PSYCHOPHARMACOLOGY ACROSS THE FEMALE REPRODUCTIVE LIFESPAN

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MISSING LINK

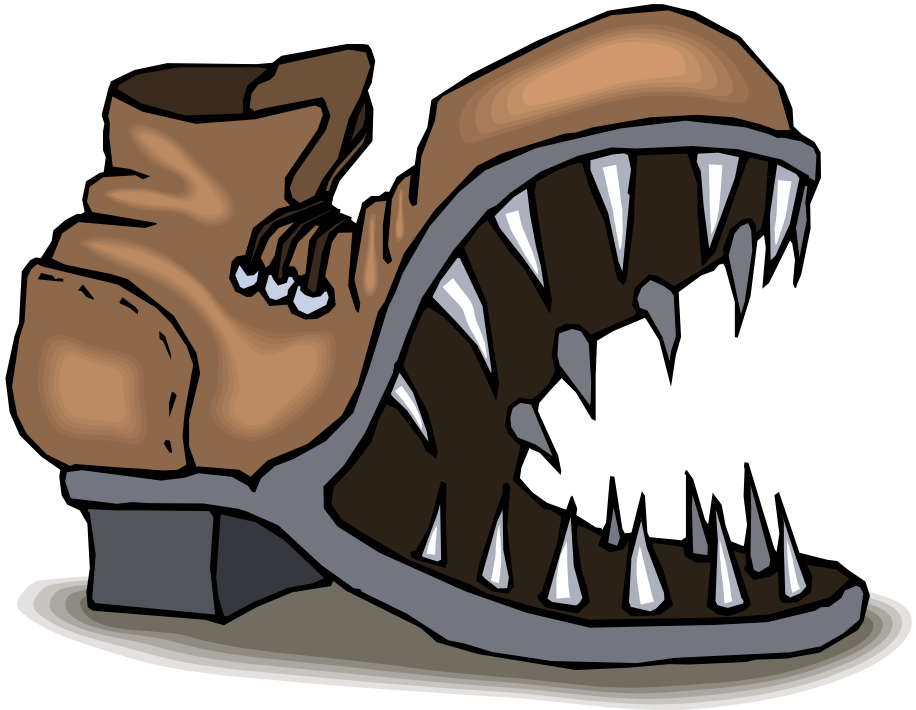
OUTLINE

- Premenstrual dysphoric disorder
- Pregnancy and lactation
  - Antidepressants
  - Antipsychotics
  - Antiepileptics and mood stabilizers
- Menopause

CAVEAT

- This is a 45-min summary of what should be a 3-day workshop.

PREMENSTRUAL DYSPHORIC DISORDER (PMD)

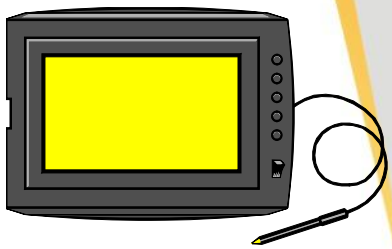


NOMENCLATURE

- Premenstrual tension
- Premenstrual syndrome
- Late luteal phase dysphoric disorder
- Premenstrual tension syndrome (ICD-10)
  - Criteria broad, easy to endorse
  - Identifies even mild s/s
- Premenstrual dysphoric disorder (DSM 5)
  - Narrow, specific
  - Labels only severe s/s

PREVALENCE

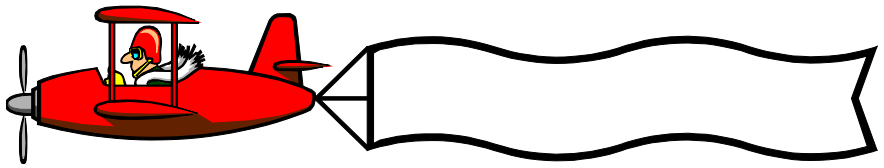
- DSM: 3-9%
  - Robinson and Ismail, Int J Womens Health 2015
- Indian data, 3.7-12.2%
  - Andrade, Indian J Psychiatry 2016
  - 37% in one outlying study (Mishra et al, Ind Psychiatry J 2015)
  - 91.4% with ICD-10 criteria (Raval et al, Indian J Psychiatry 2016)



