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REVIEW ARTICLE

The Effects of Novel and Newly Approved Antipsychotics on Serum Prolactin Levels: A Comprehensive Review

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Abstract Since the 1970s, clinicians have increasingly become more familiar with hyperprolactinemia (HPRL) as a common adverse effect of antipsychotic medication, which remains the cornerstone of pharmacological treatment for patients with schizophrenia. Although treatment with second-generation antipsychotics (SGAs) as a group is, compared with use of the first-generation antipsychotics, associated with lower prolactin (PRL) plasma levels, the detailed effects on plasma PRL levels for each of these compounds in reports often remain incomplete or inaccurate. Moreover, at this moment, no review has been published about the effect of the newly approved antipsychotics asenapine, iloperidone and lurasidone on PRL levels. The objective of this review is to describe PRL physiology; PRL measurement; diagnosis, causes, consequences and mechanisms of HPRL; incidence figures of (new-onset) HPRL with SGAs and newly approved antipsychotics in adolescent and adult patients; and revisit lingering questions regarding this hormone. A literature search, using the MEDLINE database (1966–December 2013), was conducted to identify relevant publications to report on the state of the art of HPRL and to summarize the available evidence with respect to the propensity of the SGAs and the newly approved antipsychotics to elevate PRL levels. Our review shows that although HPRL usually is defined as a sustained level of PRL above the laboratory upper limit of normal, limit values show some degree of variability in clinical reports, making the interpretation and comparison of data across studies difficult. Moreover, many reports do not provide much or any data detailing the measurement of PRL. Although the highest rates of HPRL are consistently reported in association with amisulpride, risperidone and paliperidone, while aripiprazole and quetiapine have the most favorable profile with respect to this outcome, all SGAs can induce PRL elevations, especially at the beginning of treatment, and have the potential to cause new-onset HPRL. Considering the PRL-elevating propensity of the newly approved antipsychotics, evidence seems to indicate these agents have a PRL profile comparable to that of clozapine (asenapine and iloperidone), ziprasidone and olanzapine (lurasidone). PRL elevations with antipsychotic medication generally are dose dependant. However, antipsychotics having a high potential for PRL elevation (amisulpride, risperidone and paliperidone) can have a profound impact on PRL levels even at relatively low doses, while PRL levels with antipsychotics having a minimal effect on PRL, in most cases, can remain unchanged (quetiapine) or reduce (aripiprazole) over all dosages. Although tolerance and decreases in PRL values after long-term administration of PRL-elevating antipsychotics can occur, the elevations, in most cases, remain above the upper limit of normal. PRL profiles of antipsychotics in children and adolescents seem to be the same as in adults. The hyperprolactinemic effects of antipsychotic medication are mostly correlated with their affinity for dopamine D2 receptors at the level of the anterior pituitary lactotrophs (and probably other neurotransmitter mechanisms) and their blood–brain barrier penetrating capability. Even though antipsychotics are the most common cause of pharmacologically induced HPRL, recent research has shown that HPRL can be pre-existing in a substantial portion of antipsychotic-naïve patients with first-episode psychosis or at-risk mental state.

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1 Prolactin (PRL)

Prolactin (PRL) (Lat. pro = for; lac, gen. lactis = milk), also called lactotrophin hormone, is a polypeptide hormone that is mainly synthesized and secreted in a pulsatile manner (with around 10 peaks per day in young adults) from lactotroph cells of the anterior lobe of the pituitary gland (i.e., the adenohypophysis) [1–6]. These cells comprise between 20 and 50 % of the cellular population of the gland [4, 5], with those in the more inner zones being more responsive to dopamine, a neurotransmitter playing a pivotal role in the regulation of PRL secretion. Lactotroph cells in the outer zone are more responsive to thyroid-releasing hormones, one of the other substances playing a role in PRL secretion [5]. However, although PRL is typically thought of as a pituitary-derived hormone, PRL secretion is not restricted to the pituitary gland [7]. Other organs and tissues in the body also produce PRL, including the hypothalamus, telencephalon, brain stem, spinal cord, choroid plexus, mammary gland, some immune cells and circumventricular organs [8, 9].

Prolactin, discovered more than 80 years ago [8], is composed of 199 amino acids, having a molecular weight of about 23 kDa [4–6, 8, 10–12]. It has been found to be involved in over 300 separate functions, which can be divided into the following categories: reproduction, water and electrolyte balance, growth and development, endocrinology and metabolism, brain and behavior and immunoregulation [12–14]. Its main physiological functions include the induction and maintenance of milk production, breast enlargement during pregnancy, inhibition of hypothalamic gonadotrophin-releasing hormone, and maintenance of proper ovarian function and of progesterone-secreting structures [3, 6, 12, 15–17]. Despite the fact that almost 300 functions could be identified for this hormone in various species, the question remains open as to which of them are really relevant in humans [8, 18].

2 Physiology

A large variety of stimuli, provided by the environment and the internal milieu (exercise, suckling, stress, sleep, meals, sexual intercourse, levels of ovarian steroids, etc.), are involved in the fine balance of stimulation and inhibition of PRL release. The secretion of PRL is under complex control of peptide and steroid hormones and neurotransmitters, which act as inhibitory [PRL-inhibiting factors (PIFs)] or stimulatory [PRL-releasing factors (PRFs)] factors by a direct effect on the lactotroph cells or by indirect pathways (modulators or indirect regulators) [17, 19–21].

The periventricular (periventricular nucleus and arcuate nucleus) and the medial (paraventricular nucleus and supraoptic nucleus) hypothalamic subdivisions are the major regions associated with PRL homeostatis [17, 19]. In the context of this review, two neurotransmitters are important to discuss: dopamine and serotonin (5-HT).

2.1 Role of Dopamine in PRL Secretion

Dopamine is the most important hypothalamic PIF [4]. It exerts a tonic inhibition on PRL secretion, mainly via two pathways: the tuberoinfundibular dopaminergic (TIDA) system and the tuberohypophysial tract [4, 17, 19–21]. The TIDA system, consisting of a population of dopaminergic neurons found in the arcuate nucleus of the hypothalamus, is the most important in regulating PRL release in humans. These dopaminergic neurons release dopamine into the perivascular spaces of the medial eminence. From here, dopamine is subsequently transported via long portal vessels to the anterior lobe of the pituitary [4, 17, 19–22]. The other inhibitory dopamine pathway, the tuberohypophysial tract, also originates in the arcuate nucleus and projects to the intermediary and posterior pituitary, and dopamine, released in the blood, reaches the lactotroph cells via the short portal vessels [4, 19, 21]. Dopamine binds to the dopamine D2 receptors (D2R) on the membrane of the lactotroph cells. D2R stimulation inhibits the PRL gene transcription, synthesis and release of PRL as well as lactotroph proliferation [4, 6, 11, 13, 17, 19, 21, 23–25]. The TIDA network is partially regulated by an autocrine negative feedback by PRL on its own release. An increase in circulating PRL levels results in higher activity of TIDA neurons, whereas a decrease in circulating PRL levels lowers their activity [4, 17]. As such, PRL regulates its own release by acting directly on the hypothalamic dopaminergic neurons, probably through regulating the activity of tyrosine hydroxylase, the rate-limiting enzyme in dopamine synthesis [4, 22].

A blockade of D2R counteracts the tonic inhibitory effect on the PRL secretion [26]. Inhibition of the dopamine transmission, especially through D2R blockade on the lactotroph cells, results in disinhibition of PRL secretion: the stronger the dopamine blockade, the higher the PRL elevation [27]. Antipsychotics have a D2-blocking effect and can therefore elevate the secretion of PRL [28, 29]. Conversely, dopamine agonists (e.g., bromocriptine) suppress PRL secretion [23].

2.2 Role of Serotonin in PRL Secretion

While hyperprolactinemia (HPRL) is well recognized in relation to antipsychotic medication and its antidopaminergic activity, there is relatively little awareness of the impact of substances interfering with serotonergic neurotransmission on the PRL levels [21].

Drugs that increase extracellular levels of 5-HT or are direct agonists of 5-HT receptors elicit PRL secretion, and blocking 5-HT synthesis or transmission results in blunted PRL release [30–33].

5-HT has a stimulatory role in PRL secretion through a complex, multi-level action on both the hypothalamus and the pituitary [4]. Although some research has demonstrated a direct prosecretory effect on the anterior pituitary cells [34], 5-HT is an indirect modulator of PRL secretion, with the hypothalamus as its predominant site of action, where several 5-HT receptors types have been found to play a role in PRL secretion [17, 19, 21, 35, 36].

The serotonergic pathways involved in the regulation of PRL secretion originate from cells in the dorsal raphe nucleus and terminate in the paraventricular nucleus of the hypothalamus, exerting their action via 5-HT1A and 5-HT2A/C receptors (5-HT2A/CR) [21, 35, 37]. The paraventricular nucleus contains cells producing oxytocin and vasoactive intestinal peptide (VIP), both considered to be PRFs [21]. The 5-HT-mediated PRL increase is probably mediated via stimulation of PRFs, of which oxytocin and VIP are the best studied [17, 21]. The oxytocin cells project to the posterior lobe of the pituitary, and oxytocin reaches the anterior pituitary via portal vessels as well as through the systemic circulation, and stimulates the lactotrophs via their oxytocin receptors, causing PRL release [38, 39]. The VIP cells project to the anterior pituitary, where VIP binds to the receptor on the lactotroph cell membrane, stimulating PRL release [40]. Moreover, VIP may also be produced in the pituitary itself, stimulating PRL release by autocrine and paracrine mechanisms [17]. Furthermore, animal studies suggest a link between oxytocin and VIP action on PRL release [41]. Although pharmacological and anatomic data indicate that the paraventricular nucleus represents a major regulating site of 5-HT-induced PRL release, ablation of the paraventricular nucleus does not entirely abolish the PRL response to 5-HT agonists, demonstrating that other pathways also contribute to 5-HT-induced PRL release [42, 43]. An alternate path for 5-HT-induced PRL release is inhibition of the TIDA dopamine cells. However, there is little synaptic contact between 5-HT fibers and TIDA cells, indicating that if direct inhibition of dopamine cells occurs by 5-HT, it is through volume transmission of 5-HT in this region [44]. There is more direct evidence for 5-HT stimulation of GABA-ergic neurons in the vicinity of TIDA cells. Stimulation of these GABA-ergic interneurons will result in an inhibition of TIDA neurons, releasing the tonic inhibition of PRL secretion [17, 21, 45].

2.3 Role of Other Substances in PRL Secretion

As already indicated above, PRL secretion is under the complex control of peptide and steroid hormones and neurotransmitters, which can act as inhibitory or stimulatory factors. Somatostatin, acetylcholine, endothelins, norepinephrine, growth hormone, etc. are identified as PIFs. Thyrotropin-releasing hormone (TRH) as well as angiotensin II, vasopressin, galanin, etc. stimulate PRL secretion [17, 19, 21, 46]. Estrogen is a physiological regulator of PRL synthesis in pituitary lactotroph cells [47, 48]. Estrogens can increase PRL secretion in different ways: through an augmentation of the number of PRL-secreting lactotroph cells in the pituitary gland; through an elevation of the sensitivity to TRH; through a decrease in the number of pituitary dopamine receptors; and through an upregulation of the expression of the PRL receptor gene [6, 30]. Veselinović et al. [49] showed that estrogen treatment in healthy volunteers sensitizes women for PRL-elevating properties of antipsychotic medication. It is also known that ghrelin, a peptide hormone involved in metabolic homeostasis, stimulates PRL secretion, most probably by a direct action on the pituitary somatomammotroph cells (progenitor cells of lactotroph cells that can produce both PRL and growth hormone) [50–52]. A relatively large body of evidence has shown that tachykinins can modify the secretion of PRL in a rather complex fashion, having a stimulatory effect at the pituitary level, but in some circumstances (via modulating hypothalamic dopamine release) also an inhibitory one [4]. Finally, there is some evidence to suggest that endogenous opioids play an important role in regulating PRL secretion, especially in relation to stressful stimuli. Most stressful stimuli lead to a reduction in the activity of TIDA neurons through activation of inhibitory neuronal pathways, with a consequent increase in PRL secretion [4].

