A review of the association between antipsychotic use and hyperprolactinaemia

Chris Bushe, MB BS Eli Lilly and Company Ltd, Basingstoke, UK.
Michael Shaw Elmfield House MHRC, Halifax, UK.
Robert C Peveler University of Southampton, Royal South Hants Hospital, Southampton, UK.

Abstract

Recent evidence linking hyperprolactinaemia to longer-term clinical sequelae, including osteoporosis, hip fractures and possibly breast cancer, is increasing clinical awareness of the relevance of hyperprolactinaemia. A review of the literature finds clinical trials reporting some degree of comparative prolactin data among antipsychotics. Many of the randomised clinical trials (RCTs) do not report categorical rates of hyperprolactinaemia in contrast with the naturalistic studies, making it complex for clinicians to evaluate the extent and severity of hyperprolactinaemia.

Hyperprolactinaemia is one of the commonest adverse events reported in clinical trials and can be found in association with all antipsychotics. The highest rates of hyperprolactinaemia are reported in association with risperidone and amisulpride, often as high as 80–90% of all female subjects and consistently greater than with the typical antipsychotics. Significant rates of hyperprolactinaemia of lesser severity and more transience have also been reported in association with other atypical antipsychotics.

Key words prolactin; schizophrenia; hyperprolactinaemia; osteoporosis; antipsychotics; categorical data analysis; breast cancer

Introduction

Antipsychotics are currently used for long-term treatment in the vast majority of patients with schizophrenia and bipolar disorder. There has been a longstanding awareness that typical antipsychotics can be associated with hyperprolactinaemia, although the potential long-term sequelae of this adverse event have only recently been fully recognised (Howard et al., 2007; Tworoger et al., 2007; Harvey et al., 2007). The development of the atypical antipsychotics and their adoption as first-line treatments for patients with schizophrenia was primarily on the basis that although their benefits in treating psychosis are slightly superior to the typicals, their safety profile was a significant advancement (NICE, 2002). However, replacing the concerns regarding extra-pyramidal side effects and the risk for tardive dyskinesia (prominently associated with the older agents) are new concerns regarding a variety of metabolic and endocrine abnormalities, including hyperprolactinemia.

Despite the body of evidence showing that of all the adverse effects of antipsychotic treatments hyperprolactinaemia may be one of the most commonly found (Kane et al., 2007; Potkin et al., 2003; Kinon et al., 2003), there is little evidence of regular monitoring of prolactin in UK in 2007. There are a number of possible reasons for this, including a lack of awareness of the potential longer-term sequelae of hyperprolactinaemia. Only recently have data emerged showing that hyperprolactinemia-mediated osteoporosis in schizophrenia can translate into clinically relevant hip fractures (Howard et al., 2007). Furthermore, the USA Nurses study and other data have concluded that in a general population the incidence of breast cancer may be significantly linked to prolactin levels (Tworoger et al., 2004; Tworoger and Hankinson, 2006; Tworoger et al., 2006; Tworoger et al., 2007). These data are also consistent with results from a retrospective cohort study of more than 100,000 women, which found antipsychotic dopamine antagonists to be associated with a 16% increase in breast cancer (adjusted hazard ratio 1.16; 95% CI 1.07, 1.26) with a relationship between larger doses and greater risk (Wang et al., 2002). Two further recent studies have found increased risks of breast cancer in female schizophrenia patients from 20–42% (Dalton et al., 2005; Disability Rights Commission, 2006).

The increasing knowledge of the physical manifestations of schizophrenia and its treatment are a challenge to psychiatrists, but prolactin data have not always been reported in a clinically meaningful way to clinicians. Most clinical papers report significant rates of adverse events in clinical trial cohorts categor-
ically but this is not always the case for prolactin (Lieberman et al.; 2005; David et al., 2000). For example, the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) study for schizophrenia is an example of a modern NIMH-funded pragmatic clinical randomised trial that has contributed important findings to the evidence base of efficacy outcomes when comparing antipsychotics. However, the authors report only the mean cohort values rather than the categorical numbers of subjects who developed hyperprolactinaemia in the various cohorts.

For a clinician to understand an adverse effect of a treatment they may need to know not only the prevalence but also the severity of that adverse effect. That there is increasing interest in prolactin and its association with antipsychotics is indicated by the observation that a search using the terms ‘prolactin and antipsychotics’ (solely on Medline; February 2008) yields 2653 citations. This review sets out to establish the relationship between the use of available antipsychotics and hyperprolactinaemia, and the methodology of reporting of that data.

Clinical reporting of prolactin data

Studies that report prolactin data

There are few clinical studies or papers that have the primary intent to report prolactin data (Kleinberg et al., 1999; Bushe and Shaw, 2007; Jakovljevic et al., 2007). Most data are derived from randomised controlled trials (RCTs), primarily designed to test for efficacy comparing antipsychotic treatments, in which prolactin measurements have constituted part of the set of measured laboratory parameters (Schooler et al., 2005; Kane et al., 2007a). Some further data derive from observational reporting of predominantly point-prevalence samples and case series (Montgomery et al., 2004). There has been no reported clinical trial (RCT) in which the primary sole endpoint was change in prolactin. There are also smaller studies that have evaluated sexual functioning and bone mineral density. These studies have additionally reported prolactin data (O’Keane, 2005; Meaney and O’Keane, 2003; Meaney et al., 2004).

There is an important caveat for this review, in that it is likely other prolactin data are available in addition to our review of the existing literature. The predominant focus is on the 20 studies reported in Table 1.

