Hormonal Side Effects in Women: Typical Versus Atypical Antipsychotic Treatment

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Neuroleptic-induced hyperprolactinemia can cause menstrual disorders, impaired fertility, galactorrhea, and sexual dysfunction, as well as hypoestrogenism secondary to disruption of the hypothalamic-pituitary-ovarian axis. The development of the prolactin-sparing atypical antipsychotic drugs offers prevention and resolution of these adverse reactions. Thus far, this property of the new medications has received insufficient clinical attention. The authors use case vignettes to discuss assessment and management of clinical situations that arise as a result of antipsychotic-induced endocrine changes.
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The clinical definition of "atypicality" for antipsychotic agents is controversial. Usually, it refers to efficacy against psychotic symptoms with a decreased tendency to induce neurologic movement disorders. In the case of clozapine, it also means effectiveness in treatment-resistant schizophrenia. The label has also come to mean efficacy against negative symptoms and a wider spectrum of comorbid symptoms. There has, to date, been no agreement as to whether the prolactin-sparing effect of some, but not all, of the new drugs should be included in the definition of atypicality. Despite the lack of expert consensus on this issue, the variable propensity of antipsychotic drugs to induce hyperprolactinemia does have clinical relevance for patients being treated with these medications.

Traditional typical neuroleptics elevate prolactin levels.[1] In contrast, clozapine does not cause sustained prolactin elevations.[2] Olanzapine is prolactin-sparing relative to haloperidol[3] and risperidone.[4] While prolactin increases may occur with olanzapine, they tend to be minimal and relatively transient.[5] The recently released compound quetiapine does not elevate prolactin throughout its suggested dosage range.[6] Risperidone, in contrast, is comparable to traditional neuroleptics and in premenopausal women is capable of inducing more severe hyperprolactinemia than are the first-generation antipsychotics.[7–9]

Prolactin, an anterior pituitary hormone, has a major physiologic role in human lactation. Hyperprolactinemia secondary to neuroleptic ingestion or from other causes suppresses the pulsatile secretion of gonadotropin-releasing hormone (GnRH) from the hypothalamus. Abnormal menstrual cycles or amenorrhea and erratic or absent ovulation may ensue secondary to disruption of normal hormonal production and cyclical secretion of sex steroids.[10–13] In reproductive-aged women, hyperprolactinemia may therefore induce hypoestrogenism comparable to what occurs in menopause. Galactorrhea may or may not occur concurrent with menstrual dysfunction.[14,15]

When prolactin levels are lowered, these side effects usually resolve. Menses may resume, libido may increase, and fertility (depending on age and health) may return to normal. Estrogen levels, if low, return to age-appropriate levels, therefore reducing the medical risks associated with hypoestrogenism, which include genitourinary symptoms, decreased bone mineral density,[16,17] and cardiovascular disease.[18,19] Low estrogen levels also modify psychiatric symptoms and cognitive functions.[20–22] Age, psychological state, stage in the life cycle, and the duration and severity of disruption of normal hormonal cyclicity are all factors that influence the medical and psychological impact of hormonal changes on the individual woman.

With the introduction of the second generation of antipsychotic drugs, which in general achieve good control of the symptoms of schizophrenia with fewer side effects, psychological issues that earlier had limited significance or clinical priority now become important to address. For

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instance, menstruation is a defining event in women's lives from the time it begins until the time it ends.[23] It inevitably acquires meanings vis-à-vis peer relations, femininity, desirability, fertility, and womanhood. Its meaning is, of course, influenced by upbringing, individual experience, and cultural traditions. Psychologically, amenorrhea may be experienced with indifference (case 1), as a loss of youth and generative ability (case 2), or as a welcome development (case 3). It is important that these issues be recognized and addressed in women with serious mental illnesses, as in any women undergoing psychiatric treatment.

A recent review article[24] discusses neuroleptic-induced hyperprolactinemia in both sexes. The objective of the current article is to focus on antipsychotic drugs and hyperprolactinemia in women, using case vignettes chosen to illustrate optimal assessment and management of hyperprolactinemia in the clinic.

CASE VIGNETTES

Case 1: The Young Woman With Early-Onset Schizophrenia

Ms. A, a 21-year-old sexually inactive, single woman, has adolescent-onset schizophrenia. At age 19, following an acute exacerbation of her psychotic symptoms, she was referred to a day program for medication management and rehabilitation. She experienced intermittent psychotic symptoms, dyskinetic movements of her mouth and fingers, akathisia, and a mildly elevated serum prolactin level of 26 μg/L (reference range, 1–15 μg/L) while being treated with trifluoperazine, 5 mg b.i.d., and lithium, 600 mg b.i.d. Menstrual periods were present but irregular.

