ABSTRACT

Hyperprolactinemia is one of the major adverse effects of antipsychotic agents. Although it is predominantly associated with the use of conventional or typical agents, atypical agents also cause varying degrees of hyperprolactinemia. Clinical manifestations, which tend to be underrecognized, are the result of the direct action of prolactin on its target tissues and of the sequelae of hypogonadism secondary to hyperprolactinemia. Long-term consequences of hyperprolactinemia may be serious; therefore, physicians must be alert to the signs and symptoms of hyperprolactinemia when monitoring their patients. (Adv Stud Med. 2004;4(10F):S982-S986)

A typical antipsychotic agent, first introduced in the 1990s, have several major advantages over their predecessors—the conventional or typical antipsychotics. With their broader therapeutic spectrum, atypical agents ameliorate the negative and cognitive symptoms of schizophrenia, as well as the positive symptoms. Furthermore, compared with conventional agents, their use is associated with reduced incidences of motor disturbances such as extrapyramidal symptoms. These agents have, therefore, been widely adopted and have now supplanted their older counterparts as the agents of choice for the treatment of schizophrenia. They are also being increasingly used for the treatment of other mental disorders, including bipolar disorder. Although categorized as a single class of drug, atypical antipsychotic agents vary widely in their mechanisms of action and their adverse effect profiles. For example, a growing body of clinical evidence indicates that in some patients, they are associated with a particular constellation of adverse effects, namely, metabolic and endocrine dysfunction.

However, not all drugs are equally implicated, and differences are seen among them in the extent to which they cause these adverse effects.

Metabolic adverse effects of atypical antipsychotics include weight gain, hyperglycemia (typically leading to diabetes), and atherogenic lipid profile. A full discussion of these adverse effects and their implications is beyond the scope of this article, and readers are referred to recent reviews and guideline publications for further information. The remainder of this article focuses on the issue of atypical antipsychotic-associated endocrine dysfunction, namely, hyperprolactinemia.

PATHOPHYSIOLOGIC BASIS OF HYPERPROLACTINEMIA

Prolactin is a single-chain polypeptide hormone consisting of 199 amino acids (23 kDa) stabilized by 3 disulfide bonds. Although it has traditionally been associated with lactation, recent evidence implicates prolactin in more than 300 physiologic functions related predominantly to reproduction and homeostasis. Distribution of prolactin receptors is ubiquitous; they are found in almost all tissues and organs of the body. The main site of prolactin synthesis is the anterior pituitary gland; however, the central nervous system, mammary glands, uterus, prostate, placenta,
endothelium, and immune cells have also been shown to synthesize prolactin. In these regions, prolactin is thought to function in an autocrine/paracrine capacity.

Mechanisms that control the synthesis and release of prolactin from the anterior pituitary are complex and are influenced by numerous endogenous regulatory agents and feedback loops and by the circadian rhythm. Under normal physiologic conditions, the synthesis and release of prolactin by the lactotroph cells of the anterior pituitary are under tonic inhibition by the hypothalamus. This action is mediated by a number of prolactin inhibitory factors, of which dopamine (DA) appears to be the most important. DA, released by neuroendocrine cells of the tuberoinfundibular tract, reaches the lactotrophs through the hypothalamic-hypophyseal/pituitary portal system (Figure 1). DA binds to its D2-receptor subtype on the membrane of the lactotroph. Receptor activation leads indirectly to a decrease in intracellular Ca2+ levels and the subsequent cessation of prolactin secretion.

Disinhibition of lactotrophs by DA antagonists results in unchecked prolactin release. Persistent disinhibition leads to elevated plasma prolactin concentrations or hyperprolactinemia. Tricyclic antidepressants, selective serotonin reuptake inhibitors, and some opioids have also been shown to increase prolactin levels. Nonpharmacologic causes of hyperprolactinemia include prolactin-secreting pituitary adenomas and other diseases of the pituitary gland, central nervous system diseases affecting hypothalamic function, stress, hypothyroidism, renal dysfunction, and hepatic dysfunction. A diagnosis of hyperprolactinemia is made when a plasma prolactin concentration above the upper limits of normal—typically, 18 ng/mL for men and prepubertal girls, 29 ng/mL for premenopausal women, and 20 ng/mL for postmenopausal women—is measured on 2 separate occasions.