Comparative prolactin data between antipsychotics

Overview

For all currently available antipsychotics in the UK and USA there is potential for associated hyperprolactinaemia. The terminology sometimes used to label antipsychotics as ‘prolactin elevating’ or ‘prolactin sparing’ is most likely incomplete and may lead clinicians to conclude that antipsychotics, such as olanzapine and quetiapine, can never be associated with significant hyperprolactinaemia. The trial data shown in Table 1 show that hyperprolactinaemia is reported with all antipsychotics, and prevalence rates for olanzapine and quetiapine are reported as high as 40% and 22%, respectively, in one study (Montgomery et al., 2004).

In general terms, the antipsychotics associated with the highest prevalence of hyperprolactinaemia and severity of hyperprolactinaemia are not the ‘typical’ antipsychotics, but risperidone and amisulpride. There is evidence that it is the major active metabolite of risperidone, 9-hydroxyrisperidone (paliperidone), that is responsible for the prolactin elevation (Knegtering et al., 2006) thus it can also be reasoned that paliperidone, recently licensed in the EU, will have at least similar prolactin-elevating potential to risperidone. The absence of specific trials designed to evaluate the comparative effects of antipsychotics on prolactin does lead to the provision of data sets that often are not able to address all relevant issues. In addition to incidence and prevalence, other important factors include severity and persistence of any hyperprolactinaemia and associated hypogonadism and, of course, the relationship to any longer-term clinical sequelae. Drug dosages may also be relevant and these are detailed in Table 1. Drug dosages for typical antipsychotics may differ in varying geographies.

Amisulpride

Amisulpride is probably the antipsychotic with the potential for maximum prolactin elevation. Amisulpride has rarely been included in any major comparative trials as it is not commercially available in the USA. Despite small cohort sizes there seems clarity that subjects who receive doses as low as 50 mg/day have hyperprolactinaemia in almost all cases (Kopacek et al., 2004) that is significantly high (mean 113 ng/ml, ~2400 mIU/L) and higher in females (160 ng/ml, ~3400 mIU/L) than males (48 ng/ml, ~1000 mIU/L). The Halifax data (n=7) also found 100% hyperprolactinaemia (Bushe and Shaw, 2007) and in the data reported in this supplement (n=9) 89% (Bushe et al., 2008). A Greek cohort (n=17) also found a 100% prevalence of hyperprolactinaemia for patients receiving amisulpride (Paparrigopoulos et al., 2007).

Aripiprazole

Aripiprazole is associated with a low rate of hyperprolactinemia <5% (Kane et al., 2007b; Pigott et al., 2003). In a 26-week placebo RCT aripiprazole was associated with a lower rate than placebo (5% versus 13%), consistent with the known pharmacology as a partial agonist. Prevalence rates of 3.1–5.0% seem consistent (Kane et al., 2007b; Potkin et al., 2003; Pigott et al., 2003).

Clozapine

Clozapine has weak binding affinity for the dopamine D2 receptor and is thus not expected to be associated with elevations
### Table 1  Clinical trials reporting prolactin data