A trial of risperidone was initiated. Her mental state improved and her restlessness decreased so that she was able to successfully attend the day program. The dyskinetic movements remained unchanged. Consecutive serum prolactin levels measured while she was taking risperidone, 2 mg b.i.d., were 42.4, 117.7, 148.2, and 103.4 μg/L, i.e., markedly elevated. Galactorrhea was present only with nipple manipulation and was not bothersome to the patient. She did not have a spontaneous period during the 9 months of risperidone treatment. At month 5 of risperidone treatment, progesterone challenge produced only a scanty withdrawal bleed. She was unwilling to take intermittent oral progesterone to assess functional estrogen status or, alternatively, to commence oral contraceptives as recommended by the consulting endocrinologist. Ms. A did not complain about her menstrual disturbance. She conveyed indifference and was embarrassed by questions about her menses. In contrast, her mother expressed concern that Ms. A's menstrual cessation was "abnormal."

Because of residual psychotic symptoms, extrapyramidal side effects, and absent menses, Ms. A was eventually switched to treatment with olanzapine. Her serum prolactin level normalized and was 13 μg/L at month 2, spontaneous periods occurred at months 3 and 5, and regular monthly menstrual cycles resumed by month 7 of olanzapine treatment. Serum prolactin levels on olanzapine treatment, 17.5 and 22.5 mg h.s., were 16 μg/L. While Ms. A reports that she is "happy" about resumption of menstruation, she continues to appear unconcerned about this dimension of womanhood. Her mild galactorrhea and akathisia resolved and her dyskinetic movements gradually diminished. Ms. A continued to experience positive symptoms of schizophrenia during periods of increased stress, but functionally, she improved enough to progress to a work training program.

Discussion. The development of amenorrhea in women with diagnosed schizophrenia has generally been regarded as a known but clinically benign consequence of traditional neuroleptic treatment. It has sometimes even been considered to be a desirable outcome given some psychotic women's impaired abilities to attend to hygiene and difficulty with adherence to birth control measures. Disruption of menstrual cycles, a known and common side effect of antipsychotic treatment,[25,26] is often not routinely monitored for by prescribing physicians and, if detected, may be inappropriately treated with reassurance. In this patient, markedly elevated prolactin levels occurred concurrent with the development of amenorrhea. Progesterone administration confirmed a cumulative lack of estrogen effect since only scanty withdrawal bleeding occurred. With reduction in prolactin levels, menstrual cycle resumption (as was the case with Ms. A) has been reported with clozapine[27] and olanzapine treatment,[28,29] but population studies that would provide more systematic data are not yet available.

Serum prolactin levels are affected by multiple physiologic variables including circadian rhythms,[30] phase of the menstrual cycle,[31] food intake, stress, and nipple stimulation.[11] When studying small changes in prolactin levels for research purposes, control of these factors is important. However, when screening for pathologic hyperprolactinemia in antipsychotic-treated patients, a random measurement of the nonfasting serum prolactin level is acceptable and will provide relevant clinical information. If the level is only mildly elevated, i.e., 2 to 3 times the upper limit of the reference range, repeating the test to assess whether hyperprolactinemia is in fact present is the next appropriate step. At levels greater than 3 times normal in a patient with known sequelae of neuroleptic-induced hyperprolactinemia, repeated measurements are neither diagnostically helpful nor cost-effective. The key point is that patients who are treated with antipsychotic drugs known to elevate serum prolactin must be monitored for known sequelae of hyperprolactinemia.[32] Sole reliance on prolactin levels is inadequate since effects on end organ function are individualized and variable.[33,34]

Disrupted menstrual cycles and amenorrhea have been linked with schizophrenia even prior to the introduction of

neuroleptics.[35] It is sometimes unclear in women with schizophrenia whether the menstrual disturbance is secondary to the disease or the drug or both. This is analogous to tardive dyskinesia, which is a known side effect of treatment with neuroleptics even though dyskinesias in persons with schizophrenia had been reported prior to the use of these drugs. It is possible that women with schizophrenia, given their brain disease and/or stress sensitivity and the frequent onset of this disorder during adolescence, are particularly vulnerable to drug-induced dysregulation of their hypothalamic-pituitary-ovarian axis as they are to extrapyramidal movement disorders. Documenting the menstrual history prior to antipsychotic administration is thus essential. Ongoing monitoring of menstrual function, as was done in this patient, allows for appropriate investigations and interventions should clinical status require them.

