Guidelines for Antipsychotic-Induced Hyperprolactinemia

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ABSTRACT

Treatment with antipsychotic medication can be associated with hyperprolactinemia, which may be asymptomatic or associated with a wide variety of side effects. Determining a baseline prolactin level before beginning antipsychotic therapy can assist the clinician in determining whether or not a patient’s elevated level is due to medication-induced hyperprolactinemia. If other causes of hyperprolactinemic can be ruled out, then careful consideration must be given to the risks and benefits of maintaining the patient on the therapeutic antipsychotic regimen. It is suggested that prolactin levels in patients taking antipsychotics should be monitored, but there is no consensus regarding frequency. Management of antipsychotic-induced hyperprolactinemia should be conducted on a case-by-case basis. [Psychiatr Ann. 2015;45(5):266-272.]

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T treatment with antipsychotic medication may be correlated with a rise in prolactin level due to hypothalamic dopamine blockade. Hyperprolactinemia associated with antipsychotic use can be asymptomatic or associated with a number of adverse effects. Irregular menses, male gynecomastia, osteoporosis, sexual dysfunction, and infertility in both genders are among the potential risks, necessitating that psychiatrists monitor and manage deleterious effects in patients being treated with antipsychotics. This article includes a discussion of evidence for baseline prolactin screening, suggested work-up in the event that hyperprolactinemia is detected, and possible courses of action.
SHOULD A BASELINE PROLACTIN LEVEL BE MEASURED PRIOR TO INITIATING ANTIPSYCHOTIC THERAPY?

The guidelines are not clear on this question; some clinicians recommend no screening or propose screening for higher-risk medications and patients, whereas others endorse universal pre-treatment screening. The strongest predictors of hyperprolactinemia are the type and dose of the antipsychotic prescribed, with increased levels observed at higher doses. In the case of typical antipsychotics, antipsychotic efficacy correlates with elevation in prolactin level. Therefore, haloperidol gives rise to the greatest prolactin level increase. Risperidone is among the highest elevators of the atypical antipsychotics. Olanzapine and quetiapine are less commonly associated with hyperprolactinemia. Clozapine and aripiprazole rarely elevate prolactin. Age of the female patient is also a factor in developing hyperprolactinemia. Women of reproductive age, particularly parous women, appear to be at higher risk of hyperprolactinemia than postmenopausal women.

Nonetheless, pretreatment prolactin screening in a patient started on an antipsychotic regimen allows for less diagnostic confusion in the event of potential hyperprolactinemia, permitting greater confidence in a diagnosis of medication-induced hyperprolactinemia. For example, if it is clear that an increase in prolactin level follows the initiation of antipsychotic therapy, and no features of pituitary disease (such as headache and visual disturbances) are present, then further investigation is unnecessary. The Pituitary Society recommends retesting the prolactin level 72 hours after temporarily discontinuing antipsychotic medication. Often, however, drug discontinuation is not feasible because of the patient’s clinical condition. Some authors propose not only establishing a baseline prolactin level, but also determining baseline menstruation and psychosexual function. The latter information is useful because inquiring about these more private topics provides a good segue to explaining potential antipsychotic side effects to the patient and sets the stage for revisiting these types of questions during follow-up appointments.

WHICH EVALUATION SHOULD BE PERFORMED WHEN AN ELEVATED PROLACTIN LEVEL IS DETECTED IN A PATIENT RECEIVING ANTIPSYCHOTIC THERAPY?

One must first examine the temporal relationship between prolactin level elevation and initiation of antipsychotic therapy. As mentioned above, unnecessary work-up can be avoided when the temporal relationship is clear. This is why establishing a pretreatment prolactin level is valuable. If the time course is unclear, however, a full set of testing must be conducted, including assessing liver, renal, and thyroid function. One may consider performing magnetic resonance imaging of the pituitary gland, particularly if the patient displays symptoms of a sellar space-occupying lesion, suggested by the presence of headache and visual field defects, or if the prolactin level is more than 4 times greater than the upper range of normal (ie, 300-500 mIU/L, corresponding to ~14-24 ng/mL). One may also consider determining sex steroid levels to assess for risk of osteoporosis. In addition to time course and symptomatology, the degree of rise in prolactin level is helpful in determining whether the elevation can best be attributed to use of antipsychotic drugs or another cause. If the prolactin level is less than 2,000 mIU/L (~95 ng/mL), elevated numbers are more likely due to the use of antipsychotic medication; if the level is greater than 2,500 mIU/L (~118 mg/mL), in the absence of breast-feeding or pregnancy, a pituitary tumor may be suspected.

