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*J Psychopharmacol* 2008; 22; 90
DOI: 10.1177/0269881107087373

The online version of this article can be found at:
http://jop.sagepub.com/cgi/content/abstract/22/2_suppl/90
Current guidelines and their recommendations for prolactin monitoring in psychosis

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Abstract

Guidelines on the use of second-generation antipsychotics and physical health monitoring have begun to include information on hyperprolactinemia, and generally recommend that patients should be queried about possible symptoms related to elevated prolactin: menstrual abnormalities, galactorrhea and sexual dysfunction. However, with only two exceptions, none of the guidelines suggest performing baseline plasma prolactin levels. Although several of the guidelines mention the potential for hyperprolactinemia to be associated with osteopenia and osteoporosis, there is no guidance how to monitor for this. Product labeling for the different antipsychotics inform the clinician about potential risks but are not helpful with precise monitoring recommendations. The internal medicine literature contains important information regarding the pulsatile secretion of prolactin, differential diagnosis of hyperprolactinemia, and plasma levels of prolactin usually associated with certain symptoms that would be useful for the prescriber of antipsychotics to be aware of. The prudent clinician should consider obtaining a baseline plasma prolactin level and at least one follow-up measurement when starting any patient on a new antipsychotic. This will help guide clinical decisions about antipsychotic dosage, switching antipsychotic medications, or considering ancillary treatments to protect bone mass. These decisions would be within the context of considering other adverse events as well as the overall effectiveness of the antipsychotic medication being used.

Key words
guidelines; prolactin; hyperprolactinemia; antipsychotic; schizophrenia

Introduction

The increase in plasma prolactin levels observed in many patients receiving antipsychotics was once thought to be inevitable with the use of neuroleptics, and not much was suggested regarding how to monitor for it. In the past, discussions of prolactin levels focused on their possible usefulness for monitoring antipsychotic treatment response. For example, low serum prolactin was thought to be useful in predicting who might relapse (Brown and Laughren, 1981).

The availability of clozapine in 1989 ushered in an era where some antipsychotics could be classified as prolactin-sparing, and the lack of hyperprolactinemia was considered to be an important criterion for atypicality. This may not be entirely accurate in that atypical (second-generation) antipsychotics can also elevate prolactin levels, but that these increases are usually small and/or transient (Turrone et al., 2002). These transient prolactin elevations may correspond to transient dopamine D2 receptor blockade, a property that differs between first and second-generation antipsychotics, and among the second-generation antipsychotics themselves (Kapur and Seeman, 2001).

This review summarizes the current guidance regarding the monitoring for hyperprolactinemia, as provided by government agencies, professional organizations and consensus panel reports. The discussion will include what we know about the physiology of prolactin and how that may shape the decision-making for new recommendations for monitoring prolactin.

Guidance from government agencies

Government agencies regulate the commercialization of medications and their promotion. The information about a medication is summarized in its product labeling or package insert, a
document carefully scrutinized by the regulators. In the USA, the Food and Drug Administration (FDA) has this responsibility. Below is a summary of what the product labeling suggests clinicians consider when prescribing the second-generation antipsychotics that are available in the USA.

Product labeling for clozapine (Novartis, 2005) states that clozapine therapy produces little or no prolactin elevation, and no guidance is offered as to monitoring prolactin. Labeling for aripiprazole (Bristol-Myers Squibb, 2006) notes the lack of medically important differences between aripiprazole and placebo in mean change from baseline in prolactin in a 26-week study. However, increases in serum prolactin levels were observed in female mice (but not in rats) at the doses associated with mammary gland and pituitary tumors. The label adds that the relevance for human risk of the findings of prolactin-mediated endocrine tumors in rodents is unknown. No recommendations are made regarding the measurement or monitoring of prolactin.