That Ms. A's mother was more concerned about the amenorrhea than the patient herself is a common scenario. Ms. A may have been relieved to bypass menstruation. However, without regular menses as a marker, the fear of an undetected pregnancy may create stress for both the patient and her family. Mothers are often more aware than are their young daughters that the absence of menses is abnormal, and they often express concern about the medical and psychological consequences of amenorrhea compounding the already heavy burden of a severe psychiatric illness. In addition, women today are in general more aware of the negative health consequences of hypogonadism.

Case 2: The Woman With Treatment-Resistant Schizophrenia

Ms. B, a 32-year-old sexually inactive single woman with a 12-year history of chronic treatment-resistant schizophrenia, lives at home with a protective extended family. She experienced severe recurring positive symptoms. Because of this, and since olanzapine and quetiapine were not yet available (as with case 3), she proceeded directly to a trial of clozapine.[32] On clozapine treatment, she dramatically improved and became capable of participation in a psychosocial rehabilitation program.

While taking high-dose haloperidol (oral plus depot) and lithium, her serum prolactin level was markedly elevated to 211 μg/L. At month 4 of clozapine treatment, her prolactin level had normalized to 14.7 μg/L. There was no history of galactorrhea. Menstrual periods, which had been absent during the preceding 5 years of neuroleptic treatment, resumed 5 months following clozapine initiation. She proudly announced that since she was now "a woman again," she wished to marry and have a child. Ms. B became romantically involved with a male schizophrenia patient. Shortly thereafter, they became engaged and requested a counseling session to discuss having children. Of major concern to her fiancé was Ms. B's desire to stop her medication now that she felt "normal." Her rationale was that she was now "cured," and that if she should became pregnant, she would refuse medication for fear of harming the fetus. She subsequently reduced her medication against medical advice and relapsed, and the relationship ended. Ms. B's yearning for a "normal" life as a wife and mother continues to be a significant issue in her therapy.

Discussion. In Ms. B's case, despite 5 years of amenorrhea, this medical condition was not diagnosed, investigated, and/or recognized as a significant medical and psychological issue by her psychiatric team. Secondary amenorrhea in a premenopausal woman, whether she has schizophrenia or not, warrants appropriate investigations that may include a gynecology examination, pregnancy test, serum follicle-stimulating hormone (FSH) test to rule out ovarian failure, prolactin level test to rule out hyperprolactinemia, and a progesterone challenge to determine estrogen status. In the presence of hyperprolactinemia, FSH is inappropriately suppressed such that it does not assist in diagnosis of ovarian failure as it does in non-hyperprolactinemic patients.

Libido may increase with resolution of hyperprolactinemia, but sexual dysfunction in antipsychotic-treated women is usually multifactorial.[36] Hyperprolactinemia in one study of antipsychotic-treated patients correlated with male but not female sexual problems.[25] More research in this area is indicated. In Ms. B, an increase in sexual interest occurred concurrent with resolution of chronic hyperprolactinemia, reduction in psychotic symptoms, and increased ability to socialize; perhaps all 3 contributed to her interest in engaging in a heterosexual relationship. The desire for a "normal" life and the yearning for a child is of course not confined to seriously mentally ill women whose level of function improves with atypical antipsychotic treatment.[37] In Ms. B, though, the return of regular menses precipitated her desire to be a mother as it signaled to her that she was capable of conceiving. That Ms. B had viewed herself as "less than a woman" while suffering from amenorrhea had not been comprehended by her treating physician (R.A.D.) until this side effect resolved with clozapine treatment. The availability of the new prolactin-sparing antipsychotics that interfere less with the endocrine system means that women with schizophrenia will suffer one less loss, i.e., they may be able to retain normal menstrual function.

The return of menses may be welcome, as in Ms. B, or unwelcome, as in the next case, but before switching to a prolactin-sparing antipsychotic, women with amenorrhea secondary to neuroleptic-induced hyperprolactinemia should be advised that menses may resume. With the resumption of regular cycles, normal fluctuating hormone levels may put women with schizophrenia at risk for premenstrual exacerbation of schizophrenic symptoms. This will require the clinician to consider dosage adjustments of medication over the menstrual cycle and to counsel patients about this possibility. Women should be encouraged

to record the onset of menses to assist psychiatrists in monitoring for menstrual cycle fluctuations of symptoms.