3 Diagnosis of Hyperprolactinemia (HPRL)

3.1 Normal and Elevated PRL Values

Normal serum concentration of PRL varies with sex [11, 16, 53]. Hence, normal PRL levels for men and women are different, with ranges of 10–20 and 10–25 ng/ml, respectively [54, 55]. There are also marked interindividual differences; normal PRL serum levels differ appreciably from one individual to another [17, 46, 56, 57]. Serum PRL also displays pronounced circadian variations (up to four times), with maximal concentrations occurring during sleep [5, 11, 12, 15, 16, 53, 56], with a peak of up to 30 ng/ml [5, 6] between 4 a.m. and 6 a.m. [6, 55], reaching a nadir during waking hours [5]. During sleep, PRL secretion is highest during REM sleep. PRL levels are also subject to seasonal changes (higher in the spring and summer) [5, 58, 59]. An increased release of PRL occurs during pregnancy (up to a maximum of 200 ng/ml) and breastfeeding (up to a

maximum of 300 ng/ml) [6, 15, 16, 23, 46]. Although PRL is not commonly recognized as a hormone which changes significantly within the menstrual cycle or after menopause, it has been found that PRL levels vary significantly throughout the menstrual cycle [60]. These levels are higher during the menstrual mid-cycle (particularly the second half of the cycle) [61], compared with follicular and luteal phases. It also varies significantly between pre- and postmenopausal women (higher in premenopausal women) [60]. Therefore, the utility and accuracy of PRL testing may be improved by applying specific reference intervals for each phase of the menstrual cycle, with the recommendation that PRL levels should only be measured in the follicular phase, well before the mid-cycle [60]. Whether there is a change in PRL with the onset of menopause remains controversial. In healthy normoprolactinemic subjects, both increases and decreases in PRL have been reported [62]. Finally, serum PRL rises after exercise, meals, sexual intercourse, minor surgical procedures, general anesthesia, acute myocardial infarction, an epileptic seizure (including after electroconvulsive therapy) and other forms of acute stress [5, 6, 55, 61]. Interestingly, several recent studies reported that current and ex-cigarette smokers on antipsychotic medication have significantly lower mean PRL levels, compared with nonsmokers [63–65]. It is known that cigarette smoking is a potent inducer of the hepatic cytochrome P450 1A2 enzyme, and smoking may therefore result in a reduction of serum concentration of some antipsychotic drugs, which may, in turn, result in lower PRL levels [63]. However, further studies are needed to elucidate the underlying mechanism(s) [63, 64].

Hyperprolactinemia is usually simply defined as a sustained level of PRL above the laboratory upper level of normal [5, 66, 67]. However, *pathological* HPRL has to be defined as sustained circulating PRL levels above normal range in conditions other than, for example, pregnancy and lactation, when *physiological* HPRL occurs [8]. Although the clinician/researcher needs to be aware that laboratory ranges may differ between sites [67], in most laboratories and according to the most recent and more conservative reports, the upper limits for PRL serum concentrations are set at 20 ng/ml for men and 24–25 ng/ml for non-pregnant, non-nursing women [68]. Therefore, HPRL is usually defined as fasting levels at least 2 h after waking above 20 ng/ml in men, and above 25 ng/ml in women [20]. However, these limit values show some degree of variability in clinical trial reports (or, in many reports, are simply are not stated), making the interpretation and comparison of data across studies difficult. Reviewing numerous studies, we see that limit values are set between 11 ng/ml (for men) and 50 ng/ml (for women) (see Table 1). Some laboratories also give different ranges for pre- or postmenopausal women.

Prolactin-secreting pituitary adenomas (prolactinomas) (about 40 % of pituitary tumors produce PRL) [6] are the most common cause of PRL levels greater than 100 ng/ml. Thus, pituitary tumors are an important consideration for antipsychotic-treated patients with levels above 95–118 ng/ml [67, 115]. PRL levels above 200 ng/ml almost always indicate the presence of a lactotroph adenoma [55]. PRL concentration also correlates with tumor size [5, 116]. A serum PRL level >200–250 ng/ml is usually due to a macroadenoma (>1 cm in diameter), rather than a microadenoma (<1 cm diameter) [116, 117]. In the event of a macroprolactinoma, the PRL concentration can even rise to values as high as 35,000 ng/ml (see Table 2). However, it is important to note that PRL is not a perfect tumor marker. There have been reports of tumor growth of lactotroph cells in the absence of increasing PRL levels [116–118]. Therefore, the monitoring of PRL levels alone is not adequate to exclude an expanding tumor mass [116]. Moreover, PRL-producing tumors exist "silently" (a clinically insignificant adenoma) in up to 5–10 % of the adult population [119]. Elevated PRL levels, but <100 ng/ml, are most commonly due to a medication effect [55], although increases beyond 300 ng/ml with an antipsychotic medication have been reported [67, 115].

Although some case reports have noted the resolution of prolactinoma after switching from a "PRL-raising" to a "PRL-sparing" antipsychotic [120, 121], and some studies suggest that certain "PRL-raising" antipsychotics may have a causal relationship with pituitary adenoma [122], this issue remains controversial [123]. No literature exists that establishes a causal relationship between antipsychotics and pituitary tumors, or demonstrates that HPRL can cause a pituitary adenoma, including in normal physiological states of HPRL, such as pregnancy [124]. Moreover, investigation and reporting biases may have influenced the disproportional reporting of pituitary tumor in patients on "PRL-raising" antipsychotics [125]. As there are no prospective studies or randomized trials available, this area needs further research.

Values that fall within the interval of high PRL levels can bring about clinically significant symptoms [23]. Serri et al. [126] provide some rules of thumb regarding PRL levels and clinical presentations in premenopausal women: marked PRL excess (>100 ng/ml) is commonly associated with hypogonadism, galactorrhea and amenorrhea; moderate PRL excess (51–75 ng/ml) is associated with oligomenorrhea; mild PRL excess (31–50 ng/ml) is associated with short luteal phase, decreased libido and infertility. These breakpoints help to place some of the more commonly observed elevations in plasma PRL in clinical perspective [55]. However, increased PRL levels can occur without clinical symptoms [127]. Although it has been suggested that increased PRL levels are believed to be responsible for

Table 1 Hyperprolactinemia values according to different studies in patients receiving antipsychotic treatment [14, 20, 69–114]

Study	Hyperprolactinemia values
Tsuboi et al. [69]	>18.77 ng/ml (men)
	>24.20 ng/ml (women)
Geller et al. [70]	>27 ng/ml
Citrome et al. [71]	>17.7 ng/ml (men)
	>29.2 ng/ml (women)
Kikuchi et al. [72]	>20 ng/ml (men)
	>25 ng/ml (women)
Nagai et al. [73]	>12.8 ng/ml (men + postmenopausal women)
	>30.5 ng/ml (fertile women)
Pérez-Iglesias et al. [74]	>17.7 ng/ml (men)
	>29.2 ng/ml (women)
Sugawara et al. [75]	>13.69 ng/ml (men)
	>29.32 ng/ml (premenopausal women)
	>15.39 ng/ml (postmenopausal women)
Grootens et al. [76]	>18 ng/ml (men)
	>25 ng/ml (women)
Li et al. [77]	>25 ng/ml (men)
	>35 ng/ml (women)
Gopal et al. [78]	>18 ng/ml (men)
	>30 ng/ml (women)
Aston et al. [79]	>15.2 ng/ml (men)
	>23.3 ng/ml (women)
Arakawa et al. [80]	>12.8 ng/ml (men)
Bushe et al. [81]	>18.77 ng/ml (men)
	>24.2 ng/ml (women)
Citrome et al. [82]	>18.8 ng/ml (men)
	>24.2 ng/ml (women)
Kwon et al. [83]	>23 ng/ml
Kryzhanovskaya et al. [84]	>11 ng/ml (men)
	>20 ng/ml (women)
Kim et al. [85]	>20 ng/ml
Byerly et al. [86]	>18 ng/ml (men)
	>29 ng/ml (non-lactating women)
Konarzewska et al. [87]	>17.7 ng/ml
Liu-Seifert et al. [88]	>18.77 ng/ml (men)
	>24.2 ng/ml (women)
Van Bruggen et al. [89]	≥15 ng/ml (men)
	≥22 ng/ml (women)
Tschoner et al. [90]	>20 ng/ml (men)
	>25 ng/ml (women)
Meltzer et al. [91]	>18.77 ng/ml (men)
	>24.20 ng/ml (women)
Emsley et al. [92]	>18.77 ng/ml (men)
	>24.20 ng/ml (women)
Kahn et al. [93]	>18 ng/ml (men)
	>25 ng/ml (women)
Lu et al. [94]	>25 ng/ml (women)
Hanssens et al. [95]	>18.8 ng/ml (men)
	>24.2 ng/ml (women)
Yuan et al. [96]	>20 ng/ml (men)
	>25 ng/ml (women)
Kishimoto et al. [97]	>12.78 ng/ml
Howes et al. [98]	>14.4 ng/ml
Kinon et al. [99]	>18.8 ng/ml (men)
	>24.2 ng/ml (women)
Goffin et al. [14]	>25 ng/ml
Kelly and Conley [100]	≥18 ng/ml (men and women)
Schooler et al. [101]	>18 ng/ml (men)
	>25 ng/ml (women)
Volavka et al. [102]	>20 ng/ml (men)
Addington et al. [103]	>35 ng/ml (men)
	>50 ng/ml (women)
Bobes and Timdahl [104]	>20 ng/ml (men)
	>30 ng/ml (women)
Montgomery et al. [105]	>18.4 ng/ml (men)
	>26 ng/ml (women)
Cavallaro et al. [106]	>18 ng/ml (men)
	>29 ng/ml (women)
Halbreich et al. [20]	>20 ng/ml (men)
	>25 ng/ml (women)
Kinon et al. [107]	>18.77 ng/ml (men)
	>24,20 ng/ml (women)
Potkin et al. [108]	>23 ng/ml
Canuso et al. [109]	>23.2 ng/ml (premenopausal women)
Aizenberg et al. [110]	>16 ng/ml
Huber et al. [111]	>25 ng/ml
David et al. [112]	>15 ng/ml (men)
	>20 ng/ml (women)
Peuskens and Link [113]	≥15 ng/ml
Crawford et al. [114]	>13.8 ng/ml (men)
	>18.4 ng/ml (women)

sexual impairment, one is struck by the fact that the evidence is contradictory and inconclusive [128, 129]. Some studies have shown an association between sexual side effects and PRL elevation, while others have failed to support this [129]. It is therefore important to distinguish between symptomatic and asymptomatic HPRL, although this distinction is seldom made in the scientific literature [55].

3.2 Measurement of PRL Levels

Despite the well-recognized variability in PRL levels, most reports do not provide much or any data detailing the measurement of PRL levels (e.g., the time of sampling). These may be relevant factors in individual patients who

Table 2 Normal and high prolactin values

	Prolactin plasma concentrations
Normal	20 (men) and 25 (women) ng/ml
High	From 30–60 to 150–200 ng/ml
Prolactinoma	
Microprolactinomas (≤1 cm in diameter)	50–300 ng/ml (can be as low as 30 ng/ml)
Macroprolactinomas (≥1 cm in diameter)	200–5,000 ng/ml (can be as high as 35,000 ng/ml)

have borderline raised levels. A complicating factor during measurement of PRL levels is the presence of macroprolactin[2], which is essentially biologically inactive, but may lead to falsely high PRL levels as measured by many assays [66]. Conservative estimates suggest that the presence of macroprolactin leads to misdiagnosis in as many as 10 % of all reported instances of biochemical HPRL [90]. Macroprolactinemia can, however, be revealed by polyethylene glycol precipitation of serum samples [17, 90]. Thus, awareness and understanding of the potential impact of factors that affect PRL are important in the interpretation of PRL testing results [16]. When assessing PRL levels other points to be aware of are [130]:

- All serum measurements must been done by the same laboratory.
- All bloods must have been drawn in the morning with the patient in a fasting state.
- To confirm diagnosis, at least one repeated measurement is required after the initial elevated level.

There is a variety of reported units of measurement of PRL levels. Serum PRL concentrations are usually expressed in units of either ng/ml (or the equivalent μg/l), nmol/l, pmol/l, or mIU/l [5, 6]. US data are often presented in ng/ml, whereas most UK and EU data are in mIU/l [5]. Most clinical papers do not state the conversion factor needed, while there exists variability in conversion factors that are reported. In general terms, ng/ml × 21.2 converts to mIU/l (although some conversion factors given are as high as 36) [5, 66, 67, 115], ng/ml × 43.478 converts to pmol/l [70], and ng/ml × 0.043 converts to nmol/l [6].