WHAT SHOULD BE DONE IF THE PATIENT IS ASYMPTOMATIC OR MILDLY SYMPTOMATIC?

The risks and benefits of discontinuing or changing an antipsychotic regimen versus the possibility of psychiatric illness relapse must be carefully weighed. The presence and severity of clinical symptoms, and not a rise in prolactin level alone, should dictate treatment strategy. In an asymptomatic female patient having regular periods, it is unnecessary to make changes in antipsychotic medication. Similarly, in the case of a female patient experiencing mild galactorrhea with regular periods, treatment may continue. The recommendation to discontinue antipsychotic therapy in asymptomatic patients with medication-induced hyperprolactinemia is weakly made, according to the Endocrine Society Clinical Practice Guideline. Nevertheless, known or postulated side effects from longstanding hyper-prolactinemia, such as osteoporosis and an elevated risk of pituitary adenomas, may present a justifiable reason to reevaluate established antipsychotic therapy despite a lack of symptoms.

WHAT COURSE OF ACTION SHOULD BE TAKEN WHEN SYMPTOMS ARE SIGNIFICANT?

One must weigh the benefit the patient is obtaining from antipsychotic therapy, predicted length of time the patient will continue on medication, and risk of relapse in the case of dose reduction or change in medication. Side effects (such as galactorrhea, gynecomastia, oligomenorrhea, amenorrhea, infertility, sexual dysfunction, and osteoporosis) and the level
of patient distress must be monitored. In patients who rely on depot administration of antipsychotics, benefits may outweigh the risks of switching medications. Two relatively new depot antipsychotics have recently come onto the market: (1) aripiprazole and (2) olanzapine. These drugs may provide clinicians with more options should they wish to change treatment to a prolactin-sparing depot antipsychotic medication.

TREATMENT OPTIONS
Change to a Prolactin-Sparing Antipsychotic
This class of drugs includes olanzapine, quetiapine, ziprasidone, and clozapine. Unfortunately, the cross-titration period poses a significant risk of relapse of psychotic symptoms. The decision to switch to a prolactin-sparing antipsychotic must be made individually for each patient.

Addition of Sex Steroids
In women undergoing antipsychotic therapy, a combined oral contraceptive will prevent estrogen-deficiency symptoms, possibly including bone mineral density (BMD) loss. However, symptoms of hyperprolactinemia will be unaffected.

Addition of Dopamine Receptor Agonist
Because the addition of a dopamine receptor agonist such as amantadine or bromocriptine may cause a psychotic relapse, this option is typically not recommended. Although dopamine receptor agonists have been shown to increase BMD, they may also give rise to orthostatic hypotension, gastrointestinal side effects, and exacerbation of psychosis. Addition of the receptors should therefore be considered a third-line strategy, after changing antipsychotics and supplementing with sex steroids. In such cases, the lowest possible dose of dopamine receptor agonist should be used, with close monitoring. However, in the absence of the option to alter the antipsychotic medication, addition of a dopamine receptor agonist is the only approach to improve infertility and galactorrhea symptoms.

Decrease Current Dose of Medication
As the risk of hyperprolactinemia is dose-dependent, a reduction in antipsychotic dose may theoretically be helpful, but effectiveness of such a reduction has not been systematically studied. It is unclear whether dose lowering has significant effects on prolactin levels, prolactinemia symptoms, or recurrence of psychiatric symptoms.

Is Adding Aripiprazole Safe and Effective?
Some studies have suggested treatment strategies using aripiprazole as an adjunct to reduce the prolactin level in patients treated with antipsychotics. Particularly in patients who are clinically stable on antipsychotic treatment, discontinuing current medication and switching to an atypical antipsychotic may be inappropriate, so adjunctive therapy may be a better strategy.

The rationale of aripiprazole’s use as an adjunct may be attributed to its dual agonism/antagonism at the dopamine D2 receptor, which may mitigate the effects of other antipsychotic medications on the pituitary gland. Meta-analysis of five randomized controlled trials showed a prolactin level normalization rate of 79%. No significant differences in psychiatric symptoms or side effects between control and adjunctive aripiprazole-treatment groups were detected. However, an increase in sedation, insomnia, and headache was present if the administered dose was higher than 15 mg/day. Thus, the authors suggest an aripiprazole dose of 5 mg/day.

