

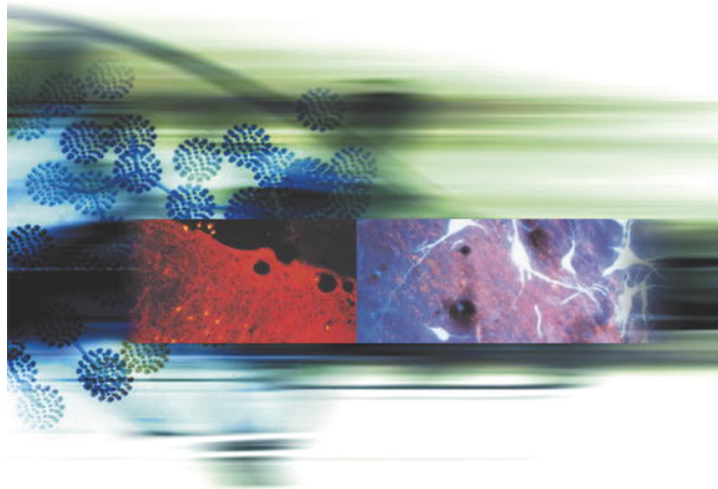
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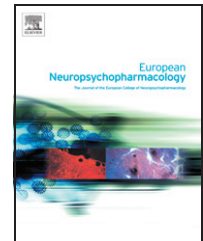
Physical Health Considerations in Psychiatry:  
Views on Recognition, Monitoring and Management

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# Prolactin awareness: An essential consideration for physical health in schizophrenia

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## KEYWORDS

Hyperprolactinaemia;  
Antipsychotics;  
Schizophrenia;  
Physical health

## Abstract

Elevations in serum prolactin levels (hyperprolactinaemia) are a common side effect of conventional and some atypical antipsychotic treatments. In patients with schizophrenia, the adverse effects of antipsychotic-induced hyperprolactinaemia on physical health (e.g. fertility problems, sexual dysfunction and reduced bone mineral density) are gaining attention. Accumulating evidence shows consistent 'prolactin-raising' effects of conventional antipsychotics and risperidone compared with other current atypical antipsychotics, which are more likely to have 'prolactin-sparing' properties. Prolactin-sparing antipsychotics (for example, aripiprazole and quetiapine) tend to show lower frequencies of hyperprolactinaemia-associated side effects. In recent studies, aripiprazole-treated patients have demonstrated lower prolactin levels compared with patients receiving other prolactin-sparing antipsychotics. There is a lack of robust recommendations for monitoring prolactin elevation among patients receiving antipsychotics. Decreasing the antipsychotic dose or switching to a prolactin-sparing medication are possible management options for antipsychotic-induced hyperprolactinaemia. There is a need to increase awareness and understanding of the impact of antipsychotic-induced hyperprolactinaemia on physical health in schizophrenia.

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## 1. Introduction

Physical health is frequently impaired in patients with schizophrenia. As well as lifestyle, the adverse effects of antipsychotic treatment are implicated in the increased risk of co-existing physical health problems, such as metabolic syndrome, diabetes and cardiovascular (CV) disease (Newcomer, 2005). Until recently, increased prolactin levels (hyperprolactinaemia), a common side effect of conventional and some atypical antipsychotic

treatments, received little attention and was rarely monitored. Hyperprolactinaemia has been shown to adversely influence fertility, sexual function and bone mineral density (Meaney et al., 2004). There is growing awareness of the detrimental effects of elevated prolactin on physical health in patients with schizophrenia treated with antipsychotics.

This paper reviews existing and emerging evidence on antipsychotic-induced hyperprolactinaemia and explores the relationship between antipsychotic effects on prolactin levels and physical health problems in patients with schizophrenia. Current monitoring and management options for antipsychotic-induced hyperprolactinaemia are also reviewed.

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## 2. Underlying causes of hyperprolactinaemia

Prolactin, a hormone secreted by the anterior pituitary gland, is primarily regulated by dopamine. Levels of prolactin rise during pregnancy and after childbirth to promote the production of milk. However, elevated prolactin levels can be attributed to non-physiological as well as physiological factors (Verhelst and Abs, 2003) (Table 1).