The reporting of PRL levels remains poor in many published studies. A baseline plasma PRL level and at least one follow-up measurement should be reported. However, several follow-up measurements over a longer (≥1 year) study period are preferable as continuity and longer-term data are needed. Moreover, there has been a tendency to report mainly mean PRL values or mean change PRL data that do not easy allow interpretation of the precise number of patients developing HPRL or the clinical significance of these elevations. Not to report categorical data (thus not telling explicitly how many patients have HPRL) makes it difficult for clinicians to advise their patients on the appropriate risk with a particular antipsychotic compound [131]. Therefore, categorical outcomes for abnormal PRL levels need to be reported, as well as outcomes on the severity of the HPRL in individual patients. PRL levels should also be measured by a morning, fasting, pre-medication sample. Lastly, it is also important to mention whether patients at baseline were switched from another antipsychotic or not, as well as to provide the thresholds used for the registered (ab)normal plasma PRL values.

3.3 Incidence of HPRL

Hyperprolactinemia is one of the most common endocrinological disorders of the hypothalamic-pituitary axis [17]. The estimated incidence of HPRL (serum PRL values >25 ng/ml) in the non-selected healthy population is low (0.4 %) [13]. However, this estimate may be too low, given that autopsy reports state that more than 10 % of the population have a pituitary tumor [14].

Considering PRL responses to antipsychotic medication, it is repeatedly found that PRL responses to these medications are greater in females than in males [49, 107, 132–141]. This difference can be explained by the ability of estrogens to elevate serum PRL levels and enhance responsiveness to PRL-releasing stimuli [49, 142]; estrogens increase the number of lactotrophic cells of the anterior pituitary and act on the hypothalamus to decrease dopamine content [49]. Among male patients, age was found to have no influence on PRL concentrations, whereas in women, a younger age was associated with higher PRL levels, as expected for their reproductive status [105, 143]; women of reproductive age experience raised PRL secondary to antipsychotic medication more frequently than postmenopausal women [107]. Although HPRL is most established in adult patients, it can be of clinical significance in children and adolescents as well [144–154]. Once again, post-pubertal girls may be more sensitive to this adverse effect, given that estrogen stimulates PRL synthesis and enhances PRL responses to antipsychotic medication [155].

4 Causes of Elevated PRL Values and HPRL

Considering the complexity of PRL regulation, many factors can cause HPRL [12, 156]. Table 3 presents the

[2] Besides monomeric PRL, which accounts for approximately 85 % of total PRL in normal sera, higher-molecular-weight variants of PRL are known. Macroprolactin, which in the majority of cases consists of antigen-antibody complexes of monomeric PRL and immunoglobulin G, contributes <1 % to circulating PRL levels. However, in some patients with supraphysiological PRL levels, macroprolactin was demonstrated to be the predominant form without eliciting the classical signs and symptoms of HPRL [90].

conditions in which elevated PRL values and/or HPRL can arise [5, 15, 17, 23, 29, 57, 115, 157–159].

5 Methods

To get a fuller picture of the relationship between antipsychotics and PRL elevation and because, at this moment, no review has been published about the effect of the newly approved antipsychotics asenapine, iloperidone and lurasidone on PRL levels, a literature search (1966 until December 2013), using the MEDLINE database, was conducted for English-language published reviews, meta-analyses and clinical trials of first-generation antipsychotics (FGAs), second-generation antipsychotics (SGAs) and newly approved antipsychotics. The following keywords were used: "antipsychotics," "neuroleptics," "clozapine," "olanzapine," "quetiapine," "amisulpride," "ziprasidone," "aripiprazole," "risperidone," "sertindole," "paliperidone (extended-release and palmitate)," "asenapine," "iloperidone," "lurasidone," "schizophrenia," "prolactin" and "hyperprolactinemia". The review is based upon studies carried out with adults as well as children and adolescents. We attempted to identify additional studies through searches of the reference lists of identified studies and reviews.

6 PRL and Antipsychotics

6.1 General Remarks

After the introduction of chlorpromazine into clinical practice more than half a century ago, antipsychotic medication rapidly became the cornerstone of pharmacological treatment for schizophrenia. Antipsychotic drugs are arbitrarily divided into first-generation and second-generation agents (including the newly approved antipsychotics). Although most antipsychotic drugs are now used to treat a broad range of symptoms and disorders, their primary indication remains psychotic disorder, more specifically schizophrenia and schizophrenia-related disorders.

It was accepted for a long time that serum PRL concentrations are not elevated in untreated schizophrenic patients, unless they have other underlying pathologies (e.g., prolactinoma) [12, 13, 160]. Several studies [138, 161–165] showed that PRL values in untreated schizophrenic patients were comparable to those of healthy control subjects. This finding would indicate that the high PRL values observed in schizophrenic patients treated with antipsychotic medication have to be attributed to the effects of this medication rather than to possible underlying effects of the disease itself [56]. The possibility that schizophrenia itself causes elevated PRL values seemed therefore excluded [14]. However, recent research showed that HPRL can be pre-existing in some patients with schizophrenia [166]. One of these studies on PRL levels in antipsychotic-free patients with schizophrenia found HPRL (>15.2 ng/ml in men and >23.3 ng/ml in women) in 23.8 % of antipsychotic-naïve patients with an at-risk mental state for psychosis and in 33.3 % of antipsychotic-naïve patients with first-episode psychosis [79]. This finding is in accordance with the results of the European First Episode Schizophrenia Trial (EUFEST) study, showing HPRL (>18 ng/ml in men and >25 ng/ml in women) in 71 % of first-episode patients of whom approximately half had never been exposed to antipsychotic treatment [93], as well as with other studies of drug-naïve patients [167–169]. The increased PRL concentrations in antipsychotic-naïve patients do not appear to be due to important confounding variables such as gender, smoking and body mass index (BMI), nor to the effects of elevated thyroid stimulating hormone (TSH), ghrelin, or cortisol [168]. Therefore, these findings suggest that HPRL in schizophrenia is not necessarily only caused by antipsychotic medication, but might already be present in antipsychotic-naïve first-episode patients and even in prodromal stages [79]. HPRL in these patients can be caused by general stress associated with the illness experience [79], or by a pre-existing vulnerability [168], including a genetic predisposition [170]. One genetic study suggested a possible abnormality of the functional −1149 G/T polymorphism of the PRL gene in schizophrenia, especially in male patients. Based on the results of this study, it may be speculated that individuals with a preponderance of the G allele of the polymorphism react more strongly to stress with a higher production of PRL [170].

The association between antipsychotic medication and HPRL has been under investigation since at least the 1970s [125]. Although HPRL can be found in association with all antipsychotic medications, these medications differ in their propensity to cause PRL elevation [171]. The highest rates of HPRL are reported in association with risperidone, amisulpride and sulpiride, often in as high as 80–90 % of all female subjects and consistently greater than with the FGAs and other SGAs (see 6.3.1.1 and 6.3.1.7). However, significant rates of HPRL of lesser severity and more transience have also been reported in association with several other antipsychotics [66]. On the basis of the scientific literature, a distinction has been made by numerous authors between antipsychotics with a "PRL-raising potential" (among which are counted the FGAs and the SGAs amisulpride, risperidone and paliperidone) and the "PRL-sparing" antipsychotics (clozapine, quetiapine, olanzapine, ziprasidone and aripiprazole) [46, 57, 105, 109, 140, 172–177]. Nevertheless, this terminology may

Table 3 Possible causes of elevated prolactin values and hyperprolactinemia

- Physiological
  - Pregnancy
  - Breast-feeding
  - Stress (causes temporary increase in prolactin secretion)
  - Physical activity: intensive effort (causes temporary increase in prolactin secretion)
  - Sexual activity
  - Sleep (causes temporary increase in prolactin secretion)
  - Neonatal age
- Pathological
  - Pituitary disorders
    - Prolactinomas
    - Mixed pituitary adenomas
    - Cushing's disease
    - Acromegaly
    - Not secreting adenomas
    - Empty sella syndrome
    - Pituitary stalk section or tumors
    - Lymphoid hypophysitis
  - CNS disorders
    - Tumors
    - Craniopharygioma
    - Sarcoidosis
    - Spinal cord lesions
    - Granulomatous diseases
    - Vascular disorders
    - Autoimmune disorders
    - Hypothalamic tumors or metastasis
    - Cranial irradiation
    - Seizures
  - Systemic diseases
    - Severe hypothyroidism
    - Empathic cirrhosis
    - Chronic renal insufficiency
    - Polycystic ovary syndrome
    - Estrogen-secreting tumors
    - Pseudocyesis
    - Chest trauma following an operation, accident, herpes zoster (shingles) [22, 145] (any disorder of the neural network between the chest and the hypothalamus can cause hyperprolactinemia) [15, 144]
    - Stage immediately following an epileptic fit
- Pharmacological
  - D2 receptor antagonists
    - First-generation antipsychotics
      - Phenothiazines
      - Thioxanthenes
      - Butyrophenones
    - Second-generation antipsychotics
      - Paliperidone
      - Risperidone
      - Quetiapine
      - Olanzapine
      - Benzamides (amisulpride)
  - Other dopamine (D2) antagonists
    - Amoxapine
    - Metoclopramide
  - Antidepressants
    - Tricyclic
      - Amitriptyline
      - Desipramine
      - Clomipramine
      - Amoxapine
    - Tetracyclic
    - MAO-inhibitors (mono-amine oxidase inhibitors)
      - Pargyline
      - Clorgyline
    - SSRIs (selective serotonin reuptake inhibitors)
      - Paroxetine, citalopram and fluvoxamine (all bring about a minimal increase, although not above normal values)
    - Other
      - Prolactin increases were not observed with the long-term use of nefazodone, bupropion, venlafaxine or trazodone
  - Opiates and cocaine
  - Antihypertensives
    - Methyldopa
    - Verapamil
    - Reserpine
    - Labetalol
  - Gastrointestinal medication
    - Metoclopramide
    - Domperidone (metoclopramide and domperidone are both dopamine receptor blockers)
  - H_2 receptor antagonists (?)
    - Ranitidine
    - Cimetidine
  - Hormone preparations
    - Estrogens
    - Oral contraceptive pills
    - Antiandrogens
  - Protease inhibitors (?)
  - Benzodiazepines (occasionally)
    - Alprazolam
  - Other
    - Fenfluramine
    - Alcohol

incorrectly lead clinicians to conclude that antipsychotic medication such as clozapine, quetiapine and even aripiprazole can never be associated with significant HPRL.

Thus, although this terminology can be helpful, it oversimplifies the picture [115]. When looking at individual studies, in order to make an adequate evaluation of the PRL-elevating propensity of antipsychotics, information on PRL baseline values and previous treatment is necessary.

A complex question relating to PRL levels concerns the persistence of HPRL [66]. With the exception of some studies (e.g., the study of Eberhard et al. [178] on risperidone; see 6.3.1.7), most of the reported PRL data are of too short duration to make definitive statements regarding this issue [179].

6.2 PRL and First-Generation Antipsychotics (FGAs)

Elevated PRL values are regularly observed when FGAs are used. In most patients, such values are an unavoidable side effect [12, 23]. FGAs induce a significant rise in serum concentrations of PRL, which are around two to three times higher than the reference values [53, 55, 56]. The PRL values that are noted with FGAs are in general lower than 100 ng/ml, although in some patients values of up to 365 ng/ml have been observed [29]. In a study by Montgomery et al. [105], HPRL (>18.4 ng/ml for men, >26 ng/ml for women, with a mean PRL level of 42.1 ng/ml) was found in 71 % of the patients treated with FGAs. In 37 % of the patients, PRL values exceeded twice the normal PRL values.

