Elevated prolactin levels in patients with schizophrenia: mechanisms and related adverse effects

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Abstract

The neurologic processes involved in schizophrenia are complex and diverse and the mechanisms through which antipsychotic agents exert their effects have been only partly elucidated. Hyperprolactinemia is a common side effect of treatment with many antipsychotics and is particularly associated with conventional (‘typical’) agents as well as the atypical antipsychotic risperidone. In contrast, other atypical agents introduced over the last decade do not elevate prolactin levels. This article discusses the regulatory mechanisms involved in prolactin secretion, the physiologic role of prolactin, and the etiology of hyperprolactinemia. Elevated prolactin levels may play important roles, both direct and indirect, in various pathologic states, including breast cancer, osteoporosis, cardiovascular disorders, and sexual disturbances. Antipsychotic-induced hyperprolactinemia may be associated with similar clinical manifestations; these are examined with particular reference to patients with schizophrenia.

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1. Introduction

Prolactin is a polypeptide hormone secreted by the lactotroph cells of the anterior pituitary gland. Prolactin release is pulsatory with approximately 13–14 pulses a day and displays a significant diurnal rhythm. Levels increase shortly after sleep onset, peak during the night, and start to decline shortly after waking, reaching a nadir around noon (Yen and Jaffe, 1991). Food, especially a midday meal, increases prolactin levels (Ishizuka et al., 1983). Levels among individuals also tend to fluctuate over time and this is particularly evident in post-menopausal women (Hankinson et al., 1995). The predominant form of prolactin is a monomer molecule (23 kDa) but the 16 kDa and 40–50 kDa dimers as well as the 70–80 kDa variant also occur (Davis et al., 1991). It has been suggested that the various prolactin molecules may have different bioavailability and some differential clinical effects. For the most part, these effects are related to reproductive endocrinology (Rogol et al., 1975; Sinha, 1995); we are not aware of differential effects in the context of central nervous system (CNS) disorders.

2. Regulation of prolactin secretion

The primary physiologic role of prolactin is the induction of lactation. However, prolactin interacts with other CNS and peripheral processes and its secretion is influenced by both stimulatory and inhibitory endogenous substances (Table 1) (Melmed, 2000). Prolactin release is also indirectly influenced by the effects of exogenous substances on endogenous ones (Melmed, 1995).

Prolactin secretion is regulated via tonic secretion of dopamine in the tubero-infundibular tract and the hypothalamo-hypophyseal vessels. Dopamine acts as a prolactin-inhibiting factor on D_2 receptors located on the surface of the pituitary lactotroph cells, whereas serotonin stimulates prolactin secretion. The serotonin-mediated increase is probably via stimulation of prolactin-releasing factors, in particular thyrotropin-releasing hormone, vasoactive intestinal polypeptide, and peptide histidine methionine (Fig. 1). Prolactin is also released in response to strong stimulatory effects on the nipple, such as breastfeeding, and in response to stress. In the context of CNS mechanisms and disorders, it is important to note that estrogen, opioids, substance P, and many other endogenous substances increase prolactin secretion while major neurotransmitters such as gamma aminobutyric acid (GABA) and acetylcholine inhibit prolactin secretion (Table 1) (Melmed, 2000). Therefore, medications that interfere with the main regulatory mechanisms of prolactin or with specific endogenous substances may cause an increase or decrease in prolactin levels with downstream effects on other systems. As conventional (typical) antipsychotic agents inhibit dopamine action at D_2 receptors, this may be one explanation for the hyperprolactinemia that can occur during treatment with these agents.
### Table 1
Endogenous substances affecting prolactin release

