PSYCHOTROPICS AND HYPERPROLACTINEMIA

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Topic Overview

Hyperprolactinemia occurs in varying degrees when psychotropic medication is used. Antipsychotic drugs carry a well-known risk of hyperprolactinemia, and clinical outcomes depend upon known physiological mechanisms and competing drug effects that flood the brain's dopamine receptor sites. An increase in serum prolactin strongly correlates with the type of psychotropic drug, mechanism of action, if prescribed alone or in combination with other medication, and endogenous factors.

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Target Audience: This educational activity is for pharmacists.

How to Earn Credit: From September 5, 2022, through September 5, 2025, participants must:

1) Read the "learning objectives" and "author and planning team disclosures;"
2) Study the section entitled "educational activity;" and
3) Complete the Post-test and Evaluation form. The Post-test will be graded automatically. Following successful completion of the Post-test with a score of 70% or higher, a statement of participation will be made available immediately. (No partial credit will be given.)

Learning Objectives: Upon completion of this educational activity, participants should be able to:

1. **Describe** the methods of controlling elevated prolactin levels used to reduce the risk of hyperprolactinemia
2. **Identify** the well-known side effects of psychotropic medication, specifically from the use of antipsychotics in people with schizophrenia and bipolar disorder
3. **Compare** the risks and corresponding complications of hyperprolactinemia in males and females
4. **Identify** treatments that may lower serum prolactin levels

Disclosures

The following individuals were involved in the development of this activity: Steve Malen, PharmD, and Susan DePasquale, MSN, PMHNP-BC. There are no financial relationships relevant to this activity to report or disclose by any of the individuals involved in the development of this activity.

Introduction

Hyperprolactinemia is a well-known occurrence in people who are treated with psychotropic medications, notably antipsychotic medication for the treatment of schizophrenia and bipolar disorder. When reviewing the clinical effects of hyperprolactinemia with patients, pharmacists and prescribers should discuss common clinical consequences and possible options for therapy. People who are treated for a serious mental illness are at higher risk of developing hyperprolactinemia than healthy people within the general population. These patients require routine serum prolactin testing and physical assessment to determine whether complications from the treatment have occurred. Hyperprolactinemia may cause clinically significant concerns that require consideration of treatment benefits and risks for a patient.

Prolactin: Secretion and Function

Prolactin (PRL) is a polypeptide hormone that is synthesized and secreted by the pituitary gland at approximately ten peaks per day in younger individuals.[1] This hormone has been known for more than eighty years and consists of 199 amino acids.[1] Prolactin is involved in hundreds of physiological processes, but it is most prominent for its role in lactation, ovulation, and breast development. The normal serum prolactin level is 10 - 20 ng/mL for men and 10 - 25 ng/mL for women.[1]

While PRL has generally been referred to as a pituitary-derived hormone, other organs and tissues in the body produce PRL besides the pituitary gland. This includes the hypothalamus, brain stem, spinal cord, mammary gland, and other cells and circumventricular organs.[1] Prolactin derives from the Latin "pro" and lactis (milk) and is also called lactotrophin hormone. 20 to 50% of the pituitary gland cellular population secretes PRL.[1] The inner zones have been described as more responsive to dopamine, which helps in the regulation of PRL secretion. The outer zone lactotroph cells are more responsive to thyroid-releasing hormones, which also influence PRL secretion.[1] Other factors that can influence PRL secretion through inhibitory or stimulatory controls include the following:[2,3]

-peptide and steroid hormones and neurotransmitters
-somatostatin
-acetylcholine
-endothelins
-norepinephrine
-growth hormone
-angiotensin II
-vasopressin
-galanin
-estrogen

Estrogen and Progesterone

Estrogen and progesterone are elevated during pregnancy, and they promote breast tissue growth and the release of prolactin.[2] The mechanical stimulation of suckling or nipple stimulation has the most potent effect on prolactin release. Sensory nerves in the nipple are stimulated, and the signal is carried via the spinal cord, which inhibits dopamine release and the action of dopamine on prolactin.[2] These signals also increase the production of oxytocin and lactation.[2]