It has been suggested that patients receiving long-term neuroleptic treatment may develop tolerance to the secondary raising effect, with serum PRL concentration returning to normal with continued treatment. However, conflicting results have been reported. A few studies reported that tolerance can develop with time. Marken et al. [180], for example, found that 37.5 % of men and 27 % of women, who had been treated with FGAs for at least 5 years, had normal PRL levels. Brown and Laughren [181] found that after 4 months of treatment, PRL reached a stable level, substantially lower than that at the onset of FGAs treatment and not differing from that after years of treatment. Other studies, however, reported that tolerance does not occur. Meltzer and Fang [182, 183] studied serum PRL levels, before and during long-term administration of phenothiazines on a twice daily schedule, in 27 newly admitted schizophrenic patients. By 72 h after the initiation of treatment, all 27 patients had persistently elevated serum PRL levels, averaging a 3.2- and 3.8-fold increase in normal PRL values in men and women, respectively. Serum PRL levels remained elevated during the 1- to 3-month period subjects were studied, suggesting there was no tolerance to this effect of phenothiazines. A Japanese study failed to demonstrate tolerance in 27 chronic inpatients with schizophrenia receiving long-term haloperidol [184]. According to an overview of Meltzer [185] concerning long-term effects of FGAs on the neuroendocrine system, serum PRL levels remain elevated in most, but not all, schizophrenic patients receiving FGAs chronically, if the dose administered is high enough. Tolerance to these PRL elevations may develop in some subjects, but even their PRL levels, though still within normal limits, are higher than baseline levels.

6.3 PRL and Second-Generation Antipsychotics (SGAs)

6.3.1 PRL and SGAs in Adults

It has been established that, as a group, the SGAs cause a lesser elevation of the PRL plasma levels than the FGAs [90, 138, 186, 187]. Their greater specificity, resulting in a lesser blockade of the dopaminergic receptors, but also their stronger 5-HT2AR blockade, is thought to explain the more limited elevation of the PRL levels [15, 188] (see also 6.5). The notable exceptions in this regard are amisulpride, risperidone and paliperidone. However, with the exception of aripiprazole and clozapine, all SGAs have a standard warning regarding PRL elevations in their US product labels.

6.3.1.1 Amisulpride Amisulpride, which is structurally related to the older high-PRL-elevating benzamide, sulpiride [11, 189], is associated with high rates of HPRL. Amisulpride also has a pronounced PRL-elevating effect which appears to be independent of dosage and duration of administration [190]. Even at relatively low doses (50 mg/day) amisulpride seems to induce substantially elevated PRL values [191–195], and brings about greater increases in PRL values than olanzapine and risperidone [193, 196, 197]. Kopecek et al. [193] found that subjects who receive doses as low as 50 mg/day have HPRL in almost all cases. This HPRL is significantly high (mean 113 ng/ml), and higher in females (160 ng/ml) than in males (48 ng/ml). Paparrigopoulos et al. [198] found a 100 % prevalence of HPRL for patients receiving amisulpride. A 12-month, open-label clinical trial with flexible doses of amisulpride (mean dose 501.4 ± 283.5 mg/day at month 12) found HPRL to be the most common (41.9 %) reported adverse effect among patients with schizophrenia. At baseline, the mean serum PRL level of all patients was 42.7 ng/ml, which increased significantly to 92.7 ng/ml at 8 weeks ($p < 0.001$) and then decreased to 73.3 ng/ml at month 12 [199]. Another 12-month trial found HPRL in 75.9 % of men and 85.7 % of women [200]. Frighi et al. [201], investigating the safety of antipsychotic medication in individuals with intellectual disability, found all participants on amisulpride/sulpiride had HPRL. Therefore, amisulpride is regarded to be the antipsychotic with the

potential for maximum PRL elevation [66]. Nevertheless, HPRL rapidly reverses following amisulpride discontinuation [190, 195].

6.3.1.2 Aripiprazole Aripiprazole belongs to the group of "PRL-sparing" antipsychotics [202–204]. In most studies with aripiprazole, PRL levels were found to decrease, even below those expected from placebo, or to remain unchanged over all dosages [83, 85, 86, 94, 108, 123, 200, 206–221]. However, new-onset HPRL with aripiprazole has been found [95, 108, 217]. In the study of McQuade et al. [217], among patients who had normal PRL levels at baseline, 8 % in the aripiprazole (15–30 mg/day) group experienced increases above the upper limit of normal (not defined) at some point during the trial. In general, HPRL prevalence rates of 3.1–9 % seem consistent [108, 191, 214, 217, 220–222], but can be sometimes higher. For example, Kwon et al. [83] found 10.7 % of patients to have an abnormal PRL level (>23 ng/ml) throughout the entire aripiprazole (10–30 mg/day) study (26 weeks). In another 26-week trial of aripiprazole (mean daily dose at endpoint 18.7 mg) versus "standard of care" agents (olanzapine, quetiapine or risperidone; mean daily dose at endpoint 12.5 mg, 386.8, and 4.6 mg, respectively), Kerwin et al. [223] found 16.8 % of aripiprazole-treated patients had potentially clinically relevant PRL elevations (compared with 54.4 % in the "standard of care" group). However, what is meant with "potentially clinically relevant PRL elevations" is not stated by the authors. Byerly et al. [224] showed that aripiprazole in combination with risperidone or olanzapine significantly reduced the PRL levels induced by these antipsychotics during the first week of treatment. In combination with risperidone, aripiprazole even decreased PRL levels to within the normal range of PRL values. These results are confirmed by other reports [86, 94, 216, 225–230]. The addition of aripiprazole 5 mg daily to long-acting risperidone was equally associated with a significant decrease in PRL levels. In an open, uncontrolled clinical trial with 13 patients with a severe mental disorder (schizophrenia and other unspecified psychoses), 12 patients showed a decrease in serum PRL levels (81 ± 46 µg/l at baseline vs. 42 ± 21 µg/l at month 1, $p < 0.001$, 52 % mean reduction) [231]. In two patients treated with adjunctive aripiprazole, PRL levels reverted to normality [231]. A recent meta-analysis of five randomized controlled trials ($n = 639$) comparing the safety and efficacy of adjunctive aripiprazole versus placebo for antipsychotic-induced HPRL found adjunctive aripiprazole to be both safe and effective as a reasonable choice treatment for patients with antipsychotic-induced HPRL. Adjunctive aripiprazole was associated with a 79.11 % (125/158) PRL level normalization rate. The appropriate dose of adjunctive aripiprazole may be 5 mg/day [232]. However, the add-on effects of aripiprazole in reversing antipsychotic-induced HPRL depend on the pharmacological properties of the pre-existing antipsychotic; adjunctive aripiprazole treatment reverses effectively HPRL induced by risperidone and olanzapine, but seems to be less effective for that induced by benzamide antipsychotics (amisulpride and sulpiride) [226, 233].

The absence of elevated PRL levels with aripiprazole can be accounted for by the partial agonism of aripiprazole with reference to the D2R [66, 234], most likely because it maintains a low level of activation of pituitary D2R [235]. As a partial D2R agonist, aripiprazole may be the drug of choice in patients suffering from both psychosis and prolactinoma [121].

Some data indicate that switching to aripiprazole also may be useful for resolving antipsychotic-induced HPRL [86, 94, 216]. Even rapid decreases of PRL levels seem to be achieved with aripiprazole switching strategies [86]. Lu et al. [94] assessed the time course of changes in antipsychotic-induced HPRL during the process of antipsychotic switching to aripiprazole (mean dose 18.5 mg/day). Twenty-three female schizophrenic subjects with risperidone (mean dose 4.8 mg/day)- or sulpiride (mean dose 500 mg/day)-induced symptomatic HPRL were recruited into the study. Serum PRL levels were measured at baseline, during the combination treatment period, and 4 weeks after having completed discontinuation of the pre-existing antipsychotic treatment. Switching antipsychotic drugs to aripiprazole was effective in reducing serum PRL levels in schizophrenic patients who received the PRL-raising antipsychotics. Mean serum PRL levels at baseline, during combination period, and after the switch were 97.0 ng/ml, 27.2 ng/ml ($p < 0.001$, vs. baseline) and 12.2 ng/ml ($p < 0.001$, vs. baseline), respectively. In a post hoc subanalysis of an 8-week, open-label study in outpatients with schizophrenia ($n = 269$), Byerly et al. [86] examined short-term effects on PRL levels during a switch from risperidone ($n = 105$) or olanzapine ($n = 164$) to aripiprazole 30 mg/day with three switching strategies (I, immediate aripiprazole initiation with simultaneous immediate discontinuation of olanzapine/risperidone; II, immediate aripiprazole initiation while tapering off olanzapine/risperidone over 14 days; III, titrating aripiprazole upwards while tapering off olanzapine/risperidone over 14 days). Mean baseline PRL levels (ng/ml) were within normal range for the three olanzapine groups (group I, 11.7; group II, 13.2; group III, 11.2), but above normal for the risperidone groups (group I 39.7; group II 48.5; group III 33.5). Following aripiprazole initiation, mean PRL levels decreased significantly ($p < 0.001$) at week 1 and were maintained to week 8 in all groups irrespective of

prior treatment. Previously elevated PRL levels in the risperidone groups were reduced to within normal range within 1 week, irrespective of switching strategy.

6.3.1.3 Clozapine Clozapine induces little or no PRL elevation [11, 15, 30, 46, 110, 131, 155, 236–240] or is associated with significant decreases of PRL levels (after switching from a PRL-elevating FGA) [102, 241]. For example, Breier et al. [241] found that, after a baseline fluphenazine treatment period, clozapine (mean dose 403.6 mg/day) significantly decreased PRL levels from 53.3 ng/ml at baseline to 12.2 ng/ml at week 6. Long-term treatment with clozapine seems not to influence PRL levels significantly. One study showed that even after a treatment duration of 36 months with clozapine (median dose 300 mg), PRL levels remain low (mean 9 ng/ml) [242]. Despite all these observations, several studies indicated that clozapine can cause a brief (a few hours) elevation of PRL levels immediately after the dose is administered [11, 15, 238, 242], or can even be associated with HPRL [105, 243]. Turrone et al. [242] established that clozapine caused a doubling of the PRL baseline values in the 1–5-h period after medication administration. Montgomery et al. [105], who analyzed the data of three electronic databases ($n = 422$), determined that 11 % of the patients treated with clozapine had HPRL (>18.4 ng/ml for men, >26 ng/ml for women). However, the authors did not specify the mean treatment time of clozapine. They only noted that treatment in these chronically mentally ill patients had been stable for at least 1 month prior to the PRL assay. Bushe and Shaw [243] reported a prevalence of HPRL of 5 % with clozapine.

6.3.1.4 Olanzapine Olanzapine, an antipsychotic with an intermediary D2R binding affinity, induces a moderate elevation of PRL levels [200, 244]. Categorical data show prevalence rates between 6 and 60 % [66, 74, 76, 99, 105, 114, 191, 245, 246]. Administration of olanzapine causes a doubling of PRL baseline values 6 h after it is taken [242].

Although switching from a PRL-raising antipsychotic to olanzapine can lead to a significant reduction [90, 247–249], even to the upper limit of normal [99], or a normalization of PRL levels [81, 205] in approximately half up to all of the patients who had elevated PRL levels at baseline, PRL levels during treatment with olanzapine remain raised in another substantial proportion (one-third to more than a half) of patients [205, 245, 246]. Moreover, olanzapine treatment can lead to new-onset HPRL in patients with normal PRL levels at baseline [87, 205].

Although Karagianis and Baksh [250], in a high-dose study ($n = 24$) on olanzapine, found no significant correlation between mean PRL values and olanzapine high-dose treatment groups (20, 25, 30 and 40 mg/day, mean duration of olanzapine therapy 15.3 months), most studies demonstrated a dose-dependent effect of oral olanzapine on the plasma PRL level of patients with schizophrenia, with higher doses associated with higher PRL levels [82, 102, 114, 251–253]. Significant dose-associated changes have also been identified with olanzapine long-acting injection [254].

Genetic polymorphisms may be associated with differences in PRL secretion mediated by SGAs. Cabaleiro et al. [255] found that some polymorphisms in D2R and 5-HTR2A are involved in PRL levels after administration of olanzapine. These results agree with those obtained in an earlier study revealing that PRL secretion induced by olanzapine (and risperidone) in healthy volunteers was modulated by Taq1A polymorphism of D2R. However, this factor was not linked to PRL secretion in quetiapine-treated healthy volunteers [256].