<table>
<thead>
<tr>
<th>Stimulatory</th>
<th>Inhibitory</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serotonin (5-HT)</td>
<td>Cholecystokinin (CCK)</td>
</tr>
<tr>
<td>Thyrotropin-releasing hormone</td>
<td>Bombesin</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Secretin</td>
</tr>
<tr>
<td>Vasoactive intestinal polypeptide</td>
<td>Gastrin</td>
</tr>
<tr>
<td>Peptide histidine isoleucine</td>
<td>Galanin</td>
</tr>
<tr>
<td>Opioid peptides</td>
<td>Calcitonin</td>
</tr>
<tr>
<td>Growth hormone-releasing hormone</td>
<td>Calcitonin gene-related peptide</td>
</tr>
<tr>
<td>GnRH</td>
<td>Tymosin factor 5</td>
</tr>
<tr>
<td>Oxytocin</td>
<td>Melatonin</td>
</tr>
<tr>
<td>Vasopressin</td>
<td>Other posterior pituitary factors (?)</td>
</tr>
<tr>
<td>Histamine (H₁)</td>
<td>Platelet activating factor</td>
</tr>
<tr>
<td>Bradykinin</td>
<td>Epidermal growth factor</td>
</tr>
<tr>
<td>Angiotensin II</td>
<td>α-Melanocyte-stimulating hormone</td>
</tr>
<tr>
<td>Neurotensin</td>
<td></td>
</tr>
<tr>
<td>Substance P</td>
<td></td>
</tr>
<tr>
<td>Corticotropin-releasing hormone?</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from the work of Melmed (2000).

3. The differential diagnosis of hyperprolactinemia

The causes of hyperprolactinemia are wide-ranging, with CNS disorders, various systemic conditions, pituitary disorders, and antidepressive and antipsychotic medications all implicated (Table 2). As such, even in patients who receive prolactin-inducing medications, other possible causes of hyperprolactinemia should be considered.

3.1. Systemic conditions

The most prevalent systemic condition associated with hyperprolactinemia is stress in response to psychologic, environmental, or internal stimuli. Together with cortisol and growth hormones, prolactin is recognized as a major stress-induced hormone but its role in the normal and abnormal stress responses has been less widely studied than that of cortisol. Physical stress, whether brought about from normal exercise, medical conditions such as hypoglycemia (Nathan et al., 1980), or induced by surgery, may also cause hyperprolactinemia. In addition, any impairment in prolactin metabolism, including advanced liver dysfunction, cirrhosis, or chronic renal failure, may result in elevated prolactin levels.

The increase in estrogen that occurs during pregnancy can lead to elevated levels
of prolactin but hormonal levels are also increased in pseudocyesis. The inter-
relationship between prolactin and estrogen is quite complex. As will be discussed
in more detail below, hyperprolactinemia-induced hypogonadism and its con-
sequences are important but estrogen itself increases levels of prolactin. This ele-
vation is effected through estrogen’s multiple influences on CNS functions
(Halbreich et al., 1981; McEwen et al., 1997), as well as through a direct influence
on lactotrophs (Melmed, 1995; Petty, 1999). Estrogen increases lactotroph mRNA
levels, influences prolactin gene transcription and expression, and affects mitotic
activity and DNA synthesis (Petty, 1999). It elevates levels of prolactin, thereby
increasing the amplitude of prolactin bursts as well as prolactin release and storage
(Veldhuis et al., 1989). Estrogen also has an indirect effect on prolactin via synthesis
of protein intermediates, modulation of the inhibiting effect of dopamine or prolactin
gene transcription, and a decrease in cellular cAMP. Any increase in levels of estro-
gen, whether from endogenous or exogenous sources, may result in increased levels
of prolactin. These levels are usually not high enough to cause prolactin-induced
hypoestrogenism.

3.2. CNS and pituitary disorders

Any space-occupying lesions or processes in the CNS that are also located in or
influence the hypothalamus may cause hyperprolactinemia. Meningiomas, craniofi-
angiomas, sarcoidosis, disseminated autoimmune disorders, and vascular impairments
are all potential causes.
Table 2
Differential diagnosis of hyperprolactinemia

<table>
<thead>
<tr>
<th>Systemic conditions</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stress</td>
<td><em>First generation neuroleptics</em></td>
</tr>
<tr>
<td>Pregnancy</td>
<td>Phenothiazines</td>
</tr>
<tr>
<td>Pseudocyesis</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Cushing’s disease</td>
<td><em>Second generation neuroleptics</em></td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>Risperidone</td>
</tr>
<tr>
<td>Chronic renal failure</td>
<td><em>Antidepressants</em></td>
</tr>
<tr>
<td>Breast stimulation</td>
<td>Some tricyclic antidepressants</td>
</tr>
<tr>
<td></td>
<td>Specific serotonin reuptake inhibitors</td>
</tr>
<tr>
<td><em>CNS disorders</em></td>
<td><em>Monoamine-oxidase inhibitors</em></td>
</tr>
<tr>
<td>Meningiomas</td>
<td>d-fenfluramine</td>
</tr>
<tr>
<td>Cranioopharingiomas</td>
<td>Reserpine</td>
</tr>
<tr>
<td>Sarcoidosis</td>
<td>α-methyldopa</td>
</tr>
<tr>
<td>Disseminated autoimmune disorders</td>
<td>Cocaine and other opiates</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Verapamil</td>
</tr>
<tr>
<td>Hypothalamic tumors and metastases</td>
<td>Cimethidine</td>
</tr>
<tr>
<td>Cranial irradiation</td>
<td>Estrogens</td>
</tr>
<tr>
<td></td>
<td>Oral contraceptives</td>
</tr>
</tbody>
</table>