### 2.1. What constitutes an abnormal serum prolactin level?

Serum prolactin values are subject to significant inter- and intra-individual variation, but the upper limit of the normal range is generally reported as 15–25 µg/L in both males and females (Mikhail and Bevan, 1988; Lenton et al., 1979; Marken et al., 1992). Serum prolactin levels in excess of 200 µg/L signal a prolactin-secreting pituitary adenoma (prolactinoma), which accounts for 30–40% of all pituitary tumours (Molitch, 2001). Increases in prolactin levels of 25–200 µg/L frequently occur as a result of treatment with some medications, which include antipsychotics, antidepressants and antiemetics (Verhelst and Abs, 2003). Hyperprolactinaemia as a consequence of antidepressant treatment has been shown to occur less frequently than antipsychotic-induced hyperprolactinaemia (Marken et al., 1992).

## 3. Antipsychotic-induced hyperprolactinaemia in schizophrenia

Antipsychotic treatment effects on serum prolactin levels are well acknowledged (Haddad and Wieck, 2004), and are

**Table 1** Underlying causes of hyperprolactinaemia (Verhelst and Abs, 2003)

	Cause
Physiological	Pregnancy
	Nursing
	Stress <sup>a</sup>
	Exercise <sup>a</sup>
	Sleep <sup>a</sup>
Pathological	Pituitary disorders – e.g. micro- or macroprolactinoma, acromegaly
	Hypothalamic disorders – e.g. craniopharyngioma, pituitary stalk section, glioma
Pharmacological	Antipsychotics (risperidone, amisulpride, and typicals)
	Antidepressants (SSRIs, clomipramine)
	Antiemetics
	Antihypertensives
	Oestrogens
	Verapamil
	Protease inhibitors
Other	Chronic renal failure
	Idiopathic hyperprolactinaemia

Causes included above are not a comprehensive list. SSRI, selective serotonin reuptake inhibitor.

<sup>a</sup> Causes temporary increase in prolactin secretion.

**Table 2** Possible direct and indirect consequences of hyperprolactinaemia (Meaney et al., 2004; Haddad and Wieck, 2004)

	Symptom
Direct	Amenorrhoea, Galactorrhoea Gynaecomastia
Indirect	Infertility
	Menstrual abnormalities
	Sexual dysfunction: Libido decreased; erectile dysfunction
	Acne/hirsutism in women
	Reduced bone mineral density (fractures)
	Breast and endometrial cancer Increase of cardiovascular risk <sup>a</sup>

<sup>a</sup> (Sun et al., 2005).

generally considered to be the cause of increased serum prolactin concentrations in patients with schizophrenia. Several studies have shown that prolactin levels are not elevated in patients who are not receiving antipsychotic treatment (Haddad and Wieck, 2004). Moreover, there is evidence to suggest that unmedicated women with schizophrenia have lower mean daily prolactin levels than their healthy counterparts (Rao et al., 1994). Treatment with conventional antipsychotics in patients with schizophrenia has been shown to increase serum prolactin concentrations 5–10 times above that of healthy control subjects (Marken et al., 1992). Furthermore, one study showed that prolactin levels rose within 30–60 min of intramuscular administration of the conventional antipsychotic, chlorpromazine (Meltzer and Busch, 1983). Elevations in serum prolactin as a result of conventional antipsychotic treatment have been observed to be dose-dependent (Smith et al., 2002).

Reports have consistently shown a higher prevalence of hyperprolactinaemia in women receiving antipsychotics. Recent cross-sectional studies in the US and UK have estimated hyperprolactinaemia prevalence rates of up to 42% in men and 75% in women with schizophrenia who were receiving conventional antipsychotics or risperidone (Kinon et al., 2003; Smith et al., 2002). The magnitude of conventional antipsychotic-induced serum prolactin elevation has also been shown to be significantly higher in women than men ( $p < 0.0001$ ) (Meltzer et al., 1983).

