Frequently Overlooked Considerations in Women's Mental Health

A Carlat Webinar

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Conflicts and Disclosures

None

Learning Objectives

After the webinar, clinicians should:

1. Be aware of common gender differences in the course of illness of bipolar disorder and schizophrenia
2. Know medication side effects that occur more commonly in female patients
3. Identify drug interactions with hormonal contraception
4. Summarize some of the current research findings in psychiatric treatment

Bipolar disorder: gender differences in course of illness

Women experience more rapid cycling, more time depressed, more seasonal variation, and more anxiety

Proposed reason for rapid cycling: gender differences in use of antidepressants

Menstrual cycle phase: not associated with rapid mood cycling

Gogos A et al Br J Pharmacol 2019;176(21):4119-4135

Gender differences in bipolar subtypes and comorbidity

There appears to be a slight overrepresentation of women with bipolar II disorder

Be careful not to mistake premenstrual dysphoric disorder (PMDD) for bipolar II disorder

Diflorio A et al Int Rev Psychiatry 2010;22(5):437-52

Schizophrenia: gender differences

- On average, age of onset is later in women than in men
- Women tend to have less severe symptoms and better outcomes
- Males show more negative symptoms and cognitive deficits
- Expressed emotion has a greater negative impact on males
- Late-onset schizophrenia occurs more often in women

Ayesa-Arriola R et al, NPJ Schizophrenia 2020;6(1):33

Adjunctive estradiol for schizophrenia

N=100 women of child-bearing age, median age 38 years (range: 34-42 years)

Received 200 mcg estradiol patch or placebo for 8 weeks

PANSS showed significant improvement but only for women > 38 years

Estradiol may be an effective add-on treatment for women of childbearing age with schizophrenia

Weiser M et al, JAMA Psychiatry 2019;76(10):1009-1017

SERMs for women with schizophrenia

- Raloxifene, a selective estrogen receptor modulator (SERM), acts similarly to estrogen on dopamine and serotonin in the brain
- It lacks estrogen's negative effects on breast and uterine tissue
- Postmenopausal women randomized to raloxifene (adjuvant to antipsychotic) have experienced
- Significantly faster recovery
- Improvement in positive symptoms

Kulkarni J et al, Front Neuroendocrinology 2019;53:100743

Antiepileptic medications: drug interactions specific to women

Many antiepileptic medications induce cytochrome P450 enzymes

Thereby, they increase metabolism of hormones and can reduce efficacy of oral contraceptives and HRT

Include:

- Carbamazepine
- Topiramate
- Oxcarbazepine

Estrogen containing oral contraceptives can increase the metabolism of lamotrigine

Lamotrigine blood levels can be reduced by 50%

Wegner et al, Acta Neurol Scand 2014;129(6):393-8

Recommendations

For women on oral contraceptives (OC) who are starting lamotrigine, instruct them:

not to stop the OC while taking lamotrigine or

to stop the OC before starting lamotrigine or

to use a progestin-only contraceptive

Gender differences in side effects from mood stabilizers: lithium-induced hypothyroidism

Hypothyroidism develops about 3-4 times more commonly in women than in men

The risk for lithium induced hypothyroidism is especially increased in women over the age of 50

Ozerdem A et al, Bipolar Disord 2014;16(1):72-82

Gender differences in side effects: lithium

Hyperparathyroidism:
Subsequent elevation of serum calcium may produce bone demineralization
May exacerbate risk of osteoporosis
Autoimmune illnesses, eg, psoriasis, lupus
80% occur more often in women
Lithium’s immuno-stimulating properties may exacerbate autoimmune illnesses

Angum F et al Cureus. 2020;12(5): e8094

Lithium: considerations of particular relevance to women

- Women should be warned not to use NSAIDs or diuretics for premenstrual symptoms
- NSAIDs and several diuretics reduce lithium clearance and can produce lithium toxicity
- Lithium should not be first-line agent for women with active eating disorders who engage in frequent purging and/or use of laxatives/diuretics

Polycystic ovary syndrome (PCOS) and valproate

- Several studies have reported an elevated rate of hyperandrogenism and menstrual disturbances among women on valproate
- For example: menstrual disturbances occurred in 45% of women on valproate vs 13-19% of women on other AEDs
- Women under aged 20 years: especially high risk
- Resolves with switch from valproate to other medications (eg, lamotrigine)

PCOS defined by:

- Chronic anovulation
- Hirsutism
- Obesity
- Acne
- Elevated androgens
- Insulin resistance

PCOS: pathogenesis

Weight gain and insulin resistance are believed to play a role in pathogenesis

Elevated levels of insulin inhibit aromatase enzyme, which converts testosterone to estrogen

Elevated androgens may initiate the reproductive dysfunction of PCO

Rosenfield RL et al, Endocr Rev 2016;37(5):467-520

PCOS and valproate

Recommended for women on valproate:

- Menstrual diary
- Serum androgens: testosterone, androstenedione, DHEA

“Conceivably neglected:” risks of valproate

A 24-month retrospective chart review of 383 charts demonstrated prescription of valproate to 20% of 98 women aged 15-45, with little evidence of advice regarding risk and contraception.