*Tumors in the anterior pituitary, particularly prolactinomas, are one of the most common causes of hyperprolactinemia. Other pituitary disorders, such as empty sella syndrome and acromegaly, may also elevate prolactin. Magnetic resonance imaging and computed tomography scans that focus on the sella turica are therefore essential in diagnosing hyperprolactinemia.*

3.3. Schizophrenia and antipsychotic-induced hyperprolactinemia

Prolactin secretion in patients with schizophrenia is important, even though schizophrenia affects only 1% of the total world population. This is because the chronicity of schizophrenia and associated long-term disability means that it is one of the 10 most common disorders documented by the World Bank and World Health Organization causing cumulative disability and lost productive years.

The influence of schizophrenia per se on prolactin secretion is not completely clear. The current broad boundaries of the clinical definition of schizophrenia, together with the diversified CNS processes involved in the pathobiology of psychotic disorders, which can increase or decrease levels of prolactin, makes a coherent explanation difficult. As the diversity of clinically effective atypical antipsychotics and functional imaging studies have shown, schizophrenic patients may display a
range of receptor abnormalities. These include, but are not limited to, D₁, D₂ and other dopamine receptors, serotonin receptors, α₁ and α₂ adrenoceptors, muscarinic cholinergic receptors, histamine, GABA, sigma opioid receptors, and glutamate systems (NMDA receptors) (Goldstein, 1999a). Therefore, prolactin levels in a given untreated schizophrenic individual are the result of the balance between multiple internal regulatory processes and external stimuli (e.g. stressful events).

Most of our knowledge concerning prolactin levels in schizophrenic patients has been gained from studies of patients treated with antipsychotic medications. The dopaminergic hypothesis for the pathobiology of schizophrenia was developed mainly because the efficacious conventional (typical) antipsychotics were all dopamine-blocking agents. Their clinical efficacy was attributed to blockade of the mesolimbic and mesocortical dopaminergic pathways, while the extrapyramidal adverse effects associated with conventional antipsychotics were due to blockade of the nigrostriatal dopamine pathway.

The tubero-infundibular system regulates prolactin secretion via dopamine neurones. Dopamine from the tubero-infundibular system is secreted from the median eminence of the hypothalamus, via the portal veins of the pituitary stalk, to the lactotrophs in the anterior pituitary where it exerts its tonic-inhibitory effect. (There is a short feedback mechanism between prolactin and dopamine released from the hypothalamus.) Therefore, any blockade of dopamine receptors in the tubero-infundibular system would reverse prolactin inhibitory effects and lead to hyperprolactinemia. Typical antipsychotic agents are nonselective, blocking all dopamine pathways including the tubero-infundibular pathway. Indeed, it has been suggested that the magnitude of hyperprolactinemia may be a biological marker for the therapeutic effects of an antipsychotic, and a very high correlation between hyperprolactinemic effect and ‘therapeutic potency’ has been demonstrated across a group of conventional antipsychotic drugs (Gruen et al., 1978). While antipsychotic-induced hyperprolactinemia is almost universal with typical agents, most atypical antipsychotics do not cause a sustained elevation in prolactin levels. Conversely, risperidone induces hyperprolactinemia at least to a similar level to that of the conventional neuroleptics (Goldstein, 1999b). In addition, there is some evidence that zotepine (von Bardeleben et al., 1987) and amisulpride (Wetzel et al., 1994) also induce hyperprolactinemia.