Estrogen is known to have varied regulation potential on PRL via the following sequence:[1]

-Increase in the number of PRL-secreting lactotroph cells
-Increase in sensitivity to TRH, thyroid-releasing hormone
-Decrease in the pituitary dopamine receptors
-Increase in expression of PRL receptor gene

In clinical studies, it has also been identified that the co-administration of estrogen and antipsychotic medication in healthy women can lead to PRL increases.[1]

Other Factors Regulating Prolactin Secretion

Ghrelin is a peptide hormone with a role in metabolic homeostasis that can also stimulate PRL secretion, as well as the production of growth hormone.[1] There is also increasing evidence that tachykinins can have both a stimulatory and inhibitory effect on PRL secretion at the pituitary gland level (increasing PRL) and by controlling hypothalamic dopamine release (inhibiting PRL).[1] Some evidence exists that during a stressful event, endogenous opioids have a significant regulatory influence over PRL secretion.[1] More research is needed to fully understand the role of external factors, physiological structures, and mechanisms that influence PRL serum levels.

Function of Prolactin

Prolactin starts and maintains breast enlargement in pregnant women and promotes milk production. Prolactin also inhibits hypothalamic gonadotropin-releasing hormone and sustains ovarian function and progesterone-secreting body systems.[1] There is an inhibitory effect on gonadotropin-releasing hormone (GnRH) through prolactin release from the hypothalamus.[2] Reduced GnRH lowers gonadotropic cell stimulation, and there is a corresponding loss of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary.[2]

Follicle-stimulating hormone and LH are important hormones that regulate menstruation and lactation and, therefore, serve as a natural contraceptive. In males, prolactin also inhibits GnRH release and leads to lowered spermatogenesis and infertility.[2]

Prolactin has more than 300 separate functions, of which these are the most important:

-Reproduction
-Water and electrolyte balance
-Growth and development
-Endocrinology and metabolism

-Brain and behavior
-Immunoregulation[1]

Prolactin has an effect on the immune system predominantly by inhibiting the negative selection of autoreactive B lymphocytes, thus promoting autoimmunity.[3] Hyperprolactinemia has an influencing role in several autoimmune diseases.[3,4] Lactating women with autoimmune diseases can experience disease relapse, which is indicative of an active influence of prolactin. More research is needed to characterize the role of PRL in autoimmune diseases.

Antipsychotic-induced Hyperprolactinemia

Typical antipsychotics may increase serum prolactin levels, and this puts the patient at risk for sexual and reproductive dysfunctions.[1,5] Concerns exist about the safety of using medications that can increase serum prolactin levels in patients who have breast cancer, have a history of breast cancer, are at risk for breast cancer, or have another prolactin-dependent tumor.[6,7] However, one study did not find a significant correlation between antipsychotics and breast cancer.[8]

Elevated prolactin levels are a common adverse effect of typical antipsychotics, occurring in approximately 40% - 90% of patients taking these drugs.[3] Elevated prolactin levels caused by a typical antipsychotic increase the risk for ejaculatory and erectile dysfunction, galactorrhea, infertility, loss of libido, and menstrual abnormalities. Due to these adverse effects, patients tend to stop taking the medication.[1] Risk factors for antipsychotic-induced hyperprolactinemia may include the use of high-potency antipsychotics, high doses, female gender, and use during adolescence.

Elevated prolactin levels caused by an antipsychotic often persist, but for some patients, they will return to normal. Elevated prolactin levels have been shown to be present in patients with schizophrenia before beginning therapy with an antipsychotic.[1] Elevated PRL serum levels in antipsychotic-naïve patients have not been linked to gender, body mass index (BMI),

elevated thyroid stimulating hormone, ghrelin, cortisol, or other lifestyle behavior such as smoking.[1]

Elevated PRL that leads to hyperprolactinemia may also be caused by general stress associated with schizophrenia. One study suggested that there may be a connection between an abnormality of the prevalence of the G allele over the T allele of the 1149 G/T polymorphism of the PRL gene in patients with schizophrenia, leading to higher PRL levels. Based on the results of the study, it may be argued that individuals with a preponderance of the G allele are more likely to react more strongly to stress and have a higher production of PRL, especially in males.[1]

