# Antipsychotics and prolactinemia: biological regulation and clinical aspects

*Antipsicotici e prolattinemia: regolazione biologica e aspetti clinici*

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## Summary

*A number of antipsychotics, including oral haloperidol, amisulpride and risperidone, are associated with hyperprolactinemia, an adverse effect that is not related to their therapeutic efficacy. This adverse reaction not only has a negative impact on sexual and reproductive function in the short-term, but also produces body weight gain and reduction in bone density, leading in the long-term to obesity, a condition that notoriously increases the risk of a broad range of medical disorders, as well as all-cause mortality, and to osteoporosis, which notoriously increases the risk of fractures and chronic disability. Other long-term adverse effects of hyperprolactinemia include an increase in the risk of breast and endometrial cancer (Table II).*

*Prolactin levels should be monitored in patients on long-term antipsychotic treatment and early signs heralding the development of hyperprolactinemia, such as body weight gain and menstrual changes, should be sought regularly.*

*Four therapeutic options are available for management: reduction in the dosage of the prolactin-raising agent; switch to a prolactin-sparing agent, such as aripiprazole, clozapine, quetiapine or olanzapine; addition of a dopamine agonist or of hormonal therapy with estrogens and progestogens. None of these options is ideal and preventive measures tailored to the needs of the individual patient are to be preferred.*

*Key words:*

*Antipsychotics • Prolactin • Biological regulation • Hyperprolactinemia • Long-term consequences • short-term consequences*

## Introduction

### *Biological effects and regulation of prolactin secretion*

Prolactin is a 199-amino acid polypeptide that is produced by the lactotroph cells located in the anterior part of the pituitary gland and cleared by the kidneys. Although prolactin receptors are ubiquitous in the body and prolactin has proved to be able to modulate numerous biological effects, its main physiological role consists in preparing the mammary glands for lactation during pregnancy and in stimulating the production of milk after delivery.

In view of its pleiotropic effect, it is secreted regularly throughout life, not just during and after pregnancy. Its secretion follows a circadian rhythm characterized by a peak after about 4 hours of sleep, a trough about 6 hours after waking and regular pulsatile release about every 95 minutes; it is influenced by everyday activities, such as meals, stress, sexual and physical activity, which produces additional mild and transient increases in prolactin concentrations. Normal plasma concentrations differ in the two sexes, the normal range being 0-20 mcg/mL in males and 0-25 mcg/mL (800 nU/L) in females; during pregnancy and nursing concentrations increase 10-20 fold [1-7].

One of the main factors that causes confusion in clinical practice is the

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use of different laboratory measurement units for prolactin levels, mainly mIU/L and ng/mL. Knowledge of the conversion factor is useful, namely 1 ng/mL = 21.1 mIU/L.

Prolactin secretion is regulated by hypothalamic hormones delivered through the hypothalamic-pituitary portal vessels. Regulation is the result of the balance between stimulation, mediated mainly by the hypothalamic hormone thyrotropin-releasing hormone and, secondarily, by serotonin via receptors 5HT1A and 5HT2, and inhibition, mediated mainly by dopamine. Inhibition usually predominates. Dopamine is released by the tuberoinfundibular neurons in the hypothalamus and binds to D2 dopamine receptors on the membrane of the prolactin secreting pituitary cells; the stimulation of these receptors influences prolactin gene transcription, synthesis and release. The balance is modulated by other substances, such as estrogens, which can bind to specific intracellular receptors in lactotroph cells, increasing prolactin gene transcription and synthesis, counteracting dopaminergic effects [3 4 8-10]. Hyperprolactinemia produces marked changes in Gonadotropin Releasing Hormone (GnRH) pulsatile secretion and, consequently, in the physiological production of Follicle Stimulation Hormone (FSH) and Luteinizing Hormone (LH). The change in FSH and LH function produces dysregulation of follicle growth and ovulation in women and of steroidogenesis and spermatogenesis in men [11]. This ultimately results in hypogonadism, which is the cause of the symptoms of hyperprolactinemia, both in the short and long-term [10 12-16].

## *Prevalence and causes of hyperprolactinemia*

The prevalence of hyperprolactinemia ranges from 0.4% in an unselected healthy adult population up to 10% in particular patient populations. For instance, it is found in 9% of young women who present with amenorrhea and in 5% of men with fertility problems or impotence [11 17-20].

The causes of hyperprolactinemia may be subdivided into 4 groups, as is shown in Table I [20]. The proposed mechanisms of medication-induced hyperprolactinemia are described in Figure 1.

## *High risk patient subgroups*

An explanation for differences among studies is the differences in demographic characteristics of the study patient population besides sex. The impact of such differences were assessed in a cross-sectional open-label study in 402 adult in- or outpatients with a diagnosis of schizophrenia, who had been on treatment with prolactin-raising antipsychotics for at least 3 months [21]. The prevalence of hyperprolactinemia was 65,6% in premenopausal women *vs*. 45.1% in postmenopausal women and 42.4% in men; in addition, an inverse relationship was found between age and risk of hyperprolactinemia, 1 year less corresponding to a 2,25% in-

**TABLE I.**
Causes of hyperprolactinemia. *Cause di iperprolattinemia*.

| **Pharmacological Causes** |
|---|
| Psychotropic drugs: antidepressants (esp. serotoninergic agents); conventional and some atypical antipsychotics; antihypertensive agents (methyldopa reserpine verapamil); antiemetic anti-dopaminergic agents (metoclopramide); H2 receptor antagonists (cimetidine, ranitidine); Hormones (estrogen, oral contraceptives); miscellaneous (amphetamines, opiates) |
| **Physiological Causes** |
| Lactation; pregnancy; sleep; stress; physical exercise; sexual activity; breast stimulation |
| **Pathological Causes** |
| Pituitary disorders; empty sella syndrome; micro- and macro-prolactinomas; stalk lesions; hypothalamic disorders; tumors; sarcoidosis; postencephalitis; endocrine disorders; cushing's syndrome; polycystic ovary syndrome; primary hypothyroidism |
| **Miscellaneous Causes** |
| Chest wall lesions due to trauma or cancer; chronic renal insufficiency; serious liver disease and cirrhosis; ectopic production of prolactin (e.g. by small cell lung carcinoma) |