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Patients</th>
<th>Mean prolactin data</th>
<th>Categorical prolactin data</th>
<th>Study conclusion</th>
<th>Study description</th>
<th>Study drug doses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schoeler et al., 2005</td>
<td>RCT</td>
<td>505</td>
<td>Yes</td>
<td>Yes</td>
<td>Risperidone significantly higher rates of HP (73.8% vs 49.8%) and mean prolactin values than haloperidol. Prolactin related ADRs also more common</td>
<td>Risperidone vs haloperidol in first episode psychosis, Median follow up 206 days</td>
<td>Risperidone 3.3mg Haloperidol 2.9 mg Mean modal dose</td>
</tr>
<tr>
<td>Kinon et al., 2003</td>
<td>Nat</td>
<td>402</td>
<td>Yes</td>
<td>Yes</td>
<td>Risperidone significantly higher rates of HP in females (88% vs 47.6%) and males and mean prolactin values than haloperidol</td>
<td>Point prevalence study in schizophrenia subjects taking medication minimum 3 months</td>
<td>Risperidone 4.2–5.2 mg Conventional 577–250 mg/day chlorpromazine equivalents Mean dose</td>
</tr>
<tr>
<td>Bushe and Shaw, 2007</td>
<td>Nat</td>
<td>194</td>
<td>Yes</td>
<td>Yes</td>
<td>HP found in 38% of asymptomatic outpatient cohort with SMI. Females 52%, males 26%. Higher prolactin levels in females. HP in 100% female risperidone and amisulpride patients</td>
<td>Naturalistic cross-sectional study including all patients in a single CMHT with SMI receiving antipsychotics</td>
<td>Risperidone 4.89 mg Risperidone LAIM 2mg/day equivalent Mean dose</td>
</tr>
<tr>
<td>Melkerson, 2005</td>
<td>Nat</td>
<td>75</td>
<td>Yes</td>
<td>Yes</td>
<td>HP in 89% risperidone and 24% olanzapine. HP linked to sexual adverse effects</td>
<td>Naturalistic cross-sectional study in schizophrenia subjects</td>
<td>Risperidone 3mg (median) Olanzapine 10 mg (median)</td>
</tr>
<tr>
<td>Kane et al., 2007a</td>
<td>RCT</td>
<td>629</td>
<td>Yes</td>
<td>No</td>
<td>Mean prolactin elevated after 6 weeks paliperidone. Females 2639 mIU/L, males 960 mIU/L.</td>
<td>Six-week placebo RCT paliperidone in schizophrenia</td>
<td>Paliperidone ER 6–12 mg</td>
</tr>
<tr>
<td>Kramer et al., 2007</td>
<td>RCT</td>
<td>207</td>
<td>Yes</td>
<td>No</td>
<td>Prolactin increased more in females than males. Compared with placebo, mean prolactin levels were four times as high among men (40 vs. 10 ng/mL) and five times as high among women (100 vs. 20 ng/mL) who received paliperidone at any dosage</td>
<td>Long-term recurrence prevention study &gt;220 days</td>
<td>Paliperidone ER 3–15 mg</td>
</tr>
<tr>
<td>Jung et al., 2006</td>
<td>Nat</td>
<td>51</td>
<td>Yes</td>
<td>Yes</td>
<td>HP females 90.5%, males 40%</td>
<td>Bone mineral density study. Cross-sectional Haloperidol-treated patients</td>
<td>Haloperidol (mean) 14.5–15.3 mg</td>
</tr>
<tr>
<td>Potkin et al., 2006</td>
<td>RCT</td>
<td>382</td>
<td>Yes</td>
<td>No</td>
<td>Mean prolactin elevation greater in risperidone than quetiapine. Mean reduction in quetiapine</td>
<td>Acute schizophrenia subjects hospitalised Randomised to risperidone, quetiapine or placebo</td>
<td>Risperidone 4.32 mg Quetiapine 523.8 mg Mean modal dose</td>
</tr>
<tr>
<td>Zhang et al., 2002</td>
<td>Nat</td>
<td>30</td>
<td>Yes</td>
<td>No</td>
<td>Mean increase in prolactin in risperidone males</td>
<td>Open label 12-weeks risperidone</td>
<td>Risperidone 6mg (fixed dose)</td>
</tr>
<tr>
<td>Costa et al., 2007</td>
<td>RCT</td>
<td>63</td>
<td>Yes</td>
<td>No</td>
<td>Decrease in mean prolactin in olanzapine patients</td>
<td>Open label 9 months olanzapine or typical antipsychotics</td>
<td>Olanzapine 17.5 mg Haloperidol 10.5 mg Chlorpromazine 300 mg (mean dose)</td>
</tr>
<tr>
<td>Volavka, 2005</td>
<td>RCT</td>
<td>133</td>
<td>Yes</td>
<td>No</td>
<td>Risperidone caused significant elevation of prolactin levels that appeared to be dose dependent. Clozapine and olanzapine were associated with decreases of prolactin, whereas haloperidol led to a minor, nonsignificant increase. Plasma olanzapine and prolactin levels were correlated</td>
<td>RCT in treatment resistant subjects 14 weeks</td>
<td>Clozapine 526 mg Olanzapine 30.4 mg Risperidone 11.6 mg Haloperidol 25/7 mg (mean dose)</td>
</tr>
<tr>
<td>Study</td>
<td>Type</td>
<td>Patients</td>
<td>Mean prolactin data</td>
<td>Categorical prolactin data</td>
<td>Study conclusion</td>
<td>Study description</td>
<td>Study drug doses</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------</td>
<td>----------</td>
<td>---------------------</td>
<td>---------------------------</td>
<td>------------------</td>
<td>-------------------</td>
<td>------------------</td>
</tr>
<tr>
<td>Kane et al., 2007b</td>
<td>RCT</td>
<td>300</td>
<td>Yes</td>
<td>Yes</td>
<td>HP 4.4% aripiprazole vs 57.7% perphenazine</td>
<td>RCT in treatment resistant subjects 6 weeks</td>
<td>Aripiprazole 28.8 mg Perphenazine 39.1 mg (mean dose)</td>
</tr>
<tr>
<td>Montgomery et al., 2004</td>
<td>Nat</td>
<td>422</td>
<td>Yes</td>
<td>Yes</td>
<td>HP found with all antipsychotics. risperidone 91%, clozapine 11%, olanzapine 40%, quetiapine 22%</td>
<td>Prevalence of HP in USA database</td>
<td>Not reported</td>
</tr>
<tr>
<td>Jung et al., 2005</td>
<td>Nat</td>
<td>60</td>
<td>Yes</td>
<td>Yes</td>
<td>HP in 66% but more common in females than males</td>
<td>Prevalence of HP in Korean inpatients</td>
<td>Haloperidol 15.0–16.3 mg (mean dose)</td>
</tr>
<tr>
<td>Kleinberg et al., 1999</td>
<td>RCT</td>
<td>2725</td>
<td>Yes</td>
<td>No</td>
<td>Mean prolactin greater with risperidone than haloperidol unless haloperidol 20 mg. Peak prolactin levels at 4 mg risperidone.</td>
<td>Mean prolactin levels from two large risperidone trials</td>
<td>Risperidone 2–16mg Haloperidol 10-20mg</td>
</tr>
<tr>
<td>Chue et al., 2005</td>
<td>RCT</td>
<td>640</td>
<td>Yes</td>
<td>Yes</td>
<td>HP in 72% of risperidone patients</td>
<td>12-week RCT in schizophrenia patients Risperidone oral vs LAIM</td>
<td>Risperidone 2–6 mg LAIM 25–75 mg (dose ranges stated only)</td>
</tr>
<tr>
<td>Lieberman et al., 2005</td>
<td>RCT</td>
<td>1493</td>
<td>Yes</td>
<td>No</td>
<td>Mean prolactin decrease (including perphenazine) in all cohorts except risperidone</td>
<td>Pragmatic NIMH funded RCT assessing all-cause discontinuation</td>
<td>Risperidone 3.9 Perphenazine 341 mg Mean modal dose</td>
</tr>
<tr>
<td>Bushe et al., 2008</td>
<td>Nat</td>
<td>178</td>
<td>Yes</td>
<td>Yes</td>
<td>HP with all antipsychotics except clozapine. Amisulpride 89%, risperidone 55%, Risperidone LAIM 67%</td>
<td>Cross sectional HP in all patients taking antipsychotics in a physical health programme</td>
<td>Risperidone 3.3–4.6 mg. Mean dose</td>
</tr>
<tr>
<td>Tran et al., 1997</td>
<td>RCT</td>
<td>339</td>
<td>No</td>
<td>Yes</td>
<td>HP at endpoint. Olanzapine 36% Risperidone 90%</td>
<td>28 week double blind olanzapine vs risperidone RCT. 50% of subjects excluded from categorical analysis due to abnormal baseline prolactin</td>
<td>Olanzapine 17.2 mg Risperidone 7.2 mg Mean modal dose</td>
</tr>
<tr>
<td>Potkin et al., 2003</td>
<td>RCT</td>
<td>404</td>
<td>Yes</td>
<td>Yes</td>
<td>Baseline mean prolactin ranged 9–12.7 ng/mL. Risperidone increased by 47.9 ng/mL vs aripiprazole decreased 6.4–6.6 ng/mL. Categorical HP- Risperidone 90.5%; aripiprazole 20mg, 4.1%; aripiprazole 30mg 3.3%; placebo 10.3%</td>
<td>Four-week double-blind aripiprazole vs risperidone RCT.</td>
<td>Risperidone 6 mg Aripiprazole 20 or 30 mg (fixed doses)</td>
</tr>
</tbody>
</table>