By contrast, the product labeling for risperidone (Janssen, 2006a) states that risperidone can elevate prolactin levels in adults, children and adolescents, that the elevation persists during chronic administration, and that risperidone is associated with higher levels of prolactin elevation than other antipsychotic agents. The labeling further warns that hyperprolactinemia may suppress hypothalamic gonadotropin-releasing hormone, resulting in reduced pituitary gonadotropin secretion, and that this, in turn, may inhibit reproductive function by impairing gonadal steroidogenesis in both men and women. The label lists galactorrhea, amenorrhea, gynecomastia and impotence as being reported in patients receiving prolactin-elevating compounds, and that long-standing hyperprolactinemia when associated with hypogonadism may lead to decreased bone density in both men and women. Because about a third of human breast cancers are prolactin dependent in vitro, prolactin elevating medications may be deleterious if prescribed in a patient with previously detected breast cancer. An increase in pituitary gland, mammary gland and pancreatic islet cell neoplasia (mammary adenocarcinomas, pituitary and pancreatic adenomas) was observed in the risperidone carcinogenicity studies conducted in mice and rats, but an association between chronic administration of this class of drugs and tumorigenesis in humans has not been evidenced. There is no guidance regarding how to monitor for hyperprolactinemia.

Labeling for ziprasidone (Pfizer, 2007) notes that ziprasidone elevates prolactin levels in humans, and that increased prolactin levels were also observed in animal studies with this compound, and were associated with an increase in mammary gland neoplasia in mice (but not in rats). The other language is similar to what was included for olanzapine. No monitoring advice is offered.

The product labeling for quetiapine (AstraZeneca, 2007) notes that although an elevation of prolactin levels was not demonstrated in clinical trials, increased prolactin levels were observed in rat studies with this compound, and were associated with an increase in mammary gland neoplasia in rats. The label contains similar language to that for olanzapine regarding potential effects of hyperprolactinemia. No monitoring advice is offered.

The product inserts for the first-generation antipsychotics, such as chlorpromazine, perphenazine and haloperidol, are no longer included in compendia such as the Physicians’ Desk Reference (2007), as these medications are now available as generic products and are no longer being commercially promoted. The product labels are available on-line depending on the individual manufacturer, but unfortunately not cross-referenced on the FDA website (see http://www.accessdata.fda.gov/scripts/cder/drugsatfda/). The product insert for haloperidol tablets (Sandoz, 2006) states that antipsychotic drugs elevate prolactin levels and that the elevation persists during chronic administration. Similar information is included as in the label for risperidone, paliperidone, olanzapine, ziprasidone and quetiapine. No monitoring advice is provided. The product insert for other representative first-generation antipsychotics, chlorpromazine (Sandoz, 2004) and perphenazine (Sandoz, 2007) contain virtually the identical information about prolactin as in the labeling for haloperidol (Sandoz, 2006).

In summary the product labels for antipsychotics do not include recommendations regarding the measuring or monitoring of plasma prolactin levels. Depending on the agent, they do describe the available evidence regarding prolactin elevation and carcinogenic potential in rodents (mice and/or rats). For the second-generation antipsychotics, the strongest language and most detailed information about prolactin elevation are provided in the product labels for risperidone and paliperidone. The most benign descriptions are included in the labels for clozapine, aripiprazole and quetiapine. The labels for olanzapine and ziprasidone fall between these two extremes.