6.3.1.5 Paliperidone Paliperidone extended-release (ER), the oral formulation, and paliperidone palmitate, the long-acting injectable formulation of paliperidone, frequently elevate PRL levels over both short- and longer-term treatment periods [257–259]. As paliperidone is the major active metabolite of risperidone, the mechanism of PRL elevation for paliperidone is likely similar to that of risperidone [260–262]. However, two recently published studies suggest that PRL levels seem to decrease after switching from risperidone to paliperidone in patients with a psychotic disorder [263, 264]. An analysis of abnormal PRL values in ten randomized clinical trials, including 3,173 patients treated with paliperidone palmitate, showed that, overall, at any time, PRL levels were elevated for 38.8 % of the subjects [265]. In general, plasma PRL levels are elevated to a greater extent in female than in male patients [77, 78, 91, 92, 257, 266–281], remain mostly elevated throughout treatment [257] and increases with increasing paliperidone ER dosage [257, 267, 269, 272, 276–279, 281, 282]. An analysis from a separate 6-day phase I study in stable subjects with schizophrenia found similar PRL pharmacokinetic profiles (maximum plasma concentration, C_{max} and area under the curve, AUC) when subjects received the highest recommended dose of paliperidone ER (12 mg/day) compared with an average dose of risperidone (4 mg/day) [283].

6.3.1.6 Quetiapine Research has shown that quetiapine, like clozapine, induces virtually no elevation of PRL in the blood [11, 15, 27, 46, 56, 104, 200, 245, 284–286]. Moreover, many studies show that PRL levels, after switching, decrease [113, 287–291], even to normal values [81, 100, 292–294], during treatment with quetiapine. However, once again, it would be a mistake to claim that quetiapine (like clozapine) can not cause an elevation of

PRL values or induce HPRL. Some data indicate that quetiapine can bring about a transient rise in PRL levels [11, 15, 30, 242]. Kapur et al. [295] showed that in some patients, 2–3 h after a single dose, quetiapine (400–450 mg) corresponded with a transiently high D2R occupancy at around 60 % and a transiently elevated PRL level of 19–28 ng/ml. These PRL values returned to normal within 24 h. In studies that report categorical rates of HPRL, low prevalence rates in association with quetiapine have been reported, ranging from 0 to 29 % [66, 104, 105, 154, 191, 296]. Montgomery et al. [105] established that 22 % of the patients treated with quetiapine presented HPRL (>18.4 ng/ml for men, >26 ng/ml for women).

6.3.1.7 Risperidone Risperidone has a high potential for PRL elevation. It causes more marked elevations in PRL than any other SGA [17, 155, 200, 297, 298]. There is also evidence to suggest that the effect of risperidone (as well as paliperidone) on PRL may exceed that of FGAs [115, 123] (with the exception of sulpiride) [299]. A number of different comparative PRL data sets find consistently that risperidone elevated PRL more commonly and to the same or a greater degree than haloperidol [66, 101, 105, 127, 140, 300].

When data are reported in a categorical manner, there is evidence that almost all subjects (72–100 %) receiving oral risperidone [66, 74, 87, 101, 108, 243, 301] and many subjects (53–85 %) receiving risperidone long-acting intramuscular injection have HPRL [66, 172, 243]. The largest randomized controlled trial ($n = 555$) reporting PRL data found an incidence of 73.8 % (>18 ng/ml in men, >25 ng/ml in women) in risperidone-treated subjects with first-episode psychosis [101]. However, there can be great interindividual differences in the elevation of the serum PRL levels due to risperidone treatment. For example, in one study PRL levels associated with risperidone treatment ranged from 26.9 to 320 ng/ml [142].

At therapeutic concentrations of risperidone, serum PRL levels reach 30–60 ng/ml [240]. However, risperidone can impact on PRL levels even at relatively low doses [115, 140, 302, 303]. Kim et al. [303] found a mean serum PRL concentration with risperidone treatment (mean daily dosage of 3.5 mg/day) of 132.2 ng/ml, after a mean duration of 7.9 weeks. Kinon et al. [140] found that even at doses of risperidone 2 mg/day, PRL levels were already above the upper limit of normal for both females (mean PRL = 76.14 ng/ml) and males (mean PRL = 24.53 ng/ml).

The PRL-elevating effect of risperidone is mostly dose dependent [102, 105, 127, 140, 240, 304–307], even with long-acting risperidone [308]. Turrone et al. [242] showed that risperidone administration results in a dose-related elevation of PRL levels, even after patients have been taking these drugs for a prolonged period of time. Patients receiving risperidone (median dose 3 mg/day, range 1–3 mg/day, baseline plasma PRL level 27 ng/ml, median duration of risperidone treatment 8 months) showed a near doubling over baseline of PRL levels after risperidone administration. Compared with olanzapine and clozapine, whereby PRL levels returned to baseline values by 12–24 h, risperidone-induced PRL levels stayed abnormally high after 24 h.

Although, compared with those on oral risperidone, PRL levels in patients treated with long-acting risperidone seem to be generally lower, even with the long-acting form PRL levels in these patients stay significantly higher than normal PRL values [308–314]. In the phase III study by Chue et al. [309], all patients were first stabilized on oral risperidone, after which they were divided into groups that received long-acting risperidone (25, 50 or 75 mg/day) or were further treated with oral risperidone (2, 4 or 6 mg/day). PRL values for many patients remained elevated in both groups. However, PRL levels dropped significantly ($p < 0.001$) over the 12-week treatment in the long-acting group, whereas they remained essentially unchanged in the oral group. Mean PRL levels after 12 weeks of treatment were 38 ng/ml for oral risperidone (baseline 38.9 ng/ml) and 32.6 ng/ml for long-acting risperidone (baseline 37.4 ng/ml). This is confirmed in other studies [308, 315]. These observed differences between oral and long-acting risperidone are probably due to the reduced peak-through fluctuations of long-acting risperidone compared with oral risperidone. Nevertheless, long-term administration of oral risperidone seems also to bring about marked decreases in PRL values. Eberhard et al. [178] tracked the course of PRL values over 5 years in psychotic patients treated with risperidone ($n = 59$). At study entry, the median PRL level of the 218 subjects initially treated with risperidone was 1,522 nmol/l (range 24–5,716 nmol/l) or 66 ng/ml. Although the administration of risperidone was associated with higher PRL values than the values observed with other SGAs during this 5 year period, the investigators noted a strong linear decrease of these values ($p < 0.001$) with risperidone (year 0: 1,192 nmol/l or 52 ng/ml; year 1: 730 nmol/l or 32 ng/ml; year 2: 533 nmol/l or 23 ng/ml; year 3: 543 nmol/l or 24 ng/ml; year 4: 396 nmol/l or 17 ng/ml; year 5: 412 nmol/l or 18 ng/ml).

Some studies [316, 317] suggest that not risperidone but its major metabolite 9-hydroxyrisperidone (or paliperidone) is the main contributor to the increased serum PRL levels observed in many risperidone-treated patients. Given that risperidone and 9-hydroxyrisperidone have shown similar receptor binding affinities for the D2R, one would expect an almost equally strong D2R blocking effect on the lactotrophs and thus equally elevated PRL levels. However, higher plasma levels of 9-hydroxyrisperidone in treated patients, as well as its longer half-life and lower

plasma protein binding, compared with risperidone, has been proposed to explain these results.

6.3.1.8 Sertindole After it has been suspended in 1998, because of its potential risk in causing cardiovascular-related death, sertindole was relaunched to the European market in 2006. Sertindole has not cause clinically significant PRL elevations (i.e., above normal reference ranges) in short- or long-term clinical studies [299, 318–322]. One study, carried out in 11 European countries, assessing the safety and tolerability of sertindole (modal dose 16 mg/day) in the long-term (18 months) treatment of schizophrenia, found mean serum PRL levels decreased [320]. However, according to a recent meta-analysis, assessing the comparative efficacy and tolerability of 15 antipsychotic drugs in schizophrenia, sertindole causes statistically significantly higher PRL increases than placebo, which are not statistically significantly less than those induced by haloperidol [299].

6.3.1.9 Ziprasidone Similar to most SGAs, ziprasidone has a lower propensity for HPRL, compared with FGAs [323]. Most reports indicate a low incidence of PRL elevation and low to moderate levels of HPRL with ziprasidone use [11, 15, 103, 234, 240, 245, 297, 324–326]. Several studies found decreased PRL levels after, respectively, 6 weeks [301], 4–8 weeks [90], 18 weeks [327], 44 weeks [328] and 1 year [329] of treatment with ziprasidone. However, ziprasidone can also be associated with HPRL. In one study, switching from aripiprazole to ziprasidone (mean dose at last observation 116.8 mg/day) in patients with schizophrenia induced a significant increase in serum PRL levels (from 7.2 ng/ml at baseline to 33.8 ng/ml at week 12). HPRL was observed in 54.5 % of the subjects receiving ziprasidone monotherapy [330]. Analysis of the Clinical Antipsychotic Trials in Intervention Effectiveness (CATIE) data showed 17.3 % in the ziprasidone group presented HPRL (men >18.77 ng/ml, women >24.20 ng/ml) [69]. Wu et al. [331] found the increase of serum PRL levels in drug-naïve schizophrenia patients treated with ziprasidone (168 ± 17 mg/day) to be 17 ± 11 and 47 ± 51 μg/l in the ziprasidone male and female group, respectively. Suzuki et al. [332] performed positron emission tomography (PET) scans with [^{11}C]-raclopride in 12 patients with schizophrenia being treated with ziprasidone 60 mg twice daily. PRL levels were highest at 5-h post-dose: PRL levels were higher than the reference range (males 3–13 μg/l; females 3–27 μg/l) in seven patients at 5 h (mean ± standard deviation, SD 23.5 ± 13.6 μg/l). None showed HPRL at 23-h scans. Treatment with ziprasidone can also result in high HPRL rates in certain vulnerable patient groups, such as first-episode patients. Grootens et al. [76], in an 8-week double-blind randomized trial, found that 40 % of patients with recent-onset schizophrenia on ziprasidone (mean study dose 104 mg/day) met criteria for HPRL (>18 ng/ml for men, >25 ng/ml for women) at endpoint. The add-on of ziprasidone to clozapine does not result in significant PRL elevations. Zink et al. [333] found no significant changes in PRL levels in patients who were, after a partial response to monotherapy with clozapine, randomized to the treatment condition in which they received clozapine in combination with ziprasidone (mean dose 134 mg/day) for 6 weeks.

6.3.2 PRL and SGAs in Children and Adolescents

Antipsychotic-induced adverse events can be especially prominent in vulnerable populations such as children and adolescents [46]. With reference to the use of antipsychotic medication in children (≤12 years) and adolescents (12–18 years), one review showed that, in general, all antipsychotic medication, except clozapine, ziprasidone and quetiapine, increase the mean PRL level from baseline values of 8.0 ng/ml to 25–28 ng/ml after 4–8 weeks of treatment (reference range 0–15 ng/ml) [334, 335]. Incidence rates of HPRL during treatment with risperidone, olanzapine and quetiapine in this population were 62, 31 and 12 %, respectively [334]. In the same line, a comprehensive review of prospective head-to-head and placebo-controlled comparisons (34 studies) on the efficacy and safety of SGAs in children and adolescents ($n = 2{,}719$) with psychotic and bipolar spectrum disorders found that PRL levels increased the most in subjects on risperidone (mean change ranging from 8.3 to 49.6 ng/ml), followed by olanzapine (−1.5 ng/ml to +13.7 ng/ml). Treatment with aripiprazole was associated with decreased PRL levels, while clozapine and quetiapine were found to be mostly neutral [336]. A recently published systematic review and meta-analysis of the effects of SGAs in children and adolescents aged ≤18 years confirmed these results [337].

6.3.2.1 Aripiprazole Treatment with aripiprazole in children and adolescents (up to age 18 years) seems, as in adults, to be associated with decreased or unchanged PRL levels [313–318, 336–343]. Moreover, there is also good evidence that PRL levels can decrease even to subnormal PRL serum levels (<3 ng/ml for females and <2 ng/ml for males) [340].

6.3.2.2 Olanzapine Children and adolescents with schizophrenia may be more susceptible than adults to PRL increases induced by olanzapine [84]. A meta-analysis of double-blind, randomized controlled trials using antipsychotic medications for the treatment of a mental disorder in a pediatric population (children up to 18 years of age) found olanzapine-treated subjects to have much higher

odds of an elevated PRL at any time during treatment, compared with placebo (odds ratio 30.52, $p < 0.00001$) [338]. Another recently published systematic review and meta-analysis confirmed these results [337].