INCIDENCE OF ANTIPSYCHOTIC-INDUCED HYPERPROLACTINEMIA

All conventional antipsychotics cause hyperprolactinemia through their antagonistic action on D2 receptors—an effect once considered an inevitable consequence of their therapeutic activity. After treatment initiation, the plasma prolactin concentration increases on average 2- to 10-fold during the first week; after a plateau is reached, most studies find persistent elevation throughout treatment, although a few studies find prolactin levels returning to normal. Plasma prolactin levels decline to baseline within 2 to 3 weeks of antipsychotic treatment cessation; this may take longer if a depot formulation is used.

Compared with conventional agents, most atypical antipsychotic agents have a reduced tendency to cause hyperprolactinemia, although the mechanism is not known. It may be that the combination of D2 and 5-hydroxytryptamine (HT)2 antagonism provides atypical agents with relative selectivity for the mesolimbic-dopaminergic pathway, thus sparing the tuberoinfundibular and nigrostriatal pathways. The latter observation also explains the reduced propensity of these agents to cause extrapyramidal symptoms.

Although the incidence is reduced compared with conventional agents, considerable variation has been noted among the atypical agents in the extent to which they cause hyperprolactinemia (Figure 2). Risperidone is associated with the greatest elevation of plasma prolactin levels; treatment results in a sustained increase in plasma prolactin levels, which exceeds that seen with haloperidol. The reason why risperidone has such a potent effect on prolactin is unclear, but it has been suggested that it may be due to the poor blood-brain barrier (BBB) penetrability of risperidone compared with that of the other marketed atypical agents. The pituitary gland lies outside the BBB and is exposed to the systemic circulation; consequently, lactotroph D2-receptor occupancy is greatest among
agents that require higher systemic concentration for efficient penetration of the BBB.

The impact of the other atypical agents on prolactin levels is not as pronounced as that of risperidone. Treatment with olanzapine results in a mild elevation of plasma prolactin levels during the first few weeks of treatment. However, given that this increase is dose dependent, patients who require higher doses may experience adverse effects caused by hyperprolactinemia. Ziprasidone and quetiapine have little impact on plasma prolactin levels. Aripiprazole, the most recent addition to the group of antipsychotic agents, has been shown to have minimal impact on prolactin levels. Indeed, in some instances, it may cause a slight reduction by virtue of its partial agonist properties. Regardless of the agent used, women, adolescents, and children tend to be more sensitive to prolactin elevation than are men.

**Clinical Sequelae of Hyperprolactinemia**

Clinical manifestations of hyperprolactinemia arise from the direct action of excessive prolactin on its target tissues and on the sequelae of hypogonadism secondary to hyperprolactinemia.

Hypogonadism is the result of a decline in gonadotrophin-releasing hormone secretion from the hypothalamus—one of the many disruptive effects of hyperprolactinemia on the hypothalamic-pituitary-gonadal axis.

Sexual symptoms observed in women include irregular menstrual cycle or amenorrhea, premature menopause, and galactorrhea. The simultaneous occurrence of the latter 2 symptoms can be disconcerting for patients. In men, sexual symptoms include gynecomastia and galactorrhea. Infertility occurs in both sexes.

Sexual dysfunction encompassing loss of libido, failure to achieve orgasm, and erectile and ejaculatory dysfunction is also a common symptom of hyperprolactinemia. Although the cause is multifactorial, a direct correlation can be seen between the extent of sexual dysfunction and the extent of prolactin elevation, that is, agents that cause significant hyperprolactinemia (conventional agents and risperidone) are associated with more severe symptoms.

Sexual dysfunction is a sensitive issue, and patients may not initiate discussions about sexual dysfunction with their healthcare provider. In a recent survey, even though 62.5% of male and 38.5% of female participants believed their medications were causing sexual dysfunction, a significant proportion (up to 80% of women) failed to discuss it with their healthcare provider. In the same survey, 42% of male and 15% of female participants stopped taking their medication as a result of this adverse effect. Sexual dysfunction has a major negative impact on adherence, yet it remains under-recognized. In another survey, psychiatrists estimated that 28% of female and 40% of male patients experience sexual dysfunction, whereas the corresponding figures reported by patients themselves are 40% and 60%.