**USA guidelines**

Several USA guidelines regarding the treatment of patients with schizophrenia have emerged. Potentially most influential
are the guidelines promulgated by the American Psychiatric Association (APA) (see http://www.psych.org/psych_pract/ treatg/pg/prac_guide.cfm). The second edition of the schizophrenia treatment guidelines (Lehman et al., 2004) suggest an initial or baseline screen for symptoms of hyperprolactinemia, including changes in libido, menstrual changes, or galactorrhea in women and changes in libido, or in erectile or ejaculatory function in men. A baseline prolactin plasma level is left at the discretion of the clinician, based on his/her assessment of the clinical history. Follow-up screening for symptoms of hyperprolactinemia at each visit is recommended until stable, and then yearly if treated with an antipsychotic known to increase prolactin. A follow-up prolactin plasma level is left at the discretion of the clinician, again based on his/her assessment of the clinical history. The guidelines recommend that choice of antipsychotic be tempered by the patient profile, and in the case of prolactin, by a history of sensitivity to prolactin elevation, in which instance antipsychotic medication selection should be made from the following list: olanzapine, quetiapine, ziprasidone, or aripiprazole. Supporting information for these recommendations come from the authors’ observations that prolactin elevation occurs frequently at the therapeutic dose for haloperidol and risperidone, sometimes at the therapeutic dose for thioridazine, perphenazine, mild or occasional at the therapeutic dose for ziprasidone, and no risk or rare at the therapeutic dose for clozapine, olanzapine, quetiapine, and aripiprazole (see also Table 4 in Lehman et al., 2004). The authors also observe that women are at particular risk because they develop higher serum prolactin levels in response to both first-generation antipsychotics and risperidone, compared with men, and thus women may be more likely to have sexual side effects. Moreover, there was concern expressed over the relationship between elevated prolactin levels and a decrease in bone-mineral density with subsequent increase in osteoporosis. An antipsychotic with no or minimal effects on prolactin is recommended for those patients with preexisting osteopenia or osteoporosis. If a drug that increases prolactin is clinically indicated, the guidelines recommend consultation with the physician treating the bone demineralization. Should menstrual or fertility problems emerge in female patients the guidelines recommend evaluation for abnormalities in prolactin secretion, and prolactin-sparking medications are suggested. A specific caveat is made to avoid antipsychotics that elevate prolactin in women with breast cancer, or prescribed only after consultation with the patient’s oncologist; aripiprazole, which partially suppresses prolactin release, may be a preferred option in these circumstances. In lactating mothers the suppression of prolactin should be avoided, suggesting avoiding aripiprazole in those instances. If during the course of treatment with an antipsychotic a patient is experiencing clinical symptoms of prolactin elevation, the APA guidelines recommend that the dose of antipsychotic be reduced or the medication switched to an antipsychotic with less effect on prolactin. Alternatives to switching include the use of dopamine agonists, such as bromocriptine or amantadine.

At an independently funded conference held at the Mount Sinai School of Medicine in New York City in 2002, the goal was to develop recommendations for the systematic health monitoring for patients with schizophrenia being treated with antipsychotics (Marder et al., 2004). Quality of evidence and cost were also commented upon. Clear evidence from multiple-randomized controlled trials was considered level 1 evidence; data from cohort studies, outcomes research, or low quality randomized, controlled studies were considered level 2 evidence; and data from case-control studies were considered level 3 evidence. Quality of evidence for an association between specific antipsychotics and elevation in prolactin level was considered as level 1. By comparison, evidence related to association with weight gain was level 1, diabetes level 2, hyperlipidemia level 2, QT prolongation level 1, extra-pyramidal side effects level 1, and myocarditis with clozapine level 3. Costs of the different evaluative tests were noted to be relatively low compared with acquisition costs of the second-generation antipsychotics (ECG $23; slit-lamp eye examination $23; plasma prolactin level $27; glucose, triglyceride, total cholesterol, high-density lipoprotein levels $30).

The Mount Sinai Guidelines provide similar background material to the APA guidelines (Lehman et al., 2004), namely that certain antipsychotics are associated with increases in plasma prolactin level and that elevated prolactin levels can cause galactorrhea and menstrual irregularities in women, and galactorrhea and sexual dysfunction in men. The concern about hyperprolactinemia and osteoporosis is also stated. The authors note that the prevalence of prolactin-related menstrual disturbances and galactorrhea are relatively common, with estimates of the prevalence of menstrual disturbances associated with antipsychotic use varying from 15% to 91% depending on the study. Although increased prolactin levels associated with antipsychotics may not be high enough to interfere with normal ovarian or testicular function, the authors note that even a small degree of hyperprolactinemia can impair libido and potency, and hyperprolactinemia associated with use of antipsychotics may sometimes be of considerable magnitude, specifically in some patients who take risperidone. However, the authors did not define what they meant by a small degree of hyperprolactinemia or what constitutes a plasma prolactin level of considerable magnitude. The conference participants recommended that clinicians should take a careful history to determine if the patient has any signs and symptoms of an elevated prolactin level before beginning treatment with antipsychotic medications. Specifically patients should be asked the following at baseline and annually: women should be asked about changes in menstruation and libido, or if they are experiencing galactorrhea; men should be asked about libido and erectile and ejaculatory function. The obtaining of a baseline plasma prolactin level is left at the discretion of the clinician, based on if hyperprolactinemia is suspected. If medications associated with prolactin elevation are used, the same questions asked at baseline should be addressed at each visit or until the dose is stable. The presence of symptoms should trigger the obtaining of a plasma prolactin level. Should eleva-
tion in prolactin occur during treatment, and is associated with symptoms, such as menstrual or sexual dysfunction, a switch to a prolactin-sparing agent is suggested, and may obviate the need for a more elaborate and expensive, workup.