Elevated PRL secondary to antipsychotic medication has been studied since around the 1970s.[1] Hyperprolactinemia has been found to occur in all cases of antipsychotic drug use, but the greatest incidence of PRL elevation has been seen with risperidone, amisulpride, and sulpiride.[1] "Prolactin-sparing" antipsychotics, namely clozapine, quetiapine, olanzapine, ziprasidone, and aripiprazole, may still be associated with hyperprolactinemia in some individuals. The PRL-elevating potential of antipsychotic drugs, PRL baseline values, and previous antipsychotic treatment of individuals are important to decipher the PRL level concerns and the persistence of hyperprolactinemia.[1]

Symptomatic patients with elevated prolactin levels may have the drug discontinued, and the serum prolactin level should return to normal within several days.[5] The dose can be reduced, a low-potency antipsychotic can be used as a replacement, or the patient can continue to take the offending drug, and a dopamine agonist can be prescribed.[9]

The incidence and risk of elevated prolactin and sexual and reproductive dysfunctions caused by antipsychotic use are not well known, and no information on the topic was located. Recent reviews (2016) have concluded that the role of prolactin in breast carcinogenesis is uncertain.[5] Also, there is no conclusive evidence that antipsychotics increase the risk of breast malignancy and mortality, and women who need treatment with an

antipsychotic should not be deprived of these medications based on an unproven contraindication.[8]

Case Study: Hyperprolactinemia and Bromocriptine

The authors of this case study reported on a 53-year-old patient who was diagnosed with Bipolar I Disorder. He was treated through an integrated multidisciplinary Program of Assertive Community Treatment (PACT).[10]

A review of the patient's health history revealed that he carried diagnoses of B12 deficiency, type IIb dyslipidemia, benign prostatic hypertrophy (BPH), gastroesophageal reflux disease (GERD), and stage III chronic kidney disease (CKD). His medication history included:

-atorvastatin
-clonazepam
-cyanocobalamin injection
-divalproex ER
-hydroxyzine pamoate
-omeprazole, quetiapine
-risperidone oral and long-acting injections (LAI)
-laxative.

The patient was noted to show adherence to his medication regime and had no reported side effects.

The patient's lifestyle risk factors included smoking tobacco, one pack per day. Laboratory testing showed an elevated serum creatinine (SCr) level of 2.0 and a calculated creatinine clearance of 46.9 mL/min. All other baseline laboratory results were within normal limits.

The patient's history of present illness noted a problem of erectile dysfunction and ejaculation. There was no evidence of gynecomastia. An elevated prolactin level of 49 ng/mL (normal range 2.0–18.0 ng/mL) was

identified; therefore, antipsychotic-induced hyperprolactinemia was diagnosed.

Primary psychiatric symptoms were noted to be mood dysregulation and impulsive traits. Antipsychotic medication reduction, including a lower dose of quetiapine, led to symptom relapses. A trial of bromocriptine 10 mg daily was started and then increased to 7.5 mg twice daily. The patient showed no symptoms of mood dysregulation or psychosis. Eventually, the quality of his erections improved with some ongoing ejaculation issues.

Bromocriptine was increased to 10 mg twice daily nine months later, and the patient reported some improvement. Risperidone long-acting injection (LAI) was tapered slowly and discontinued. In addition to bromocriptine, he continued on total daily doses of risperidone 4 mg, quetiapine 500 mg, divalproex 1500 mg, clonazepam 1.5 mg, and aripiprazole 5 mg. He remained psychiatrically stable on this medication regime. The prolactin level returned to the normal range; over an 8-month period, prolactin reduced from 49.0 to 37.5. Over another 10 months, the prolactin level was at 32.4, and in another 6 months, the prolactin level was 17.9 (normal limits).