CLINICAL FEATURES: 1

- Mood s/s
  - Anxiety, depression, irritability, anger, affective lability
- Physical s/s
  - Bloating, muscle pain
- Other symptoms
  - Poor concentration, decreased interest, lethargy, disturbed sleep/appetite

CLINICAL FEATURES: 2



- S/s present across several menstrual cycles
- Appear in the week before onset of period
- Diminish and disappear soon after onset of period
- Cause significant distress/impairment

CONTROVERSIES

- Stigmatizes/marginalizes women
- Medicalizes a normal experience
- May be a culture-specific syndrome
- Is a pharmaceutical target
- The above notwithstanding, the occurrence of distress and impairment justify attention and treatment

(Hartlage et al, J Clin Psychiatry 2014)

TREATMENT: 1

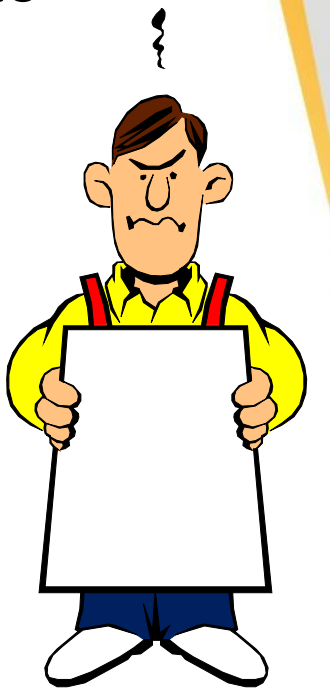
- Psychological treatments
  - From stress management to formal psychotherapy
- Hormonal treatment
- Physical treatments
  - Yoga, aerobic exercise
- Mineral supplements
  - Calcium
- Nutritional supplements
  - Vitamins, omega-3 fatty acids

TREATMENT: 2

- Herbal supplements
  - Ginkgo biloba, Crocus sativus
- Antidepressant drugs
  - SSRIs
  - In different doses and schedules
- Miscellaneous
  - Diuretics, salt restriction, caffeine restriction, NSAIDs
    (Andrade, Indian J Psychiatry 2016)

SSRIs for PMD

- Fluoxetine, the first marketed SSRI, was the first to demonstrate efficacy in RCTs
- Marjoribanks et al (Cochrane, 2013):
  - 31 RCTs of an SSRI for PMD
  - Small to medium effect sizes for self-reported improvement



CONTINUOUS vs LUTEAL PHASE DOSING

- In the initial RCTs, SSRIs were dosed all through the cycle.
  - Benefits seen from the 2nd cycle, itself.
- Later, dosing only during the luteal phase
- Both strategies are > placebo
- Which is better is presently unclear

  Marjoribanks et al (Cochrane, 2013)

CRITICAL ISSUES

- SSRIs are associated with AEs
- Continuous or luteal phase dosing increase the risk of AEs and drop out due to AEs
- Might SSRIs have an immediate symptomatic effect?
- Possibility explored as early as in 2005
  Freeman et al (J Clin Psychiatry 2005)

RECENT STUDY

(Yonkers et al, JAMA Psychiatry 2015)

- Industry-independent, 3-center RCT (n=252)
- Sert (50-100 mg/day) vs placebo
  - Starting from symptom onset
  - Abrupt d/c a few days after onset of period
  - For 6 cycles
- Sert > placebo on many but not all outcomes
- No withdrawal s/s on drug discontinuation

SUGGESTION

- Start with symptom-onset dosing
  - E.g. Sert 50-100 mg/day or Escit 5-10 mg/day
  - If no benefit with one drug, try another
- If no benefit with 2 drugs, shift to luteal phase dosing
- If inefficacy or withdrawal issues are observed, try continuous dosing
- Thought: If physical s/s > mood s/s, would an SNRI be better?

PREGNANCY

ANTIPSYCHOTICS IN PREGNANCY

- Benefits out weight risks.
- Continue whatever worked.
- Risk of teratogenicity is small to negligible.
  Huybrechts et al, JAMA Psychiatry 2016
- Risk of gestational diabetes seen with some drugs, especially the atypical antipsychotics.
- Risk of other adverse outcomes related to gestation may be due to the diagnosis, not the drug.

