BEST TREATMENT PRACTICES FOR PERINATAL MOOD AND ANXIETY DISORDERS

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PMADs are the #1 complication of Pregnancy

Etiology

- Biological
- Psychological
- Social/Environmental
- Spiritual/Existential Crisis
- Cultural Myths of Motherhood

Biology

Genetics

- Mood disorders run in families
- At higher risk if mother, siblings or other family members had PMADs or other mental health disorder
- At higher risk if already have an existing mental health disorder
- At higher risk if have History of PMS or PMDD

Spectrum of PMADs

- Depression
- Anxiety/panic
- OCD (Obsessive/Compulsive Disorder)
- Bipolar Disorder
- PTSD (Post Traumatic Stress Disorder)
- PP psychosis

Biological contributions

- PMADs may be psycho-neuro-immunological disorders that come from an exaggerated inflammatory response to labor and delivery.
- The body attempts to limit damage from stress, injury, or infection by releasing both pro-inflammatory and anti-inflammatory cytokines.
- Pro-inflammatory cytokines are linked to fatigue, hypersomnia, fever, decreased appetite, and depression.

Biological contributions

- Early postpartum is a state of serotonin deficiency (Bailara, 2006).
- Studies show that women with postpartum depression have decreased tryptophan levels, decreased platelet serotonin (Maurer-Spurej, 2007) and altered binding of platelet serotonin transporter sites (Newport et al, 2004).
- Cortisol, estradiol, and progesterone all have an impact on the serotonin system, and the latter two decrease precipitously after birth.

Biological contributions

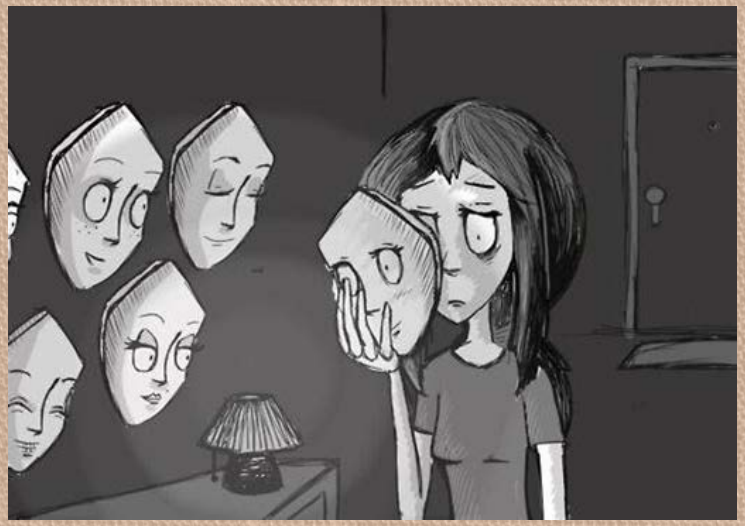
- Ilona Yim at UC-Irvine has found a correlation between the rapid release of cortico-releasing hormone at 25 weeks and the development of postpartum depression. (Yim, Glynn, Dunkel-Schetter, Hobel, Chicz-DeMet, Sandman, Archives of General Psychiatry. 2009)

- This hormone is typically produced by both the placenta and the hypothalamus.

Incidence of Clinical PMADs

- Approximately 15 - 20% of all **pregnant** and **postpartum** women may experience some form of PMAD
- Anxiety may now be more prevalent that depression (2013, Paul, Downs,Schaefer, Beiler, Weisman, Pediatrics)
- Up to 51% in low SES populations (Bennett, et al, 2004)
- 10% of Men in US experience PPD (2006, Paulson, Dauber, and Leiferman, Pediatrics)

- PMADs onset **peaks at 3 months** postpartum but can onset during pregnancy and at anytime during the first year
- May last well into the 2nd year or longer if untreated/ mistreated.
- Maternal depression is more common at 4 years following childbirth than at any other time in the first 12 months after childbirth (Woolhouse, Mensah, and Brown; British Journal of Obstetrics and Gynecology; 2014)



PMADs & Pregnancy

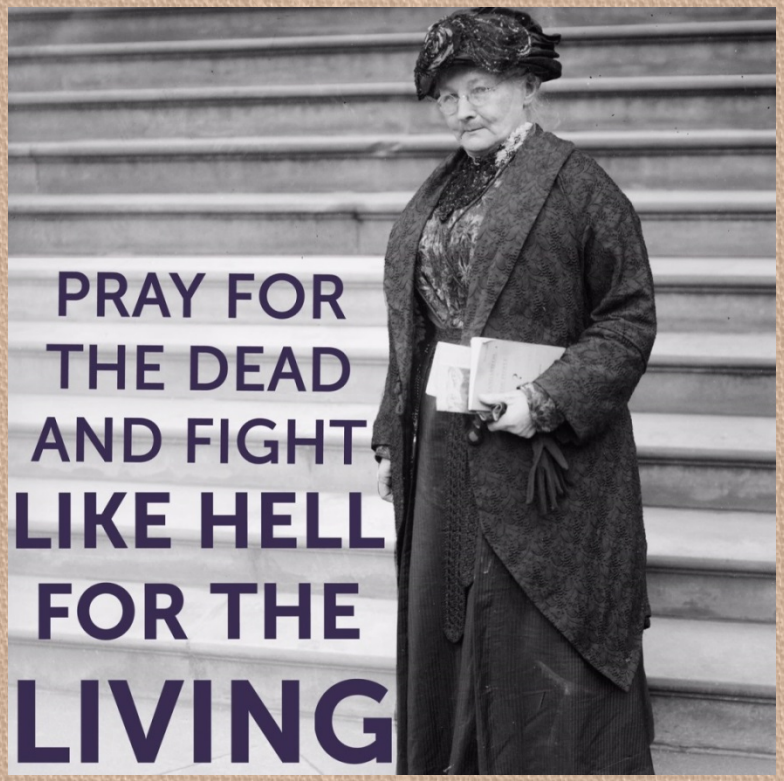
- About 1/3 start during PREGNANCY – often predominantly Anxiety
- Over 40% resume medication during pregnancy (Cohen, 2004)
- 50-75% relapse during pregnancy if discontinue existing psychiatric medications (Cohen, 2004)
- Most cases are undetected and untreated (Marcus, 2009)

Suicide is the leading cause of maternal death

(Oates, British Medical Bulletin 2003, *Perinatal psychiatric disorders: a leading cause of maternal morbidity and mortality*)

Suicide Rates increase 44% in the postpartum year

(Schiff & Grossman; Pediatrics, 2006)



Pregnancy vs. Depression

- Labile mood, teary
- Self-esteem normal
- Sleep disruptions: bladder or heartburn, can fall back asleep
- Energy – may tire, but rest restores
- Pleasure: joy and anticipation
- Appetite normal
- Appropriate worry

- Mood: dark, gloomy, down
- Anhedonia
- May have suicidal ideation, or plans with intention
- Low self-esteem, guilt
- Sleep disruptions – can't fall back asleep, often early a.m.
- Energy low – rest not restorative, chronic fatigue
- Appetite disturbances

Anxiety Symptoms

- Agitated
- Hypervigilent
- Mind Racing
- Rapid weight loss
- Difficulty falling/staying asleep
- Shortness of breath
- Heart palpitations
- Diarrhea
- GI disturbances
- Excessive worries – often about baby or own health

Panic Symptoms

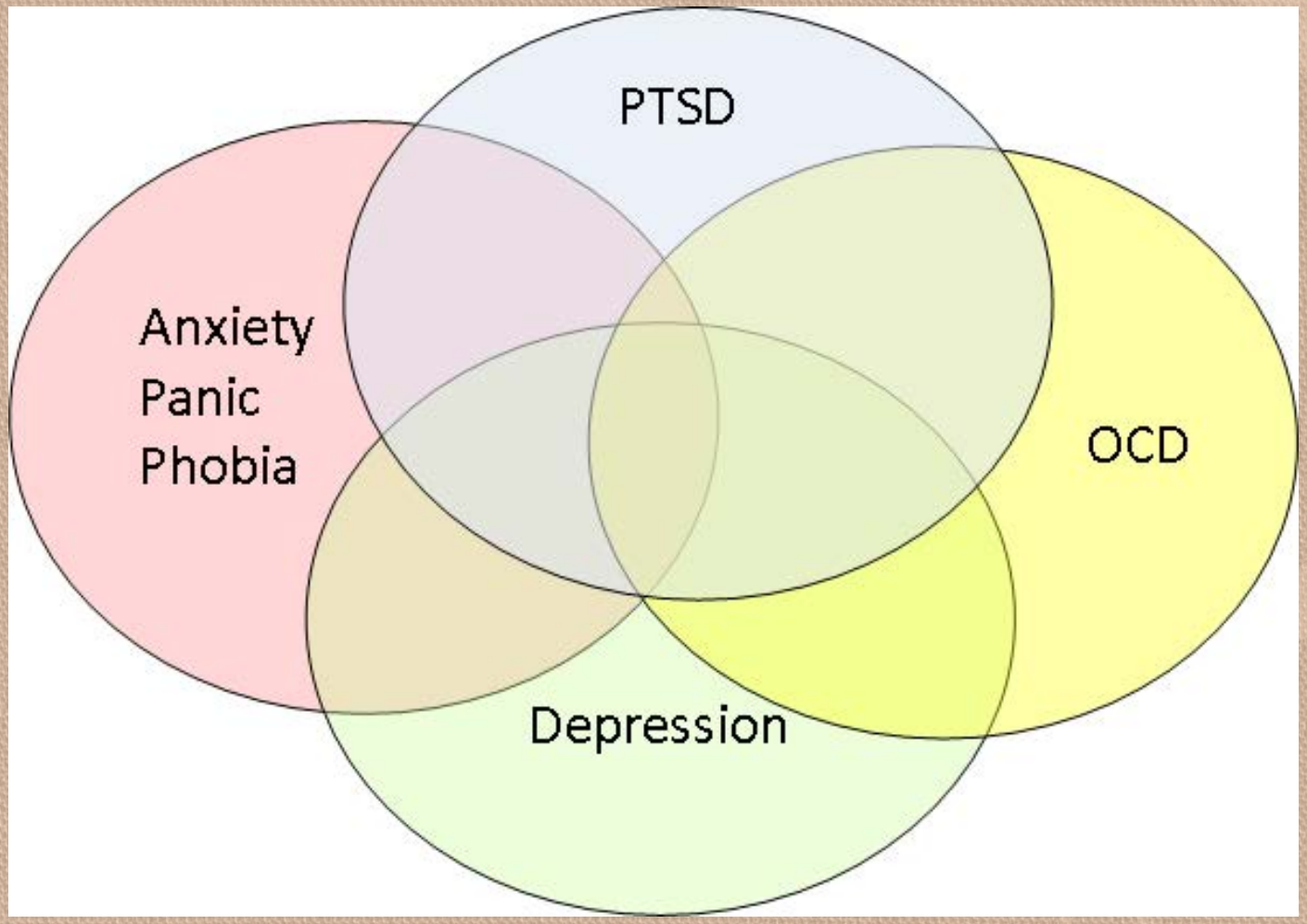
- Episodes of Extreme Anxiety
- Shortness of breath, chest pain, sensations of choking, dizziness
- Hot or cold flashes, shaking, tremors, rapid heart rate, numbness or tingling sensations
- Restlessness, agitation, irritability
- Excessive worry or fear, catastrophic thinking
- 3 greatest fears:
  - Fear of dying
  - Fear of going crazy
  - Fear of losing control