The authors highlighted the regulatory role of dopamine (D2 receptors) in prolactin secretion. The symptoms of hyperprolactinemia can include gynecomastia, galactorrhea, acne, infertility, sexual dysfunction in men and women, and menstrual disturbances and hirsutism in women. Osteoporosis, fractures, and certain types of cancer have been associated with hyperprolactinemia.[10] A ten-fold increase in prolactin levels exists in individuals who are taking antipsychotics. The effect of hyperprolactinemia can vary, depending on the type of drug used.[10]

The treatment of hyperprolactinemia is often difficult, and the use of a dopamine agonist, like bromocriptine, can help to normalize prolactin levels; however, there is the risk that the patient may decompensate and develop psychosis.[10] In this case, the patient reportedly was psychiatrically stable, and prolactin levels were rechecked every 6 months along with monitoring the patient's self-reporting of sexual function.

Based on this case study, the authors recommended the following treatment regime to control antipsychotic-induced hyperprolactinemia with sexual dysfunction:

1) initiate bromocriptine at 2.5 mg daily
2) titrate bromocriptine until 20 to 40 mg is reached over 5 to 7 days for proper treatment.[10]

Prescribers should warn patients that bromocriptine should be used cautiously in patients with diagnoses of schizophrenia or bipolar disorder due to the risk of worsening symptoms, although evidence shows the risk of psychiatric decompensation is rare. Also, a review of the literature suggests that the use of bromocriptine has risks, and administration of this medication should be done cautiously with the patient's informed consent of the potential risk involved. Two large reviews of the current clinical studies as of 2017 and 2019 caution against the use of a dopamine agonist like bromocriptine in persons with serious chronic mental illness.[11,12]

Should bromocriptine worsen psychiatric symptoms, treatment with aripiprazole can be attempted. Asymptomatic hyperprolactinemia may not require any intervention; however, when symptoms are present, the drug(s) may be discontinued, lowered, or switched to another treatment or combined with treatment.[10]

Case Study: Aripiprazole and Levels of Hyperprolactinemia

The authors of this case study reported on a 36-year-old female with a delusional disorder that corresponded with significant socio-occupational disruption due to poor sleep and appetite.[13] On physical evaluation, the patient's vital signs were stable, and her body mass index (BMI) indicated slightly overweight at 26. There were no acute health concerns, and she was evaluated as medically stable. Laboratory testing revealed a prolactin level of 14 ng/ml.

The patient was described as having poor insight, within the setting of a delusional disorder, and oral aripiprazole 5 mg daily was selected for treatment. Aripiprazole was titrated up to 10 mg and then 15 mg daily as maintenance. Three weeks later, the patient reported the delusions had subsided; however, she had developed symptoms of galactorrhea and irregular menses.

Pregnancy was ruled out. Other laboratory testing revealed a serum prolactin level of 96 ng/ml. Neuroimaging was completed to determine whether the patient had developed a prolactinoma. Aripiprazole-induced hyperprolactinemia was suspected, and therefore aripiprazole was discontinued. Galactorrhea was noted to subside on a one-month follow-up examination, and the patient's menses had normalized. The prolactin level was 18 ng/ml on follow-up laboratory testing. While off aripiprazole treatment, the patient initially remained psychiatrically stable, but a spontaneous relapse of psychosis occurred 3 months later.

The treatment of this relapse of psychosis involved a lower dose of aripiprazole at 10 mg to avoid the recurrence of hyperprolactinemia. The patient developed galactorrhea once again associated with amenorrhea, although her symptoms of psychosis resolved. Serum prolactin was recorded at an elevated level (84 ng/ml). Aripiprazole was discontinued and the serum prolactin levels normalized (19 ng/ml), and the patient's symptoms of hyperprolactinemia resolved within 1-month.

The authors commented that although many factors regulate prolactin, dopamine is the "most important hypothalamic prolactin-inhibiting factor."[13] However, prescribers should be aware that the D2 receptor blockade by antipsychotics can also counteract "the tonic inhibitory effect of dopamine on prolactin secretion, thus elevating serum prolactin levels."[13] In individuals who are prescribed antipsychotic drugs, the blood-brain barrier and degree of dopamine blockade influence the level of hyperprolactinemia that can occur.[13] Since aripiprazole is a partial agonist at the D2 receptor, the use of other full agonists and antagonists has an added effect. The *absence* of a full agonist leads to partial agonist functional activity by binding to the receptor and

leading to a physiological response. On the other hand, the *presence* of a full agonist in addition to the partial agonist leads to functional antagonist activity by competing with the full agonist for receptor occupancy, which leads to a reduced response than with agonist monotherapy.[13]