ANTIDEPRESSANTS IN PREGNANCY

EFFECT OF PREGNANCY ON DEPRESSION

- It is a myth that pregnancy protects against psychiatric illness.
- Pregnancy is associated with
  - Emotional stress
  - Physical stress
  - Physiological stresses

- Pregnancy can therefore trigger new-onset depression or depressive relapse.

EFFECT OF UNTREATED DEPRESSION ON PREGNANCY: 1

- Increased risk of maternal mortality (Brettingham, BMJ 2004).
- Increased risk of poor weight gain, alcohol or illicit drug use, pre-eclampsia, poor mother-child bonding (Kurki et al, Obstet Gynecol 2000; Nonacs and Cohen, Psychiatr Clin North Am 2003; Davalos et al, Arch Womens Ment Health 2012).
- Increased risk of preterm delivery, low birth weight, operative delivery, neonatal ICU admission (Chung et al, Psychosom Med 2001; Bonari et al, Can J Psychiatry 2004; O'Keane and Marsh, BMJ 2007).

EFFECT OF UNTREATED DEPRESSION ON PREGNANCY: 2

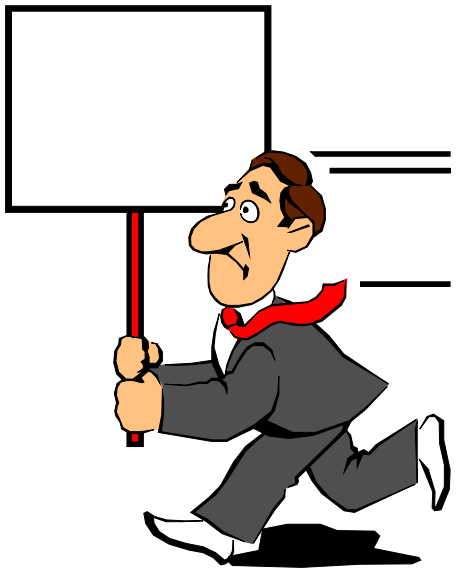
- Meta-analysis of 29 prospective studies from 12 countries: Approximately 50% increased risk of each of the following:
  - IUGR
  - Preterm birth
  - Low birth weight

(Grote et al, Arch Gen Psychiatry 2010)

(Grigoriadis et al, J Clin Psychiatry 2013)

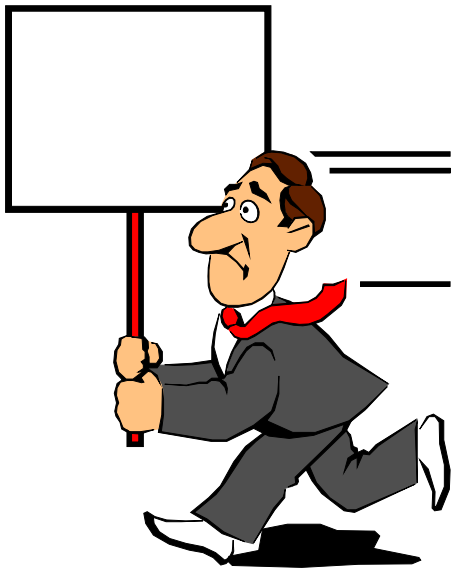
MECHANISMS OF FETOTOXICITY OF UNTREATED DEPRESSION: 1

- Neuroendocrinological changes
- Immunological impairments
- Abnormal eating patterns
- Nutritional disorders
- Neglect of health



MECHANISMS OF FETOTOXICITY OF UNTREATED DEPRESSION: 2

- Poor adherence to medical regimes
- Smoking, drinking, and illicit drug use
- Impulsive behavior
- Deliberate self-harm



IMPLICATIONS AND CAVEATS

- It may be better to treat depression during pregnancy than to leave it untreated.
- We do not have Indian data to know whether harmful maternal behavior and harmful maternal internal environment associated with untreated depression would result in the same harmful outcomes.