Long-term hyperprolactinemia has been associated with 2 potential consequences that are of major concern: osteoporosis and cancer. The association between hyperprolactinemia and osteoporosis is attributed to the downregulation of estrogen and testosterone levels by prolactin. Estrogen and, to a lesser extent, testosterone regulate bone mineral turnover such that low estrogen levels result in an increased rate of turnover and thus the development of osteoporosis. Patients with prolactin-secreting tumors lose bone mineral density, a measure of bone mass. These observations have provided the impetus for a number of studies evaluating the impact of antipsychotic treatment on bone mineral density. The few available studies sug-
gest a link between the use of prolactin-elevating antipsychotics and osteoporosis; however, these studies are methodologically flawed, and well-designed prospective studies are needed to address this issue.\textsuperscript{23,24} Interpretation of these results is further complicated by the lifestyles of many patients with schizophrenia (excessive alcohol intake, poor diet, polydipsia, sedentary routine, lack of exposure to sunlight, smoking), which place them at higher risk for osteoporosis.

Limited and inconsistent data are available for use in evaluating the relationship between hyperprolactinemia and breast cancer.\textsuperscript{25} One large prospective study found that hyperprolactinemia is associated with an increased risk for breast cancer in postmenopausal women, and another study that looked specifically at dopamine antagonist-induced hyperprolactinemia revealed a 16% increased risk for breast cancer (and not for the control condition, colon cancer).\textsuperscript{26,27} A recent study reported that prolactin protects human breast cancer cell lines against apoptosis—a finding that confirms previous observations that prolactin acts as a mitogenic factor and a promoter of neoplastic cell survival.\textsuperscript{25,28}

The use of antipsychotics has also been identified as a risk factor for endometrial cancer in premenopausal women.\textsuperscript{29} A potential link between neoplastic changes in the endometrium of patients and hyperprolactinemia had been reported in 2 earlier case studies.\textsuperscript{30} Clearly, more study is needed to discern whether a link between hyperprolactinemia and endometrial cancer can be found.

\section*{Management of Hyperprolactinemia}

Given the potential significance of hyperprolactinemia, it is prudent for the healthcare provider to routinely inquire about sexual function, breast changes, and menstrual function during the initial few weeks of treatment with a medication that may elevate prolactin and to inquire about these matters semianually thereafter. In addition, although the relationship between drug-induced hyperprolactinemia and osteoporosis, breast cancer, and endometrial cancer is not definitively known, the use of prolactin-sparing antipsychotic agents would be prudent whenever possible for patients who have or are at high risk for these diseases. If symptoms related to hyperprolactinemia develop, switching to a prolactin-sparing agent is the best option for decreasing prolactin levels. If switching is not clinically feasible or advisable, then pharmacologic intervention with a DA agonist such as cabergoline or bromocriptine may be considered as a last resort after careful evaluation of the risk/benefit ratio and careful monitoring for worsening of psychosis.

\section*{Conclusion}

Hyperprolactinemia is a major adverse effect of many antipsychotic agents. It is frequently neglected because clinical manifestations, such as sexual dysfunction, tend to be under-reported by patients and because healthcare providers tend to be reluctant to ask about these manifestations. In addition, the long-term prospective follow-up studies needed to evaluate the relationship between hyperprolactinemia and osteoporosis, breast cancer, and endometrial cancer are expensive, difficult to implement, and thus have not been performed.

The consequences of hyperprolactinemia are potentially serious and merit serious attention. It is, therefore, necessary for clinicians to monitor patients regularly and to question them about symptoms. Switching to a prolactin-sparing agent should be considered for patients who show signs of hyperprolactinemia. A growing body of evidence suggests a link between antipsychotic-induced hyperprolactinemia and the development of cancer and osteoporosis. Additional long-term, large-scale studies are required to clearly establish this link.

\section*{References}