3.4. Antidepressants and other medications

Some tricyclic antidepressants cause hyperprolactinemia, as do selective serotonin reuptake inhibitors, due to their increased serotonergic stimulatory effects. Similarly, d-fenfluramine, an ingredient in some weight-reduction products, increases serotonin activity and can produce elevated prolactin levels (Asnis et al., 1988). Monoamine oxidase inhibitors, which increase activity of dopamine but also norepinephrine and serotonin, have also been shown to induce hyperprolactinemia. We reported that depletion of dopamine with reserpine has been shown to increase levels of prolactin (Asnis et al., 1980).

Several opioids, including morphine, cocaine, and β-endorphin, have been reported to increase prolactin secretion through dopamine interaction (Gold et al., 1978). The
opioid antagonist naloxone and its long-acting counterpart naltrexone block increase in prolactin, which might be caused by other stimuli such as stress and surgery. However, it is not yet clear whether these opioids actually decrease prolactin levels if they are not already elevated.

4. Clinical effects of hyperprolactinemia

For clinical purposes, hyperprolactinemia can be defined as a plasma prolactin level of >20 ng/ml for men and >25 ng/ml for women. The diurnal rhythm of prolactin levels makes it preferable to obtain a fasting blood sample at least 2 h after waking.

Most of the clinical adverse effects of hyperprolactinemia (Table 3) may be attributed to prolactin interference with the hypothalamic–pituitary–gonadal system. This interference takes place on multiple levels (Malarkey et al., 1980; O’Dell et al., 1990). Prolactin suppresses gonadotropin-releasing hormone (GnRH) pulsatile secretion from the hypothalamus and directly interferes with the pituitary action of the gonadotropin luteinizing hormones (LH) and follicle-stimulating hormone (FSH) on the gonads. Additionally, prolactin interferes with steroid feedback mechanisms at all levels, from the pituitary up to the hypothalamus, and with the extra hypothalamus CNS processes which regulate the hypothalamus. It also inhibits aromatase activity and causes blockade of 5α-reductase. These interactions produce a major dysregulation of the hypothalamic–pituitary–gonadal system, as well as of the systems and processes affected by the pituitary and gonadal hormones.

<table>
<thead>
<tr>
<th>Clinical adverse effects of hyperprolactinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decreased BMD and osteoporosis</td>
</tr>
<tr>
<td>Infertility</td>
</tr>
<tr>
<td>  Disturbed menstrual cycles</td>
</tr>
<tr>
<td>  Anovulation</td>
</tr>
<tr>
<td>  Amenorrhea</td>
</tr>
<tr>
<td>  Irregular cycles</td>
</tr>
<tr>
<td>Decreased testosterone levels and sperm mobility</td>
</tr>
<tr>
<td>Sexual dysfunction</td>
</tr>
<tr>
<td>  Decreased libido and arousal</td>
</tr>
<tr>
<td>  Un- or hypo-orgasmia</td>
</tr>
<tr>
<td>Increased risk of CV disorders</td>
</tr>
<tr>
<td>Galactorrhea</td>
</tr>
<tr>
<td>  Breast engorgement</td>
</tr>
<tr>
<td>Increased risk of tardive dyskinesia?</td>
</tr>
<tr>
<td>Increased risk of breast cancer</td>
</tr>
<tr>
<td>Abnormal function of the immune system?</td>
</tr>
<tr>
<td>Anxiety, depression, hostility</td>
</tr>
</tbody>
</table>
4.1. Decreased bone mineral density (BMD) and osteoporosis

The consequences of hyperprolactinemia-induced decreases in estrogen and testosterone levels may lead to debilitating and long-term disease. Probably the least obvious in the short term, but one of the most serious in the long term, is osteoporosis. This prevalent bone disorder is characterized by a decrease in BMD or bone mass and is associated with significant morbidity, particularly in the elderly. Several studies (Rojansky et al., 1990; Schweiger et al., 1993; Abraham et al., 1995; Halbreich et al., 1995; Michelson et al., 1996; Keeley et al., 1997) have reported a decrease in BMD in psychiatric patients treated with neuroleptics and/or antidepressants. In patients with schizophrenia, osteoporosis does not follow the usual pattern of age-related decreases in BMD. The magnitude of decreased BMD and the ensuing increased susceptibility to osteoporosis and bone fractures is higher in men with schizophrenia than women with schizophrenia.