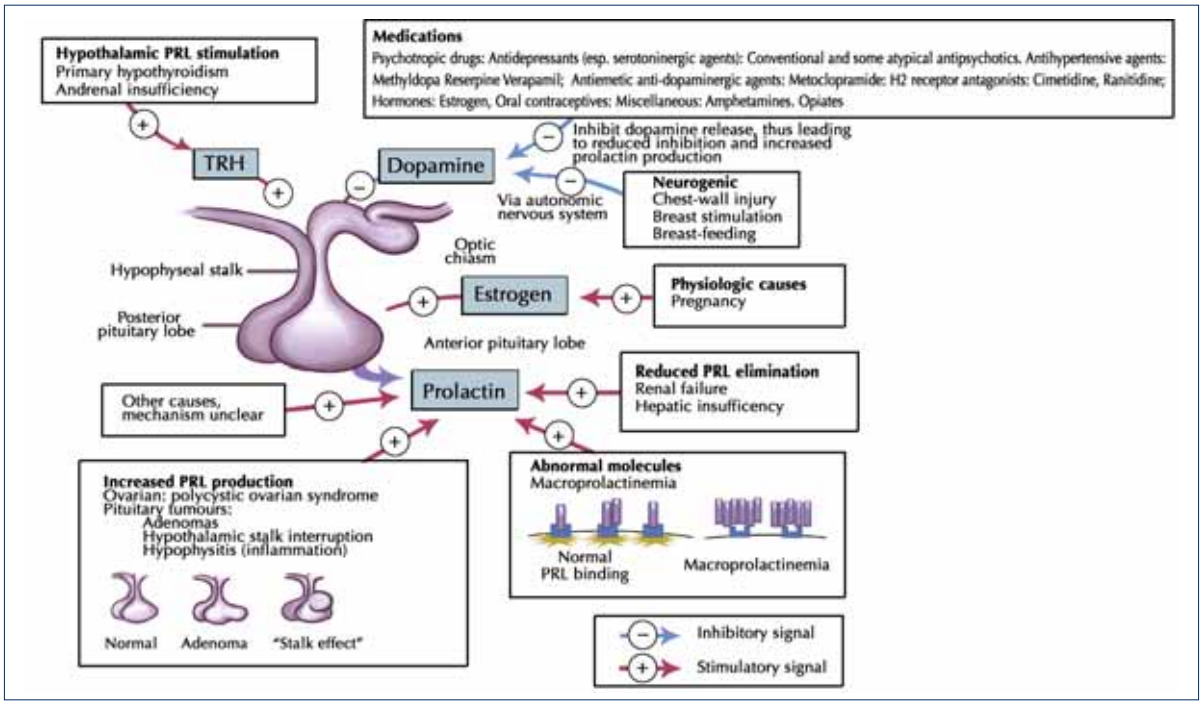


**FIGURE 1.**
Pathways of prolactin production by hypophysis and major causes of altered prolactin production. *Vie di produzione della prolattina dap arte dell'ipofisi e principali cause di alterata produzione di prolattina.*

crease in risk [Index for Age Normalization of Prolactinemia (IANP)]. The age in women was found to be important also in the previously mentioned US study by Montgomery et al. 2004 [22], in which hyperprolactinemia was significantly more common below the age of 50 years than in those who were older ($p < 0.008$). Race, on the contrary, did not appear to play a role in the development of hyperprolactinemia [21].

In addition, amongst premenopausal women, mothers in the immediate postnatal period appear to be particularly sensitive to the prolactin-raising effect of antipsychotics and preliminary data suggest that also children and adolescents are particularly susceptible to the prolactin-raising effects of antipsychotics [4 23 24].

## Antipsychotics as a cause of hyperprolactinemia

Clinical symptoms of schizophrenia appear between 16 and 25 years [8 9]. Early pharmacological treatment is identified as one of the most valuable factors for the prevention of schizophrenia relapse and improvement of patient disability [25]. Antipsychotics are an important cause of hyperprolactinemia in young adults.

They are prescribed mainly for schizophrenia, which has a prevalence of 1%, equivalent to more than 60 million people worldwide, and is amongst the top ten disorders in terms of cause of disability and loss of human productive years [2 3 13]. In view of all previous considerations, the effects of hyperprolactinemia in schizophrenic patients have to be taken into particular account.

The phenomenon was ascertained for the first time by Kleinberg in the 1971 [26] more than 30 years ago and was considered to be an inevitable consequence of essential treatment.

The dimensions of the phenomenon have been ascertained by Montgomery et al. 2004 [23] in the US and Bushe and Shaw 2007 [36] in the UK. The former carried out a retrospective study based on data-base retrieval in a large sample ($n = 470$) of chronically psychotic inpatients residing in state-funded hospitals in the US, the latter performed a cross-sectional study in 230 outpatients with severe mental disorders serviced by a community mental health team in the UK, both with the aim of assessing the prevalence and severity of hy-

perprolactinemia in psychotic patients. The rate of hyperprolactinemia was 71% amongst the US in-patients on treatment with antipsychotics with no important difference between sexes (men 72%, women 68%), whereas in the UK study in out-patients the rate was considerably lower, 38%, with a notable difference between sexes, the rate being twice as high in women as in men (52% *vs*. 26%). The difference in prevalence may be due to a recruitment bias in the retrospective study or to in- *vs*. out-patient status, the lower rate being due to lower compliance with medication amongst out-patients, whereas there is no immediate explanation for the inconsistency in the finding of differences between the sexes. The rate of severe hyperprolactinemia was similar in females in the two studies (42% in the female US in-patients *vs*. 38% in the female UK outpatients; the difference was due to the gap between the rate in male US in-patients – 36% – and male UK out-patients, only 7%). The two results are at the extremes of the findings of other studies reported in the literature, which have shown that from 38% to 75% of patients on antipsychotic therapy have hyperprolactinemia; differences between the sexes have been found in some, but not all the other studies published in the literature [5 6 15 17 21 28 30-34].

## *Comparison of hyperprolactinemic effects of different antipsychotics*

Another explanation for differences in hyperprolactinemia values is the use of different antipsychotics, as not all antipsychotics seem associated with this undesirable effect.

Any direct comparison between antipsychotics has some major concerns because of the different populations included in terms of gender and age (both independent variables with a substantial influence on prolactinemia), variability in study length, dosage used and type of study.

As different publications report prolactin levels in very different and inconsistent manners, the prevalence of hyperprolactinemia in patients treated with different antipsychotics is the most clinically relevant variable that could be roughly compared between different studies. Because of the relevant biases described above, only minimal and maximal incidences reported in the literature have been considered for the description the hyperprolactinemic effect of different antipsychotics when used in adult population.

## *Antipsychotics classification*

Indeed, antipsychotics can be subdivided into "prolactin-raising" and "prolactin-sparing" agents. The former include conventional neuroleptics, such as oral haloperidol [35 36], depot haloperidol [35 37 38], amisulpride [35 38-40], risperidone long-acting intramuscular injection (LAIM) [35 38] and risperidone [21 22 27 41-47] and the latter clozapine [27 48 49], olanzapine [22 27 47 50], quetiapine [22 27 49 51], and aripiprazole [52-54]. For accuracy it is interesting to note what is reported in the Summary of Product Characteristics (SpC) of the defined "prolactin sparing" antipsychotics. The SpC of aripiprazole does not mention at all hyperprolactinemia among the possible adverse events [55]. The SpC of clozapine states, in the pharmacodynamic properties section, that "*in contrast to classic antipsychotics, Clozaril produces little or no prolactin elevation…"* [56]. About quetiapine, the SpC states that " … *does not produce sustained elevations in prolactin. In a multiple fixed-dose clinical trial, there were no differences in prolactin levels at study completion between quetiapine, across the recommended dose range, and placebo ..."* [57].

Olanzapine's SpC reports elevated prolactinaemia among the very common adverse events when olanzapine is used, but associated clinical manifestations (e.g., gynecomastia, galactorrhea, and breast enlargement) are rare in adults. In most patients, levels returned to normal ranges without cessation of treatment [58].

On the other side prolactin-raising antipsychotics may increase prolactin concentrations 2 to 10 fold and, most importantly, increase the prevalence of hyperprolactinemia (Fig. 2); this untoward effect is not related to therapeutic efficacy. The extent of the increase is particularly pronounced with risperidone, although it is not a conventional antipsychotic. It has been shown that this drug increases prolactin levels to a significantly higher extent than conventional antipsychotics, such as haloperidol; the increase occurs independently of its dosage form [4 29 59 60 61]; its major metabolite (9-hydroxyrisperidone or paliperidone) seems to be responsible for the prolactin elevation [62].

