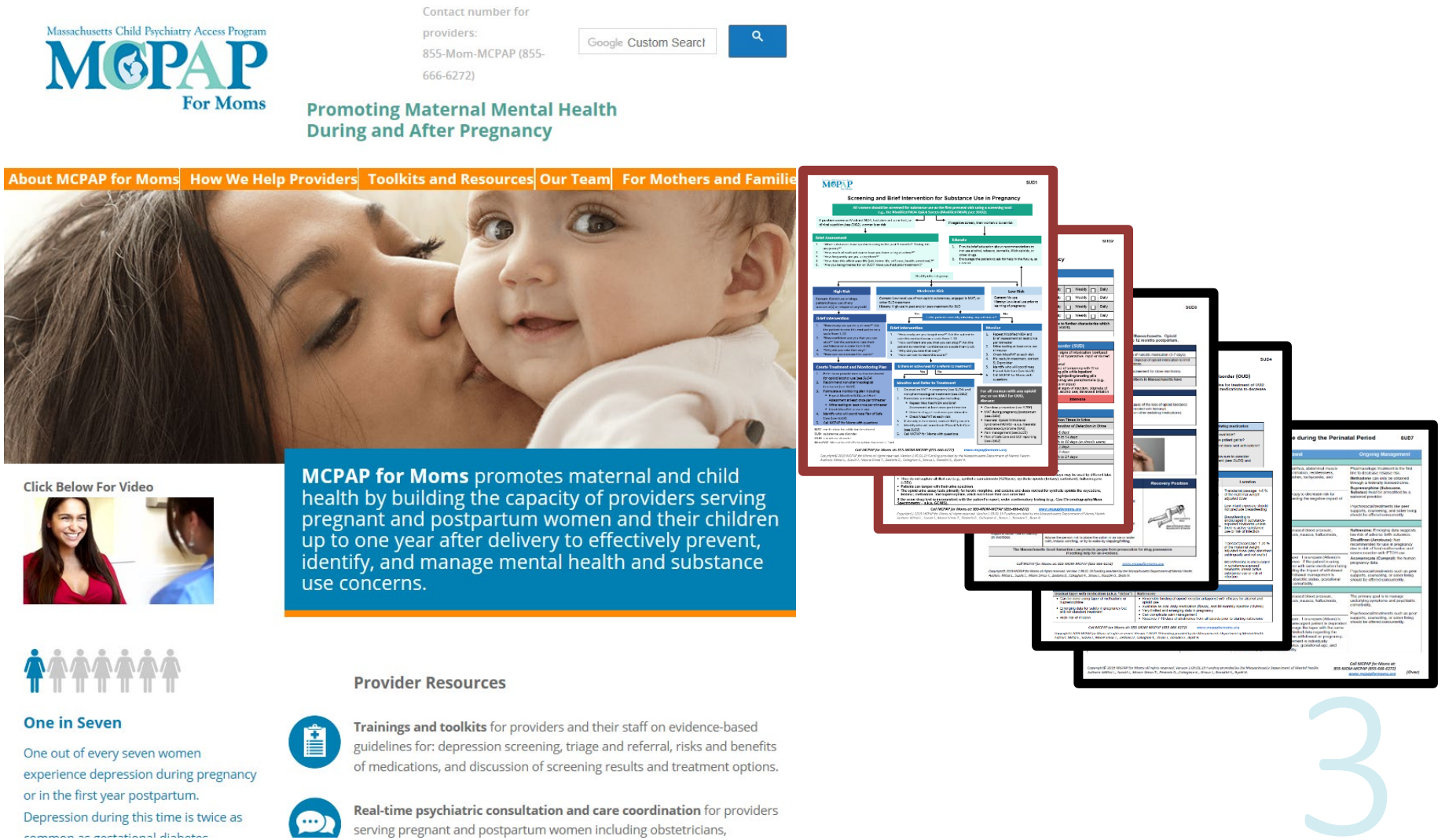
Real-time provider to provider phone consultation



Linkages with community-based resources

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Our website has resources for providers as well as patients and families - www.mcpapformoms.org



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Please call us with any questions. We are to here to help

1-855-Mom-MCPAP

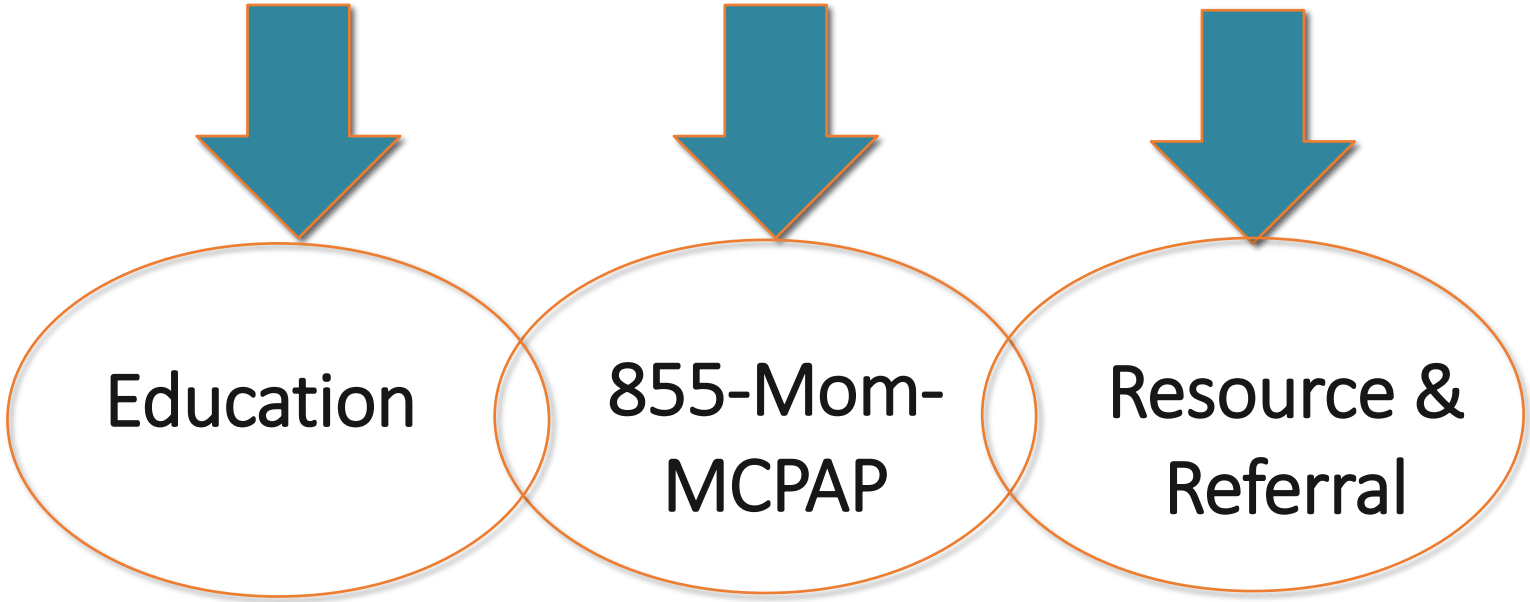
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Acknowledgements

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