Consequences of Unmanaged Anxiety and Depression in the Mother

- Poor prenatal care
- Risk of medical / obstetrical complications
- Exacerbation of psychiatric illness through postpartum
- Self-medication / substance abuse
- Impaired bonding

(Stewart, CMAJ, 2006; Marcus SM et al., Journal of Women's Health 2003; Orr et al., Pediatric & Perinatal Epidemiology, 2000)

Co-Morbidity

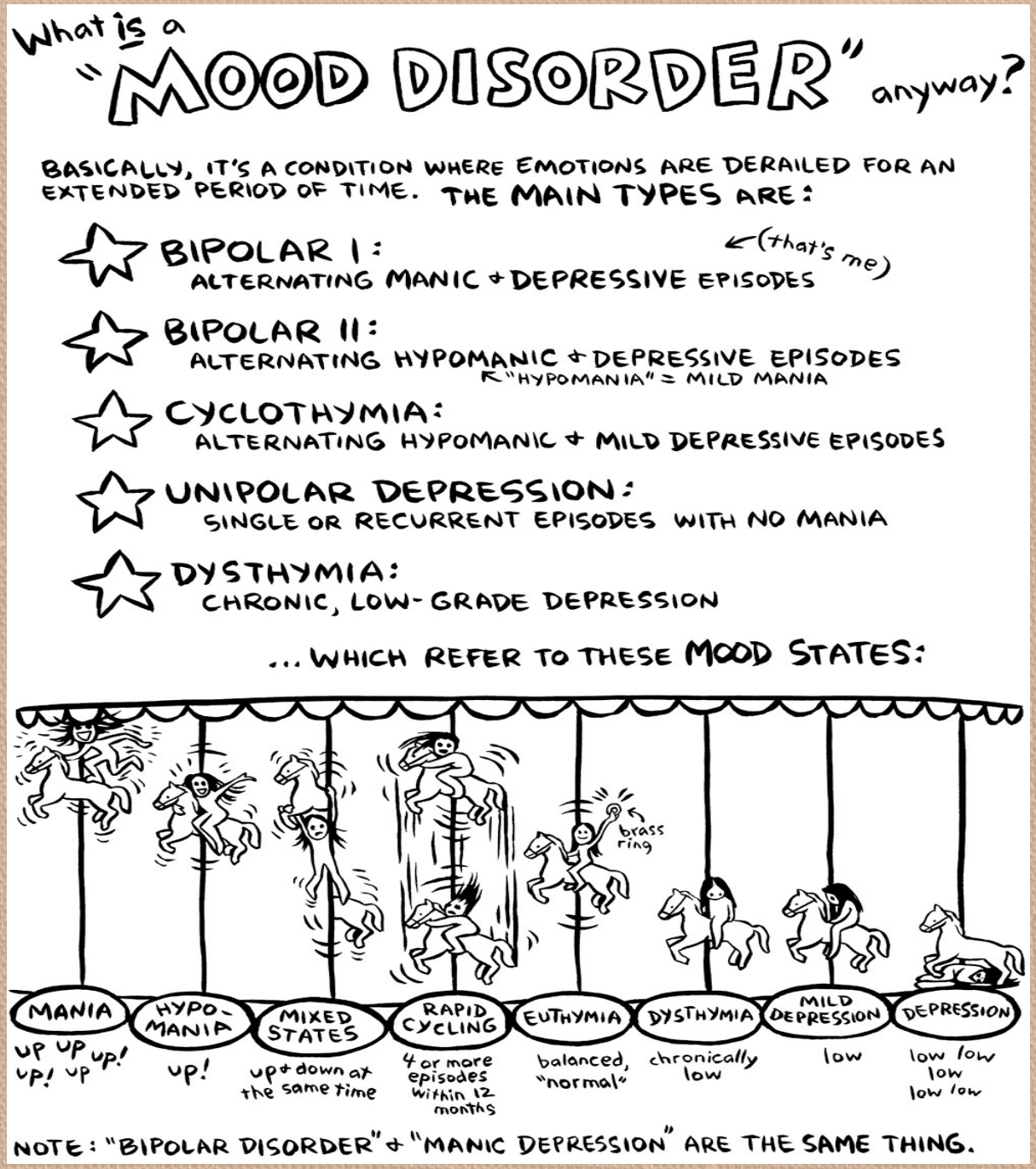


Mood Disorders and Bipolar

The “Postpartum Depression Imposter”

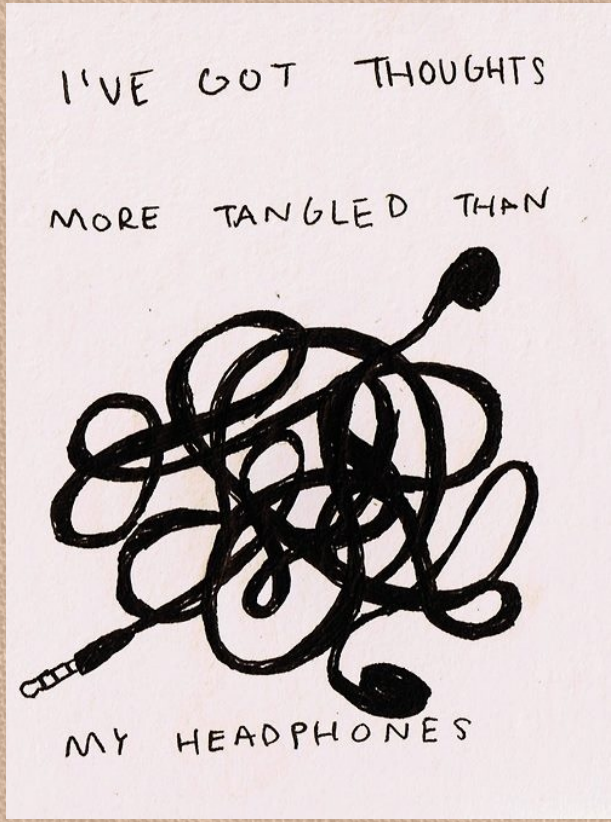
Illustrations from the book, *"Marbles: Mania, Depression, Michelangelo, and Me: A Graphic Memoir"*

by Ellen Forne (2012)



Bipolar I Disorder

- defined by manic or mixed episodes that last at least seven days, or
- Manic symptoms that are so severe that the person needs immediate hospital care.
    - Usually, depressive episodes occur as well, typically lasting at least 2 weeks.