Neuroimaging data have shown that the effects on prolactin levels depend on dopamine D2 receptor occupancy, the threshold for hyperprolactinemia being about 72% [8 10 63]. Additional evidence supporting the importance of receptor occupancy has been provided by studies in D2 dopamine receptor gene A1 allele carriers, in whom D2 receptor

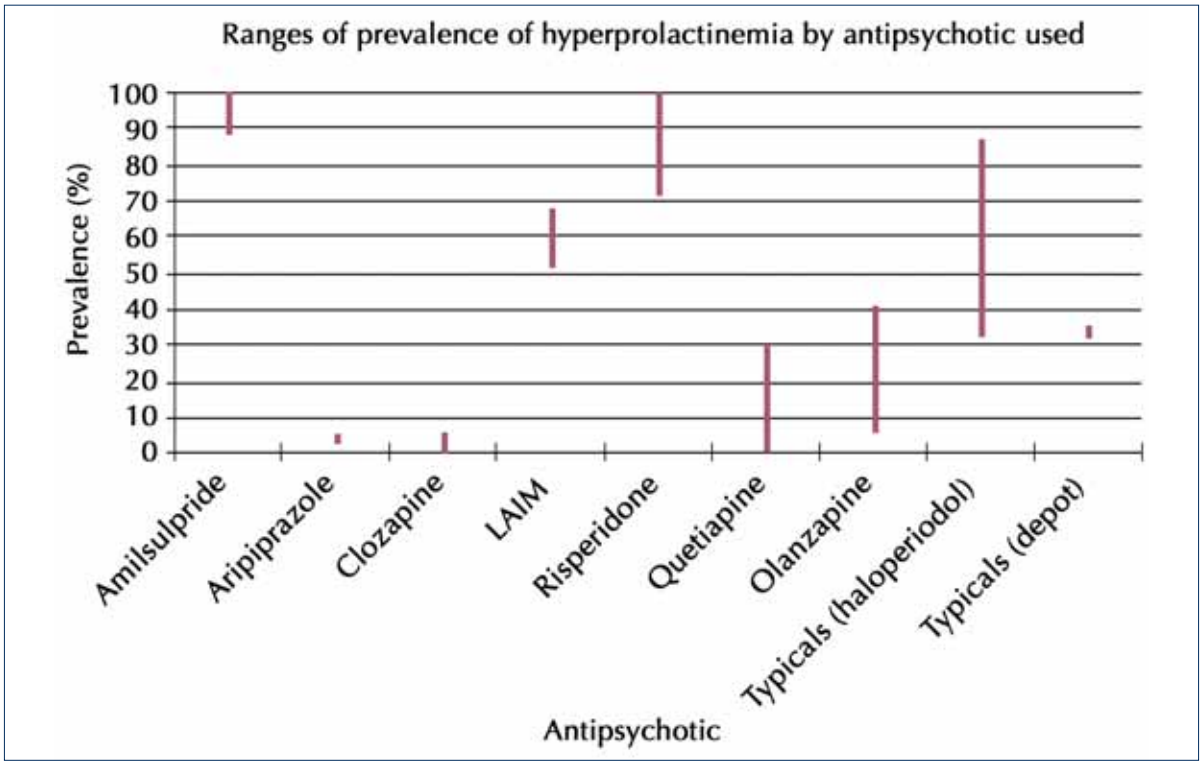


**FIGURE 2**
Ranges of prevalence of hyperprolactinemia by antipsychotic used ordinate: range of prevalence (min-max) of hyperprolactinemia belonging to different studies available in the literature. *Intervalli di prevalenza di iperprolattinemia da antipsicotici utilizzati. Ordinata: intervallo di prevalenza (min-max) di iperprolattinemia in vari studi disponibili in letteratura.*

density is significantly reduced. Prolactin levels are significantly higher in this patient population than in non-carriers and the DRD2 A1 allele can be used as a clinical marker to identify patients at risk of developing hyperprolactinemia [64]. A classical parameter of receptor occupancy is receptor affinity K, which is the concentration of the drug that is required to occupy 50% of receptors after 2 hours of incubation, at equilibrium, with receptor-bearing tissue. The K cut-off value, at which receptor binding is tight and results in hyperprolactinemia, is 1,5 nM (Fig. 2) [65]. It has also been suggested that rapid dissociation from D2 receptors may be an important pharmacological feature that ensures that an antipsychotic compound can exert its therapeutic effects without causing increasing prolactin levels [66].

## The consequences of hyperprolactinemia

In the past, hyperprolactinemia was considered a minor complication of antipsychotic treatment [26] and this approach has not substantially changed nowadays. This is reflected by the fact that more than twice as many papers have been published on "antipsychotics and extrapyramidal symptoms" than on "antipsychotics and hyperprolactinemia" (n = 3984 *vs.* n = 622 – Medline research, October 2009).

In the meantime, it has been ascertained that hyperprolactinemia is associated not only with a number of short-term untoward effects confined mainly to sexual function, which differ in the two sexes, but also with important long-term general effects mostly shared by the two sexes (Table II) [1 13 17 20 65].

### *Short-term consequences*

The sexual disorders in the acute phase are the result of changes in reproductive hormone levels produced by hyperprolactinemia. In the open-label study by Kinon et al. [21] in 396 adult patients with schizophrenia on treatment with prolactin-raising antipsychotics, i.e. conventional antipsychotics or

**TABLE II.**
Untoward effects of hyperprolactinemia. *Effetti collaterali negativi dell'iperprolattinemia.*

| Short-term effects | |
|---|---|
| **Both sexes** | |
| • | Loss of libido |
| • | Galactorrhea |
| **Women** | |
| • | Menstrual disorders (oligomenorrhea, amenorrhea, lutein phase shortening) |
| • | No ovulation (infertility) |
| • | Breast tension |
| • | Orgasmic dysfunction |
| • | Skin disorders (acne and hirsutism) |
| **Men** | |
| • | Impotence |
| • | Ejaculation disorders |
| • | Reduction in spermatogenesis |
| • | Gynecomastia |
| **Long-term effects** | |
| **Both sexes** | |
| • | Osteoporosis |
| • | Weight gain |
| • | Mood changes? |
| **Women** | |
| • | Breast and endometrial cancer? |
| • | Cardiovascular disorders? |

risperidone, hyperprolactinemia was associated with the following significant hormonal changes [21]:

*premenopausal women*

- reduction in estradiol and progesterone in patients using risperidone
- increase in total testosterone

*postmenopausal women*

- reduction in estradiol
- increase in total testosterone in patients using risperidone
- decrease in sex hormone binding globulin

*men*

- reduction in total testosterone in patients using conventional antipsychotics
- reduction in estradiol.

Literature reports a possible direct trending relationship ($p = 0.06$) between increase in prolactin concentrations and increase in the probability of menstrual disorders in premenopausal women, an increase of 1 ng/mL prolactin corresponding to a 1.1% increase in the risk of menstrual disorders. When the effects of the reduction in estrogen concentrations and on the increase in testosterone concentrations were taken into consideration in a composite scale, a significant correlation was found between composite score and menstrual disorders ($p = 0.04$), and an increase in 1 unit corresponding to a 17.5% increase in the risk of menstrual disorder [21].