Depending on existing dopamine levels, aripiprazole can show less activity at the D2 receptor and can act as a functional agonist and antagonist. If a patient is being prescribed an antipsychotic with a known risk of hyperprolactinemia, adjunctive aripiprazole competes at receptors with the potential to act as an agonist and hence lowering prolactin levels. As monotherapy, the way aripiprazole functions will depend entirely on dopamine levels.[13] Without a competing D2 antagonist, aripiprazole may function as an antagonist (including lower doses) and cause an elevation of serum prolactin. More could be said about the role of aripiprazole in regulating hyperprolactinemia in combination with other specific first-generation and second-generation antipsychotics that are used in people diagnosed with schizophrenia and bipolar disorder.

Summary

Hyperprolactinemia is a well-known occurrence in people who are treated with psychotropic medications, notably antipsychotic medication for the treatment of schizophrenia and bipolar disorder. When reviewing the clinical effects of hyperprolactinemia with patients, common clinical consequences and possible options for therapy should be discussed. People who are diagnosed with a serious mental illness are at higher risk of developing hyperprolactinemia than healthy people within the general population and will require routine serum prolactin testing and physical assessment to determine whether complications from the treatment have occurred. Hyperprolactinemia may cause clinically significant concerns that require careful consideration of pre-existing conditions, risk factors, and the treatment benefits and risks on a case-by-case basis.

Clinicians need to weigh the risks and benefits of hyperprolactinemia treatment carefully. The case reviews discussed the effect of dopamine agonists and partial agonists as adjunctive treatment with psychotropic medications to prevent or treat hyperprolactinemia. Aripiprazole specifically holds potential at lower doses or in combination with other psychotropic medications to lower the risk of hyperprolactinemia. The use of a dopamine agonist, like bromocriptine, can help to normalize prolactin levels; however, a risk exists of decompensation and spontaneous relapse of psychosis. Asymptomatic hyperprolactinemia may not require any intervention; however, when symptoms are present, the drug regimen may be changed.

Course Test

1. **Prolactin (PRL) is a(n) _____ that is synthesized and secreted by the pituitary gland.**

    a. steroid hormone
    b. amino acid derivative
    c. polypeptide hormone
    d. lipid-derived hormone

2. **True or False: Prolactin is referred to as a pituitary-derived hormone and is only produced by the pituitary gland.**

    a. True
    b. False

3. **The inner zones of the pituitary gland are described as more responsive to**

    a. dopamine.
    b. serotonin.
    c. thyroid-releasing hormones.
    d. adrenaline.

4. **The sensory signals in the nipples increase the production of lactation and**

    a. insulin.
    b. estrogen.
    c. progesterone.
    d. oxytocin.

5. **In males, prolactin inhibits _____ and leads toward lowered spermatogenesis and infertility.**

    a. ACTH release
    b. TSH release
    c. LH release
    d. GnRH release

6. **True or False: Prolactin has more than 300 separate functions.**

    a. True
    b. False

7. **Typical antipsychotics may increase serum prolactin levels, which puts the patient at risk**

    a. for suicidal thoughts and depression.
    b. for dangerously high blood pressure.
    c. for sexual and reproductive dysfunction.
    d. for a weakened immune system.

8. **Which drug below is one of the drugs with the *greatest* incidence of hyperprolactinemia?**

    a. Olanzapine
    b. Risperidone
    c. Ziprasidone
    d. All of the Above

9. **General stress may lead to higher prolactin levels in patients with schizophrenia who have a preponderance of the _____ of the 1149 G/T polymorphism of the PRL gene.**

    a. T allele
    b. D allele over the G/T allele
    c. G allele
    d. Treg cells

10. **Symptomatic patients with elevated prolactin levels**

    a. must discontinue the offending drug.
    b. must discontinue the offending drug and replace it with a full dopamine agonist.
    c. should switch to a high-potency antipsychotic.
    d. may continue the drug and may add a full or partial dopamine agonist.

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