Drug-induced amenorrhea: How we do it

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Definitions

• **Amenorrhea**: absence of menses
  - Primary: absence of menarche by age 16
  - Secondary: absence of menses in women who previously had menses. Absence must be for
    • > 3 cycles according to certain sources
    • > 6 months according to most sources
Most Common Etiologies of Secondary Amenorrhea

- Pregnancy
- Ovarian disease (40%)
- Hypothalamic dysfunction (35%)
- Pituitary disease (19%)
- Uterine disease (5%)
- Other (1%)
<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Causes</th>
</tr>
</thead>
</table>
| Hypothalamic Dysfunction| Functional hypothalamic amenorrhea  
Wt loss, stress, severe prolonged illness, exercise  
Congenital GnRH deficiency  
Inflammatory or Infiltrative disease  
Brain tumors – craniopharyngioma  
Pituitary stalk dissection or compression  
Cranial irradiation  
Brain Injury – trauma, hemorrhage, hydrocephalus  
Other syndrome – Prader-Willi, Laurence-Moon-Biedl |
| Pituitary Dysfunction   | Hyperprolactinemia  
Other pituitary tumors (acromegaly, corticotrophic adenoma)  
Other tumors (meningioma, glioma)  
Empty sella syndrome  
Pituitary infarct or apoplexy |
| Ovarian dysfunction     | Ovarian failure (menopause)  
PCOS |
| Uterine                 | Asherman syndrome |
The Hypothalamic-Pituitary-Ovarian Axis

- **Gonadotropin-releasing Hormone (GnRH)**
  - **Hypothalamus**
  - **Pituitary gland**
  - **Luteinizing Hormone (LH)**, **Follicle Stimulating Hormone (FSH)**

- **Pancreas**, **Adrenal gland**, **thyroid**

- **Other endocrine glands**

- **Uterus**

- **Progesteron**, **Estrogen**

- **Ovaries**
Amenorrhea due to hyperprolactinemia

Amenorrhea develops at serum PRL level above 60–100 µg/L (approximately 2000–3000 mU/L), amenorrhea can be caused by much lower PRL values.

Hyperprolactinemia
Normal physiology
Figure 1: Major agents regulating prolactin secretion.
Stimulation

TRH, noradrenaline, opioids, estrogen, prostaglandin, CCK, GABA, serotonin

Inhibition

dopamine

prolactin
Major physiological actions of prolactin

- **Males**
  - Able to suppress gonadal function

- **Females**
  - Essential for the secretion of milk
    - *During pregnancy,*
      - breast enlargement to prepare mammary gland to lactation
        - (together with estrogens & progesteron)
    - *After delivery,*
      - maintainance and promotion of milk production
  - Able to suppress gonadal function
<table>
<thead>
<tr>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amenorrhea/oligomenorrhea</td>
<td>Decreased libido</td>
</tr>
<tr>
<td>Infertility</td>
<td>Erectile dysfunction</td>
</tr>
<tr>
<td>Galactorrhea</td>
<td>Infertility</td>
</tr>
<tr>
<td>Dyspareunia</td>
<td>Gynecomastia</td>
</tr>
<tr>
<td>Acne/hirsutism</td>
<td>Galactorrhea</td>
</tr>
<tr>
<td>Osteopenia</td>
<td>Osteopenia</td>
</tr>
</tbody>
</table>
**Causes of hyperprolactinaemia**

**Physiological**
- Lactation
- Pregnancy
- Sleep
- Stress
- Sexual activity
- Breast stimulation

**Pharmacological**
- Psychotropic drugs: e.g. antidepressants (particularly serotonergic agents), conventional antipsychotics, some atypical antipsychotics
- Antihypertensive drugs: e.g. methyldopa, reserpine, verapamil
- Antidopaminergic antiemetics: e.g. metoclopramide
- Histamine H₂ receptor antagonists: e.g. cimetidine, ranitidine
- Hormones: e.g. estrogens (e.g. oral contraceptives), protirelin (thyrotropin-releasing hormone)
- Miscellaneous: amphetamine (amphetamine), opioids

**Pathological**
- Pituitary disease: empty sella syndrome, micro-prolactinomas, macro-prolactinomas and pituitary stalk lesions (prevent dopamine reaching the pituitary)
- Hypothalamic disease: hypothalamic tumours, hypothalamic sarcoidosis and postencephalitis
- Endocrine disease: acromegaly, Cushing's disease, polycystic ovary syndrome and primary hypothyroidism
- Miscellaneous: chest wall lesions (e.g. trauma, neoplasms), chronic renal failure, cirrhosis/severe liver disease, ectopic production of prolactin (e.g. small-cell bronchial carcinoma) and idiopathic

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Peter M. Haddad & Angelika Wieck Antipsychotic-Induced Hyperprolactinaemia Mechanisms, Clinical Features and Management Drugs 2004; 64 (20): 2291-2314
Drug-induced hyperprolactinemia

• Medication use is a common cause of hyperprolactinemia, and it is important to differentiate this cause from pathologic causes, such as prolactinomas.