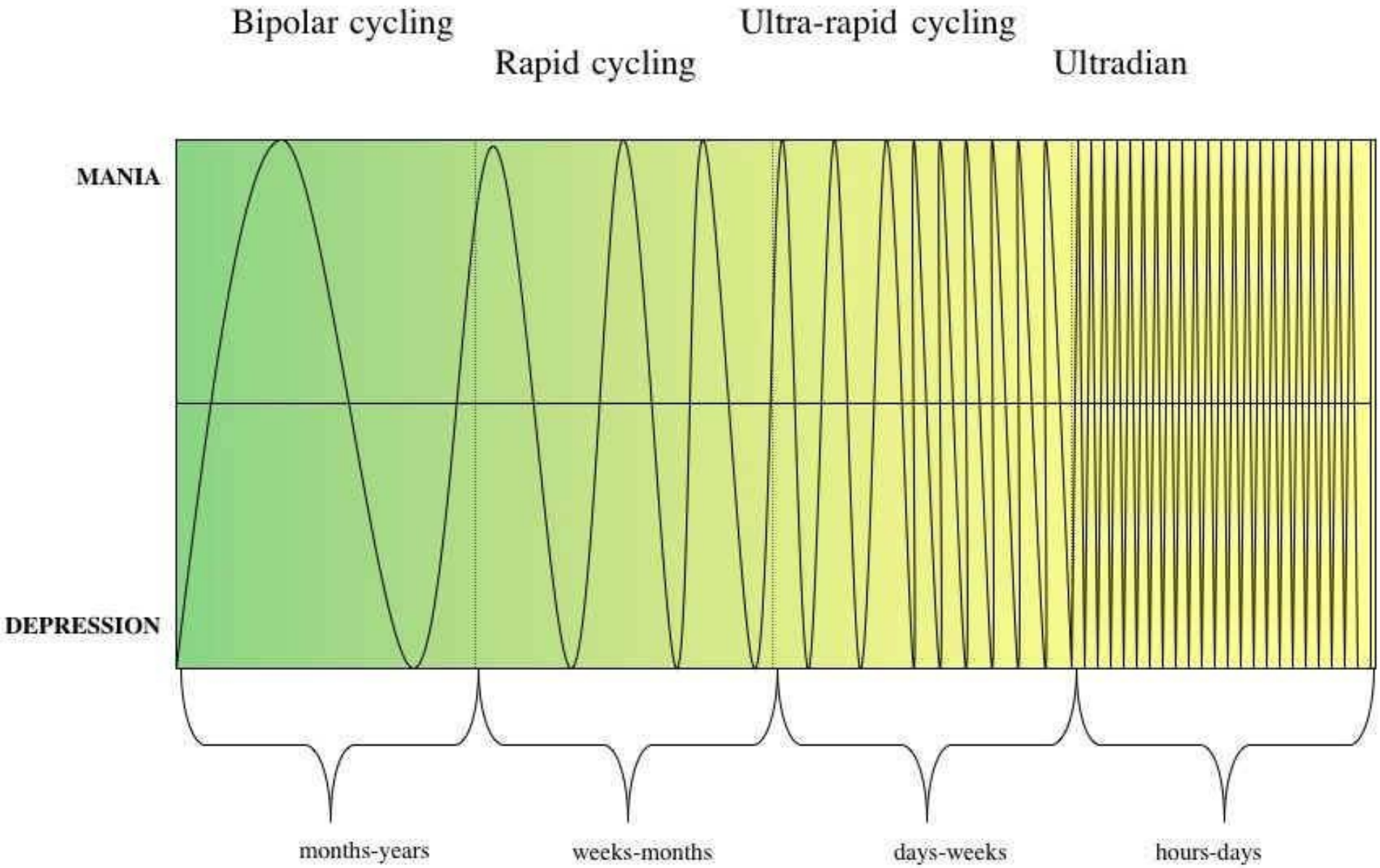


Bipolar II Disorder

- defined by a pattern of depressive episodes and
- HYPOMANIC episodes
- but no full-blown mania.

Rapid-cycling Bipolar Disorder

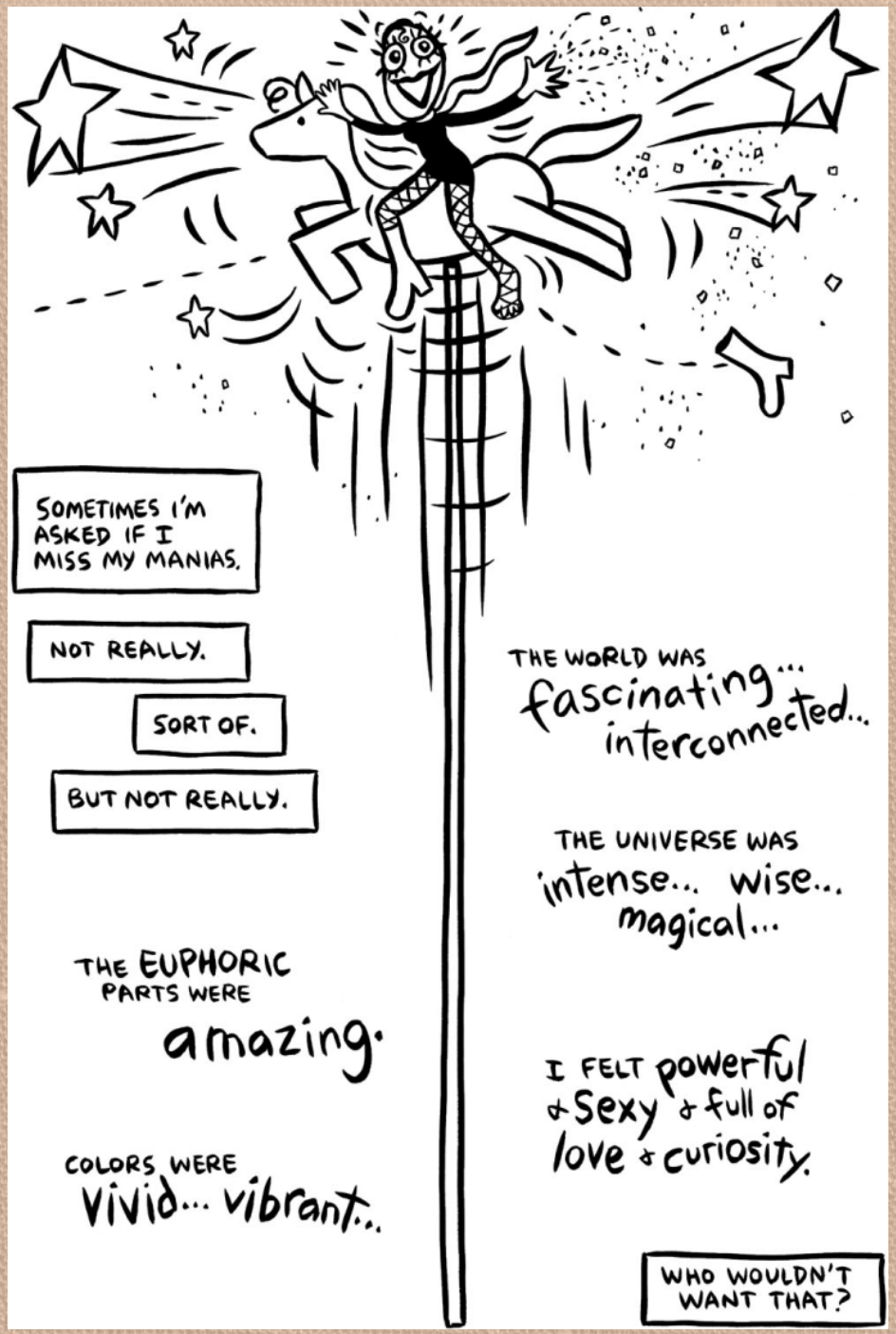
- A severe form , rapid cycling occurs when a person has four or more episodes of major depression, mania, hypomania, or mixed states, all within a year.
- Rapid cycling seems to be more common in people who have their first bipolar episode at a younger age.


Bipolar cycling
Rapid cycling
Ultra-rapid cycling
Ultradian
MANIA
DEPRESSION
months-years
weeks-months
days-weeks
hours-days

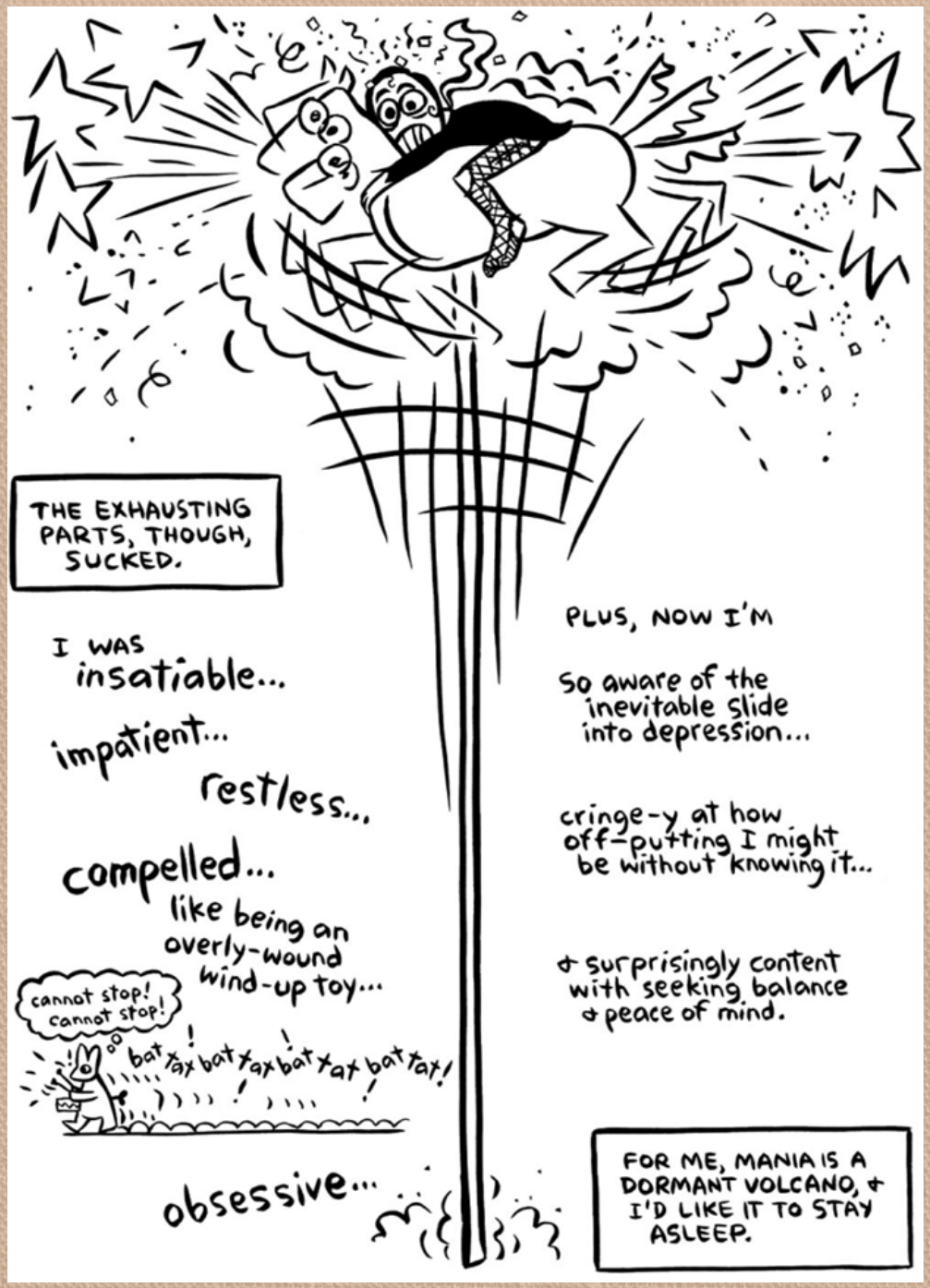
Mania

- Abnormally and persistently elevated, euphoric mood
- Agitation or irritable mood
- Inflated self-esteem or grandiosity
- Decreased need for sleep
- More talkative than usual or pressured speech
- "Flight of ideas" or racing thoughts
- Distractibility
- Increase in goal-directed activity & productivity
- Excessive involvement in pleasurable activities that have a high potential for painful consequence
- May have psychotic features (delusions, hallucinations, paranoia or disorganized thinking – not oriented x3)
- Must last at least 7 days in length or require hospitalization

What Does Hypomania Look Like?