### 3.1. Consequences of hyperprolactinaemia

Evidence suggests a causal relationship between hyperprolactinaemia and several physical health problems in males and females (Table 2). Notably, hyperprolactinaemia is associated with endocrinological changes (e.g. cortisol, testosterone modifications) (Kovacs and Kovacs, 2006), immunological system changes (Clevenger et al., 1998), as well as growth hormone alterations (Goffin and Kelly, 1996).

Although empirical data supporting a definitive effect of antipsychotic-induced hyperprolactinaemia on physical illnesses are currently limited, secondary evidence indicates a relationship between antipsychotic treatment and prolactin-related physical health problems. For example, in one study

that included 150 women, 14% were observed to develop galactorrhoea within 75 days of initiating treatment with conventional antipsychotics (Windgassen et al., 1996), whereas another study demonstrated menstrual irregularities in up to 48% of women receiving antipsychotic treatment (Haddad and Wieck, 2004; Kinon et al., 2003). Furthermore, reduced bone mineral density has been demonstrated in 57% of men and 32% of women treated with prolactin-raising antipsychotics for more than 10 years (Meaney et al., 2004). More recently, a case-control study investigated whether potential antipsychotic-induced decreases in bone mineral density could confer an increased risk of hip fractures in patients with a history of schizophrenia (Howard et al., 2007). Following a search of the General Practice Research Database, which identified 16,341 cases of hip fracture and 29,889 controls, analyses revealed a significant association between the risk of hip fracture and schizophrenia (OR=1.73, 95% CI 1.32–2.28) and prolactin-raising antipsychotics (OR=2.6, 95% CI 2.43–2.78). Multivariate analyses attributed the association between schizophrenia and hip fracture risk to antipsychotic use.

Sexual dysfunction appears to be inherent in patients with schizophrenia, but is also frequently associated with antipsychotic treatment. More than 50% of males and 30% of females have been shown to experience sexual dysfunction during conventional antipsychotic treatment (Ghadirian et al., 1982). The extent to which hyperprolactinaemia contributes to the observed antipsychotic effects on sexual dysfunction is unclear, but there is some indication that sexual dysfunction worsens with serum prolactin elevation (Burke et al., 1994; Ghadirian et al., 1982).

Although early epidemiological studies (which may have been subject to methodological limitations) of patients with

schizophrenia were inconsistent (Haddad and Wieck, 2004), a more recent large retrospective study has implied an association between the use of prolactin-raising antipsychotics and an increased risk of breast cancer among women (Wang et al., 2002). Women who had received dopamine receptor antagonists ( $n=52,819$ ), when compared with women who had not been exposed to these agents ( $n=55,289$ ), demonstrated a 16% increase in the incidence of breast cancer. Moreover, larger cumulative doses of antipsychotics were associated with a higher risk of breast cancer. Use of antipsychotics may also be associated with an increased risk of endometrial cancer (risk estimate of 5.4) according to a case-control study of 41 premenopausal women with confirmed endometrial cancer who were matched with 123 controls (Yamazawa et al., 2003). In this study, the investigators concluded that antipsychotic-induced hyperprolactinaemia may account for the heightened risk of endometrial cancer. A retrospective pharmacovigilance study has also suggested an association between antipsychotic-induced hyperprolactinaemia and development of pituitary tumours (Szarfman et al., 2006).

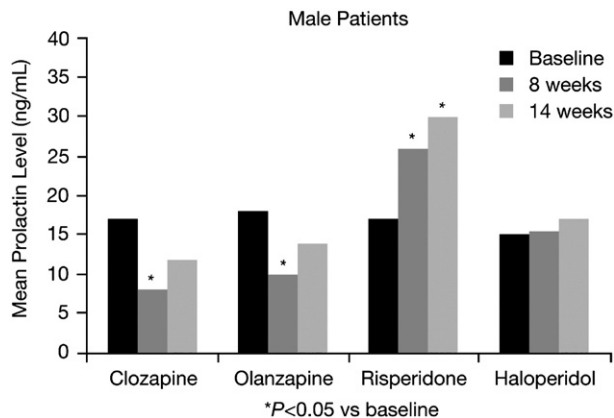
#### 4. Prolactin-sparing vs. prolactin-raising antipsychotic treatment effects