An expert consensus survey of 47 experts on psychotic disorders was conducted by a commercial enterprise pursuant to an unrestricted educational grant from Janssen Pharmaceutica, LP, the manufacturer of risperidone (Expert Consensus Panel, 2003). Amenorrhea and galactorrhea were endorsed as simple clinical markers that were important to screen for. It was noted that other assessments, such as that for osteoporosis, would be more difficult to implement. The narrative of the published report repeated the recommendations from the Mount Sinai Conference (Marder et al., 2004) regarding being aware of, and monitoring for, symptoms of increased prolactin, and consideration of switching to a prolactin-sparing medication if symptomatic hyperprolactinemia is present.

The International Psychopharmacology Algorithm Project (IPAP) is a USA-based not-for-profit corporation with substantial international input (see http://www.ipap.org/). A summary statement on antipsychotic-induced hyperprolactinemia is available from the group (International Psychopharmacology Algorithm Project, undated). The authors note that first-generation antipsychotics are associated with a 2–10-fold increase in prolactin levels, and that this is dose dependent and reversible after discontinuation of the offending medication. They also note that these elevations may not necessarily be sustained over extended periods of time. Nonetheless, the authors note that at least in adults, clozapine, olanzapine, quetiapine and ziprasidone have been shown to produce no significant sustained prolactin increase. Specific mention is made of cases of increased prolactin in children and adolescents with olanzapine (the only one of these drugs studied in this younger population as per the authors). As per the IPAP, amisulpride, risperidone and possibly zotepine lead to increased plasma prolactin in adults. A gap in knowledge was identified in that most data concerning the medical consequences of hyperprolactinemia, namely sexual dysfunction, menstrual disturbance, reduction of bone mineral density, and increased risk of breast cancer, stem from studies of patients with prolactinomas rather than studies of antipsychotic-induced hyperprolactinemia. The authors note that sexual dysfunctions in particular are commonly associated with schizophrenia per se and may or may not be related to hyperprolactinemia. Other confounding issues include the use of oral contraceptives among pre-menopausal female patients enrolled in registration trials, so that assessing menstrual irregularities in these samples may be futile. Regarding chronic antipsychotic treatment and breast cancer, the IPAP group notes that a very small effect size was evidenced and consequently no change in current treatment practice was recommended. Much like the other guidelines presented above, the IPAP authors suggest that a rise in prolactin concentrations in the absence of symptoms (sexual dysfunction, galactorrhea, menstrual irregularities) is not a source of concern. Should symptoms occur, prolactin levels, if elevated, may trigger a need to switch to a prolactin-sparing agent.