The down side…



Why is this Distinction Important?

- Many women with bipolar are 1st diagnosed in the postpartum period
- Over 60% misdiagnosed with Major Depressive Disorder, with dire wrong medication consequences
- Most women who go off their medications during pregnancy will have a relapse before the end of their pregnancy
- Over 35% suffered for 10+ years with incorrect diagnosis (Bipolar Depression, Current Psychiatry, 2004)
- High rates suicide (esp. with Mixed States)

Clinical interview tips for Bipolar

- Get a good family history!
- Don't just ask postpartum depression oriented questions – ask about manic symptoms – this is why it is important to have a paradigm shift to PMADs, not just PPD

Depression Becoming Bipolar Disorder

Dr. Verinder Sharma (2014, Western University, Canada)

- Childbirth can be the catalyst that triggers the onset of mania and hypomania
- Many have a prior history of depression that then BECOMES Bipolar disorder after birth.
- Again, the importance of careful monitoring and education of women to prevent misdiagnosis and medication mismanagement.

Sharma, et al. A prospective study of diagnostic conversion of major depressive disorder to bipolar disorder in pregnancy and postpartum. Bipolar Disorders. 2014; 16: 16-21. Schulich School of Medicine, Western University, Canada

Postpartum Psychosis

Usually correlates with either Bipolar I Disorder or Schizophrenia

Symptoms of Postpartum Psychosis:

- Delusions or strange beliefs
- Hallucinations (seeing or hearing or feeling things that aren't there)
- Feeling very irritated & agitated
- Hyperactivity
- Decreased need for or inability to sleep
- Paranoia and suspiciousness
- Rapid mood swings
- Difficulty communicating at times

Hypervigilence vs. Paranoia

- Many mothers with perinatal anxiety and OCD disorders become extremely **hypervigilent**
  - "Hover Mother"
  - "Possessive of their Baby"
  - Difficulties letting others watch, hold, diaper baby
  - Difficulties leaving the baby
  - Difficulties sleeping
  - Excessive Hyper-hearing

Postpartum Paranoia

- Hypervigilance PLUS:
- Suspiciousness
- Delusional beliefs of persecution
  - "People are lying to me"
  - "They are hiding things from me"
  - "You are reading my thoughts and will KNOW I'm a bad mother"
  - "They are plotting about me and my baby"
  - "They are all mad at me"
  - "My baby HATES me"
- Preoccupation with trivial things

Samples of Postpartum Psychosis

- "I heard voices while I was in the shower telling me I should go ahead and just kill myself."
- "I thought the devil was living inside of me—that my children would be better in heaven with God than with me."
- "I hear music playing all day in the background that is not there"
- "I believed I was Shania Twain and I needed to leave my family and go on tour."

Infanticide

- Rare -- 4% rate – greater risk with psychosis
- Rarely has a history of abusing children
- Most often part of a suicide attempt
  - 54-67% coincide with suicide attempt
  - 83% killed or tried to kill all their children
  - No anger towards child, wishes not to abandon child, often a severely distorted attempt to “save the child”

Infanticide

- Her thoughts “make sense” to her, because she is experiencing a break from reality.
- She often believes that she is being a ‘good mother’ and ‘saving her children’ by delivering them from evil.

Immediate treatment for these women is imperative

- It is also important to know that many survivors of postpartum psychosis **NEVER** had delusions containing violent commands.
- Delusions take many forms, and not all of them are destructive.

Most women who experience postpartum psychosis Do NOT harm themselves or others.

Mother/Baby Safety Concerns

- If we have concerns about the safety of a child with the mother, order 24/7 supervision for the mother and child, to ensure that they are safe.
- Assess the capacity of the mother to respond to the emotional states of the infant and, if thought to be too severely impaired, order a nurse, doula, family member or other alternative care to temporarily care for the baby
- This is usually tolerated well by the patient.

The most significant risk factors for postpartum psychosis are:

- a personal or family history of bipolar disorder or
- a previous psychotic episode.

- Postpartum psychosis is temporary and treatable
- BUT, it is an emergency and it is essential that these moms receive immediate help
- Hospitalization is frequently necessary

A word about Sleep & Psychosis

Obsessive-Compulsive Disorder

- Approximately 9% of mothers develop OCD (Abramowitz, et al; Anxiety Disorders, 2006; Zambaldi, et al; Comprehensive Psychiatry, 2009)
- Often misdiagnosed as psychosis
- Intrusive thoughts, fears, images ("Scary Movie in my Head")
- Person cannot control thoughts
- Mom is horrified by the thoughts, Tremendous Guilt and Shame
- Mom understands that to act on these thoughts would be wrong (hence she is in her 'right' mind)

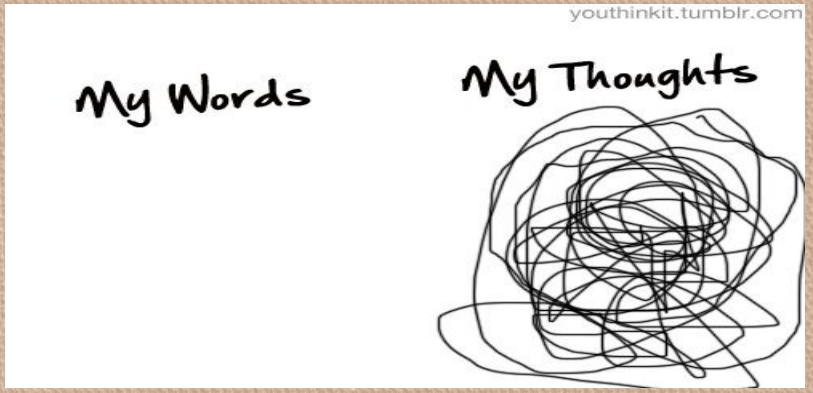
Obsessive-Compulsive Disorder

- Ritual behaviors done to avoid harming baby (e.g., put away knives, counting) or to create protection for baby (e.g., excessive cleaning, doesn't leave the house) constantly checking the baby, house, etc.
- Hyper vigilant (e.g., can't sleep for fear that something will happen to baby; constant "fight or flight" mode) – can be misconstrued as paranoia
- NORMALIZE AS A SYMPTOM & Educate Mom that thoughts do not equate with action

OCD vs. Psychosis

OCD:

- Low Risk Harm to Baby
- Recognizes thoughts/ images are wrong, and experiences worry and anxiety about thoughts
- Mother takes steps to protect baby



Psychosis:

- High Risk to Harm Baby
- Mom might have delusional beliefs about the baby
- Thoughts of harming baby are ego syntonic (she thinks they are reasonable and has urges to act on them)

Post Traumatic Stress Disorder

"It is in the eye of the Beholder"

(Beck, 2004; Birth Trauma: In the Eye of the Beholder, Nursing Research)

Prevalance:

- 18% experience a Traumatic Birth Experience
- About 5.6% to 9% of these women develop PTSD

(Creedy, Shochet, & Horsfall, 2000; Beck, Gable, Sakala & Declercq, 2011)

Postpartum PTSD Themes

- Perception of lack of care/ respect by providers
  - Feeling abandoned
  - Stripped of dignity
  - Lack of support and assurance
  - lack of continuity of care providers
- Poor Communication
  - perceived lack of communication by medical staff
  - Mom feels invisible
- Feeling powerless or out of control
- Feels actions done TO her, not WITH her – perceived lack of choice or consent
- Betrayal of trust
- Didn't feel protected, safe
- Do the ends justify the means?

  Minimized: "all that matters is your baby is healthy"

(Creedy, Shochet, Horsfall, Birth, 2000; Beck, 2004)

Treatment of PMADs during pregnancy and postpartum

A good approach should include:

- Therapy
- Medications
- Sleep
- Diet
- Self-care
- Social Supports

Social Supports

- Family & Friends
- Peer support groups
- Faith communities
- Telephone Warm-lines
- Childcare providers
- Parent Educators
- Doulas, CBEs, IBCLCs
- 12-step programs
- Childcare

NURSE Program – Self Care

Nourishment
Understanding
Rest and **R**elaxation
Spirituality or "**S**oul food"
Exercise

Sichel & Driscoll, "Women's Moods: What every woman must know about hormones, the brain and emotional health" (2000)

Mental Health Assessment – A Review

- Family history
- Symptoms
- Life Stressors
- Adequate Social Support System?
- Sleep
- Eating/Appetite
- Mental health & Trauma history
- Health/Habits
- Reproductive History & prior Birth Experiences
- Risk Assessment
- Abuse history
- Drug & Alcohol Use
- Domestic Violence

Universally, recommend screening and provide patients with literature on PMADs at the 20 week appointment, the 36 week appointment, 2 weeks postpartum and at final postpartum visit (4 times total across her perinatal care)

FREE brochures to give to patients are available through Postpartum Support International of WA. Just call to be supplied with as many as you need. www.ppmdsupport.com 1-888-404-7763 (PPMD) or info@ppmdsupport.com

Psychoeducation is Critical

- This should be your FIRST and ONGOING step with PMADs, as for many women, this is the first time they are being diagnosed.
- Address the stigma of mental illness that can be a barrier to accessing treatment.