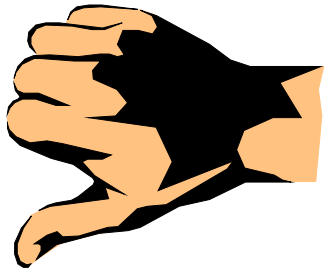
EFFECT OF DRUG-TREATED DEPRESSION ON PREGNANCY: 1

- Planned abortion
- Spontaneous abortion
- Preterm labour
- Morphological teratogenicity
  - Major, e.g. cardiac defects
  - Minor, e.g. minor finger, toe, or ear defects
  - Qualitative, e.g. cleft palate
  - Quantitative, e.g. small head circumference

EFFECT OF DRUG-TREATED DEPRESSION ON PREGNANCY: 2

- Neonatal toxicity (because of immature liver)
- Neonatal withdrawal (e.g. SSRIs, BDZP)
- Physiological teratogenicity (e.g. persistent pulmonary hypertension with SSRIs)
- Behavioral teratogenicity (e.g. low IQ, behavioral or personality problems in later life)
- Maternal adverse outcomes
  - Extra weight gain
  - Pregnancy-induced hypertension

PSYCHOTHERAPY: NEGATIVES



- May not be available.
- May not be accessible.
- May not be affordable.
- May not be acceptable.
- May not be appropriate.
  (e.g. poor motivation, severe depression).
- Onset of efficacy may be delayed.

PSYCHOTHERAPY: POSITIVES

- Treats only the mother.
- Can be used to augment drug management and hence:
  - Improve efficacy of drugs.
  - Reduce the need for polypharmacy.
  - Reduce the need for higher doses.
- Note: Involve family in therapy
  [e.g. for support and stress management].

OTHER GUIDANCE FOR MANAGEMENT DURING PREGNANCY

- Do not use lowest historically-effective doses (these may be ineffective during the stressful period that is pregnancy; the whole point in treatment is to treat EFFECTIVELY).
- In this regard, note that drug metabolism is upregulated as pregnancy progresses.
- Administer drugs in divided doses to lower dosage peaks.
- Avoid polypharmacy.

ANTIEPILEPTIC TERATOGENICITY (Weston et al, Cochrane, 2016)

- 50 observational studies
- Carbamazepine, phenobarbitone, phenytoin, topiramate increase the risks.
- Valproate is associated with the highest risk.
  - The risk is dose-dependent and can be as high as 10%.
- Lamotrigine is not associated with increased risk.
- Limited data also suggest safety with oxcarbazepine, levetiracetam, zonisamide, gabapentin.

VALPROATE IN PREGNANCY: NEURODEVELOPMENTAL EFFECTS

- Valproate exposure during pregnancy increases the risk of
  - Low IQ
  - Other neurocognitive impairments in childhood

(Gentile, CNS Spectr 2014; Bromley et al, Neurology 2016)

LITHIUM IN PREGNANCY (Patorno et al, NEJM 2017)

- Dose-dependent increase in the risk of cardiac malformations
- Significant risk at dose >900 mg/day
- But dose will need to increase as pregnancy advances
  - Issues related to increased in fluid volume
  - Need for monitoring
  - Dosing peripartum and postpartum

LACTATION: 1

- Maternal benefits of breastfeeding
  - Reduced risk of conception
  - Emotional satisfaction and bonding
  - Reduced risk of certain cancers
- Infant benefits of breastfeeding
  - Emotional
  - Cognitive
  - Resistance against infection

LACTATION: 2

- Concept of maternal weight-adjusted dose
  - <10% infant exposure is probably OK
- Many drugs are probably safe during lactation
  - Sertraline, olanzapine, valproate
- Some drugs are generally advised to be avoided during lactation
  - Lithium
- Guidance: Examine the individual risk-benefit ratio

LACTATION: 3

- Possible issues
  - Foremilk vs hindmilk
  - Feeding during troughs
  - Pump and dump at peaks
  - All controversial

MENOPAUSE

MENOPAUSE

- Affects 50% of persons after 40-50 years of age!
- Types
  - Natural
  - Surgical
  - Chemical
- Symptoms
  - Vasomotor symptoms
  - Mood symptoms
  - Other symptoms

MENOPAUSE

- Vasomotor s/s: hot flushes (hot flashes)
  - Sympathetic surges
  - Characterized by unpleasant warmth, sweating, tachycardia
  - Night sweats
- Mood symptoms:
  - Depression
  - Anxiety

MENOPAUSE

- Other symptoms
  - Insomnia
  - Cognitive disturbance
- Menopause is associated with:
  - Impaired functioning when hot flushes are severe.
  - Impaired quality of life.
- Severity varies widely
- Can last for 1-2 years.