Antipsychotic treatments differ in the extent to which they affect serum prolactin levels (Table 3). There is general agreement that conventional antipsychotics and some atypical antipsychotics (risperidone and amisulpride) elevate prolactin levels ('prolactin-raising'), whereas the atypical antipsychotics, aripiprazole, clozapine, olanzapine, quetiapine and ziprasidone are less likely to increase prolactin

**Table 3** Effects on serum prolactin levels in comparative studies of antipsychotic treatments

Antipsychotic	Study design	Effect on serum prolactin levels
Aripiprazole vs. olanzapine (Chrzanowski et al., 2006)	52-week, open-label, extension study of patients with acute relapsing or chronic schizophrenia	Higher mean prolactin levels with olanzapine than aripiprazole at study endpoint (9.30 ng/mL vs. 0.78 ng/mL; $p=0.003$ )
Olanzapine vs. risperidone (Perlis et al., 2006b)	3-week, randomized, double-blind study of patients with bipolar I disorder	Risperidone-treated patients more likely to experience elevated prolactin levels than olanzapine (51.73 ng/mL vs. 8.23 ng/mL; $p<0.001$ )
Risperidone vs. olanzapine vs. quetiapine (Staller, 2006)	Naturalistic, cross-sectional study for $\geq 6$ months in outpatient youths with psychiatric disorders	Significantly higher mean prolactin levels among risperidone-treated patients than controls or quetiapine- or olanzapine-treated patients (22 ng/mL vs. 6.4, 10.4, 6.7 ng/mL; $p<0.05$ )
Risperidone vs. haloperidol (Schooler et al., 2005)	Long-term (median duration of treatment=206 days), double-blind, randomized study in patients with first-episode psychosis	Higher mean prolactin levels in risperidone-treated patients than those treated with haloperidol (73.69 ng/mL vs. 48.16 ng/mL for women, $p<0.003$ ; 34.08 ng/mL vs. 21.81 ng/mL for men, $p<0.0001$ )
Clozapine vs. olanzapine vs. risperidone vs. haloperidol (Volavka et al., 2004)	14-week, randomized, double-blind study of patients with schizophrenia or schizoaffective disorder	Elevation of prolactin levels with risperidone ( $p<0.05$ vs. comparators) and haloperidol (ns) Decreased prolactin levels with clozapine and olanzapine

ns, non significant.



**Figure 1** Comparative analyses of antipsychotics – prolactin level changes over 14 weeks (Volavka et al., 2004). Prolactin levels in schizophrenia and schizoaffective disorder patients treated with clozapine, olanzapine, risperidone, or haloperidol, *The Journal of Clinical Psychiatry*. 65, 57–61, 2004. Copyright 2004, Physicians Postgraduate Press. Adapted or Reprinted by permission.

levels ('prolactin-sparing') (Chrzanowski et al., 2006; Perlis et al., 2006a; Staller, 2006; Volavka et al., 2004). Risperidone, in particular, is associated with markedly increased prolactin levels that appear to be sustained for long periods of time (David et al., 2000; Kleinberg et al., 1999; Volavka et al., 2004). In some studies, risperidone-associated prolactin elevation has been reported to be dose-dependent (4–30 mg/day) (Kleinberg et al., 1999; Volavka et al., 2004). In Fig. 1, the results of one comparative study are shown to illustrate the increase in prolactin with some agents but not others and the comparative table collated in the APA guidelines showing their interpretation of the side effect profiles, including prolactin effects, of the atypicals is shown in Table 4.