Therapy

- Interpersonal Psychotherapy (IPT)
- Psychoeducation
- Cognitive Behavioral Therapy (CBT)
- Modified Dialectical Behavioral Therapy (DBT)
- Mindfulness & Meditation (especially with Anxiety disorders, trauma, hypomania and mania)
- Somatic Resourcing (especially with Trauma Hx)

CBT and DBT

- Especially addressing distorted thoughts leading to dysfunctional behaviors,
- Negative internal dialogue,
- Increasing their Distress Tolerance,
- How this illness impacts interpersonal relationships

Mindfulness & Somatic Therapy

- A component of DBT or used alone
- Increasing Self Awareness
- Quieting the Mind
- Tuning into the Body

Medication Management

Disclaimer:

I am not licensed to prescribe medications and am merely reporting findings based on published research and reported case documentation.

*I am **NOT** directing anyone on how to prescribe medications.*

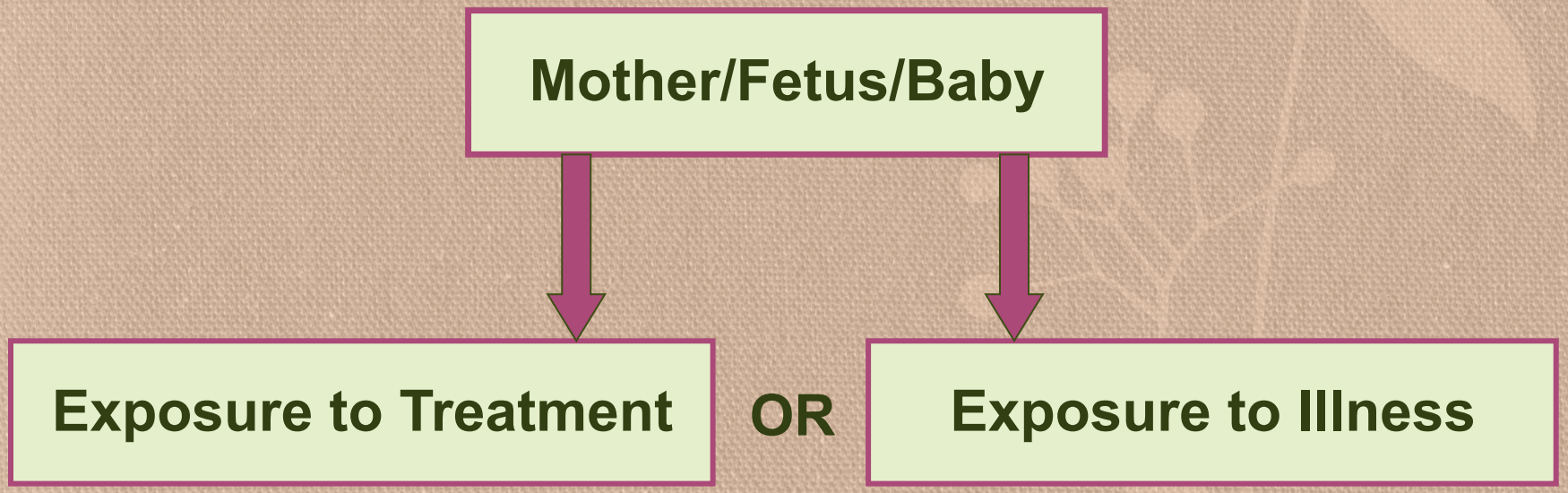
Good Resources for Meds During Pregnancy

- CDC http://www.cdc.gov/pregnancy/meds/treatingfortwo/research.html
- Motherisk www.motherisk.org
- Organization of Teratology Information Specialists www.otispregnancy.org
- Massachusetts General Hospital Center for Women's Mental Health. www.womensmentalhealth.org Subscribe to their e-newsletter!!!

Should women who are pregnant or may become pregnant take medication?

- “Stuck between a rock and a hard place”
- Some mood stabilizing medications can harm a developing fetus or nursing infant.
- HOWEVER, stopping medications, either suddenly or gradually, greatly increases the risk that symptoms will recur during pregnancy.

To Treat or not to Treat: A Clinical Conundrum



There is no such thing at no exposure

Antidepressants

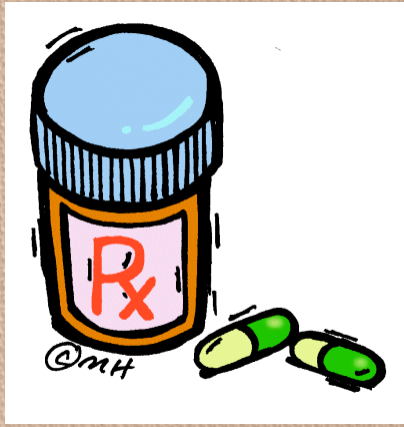
2013 Article: "Antidepressant use during pregnancy: How to avoid clinical and legal pitfalls." (Friedman and Hall, Current Psychiatry, 2013)

Conclusion: Overall risks are low, and fears of lawsuits should not deter appropriate care

http://www.currentpsychiatry.com/home/article/antidepressant-use-during-pregnancy-how-to-avoid-clinical-and-legal-pitfalls/7b2ba0f17ac723309ffdaef6770368e0.html

Med Management During Pregnancy

- Dose adjustment across the pregnancy may be required
- Account for Physiological changes: plasma volume, metabolic changes, hepatic enzymes



Hostetter, et al. *Depress Anxiety* 2000;
Wisner, *Am J Psychiatry* 1993

Med Discontinuation

- In mother
  - Avoid "cold turkey" – Taper
  - "Discontinuation Syndrome" – flu like Sx, insomia, nausea, irritability, sensory disturbances, hyperarousal
- In neonate (upon birth, when in-utero exposure)
  - Symptoms: fussy, reflux, cry
  - Up to 2 weeks
  - No long term effects

Good Medication Overview Charts:

(2012) Pictured in next 3 slides: http://www.perinatalweb.org/assets/cms/uploads/files/WAPC_Med_Chart_2012_v9.pdf

(2009) www.hfs.illinois.gov/assets/070109mch.pdf

ACOG Guidelines on Psychiatric Medication Use During Pregnancy and Lactation (2008) http://www.aafp.org/afp/2008/0915/p772.html

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ANTIDEPRESSANT MEDICATION CHART

(This chart is intended for clinicians who provide primary care to pregnant and postpartum women)

Data current as of April 2012

Antidepressants	Trade Name	Usual Daily Dose	Benefits	Maternal Risks	Fetal/Neonatal Risks	Breastfeeding: Relative infant dose=(RID)	Breastfeeding: Half-life (t1/2)/ metabolites	Breastfeeding: Reported side effects in breastfed infants
DRUG CLASS: Selective Serotonin Reuptake Inhibitors (SSRIs)								
Citalopram	Celexa®	20-40mg	• No adverse morphologic consequences for infant found • Few interactions with other medications	• Side effects include nausea, insomnia, dizziness, and somnolence	• Behavioral consequences for infant unknown • Possible increased risk of growth restriction • Possible increased risk of neural tube defects and cardiac defects (ASD)	3.60%	• Drug has intermediate t1/2 (1-2 days) • 3 weak metabolites with little activity	• Somnolence • Decreased feeding • Weight loss
Escitalopram	Lexapro®	10-20mg	• Few interactions with other medications • No adverse morphologic consequences for infant found	• Side effects include nausea, insomnia, somnolence, dizziness, fatigue, diarrhea, sexual dysfunction, and dry mouth	• No systematic studies in human pregnancy • Morphologic and behavioral consequences for infant unknown • Possible increased risk of growth restriction • Possible increased risk of necrotizing enterocolitis	5.2-8%	• Drug and active metabolite have intermediate t1/2 (1-2 days)	• Somnolence • Decreased feeding • Weight loss
Fluoxetine	Prozac®	20-60mg	• More studies in human pregnancy, including meta-analysis and neurodevelopmental follow-up • No adverse behavioral consequences for infant found	• Side effects include nausea, drowsiness, and sexual dysfunction • Possible drug interactions	• More reports of neonatal side effects than some other antidepressants • Possible morphological changes	1.6-14.6%	• Drug and active metabolites have very long t1/2 (days to weeks) • Serum levels similar to those in adults reported in some symptomatic infants	• Severe colic • Fussiness • Crying
Fluvoxamine	Luvox®	50-200mg	• No adverse morphologic consequences for infant found	• Side effects include nausea, drowsiness, anorexia, anxiety, and sexual dysfunction • Possible drug interactions	• Behavioral consequences for infant unknown	0.3-1.4%	• Drug has short t1/2 (hours) • Major metabolite not active	• No reported concerns
Paroxetine	Paxil®	20-60mg	• None--avoid during pregnancy if possible	• May increase risk of miscarriage • Side effects include nausea, drowsiness, fatigue, dizziness, and sexual dysfunction.	• Behavioral consequences for infant unknown • More reports of neonatal side effects than most other antidepressants • Possible association with cardiovascular malformations in infant	1.2-2.8%	• Drug has relatively short t1/2, but variable (hours to days) • No active metabolites	• Numerous studies suggest minimal to no effect on breastfed infants
Sertraline	Zoloft®	50-200mg	• Relatively well-studied in human pregnancy • No adverse behavioral consequences for infants found • Fewer reports of neonatal side effects than other antidepressants	• Side effects include nausea, loose stools, tremors, insomnia, and sexual dysfunction • Possible drug interactions	• Possible specific association with omphalocele and cardiac septal defects	0.4-2.2%	• Drug and weakly active metabolite have intermediate t1/2 (1-2 days) • Detectable levels in some infants, but no adverse effects	• 1 report of benign neonatal sleep myoclonus (relationship unknown)