• Hyperprolactinemia caused by medications is commonly symptomatic, causing galactorrhea, menstrual disturbance, and erectile dysfunction (impotence).

• It is important to differentiate hyperprolactinemia due to a medication from a structural lesion in the hypothalamic-pituitary area.
Figure 1: Major agents regulating prolactin secretion.
Figure 2 Schematic representation of mechanisms of drug-induced hyperprolactinemia.
<table>
<thead>
<tr>
<th>Class</th>
<th>Type</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antipsychotics</td>
<td>Typical</td>
<td>Haloperidol, Chlorpromazine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Thioridazine, Thiothixene</td>
</tr>
<tr>
<td></td>
<td>Atypical</td>
<td>Risperidone, Amisulpride,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Molindone, Zotepine</td>
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<tr>
<td>Antidepressants</td>
<td>Tricyclics</td>
<td>Amitriptyline, Desipramine,</td>
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<tr>
<td></td>
<td></td>
<td>Clomipramine, Amoxapine</td>
</tr>
<tr>
<td></td>
<td>SSRI</td>
<td>Sertraline, Fluoxetine, Paroxetine</td>
</tr>
<tr>
<td></td>
<td>MAO-I</td>
<td>Pargyline, Clorgyline</td>
</tr>
<tr>
<td>Other Psychotropics</td>
<td></td>
<td>Buspirone, Alprazolam</td>
</tr>
<tr>
<td>Prokinetics</td>
<td></td>
<td>Metoclopramide, Domperidone</td>
</tr>
<tr>
<td>Antihypertensive</td>
<td></td>
<td>Alpha-methyldopa, Reserpine,</td>
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<tr>
<td></td>
<td></td>
<td>Verapamil</td>
</tr>
<tr>
<td>Opiates</td>
<td></td>
<td>Morphine</td>
</tr>
<tr>
<td>( H_2 ) Antagonists</td>
<td></td>
<td>Cimetidine, Ranitidine</td>
</tr>
<tr>
<td>Others</td>
<td></td>
<td>Fenfluramine, Phystostigmine,</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Chemotherapics</td>
</tr>
</tbody>
</table>

**Note:** Only drugs with demonstrated ability to induce hyperprolactinemia above the normal range have been included in this table.
Atypical antipsychotics & hyperprolactinemia

Amisulpride (Solian)
Risperidone (Risperdal)
Zotepine (Lodopin)  }  Marked and sustained increase in PRL levels

Ziprasidone (Zeldox)  }  Transient elevations of PRL levels
Olanzapine (Zyprexa)  }  Little effect on PRL levels

Aripiprazole (Abilify)  }  Do not increase PRL levels
Clozapine (Clozaril)  }  Do not increase PRL levels, even at full doses
Quetiapine (Seroquel)  }
Figure 2.1. The regulation of serum prolactin levels

Serotonin

Nipple reflex (5HT1a)
Pregnancy (5HT2a)
Circadian rhythm (5HT3/1)

Anterior pituitary

Prolactin secretion

LH?

Estrogen

Libido

Erection

Libido

Progesterone

Erection

Testosterone

Lubrication

Orgasm

Dopamine

VIP

TRH

Estrogen

Breast development

Menstruation
Figure 2.2. The influence of classical antipsychotics on serum prolactin levels and possible secondary effects of serum prolactin elevation.

- Serotonin
  - Nipple reflex (5HT1a)
  - Pregnancy (5HT2a)
  - Circadian rhythm (5HT3/1)

- Anterior pituitary
  - VIP
  - TRH
  - Estrogen
  - Galactorrhea
  - Amenorrhea

- Prolactin↑
  - LH?

- Estrogen↓?
- Progesterone↓?
- Testosterone↓?