6.3.2.3 Quetiapine Incidence data of HPRL in children and adolescents treated with quetiapine seem not to be higher than those found for adult patients. A review of 29 studies [334] reported an overall incidence of 12 % during treatment with quetiapine. In the study by Stevens et al. [304], 20 % of the young male adolescents, who had been treated for at least 6 weeks with quetiapine (317.5 ± 238 mg/day), had PRL values that exceeded the normal values (0–15 ng/ml). A comprehensive review of prospective head-to-head and placebo-controlled comparisons (34 studies) on the efficacy and safety of SGAs in children and adolescents ($n = 2{,}719$) with psychotic and bipolar spectrum disorders found treatment with quetiapine mostly to be neutral [336].

6.3.2.4 Risperidone The most and best data concerning children and adolescents are available for risperidone [334]. The meta-analysis of Pringsheim et al. [338] found a change in PRL level from baseline to endpoint to be higher in risperidone-treated versus placebo-treated children, with a mean difference of 44.57 ng/ml ($p < 0.00001$). Geller et al. [70], in the initial management of children (mean age 11 years) with mania, found risperidone to be associated with HPRL (44.8 ng/ml after 8 weeks of treatment, baseline 7.2 ng/ml, $p < 0.001$), which raises concern for long-term treatment. Ercan et al. [344] found a significant increase ($p < 0.05$) in PRL levels after 8 weeks of treatment with risperidone (70 ng/ml at week 8, baseline 5.3 ng/ml) in preschool children (mean age 42.4 months) with conduct disorder and severe behavioral problems. In another study with adolescents and young adults (mean age 16 years) with anorexia nervosa, PRL levels were significantly increased for risperidone-treated subjects at week 7 (54.4 ng/ml, baseline 15.4 ng/ml vs. placebo 8.9 ng/ml, baseline 13.7 ng/ml, $p < 0.001$) [345]. In a report on a large population of adolescents with schizophrenia ($n = 257$, mean patient age 15.6 years), Haas et al. [346] observed elevations in PRL to levels >100 ng/ml in 18 % of adolescent schizophrenic patients after 8 weeks of treatment with 4 mg/day of risperidone. Eight short-term risperidone studies ($n = 739$) with an average duration of 4.6 weeks showed an increase of PRL from 7.9 ng/ml at baseline to 27.6 ng/ml at endpoint. Further treatment showed a decrease to 17.7 ng/ml after 1 year of treatment and to 24.9 ng/ml after 2 years of treatment [334]. In children and adolescents treated with risperidone, this pattern, consistent with the development of PRL tolerance over time, has also been shown by other research. Migliardi et al. [153] found mean PRL levels at 6 and 12 months to be lower than at the first month (baseline 8.4 ng/ml, 1 month 30 ng/ml, 6 months 27.9 ng/ml, 12 months 23.4 ng/ml). Nevertheless, as with olanzapine, vigilance to PRL elevation in all children treated with risperidone is necessary. More rapid CYP2D6 metabolism as well as polymorphic variation in the D2R may be important pharmacogenetic factors determining the risk for risperidone-induced HPRL in children and adolescents [61].

Lawsuits have been filed against Johnson & Johnson alleging that risperidone causes male breast tissue enlargement. The Risperdal FDA warning label states that clinical trials found gynecomastia in 2.3 % of children and adolescents treated with risperidone [347]. Trials have already begun, resulting in some noteworthy settlements [348]. Currently, several law firms are investigating the potential for more side-effect lawsuits regarding gynecomastia in young boys treated with risperidone [348, 349]. Although risperidone, according to a recent evidence-based review, has been identified as one of the medications probably associated with gynecomastia, the authors of this review state that most of the reported drug–gynecomastia associations are based on poor quality evidence [350]. Moreover, gynecomastia has also been mentioned as a potential side effect in other FDA product labels of SGAs (e.g., olanzapine, ziprasidone, quetiapine), FGAs, and selective 5-HT reuptake inhibitors (e.g., sertraline).

6.3.2.5 Ziprasidone Data on the use of ziprasidone in children are scarce [334, 338]. In general, PRL levels with ziprasidone appear to be lower than what is typically seen in children or adolescents taking olanzapine or risperidone [334, 346]. Moreover, PRL changes with ziprasidone in younger patients mostly are small and transient [351].

6.3.3 PRL and SGAs in First-Episode Patients

Studies have identified younger, antipsychotic-naïve patients with first-episode psychosis as a population vulnerable to cardiovascular and metabolic adverse effects with any antipsychotic [352–354]. As already mentioned above, research has shown that HPRL can occur in about one-third of antipsychotic-naïve first-episode schizophrenic patients, and in about one-fifth of antipsychotic-naïve patients with an at-risk mental state for psychosis [79, 93, 169]. There are indications that this HPRL might be due to a general stress associated with the illness experience and/or to a pre-existing vulnerability [168]. These findings have implications for clinical practice in that PRL should be measured in first-episode patients before starting treatment with antipsychotics [79, 169], not only to ensure that HPRL is not a pre-existing condition, but also, if necessary, to consider choosing a "PRL-sparing" antipsychotic [79].

Furthermore, it might be speculated that stress-induced HPRL plays a role in triggering the outbreak of acute psychotic symptomatology as PRL, through feedback, can increase dopamine. This would make this population even more vulnerable for "PRL-elevating" antipsychotics. However, the latter is certainly speculative and still needs further research [169, 355]. Moreover, the high level of stress, inducing PRL elevations in a substantial proportion of first-episode patients, can be secondary to the acute psychotic symptoms at the moment of admission.

Only a few studies are available that describe PRL changes in first-episode patients treated with SGAs. The results of these studies suggest that the effects of SGAs on PRL-levels in this population follow the same pattern as in adult schizophrenic patients. The presented data do not suggest that, at least for adults, first-episode patients, as a group, are more sensitive to PRL elevations, compared with adult schizophrenic patients. Nevertheless, careful attention should be given to drug selection and the lowest possible effective doses for first-episode patients with HPRL at baseline.

6.3.3.1 Amisulpride According to the results of the EUFEST study, more first-episode patients on amisulpride (89 %) had HPRL (>18 ng/ml in men and >25 ng/ml in women) than those on the other SGAs [olanzapine (50 %), quetiapine (41 %) and ziprasidone (46 %)] ($p = 0.017$). Moreover, taking amisulpride resulted in greater increases in PRL values per month ($p < 0.0001$) [93].

6.3.3.2 Aripiprazole Aripiprazole seems to be a well-tolerated antipsychotic agent in patients with first-episode schizophrenia. However, few studies have been specifically designed to test the safety of aripiprazole for the treatment of these patients. Lee et al. [211] investigated the therapeutic efficacy and tolerability of aripiprazole for treating first-episode schizophrenia following 8 weeks of treatment in routine clinical conditions. PRL levels after 8 weeks of treatment with aripiprazole were not significantly different from those at baseline. A 26-week prospective study with 300 schizophrenic patients, of whom 106 patients were drug-naïve first-episode patients, found that serum PRL levels significantly decreased from baseline levels (week 8, −20.55 ng/ml, $p < 0.001$; week 26, −14.46 ng/ml, $p < 0.001$). Only 10.7 % of patients had an abnormal PRL level (>23 ng/ml) throughout the entire study. There was no significant difference in serum PRL levels between first-episode patients and recurrence patients [83].

6.3.3.3 Olanzapine Pérez-Iglesias et al. [74] investigated the long-term (up to 1 year) effect of haloperidol, olanzapine and risperidone on serum PRL levels in a naturalistically treated first-episode psychosis population ($n = 110$). After 1 year, most of the patients in the olanzapine arm had PRL levels that fell within the reference range (<29.2 ng/ml for women and <17.7 ng/ml for men). These findings are in agreement with other studies that have reported no significant or transient PRL elevations with olanzapine treatment [356, 357].

6.3.3.4 Quetiapine In a small study with only 14 first-episode schizophrenic patients, comparing PRL levels at baseline with those after 12 weeks of treatment with quetiapine, Tauscher-Wisniewski et al. [358] found no significant difference in the elevation of PRL. All PRL levels at baseline and after 12 weeks of quetiapine treatment were in the normal range, with the exception of a slightly elevated level in an antipsychotic-naïve patient at baseline, which resolved at follow-up.

6.3.3.5 Risperidone A long-term (up to 1 year) study [74], investigating the effect of haloperidol, olanzapine and risperidone on serum PRL levels in a naturalistically treated first-episode psychosis population ($n = 110$), found that after 1 year of treatment, elevated PRL levels (≥29.2 ng/ml for women and ≥17.7 ng/ml for men) persisted in most patients treated with risperidone. Patients treated with risperidone experienced a substantial increase at 3 months, resulting in PRL levels above the reference range in 90 % of men and 87 % of women. The levels decreased at 1 year, although still more than 70 % of the patients remained above the normative range. Van Bruggen et al. [89] compared the effect of olanzapine and risperidone on hormonal state in 40 patients with a first-episode psychosis (HPRL defined as ≥15 ng/ml for men and ≥22 ng/ml for women). All patients (100 %), both male and female, using risperidone had increased PRL levels, whereas only four patients (17.4 %) (males) using olanzapine had increased PRL levels. Takahashi et al. [357] found that, after an unsuccessful 12-week treatment with olanzapine (mean dose 16.4 mg), plasma PRL concentration significantly increased after switching from olanzapine to risperidone in first-episode patients. Mean PRL concentration of both men and women significantly increased from 6.5 to 16.9 ng/ml and from 17.4 to 54.2 ng/ml, respectively ($p < 0.001$).

6.3.3.6 Ziprasidone In an 8-week, open-label, multicenter trial with 27 first-episode patients [359] treated with ziprasidone (mean total daily and endpoint doses were 120.30 ± 40.34 and 131.85 ± 51.22 mg/day, respectively), no significant differences in PRL levels from baseline to last observation were found.

6.4 PRL and Newly Approved Antipsychotics

In 2009 and 2010, three new antipsychotics were approved by the FDA: asenapine (Saphris™, Schering-Plough,

Kenilworth, NJ, USA), iloperidone (Fanapt™, Vanda Pharmaceuticals, MD, USA), and lurasidone (Latuda™, Sunovion Pharmaceuticals, Inc., Marlborough, MA, USA) [360]. These newly approved antipsychotics appear to share the same primary mechanism of action with the SGAs. Like most other SGAs, each of these newly approved antipsychotics binds with relatively high potency to 5-HT2A and D2R: iloperidone and asenapine display more potent antagonist activity at 5-HT2AR than D2R, while lurasidone displays relatively equivalent binding at both sites [361, 362]. All three agents are FDA approved for the acute treatment of schizophrenia in adults. Asenapine is also approved for the maintenance treatment of schizophrenia and as a monotherapy or as an adjunct to lithium or valproate for the acute treatment of bipolar manic or mixed episodes, with or without psychotic features [361, 363–370].

6.4.1 Asenapine

Asenapine has a low propensity to cause PRL elevation [361, 371–375]. The PRL profile of asenapine appears to be similar to that of clozapine [376]. Thus, PRL elevation can occur, but at a rate lower than that observed for olanzapine [299, 377, 378] or risperidone [299, 369]. Incidence rates of clinically significant HPRL are generally low [379]. In studies with patients with acute schizophrenia, HPRL (≥2 × upper limit of normal) occurred in 9 % of asenapine recipients (asenapine 5 mg/day) [379, 380]. Incidence rates of marked HPRL (≥4 × upper limit of normal) with asenapine in acute and stable schizophrenia, and bipolar patients were 4–5 % (asenapine 5 and 10 mg BID or twice a day) [376], 2.8 % (asenapine mean dose 17.5 mg/day) [381] and 6.5 % (asenapine mean dose 16.3 mg/day) [382], respectively. Studies [382–385] examining the long-term safety of asenapine in patients with schizophrenia and bipolar disorder showed small mean declines in PRL levels. In the 52-week, double-blind comparison of asenapine (5 or 10 mg BID, $n = 913$) and olanzapine (10–20 mg once daily, $n = 312$) by Schoemaker et al. [384], plasma PRL levels decreased within the first 2 weeks from elevated levels at baseline (between 28 and 30 ng/ml) to normal PRL levels in both treatment groups and remained relatively stable during the remainder of the study. During the extension phase [385], there were only minor further changes in PRL levels.

