Late luteal phase dysphoric disorder

- Mrs S is a 36 yo G3P3 with no significant health problems who was treated by her gynecologist for late luteal phase dysphoric disorder for monthly recurring luteal phase sad feelings and emotional lability. She was started on fluoxetine 20 mg daily, with good relief of her depressive symptoms. Within 6 months her menses became erratic, first skipping cycles, and then later she became amenorrheic. She was therefore referred to the reproductive endocrinology clinic for evaluation of absent menses.
Fluoxetine treated LLPDD and secondary amenorrhea

• History and physical revealed:
  – ROS: Normal energy levels, no recent weight loss or gain, regular exercise regimen, no nipple discharge, and no headaches
  – PE: BMI 22, normal vital signs, non-focal neurologic examination, normal female hair pattern, a generally normal pelvic examination, however the vaginal mucosa was thin and atrophic, and the cursory in office ultrasound found ovaries with multiple small follicles (less than 10 mm in diameter) and an endometrial echo complex of 4.6 mm.
Impression

• Late luteal phase dysphoric disorder treated with fluoxetine now with secondary amenorrhea.

• Evidence of hypogonadism on physical examination, with a thin endometrial echo complex, indicating a lack of estrogen effect.

• Presence of multiple small ovarian follicles indicate that ovarian failure is unlikely.
Secondary amenorrhea

- A progestin challenge test was performed: 10mg of medroxyprogesterone acetate was given for ten days, then stopped, and no vaginal bleeding occurred.
- Lab tests were ordered.
Lab tests ordered

• TSH
• Prolactin
Lab test results

- TSH 2.7 mcIU/ml
- Prolactin 39.7 ng/ml
Impression

• Late luteal phase dysphoric disorder treated with fluoxetine now with secondary amenorrhea.

• Evidence of hypogonadism on physical examination AND confirmed with a negative progestin challenge test.

• Hyperprolactinemia.
SSRI induced hyperprolactinemia

- Affects 5% of males and 22% of females
Prolactin elevation in major depressive disorder during the acute phase of treatment with fluoxetine

- Serum prolactin levels among outpatients with major depressive disorder during the acute phase of treatment with fluoxetine.
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- Abstract
- OBJECTIVE: To determine changes in serum prolactin levels in outpatients with DSM-IV-diagnosed major depressive disorder (MDD) following a 12-week open-label trial of fluoxetine. METHOD: 87 outpatients enrolled in the trial had serum prolactin levels determined at baseline and during their final visit (week 12 or discontinuation visit). In addition, serum testosterone levels were measured in 44 of the 46 men during these 2 visits. Hyperprolactinemia was defined as a serum prolactin level greater than 16.5 ng/mL or 18.9 ng/mL for men and women, respectively. The study was conducted from September 1997 to March 2002. RESULTS: Of 80 patients with normal prolactin levels at baseline, 10 (12.5%) developed hyper-prolactinemia following fluoxetine treatment. Specifically, 2 (4.5%) of 44 men and 8 (22.2%) of 36 women with normal prolactin levels at baseline developed hyperprolactinemia following treatment with fluoxetine (p = .0174 for between-gender difference). In addition, there was a significant increase in mean +/- SD serum prolactin levels following treatment with fluoxetine in all patients with normal baseline prolactin levels (6.4 +/- 3.4 to 10.0 +/- 7.0 ng/mL, p = .002). There were no significant changes from baseline in testosterone levels in men following fluoxetine treatment (448.4 +/- 139.6 to 439.5 +/- 142.1 ng/dL, p > .05; normal above 245 ng/dL), while none of the 44 men developed low testosterone levels following fluoxetine treatment. CONCLUSION: 4.5% of men and 22.2% of women with MDD developed new onset hyper-prolactinemia following fluoxetine treatment.
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Drug induced hyperprolactinemia

- Neuroleptics
- SSRI
- Opiates
- Antihypertensives
- Dopaminergic antagonists
- H2 blockers
Drugs which cause hyperprolactinemia

Antipsychotics

Typical: Haloperidol, Chlorpromazine, Thioridazine, Thiothixene
Atypical: Risperidone, Amisulpride, Molindone, Zotepine

Antidepressants

Tricyclics: Amitriptyline, Desipramine, Clomipramine, Amoxapine
SSRI: Sertraline, Fluoxetine, Paroxetine
MAO-I: Pargyline, Clorgyline

Psychotropics: Buspirone, Alprazolam

Prokinetics: Metoclopramide, Domperidone

Antihypertensive: Alpha-methyldopa, Reserpine, Verapamil

Opiates: Morphine

H2 Antagonists: Cimetidine, Ranitidine

Others: Fenfluramine, Physostigmine, Chemotherapautics
Hyperprolactinemia and antipsychotic and mood stabilizing drugs

- Risk for hyperprolactinemia increases with degree of D2 blockade
  - High Risk: butyrophenones, phenothiazines, risperidone
  - Intermediate Risk: olanzapine, quetiapine
  - Low Risk: aripiprazole, ziprasidone
- Other agents: SSRIs, opioids, phenothiazine antiemetics
- Hyperprolactinemia induces hypogonadism, lowering E in women and T in men
- Decreased E and T are associated with decreased bone mineral density and osteoporosis
AP-induced Hyperprolactinemia and Osteoporosis

• Decreased bone mineral density (BMD) in 32-60% of young to middle aged women and men treated 10+ years with antipsychotics (Meaney et al. 2004).

• Proportional to:
  – Medication dose
  – Reduction in serum T in men

• Patients receiving PRL-raising (risperidone, amisulpride, depot) compared to olanzapine developed decline in BMD over 1 year. (Meaney and O’Keane 2007).
  – Effect mitigated by treatments to augment BMD.
Monitoring

- PRL monitoring currently recommended only for symptomatic patients
- No specific recommendations for BMD measurement
- Appears prudent to monitor:
  - For evidence of sexual dysfunction, menstrual disturbance, galactorrhoea and gynaecomastia
  - PRL yearly in patients receiving high potency and/or high dose D2 antagonists
- BMD in patients with sustained elevations in PRL
Osteoporosis prevention

• Prevention: Calcium and Vitamin D supplements, exercise
• Decrease dose of AP
• Change to lower-risk AP (e.g., aripiprazole – Mir et al., 2008)
• Treat with dopamine agonist (e.g., bromocriptine – Smith 1992 - warning re: exacerbation of psychosis)
• Medications to increase BMD
  – Bisphosphonates, raloxiphene (women only)
  – HRT (estrogens in women, testosterone in men)
For our patient?

• Cessation of fluoxetine and institution of the lowest dose and duration of an alternative SSRI (citalopram 10 mg daily during the luteal phase). Other option: a trial of bupropion.

• Vitamin D (800IU) and calcium (1600mg)