Abbreviations: CMHT, community mental health team; HP, hyperprolactinaemia; LAIM risperidone, long-acting intramuscular risperidone depot; NAT, naturalistic study; RCT, randomised controlled trial.
in prolactin. We reported a prevalence of hyperprolactinaemia with clozapine of 5% (1/21) (Bushe and Shaw, 2007). Another two recent though small data sets found 0% (0/7) (Wong and Seeman, 2007) and 0% (0/15) (Bushe et al., 2008). Patients switched to clozapine can show large reductions in prolactin (593 mIU/L) (Howes et al., 2006). Among 40 male patients randomized to clozapine in a study of treatment-resistant schizophrenia, clozapine was associated with decreases of prolactin (Volavka et al., 2004). The occasional finding of hyperprolactinaemia in clozapine-treated patients may be explained by transient dose elevations in the first few hours after medicating (Turrone et al., 2002) and is unlikely to have clinical relevance.

**Risperidone and paliperidone**

**Risperidone** When data are reported in a categorical manner there is evidence that almost all subjects (Table 2) receiving oral risperidone (72–100%) and risperidone long-acting intramuscular injection (LAIM) (53–67%) (Bushe and Shaw 2007; Bushe 2008) have hyperprolactinaemia. This is particularly the case in females. Categorical data derives from naturalistic and RCT studies. The largest RCT reporting prolactin data finds an incidence of 73.8% in risperidone-treated subjects with first-episode psychosis (Schooler et al., 2005). Although breakdown into gender for categorical rates of hyperprolactinaemia is not reported, the maximum prolactin level in females 73.69 ng/ml (~1500 mLUL (SD 53.18 ~1130 mLUL) is higher than in males 34.08 ng/ml ~725 mLUL (SD 21.9 ~460 mLUL). A similarly large RCT comparing aripiprazole and risperidone over 4 weeks found hyperprolactinaemia in 91% of risperidone patients (Potkin et al., 2003) although the risperidone dosage of 6 mg is higher than most doses currently reported (Table 1 and Table 2). The data from small and large RCT as well as naturalistic studies show consistent results (Table 1). In a similar manner where only mean prolactin levels are reported, 153 risperidone subjects had a mean change from baseline of 40.3 ng/ml (~880 mLUL) (SD 3.5~75 mLUL) at 14 days, which when added to the baseline value gives a mean 14 day level of 62.6 ng/ml (1330 mLUL) (Potkin et al., 2006). Levels would be expected to rise further, reaching maximal levels only after 1–2 months (David et al., 2000) and these are maintained long term (Risperidone USA Product label). Although the categorical prevalence is not reported, the small standard deviation of only 3.5 ng/ml suggests that almost all patients would have had hyperprolactinaemia. Other naturalistic studies find hyperprolactinaemia in 89% of risperidone subjects (n=18) (Melkersson, 2005). Many other data sets give consistently high prevalence rates for risperidone-associated hyperprolactinaemia in the 80–100% range (Kopacek et al., 2006) with very high median levels 1598 mLUL (~75 ng/ml). The dose of risperidone used may be important because, in general terms, mean doses have decreased in clinical trials over the past 10 years and doses less than 4 mg may have lower prolactin elevating potential (Klieberg et al., 1999).

**Paliperidone** Paliperidone (9-hydroxylrisperidone) was licensed in USA in 2006 and has been licensed in Europe in 2007, and is the major active metabolite of risperidone. Indeed, it is probably predominantly responsible for the prolactin elevation found with both drugs (Knechttering et al., 2006). The USA product label for Paliperidone despite containing incidence rates for seizures 0.22% (and 0.25% placebo) contains no actual data on the prevalence or severity of prolactin elevations measured in clinical trials including 1665 patients. No specific laboratory tests are recommended in the product label. The prolactin data reported in the individual publications is mean cohort values only for the Paliperidone study cohorts (Kane et al., 2007a; Kramer et al., 2007). These data are, however, salient. The mean value at 6 weeks in females was 124.5±65.5 ng/ml and as expected lower in males 45.3±23.19. Using a conversion factor of 21.2 this equates to 2639.4 mLUL in females and 960.6 mLUL in males. These values are approximately double those reported for risperidone in the first-episode study discussed above (Schooler et al., 2005). In a similar manner the longer-term RCT evaluating paliperidone ER in recurrence prevention that provides 6–9 months follow up reports no prolactin data other than stating that levels were raised and greater in females than males (Kramer et al., 2007). Data are, however, reported on the internet that compared with placebo, mean prolactin levels were four times as high among men (40 versus