For additional information contact: Wisconsin Association for Perinatal Care | 211 S. Paterson St., Suite 250 | Madison, WI 53703 | www.perinatalweb.org Email: wapc@perinatalweb.org

WISCONSIN ASSOCIATION for Perinatal Care

ANTIDEPRESSANT MEDICATION CHART

(This chart is intended for clinicians who provide primary care to pregnant and postpartum women)

Data current as of April 2012

Antidepressants	Trade Name	Usual Daily Dose	Benefits	Maternal Risks	Fetal/Neonatal Risks	Breastfeeding: Relative infant dose=(RID)	Breastfeeding: Half-life (t1/2)/ metabolites	Breastfeeding: Reported side effects in breastfed infants
DRUG CLASS: Tricyclic antidepressants (TSAs)								
Desipramine	Norpramin®	100-300mg	• More studies in human pregnancy, including neurodevelopmental follow-up • No adverse morphologic consequences for infant found • No adverse behavioral consequences for infant found • May be useful if sedation desired	• Side effects include sedation, weight gain, dry mouth, constipation, and orthostatic hypotension--baseline ECG recommended • Possible drug interactions	• Fetal and neonatal side effects include tachycardia and urinary retention	0.2-0.9%	• Drug and active metabolite have intermediate t1/2 (1-2 days) • Not detected in infants	• No reported adverse events in infants found
Nortriptyline	Pamelor®	50-150mg	• More studies in human pregnancy, including neurodevelopmental follow-up • No adverse morphologic consequences for infant found • No adverse behavioral consequences for infant found • May be useful if sedation desired	• Side effects include sedation, weight gain, dry mouth, constipation, and orthostatic hypotension--baseline ECG recommended • Possible drug interactions	• Fetal and neonatal side effects include tachycardia and urinary retention	1.7-3.1%	• Drug has intermediate t1/2 (≥1 day) • No active metabolites	• No reported adverse events in infants found
DRUG CLASS: Serotonin Norepinephrine Reuptake Inhibitors (SNRIs)								
Duloxetine	Cymbalta®	40-60mg	• Balanced antidepressant; may be effective when selective agents are not • Low cord to maternal serum ratio suggests limited transfer across the placenta	• Common side effects include nausea, dry mouth, constipation, diarrhea, vomiting, decreased appetite, fatigue, dizziness ,somnolence, tremors, sweating, blurred vision, and insomnia	• No systematic studies in human pregnancy • Morphologic and behavioral consequences for infant unknown	0.10%	• Drug has short t1/2 (hours) • No active metabolites • Relative infant dose low	• No reported adverse events in infants found
Venlafaxine	Effexor®	75-300mg	• Balanced antidepressant; may be effective when selective agents are not • No adverse morphologic consequences for infant found	• May increase risk of miscarriage • Maternal side effects include nausea, sweating, dry mouth, dizziness, insomnia, somnolence, and sexual dysfunction	• No behavioral studies in human pregnancy • Possible neonatal risk of respiratory, cyanosis, apnea, seizures, and temperature instability	6.8-8.1%	• Drug and active metabolite have short t1/2 (approx 5 h)	• Detectable plasma levels in several breastfed infants were not associated with any adverse effects
DRUG CLASS: Other								
Bupropion	Wellbutrin® Zyban®	300-450mg	• No adverse morphologic consequences for infant found • Helps with smoking cessation (never tested in pregnancy)	• May increase risk of miscarriage • Maternal side effects include dizziness, headache, dry mouth, sweating, tremor, agitation, insomnia, and rare seizures • Possible drug interactions	• Behavioral consequences for infant • Possible increased risk of CHD (left outflow tract defects) • Possible increased risk of fetal cardiac arrhythmia	0.6-2%	• Drug and active metabolite have intermediate t1/2 (~ 1 day) • Plasma levels undetectable in breastfed infant	• One reported case of seizure in a 6 month old
Mirtazapine	Remeron®	15-45mg	• No adverse morphologic consequences for infant found • Helps restore appetite in women who are not gaining weight • Less likely to exacerbate nausea and vomiting	• May increase risk of miscarriage • Maternal side effects include somnolence, nausea, weight gain, and dizziness	• Behavioral consequences for infant unknown • May increase risk of preterm birth • Possible hypothermia	1.6-6.3%	• Drug and active metabolite have intermediate t1/2 (1-2 d) • Very low plasma level detected in 1 of 3 infants tested	• No adverse effects reported • Observe for sedation

WAPC
WISCONSIN ASSOCIATION for Perinatal Care

ANTIDEPRESSANT MEDICATION CHART

(This chart is intended for clinicians who provide primary care to pregnant and postpartum women)

Breastfeeding and Medications: Maternal Considerations

1. Avoid random switching of medications based on data alone. Choose drugs for which published data is available, rather than those recently introduced.
2. Most drugs are quite safe in breastfeeding mothers. The risk of not breastfeeding and instead using infant formula is much higher for the infant.
3. If the Relative Infant Dose (RID) is less than 10%, most medications are quite safe to use. The RID of the vast majority of drugs is <1%.
4. Choose drugs with a short half-life, high protein binding, low oral availability, or high molecular weight.
5. Medications used in the first 3-4 days postpartum generally produce sub-clinical levels in the infant due to the limited volume of milk.
6. Avoid using medications when possible. Herbal drugs, high dose vitamins, unusual supplements, etc. that are simply not necessary should be avoided.

Adapted from Hale, T.W. (2010). *Medications and Mothers' Milk (14th ed.)*.

Breastfeeding and Medications: Neonatal Considerations

1. Evaluate the infant for risks: Be slightly more cautious with premature infants or neonates. Be less concerned about older infants.
2. Inquire about the infant: Always inquire about the infant's age, size, and stability. This is perhaps the most important criteria to be evaluated prior to using the medication.
3. Infant age: Premature and newborn infants are at somewhat greater risk. Older mature infants can metabolize and clear medications much easier.
4. Infant stability: Unstable infants with poor GI stability may increase the risk of using medications.
5. Pediatric Approved Drugs: These generally are less hazardous if long-term history of safety is recognized.

Adapted from Hale, T.W. (2010). *Medications and Mothers' Milk* (14th ed.).

This chart was compiled by a multidisciplinary work group of leaders in their respective disciplines including OB/GYN, family practice, psychiatry, nursing, genetics, and pharmacy, practicing in Wisconsin and representing WAPC and/or the Wisconsin Section of the American Congress of Obstetricians and Gynecologists.

Updated April 2012
Funded in part by the Perinatal Foundation.

For additional information, contact Wisconsin Association for Perinatal Care | 211 S. Paterson St., Suite 250 | Madison, WI 53703 | www.perinataIweb.org | Email: wapc@perinatalweb.org

APA & ACOG Joint Report on Antidepressants

- Acknowledges use during pregnancy has slight increased risk of miscarriage and may deliver their babies early, before 37 weeks of gestation.
- Both depressive symptoms and antidepressant exposure are associated with fetal growth changes and shorter gestations, but **the majority of studies that evaluated antidepressant risks were unable to control for the possible effects of a depressive disorder.**
- Short-term neonatal irritability and neurobehavioral changes are also linked with maternal depression and antidepressant treatment.
- The association between paroxetine (Paxil) and cardiac defects is more often found in studies that included all malformations rather than *clinically significant* malformations. (ie, no difference than background levels of malformations)
- Late gestational use of selective serotonin reuptake inhibitor antidepressants is associated with transitory neonatal signs and a low risk for persistent pulmonary hypertension in the newborn

(Yonkers, Wisner, Stewart, Oberlander, Dell, Stotland, Rami; Obstetrics and Gynecology, 2009)

PTSD Treatment

Therapy

- Exposure therapy
- Cognitive restructuring (CBT)
- Stress inoculation training
- EMDR

Medications

- Prazosin – blocks release of adrenaline and reduces nightmares
- D-cycloserine (Seromycin), which boosts the activity of a brain chemical called NMDA, which is needed for fear extinction
- Propranolol (Inderal) – Beta Blocker, reduces heart rate, interrupts memory recall to inhibit flashbacks

In my clinical experience, I have yet to have a patient with Bipolar Disorder, Schizophrenia, or cycling Mood Disorders stabilize WITHOUT medications.

When to start Meds for Bipolar Disorder?

- Starting a mood stabilizer in the third trimester ensures lower risk of relapse, but still some risk of fetal exposure. (But greatly reduces effects on fetal development than in the first 8 weeks gestation).
- If the mood stabilizer is started immediately postpartum, the risk of a mood episode is low to medium, but infant exposure to medication is greatly reduced.
- Planning to start mood stabilizer therapy at the onset of symptoms is associated with a much higher risk of relapse

Medications for Mood Disorders

Mood Stabilizers:

- Lithium
- Atypical antipsychotics
  - Quetiapine (Seroquel)
  - Olanzapine (Zyprexa)
  - Aripiprazole (Abilify)
  - Risperidone (Risperdal)
  - Ziprasidone (Geodon)

Anticonvulsants:

- Valproic acid or divalproex sodium (Depakote)
- Lamotrigine (Lamictal)
- Gabapentin (Neurontin), Topiramate (Topamax), and Oxcarbazepine (Trileptal).