Among the prolactin-sparing antipsychotics, short- and long-term studies have demonstrated minimal elevations or decreases in prolactin levels following aripiprazole treatment (Chrzanowski et al., 2006; Marder et al., 2003; Potkin et al., 2003). In comparisons with other prolactin-sparing antipsychotics, aripiprazole has shown a lower likelihood of increasing prolactin levels (Chrzanowski et al., 2006; Kerwin et al., 2007). The 26-week, open-label community-based Schizophrenia Trial of Aripiprazole (STAR) study of aripiprazole or standard of care (SoC) agents (olanzapine, quetiapine or risperidone) found that a higher proportion of patients in the SoC group had potentially clinically relevant prolactin elevations (54.4%) compared with the aripiprazole-treated group (16.8%) (Kerwin et al., 2007). Similarly, a 52-week, open-label comparison of olanzapine and aripiprazole in patients with acutely relapsing or chronic, stable schizophrenia reported minimal effects of aripiprazole on mean serum prolactin concentrations at study endpoint (9.30 ng/mL vs. 0.78 ng/mL;  $p=0.003$ ) (Chrzanowski et al., 2006). Furthermore, no dose-dependent effects on prolactin were evident in a pooled analysis of 932 patients with schizophrenia treated with aripiprazole across the full dose range of 2–30 mg/day (Marder et al., 2003).

As with serum prolactin elevations, antipsychotics demonstrate differential propensities for inducing side effects potentially related to hyperprolactinaemia. Antipsychotics differ, in particular, with respect to their effects on sexual function (Cutler, 2003). A combined analysis of open-label and controlled data from 199 patients revealed that prolactin-raising antipsychotics (conventional antipsychotics and risperidone) were associated with higher frequencies of sexual dysfunctions than the prolactin-sparing antipsychotics clozapine, olanzapine, quetiapine and sertindole (libido loss 43.9% vs. 11.8%; orgasm disturbance 31.7% vs. 5.2%) (Knegtering et al., 2003). These results are in agreement with other reports of a higher degree of sexual dysfunction with conventional antipsychotics and risperidone (Dorevitch et al., 1999; Knegtering et al., 2004).

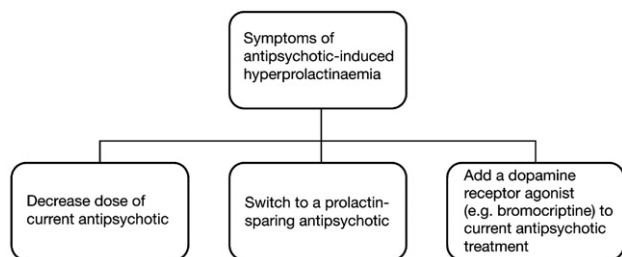
**Table 4** Selected side effects of commonly used antipsychotic medications (Tandon, 1998)

Medication	Extra pyramidal side effects/tardive dyskinesia	Prolactin elevation	Weight gain	Glucose abnormalities	Lipid abnormalities	QTc prolongation	Sedation	Hypotension	Anti-cholinergic side effects
Thioridazine	+	++	+	+ <sup>#</sup>	+ <sup>#</sup>	+++	++	++	++
Perphenazine	++	++	+	+ <sup>#</sup>	+ <sup>#</sup>	0	+	+	0
Haloperidol	+++	+++	+	0	0	0	++	0	0
Clozapine*	0 <sup>+</sup>	0	+++	+++	+++	0	+++	+++	+++
Risperidone	+	+++	++	++	++	+	+	+	0
Olanzapine	0 <sup>+</sup>	0	+++	+++	+++	0	+	+	++
Quetiapine <sup>†</sup>	0 <sup>+</sup>	0	++	++	++	0	++	++	0
Ziprasidone	0 <sup>+</sup>	+	0	0	0	++	0	0	0
Aripiprazole <sup>§</sup>	0 <sup>+</sup>	0	0	0	0	0	+	0	0

0 = no risk or rarely causes side effects of therapeutic dose; + = mild or occasional side effects at therapeutic dose; ++ = sometime causes side effects at therapeutic dose; +++ = frequently causes side effects at therapeutic dose; # = data too limited to rate with confidence.

\*Also causes agranulocytosis, seizure and myocarditis; <sup>†</sup>possible exception of akathisia; <sup>‡</sup>also carries warning about potential development of cataracts; <sup>§</sup>also causes nausea and headache.