## Long-term consequences

### Body weight gain

A wealth of studies in animals and in humans shows that prolactin plays an important role in body weight regulation, although the mechanisms whereby this occurs have not been fully elucidated. It is believed that the change in the estrogen-testosterone ratio produced by hyperprolactinemia in the ventral medial and paraventricular nuclei of the hypothalamus increases appetite to abnormal levels [68]. In a cross-sectional study in 227 psychiatric patients who had been treated with psychotropic drugs for at least 6 months, there was a significant correlation between body mass index (BMI) and prolactin levels in male out-patients ($p = 0.03$), but not in male in-patients given a fixed diet, indicating that the cause was an increase in the ingestion of food, not a decrease in energy consumption [68]. In addition, in vitro studies have shown that chronic hyperprolactinemia significantly increases insulin resistance of adipocytes [69]. Consequently, body weight gain and increased insulin resistance induced by hyperprolactinemia might trigger a cascade of events leading to glucose intolerance and, ultimately, diabetes mellitus [70]. Even if this speculation should not prove to be the case, body weight gain induced by hyperprolactinemia should be considered a major long-term complication in young adult patients, as it contributes to obesity, a condition that is notoriously associated with an increased risk of a broad range of medical disorders, as well as an increase in all-cause mortality [71 72].

### Osteoporosis

It is well known that low estrogen levels, such as those induced by hyperprolactinemia, lead to

osteopenia and, ultimately, to osteoporosis. Low estrogen levels increase bone remodelling excessively by activating osteoclasts that are responsible for bone resorption and inhibiting osteoblasts that mediate bone formation; in addition, estrogen may also affect the rate of bone cell apoptosis by increasing the life span of osteoclasts and reducing the life span of osteoblasts [73 74]. Indeed, in women with hyperprolactinemia due to a pituitary adenoma, bone mineral density (BMD) has been found to be reduced by 17% in cortical bone and by 15-30% in trabecular bone. The amenorrhea associated with low estrogen levels is directly correlated to the severity of the reduction in BMD and cortical osteopenia is closely related to the duration of hyperprolactinemia. The phenomenon is not confined to women, as low testosterone levels have similar effects in men [74].

BMD has been measured in patients affected by schizophrenia on treatment with prolactin-raising psychotropic medications in a number of trials. Preliminary cross-sectional trials suggested that BMD, as well as bone speed of sound, is significantly reduced in such patients, but did not provide any conclusive evidence that hyperprolactinemia plays an important role in its development [4].

In particular, Hummer et al. 2005 [33] found a significant reduction in BMD in males ($p < 0.001$) included in their cross-sectional study of 75 in- and outpatients aged 19-50 years that suffered from schizophrenia and had been treated with antipsychotics for at least 1 year. The authors pointed out that there are many other factors that may contribute to a reduction in BMD in schizophrenic patients besides hyperprolactinemia, such as immobility in patients with negative symptoms (which were indeed inversely correlated to BMD $p < 0.04$), cigarette smoking, excessive alcohol consumption, poor nutrition with diet low in calcium and protein, and polydipsia leading to calciuria. According to the literature, high proportions of schizophrenic patients have these risk factors: 85% are smokers, 35 to 65% consume too much alcohol and 10 to 15% suffer from polydipsia that is sufficiently severe to lead to calciuria [74].

Clear cut data providing evidence of the role of hyperprolactinemia in the development of osteoporosis in young women with schizophrenia was provided by O'Keane and Meaney 2005 [16], who carried out a cross sectional comparative trial in 38 premenopausal females with a diagnosis of schizophrenia. The patients were divided into two groups according to treatment with prolactin-raising (n = 26 risperidone, amisulpride, haloperidol, mean ± SD exposure 8.4 ± 4.7 years) or a prolactin-sparing antipsychotic (n = 12 olanzapine, mean ± SD expo-

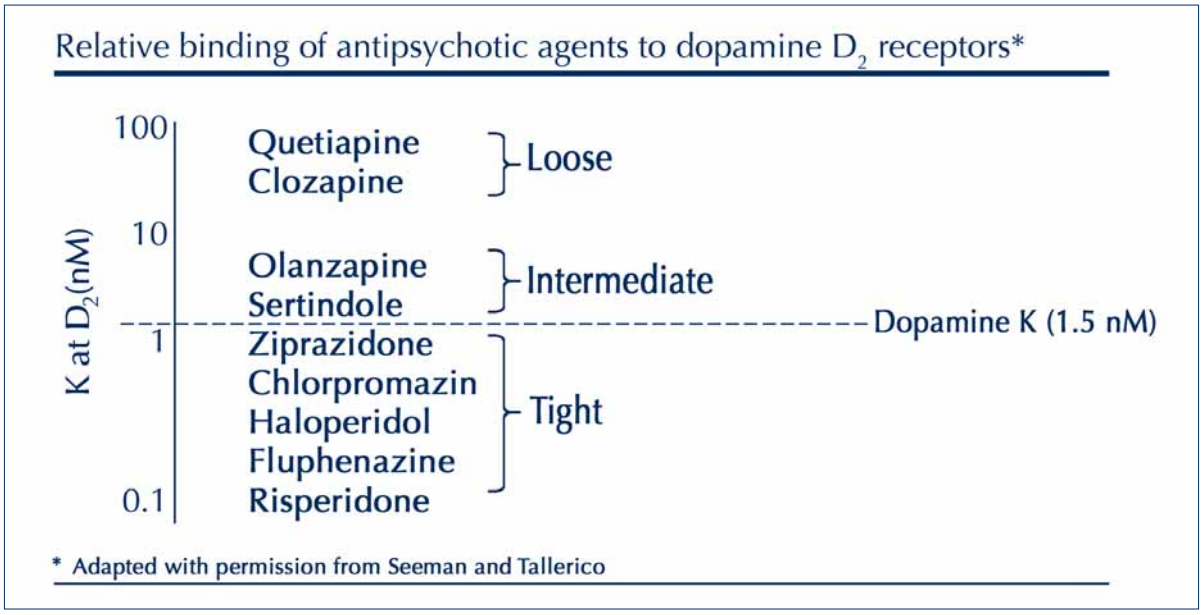


**FIGURE 3**
Proportions of patients with normal, osteopenic and osteoporotic BMD values by treatment. *Percentuali di pazienti con valori BDM normali, osteopenici e osteoporotici.*

sure 6.3 ± 3.8 years). Patients taking concomitant medications and/or with concomitant disorders that were potential confounding factors were excluded and the presence of the other known confounding factors, such as smoking and alcohol intake, were similar in the two groups. Sixty-five percent of the patients in the prolactin-raising group (96% of whom had hyperprolactinemia) had abnormally low BMD values *vs*. 17% patients in the olanzapine group (33% of whom had hyperprolactinemia); all 4 patients with osteoporosis were in the prolactin-raising group (Fig. 2). Prolactin values were predictive of reduced lumbar BMD values ($p = 0.003$) and hyperprolactinemia was significantly associated with low sexual hormone levels (estradiol, progesterone, testosterone) and high FSH levels ($p < 0.05$). Thus, long-term exposure to prolactin-raising antipsychotics is associated with a significant reduction in bone mineral density. Worthy of note is the fact that schizophrenia usually is diagnosed during late adolescence when peak bone mass has not been achieved, so the risk of osteoporosis due to prolactin-raising antipsychotic therapy may actually be higher than the extent of the bone mineral density reduction recorded might suggest. What is more, osteoporosis is a silent disease that does not produce any symptoms until a fracture has actually occurred, so BMD monitoring is mandatory to prevent its complications [16 75].