How Should the Side Effects of Osteopenia and Osteoporosis Be Addressed?
If amenorrhea has lasted 12 months or longer in a female patient on an antipsychotic regimen, BMD measurements should be undertaken. If osteopenia or osteoporosis is discovered, Haddad and Wieck recommend referring the patient to a specialist for further management. Others suggest the approach to treating bone loss is to lower prolactin, which will normalize the sex steroids, or alternatively, to provide exogenous sex steroids. Hyperprolactinemia alone is not a direct risk factor for the development of osteoporosis; data appear to point toward a prolonged decrease in sex steroid levels as the cause of osteoporosis due to hyperprolactinemia. BMD loss is possible in both genders. Monitoring BMD for 2 years after osteoporosis detection allows the clinician to determine whether one of the aforementioned interventions has been successful. If BMD level does not respond, only then should one consider alternative treatments such as bisphosphonates. On the other hand, some sources recommend the introduction of bisphosphonates immediately upon discovery of osteoporosis. Therefore, there is no clear recommendation on how to prevent or treat osteoporosis in this population.

Does Prolonged Hyperprolactinemia due to Long-Term Antipsychotic Therapy Increase the Risk of Breast Cancer, Pituitary Tumors, or Sexual Dysfunction?
Breast Cancer. More data are needed to answer this question. Some authors cite lower rates of breast cancer in women with schizophrenia,
whereas others claim higher rates. A study of female patients with operable breast lesions showed the presence of hyperprolactinemia in comparable proportions in the case of breast cancer and benign breast conditions. Similarly, a Dutch investigation of women with idiopathic hyperprolactinemia or prolactinomas demonstrated no increase in breast cancer rates when compared with national breast cancer incidence. However, two studies have lent support to a potential association between hyperprolactinemia and breast cancer. A prospective cohort study demonstrated that the use of prolactin-raising antipsychotics was associated with a 16% increase in breast cancer.

**Pituitary Tumors.** There is an increased prevalence of prolactinoma in patients receiving risperidone and haloperidol, but not in those receiving ziprasidone, olanzapine, clozapine, or quetiapine. This finding, however, may be attributed to surveillance and reporting bias. In fact, patients receiving antipsychotic therapy, particularly when taking medications more likely to induce hyperprolactinemia, such as risperidone and haloperidol, are more likely to undergo pituitary imaging screening. Although the relationship is currently unclear, correlations have been shown between affinity for the dopamine D2 receptor and strength of association with pituitary tumor, with risperidone having the highest receptor affinity and strength of association, followed by haloperidol, ziprasidone, and olanzapine.

**Sexual Dysfunction.** Research on this topic has been limited by the confounding factors of patients taking more than one medication and the difficulty of distinguishing sexual dysfunction attributed to medication versus the effect of the psychiatric illness itself. Studies have demonstrated higher rates of sexual dysfunction in patients with prodromal signs of psychosis as well as first-episode psychosis compared with healthy controls, suggesting that sexual dysfunction may be...
inherent to the illness itself. Nevertheless, observations have been made on the association between antipsychotic medications known to significantly increase prolactin and the incidence of sexual dysfunction. For instance, risperidone is well known to increase prolactin levels, and its use has also been correlated with some of the highest rates of anorgasmia. The risks of medication nonadherence are particularly high when patients develop sexual dysfunction as a side effect, indicating the importance of screening for sexual side effects over the course of antipsychotic treatment.

How Often Should Prolactin Be Measured in Patients Taking Antipsychotics?

Monitoring of prolactin is “generally not recommended” in clinical guidelines. Thus, an elevated prolactin level will frequently be detected only after inquiring about the patient’s side effects to medication. It is important to ask about them, as patients will not often reveal symptoms of a more personal nature. Despite the fact that no guidelines exist for routine prolactin monitoring, some symptoms, such as osteoporosis and infertility, are silent, and guidelines for routine monitoring in patients on antipsychotic regimens should perhaps be implemented. Some authors suggest testing prolactin levels 3 months after initiation of an antipsychotic, because blood will be drawn for diabetes and dyslipidemia monitoring at this time, followed by subsequent testing as undesirable symptoms appear. Other authors propose annual testing.

CONCLUSION

Treatment with antipsychotic medication can be associated with hyperprolactinemia, which may be asymptomatic or associated with a wide variety of side effects. Prior to initiating antipsychotic therapy, determining a baseline prolactin level may assist the clinician in determining whether a patient’s elevated level is due to medication-induced hyperprolactinemia or another cause. One must conduct a thorough work-up of hyperprolactinemic patients to rule out other causes, and then carefully consider the risks and benefits of maintaining the patient on the therapeutic antipsychotic regimen, altering the dose, changing the medication, or adding other medications to specifically address adverse effects. It is suggested that prolactin levels in patients taking antipsychotics should be monitored, although no consensus as to frequency has been reached. Management of antipsychotic-induced hyperprolactinemia should be on a case-by-case basis.

REFERENCES