**Canadian guidelines**

The Canadian Psychiatric Association has provided guidelines for the treatment of schizophrenia, and similar to the guidelines in the USA, includes pertinent questions to ask when evaluating endocrine and sexual functioning (Canadian Psychiatric Association, 2005). For women, the functional inquiry would include questions concerning menstruation, libido and galactorrhea. For men, the concerns revolve around libido, erectile and ejaculatory function. Plasma prolactin levels are recommended where clinically indicated. Baseline assessment would be followed by monthly inquiry for 3 months after initiating a new antipsychotic, and then annually. The authors suggest asking about masturbatory activities, using a menstrual calendar for women, and asking men about spontaneous morning erections. The authors note that isolated hyperprolactinemia without clinical symptoms may still however be a concern in the long-term, but do not provide guidance as to what levels are problematic or the length of time of the asymptomatic hyperprolactinemia that would be clinically relevant. The guidelines are supported by a literature review similar to that found in the USA reports. The authors caution that sexual dysfunctions may be seen with all available antipsychotics, whether they are prolactin-sparing or not. The presence of endocrine or sexual symptoms may be addressed by reducing the dose of the antipsychotic or by switching to another antipsychotic with a lower propensity to cause prolactin elevation. In the individual with sexual dysfunction, confounding medications, such as selective serotonin reuptake inhibitors, should be reassessed as to their need. Caution is urged for women switching from a first-generation antipsychotic or risperidone to a prolactin-sparing antipsychotic – fertility may be restored and appropriate birth control may be needed.

**Australia and New Zealand guidelines**

The guidelines for the treatment of schizophrenia from Australia and New Zealand (Royal Australian and New Zealand College of Psychiatrists, 2005) are a review of the definition, clinical presentation, and course of illness, together with an overview of biopsychosocial treatments. The physical health monitoring, although mentioned, is not described in detail. Regarding hyperprolactinemia, the authors simply recommend that sexual function and side effects should be reviewed regularly, and prolactin levels be measured where indicated.

**UK guidelines**

The National Institute for Clinical Excellence (NICE) of the National Health Service has produced a guideline regarding core interventions in the treatment of schizophrenia (National Collaborating Centre for Mental Health, 2002). Prolactin is mentioned only once. It is noted that physical health checks
should pay particular attention to endocrine disorders such as diabetes and hyperprolactinemia, cardiovascular risk factors such as blood pressure and lipids, side effects of medication, and lifestyle factors such as smoking. No guidance is offered on what specific questions to ask regarding hyperprolactinemia, or what to do in the event of an elevated prolactin level. An update to the NICE document is underway (see http://www.nice.org.uk). A 2006 quick reference guide for bipolar disorder does provide additional information (National Collaborating Centre for Mental Health, 2006), in that children and adolescents should be monitored for prolactin abnormalities, and that women should be advised that the raised prolactin levels associated with some antipsychotics can reduce the chances of conception. Monitoring for specific drugs is recommended for risperidone only with prolactin levels checked at baseline and repeated if symptoms of raised prolactin develop.

The Maudsley Prescribing Guidelines is currently in its 8th edition (Taylor et al., 2005), although the 9th edition is anticipated shortly. For amisulpride, olanzapine, risperidone and zotepine, the monitoring of baseline prolactin is recommended, with additional monitoring if symptoms occur (noted to be rare for olanzapine). If prolactin-related effects are intolerable, the recommendation is to stop the offending agent. As per the guidelines, prolactin monitoring is not necessary for clozapine, quetiapine, ziprasidone, or aripiprazole. Supporting these recommendations are the observations that although all antipsychotics cause measurable changes in prolactin, some do not increase prolactin above the normal range at standard doses (these include clozapine, olanzapine, quetiapine, aripiprazole and ziprasidone). By contrast to the other guidelines presented so far, baseline prolactin levels in the absence of symptoms are recommended, at least for some of the antipsychotics. The authors note that hyperprolactinemia is often superficially asymptomatic (i.e. the patient does not spontaneously report problems) and that there is the possibility that hyperprolactinemia does not affect subjective quality of life. The authors note that persistent elevation of plasma prolactin is associated with sexual dysfunction, reductions in bone mineral density, menstrual disturbances, breast growth and galactorrhea, suppression of the hypothalamic–pituitary–gonadal axis, and a possible increase in the risk of breast cancer. Should symptomatic hyperprolactinemia occur, the first choice for most patients would be switching to an antipsychotic that is prolactin sparing. The guidelines note that symptoms may resolve slowly and symptom severity may not correlate with prolactin changes. Alternatively, dopamine agonists, such as amantadine, carbarogline and bromocriptine may be effective.