6.4.2 Iloperidone

As with other drugs that antagonize D2R, iloperidone elevates PRL levels [386]. However, the effect of iloperidone on PRL is reported to be low [360, 361, 387–395] and transient with acute onset of treatment [362]. Short-term [389, 396] as well as long-term studies [397] showed PRL levels generally decrease or remain unchanged during iloperidone treatment. However, there does appear to be a potential for PRL elevations in some subjects [389, 398, 399]. In a pooled analysis of three 6-week, prospective, randomized, multicenter, double-blind, placebo- and comparator-controlled trials ($n = 1,943$), patients were exposed to three dose ranges of iloperidone (4–8, 10–16 and 20–24 mg/day). PRL levels were generally decreased after treatment with two iloperidone dosages; least squares mean changes in PRL from baseline to endpoint were −38 and −23.1 ng/ml in patients receiving iloperidone 4–8 and 10–16 mg/day, respectively. PRL levels were not available for the iloperidone 20–24 mg/day group [396]. However, some other data suggest that higher doses of iloperidone can actually induce HPRL. In a 4-week, double-blind, placebo-controlled trial, 14.8 % of iloperidone (24 mg/day)-treated patients with acute exacerbations of schizophrenia had values outside the upper extended reference range for PRL (not defined), compared with 1.5 % of patients in the placebo group [389]. The insert label of iloperidone, referring to the same trial, however, mentions that elevated plasma PRL levels were observed in 26 % of adults treated with iloperidone 24 mg/day, compared with 12 % in the placebo group [386]. Nevertheless, mean PRL change from baseline remained almost unchanged (+2.6 ng/ml) compared with a decrease of 6.3 ng/ml in the placebo group [389]. Results from a very recent open-label extension trial showed essentially unchanged or decreased levels of serum PRL during long-term (25-week) treatment with iloperidone 24 mg/day (12 mg BID). PRL mean changes from baseline to endpoint for patients switched from ziprasidone and placebo to iloperidone were −7.7 ng/ml (SD 38.7) and +5.1 ng/ml (SD 14.6), respectively. For patients who continued iloperidone treatment, mean PRL change from baseline to endpoint was −15.2 ng/ml (SD 27.9) [397].

6.4.3 Lurasidone

Although lurasidone is reported to induce modest, dose-dependent PRL elevations [400, 401], especially at the beginning of treatment [402], as well as HPRL in some patients [71, 403, 404], in many patients it seems to be associated with no clinically meaningful PRL alterations [71, 405–408].

Product labeling notes that short-term, placebo-controlled trials found small dose- and gender-related (higher in females) effects on PRL levels, with a median change from baseline to endpoint of 0.4 ng/ml for all lurasidone-treated schizophrenic patients (−1.1 ng/ml with 20 mg/day, −1.4 ng/ml with 40 mg/day, −0.2 ng/ml with 80 mg/day, 3.3 ng/ml with 120 and 160 mg/day), compared with

−1.9 ng/ml for placebo [404]. The proportion of patients with PRL elevations ≥5 × upper limit of normal (not defined) was 2.8 % for lurasidone-treated patients versus 1 % for placebo-treated patients. For women, this occurred in 5.7 % for lurasidone versus 2 % for placebo; for men in 1.6 % for lurasidone versus 0.6 % for placebo [404]. In a 6-week, double-blind, placebo-controlled trial with a fixed dose of lurasidone 80 mg ($n = 90$) or placebo ($n = 90$), treatment with lurasidone was associated with a small but significant median increase in PRL levels at endpoint compared with placebo (+2.4 vs. −0.3 ng/ml, $p < 0.05$). Larger median increases were observed in the small group of women (+9.2 ng/ml) compared with in men (+1.4 ng/ml). A moderate correlation was seen between serum lurasidone concentrations and PRL levels. Three patients had treatment-emergent PRL concentrations between 50 and 100 ng/ml at endpoint [409]. Pooled data from five double-blind, placebo-controlled, short-term studies of schizophrenia patients ($n = 1{,}004$) with an acute exacerbation showed the mean end-point change in PRL (ng/ml) was +1.1 for lurasidone vs. −0.5 for placebo [410].

Consistent with prior short-term studies of lurasidone, there was no indication for clinically relevant changes in PRL in four very recently published short-term studies on lurasidone [401, 403, 411, 412]. In the randomized, 6-week, open-label study of McEvoy et al. [411] (lurasidone 40–120 mg/day), mean changes from baseline to last-observation-carried-forward (LOCF) endpoint in PRL concentrations were −0.5 and 2.0 ng/ml for male and female patients, respectively. PRL ≥5 × upper limit of normal (not defined) was observed in 2/219 subjects (0.9 %), all in the randomized group that initially received lurasidone 80 mg/day for 14 days. Mean change from baseline to LOCF endpoint in PRL concentrations in this dosage group was also higher (9.6 ng/ml) for female patients, compared with all other dosages/gender groups [40 mg/day for 2 weeks and 40 mg/day for 1 week, increased to 80 mg/day on day 8 for week 2 (up-titration group)], where mean changes in PRL concentrations decreased or remained almost unchanged. In the same line, the 6-week, randomized, placebo-controlled study of Nasrallah et al. [403] showed modest increases in PRL following treatment with lurasidone (40, 80 or 120 mg/day), compared with placebo. Median changes from baseline PRL levels were −0.9, 1.3 and 2.4 ng/ml for patients receiving lurasidone 40, 80 and 120 mg/day, respectively, compared with 0.4 ng/ml for those receiving placebo. Changes were greater among female than among male patients, particularly in those receiving lurasidone 120 mg/day (median change, 1.4 ng/ml for men and 6.4 ng/ml for women). However, a change from normal to high (>17.7 ng/ml for men, >29.2 ng/ml for women) PRL levels occurred in 8.3, 16.1 and 19.7 % of patients receiving lurasidone 40, 80 and 120 mg/day, respectively, compared with 4.9 % of patients receiving placebo. Ogasa et al. [401] found median PRL levels at the week 6 LOCF endpoint were modestly increased relative to baseline in the lurasidone 40 (3.5 ng/ml) and 120 mg/day (7.7 ng/ml) groups, but not in the placebo group (−1.3 ng/ml). Again, a sex difference was observed, with lurasidone producing greater increases in PRL in women (3.8 and 21.1 ng/ml in the lurasidone 40 and 120 mg/day, respectively) than in men (3.4 and 5.6 ng/ml in the lurasidone 40 and 120 mg/day, respectively). Two patients discontinued the study because of elevated PRL >200 ng/ml. Finally, Loebel et al. [412], in another 6-week, randomized, double-blind, placebo- and active-controlled trial, found dose-related median changes in PRL levels at the 6-week LOCF endpoint for the lurasidone 80 and 160 mg/day treatment groups to be 0.8 and 3 ng/ml, respectively. This increase in PRL levels was found primarily in female subjects.

Uncontrolled longer-term trials (primarily open-label extensions) reported decreases in PRL concentrations. Lurasidone was associated with a median change in PRL of −0.9 ng/ml at week 24, −5.3 ng/ml at week 36, and −2.2 ng/ml at week 52 [404]. One uncontrolled open-label extension study even reported a mean change of −12.7 ng/ml at week 52 [413]. A very recently published open-label extension study by Stahl et al. [414] observed small changes in PRL levels. PRL mean changes from baseline to endpoint (month 6) for patients switched from olanzapine and placebo to lurasidone were −5.6 ng/ml (SD 10.8) and +6.0 ng/ml (SD 18.9), respectively. For patients who continued lurasidone treatment, mean PRL change from baseline to endpoint was +2.7 ng/ml (SD 37.0). Little change in PRL concentrations from baseline to endpoint were equally reported in controlled trials. A 12-month, double-blind, active-controlled study on the long-term safety and tolerability of lurasidone in schizophrenia showed essentially no change in PRL levels for male as well as female patients treated with once-daily, flexible-dosed lurasidone (40–120 mg). Median changes from baseline to endpoint (month 12) were −0.5 and +0.1 ng/ml for male and female patients, respectively [71].

Recently, a systematic review and exploratory meta-analysis [415] of randomized, placebo-controlled trials was conducted by our research group to assess the efficacy of paliperidone (ER formulation), iloperidone, lurasidone and asenapine on several dimensions of symptoms (positive, negative, general psychopathology, depression, anxiety), as well as their tolerability profile in the short-term treatment (≤12 weeks) of schizophrenia and bipolar disorder, compared with placebo. Although all these antipsychotics statistically significantly ($p < 0.05$) increased PRL levels more than placebo, paliperidone especially was associated with a higher risk to produce PRL increase, compared with

placebo [relative risk 8.52, confidence interval (CI) 4.94–14.67; number needed to harm 2.3, CI 1.3–4.4]. Whereas, compared with placebo, mean changes in PRL levels (ng/ml) with asenapine [weighted mean difference (WMD) 4.517, CI 1.882–7.152] and lurasidone (WMD 9.13, CI 4.9–13.3) treatment were low to moderate, paliperidone was associated with substantial and consistent increases in serum PRL, both in men (WMD 23.85, CI 18.56–29.14) and women (WMD 71.23, CI 54.57–87.89). The mean change in PRL levels (ng/ml) with iloperidone treatment, compared with placebo, was also high (WMD 26.87, CI 12.27–41.47). However, as only one report (containing four trials) on iloperidone was included in this analysis and the heterogeneity value for these results was extremely high (98.5 %), one should consider this result to be unreliable. Therefore, we concluded that asenapine, showing a low propensity to cause PRL elevation at the beginning of treatment, has a PRL profile that appears to be similar to that of clozapine; lurasidone is probably more comparable to ziprasidone and olanzapine; paliperidone elevates PRL levels in a fashion similar to risperidone.

A recently published meta-analysis of 212 blinded, randomized controlled trials ($n = 43{,}049$), comparing the efficacy and tolerability of 15 antipsychotic drugs in schizophrenia, found that aripiprazole, quetiapine, asenapine and iloperidone did not cause significantly increased PRL concentrations, compared with placebo. Paliperidone and risperidone were associated with significantly greater PRL increases than all other drugs. Because of methodological reasons, clozapine and amisulpride could not be included in the analysis. The ranking in order of PRL increase presented by these authors is as follows: amisulpride > paliperidone > risperidone > lurasidone > ziprasidone > iloperidone > olanzapine > asenapine > placebo > quetiapine > aripiprazole [299].

Based on our review, PRL side-effect profiles of SGAs and newly approved antipsychotics are given in Table 4.

Table 4 Prolactin side-effect profile of novel and newly approved antipsychotics

	Prolactin elevation
Amisulpride	+++
Aripiprazole	0
Asenapine	+
Clozapine	+
Iloperidone	+
Lurasidone	++
Olanzapine	++
Paliperidone	+++
Quetiapine	+/−
Risperidone	+++
Sertindole	+
Ziprasidone	++

0 minimal to no risk, +/− minimal risk, + low risk, ++ moderate risk, +++ high risk

6.5 Possible Explanations of the PRL-Elevating Tendency of Antipsychotics

Several hypotheses have been put forward to explain the different PRL profiles of antipsychotic medication. A correlation has been proposed between the fastness of dissociation from the D2R and the PRL-sparing properties of certain antipsychotics ("fast dissociation hypothesis"); antipsychotics associated with lesser degrees of PRL elevation have fast D2R dissociation [5]. Clozapine and quetiapine have the fastest rate of dissociation from D2R; olanzapine has an intermediate rate of dissociation [416]. Quetiapine, as an example of an antipsychotic with fast dissociation, is associated with central D2R occupancy that falls from initial blockade of 60–70 % at 2 h post-dosing to around 30 % at 24 h [417]. Conversely, FGAs, as a group, and risperidone dissociate slowly from the D2R, resulting in more prolonged blockade and therefore greater PRL release [5, 418]. However, although its high PRL risk is well known, amisulpride is rapidly dissociated from the D2R [416, 419]. Moreover, according to a recent study, haloperidol, also a highly PRL-releasing antipsychotic, showed a rather fast dissociation profile [420]. It is thus conceivable that other factors, in addition to kinetic properties, contribute to the PRL-releasing properties of antipsychotics.