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**Figure 2** Management options for antipsychotic-induced hyperprolactinaemia (Haddad and Wieck, 2004).

As a consequence of their prolactin-raising properties, some antipsychotics may be associated with an increased risk of pituitary tumour development (Duggal and Mendhekar, 2006; Szarfman et al., 2006). Investigators screened the US FDA Adverse Event Reporting System Database (a voluntary reporting system with a database of >2.5 million reported adverse events) to determine the relative frequency and association between seven antipsychotic medications (aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone and haloperidol) and reports of pituitary tumours, as well as hyperprolactinaemia and galactorrhea (Szarfman et al., 2006). Risperidone demonstrated the highest adjusted reporting ratio (i.e., the strongest association between the drug and an adverse event) for pituitary tumours followed by haloperidol, ziprasidone and olanzapine. The incidence of reports of hyperprolactinaemia and galactorrhea were also higher with risperidone than with other antipsychotics.

**4.1. Are differences in antipsychotic treatment effects on serum prolactin related to their mechanism of action?**

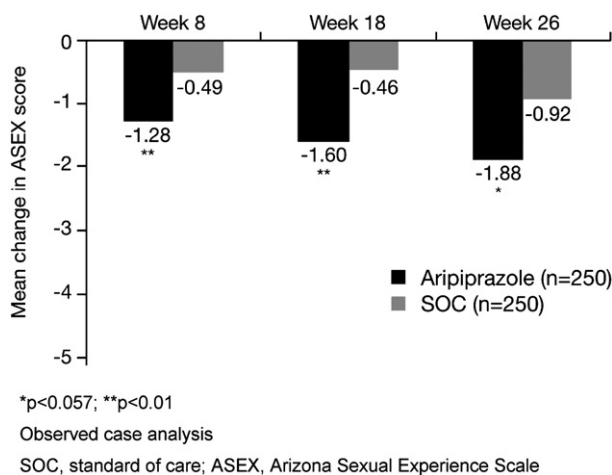
The pharmacological profile of antipsychotic treatments may underlie their differential effects on prolactin levels. Prolactin elevation is proposed to occur as a consequence of striatal dopamine D<sub>2</sub> receptor blockade and the rate at which a particular antipsychotic dissociates from these receptors (Haddad and Wieck, 2004). The underlying action of conventional antipsychotic treatment on prolactin secretion was demonstrated in one report in which the addition of haloperidol to ongoing clozapine treatment was shown to increase striatal D<sub>2</sub> receptor occupancy and elevate prolactin levels (Kapur et al., 2001). In contrast to other current antipsychotic treatments, aripiprazole possesses a distinct mechanism of action that encompasses partial agonist activity at dopamine D<sub>2</sub> receptors (Burris et al., 2002; Shapiro et al., 2003; Stahl, 2001), which may account for its 'prolactin-sparing' profile.

**5. Monitoring and management of antipsychotic-induced hyperprolactinaemia**

Screening for hyperprolactinaemia is not currently undertaken routinely (Bushe and Shaw, 2007; Maguire, 2002). Moreover, in the case of sexual side effects, professionals may be uncomfortable or under-rate this aspect of their patients' health. It has been demonstrated that the prevalence of sexual dysfunction is higher when rated by patients than when rated

by their psychiatrists (Cutler, 2003). Despite the established evidence of antipsychotic-induced hyperprolactinaemia, published guidance on the monitoring and management of elevated prolactin levels in patients receiving antipsychotic treatment is lacking. Current guidance does not recommend regular monitoring of antipsychotic-induced hyperprolactinaemia. Instead, recommendations for screening of antipsychotic-induced serum prolactin elevation are restricted to questioning patients on possible signs and symptoms of elevated prolactin levels (at treatment initiation and annually once treatment is underway) or a morning random measurement of serum prolactin concentrations in patients with side effects indicative of hyperprolactinaemia (Compton and Miller, 2002; Marder et al., 2004). For prolactin-raising antipsychotics, it has been recommended that patients are questioned on possible prolactin-related effects until a stabilized dose is achieved (Marder et al., 2004). In patients with elevated prolactin levels, other potential causes of hyperprolactinaemia should be ruled out (Table 1) (Haddad and Wieck, 2004; Marder et al., 2004). Several management options are available to counteract the effects of antipsychotic-induced hyperprolactinaemia (Haddad and Wieck, 2004) (Fig. 2). Although the simplest strategy is to decrease the dose of the current antipsychotic, this may increase the risk of exacerbating symptoms or a relapse.