International guidelines

The World Federation of Societies of Biological Psychiatry (WFSBP) has produced two schizophrenia treatment guidelines, one for acute treatment (Falkai et al., 2005), the other for long-term treatment (Falkai et al., 2006). After a systematic review of all available evidence, a consensus was reached regarding practice recommendations. Data was extracted from various national treatment guidelines and panels for schizophrenia, as well as from meta-analyses, reviews and randomized clinical trials. The data was also evaluated with respect to the strength of evidence in a similar fashion used by the Mount Sinai Conference (Marder et al., 2004). The panel noted that antipsychotics, particularly first-generation antipsychotics, amisulpride and risperidone can cause hyperprolactinemia by blocking dopamine D2 receptors. The authors quantified the frequency of elevation in a table (Falkai et al., 2005, Table 5) where prolactin elevation was noted as ‘frequent’ (>10%) with haloperidol and amisulpiride, ‘sometimes’ (<10%) with risperidone, ‘occasionally, may be no different than placebo’ for olanzapine, quetiapine, ziprasidone, and ‘no risk’ for clozapine and aripiprazole. The authors note that women tend to develop both more EPS and higher prolactin levels during antipsychotic treatment than men. As in most of the other guidelines reviewed here, the authors note that hyperprolactinemia can lead to galactorrhea, menstrual, cyclical and sexual disturbances in women, and reproductive and sexual dysfunction and galactorrhea/gynecomastia in men. The duration of plasma prolactin elevation is noted: elevated levels may be observed up to 2 weeks after stopping an oral first-generation antipsychotic, and up to 6 months after stopping a depot first-generation antipsychotic. By contrast, the authors note that with the exception of amisulpride and risperidone, the second-generation antipsychotics only transiently elevate prolactin levels and these return to normal within a few days. The guidelines caution that effects on sexual function can be confounded by receptor binding at other than dopamine D2 receptors, making it difficult to attribute cause and effect when evaluating sexual dysfunction in the presence of hyperprolactinemia. The WFSBP guidelines further caution the clinician that there is still an ongoing debate as to whether hyperprolactinemia increases the risk of breast cancer, and that the data is so far inconclusive. If hyperprolactinemia impairs sex steroid production, osteoporosis can result – thus, for patients with preexisting osteopenia or osteoporosis, a prolactin-sparing antipsychotic is recommended. Repeating the caution in the American Psychiatric Association guidelines (Lehman et al., 2004), for women with breast cancer antipsychotics with prolactin-elevating effects should be avoided or prescribed only after consultation with the patient’s oncologist. The WFSBP guidelines suggest that sexual dysfunction can be prevented by using an antipsychotic with no or minimal prolactin elevation (Falkai et al., 2006, Table 4). If sexual dysfunction is observed and an elevated prolactin level is found, the suggestion is to switch to an antipsychotic that is prolactin-sparing. An alternative is the use of an agent such as bromocriptine.

How might the guidelines be improved?