<table>
<thead>
<tr>
<th>Study</th>
<th>All</th>
<th>Females</th>
<th>Males</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kinon et al., 2003</td>
<td>Not reported</td>
<td>88% (n=38)</td>
<td>70% (n=84)</td>
<td>4.2–5.2 mg (mean)</td>
</tr>
<tr>
<td>Melkersson, 2005</td>
<td>89%</td>
<td>100% (n=9)</td>
<td>78% (n=9)</td>
<td>3 mg (median)</td>
</tr>
<tr>
<td>Schooler et al., 2005</td>
<td>73.8%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>3.3 mg (mean modal)</td>
</tr>
<tr>
<td>Bushe and Shaw, 2007</td>
<td>83%</td>
<td>100% (n=10)</td>
<td>63% (n=8)</td>
<td>4.89 mg (mean)</td>
</tr>
<tr>
<td>Montgomery et al., 2004</td>
<td>91%</td>
<td>Not reported</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Kropacek et al., 2006</td>
<td>92%</td>
<td>100% (n=8)</td>
<td>75% (n=4)</td>
<td>1.25 mg (median)</td>
</tr>
<tr>
<td>Lee et al., 2006</td>
<td>100%</td>
<td>100% (n=15)</td>
<td>100% (n=12)</td>
<td>4 mg (mean)</td>
</tr>
<tr>
<td>Potkin et al., 2003</td>
<td>91%</td>
<td>–</td>
<td>–</td>
<td>6 mg (fixed)</td>
</tr>
<tr>
<td>Chue et al., 2005</td>
<td>72%</td>
<td>–</td>
<td>–</td>
<td>2–6 mg (range of fixed doses)</td>
</tr>
</tbody>
</table>

A review of the association between antipsychotic use and hyperprolactinaemia

Table 2 Prevalence of hyperprolactinaemia in risperidone-treated subjects (males and females)
Comparative prolactin data – risperidone and typical antipsychotics

A number of different data sets find consistently that risperidone elevates prolactin more commonly and to a greater degree than haloperidol. A large long term first episode psychosis trial (median treatment length 206 days) in 555 subjects randomised to risperidone or haloperidol found significantly higher prolactin levels in risperidone subjects (Schooler et al., 2005). Hyperprolactinaemia was also diagnosed significantly more commonly (73.8% and 49.8%, respectively). Consistent with these data are findings from a large point-prevalence study in 402 schizophrenia subjects receiving risperidone or typicals (Kinon et al., 2003). Hyperprolactinemia was more common among females taking risperidone (88 versus 47.6%; p=0.0001) than conventional and in those risperidone subjects of reproductive age the prevalence was 96%. Perhaps, the most robust data derive from the analysis from Kleinberg in 1999 from over 2000 patients, who found that risperidone was associated with greater mean increase in prolactin in both men and women than haloperidol 10 mg at risperidone doses from 4–16 mg and equivalence with haloperidol 20 mg (Kleinberg et al., 1999). The study data reveal that almost the maximum prolactin mean level around 50 ng/ml in females was reached at 4 mg risperidone. Further dose increases did not appear to increase the prolactin levels additionally. Furthermore, prolactin levels did not differ between the pre- and post-menopausal cohorts. These findings are replicated in other studies. Prevalence rates for hyperprolactinemia in patients taking typical antipsychotics are around 50% those of risperidone treated patients. In a naturalistic cohort of 194 outpatients in a single community mental health team risperidone oral monotherapy was associated with hyperprolactinemia in 89% compared with 33% of those taking predominantly depot typical antipsychotic medications (Bushe and Shaw, 2007). Risperidone LAIM was associated with a lower rate of hyperprolactinemia than oral risperidone relating to the lower dosage used (2 mg/day equivalent RAIM versus 4.89 mg/day oral). This again is consistent with previous data (Chue et al., 2005). A relationship between dose of risperidone and prolactin level has been demonstrated (Kinon et al., 2003). A large cross-sectional prevalence study using three electronic databases in USA (Montgomery et al., 2004) reports risperidone associated hyperprolactinemia in 91% (n= 56) with 64% (n=56) having greater than twofold increase (>56 ng/ml or 1176 mIU/L) contrasting with 68% on typical antipsychotics. The CATIE study does not report categorical prolactin data but does show that there was an exposure-adjusted decrease in prolactin for all antipsychotic medications except risperidone (p=0.001) where an increase of 13.8 ng/ml ~290 mIU/L was observed contrasting with a decrease of 1.2 ng/ml ~25 mIU/L seen with perphenazine (mean modal dose of 20.8 mg/day) (Liebermann et al., 2005).

Quetiapine

RCTs have supported the notion that quetiapine is a relatively prolactin-sparing antipsychotic (Arvenitis et al., 1997; Potkin et al., 2006). A recent RCT in patients with acute psychosis reports significantly greater prolactin elevation at 14 days with risperidone (mean change from baseline 40.3 ng/ml ~850 mIU/L) than quetiapine (10.1 ng/ml ~215 mIU/L) (Potkin 2006). In this study the mean prolactin at baseline was already high (22.3 ng/ml and 24.8 ng/ml, respectively for both groups) and the reduction measured may be reflective of exposure to prior antipsychotics. In studies that report categorical rates of hyperprolactinaemia low prevalence rates in association with quetiapine have been reported ranging from 0–29% (Wong and Seeman, 2007; Montgomery et al., 2004; Bushe and Shaw, 2007; Bushe et al., 2008).

Olanzapine

Olanzapine is associated with hyperprolactinaemia that is regarded as mild and transient (Olanzapine SPC). In one of the early dose finding studies for olanzapine at week 2 between 13–38% of olanzapine subjects had hyperprolactinaemia dependent upon dosage (5–15 mg/day) that had reverted to placebo incidence levels by week 6 (Crawford et al., 1997). Significant hyperprolactinaemia however can be reported. Categorical data shows prevalence between 6–40% (Montgomery et al., 2004; Bushe and Shaw, 2007; Tran et al., 1997, Crawford 1997) and in the Halifax cohort we found a female subiect with a level of 1716 mIU/L ~80 ng/ml (Bushe and Shaw, 2007).