- Libido↓?
- Erection↓
- Lubrication↓?
- Orgasm↓
Figure 2.3. The influence of new antipsychotics on dopaminergic and serotonergic pathways, the possible consequences for serum prolactin levels and other effects.
Ranges of prevalence of hyperprolactinemia by antipsychotic used

<table>
<thead>
<tr>
<th>Antipsychotic</th>
<th>Prevalence (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amisulpride</td>
<td>100</td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>90</td>
</tr>
<tr>
<td>Clozapine</td>
<td>80</td>
</tr>
<tr>
<td>LAIM</td>
<td>70</td>
</tr>
<tr>
<td>Risperidone</td>
<td>60</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>50</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>40</td>
</tr>
<tr>
<td>Typical (haloperidol)</td>
<td>30</td>
</tr>
<tr>
<td>Typical (depot)</td>
<td>20</td>
</tr>
<tr>
<td></td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>0</td>
</tr>
</tbody>
</table>
Medical Monitoring for drug-induced hyperprolactinemia

Psychiatrists should follow the treatment guidelines and ask patients questions that would indicate whether or not they might have elevated prolactin:

✓ **Women** should be asked about changes in menstruation, libido, lactation
✓ **Men** should be asked about changes in libido, erectile and ejaculatory functions

Drug-induced hyperprolactinemia

Asymptomatic
Continue the drug

Symptomatic
Switch the drug
Replace Testosterone/Estrogen

Dopamine agonists may exacerbate psychosis
Treatment of drug-induced hyperprolactinemia

Box 2: Objectives of treatment of hyperprolactinemia

- Restoration and maintenance of normal gonadal function
- Restoration of normal fertility
- Prevention of osteoporosis

If a pituitary tumour is present:
- Correction of visual or neurological abnormalities
- Reduction or removal of tumour mass
- Preservation of normal pituitary function
- Prevention of progression of pituitary or hypothalamic disease
TABLE 3. Treatment Strategies for the Patient With Symptomatic Medication-Induced Hyperprolactinemia

<table>
<thead>
<tr>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confirm that the medication is the cause of hyperprolactinemia</td>
</tr>
<tr>
<td>Discontinue medication for 3 or 4 days*</td>
</tr>
<tr>
<td>Image hypothalamic/pituitary area with use of magnetic resonance imaging or computed tomography</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Switch to an alternative medication that does not cause hyperprolactinemia* or</td>
</tr>
<tr>
<td>Treat the problem caused by the hyperprolactinemia</td>
</tr>
<tr>
<td>Estrogen or progesterone</td>
</tr>
<tr>
<td>Testosterone</td>
</tr>
<tr>
<td>Bisphosphonate or</td>
</tr>
<tr>
<td>Add dopamine agonist cautiously (rarely necessary)</td>
</tr>
</tbody>
</table>

*With psychoactive medications, this must be done cautiously in consultation with the patient’s psychiatrist.
Dopamine agonists

**Bromocriptine** *(Parlodel 2.5 mg, 5 mg, 10 mg)*
Starting dose 1.25 mg (half a tablet) at bedtime for the 1st week, then up to 2.5 - 5 mg twice a day

**Lisuride** *(Dopergin, Revanil 0.2 mg, 0.5 mg, 1 mg)*
Starting dose 0.1 mg daily increasing slowly after 1-2 weeks to a standard dose of 0.2 mg three times daily

**Cabergoline** *(Cabaser, Dostinex 1mg, 2mg)*
First line treatment, longer acting with fewer side effects 0.25-1.5 mg two times/week

**Quinagolide** *(Norprolac 150 μg)*
second line treatment more potent then bromocriptine. Starting dose 25 μg/day, then up to 150-300 μg/day
Partial agonists of DA receptors

can treat both the:

- **positive symptoms**, arising from dopamine overactivity (mesolimbic pathway)
- **negative symptoms**, related to reduced dopamine activity (mesocortical pathway)

**Aripiprazole** (Abilify), shows partial agonist activity at D2 and serotonin 5–HT$_{1A}$ receptors and has antagonist activity at serotonin 5–HT$_{2A}$ receptors
Aripiprazole slightly lowers serum prolactin levels prolactin

Conclusions

- Drug-induced amenorrhea is associated with hyperprolactinemia.

- Hyperprolactinemia is an undesirable effect of conventional antipsychotics, amisulpride, and risperidone.

- Hyperprolactinemia is associated not only with an immediate negative impact on sexual and reproductive function, but also with important long-term effects, such as body weight gain and osteoporosis.

- Prolactin levels should be monitored in all patients on treatment with prolactin-raising antipsychotics.