Osteoporosis is a disease of impaired homeostatic regulation (Riggs, 1981). The bone normally undergoes constant change and remodeling and is vulnerable to multiple influences (Steele, 1985), many of which might occur in patients with schizophrenia (Halbreich and Palter, 1996). Hyperprolactinemia has been linked to hypogonadism secondary to disruption of the hypothalamic–pituitary–gonadal axis (Dickson and Glazer, 1999). However, the relative contribution of hypogonadism or of prolactin elevation itself to the development of osteoporosis is not entirely clear. For instance, a preclinical study found that estrogen deficiency was more important in determining BMD than prolactin excess and concluded that osteoporosis was probably due to prolactin-induced hypogonadism rather than a direct effect of prolactin on calcium homeostasis (Adler et al., 1998). Support for this finding was provided in a clinical study of women with hyperprolactinemia and amenorrhea. Those with the most severe reduction in BMD had the lowest levels of estradiol, indicating that the bone loss was caused by reduced estrogen not directly by elevated prolactin (Klibanski et al., 1980).

Patients with schizophrenia, especially those who are treated with conventional antipsychotics, appear particularly susceptible to decreases in BMD (Lacro and Jeste, 1994). Chronic psychotropic-induced hyperprolactinemia is associated with hypogonadism in both men and women (Levinson and Simpson, 1987). For instance, a study examining antipsychotic-induced body-weight gain in pre-menopausal women found that the atypical agent sulpiride significantly increased prolactin levels and significantly reduced estradiol levels, surmizing that the decreased serum estradiol level was secondary to hyperprolactinemia (Baptista et al., 1997). This in turn may lead to osteoporosis in both genders (Klibanski et al., 1980; Ataya et al., 1988).

It is suggested that the neuroleptic-induced decrease in gonadal hormones may be responsible for a decrease in 1α hydroxylate in the kidney, in 1,25 dihydroxy vitamin-D synthesis, and reduced calcium absorption in the intestine, all of which may contribute to decreases in BMD. Low levels of estrogen also influence interleukin activity, which, following a complex process (Halbreich and Palter, 1996), leads to increased bone resorption and decreased bone formation, resulting in decreased BMD. Indeed, in patients with schizophrenia, pathways other than hyperprolactinemia-induced
bone processes may be involved in the development of osteoporosis. Polydipsia and impaired fluid and electrolyte balance (mostly calcium), smoking, dietary and vitamin deficiencies, as well as a lack of exercise and limited exposure to sunlight may all contribute. Nevertheless, hypogonadism remains a major contributing factor.

4.2. Prolactin and the immune system

As discussed previously, prolactin influences several interleukins and in turn is influenced by changes in interleukin-2 and other interleukins. Prolactin receptors have been identified on several blood cells, notably B-cells, T-cells, and monocytes. Prolactin synthesis by normal lymphocyte cells has also been confirmed. It has been suggested that prolactin is secreted from mononuclear cells and has an autocrine/paracrine effect on immune-cell function (Pellegrini et al., 1992). Though it is clear that pituitary prolactin and mononuclear-secreted prolactin modulate the immune system, the hormonal effects are multifaceted and diverse. It is still unclear whether antipsychotic-induced hyperprolactinemia per se influences the immune system and if so in what way, because several immune-related processes are impaired in untreated patients with schizophrenia.

4.3. Prolactin and the cardiovascular (CV) system

It is well documented that women of reproductive age suffer less from CV disorders and cardiac infarction than men. However, following menopause this gender difference disappears. It has been suggested that the decreased prevalence of CV disorders in pre-menopausal women is attributable to the protective effects of estrogen against arteriosclerosis, hypertension, and raised cholesterol and triglyceride levels (Schenck-Gustafsson, 1996). As such, the low estrogen levels that commonly occur with hyperprolactinemia may increase the rate of CV disorders in this group. Shaarawy et al. (1997) reported high blood pressure and decreased nitric oxide in women with hyperprolactinemia and low estrogen, which were normalized following treatment with bromocriptine. We are not aware of any similar studies in treated patients with schizophrenia, or whether a hypo-estrogenic state resulting from antipsychotic-induced hyperprolactinemia increases the prevalence of CV disorders and accelerates vulnerability to myocardial infarcts in female patients.