In a recent study that randomised patients with hyperprolactinemia to remain on current treatment (risperidone or typical antipsychotics) or receive olanzapine for 16 weeks, by study end prolactin levels had only normalised in 90% of olanzapine subjects (Kinon et al., 2006). In an osteoporosis study, hyperprolactinemia was found in 33% of olanzapine subjects (n=12) (mean 446.4 mIU/L ~21 ng/ml contrasting with 96% of the prolactin ‘elevating’ cohort (risperidone, typical antipsychotics and amisulpride) (O’Keane and Meaney, 2005). In 2002 Turron (Turron et al., 2002) found that in a small cohort of male schizophrenia subjects, dose-related elevations (transiently) were found in patients receiving clozapine, risperidone and olanzapine. Although the olanzapine changes were not statistically significant due to small numbers, there was a doubling of the basal values from 9 to 18 ng/ml. Peak prolactin values were found after risperidone at 120 minutes, olanzapine 290 minutes and clozapine 180 minutes. These data are consistent with our findings in that hyperprolactinaemia can be found in patients taking any antipsychotic. This provides some support for the suggestion that prolactin levels should be taken before medication as a trough level and 3 hours afterwards as a peak. The averaging of these values may be taken as the overall figure.

Typical and/or conventional antipsychotics

Rates of hyperprolactinaemia with typical antipsychotic medications are high. The lowest prevalence rate reported 33% compares with the
highest 87% (Bushe and Shaw, 2008; Jakovljevic et al., 2007). There is, however, the probability that lower rates reflect lower doses used and the UK data are supportive of this. In the three recent naturalistic data sets reported from UK data, prevalence rates for hyperprolactinemia in patients receiving predominantly depot formulations were consistently between 33–35% (Crockett et al., 2005; Bushe and Shaw, 2008; Bushe et al., 2008). Where higher rates are found, 66% in a Korean cohort in a cross-sectional prevalence study (Jung et al., 2005), the mean dose of haloperidol was higher (15–16.3 mg) than is often the case in other countries. An early dose-ranging olanzapine trial also using haloperidol 15 mg found hyperprolactinemia in the haloperidol cohort in 72% at 2 weeks and around 60% at 6 weeks (Crawford et al., 1997).

### Complex questions relating to prolactin levels

#### Persistence of hyperprolactinaemia

Many if not all of the reported prolactin data are of too short duration to make definitive statements regarding the persistence of hyperprolactinaemia. However, information is available from product labelling as approved by regulatory authorities. For example, product information as approved in the USA notes that for some drugs that prolactin elevation persists during chronic administration. However there is a 5-year naturalistic study of risperidone that suggests that prolactin levels may lower over time (Eberhard et al., 2007). Additional long-term studies are needed.

#### What level of prolactin matters?

This is a difficult question to address and a full discussion is beyond the scope of this review but is discussed elsewhere in the supplement. In terms of sexual side effects, these symptoms are overt and the prolactin level is less relevant. For the ‘hidden’ consequences of long term hyperprolactinaemia there is a little guidance. In three studies that have found bone mineral density loss have mean cohort prolactin values of 908–3024 mIU/L (~43–142 ng/ml) with treatment with typical antipsychotics or risperidone for between 8–21 years (Meaney et al., 2004; O’Keane and Meaney 2005; Becker et al., 2003). Prolactin levels

### Table 3. Categorical prevalence of hyperprolactinaemia in studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Patients (n) in study</th>
<th>Females</th>
<th>Males</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bushe and Shaw, 2007</td>
<td>194</td>
<td>52%</td>
<td>26%</td>
<td>38%</td>
</tr>
<tr>
<td>Kinon et al., 2003</td>
<td>402</td>
<td>60%</td>
<td>42%</td>
<td>49%</td>
</tr>
<tr>
<td>Montgomery et al., 2004</td>
<td>422</td>
<td>68%</td>
<td>72%</td>
<td>69%</td>
</tr>
<tr>
<td>Meaney et al., 2004</td>
<td>55</td>
<td>64%</td>
<td>60%</td>
<td>62%</td>
</tr>
<tr>
<td>Smith et al., 2002a</td>
<td>101</td>
<td>75%</td>
<td>34%</td>
<td>–</td>
</tr>
<tr>
<td>Hummer et al. (2005)</td>
<td>75</td>
<td>44%</td>
<td>23%</td>
<td>28%</td>
</tr>
<tr>
<td>Smith et al., 2002b</td>
<td>67</td>
<td>75%</td>
<td>34%</td>
<td>46%</td>
</tr>
<tr>
<td>Schooler et al., 2005</td>
<td>555</td>
<td>–</td>
<td>–</td>
<td>62%</td>
</tr>
<tr>
<td>Melkersson, 2005</td>
<td>75</td>
<td>42%</td>
<td>21%</td>
<td>31%</td>
</tr>
<tr>
<td>Jung et al., 2006</td>
<td>51</td>
<td>91%</td>
<td>40%</td>
<td>61%</td>
</tr>
<tr>
<td>Jung et al., 2005</td>
<td>60</td>
<td>93%</td>
<td>47%</td>
<td>66%</td>
</tr>
<tr>
<td>Bushe et al., 2008</td>
<td>178</td>
<td>47%</td>
<td>18%</td>
<td>33%</td>
</tr>
</tbody>
</table>
of this severity are not uncommon in risperidone-treated patients in the UK (Bushe and Shaw, 2007). In relationship to breast cancer, the no-effect level for prolactin has not been established (Harvey et al., 2007) and the increased risk for breast cancer demonstrated in mentally well USA nurses is shown for levels of around 500 mIU/L (Tworoger et al., 2006; Tworoger et al., 2004), although the attributable risk may be quite small.