Antidepressants & Bipolar Disorder

- Often used to treat symptoms of depression in bipolar disorder.
- HOWEVER, Taking only an antidepressant can increase the risk of inducing mania or hypomania, or of developing rapid-cycling symptoms.
- To prevent this switch, prescribers often first start a mood-stabilizing medication before starting an antidepressant.

Antidepressant Safety in Pregnancy

- Based on recent data from the Metropolitan Atlanta Congenital Defects Program, the risk of major structural or genetic birth defects in the United States is approximately 3% of all births
- This report suggesting that the use of antidepressants during pregnancy **DOES NOT** increase the risk above the general population risk of 2%–3%, nor is there evidence to indicate that they might cause organ-specific defects.

Steiner; Prenatal Exposure to Antidepressants: How Safe Are They? *Am J Psychiatry* 2012;169:1130-1132

Antidepressant Safety in Pregnancy

- N = 36,772 infants exposed to any SSRI in early pregnancy
- To summarize, this large Nordic study found **NO** substantial increase in the overall prevalence of birth defects among infants exposed to SSRIs or venlafaxine (Effexor) in utero.

(Furu, Kieler, Haglund, Engeland, et al. BMJ. 2015; *Selective serotonin reuptake inhibitors and venlafaxine in early pregnancy and risk of birth defects: population based cohort study and sibling design*)

- N = 64,389 women who used antidepressants during the first trimester
- there was **NO** substantial increase in the risk of cardiac malformations attributable to antidepressant use during the first trimester of pregnancy

(Huybrechts, Palmsten, Avorn, Cohen, Holmes, Franklin, Mogun, Levin, Kowal, Setoguchi, Hernández-Díaz. N Engl J Med. 2014, *Antidepressant use in pregnancy and the risk of cardiac defects*)

Antidepressants in pregnancy and Autism?

New 2014 Study found:

- In **boys only** (Not girls), prenatal exposure to SSRIs may slightly increase susceptibility to Autism Spectrum Disorder (ASD)
- They admit, however, that underlying depression and its genetic underpinnings may be a confounding variable.

TOO SOON TO SAY…

(Harrington, Lee, Crum, Zimmerman, Hertz-Picciotto, Pediatrics, 2014 May. Prenatal SSRI use and offspring with autism spectrum disorder or developmental delay)

Anxiety Meds

- Benzos used prenatally does **NOT** carry a significant teratogenic risk.
- Prenatal exposure to diazepam (Valium) increases the risk of oral cleft, but the absolute risk increases by only 0.01 percent (from six to seven in 10,000 infants).
- Use of benzos shortly before delivery is associated with floppy infant syndrome and withdrawal syndromes may persist after delivery in infants whose mothers took alprazolam (Xanax), chlordiazepoxide (Librium), or diazepam.
- Benzodiazepines during breastfeeding affects the infant only if they have an impaired ability to metabolize the drug. In this situation, the infant may demonstrate sedation and poor feeding.

(ACOG Guidelines on Psychiatric Medication Use During Pregnancy and Lactation,American Family Physician, 2008)

Antipsychotic use in 1st & 2nd Trimester

2015 Study Results:

Compared with non-users, women prescribed an antipsychotic medication in pregnancy did **NOT** seem to be at higher risk of:

- gestational diabetes
- hypertensive disorders of pregnancy
- venous thromboembolism
- preterm birth
- birth weight differences

(Vigod, Gomes, Wilton, Taylor, Ray, British Medical Journal 2015; *Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study*)

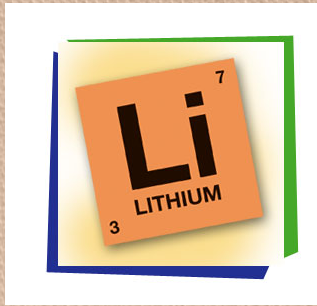
2015 meta-analysis of adverse associated outcomes with exposure to antipsychotics during pregnancy

- Antipsychotic (typical and atypical) exposure was associated with:
  - Increased risk of major malformations
  - Increased risk of cardiac defects
  - Increased risk of preterm delivery
  - Lower birth weight
  - Small for gestational age
- **Association does not necessarily imply causation**
- The most important confounding factor is psychiatric illness itself
- **We cannot conclude if the worse outcomes we observe are the result of medication exposure or the result exposure to psychiatric illness and/or certain behaviors that go along with illness (i.e., poor prenatal care, smoking, substance use).**

(Coughlin, Blackwell, Bartley, Hay, Yonkers, Bloch. Obstet Gynecol. 2015: *Obstetric and neonatal outcomes after antipsychotic medication exposure in pregnancy*)

Lithium

- Class D
- use during the first trimester is associated with a 10- to 20-fold increase in the risk of Ebstein's anomaly, but the absolute risk is approximately 1 per 1,000 births.
- use in the third trimester has been associated with floppy baby syndrome.
- Only one study has assessed long-term outcomes of children exposed to lithium *in utero* and found no developmental delay in 80 children followed for 5 years prospectively



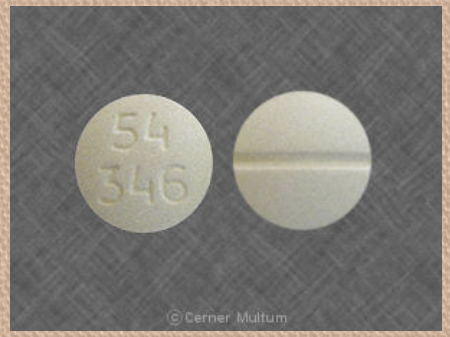
u M. What happened to the lithium babies? A follow-up study of children born without malformations. *Act Psychiat Scand*1976; **54**: 193–7)

Lithium

- Teratogenic in 1st trimester exposure, causing cardiovascular defects.
- Possible association with neural tube defects, hip dislocation, cerebral palsy, and polydactyly (extra fingers).
- ***However**, more recent research reports that teratogenicity associated with lithium may have been **overestimated** in the past.* (Yonkers, Wisner, Stowe, Leibenluft, Cohen, Miller, Manber, Viguera, Suppes, Altshuler; Management of Bipolar Disorder During Pregnancy and the Postpartum Period; *Am J Psychiatry* 2004;161:608-620.
- Lithium overdose in the mother can cause preterm labor, and abnormal fetal heart pattern

Lithium

- Additionally, stopping lithium before conception or during early pregnancy is associated with a three-fold increase in the risk of postpartum bipolar relapse
- Regular monitoring of lithium blood levels is important, because lithium requirement increases markedly with pregnancy and reduces dramatically post-partum.



Quetiapine (Seroquel)

- Has the **least** amount of passage through the placenta compared to other atypical antipsychotics (i.e. olanzapine, haloperidol, and risperidone
- There is no apparent increased risk of birth defects with quetiapine (Seroquel), but the number of studies that have been conducted is small.

Atypical Antipsychotic Administration During Late Pregnancy: Placental Passage and Obstetrical Outcomes; Newport, et al; *Am J Psychiatry 2007*

Quetiapine (Seroquel)

- Class C in pregnancy
- There is a risk of maternal weight gain with subsequent increase in diabetes mellitus and thromboembolic events (blood clots) with quetiapine use.
- There is an increased risk of having an infant who is large for gestational age.
- There is a small risk of neonatal poor adaptation syndrome at birth although. The infant should be observed for 48 hours after delivery and examined for low muscle tone and poor feeding, just in case.

Lamotrigine (Lamictal)

- Class C in pregnancy
- Lamotrigine does not appear to increase the risk of birth defects in several studies so far.
- Considered the first choice of antiepileptic drug for women wishing to become pregnant due to such low risk both in terms of fetal malformations and postpartum cognitive development.

Moore, Aggarwal ; Lamotrigine use in pregnancy. *Expert Opin Pharmacother*. 2012 Jun;13(8):1213-6.

Valproate (Depakote)

- Pregnancy category D
- Linked with an increase in neural tube defects as well as craniofacial, skeletal, cardiovascular, urogenital and cerebral defects
- 4 to 11-fold increase in the risk of orofacial clefts
- 4 to 7-fold increase in congenital heart defects, compared with the general population

Yonkers, Wisner, Stowe, Leibenluft, Cohen, Miller, Manber, Viguera, Suppes, Altshuler; Management of Bipolar Disorder During Pregnancy and the Postpartum Period; *Am J Psychiatry* 2004;161:608-620

Valproate (Depakote)

- **It is important to advise patients that, often by the time pregnancy is discovered, the risk period for most teratogenic effects has already passed;**
- Cleft palate occurs less than 60 days after conception, anterior neural plate anomalies occur during weeks 2–3 and spina bifida may occur in the late pre-implantation phase, according to studies in an animal model.
- **Beyond 8 weeks, no major morphological anomalies are thought to occur, so stopping or changing treatment will not reduce the risk for birth defects.**

Yonkers, Wisner, Stowe, Leibenluft, Cohen, Miller, Manber, Viguera, Suppes, Altshuler; Management of Bipolar Disorder During Pregnancy and the Postpartum Period; *Am J Psychiatry* 2004;161:608-620

Long-term Neurodevelopmental Effects

- Pregnant women with epilepsy receiving monotherapy (ie, carbamazepine (Tegratol), lamotrigine (Lamictal), phenytoin (Dilantin), or valproate (Depakote) were followed from pregnancy through 6 yrs.

- No adverse effects of exposure via breast milk were observed at age 6 years.