4.4. Prolactin and breast cancer

Increased levels of prolactin have been identified as a risk factor for breast cancer (Adams, 1992), which is the most common malignant disorder among women and is a major cause of death (Kelsey and Horn-Ross, 1993). Once the link between conventional antipsychotics and hyperprolactinemia was established, the publication of several reports focusing on breast cancer followed (Katz et al., 1967; Oriana et al., 1991). However, the results from these studies were inconclusive and did not confirm either an increased prevalence of breast cancer in psychiatric patients or any
connection with hyperprolactinemia. These inconclusive findings were in contrast to those from our own study. We reviewed the mammograms, psychiatric history, and treatment of 275 women patients aged >40 years in a psychiatric state hospital and compared these to 928 women of similar age at a general hospital radiology clinic (Halbreich et al., 1996). The incidence of breast cancer documented by pathology was >3.5 times higher among psychiatric patients than among patients in the specialized radiology clinic and 9.5 times higher than the reported incidence in the general population. While this increased incidence may be attributed to antipsychotic-induced hyperprolactinemia, cigarette smoking and alcohol consumption may also play a role.

The study drew criticism, which was amplified due to the sensitivity of the issue. However, the hyperprolactinemia connection is supported by a large prospective study of >30,000 post-menopausal women (Hankinson et al., 1999). Blood sampling resulted in 306 of the women being diagnosed with breast cancer and this group was compared with 448 matched control individuals. The prospective data suggests that higher plasma prolactin levels are associated with an increased risk of breast cancer in post-menopausal women. This increased risk also held after controlling for plasma estrogen and androgens and IGF-1.

Several putative mechanisms have been put forward to explain the role of prolactin in breast cancer. These include expression of prolactin in both normal and malignant breast tissue, the existence of receptors for prolactin in >50% of breast tumors, and a prolactin-induced increase in DNA synthesis of breast cancer cells in vivo (Hankinson et al., 1999). It is of interest that prolactin administration has been shown to increase the rate of mammary tumors in mice (Welsch and Nagasawa, 1977). As the magnitude of a positive relationship between plasma prolactin levels and the risk of breast cancer has been reported to be similar to that observed between estrogen levels and breast cancer, this association should not be ignored. In younger women, increased prolactin and decreased estrogen levels may counteract each other to some extent but this is not the case in post-menopausal women who have been exposed to long-term treatment with typical antipsychotics. It is not yet known whether women who were administered conventional neuroleptics for a long time and then switch to those atypical agents that do not induce prolactin elevation, reduce their risk of breast cancer. In any case, regular mammograms are a necessary minimum precaution in women receiving antipsychotic treatment for schizophrenia.

4.5. Galactorrhea

Galactorrhea has been reported in 30–80% of women with hyperprolactinemia associated with pituitary tumors (Franks and Nabarro, 1977) but the reported prevalence of galactorrhea in patients with schizophrenia taking antipsychotics is much lower (Wessellmann and Windgassen, 1995: Windgassen et al., 1996). One explanation for this apparent difference might be that, as breast milk is not spontaneously secreted (nipple stimulation is necessary), galactorrhea goes unnoticed and is therefore under-reported. Not all women with hyperprolactinemia suffer from galactorrhea and, conversely, the symptom may be present in women with normal levels of prolactin. Galactorrhea also occurs in men although to a lesser degree. Even though
galactorrhea is a mild and harmless side effect of some antipsychotics, its confirmation is simple (diagnosis can be made by squeezing the nipple) and its occurrence could point to other, more serious, adverse effects.

4.6. Influence of hyperprolactinemia on the menstrual cycle and fertility

As hyperprolactinemia is associated with suppressed estrogen levels, initial evidence of elevated prolactin is often identified by reproductive-related symptoms, particularly in women. Symptoms include menstrual irregularities, anovulation and its sequelae, and amenorrhea. These symptoms are often accompanied by galactorrhea, breast enlargement, or a feeling of engorgement (Knegtering et al., 2000). However, the percentage of women on antipsychotics who report amenorrhea (≥33%) is approximately twice the proportion who report galactorrhea (Santoni and Saubadu, 1995). This may be attributed to reports that galactorrhea depends on the duration of hyperprolactinemia and hypogonadism. Women with long-standing amenorrhea are less likely to have galactorrhea (Thorner et al., 1998) even though self-reports of the latter are few even when it exists. Amenorrhea is accompanied by infertility so antipsychotic-induced hyperprolactinemia can, indirectly, serve as a contraceptive for women with schizophrenia. Our own experience is that not all women consider drug-induced amenorrhea to be an undesirable adverse effect. However, they might be more concerned about sexual dysfunction, which has been linked to elevated levels of prolactin.