Methodological issues

Many psychiatrists will not consider themselves expert in endocrinology, and there is a challenge in interpreting appropriately the varied prolactin data and its relationship to clinical sequelae. Potentially there are many areas for confusion.

Units of measurement

There is a variety of reported units of measurement of prolactin levels. Studies done in th USA and outside of the UK currently report data as ng/ml whereas most UK data is in mIU/L. Other units include nmol, µg/l (equivalent to ng/ml) and pmol. The commonest conversion that is needed is from ng/ml to mIU/L or vice versa. Traditionally mIU/L is regarded as SI units and ng/ml as conventional. Most clinical papers do not state the conversion factor needed and there is 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. The conversion factors are specific to the assay type used in the prolactin measurement and are rarely reported in clinical data reports. Although most assays are complex and use radioimmunoassay techniques that require a specialised technician, kits are in development that use monoclonal antibody techniques and could be performed in outpatient settings. A further complicating factor is the presence of macroprolactin, which is essentially biologically inactive, but may lead to falsely high prolactin levels as measured by many assays.

Definition of hyperprolactinemia

The only applicable current definition is that the prolactin level is greater than the laboratory normal range, in which there is tremendous variability dependent on many factors including types of measurement kits used. These normal ranges show some degree of variability in clinical trial reports but in some cases are not stated making interpretations of that data complex. Where normal ranges are given the upper limit of normal (ULN) for females tends to be often higher by as much as 30% than for males.

Methodology of reporting details of prolactin measurements

Despite well-recognised diurnal variability in prolactin levels most reports do not provide much or any data detailing the time of sampling, fasting status and whether duplicate samples were taken. These may be relevant factors in individual patients who have borderline raised levels. Studies in healthy subjects do find such variability but the prolactin levels tend to be significantly lower than those in patients receiving antipsychotics. Garde et al. (2000) reported in healthy female subjects a mean prolactin level after multiple sampling of 136 mIU/L (~6 ng/ml) with cyclical seasonal variation accounting of 23%. Prolactin was highest in March–May (153 mIU/L ~7 ng/ml) and lowest in September–November (98 mIU/L). In SMI subjects receiving antipsychotics, such variability would be expected to be less relevant due to the already significant elevations associated with antipsychotic usage. Sampling in relation to medication dosing may however be relevant as prolactin levels even when significantly elevated on risperidone, become further elevated after dosing (Turrone et al., 2002).

Cohort sizes

Cohort sizes are highly variable. The largest data sets reporting prolactin include the recently reported 6-week Paliperidone study in 628 schizophrenia subjects (Kane, 2007a) and the risperidone and haloperidol in first episode psychosis study in 555 subjects (Schooler et al., 2005). The cohort sizes of relevant studies in which prolactin data is available are shown in Table 1.

Methodology for reporting prolactin data in clinical studies

Data can be reported as mean values for a cohort or in categorical terms of hyperprolactinemia. Data reported as mean values either from a whole cohort or as the degree of change from a baseline figure are intuitively less valuable to clinicians. In Table 1 where the major clinical studies providing prolactin data are summarised 12/20 (60%) provides some categorical analysis, however this derives predominantly from the naturalistic studies (78%) as opposed to the RCTs (5/12) (42%). Furthermore, even when reported categorically as rates of incidence or prevalence of hyperprolactinaemia, rarely is the severity also stated. This has made it a complex task for clinicians to appreciate that hyperprolactinaemia is a common finding in SMI patients receiving antipsychotics. Furthermore, mean change data are unhelpful when advising patients about the likelihood of a specific adverse event. At present the longer-term possible sequelae to hyperprolactinemia are unlikely to be observed or reported within clinical trials (osteoporosis, hip fractures) and hence the risk of hyperprolactinaemia remains the best predictor they can be advised on.

Summary

Recent evidence linking hyperprolactinaemia to longer-term clinical sequelae including osteoporosis, hip fractures and possibly breast cancer is increasing clinical awareness of the relevance of hyperprolactinaemia. A review of the literature finds
many clinical trials reporting some degree of comparative pro-
lactin data amongst antipsychotics.

Hyperprolactinemia is common and there is little doubt that
cases of hyperprolactinaemia will be found in subjects receiving
all antipsychotics. The prevalence of hyperprolactinaemia is
consistently highest with risperidone and amisulpride, reaching
80–90% in females. Olanzapine is also associated with hyper-
prolactinaemia but with lower categorical rates, less severity
and often transient in nature. The lowest categorical rates are
found with quetiapine and aripiprazole. Clozapine rarely in-
duces hyperprolactinaemia.

Declarion of interest
Chris Bushe is an employee of Eli-Lilly UK.
Michael Shaw, declaration of interest, none.
Robert Peveler has received hospitality, fees for speaking or
consultancy from makers of antipsychotics including, Lilly,
Bristol Myers Squibb, Sanofi, Astra Zeneca, Lundbeck,
Janssen and Pfizer.

References
Arvanitis LA, Miller BG (1997) Multiple fixed doses of ‘Seroquel’
(quetiapine) in patients with acute exacerbation of schizophrenia:
a comparison with haloperidol and placebo. The Seroquel Trial
Becker D, Liver O, Mester M, Rapoport M, Weizman A, Weiss M
(2003). Risperidone but not olanzapine decreases bone mineral
density in female premenopausal schizophrenia patients. J Clin Psy-
chiatry 64: 761–766
Bushe C, Shaw M (2007) Prevalence of hyperprolactinaemia in a nat-
uralistic cohort of schizophrenia and bipolar outpatients during
treatment with typical and atypical antipsychotics. J Psychophar-
macol 21: 768–773
and often transient in nature. The lowest categorical rates are
found with quetiapine and aripiprazole. Clozapine rarely in-
duces hyperprolactinaemia.