The high rates of osteoporosis associated with schizophrenia may result from hypogonadism secondary to antipsychotic-induced hyperprolactinemia, and the prolactin-raising profile of antipsychotic drugs should be considered when choosing an antipsychotic drug.

Summary of the mechanisms of hyperprolactinemia:

- hyperprolactinemia reduces BMD via a reduction in estrogen levels;
- low estrogen levels stimulate osteoclasts responsible for bone resorption and inhibit osteoblasts that mediate formation of new bone tissue;
- insufficient estrogen levels reduce mean survival of osteoblasts and increase mean survival of osteoclasts;
- hyperprolactinemia may reduce BMD also via:
  – changes in androgen levels;
  – direct effects on the bone matrix (probably produced by a reduction in calcitonin);
  – direct inhibition of osteoblasts [16].

*Risk of breast and endometrial cancer*

Prolactin increases the rate of spontaneous mammary tumors in mice and promotes the growth of carcinogen-induced mammary tumors in rats. These findings cannot be directly extrapolated to the human species, because the hormonal sensitivity of the tumors differs, but nevertheless, are reason for concern [4]. For this reason a number of investigations have been performed in women with inconclusive results. The strongest evidence has been provided by a retrospective cohort study, comparing 52,819 women exposed to prolactin-raising antipsychotics to 55,289 age-matched women who were not exposed, according to medical prescriptions filled and reimbursed by medical insurance programs in New Jersey (US) in the period 1989-1995 [48]. The incidence of breast cancer in the two groups was established by consulting a mandatory state cancer registry in July 1996. The use of prolactin-raising antipsychotics was associated with a 16% increase in the risk of breast cancer (95% CI of the hazard ratio: 1.07-1.26). The extent of the risk is similar to that associated with estrogens. As prolactin reduces estrogen levels, it is likely that the risk of breast cancer associated with hyperprolactinemia is counterbalanced in young women by the reduction in estrogen levels; obviously this is not the case in postmenopausal women. In view of the modest increase in risk, this finding does not contraindicate the use of prolactin-raising antipsychotics in women, provided that mammograms are performed regularly in female patients with hyperprolactinemia [5 17]. In addition, the agents should not be prescribed to the subgroup of patients with a history of breast cancer, as a few types of human breast carcinomas are sensitive to prolactin [4].

It has been suggested that hyperprolactinemia may also be associated with an increase in the risk of endometrial cancer, as some young women with drug-induced hyperprolactinemia do not ovulate, but nevertheless, produce enough estradiol to stimulate the endometrium. However, no evidence substantiating this speculation is available to date [4].

The comparison of the incidence of adverse events from NIH database has confirmed that risperidone had the highest ratios for hyperprolactinemia (34.9, 90% confidence interval [CI] 32.8-37.1), galactorrhea (19.9, 90% CI 18.6-21.4), and pituitary tumors (18.7, 90% CI 14.9-23.3) when compared with other antipsychotics [76].

The ability of prolactin to induce mitosis and inhibit apoptosis is considered to be a risk factor also for prostate tumors in males [77-79].

*Immune function*

Prolactin has proved to be a compound that stimulates and facilitates immune function. A number of in vitro and in vivo studies have documented that it potentiates lymphocyte functions in B, T and natural killer cells; in addition, antigen-driven clonal expansion and increased antibody production by plasma cells are facilitated by the presence of prolactin. Within the setting of bone marrow transplantation, prolactin promotes hematopoietic and immune recovery, albeit to a lesser extent than major cytokines. On the other hand, in cases of allogeneic bone marrow transplantation, the stimulation of immune function by prolactin may actually be counterproductive, as prolactin levels are significantly higher in patients who develop graft-versus-host disease than in those who do not have this complication. Consequently, the stimulation of immune function by prolactin-raising medications should be borne in mind for the management of patients undergoing transplantation [80].

*Other long-term effects*

Speculations have been made that the long-term reduction in estrogen levels in women may be associated with an increase of cardiovascular risk, but at present no clinical trials have been conducted to verify this hypothesis.

Another speculation is that hyperprolactinemia may have an impact on mood in both sexes either as a consequence of the effects on estrogen and testosterone levels or via a direct effect. Studies in women have shown that hostility, depression and anxiety are more frequent in amenorrheic women with hyperprolactinemia than in amenorrheic women with normal prolactin levels and in women with normal menstrual cycles, as well as in normal women with elevated prolactin levels. These findings support the hypothesis that hyperprolactinemia has an impact on mood, but do not enable us to draw any conclusion on the mechanisms of action [4].

An FDA review of adverse reactions to antipsychotics has disclosed a potential association between potent D2 agonists and pituitary tumors [76].

Furthermore, the possibility of an increase in pituitary volume by 12% following treatment with prolactin-raising antipsychotics for 12 months has been reported [81 82].

## Diagnostic work-up of the patient with hyperprolactinemia

The diagnostic work-up of the patient with hyperprolactinemia on treatment with prolactin-raising antipsychotics should include a complete medical history, including information on menstrual cycles, family history of breast, uterine and prostate cancer, as well as of osteoporosis (especially if the mother experienced a hip fracture) a physical examination and a standard battery of laboratory tests (renal, liver and thyroid function tests plus pregnancy test). If the patient reports headache and visual field defects are detected, magnetic resonance images of the sellar space should be obtained to exclude any space occupying lesion [4]. Particular attention should be taken when concomitant drug use is collected, to determine if any other "prolactin-release-affecting" drug is used, to avoid possible synergistic addenda.

Important information for the differential diagnosis is provided by prolactin values: values > 150 mcg/mL indicate the presence of prolactinoma; values of approximately 100 mcg/mL indicate the presence of a micro- or hypofunctioning prolactinoma, whereas values ranging from 70 to 100 mcg/mL often are due to prolactin-raising pharmacological agents. An additional indication is provided by the presence of a temporal relationship between appearance of hyperprolactinemia symptoms and introduction of prolactin-raising treatment: it usually occurs after about 20 days when the drug is the cause, but the interval may range from 7 to 75 days [1 4 19].

When the patient is on treatment with a pharmacological agent that notoriously causes hyperprolactinemia, prolactin levels are below 80 mcg/mL, the onset of hyperprolactinemic symptoms occurs a few weeks after the introduction of the agent, there are no signs or symptoms that suggest a sellar space-occupying lesion and other laboratory tests are normal, the diagnosis of iatrogenic hyperprolactinemia is likely. However, the only way to make this diagnosis with certainty is to stop treatment with the drug (dechallenge) and verify whether prolactin levels normalize within a few days (oral medication); this is not feasible with depot formulations, whose effects may last months [4].

Prolactin levels should be monitored during treatment with antipsychotics, especially those known to increase prolactin: the prolactin level should be determined before initiation of treatment, together with blood sugar and the lipid profile, after one month of treatment and every three months thereafter. Prolactin levels are to be repeated if the dosage of the antipsychotic is increased or if the patient is switched to a different compound. During therapy, libido, sexual function status, body weight and the menstrual cycle are to be monitored; even modest changes may herald hyperprolactinemia. The use of sexual dysfunction questionnaires is recommended [7 15 83-85].

During prolactin monitoring, in the event of doubtful values, blood sampling should be repeated after at least one hour of rest, before intake of the antipsychotic. Ideally, a cannula should be inserted into the vein and blood should be drawn after 20-30 minutes in order to avoid puncture stress, according to the recommendations of the Pituitary Society.