Basic elements of the prolactin monitoring recommendations for each of the reviewed guidelines are summarized in Table 1. With the exception of the Maudsley Guidelines (Tay-
<table>
<thead>
<tr>
<th>Guideline</th>
<th>Baseline plasma prolactin levels</th>
<th>Periodic plasma prolactin levels</th>
<th>Baseline functional inquiry</th>
<th>Periodic functional inquiry</th>
<th>Guidance on what plasma prolactin levels are clinically important</th>
<th>General guidance on management of hyperprolactinemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manufacturer’s product labeling</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No, at each visit until stable, and then yearly if treated with an antipsychotic known to increase prolactin.</td>
<td>No</td>
</tr>
<tr>
<td>American Psychiatric Association (Lehman et al., 2004)</td>
<td>If indicated on the basis of clinical history</td>
<td>No</td>
<td>Yes</td>
<td>No</td>
<td>For patients who are receiving antipsychotics known to be associated with elevation in prolactin levels, the screening questions should be asked at each visit for the first 12 weeks after starting the antipsychotic or until the dose is stable, and then annually; otherwise annually for all patients</td>
<td>No</td>
</tr>
<tr>
<td>Mount Sinai Conference (Marder et al., 2004)</td>
<td>If symptoms are present</td>
<td>If symptoms are present</td>
<td>Yes</td>
<td>No</td>
<td>Unclear</td>
<td>No</td>
</tr>
<tr>
<td>Expert Consensus Survey (Expert Consensus Panel, 2003)</td>
<td>See Mount Sinai Conference (Marder et al., 2004)</td>
<td>See Mount Sinai Conference (Marder et al., 2004)</td>
<td>See Mount Sinai Conference (Marder et al., 2004)</td>
<td>See Mount Sinai Conference (Marder et al., 2004)</td>
<td>See Mount Sinai Conference (Marder et al., 2004)</td>
<td>No</td>
</tr>
<tr>
<td>International Psychopharmacology Algorithm Project (International Psychopharmacology Algorithm Project, undated)</td>
<td>No</td>
<td>If symptoms are present</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Canadian Psychiatric Association (Canadian Psychiatric Association, 2005)</td>
<td>When clinically indicated</td>
<td>When clinically indicated</td>
<td>Yes</td>
<td>Monthly inquiry for 3 months after initiating a new antipsychotic, and then annually</td>
<td>Sexual function and side effects should be reviewed regularly</td>
<td>No</td>
</tr>
<tr>
<td>Australia and New Zealand (Royal Australian and New Zealand College of Psychiatrists, 2005)</td>
<td>When indicated</td>
<td>When indicated</td>
<td>Unclear</td>
<td>No</td>
<td>Sexual function and side effects should be reviewed regularly</td>
<td>No</td>
</tr>
<tr>
<td>UK National Institute for Clinical Excellence (National Collaborating Centre for Mental Health, 2002)</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Physical health checks should pay particular attention to endocrine disorders, such as diabetes and hyperprolactinemia...</td>
<td>No</td>
</tr>
<tr>
<td>UK National Institute for Health and Clinical Excellence (National Collaborating Centre for Mental Health, 2006)</td>
<td>For risperidone only; For children and adolescents only</td>
<td>If symptoms of raised prolactin develop</td>
<td>No</td>
<td>No</td>
<td>No, No, No</td>
<td>No</td>
</tr>
<tr>
<td>Maudsley Prescribing Guidelines (Taylor et al., 2005)</td>
<td>For amisulpride, olanzapine, risperidone, and zotepine</td>
<td>For amisulpride, olanzapine, risperidone, and zotepine if symptoms occur</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>World Federation of Societies of Biological Psychiatry (Falkai et al., 2005; Falkai et al., 2006)</td>
<td>No</td>
<td>If hyperprolactinemia is suspected</td>
<td>Unclear</td>
<td>Unclear</td>
<td>No, Yes</td>
<td>No</td>
</tr>
</tbody>
</table>
found in general texts of internal medicine, such as Harrison’s Principles of Internal Medicine (Melmed and Jameson, 2005). From these sources, we note that the normal adult serum prolactin level is 10–25 ng/ml (~210–530 mIU/L) in women and 10–20 ng/ml (~210–420 mIU/L) in men. Not always noted in reviews for psychiatrists is that prolactin secretion is pulsatile, and highest during REM sleep, with a peak of up to 30 ng/ml (~640 mIU/L) between 0400h and 0600h. Prolactin’s circulating half-life is a mere 50 minutes. Moreover serum prolactin rises after exercise, meals, sexual intercourse, minor surgical procedures, general anesthesia, acute myocardial infarction, and other forms of acute stress. These factors need to be considered when making recommendations as to when prolactin levels ought to be measured and how they are to be interpreted. Basal fasting morning prolactin levels may be the easiest way to standardize the sampling procedure, and can be done at the same time fasting glucose and lipids are obtained. It may be necessary to measure levels on several different occasions when clinical suspicion is high because levels may vary widely due to prolactin’s pulsatile secretion pattern. Measuring transient prolactin elevations by sampling plasma within the 1–5 hour period after antipsychotic medication administration may be of interest, but the adverse long-term consequences of these transient elevations are unknown (Turrone et al., 2002).