Changes in reproductive fitness secondary to treatment with prolactin-sparing antipsychotics have not been systematically studied,[38] but case reports[27–29,39–42] coupled with the known adverse effects of hyperprolactinemia on fertility[10,11] suggest that switching from traditional neuroleptics or risperidone to these new prolactin-sparing medications improves reproductive fitness. This change may be unexpected by the patient, the family, and the care providers. Pregnancies, both desired[39] and unwanted,[40] have been described in clozapine-treated women as a possible consequence of normalization of prolactin levels and, subsequently, more regular ovulation. An undesired pregnancy in a woman switched from depot neuroleptic treatment to olanzapine has also been reported.[41] While it is essential to assist all seriously mentally ill women with family planning,[37] the potentially increased risk of pregnancy with resolution of hyperprolactinemia following medication change to clozapine, olanzapine, and quetiapine warrants intensified efforts to provide contraceptive counseling.

Case 3: The "Menopausal" Woman With Chronic Schizophrenia

Ms. C, a 52-year-old married grandmother, has a 20-year history of schizophrenia. At age 47, she began to experience increased psychotic symptoms with severe hallucinations and paranoid delusions that required multiple emergency hospitalizations. Despite trials of both oral and depot typical neuroleptics and risperidone, her ability to function in her chosen roles as a housewife and spouse continued to deteriorate. Following clozapine initiation, she experienced marked symptom reduction and no longer required hospital admissions.

According to Ms. C, menopause had occurred in her mid-40s. Galactorrhea was not present. Nine months after clozapine initiation and 1 year after discontinuing pipotiazine palmitate injections (a piperidine phenothiazine), her serum prolactin levels, which had been markedly increased at 126, 120, and 126 μg/L prior to initiating clozapine, remained elevated at 55 μg/L. Given the decline from previous levels, and since depot neuroleptics can produce prolonged dopamine blockade and, therefore, prolactin elevations, further endocrine and neurologic investigations were not considered to be clinically justified at that point.

Seventeen months after clozapine initiation, Ms. C developed uterine bleeding and became very alarmed. Since her interpretation was that her periods had resumed, she was afraid that she could become pregnant. She was referred to a gynecologist for investigation of postmenopausal bleeding and underwent a diagnostic dilatation and curettage. The pathology report stated that the endometrium was "hypoactive in appearance. The stroma still retains a slight amount of edema, indicating at least a recent, low-level estrogen effect." A prolactin level drawn 1 day before surgery was 6 μg/L. At 2-year follow-up, no further episodes of vaginal bleeding had occurred.

Discussion. Postmenopausal vaginal bleeding requires investigation and may necessitate a surgical diagnostic procedure, as occurred in Ms. C's case. The timing of her bleeding suggested estrogenization of the endometrium concomitant with resolution of neuroleptic-induced hyperprolactinemia, but we cannot be certain, given that postmenopausal women frequently present with vaginal bleeding from other causes.

When hyperprolactinemia is detected while utilizing a known prolactogenic drug, it is presumptive that the drug is the cause, but other etiologies must be considered. Clinical examination to eliminate chest wall irritation, signs of a sellar mass, and hypothyroidism and laboratory measurement of thyroid-stimulating hormone and creatinine (to rule out early renal failure) as causes of hyperprolactinemia are all necessary. In the absence of clinical findings, diagnostic imaging of the pituitary is not generally indicated since the 10% to 30% incidence of hypodense pituitary lesions on computed tomography (CT) or magnetic resonance imaging (MRI) scans in the normal population may confuse the issue and needlessly worry the patient.[43] Consultation with an endocrinologist may assist in clarifying how extensive investigations should be. With the introduction of prolactin-sparing antipsychotics, discontinuation of the neuroleptic and monitoring for prolactin normalization after switching to olanzapine, quetiapine, or clozapine may be diagnostic, as it was in these cases.

When a perimenopausal neuroleptic-treated woman develops amenorrhea, the presumption that she has become menopausal may be incorrect. Amenorrhea may be secondary to neuroleptic-induced hyperprolactinemia and may resolve if the patient is prescribed a prolactin-sparing antipsychotic or other treatment for hyperprolactinemia. Treatment with drugs that increase prolactin levels, combined with age-related decline in estrogen levels, may put perimenopausal women at increased risk for premature cessation of menses and an earlier decline in estrogen levels than women who are not taking antipsychotics. This earlier onset of hypoestrogenism is a risk factor for decreased bone mineral density[17] and cardiovascular disease.[18,19] Treatment of hyperprolactinemia has been shown to increase bone mass in amenorrheic women with osteopenia, therefore making identification of this at-risk group of medical importance.[44]

If a woman believes that she is menopausal, she may also believe that birth control measures are no longer required. Because Ms. C was presumed to be postmenopausal at the time of clozapine initiation, she was not warned of the possibility of vaginal bleeding, and she subsequently suffered significant psychological distress. Clinicians who treat perimenopausal women should, as with

younger women, consider the possibility that a switch to a prolactin-sparing antipsychotic may cause menses to resume. The chance of conceiving therefore increases, so patient education must accompany medication change.