Patients younger than 25 years of age, in whom bone formation is incomplete, are at risk of osteopenia or even of osteoporosis, especially young women [12 15 16], DEXA (Dual Energy X-ray Absorptiometry) is indicated in patients on treatment with antipsychotics who are older than 65 years of age, report amenorrhea lasting for more than 6 months, have experienced early menopause (< 35 years), have a diagnosis of hypogonadism or have Body Mass Index (BMI) < 19 and a family history of osteoporosis or of spontaneous fractures.

## Treatment

The main objectives of treatment are to restore fertility, normal gonad function and prevent long-term complications, mainly osteoporosis.

Four options are available [1 4 5 7 17]:

- reduction in the dosage of the prolactin-raising agent. This option has the advantage of simplicity, but there is the risk of relapse due to inefficacy on psychotic symptoms;
- switch to a prolactin-sparing agent. This option has the advantage that it may confirm the diagnosis, but it is also associated with the risk of relapse;
- addition of a dopamine agonist. This enables continuation of treatment with an effective prolactin-raising agent when the risk of relapse is high, but is associated with the risk of undesirable effects. In particular, the dopamine agonists that are approved for therapeutic use in this indication (bromocriptine, cabergoline and pergolide) are all ergot-derivatives, which have recently been found to be associated with a high risk of cardiac valvulopathy [86 87]. The studies that revealed this risk assessed the effects of cabergoline and pergolide in patients with Parkinson's disease given higher doses than those used for hyperprolactinemia; the use of these drugs has been restricted by regulatory authorities only in this neurological indication. However, a safe threshold has not been established and continuation of use for hyperprolactinemia is currently a topic for debate. Psychiatrists should implement this option with great caution, on account of the risk of induction or exacerbation of psychotic symptoms due to D2 receptor stimulation;
- addition of hormonal therapy with estrogens and progestogens. Also this therapeutic option is associated with the risk of important undesirable effects, such as an increase in the risk of thrombotic events and of breast cancer.

Thus, none of the current therapeutic options is ideal. At present pure prolactin-receptor antagonists are in development [88], which hopefully will provide a valid alternative.

In any case, patients and their families should be comprehensively informed about the risk of long-term iatrogenic damage produced by prolactin raising antipsychotics, covering osteoporosis, tumors, immune function changes and reduction in fertility, in order to avoid legal complications.

## Conclusions

Hyperprolactinemia is an undesirable effect of conventional antipsychotics and risperidone, while second generation antipsychotics as quetiapine, aripiprazole, clozapine given at therapeutic doses, in the acute as in the long term period use, are not related with a clinically relevant elevation of prolactine for most patients. 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

in order to take preventive measures tailored to the needs of the individual patient, taking into particular consideration the risk-benefit ratio when such therapeutic choice is adopted.

## References


1 Prabhakar VK, Davis JR. *Hyperprolactinaemia* Best Pract Res Clinical Obstet Gynaecol 2008;22:341-53.

2 Halbreich U, Kinon BJ, Gilmore JA, Kahn LS.. *Elevated prolactin levels in patients with schizophrenia: mechanisms and related adverse effects*. Psychoneuroendocrinology 2003;28(Suppl 1):53-67.

3 Halbreich U, Kahn L. *Hyperprolactinemia and schizophrenia: mechanism and clinical aspect*. J Psychiatr Pract 2003;9:344-53.

4 Haddad PM, Wieck A. *Antipsychotic-induced hyperprolactinemia. Mechanisms, clinical features and management.* Drugs 2004;64:2291-314.

5 Byerly M, Suppes T, Tran Q, Baker RA. *Clinical implications of antipsychotic-induced hyperprolactinemia in patiens with schizophrenia spectrum or bipolae spectrum disorders*. J Clin Psychopharmacol 2007;27:639-61.

6 Montejo AL. *Prolactin awarennes: an essential consideration for fisical health in schizophrenia.* Eur Neurophycopharmacol 2008;18:S108-14.

7 Peveler CR et al. *Antipsychoticts and hyperprolactinaemia: clinical recommendations.* J Psychopharmacol 2008;22(Suppl):98-103.

8 Thomasson-Perret N, Penelaud PF, Theron D, Gautteganges S, Mocaer E. *Markers D2 and D3 receptor activity in vivo: PET scan and prolactin*. Therapie 2008;63:237-42.

9 La Torre D, Falorni A. *Pharmacological causes of hyperprolactinaemia*. Ther Clin Risk Manag 2007;3:929-51.

10 Fitzgerald P, Dinan TG. *Prolactin and dopamine: what is the connection? A review article*. J Psychopharmacol 2008;22(Suppl):12-9.

11 Konarzewska B, Wołczyński S, Szulc A, Galińska B, Popławska R, Waszkiewicz N. *Effect of risperidone and olanzapine on reproductive hormones, psychopathology and sexual functioning in male patients with schizophrenia*. Psychoneuroendocrinology 2009;34:129-39.

12 O'Keane V. *Antipsychotic-induced hyperprolactinaemia, hypogonadism and osteoporosis in the treatment of schizophrenia.* J Psychopharmacol 2008;22(Suppl 2):70-5.

13 Holt RI. *Medical causes and consequences of hyperprolactinemia. A context for psychiatrists*. J Psychopharmacol 2008;22(Suppl 2):28-37.

14 Dickson RA, Seeman MV, Corenblum B. *Hormonal side effects in women: typical versus atypical antipsychotic treatment.* J Clin Psychiatry 2000;61(Suppl 3):10-5.

15 Smith SM, O'Keane V, Murray R. *Sexual dysfunction in patients taking conventional antipsychotic medication.* Br J Psychiatry 2002;181:49-55.

16 O'Keane V, Meaney M. *Antipsychotic drugs: a new risk factor for osteoporosis in young women with schizophrenia?* J Clin Psychopharmacol 2005;25:26-31.

17 Bostwick JR, Guthrie SK, Ellingrod VL. *Antipsychotic-induced hyperprolactinemia*. Pharmacotherapy 2008;29:64-73.

18 De Rosa M, Zarrilli S, Di Sarno A, Milano N, Gaccione M, Bossia B, Lombardi G, Colao A. *Hyperprolactinemia in man: clinical and biochimical features and response to treatment*. Endocrine 2003;20:75-82.

19 Verhelst J, Abbs R. *Hyperprolactinaemia, phatophisiology and management*. Treat Endocrinol 2003;2:23-32.

20 Serri O, Chik CL, Ur E, Ezzat S. *Diagnosis and management of hyperprolactinemia*. CMAJ 2003;169:575-81.

21 Kinon B, Gilmore JA, Liu H, Halbreich UM. *Prevalence of hyperprolactinemia in schizophrenia patients treated with conventional antipsychotic medications or risperidone.* Psychoneuroendocrinology 2003;28(Suppl 2):55-68.

22 Montgomery J, Winterbottom E, Jessani M, Kohegyi E, Fulmer J, Seamonds B, Josiassen RC. *Prevalence of hyperprolactinemia in schizophrenia: association with typical and atypical antipsychotic treatment*. J Clin Psychiatry 2004;65:1491-8.

23 Roke Y, van Harten PN, Boot AN, Buitelaar JK. *Antipsychotic medication in children and adolescents: a descriptive review of the effects on prolactin level and associated side effects*. J Child Adol Psychopharcol 2009;19:403-14.