Prolactin-secreting pituitary adenomas (prolactinomas) are the most common cause of prolactin levels greater than 100 ng/ml (~2120 mIU/L). Prolactin levels above 200 ng/ml (~4240 mIU/L) almost always indicate the presence of a lactotroph adenoma (Serri et al., 2003). Elevated prolactin levels, but less than 100 ng/ml (~2120 mIU/L), is most commonly due to a medication effect, but can more rarely be seen with a microprolactinoma, pituitary stalk compression, hypothyroidism or renal failure. These thresholds and differential diagnosis can be helpful to include in guidelines intended for psychiatrists.

Serri et al. (2003) provide some rules of thumb regarding prolactin levels and clinical presentations in pre-menopausal women: marked prolactin excess (>100 ng/ml (~2120 mIU/L]) is commonly associated with hypogonadism, galactorrhea and amenorrhea; moderate prolactin excess [51–75 ng/ml (~1080–1590 mIU/L)] is associated with oligomenorrhea; mild prolactin excess [31–50 ng/ml (~660–1060 mIU/L)] is associated with short luteal phase, decreased libido and infertility. These breakpoints help place some of the more commonly observed elevations in plasma prolactin in clinical perspective.

Although this review has focused on antipsychotic medications and their association with elevated plasma prolactin levels, drug induced hypersecretion can also be seen with dopamine synthesis inhibitors (alpha-methylldopa), catecholamine depletors (reserpine), opiates, H2 antagonists (cimetidine, ranitidine), imipramines (amitriptyline, ranitidine), serotonin-reuptake inhibitors (fluoxetine), calcium channel blockers (verapamil), and hormones (estrogens, antiandrogens). Normalizing prolactin levels is the treatment goal in order to alleviate suppressive effects on gonadal function, halt galactorrhea, and preserve bone mineral density. It remains unclear what thresholds or cut-off points ought to be considered when managing prolactin elevation in the absence of symptoms.

Selection of an antipsychotic and monitoring for prolactin abnormalities should be done within the context of evaluating other side-effect profiles, such as extra-pyramidal symptoms, as well as potential metabolic consequences, such as weight gain, hyperlipidemia and glucose abnormalities. Overall effectiveness of an antipsychotic medication involves consideration of both efficacy and tolerability, both of which varies from drug to drug, and patient to patient. The use of evidence-based medicine tools, such as number needed to treat and number needed to harm, may be helpful in this regard (Citrome and Stroup, 2006).

Conclusions

Guidelines regarding the monitoring for hyperprolactinemia in patients receiving antipsychotics are limited. Although they encourage the clinician to ask about symptoms that may be related to elevated plasma prolactin levels, they do not provide sufficient guidance regarding risks that are not so easy to ascertain, such as osteopenia or osteoporosis. Moreover, the guidelines do not for the most part address when and how to measure plasma prolactin levels, nor how to interpret them if they are moderately elevated. A major obstacle are the gaps in our knowledge of the consequences of moderate hyperprolactinemia among patients receiving antipsychotics, including the unknown consequences of transient elevations of prolactin that may be evidenced with medications that bind loosely to the dopamine D2 receptor. The prudent clinician should consider obtaining a baseline plasma prolactin level and at least one follow-up measurement when starting any patient on a new antipsychotic. This will help guide clinical decisions about antipsychotic dosage, switching antipsychotic medications, or considering ancillary treatments to protect bone mass. These decisions would be within the context of considering other adverse events as well as the overall effectiveness of the antipsychotic being used.
Declaration of interest

Leslie Citrome, MD, MPH, is a consultant for, has received honoraria from, or has conducted clinical research supported by the following: Abbott Laboratories, AstraZeneca Pharmaceuticals, Avanir Pharmaceuticals, Azur Pharma Inc., Barr Laboratories, Bristol-Myers Squibb, Eli Lilly and Company, Forest Research Institute, GlaxoSmithKline, Janssen Pharmaceuticals, Jazz Pharmaceuticals, Pfizer Inc., and Vanda Pharmaceuticals.

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Accessed April 16, 2007