Robust evidence of teratogenic and neurodevelopmental risk underpins increased regulation, and recommendations that valproate not be prescribed to this cohort.

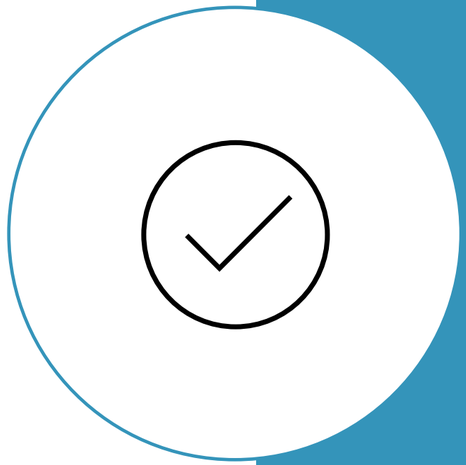
Perera C et al Australas Psychiatry 2019;27(2):125-128

U.K. restricts use of valproate for women of childbearing age

- In April 2018: the Medicines and Healthcare Products Regulatory Agency (MHRA) banned valproate in the U.K. for all women of childbearing potential who are not enrolled in a pregnancy prevention program
- This includes completion of a signed risk acknowledgement form, at least annually; agreement to use contraception; and pregnancy tests before starting and during treatment

U.K. restrictions (cont’d)

- The program is consistent with those for other highly teratogenic drugs such as thalidomide and isotretinoin.
- Valproate is dispensed
  - In smaller pack sizes to encourage monthly prescribing
  - In packages including pictograms/warning images



France bans use of valproate in pregnancy

- France has imposed a partial ban on prescribing valproate for women and girls as of July 2017
- The French National Agency for the Safety of Medicines and Health Products announced a ban on the use of the drug by women and girls who suffer from bipolar disorder and are either pregnant or of childbearing age, with no efficient form of contraception

Bo QJ et al, Psychiatry Res 2016;237:257-263
Li et X al, PLoS One 2013;8(8):e70179

Hyperprolactinemia and antipsychotic meds

Has been reported with most 2nd-generation antipsychotics, not only risperidone

Once prolactin levels > 60 ng/ml, amenorrhea is likely

Hypo-estrogenic state increases risk of bone loss.

Risk of breast cancer among schizophrenic women appears LOWER than expected

Barak Y et al, Schizophr Res 2008;102(1-3):249-253
Crews MPK et al. Hum Psychopharm 2012 Jan;27(1):15-23

Medication-induced hyperprolactinemia

Can be treated with:

- dosage reduction
- switch to another agent
- birth control pill
- add aripiprazole 5-15 mg/day
- add metformin 750-1500 mg daily
- dopamine agonist, eg, bromocriptine 2.5-15 mg daily

Bo QJ et al, Psychiatry Res 2016;237:257-263
Li X al, PLoS One 2013;8(8):e70179

Psychiatric meds and bone disease

Certain AEDs and antipsychotic agents may increase risk of bone disease

For AEDs (eg, carbamazepine):

- Induction of vitamin D metabolism
- Interference with intestinal absorption of Calcium

Ucan Tokuc FE et al Ideggyogy Sz 2021;30;74(7-08):257-265

Psychiatric meds and bone disease (cont'd)

1

Counsel patients about good bone health practices

2

Recommend calcium and vitamin D

3

Consider BMD measurement after 5 years of treatment (or before) in postmenopausal women

Orleans RJ et al N Engl J Med 2014;8;370(19):1777-1779

Premenstrual exacerbation of psychiatric symptoms

Every major psychiatric disorder has been reported to worsen in at least some women premenstrually

When women of reproductive age appear to have monthly exacerbations or relapses of symptoms, explore where they are in their menstrual cycle

Ray P et al Arch Womens Ment Hlth 2020;23(1):113-122

Menopause, hot flashes, and antidepressants

- In menopausal women, hot flashes and night sweats can contribute to insomnia and anxiety
- Up to 75% of women experience hot flashes
- SSRIs and SNRIs have been found (in some studies) to significantly reduce hot flashes/night sweats
- In April 2014, the FDA approved Brisdelle (paroxetine 7.5 mg), the first nonhormonal option for menopausal vasomotor symptoms

Orleans RJ et al N Engl J Med 2014;8;370(19):1777-1779

Reproductive-related mood changes?

Is there a correlation of depressive mood before menstruation, during pregnancy, after delivery and around the menopause?

N = 110 women, mean age 52 years

Current and retrospective ratings, using a visual analogue scale

Present mood was significantly associated with mood in the premenstrual period, but not with pregnancy or postpartum

Becker D et al Climacteric 2007;10(1):46-50

Summary

- Gender differences are frequently seen in:
  - Course of illness (eg, schizophrenia, bipolar disorder)
  - Medication side effects
  - Drug interactions
  - Treatment options
- Female patients may experience exacerbations of mental illnesses at times of hormonal changes (premenstrually; pregnancy/postpartum; menopause)