An alternative option is to switch to a prolactin-sparing antipsychotic treatment. Consistent with the findings of lower sexual dysfunction in patients receiving prolactin-sparing antipsychotics, findings from the STAR study have demonstrated significant improvements in sexual functioning among patients with schizophrenia when switched to aripiprazole treatment due to tolerability issues and/or suboptimal control of their clinical symptoms with their previous antipsychotic medication (Fig. 3) (Kerwin et al., 2007 and unpublished further analyses of this study). Using the Psychotropic-Related Sexual Dysfunction Questionnaire (PRSexDQ), a naturalistic study of 86 outpatients with schizophrenia or schizophreniform disorder receiving various antipsychotic treatments, a significant improvement in PRSexDQ total scores was observed following a switch to open-label quetiapine treatment for 6 months ( $p < 0.001$ ) (Montejo



**Figure 3** Change in sexual functioning at Week 26 in the Schizophrenia Trial of Aripiprazole (STAR) study (Kerwin et al., 2007 and unpublished further analyses of this study).

Gonzalez et al., 2005). PRSexDQ scores remained stable in patients who had initiated quetiapine treatment showing a lack of sexual dysfunction. A small study of 29 patients who demonstrated abnormal serum prolactin levels during conventional antipsychotic treatment showed that subsequent switching to clozapine decreased prolactin levels in patients to within normal ranges, whereas those who switched to risperidone did not demonstrate a marked change in their prolactin levels (Breier et al., 1999). Switching to the newer atypical antipsychotic, aripiprazole, from previous antipsychotic (risperidone, thioridazine, or olanzapine) in a multicentre, randomized, open-label study has provided reduction in prolactin levels (Casey et al., 2003). A number of case reports in the literature also cite positive experience of switching to aripiprazole with respect to prolactin levels (Anghelescu and Wolf, 2004; De Hert et al., 2007).

The addition of a D<sub>2</sub> receptor agonist to an existing antipsychotic treatment is another management option. The dopamine agonist, bromocriptine, corrects elevated prolactin levels and has been shown to increase mean bone mineral density (Stampfer et al., 1990). However, bromocriptine may be associated with adverse effects such as postural hypotension and gastrointestinal symptoms (Haddad and Wieck, 2004).

## 6. Conclusion

Antipsychotic-induced hyperprolactinaemia is evident among patients with schizophrenia, and research suggests that elevations in prolactin levels may account for specific physical health problems that are frequently observed in these patients. Conventional antipsychotics and risperidone are consistently associated with 'prolactin-raising' effects, whereas other current atypical antipsychotics are more likely to have 'prolactin-sparing' properties. Studies have shown that aripiprazole has a minimal effect on prolactin and is associated with lower prolactin levels when compared with other prolactin-sparing antipsychotics. Robust recommendations for the monitoring of prolactin elevations induced by antipsychotic treatments are sparse. Current management options for antipsychotic-induced hyperprolactinaemia include a decrease in antipsychotic dose or switching to a prolactin-sparing medication. Further controlled studies and adequate guidance are essential to increase awareness and understanding of the impact of antipsychotic-induced hyperprolactinaemia on physical health in schizophrenia.

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## Conflict of interest

Dr Montejo has been a speaker for Lilly, AstraZeneca, Bristol-Myers Squibb, Servier, Glaxo-SmithKline, Lundbeck, Sanofi Synthelabo and Wyeth. He is an advisor for Lilly and AstraZeneca and he had received grants from Astra Zeneca, Bristol-Myers Squibb, Lilly, Servier, Glaxo-SmithKline, Lundbeck, Sanofi Synthelabo and Pfizer.

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