Declarion of interest
Chris Bushe is an employee of Eli-Lilly UK.
Michael Shaw, declaration of interest, none.
Robert Peveler has received hospitality, fees for speaking or
consultancy from makers of antipsychotics including, Lilly,
Bristol Myers Squibb, Sanofi, Astra Zeneca, Lundbeck,
Janssen and Pfizer.

References
Arvanitis LA, Miller BG (1997) Multiple fixed doses of ‘Seroquel’
(quetiapine) in patients with acute exacerbation of schizophrenia:
a comparison with haloperidol and placebo. The Seroquel Trial
Becker D, Liver O, Mester M, Rapoport M, Weizman A, Weiss M
(2003). Risperidone but not olanzapine decreases bone mineral
density in female premenopausal schizophrenia patients. J Clin Psy-
chiatry 64: 761–766
Bushe C, Shaw M (2007) Prevalence of hyperprolactinaemia in a nat-
uralistic cohort of schizophrenia and bipolar outpatients during
treatment with typical and atypical antipsychotics. J Psychophar-
macol 21: 768–773
and severity of hyperprolactinaemia in two UK cohorts of patients
with severe mental illness during treatment with typical and utyipi-
cal antipsychotics. J Psychopharmacol 22 (Suppl): 56–62
Chue P, Eerdekkens M, Augustyns I, Lachaux B, Molcan P, Eriksson
L, Pretorius H, David AS (2005) Comparative efficacy and safety
of long-acting risperidone and risperidone oral tablets. Eur Neu-
ropsychopharmacol 15: 111–117
Costa AM, de Lima MS, Faria M, Filho SR, de Oliveira IR, de Jesus
Mari J (2007) A naturalistic, 9-month follow-up, comparing olan-
zapine and conventional antipsychotics on sexual function and hor-
monal profile for males with schizophrenia. J Psychopharmacol.
21: 165–170
Crawford AM, Beasley CM, Tollesford GD (1997) The acute and long-
term effect of olanzapine compared with placebo and haloperidol
on serum prolactin concentrations. Schizophr Res 26: 41–54
Crockett A, Goldstein M, Bushe C (2005) How has NICE guidelines
affected prescribing in depot clinic schizophrenia patients? The
Dewsbury experience. British Association of Psychopharmacology
2005 Summer Meeting 24–27 July, 2005; Harrogate, UK
Dalton SO, Mellemkjaer L, Thomassen L, Mortensen PB, Johansen C
(2005) Risk for cancer in a cohort of patients hospitalized for
risperidone and haloperidol on plasma prolactin levels in patients

the gap
level during 5 years of risperidone treatment in patients with psy-
Garde AH, Hansen AM, Skovgaard LT, Christensen JM (2000) Sea-
sonal and biological variation of blood concentrations of total cho-
lesterol, dehydroepiandrosterone sulfate, hemoglobin A (1c), IgA,
prolactin, and free testosterone in healthy women (2000). Clin
 Chem. 246: 551–559; Erratum in: Clin Chem 47: 1877
Harvey PW, Everett DJ, Springall CJ (2007). Adverse effects of pro-
lactin in rodents and humans: breast and prostate cancer. J Psycho-
pharmacol 22 (Suppl): 20–27
Howes OD, Smith S, Gaughran FP, Amiel SA, Murray RM, Pilowsky
LS (2006) The relationship between prolactin levels and glucose ho-
meostasis in antipsychotic-treated schizophrenic patients (2006)
Clin Psychopharmacol 26: 629–631
Jakolvijec M, Pivac N, Mihaljevic-Peles A, Muntapic M, Relja M,
Ljubicic D, Marcinko D, Muck-Seler D (2007) The effects of olan-
zapine and fluphenazine on plasma cortisol, prolactin and muscle
rigidity in schizophrenic patients: a double blind study. Prog Neu-
ropsychopharmacol Biol Psychiatry 31: 399–402
Jung DU, Sea YS, Park JH, Jeong CY, Conley RR, Kelly DL, Shim
haloperidol use in patients with chronic schizophrenia. J Clin Psy-
chopharmacol 25: 613–615
Jung DU, Conley RR, Kelly DL, Kim DW, Yoon SH, Jang JH, Shin
orean patients with schizophrenia: a cross-sectional study. J Clin Psy-
chiatry 67: 1391–1396
Kane J, Canas F, Kramer M, Ford L, Gassmann-Mayer C, Lim P,
Eerdekkens M (2007a) Treatment of schizophrenia with paliperidone
extended-release tablets: a 6-week placebo-controlled trial Schi-
zophr Res 90: 147–161
Kane J, Meltzer H, Carson W, McQuade R, Marcus R, Sanchez R
(2007b). Aripiprazole for treatment resistant schizophrenia: results
of a multicenter randomised double-blind comparison study versus
perprolactinaemia in schizophrenic patients treated with conven-
tional antipsychotic medications or risperidone. Psychoneuroendo-
crinol 28: 55–68
hyperprolactinaemia and reproductive comorbidities in patients
with schizophrenia switched from conventional antipsychotics to
risperidone to olanzapine. Psychoneuroendocrinol 31: 577–588
Kleinberg DL, Davis JM, De Coster R (1999) Prolactin levels and ad-
verse effects in patients treated with risperidone. J Clin Psychophar-
macol 19: 57–61
den Bosch RJ (2005) Predominant role of the 9-hydroxy metabolite
of risperidone in elevating blood prolactin levels. Am J Psychiatry
162: 1010–1012
Kopecek , Bares MM, Svare J, Dockery C, Horacek J (2004) Hyper-
prolactinemia after low dose of amisulpride. Neuro Endocrinol
Lett 25: 419–422