The onset of menopause in women with schizophrenia should prompt referral to a gynecologist or family practitioner to determine appropriate hormone replacement therapy. At a minimum, psychiatric care providers should monitor for the onset of menopausal symptoms in antipsychotic-treated women, assess the role of neuroleptic-induced hyperprolactinemia in any menstrual disturbance, and facilitate and advocate that these women receive the same standard of care as is provided to menopausal women who are not mentally ill.

While galactorrhea is a known consequence of neuroleptic-induced hyperprolactinemia and perhaps the side effect that clinicians most often associate with hyperprolactinemia, only the young woman with schizophrenia (case 1) had mild galactorrhea. This side effect was reported as not bothersome and was elicited only on direct questioning. Subjective responses to galactorrhea have been reported to be highly individual. In some women this side effect can be misinterpreted as evidence of pregnancy or generative potential.[45] It is not surprising that cases 2 and 3 did not present with galactorrhea despite high levels of prolactin, as milk production requires appropriate hormonal priming of breast tissue.[10–13] Both of these women were probably estrogen deficient secondary to chronic hyperprolactinemia and in the second case, also to a concomitant age-related decline in estrogen production. There is a poor correlation between hyperprolactinemia and the clinical presence and severity of galactorrhea.

The impact of chronic neuroleptic-induced hyperprolactinemia, as well as normalization of prolactin levels and hormonal cyclicity following treatment with prolactin-sparing antipsychotics, on symptoms of schizophrenia, emotions, and behavior warrants investigation. Psychological distress, in particular anxiety, depression, and hostility, secondary to nonphysiologic hyperprolactinemia has been reported in nonpsychotic women independent of hypoestrogenism.[46] Also, symptom severity in women with schizophrenia has been found to be inversely related to estrogen levels,[47] and changes in psychopathology have been reported with estrogen administration.[48–50] In Ms. C, a trial of estrogen replacement at the time of symptom exacerbation that was coincident with the onset of apparent menopause during her late 40s might have been a reasonable intervention. Improvement in psychopathology after switching from typical to atypical antipsychotics has been attributed to a new balance of neurotransmitter receptor blockade. It is possible, however, that normalization of endocrine function also contributes to improvement in symptoms, at least for a subgroup of women.

If side effects are present secondary to neuroleptic-induced hyperprolactinemia, various approaches are possible, including (1) switching to a prolactin-sparing antipsychotic, i.e., olanzapine, quetiapine, or clozapine (the latter if the woman is treatment resistant); (2) lowering the dose of the typical neuroleptic or risperidone; (3) adding a dopamine agonist, such as bromocriptine; or (4) adding cyclical or combined estrogen and progesterone hormone replacement to treat the estrogen deficiency.[24,32] The last approach addresses hypoestrogenism and its consequences, but direct symptoms of hyperprolactinemia will not be solved by this intervention.

CONCLUSION

Reproductive and sexual functioning are important dimensions of womens' lives. The availability of atypical antipsychotics that do not induce hyperprolactinemia is good news, since the risk of developing disturbed menstrual cycles, hypogonadism, galactorrhea, and sexual dysfunction is reduced with these drugs. The use of the drugs can normalize the lives of women with schizophrenia, but that in turn calls for extra attention by care providers to issues of sexual activity, contraception, and decision making regarding child bearing. By understanding the multiple factors that affect reproduction and sexuality, clinicians can improve the quality of life of women with schizophrenia, who often must receive life-long treatment with antipsychotic medications.

Drug names: bromocriptine (Parlodel and others), clozapine (Clozaril), haloperidol (Haldol and others), olanzapine (Zyprexa), quetiapine (Seroquel), risperidone (Risperdal), trifluoperazine (Stelazine).

Disclosure of off-label usage: The authors of this article have determined that, to the best of their knowledge, no investigational information about pharmaceutical agents has been presented herein that is outside U.S. Food and Drug Administration–approved labeling.

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