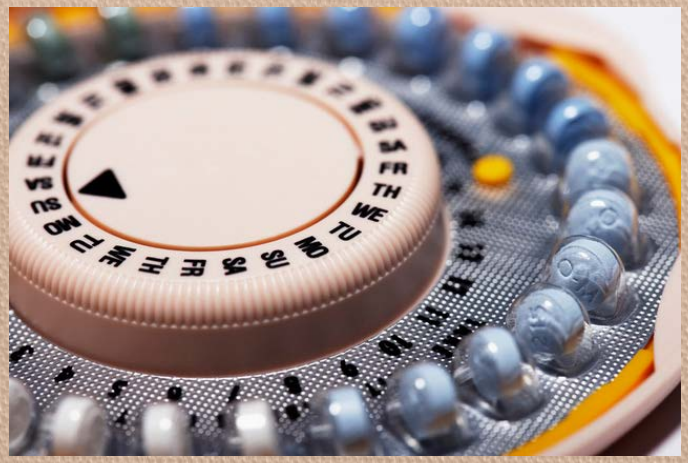
Meador, Baker, Browning, Cohen, Bromley, Clayton-Smith, Kalayjian, Kanner, Liporace, Pennell, Privitera, Loring; Breastfeeding in children of women taking antiepileptic drugs: cognitive outcomes at age 6 years. Neurodevelopmental Effects of Antiepileptic Drugs (NEAD) Study Group. *JAMA Pediatr*. 2014 Aug;168(8):729-36

Risk of Bipolar Relapse in Pregnancy

- The overall risk of at least one recurrence in pregnancy was 71%.
- Among women who discontinued versus continued mood stabilizer treatment, recurrence was 2x greater
- the proportion of weeks ill during pregnancy was 5x greater.
- Median recurrence latency was 11x faster after abrupt/ rapid versus gradual discontinuation of mood stabilizer.
- Most recurrences were depressive or mixed 74%, and 47% occurred during the 1st trimester.

Viguera, et al; Am J Psychiatry 2007

Future Pregnancies



- In practice, pre-conception planning of drug management during pregnancy is difficult in women with bipolar disorder.
- Even in the general population, approximately 50% of pregnancies are unplanned.
- Bipolar Disorder requires very mindful pregnancy planning, if possible, due to the teratogenic nature of many mood stabilizers on the fetus.
- Discuss Birth Control options between pregnancies if you get the chance

An ounce of prevention…

Folate supplementation is crucial in women taking any drug associated with risk for neural tube defects

Check for MTHFR Gene Mutation

- Methylenetetrahydrofolate Reductase
- Dx with simple blood test
- Those with this mutation CANNOT properly metabolize folic acid, and need to INSTEAD take a methylated version (such as Rx for Deplin)
- For more information:
  - http://ghr.nlm.nih.gov/gene/MTHFR
  - http://mthfrsupport.com
  - http://mthfr.net

MTHFR Gene Mutation

Correlated with:

- Miscarriages
- Pre-eclampsia
- Premature Death
- Placental Abruption
- Congenital Heart Defects
- Infant depression via epigenetic processes caused by maternal depression
- Pulmonary embolisms
- Depression, Bipolar disorder, Schizophrenia
- Stroke
- Cancer
- Spina bifida
- Tongue Tie
- Oral Clefts
- Midline Defects
- Blood clots
- Deficits in childhood cognitive development
- Migraines with aura
- Low HDL
- High homocysteine
- Atherosclerosis
- Potential drug toxicities: methotrexate, anti-epileptics
- Myocardial Infarction (Heart Attack)
- Heart Murmurs
- Nitrous Oxide Toxicity
- And others

Medications and Breastfeeding

- Informed Choice
- Most Anti-depressants are considered safe with breastfeeding
- Proceed with Caution with other categories of medications such as mood stabilizers, anti-psychotics and sleep meds

Antidepressants and Breastfeeding

- Sertraline (Zoloft) is one of the most frequently prescribed antidepressants perinatally and has low concentration in breast milk and infant serum (Berle and Spigset, *Antidepressant use during breastfeeding*. Curr Womens Health Rev. 2011; Friedman, Nagle-Yang, Parsons, *Maternal mental health in the neonatal intensive care unit*. NeoReviews. 2011)

- "Most newer antidepressants produce very low or undetectable plasma concentrations in nursing infants. The highest infant plasma levels have been reported for fluoxetine (Prozac), citalopram (Celexa) and venlafaxine (Effexor)." (Berle and Olav, Curr Womens Health Rev. 2011, *Antidepressant Use During Breastfeeding*)

Mood Stabilizing Meds and Breastfeeding

- Olanzapine (Zyprexa) is the best-studied with respect to breastfeeding.
- the relative infant dose was only 1%
- No olanzapine was detected in infants exposed via milk and no adverse effects were observed in the infants

Croke S, Buist, Hackett LP et al. Olanzapine excretion in human breast milk: estimation of infant exposure. Int J Neuropsychopharmacol. 2003;5:243-7.; Gardiner SJ, Kristensen JH, Begg EJ et al. Transfer of olanzapine in to breast milk, calculation of infant drug dose, and effect on breast-fed infants. Am J Psychiatry. 2003;160:1428-31.; Lutz UC, Wiatr G, Orlikowsky T et al. Olanzapine treatment during breast feeding: a case report. Ther Drug Monit. 2008;30:399-401.; Whitworth A, Stuppaeck C, Yazdi K et al. Olanzapine and breast-feeding: changes of plasma concentrations of olanzapine in a breast-fed infant over a period of 5 months. J Psychopharmacol. 2008;99:379-83.; Var L, Ince I, Topuzoglu A, Yildiz A. Management of postpartum manic episode without cessation of breastfeeding: A longitudinal follow up of drug excretion into breast milk. Eur Neuropsychopharmacol. 2013;23

Mood Stabilizing Meds and Breastfeeding

Lithium: Mixed Results

- Some studies showed infant plasma concentrations that may be up to 50% of maternal plasma concentrations. (Gardiner, and Begg, Clinical Pharmacologist, Christchurch School of Medicine; Drug Safety in Lactation; *Prescriber Update* 21: 10-23; May 2001)
- If this is the case, Infant exposure is sufficiently high that it should be regarded as **unsafe** for use in breastfeeding.
- While others found low serum concentration in infants, pointing to the possibility that it is tolerated well. (Viguera, Newport, Ritchie, Stowe, Whitfield, Mogielnicki, Baldessarini, Zurick, Cohen; Lithium in Breast Milk and Nursing Infants: Clinical Implications; *Am J Psychiatry* 2007;164:342-345)

Mood Stabilizing Meds and Breastfeeding

Lamotrigine

- Newport (2008) found measuring maternal and infant plasma concentrations, that the relative infant dose (RID) of lamotrigine was 9.2% and that the theoretical infant dose (TID) was 0.51 mg/kg per day. This RID of 9.2% is lower than the RID cutoff of 10% frequently used as an empiric cutoff for assuming safety during lactation.
- It is reassuring, however, that **this dose is considerably lower than doses of lamotrigine used to treat seizures in infants**.

Newport DJ, Pennell PB, Calamaras MR, et al. Lamotrigine in Breast Milk and Nursing Infants: Determination of Exposure. *Pediatrics*. 2008. 122(1):e223-e231

Mood Stabilizing Meds and Breastfeeding

Risperidone (Risperdal)

- limited case studies, however, it appears to have a favorable safety profile for breastfeeding, with a low relative infant dose

(Aichhorn, Stuppaeck, Whitworth. Risperidone and breast-feeding. *J Psychopharmacol*. 2005 Mar; 19(2):211-3.; Hill RC, McIvor RJ, Wojnar-Horton RE, Dip G et al. Risperidone distribution and excretion into human milk: case report and estimated infant exposure during breast-feeding. *J Clin Psychopharmacol.* 2000;20:285-6.; Ilett KF, Hackett LP, Kristensen JH, Vaddadi KS et al. Transfer of risperidone and 9-hydroxyrisperidone into human milk. Ann *Pharmacother*. 2004;38:273-6.; Aichhorn W, Stuppaeck C, Whitworth AB. Risperidone and breast-feeding. *J Psychopharmacol.* 2005;19: 211-3.; Weggelaar NM, Keijer WJ, Janssen PK. A case report of risperidone distribution and excretion into human milk: how to give good advice if you have not enough data available. *J Clin Psychopharmacol*. 2011 ;31:129-31.; Ratnayake T, Libretto SE. No complications with risperidone treatment before and throughout pregnancy and during the nursing period. *J Clin Psychiatry*. 2002;63(1):76-7.)

Meds & Breastfeeding Resources

- www.mothertobaby.org
- http://toxnet.nlm.nih.gov (LactNet)
- www.motherisk.org/women/breastfeeding
- www.infantrisk.com (Thomas Hale)
- www.uppitysciencechick.com/PPD-Treatments-Medications.html (Kathleen Kendall-Tackett)

Psychotherapy in combination with Medication Management is best practices. Medication alone is usually not sufficient.

Sites to download PMAD Screening Tools

- Edinburgh Scale http://www.fresno.ucsf.edu/pediatrics/downloads/edinburghscale.pdf
- Patient Health Questionnaire (PHQ-9) http://www.phqscreeners.com/overview.aspx?Screener=02_PHQ-9
- Postpartum Depression Screening Scale (PDSS) http://www.wpspublish.com/store/p/2902/postpartum-depression-screening-scale-pdss

Resources for Mothers

- Postpartum Support International of WA state www.ppmdsupport.com
- Postpartum Support International www.postpartum.net
- Postpartum Progress Blog by Katherine Stone www.postpartumprogress.com
- *Bipolar Mom Life* Blog by Jennifer Marshall http://bipolarmomlife.com/
- Moms with Bipolar online support group http://www.bphope.com/Social/Groups/Details/MomswithBipolarDisorder