HORMONE REPLACEMENT THERAPY

- Position statement of the North American Menopause Society
- Expert consensus statement
- Updates the 2012 position statement
- Endorsed by about 30 academic organizations across the world, including the Indian Menopause Society

  (North American Menopause Society, Menopause, 2017)

HORMONE THERAPY: POSITION STATEMENT

Benefits

- HRT is the most effective treatment for
  - Vasomotor symptoms of menopause
  - Genitourinary syndrome of menopause
- HRT prevents bone loss and fracture.
- Note: Genitourinary syndrome includes vulvovaginal atrophy and its functional consequences

HORMONE THERAPY: POSITION STATEMENT

Optimization

- HRT risks depend on type, dose, duration of use, route of admn, timing of initiation, and whether a progestogen is used.
- Treatment should be individualized to identify the most appropriate HRT type, dose, formulation, route of admn, and duration of use
- Periodic risk-benefit reevaluation is necessary.

HORMONE THERAPY: POSITION STATEMENT

Early use

- For women aged <60 years or who are <10 years of menopause onset and have no contraindications: the benefit-risk ratio is most favorable for
  - Treatment of bothersome vasomotor s/s
  - For those at elevated risk for bone loss or fracture.

HORMONE THERAPY: POSITION STATEMENT

Late use

- For women aged > 60 years or who are >10 years from menopause onset, the benefit-risk ratio is less favorable because of the greater absolute risks of
  - Coronary heart disease
  - Stroke
  - Venous thromboembolism
  - Dementia.

HORMONE THERAPY: POSITION STATEMENT

Other issues

- Longer durations of HRT should be for documented indications
  - E.g. Persistent vasomotor s/s or bone loss
- There should be shared decision making and periodic reevaluation.
- For bothersome genitourinary syndrome not relieved with over-the-counter therapies and without indications for oral HRT, low-dose vaginal estrogen or other therapies are recommended.

NON-HRT TREATMENT OF VASOMOTOR SYMPTOMS

- Position statement of the North American Menopause Society
- Expert consensus statement
- Updates an earlier position statement
- North American Menopause Society (Menopause, 2015)

NON-HRT TREATMENT OF VASOMOTOR SYMPTOMS: 1

- Recommended treatments:
  - Paroxetine is the only FDA-approved nonHRT drug.
  - Other SSRIs and SNRIs probably also help.
  - CBT and, perhaps, hypnosis can also help.
  - Gabapentin and related drugs, and clonidine may also help.

NON-HRT TREATMENT OF VASOMOTOR SYMPTOMS: 2

- Treatments recommended with caution:
  - Weight loss
  - Mindfulness-based stress reduction
  - S-equol derivatives of soy isoflavones
  - Stellate ganglion block
- These treatments need further study for firm guidance.

NON-HRT TREATMENT OF VASOMOTOR SYMPTOMS: 3

- Treatments not recommended:
  - Avoidance of triggers
  - Paced respiration,
  - Exercise, yoga, relaxation
  - Cooling techniques
  - OTC supplements, herbal therapies
  - Acupuncture, chiropractice
  - Calibration of neural oscillations
- Studies are negative, insufficient, or inconclusive.

STRESS URINARY INCONTINENCE

- Interventions range from Kegel exercises to surgery
- Adrenergic antidepressants provide symptomatic benefits
- Duloxetine (120 mg/day) has been best studied.
  - Approved in Europe but not the USA

SUGGESTED READING

E-LEARNING INITIATIVES

Send a blank email to:

- synergytimes-subscribe@yahoogroups.com
  - For Synergy Times, an e-newsletter on psychiatry and the allied medical and mental health sciences
- eJCIndia-subscribe@yahoogroups.com
  - To join the Journal Club e-group of the Dept of Psychopharmacology and Indian Psychiatric Society.
- My email: andradec@gmail.com

ENFIN…

That’s it, folks; thanks for listening!