A similar situation exists for men with hyperprolactinemia. The prolactin-induced decrease in GnRH levels, pulsatility, and activity causes decreases in LH, FSH, and testosterone. Prolactin is actively concentrated in the testes and decreases sperm production and motility (Rogol et al., 1975), therefore decreasing male fertility even when sexual function is maintained. It is of note that, when examined, up to 33% of men with hyperprolactinemia had galactorrhea. This suggests that breast examination should be part of routine clinical examination of both women and men on antipsychotics and should not be left to self report.

4.7. Sexual dysfunction

Normal sexual function comprises a combination and culmination of several components: libido, arousal, and orgasm. All three are regulated by complex multiple processes, only some of which will be discussed here. Increased dopamine and decreased prolactin are associated with increased libido. Increased nitric oxide and increased cAMP, as well as increased acetylcholine, are needed for arousal and orgasm is associated with a decrease in serotonin and an increase in norepinephrine levels. Thus, it is apparent that hyperprolactinemia is only part of the sexual dysfunction equation.

In patients undergoing dialysis for renal dysfunction, those reporting sexual function disturbances had significantly higher serum prolactin levels than patients with normal sexual function. Treatment with the dopamine agonist bromocriptine nor-
malized prolactin levels and improved libido and the frequency of sexual activity (Weizman et al., 1983).

In men, neuroleptic-induced hyperprolactinemia has been reported to cause impaired sexual function on several levels: reduced libido, erectile dysfunction, partial to complete impotence, delayed orgasm, retrograde ejaculation, painful ejaculation, and anorgasmia (Keks et al., 1987; Knegtering et al., 2000). These symptoms have been reported by up to 50% of patients on typical antipsychotics (Ghadirian et al., 1982). Reduced libido has also been noted in women. Among the atypical agents, clozapine has been reported to be associated with fewer sexual side effects than conventional antipsychotics (Peacock et al., 1994) and sexual side effects from olanzapine were reported infrequently during clinical trials. Risperidone, on the other hand, is associated with a higher incidence of sexual dysfunction (Claus et al., 1992; Marder and Meibach, 1994). This may be a reflection of risperidone-induced hyperprolactinemia (Goldstein, 1999b). It is also of interest that female reports of decreased ability to reach orgasm are high with risperidone when compared with typical neuroleptics (Knegtering et al., 2000). The few spontaneous reports of sexual problems from patients in the quetiapine clinical trials program are consistent with evidence that quetiapine does not elevate prolactin levels (Borison et al., 1996; Arvanitis and Miller, 1997; Small et al., 1997).

4.8. Mood and behavioral effects of hyperprolactinemia

Hostility, depression, and anxiety were reported to be more frequent in amenorrheic women with hyperprolactinemia than in both amenorrheic women with normal levels of prolactin and in women with regular menstrual cycles (Fava et al., 1983, 1988). Similar mood symptoms have also been reported in response to elevated prolactin in healthy women (Buckman, 1985). However in men, the direct impact of increased prolactin on mood and behavior is still unclear. Furthermore, prolactin has been suggested to induce dysphoric states in its own right (Kellner et al., 1984). The issue is further complicated because the influence of increased prolactin on estrogen and testosterone means that some of the long-term hormonal effects of hyperprolactinemia are difficult to distinguish from those related to hypogonadism and to the effects of decreased estrogen and testosterone on the CNS.

5. Conclusions

In recent years, increased prescribing of atypical antipsychotics would suggest that the prevalence of hyperprolactinemia in patients with schizophrenia is probably declining, at least in developed countries, although this assumption needs to be confirmed. Whether a switch to those atypical antipsychotics that do not induce hyperprolactinemia will completely rectify the long-term hyperprolactinemic effects of the typical antipsychotics, or just prevent further deterioration, has not yet been determined. Long-term follow-up studies are required to answer this question.

From a public-health and cost-effectiveness perspective, the disability and pro-
jected costs associated with the long-term effects of hyperprolactinemia, as well as with other drug-induced adverse effects, should be taken into account when selecting antipsychotic medications. This is particularly true for the treatment of schizophrenia in developing countries and for patients elsewhere whose treatment is paid for from public or institutional funds.

**References**