24 Correll CU. *Effect of hyperprolactinaemia during development in child and adolescent*. J Clin Psychiatry 2008:69;24.

25 Lieberman JA, Perkins DO, Jarskog LF. *Neuroprotection: a therapeutic strategy to prevent deterioration associated with schizophrenia*. CNS Spect 2007;12(Suppl):1-13.

26 Kleinberg DL. *Human prolactin: measurement in plasma by vitro bioassay*. J Clin Invest 1971;50:1557-68.

27 Busche C, Shaw M. *Prevalence of hyperprolactinemia in a naturalistic cohort of schizophrenia and bipolar outpatients during treatment with typical and atypical antipsychotics.* J Psychopharmacol 2007;21:768-73.

[28] Molitch ME. *Drugs and prolactin*. Pitutary 2008;11:209-18.

[29] Volavka J, Czobor P, Cooper, TB, Sheitman B, Lindenmayer JP, Citrome L, McEvoy JP, Lieberman JA. *Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol*. J Clin Psychiatry 2004;65:57-61.

[30] Kopecek M, Bares M, Horacek J, Mohr P. *Low-dose risperidone augmentation of antidepressants or anxiolytics is associated with hyperprolactinemia*. Neuro Endocrinol Lett 2006;27:803-6.

[31] Smith S, Wheeler MJ, Murray R. *The effects of antipsychotic induced hyperprolactinemia on the hypothalamic-pituitary-gonadal axis*. J Clin Psychopharmacol 2002;22:109-14.

[32] Meaney AM, Smith S, Howes OD, O'Brien M, Murray RM, O'Keane V. *Effects of long-term prolactin-raising antipsychotic medication on bone mineral density in patients with schizophrenia*. Br J Psychiatry 2004;184:503-8.

[33] Hummer M, Malik P, Gasser RW, Hofer A, Kemmler G, Moncayo Naveda RC, Rettenbacher MA, Fleischhacker WW. *Osteoporosis in patients with schizophrenia*. Am J Psychiatry 2005;162:162-7.

[34] Molitch ME. *Medication-induced hyperprolactinemia*. Mayo Clin Proc 2005;801050-7.

[35] Bushe C, Shaw M, Peveler RC. *A review of the association between antipsychotic use and hyperprolactinaemia*. J Psychopharmacol, 2008;22(Suppl):46-55.

[36] Jakovljevic M, Pivac N, Mihaljevic-Peles A, Mustapic M, Relja M, Ljubicic D, Marcinko D, Muck-Seler D. *The effects of olanzapine and fluphenazine on plasma cortisol, prolactin and muscle rigidity in schizophrenic patients: a double blind study*. Prog Neuropsychopharmacol Biol Psychiatry 2007;31:399-402.

[37] Crockett A, Goldstein M, Bushe C. *How has NICE guidelines affected prescribing in depot clinic schizophrenia outpatients? The Dewsbury experience*. British Association of Psychopharmacology, Summer Meeting 24-27 July, 2005; Harrogate, UK.

[38] Halbreich U, Kahn LS. *Hormonal aspects of schizophrenias: overview*. Psychoneuroendocrinology 2003;28(Suppl):1-16.

[39] Kopecek M, Bares M, Svarc J, Dockery C, Horácek J. *Hyperprolactinemia after low dose of amisulpride*. Neuro Endocrinol 2004;25:419-22.

[40] Paparrigopoulos T, Liappas J, Tzavellas E, Mouriklis I, Soldatos C. *Amisulpride-induced hyperprolactinemia is reversible following discontinuation*. Prog Neuro-Psychopharmacol Biol Psychiatry 2007;31:92-6.

[41] Melkersson K. *Differences in prolactin elevation and related symptoms of atypical antipsychotics in schizophrenic patients*. J Clin Psychiatry 2005;66:761-7.

[42] Schooler N, Rabinowitz J, Davidson M, Emsley R, Harvey P, Kopala L, McGorry PD, Van Hove I, Eerdekens M, Swyzen W, De Smedt G. *Early Psychosis Global Working Group. Risperidone and haloperidol in first-episode psychosis: a long-term randomized trial*. Am J Psychiatry 2005;162:947-53.

[43] Kopecek M, Bares M, Horacek J, Mohr P. *Low-dose risperidone augmentation of antidepressants or anxiolytics is associated with hyperprolactinemia*. Neuro Endocrinol Lett 2006;27:803-6.

[44] Lee BH, Kin YK. *The relationship between prolactin response and clinical efficacy of risperidone in acute psychotic inpatients*. Prog Neuropsychopharmacol Biol Psychiatry 2006;30:658-62.

[45] Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, Stringfellow J, Ingenito G, Marder SR. *Aripiprazole, an antipsychotic with a novel mechanism of action, and risperidone vs. placebo in patients with schizophrenia and schizoaffective disorder*. Arch Gen Psychiatry 2003;60:681-90.

[46] Chue P, Eerdekens M, Augustyns I, Lachaux B, Molcan P, Eriksson L, Pretorius H, David AS. *Comparative efficacy and safety of long-acting risperidone and risperidone oral tablets*. Eur Neuropsychopharmacol 2005;15:111-7.

[47] Tran PV, Hamilton SH, Kuntz AJ, Potvin JH, Andersen SW, Beasley AJ et al. *Double-blind comparison of olanzapine versus risperidone in the treatment of schizophrenia and other psychotic disorders*. J Clin Psychopharmacol 1997;17:407-18.

[48] Wang PS, Walker AM, Tsuang MT, Orav EJ, Glynn RJ, Levin R, Avorn J. *Dopamine antagonists and the development of breast cancer*. Arch Gen Psychiatry 2002;59:1147-54.

[49] Bushe C, Yeomans D, Floyd T, Smith S. *Categorical prevalence and severity of hyperprolactinaemia in two UK cohorts of patients with severe mental illness during treatment with typical and atypical antipsychotics*. J Psychopharmacol 2008;22(Suppl):56-62.

[50] Crawford AM, Beasley CM Jr, Tollefson GD. *The acute and long term effect of olanzapine compared with placebo and haloperidol on serum prolactin concentrations*. Schizophr Res 1997;26:41-54.

[51] Wong J, Seeman MV. *Prolactin, menstrual irregularities, quality of life*. Schizophr Res 2007;91:270-1.

[52] Kohen D, Wildgust HJ. *The evolution of hyperprolactinemia as an entity in psychiatric patients*. J Psychopharmacol 2008;22(Suppl):6-11.

[53] Potkin SG, Saha AR, Kujawa MJ, Carson WH, Ali M, Stock E, Stringfellow J, Ingenito G, Marder SR. *Aripiprazole, an antipsychotic with a novel mechanism*

*of action, and risperidone vs. placebo in patients with schizophrenia and schizoaffective disorder*. Arch Gen Psychiatry 2003;60:681-90.

54 Pigott TA, Carson WH, Saha AR, Torbeyns AF, Stock EG, Ingenito GG. *Aripiprazole for the prevention of relapse in stabilised patients with chronic schizophrenia - a placebo-controlled 26 week study*. J Clin Psychiatry 2003;64:1048-56.