The different penetration potencies of the various antipsychotics with reference to the blood–brain barrier are another explanation that has been put forward. While the antipsychotic effect is based on the antagonism of receptors situated within the central nervous system, PRL elevation is associated with blockade of D2R at the level of the anterior pituitary lactotroph cells [420]. Anatomically, the pituitary gland lies outside the blood–brain barrier [5, 27]. The lesser ability of amisulpride, sulpiride and risperidone, in comparison with olanzapine and quetiapine, to penetrate this barrier could explain the tendency of these compounds to induce elevated PRL values [80, 316, 418]. Their lesser penetration at therapeutic dose levels leads to a greater D2R occupancy in the pituitary area and therefore to a greater increase of the PRL values [316]. Especially for amisulpride, a decreased penetration of the blood–brain barrier would explain the marked tendency of this medicine to cause a rise in PRL values [195, 421]. This hypothesis is supported by the observation that domperidone, a D2 blocker that does not cross the blood–brain barrier, is associated with significant PRL elevation [422].

The quantification of dopamine D2R occupancy in the pituitary by several antipsychotics using PET scans has not

been reported until recently. Arakawa et al. [80] demonstrated that the D2R occupancy in the pituitary was a predictor of HPRL. These researchers measured dopamine D2R binding of risperidone, olanzapine, haloperidol and sulpiride in the pituitary (and temporal) cortex in schizophrenic patients. A significant positive correlation was observed between the plasma concentration of PRL and dopamine D2R occupancy in the pituitary ($p = 0.001$) by the various antipsychotic drugs. The study also indicated that a 50 % D2R occupancy in the pituitary might represent a threshold level of HPRL. The brain/plasma concentration ratio, indicating the penetrating capability across the blood–brain barrier, seemed to be a good characteristic biomarker of each antipsychotic drug for the risk of HPRL at therapeutic dose.

The largest study to date ($n = 481$) [69], investigating the relationship between serum PRL concentration and estimated D2R blockade with risperidone ($n = 172$), olanzapine ($n = 211$) or ziprasidone ($n = 98$) in patients with schizophrenia, demonstrated a threshold of HPRL at 73 % of striatal D2R occupancy. However, this threshold seems to differ among antipsychotic drugs. The cut-off points for HPRL were 68–70 % for risperidone, 77 % for olanzapine and 55 % for ziprasidone. This means the threshold for HPRL in D2R occupancy may lie somewhat on the lower side of the established therapeutic window with antipsychotics (i.e., 65–80 %), and therefore highlights the need for the use of the lowest possible dose to avoid this hormonal side effect.

However, D2R blockade on the lactotrophs certainly is not the sole major cause leading to HPRL [49, 420]. In the first systematic examination of the effects of different antidopaminergic mechanisms on PRL concentration in healthy volunteers, Veselinović et al. [49] performed a 7-day intervention with three substances with entirely different mechanisms of action: aripiprazole (partial D2R agonist), haloperidol (D2R antagonist) and reserpine (a vesicular monoamine transporter type 2 blocker). The completely different antidopaminergic mechanisms of haloperidol and reserpine both resulted in a significant increase in PRL levels. PRL levels changed significantly with haloperidol (from 177.2 ± 74.6 to 350.7 ± 202.6 mU/l, $p < 0.0001$) but not after aripiprazole (from 160.9 ± 65.0 to 189.6 ± 209.6 mU/l, $p = 0.69$) or placebo (from 211.6 ± 113.4 to 196.1 ± 85.6 mU/l, $p = 0.8$). However, reserpine, not directly interacting with D2R, caused the most distinct increase (from 149.6 ± 80.2 to 540.3 ± 280.8 mU/l, $p < 0.0001$). Thus, these findings indicate that the dopaminergic regulation of PRL secretion is not only related to the D2-like dopamine receptors on the lactotroph cells itself. Although PRL release is controlled primarily by dopamine acting on D2R, other neurotransmitter receptor systems probably are involved. Therefore, the serotonergic antagonistic activity of the SGAs has also been proposed as another explanation [423].

Finally, genetic factors also seem to play an important role. Genetic D2R polymorphisms may explain why some individuals are more prone to develop HPRL [424, 425]. The TaqIA A1 [26, 424] and the A-241G alleles are associated with higher PRL concentration, and adverse events potentially related to HPRL were found to be four times more common in TaqIA A1 allele carriers [425].

7 Consequences of HPRL

Multiple signs and symptoms are associated with HPRL (see Table 5) [6, 15, 23, 46, 57, 159, 426, 427].

For years there has been considerable debate about the impact of HPRL in schizophrenic patients. Frequently, HPRL in these patients has been linked to sexual dysfunctions, osteoporosis and even breast cancer.

Although it is often suggested that increased PRL levels are responsible for sexual dysfunctions in schizophrenic patients, one is struck by the fact that the literature on this topic is limited [128, 428] and that the evidence is contradictory and inconclusive [128, 129, 429, 430]. Some studies have shown an association between sexual side effects and PRL elevation, while others have failed to support this [431]. From all evidence taken together, one can conclude that it is highly unlikely that PRL elevation is the sole cause of sexual dysfunctions, and that multiple causes for sexual dysfunction in schizophrenic patients should be considered [5]. Specific pharmacological profiles, especially with regard to the noradrenergic and serotonergic receptors, the impact of the illness itself (e.g., the presence of negative or depressive symptoms), and the impact of patients' psychosocial settings need to be considered as well [129, 429]. Moreover, a recent study, assessing sexual function in individuals at ultra-high risk of psychosis, showed that sexual function is already impaired prior to the onset of the first episode (and thus initiation of treatment with antipsychotics), with half of these individuals showing evidence of sexual dysfunction. These high rates of dysfunction were not specific to particular domains of sexual function [432].

Also regarding antipsychotic medication and osteoporosis conflicting results exist. Some studies [433–437] suggest antipsychotics contribute to a small increase in the risk of fractures, while others do not [438, 439]. Of the studies examining the relationship between antipsychotic-induced HPRL and bone mineral density loss, about 60 % found some effects of HPRL on bone mineral density [440]. However, as in the case of sexual dysfunctions, the etiology of osteoporosis is multifactorial [441] and the relative contributions of antipsychotic-related HPRL and

Table 5 Consequences of hyperprolactinemia

Irregular menstrual cycle
Amenorrhea: complete absence of menstruation
Menorrhagia: excessive menstrual bleeding
Oligomenorrhea: long and irregular intervals between two successive menstrual periods
Anovulation (absence of ovulation)
Polymenorrhea: short and irregular intervals between two menstrual periods
Abnormal semen production
Hypospermia (low sperm count)
Azoospermia (complete absence of sperm cells in the semen)
Fertility disorders/infertility
Galactorrhea (secretion of milk from the nipples in men and the same phenomenon in non-lactating women) and gynecomastia (excessive development of the male mammary glands)
Sexual dysfunction
Decreased libido, impaired arousal, impaired orgasm
Erectile dysfunction and ejaculation dysfunction
Impotence
Hypogonadism
Inadequate functioning of the sex glands (gonads), as a result of which the levels of testosterone in the blood in men and of estrogen in women are abnormally low
Hirsutism (male hair growth) and acne in women, due to relative androgen excess compared with low estrogen levels
Obesity
Decreased bone mineral density, which may lead to increased risk of osteoporosis
Breast cancer (?)

the influence of important unhealthy lifestyle behaviors in this population (such as smoking and reduced physical activity) remain unclear; more definitive, prospective, long-term studies that directly assess relevant confounding variables are needed [440]. The precise link between HPRL and osteoporosis also remains to be elucidated [5]. There are two potential mechanisms by which HPRL may result in bone mineral density reductions: a direct one in the absence of hypogonadism, and an indirect one mediated (via the hypothalamic–pituitary–gonadal axis) through suppression of gonadal hormone levels [9, 442].

There is accumulating epidemiological, clinical, and biological evidence confirming a role of PRL in human breast cancer risk [8, 443, 444]. However, although an association has been demonstrated, a cause and effect relationship is yet to be established [445]. In vitro and in vivo studies strongly support that PRL is involved in processes related to late-stage carcinogenic effects of breast cancer, including increasing cell proliferation and reducing apoptosis. Thus, it is possible that high circulating PRL levels are important only after a preclinical lesion has developed and promotes late-stage carcinogenesis [443]. The majority of the limited number of studies in which the risk of breast cancer has been investigated in patients treated with FGAs (e.g., [446–448]) or SGAs [449] did not disclose an increased risk of breast cancer. Even exclusive users of PRL-elevating SGAs, such as risperidone, were found not to be at an increased risk of breast cancer [449]. However, based on the above mentioned cancer research on the association between breast cancer risk and PRL, it seems prudent to avoid PRL-elevating medications in women with a history of breast cancer and possibly in those with a strong family history of breast cancer [46, 55, 67, 427].

8 Conclusion

Hyperprolactinemia is often defined as a PRL concentration greater than the upper reference limit of the local laboratory. However, a critical review of the literature shows a substantial variation in reference intervals for serum PRL. Differences in study design, the use of concomitant PRL-elevating medication, the short overall study duration of most studies, the lack of PRL baseline values and information on previous treatments and/or PRL measurements in a substantial number of studies, make the interpretation and comparison of data even more difficult. As rates of HPRL will be dependent on many factors, such as the timing of PRL measurement, these factors may be relevant confounders for some data sets. Units of measurement also cause some confusion: US data are often presented in ng/ml whereas most UK and EU data are in mIU/l; conversion rates are not standardized and vary depending on the assay employed. Finally, clinical reports do not always report the reference interval for serum PRL while speaking about HPRL. Although many studies on PRL are done by pharmaceutical companies, a recent large-scale meta-analysis on antipsychotics (including an analysis on the PRL-inducing properties of these compounds) showed efficacy outcomes did not change substantially when pharmaceutical industry sponsorship was accounted for in meta-regressions and sensitivity analyses [299].

Antipsychotics differ in their propensity to cause PRL elevation. Although a discrimination of "PRL-sparing" versus "PRL-elevating" antipsychotic drugs may provide the clinician with treatment choices in order to avoid or mitigate HPRL, these terms can be misleading for clinicians, concluding that antipsychotic medications such as aripiprazole, clozapine and quetiapine can never be associated with significant HPRL. Actually, all antipsychotics (FGAs, SGAs and newly approved antipsychotics) have the propensity, especially during the first hours of treatment, to elevate PRL levels above the upper limit of normal and to induce HPRL. However, differences between antipsychotic

drugs with respect to PRL elevation are large. Among the FGAs, especially the high PRL risk of sulpiride is known. Among the SGAs, amisulpride, risperidone and paliperidone are associated with the greatest elevation of PRL. Olanzapine and ziprasidone do this with a moderate severity. Although clozapine can raise (generally transiently) PRL levels, these mostly remain within normal range. During treatment with quetiapine, PRL levels are mostly found to remain unchanged or to decrease over all dosages, in most cases from levels at switch of treatment. Aripiprazole shows the most benign PRL profile as, in most studies, PRL levels were found to remain unchanged or to decrease, even below those expected from placebo, in adults as well as in children and adolescents. Nevertheless, important consideration must always be given to adolescents and children, who may be more vulnerable than adults to PRL increases and at higher risk of developing HPRL. Recent research also has shown that HPRL can be pre-existing in a substantial proportion of antipsychotic-naïve patients with first-episode psychosis or at-risk mental state. This pre-existing vulnerability and/or a genetic predisposition must therefore be taken into account when considering this important antipsychotic side effect in these populations. Due to the overall paucity of data on the newly approved antipsychotics, there is still insufficient evidence to draw firm conclusions concerning the PRL safety profile of these compounds. Therefore, there is a clear need for further controlled trials to evaluate how safe these newly approved antipsychotics really are and which of these agents are potentially less problematic regarding PRL than most other "older" SGAs.

Prolactin elevations with antipsychotic medication are mostly gender-related and dose-related. However, antipsychotics having a high potential for PRL elevation (amisulpride and risperidone) can have a profound impact on PRL levels even at relatively low doses, while PRL levels with antipsychotics having a minimal effect on PRL (aripiprazole) can remain unchanged over all dosages. Although tolerance and decreases in PRL values after long-term administration of PRL-elevating antipsychotics can occur, these elevations, in most cases, remain above the upper limit of normal.

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