55 Abilify SpC: http://www.emea.europa.eu/humandocs/PDFs/EPAR/abilify/H-471-PI-en.pdf

56 Clozaril SpC: http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=1277

57 Seroquel SpC: http://emc.medicines.org.uk/emc/assets/c/html/DisplayDoc.asp?DocumentID=2295

58 Zyprexa SpC: http://www.emea.europa.eu/humandocs/Humans/EPAR/zyprexa/zyprexa.htm/H-115-PI-EN[1].pdf

59 Schlösser R, Gründer G, Anghelescu I, Hillert A, Ewald-Gründer S, Hiemke C, Benkert O. *Long-term effects of the substituted benzamide derivative amisulpride on baseline and stimulated prolactin levels*. Neuropsychobiology 200;46:33-40.

60 Marder SR, McQuade RD, Stock E, Kaplita S, Marcus R, Safferman AZ, Saha A, Ali M, Iwamoto T. *Aripiprazole in the treatment of schizophrenia: safety and tolerability in short-term, placebo-controlled trials*. Schizophr Res 2003;61:123-36.

61 Svestka J, Synek O, Tomanová J, Rodáková I, Cejpková A. *Differences in the effect of second-generation antipsychotics on prolactinaemia: six weeks open-label trial in female in-patients*. Neuro Endocrinol Lett 2007;28:881-8.

62 Knegtering R, Baselmans P, Castelein S, Bosker F, Bruggeman R, van den Bosch RJ. *Predominant role of the 9-hydroxy metabolite of risperidone in elevating blood prolactin levels*. Am J Psychiatry 2005;162:1010-2.

63 Kapur S, Zipursky R, Jones C, Remington G, Houle S. *Relationship between dopamine D(2) occupancy, clinical response and side effects: a double-blind PET study of first-episode schizophrenia*. Am J Psychiatry 2000;157:514-20.

64 Young R, Lawford B, Barnes M, Burton SC, Ritchie T, Ward WK, Noble EP. *Prolactin levels in antipsychotic treatment of patients with schizophrenia carrying the DRD2*A1 allele*. Br J Psychiatry 2004;185:147-51.

65 Maguire GA. *Prolactin elevation with antipsychotic medications: mechanism of action and clinical consequences*. J Clin Psychiatry 2002;63(Suppl):56-62.

66 Kapur S, Seeman P. *Does fast dissociation from the dopamine d(2) receptor explain the action of atypical antipsychotics? A new hypothesis*. Am J Psychiatry 2001;158:360-9.

67 Kinon BJ, Gilmore JA, Blake DS, Dean RA, Liu H. *Preliminary exploration of the prevalence of hyperprolactinemia and reproductive hormone reduction during antipsychotic drug treatment*. International Congress on Schizophrenia research (ICSR), Whistler, British Columbia (Canada), 4/28-5/2/2001.

68 Baptista T, Lacruz A, Meza T, Contreras Q, Delgado C, Mejias MA, Hernandez L. *Antipsychotic drugs and obesity: is prolactin involved?* Can J Psychiatry 2001;46:829-34.

69 Cabrera R, Mayor P, Fernández-Ruiz J, Calle C. *Insulin binding and action on adipocytes from female rats with experimentally induced chronic hyperprolactinemia*. Mol Cell Endocrinol 1988;58:167-73.

70 McIntyre RS, McCann SM, Kennedy SH. *Antipsychotic metabolic effects: weight gain, diabetes mellitus and lipid abnormalities*. Can J Psychiatry 2001;46:273-81.

71 National Institutes of Health; National Heart, Lung and Blood Institute Obesity Task Force. *Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults – the evidence report*. Obes Res 1998;6(Suppl 2):S51-209.

72 Manson JE, Willett WC, Stampfer MJ, Colditz GA, Hunter DJ, Hankinson SE, Hennekens CH, Speizer FE. *Body weight and mortality among women*. N Engl J Med 1995;333:677-85.

73 Stubbs B. *Antipsychotic-induced hyperprolactinaemia in patients with schizophrenia: consideration in relation to bone mass density*. J Psych Ment Heart Nurs 2009;16:838-42.

74 Naidoo U, Goff DC, Klibanski A. *Hyperprolactinemia and bone mineral density: the potential impact of antipsychotic agents*. Psychoneuroendocrinology 2003;28,97-108.

75 Rey-Sanchez P, Lavado-Garcia J et al. *Ultrasone bone mass in schizophrenic patients on antipsychotic therapy*. Hum Psychopharmacol. Clin Exp 2009;24:49-54.

76 Szarfman A, Tonning JM, Levine JG, Doraiswamy PM. *Atypical antipsychotics and pituitary tumors: a pharmacovigilance study*. Pharmacotherapy 2006;26:748-58.

77 Vonderhaar BK. *Prolactin: the forgotten hormone of human breast cancer*. Pharmacol Ther 1998;79:169-78.

78 Das R, Vonderhaar BK. *Prolactin as a mitogen in mammary cells*. J Mammary Gland Biol Neoplasia 1997;2:29-39.

[79] Perks CM, Keith AJ, Goodhew KL, Savage PB, Winters ZE, Holly JM. *Prolactin acts as a potent survival factor for human breast cancer cell lines*. Br J Cancer 2004;91:305-11.

[80] Foley K, Kast RE. *Review of evidence that post-transplantation psychiatric treatment commonly affects prolactin levels and thereby influences graft fate*. Gen Hosp Psychiatry 2006;28:230-33.

[81] Kane JM, Meltzer HY, Carson WH, McQuade RD, Marcus RN, Sanchez R, Aripiprazole Study Group. *Aripiprazole for treatment resistant schizophrenia: results of a multicenter randomized double-blind comparison study versus perphenazine*. J Clin Psychiatry 2007;68:213–23.

[82] MacMaster FP, El-Sheikh R, Upadhyaya AR, Nutsche J, Rosenberg DR, Keshavan, M. *Effect of antipsychotics on pituitary gland volume in treatment-naïve first-episode schizophrenia: a pilot study*. Schizophr Res 2007;92:207-10.

[83] Citrome L. *Current guidelines and their recommendations for prolactin monitoring in psychosis*. J Psychopharmacology 2008;22(Suppl):90-7.

[84] McGahuey CA, Gelenberg AJ, Laukes CA, Moreno FA, Delgado PL, McKnight KM, Manber R. *The Arizona Sexual Experience Scale (ASEX): reliability and validity*. J Sex Marital Ther 2000;26:25-40.

[85] Lingjaerde O, Ahlfors UG, Bech P, Dencker SJ, Elgen K. *The UKU side effect rating scale. A new comprehensive rating scale for psychotropic drugs and a cross-sectional study of side effects in neuroleptic-treated patients*. Acta Psychiatr Scand Suppl 1987;334:1-100.

[86] Schade R, Andersohn F, Suissa S, Haverkamp W, Garbe E. *Dopamine agonists and the risk of cardiac valve regurgitation*. N Engl J Med 2007;356:29-38.

[87] Zanettini R, Antonini A, Gatto G, Gentile R, Tesei S, Pezzoli G. *Valvular heart disease and the use of dopamine agonists for Parkinson's disease*. N Engl J Med 2007;356:39-46.

[88] Goffin V, Touraine P, Culler MD, Kelly PA. *Drug insight: prolactin-receptor antagonists, a novel approach to treatment of unresolved systemic and local hyperprolactinemia?* Nature Clinical Practice Endocrin Metab 2006;2:571-81.

[89] British Columbia Schizophrenia Society. *Basic Facts About Schizophrenia*. 9th edition, April 2001 (http://www.mentalhealth.com/book/p40-sc02.html).