Secondary Effects of Antipsychotics: Women at Greater Risk Than Men

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Context: The health burden of antipsychotic medication is well known, but the disproportionate effect on women as compared with men is underappreciated. *Objective:* The goal of this article is preventive—to better inform clinicians so that the risks to women and to their offspring can be diminished. *Method:* All PubMed sources in which the search term gender (or sex) was linked to a side effect of antipsychotic medication were reviewed. *Result:* There is general agreement in the literature on women's increased susceptibility to weight gain, diabetes, and specific cardiovascular risks of antipsychotics, with less consensus on malignancy risks and risks to the fetus. Cardiovascular death, to which men are more susceptible than women, is disproportionately increased in women by the use of antipsychotics. Sedating antipsychotics raise the risk of embolic phenomena during pregnancy, and postpartum. Prolactin-elevating drugs suppress gonadal hormone secretion and may enhance autoimmune proclivity. *Conclusions:* Clinicians need to be aware of the differential harm that women (and their offspring) can incur from the side effects of antipsychotics.

Key words: antipsychotics side effects/women/cardiovascular risk/autoimmunity/thromboembolism/malignancy/blood dyscrasia

A systematic PubMed search entering search terms for the various side effects of second-generation antipsychotics (blood dyscrasia, cardiovascular event, diabetes mellitus (DM), hypertension, metabolic syndrome, neuroleptic malignant syndrome, prolactin elevation, QT interval, sleep apnea, thromboembolism, and weight gain) plus "gender" and "antipsychotic" linked to "malignancy" and "birth complication" yielded a long list of publications. Those with the greatest clinical relevance are examined in this article, which reviews the potential harm of antipsychotics to women and their offspring.

Prolactin Elevation

Antipsychotic medication blocks type 2 dopamine (D2) receptors on the lactotrophs of the anterior pituitary gland, releasing these cells from dopamine inhibition, which results in increased prolactin secretion. This complication is most associated with conventional antipsychotics, amisulpride, and risperidone, which can raise prolactin levels 10-fold above pretreatment values in both men and women, but because women start off at higher levels, they are more likely to experience symptoms—gynecomastia, galactorrhoea, sexual dysfunction, atrophic changes in the urethra and vaginal mucosa, reduced vaginal lubrication and dyspareunia, loss of libido, ovarian dysfunction, infertility, oligomenorrhoea, and amenorrhoea.[1] Sexual dysfunction while on antipsychotics, for instance, is much more frequent in women than in men, an underappreciated clinical fact. Compared with sex-matched controls, the odds ratio (OR) is 15.2 for women and 3.7 for men.[2]

Prolactin elevation, defined as a level above 18.77 ng/ml for males and above 24.20 ng/ml for females, was found in 42.4% of males on antipsychotics, 45.1% of postmenopausal women, but in as many as 65.6% of reproductive age women. Because high prolactin inhibits the pulsatile production of gonadotrophin-releasing hormone from the hypothalamus and, more directly, the ovarian secretion of estrogen, one-third of premenopausal females in this study whose prolactins were elevated showed postmenopausal levels of estradiol, ie, levels $\leq$19.8 pg/ml.[3] The consequently high androgen-to-estrogen ratio can induce symptoms such as acne and hirsutism, common and distressing complaints of women treated with older antipsychotics and with risperidone.

Osteoporosis

As a result of postmenopausal estrogen loss, 30% of women over the age of 50 suffer from osteoporosis. Given the higher prevalence of secondary hyperprolactinemia in women compared with men, osteoporosis would be expected to be more prevalent among antipsychotic-using women than among their male peers, but the evidence is far from clear. In a cross-sectional Korean study, female patients who had been on haloperidol monotherapy

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for at least 2 years, but not male patients, showed significantly lower bone mineral density (BMD) than age and sex-matched controls. In the 18 female patients with BMD loss, 17 had hyperprolactinemia and 7 also had hypoestrogenemia.[4] Meaney et al.,[5] however, found more age-related reductions in BMD in men (57%) receiving prolactin-raising antipsychotics than in women (32%), the higher the dose the lower the BMD. Similarly, in a cross-sectional study of 75 patients with schizophrenia treated with antipsychotics for at least 1 year, only men (not women) showed lowered BMD in the lumbar region. Exposure to antipsychotics known to increase prolactin was not related to BMD in this study. What the investigators found was that the body mass index (BMI) correlated positively with BMD: the more weight, the denser the bone in both sexes.[6] Howard et al.[7] found a significant interaction between prolactin-raising antipsychotics and hip fracture for both men and women: OR = 2.12 for men and OR = 1.93 for women. In general, fractures that result from osteoporosis are more common in women than in men because of women's smaller skeletons.[8,9] As stated by Halbreich,[10] "Despite many publications, the epidemiology of abnormal bone structure, mineralization and dynamics in patients with schizophrenia is still not fully determined." It is not yet clear which drugs, over what period of time, do what to bone and whether women are more affected than men, and at what ages.

It is important to keep in mind that antipsychotic drugs, while raising prolactin levels, also lead to increases in lipid stores from which steroids, including estrogens and androgens, are synthesized. The sex hormone deficiency that results from high prolactin may be offset by the increased gonadal hormone level that results from extra adiposity. At this time, it is not clear that antipsychotics raise the risk for osteoporosis although some may, especially at high doses. If they do, there is no current evidence that women are at greater risk than men.

Breast and Prostate Cancer

Similar doubts about specific antipsychotic risk exist with respect to breast and prostate cancer. Although higher prolactin levels are associated with increased breast cancer risk,[11] there is no evidence that women on antipsychotics show a higher prevalence of breast cancer than occurs in the general population. Prolactin is mitogenic in that, locally produced by breast cancer cells, it stimulates their proliferation and suppresses apoptosis.[12] However, using nationwide computerized registers of death data on 12 430 473 individuals (144 364 of whom suffered from Parkinson's disease [PD]), patients with PD (who have low dopamine and high prolactin levels) showed lower rates of breast and other types of malignancies than the population at large.[13] Epidemiological studies have been limited and inconsistent, often not taking into account important factors such as family history and parity when estimating breast cancer risks in antipsychotic-using women.[14] With appropriate confounders accounted for, a recent study found *no* association between the use of antipsychotic medications and breast cancer and an *inverse* association with prostate cancer.[15] There is no evidence at present that high prolactin secondary to antipsychotics can be held responsible for increasing the risk of either breast or prostate malignancy.

Prolactin and Autoimmunity

Hyperprolactinemia is associated with autoimmune diseases such as systemic lupus erythematosus, rheumatoid arthritis, Sjogren's syndrome, Hashimoto's thyroiditis, celiac disease, type 1 DM, Addison's disease, and multiple sclerosis.[16,17] This may be a result of a prolactin-induced proliferation of immature autoreactive B lymphocytes, immunoglobulins, and autoantibodies. These diseases, more common in women than in men, are frequently seen in schizophrenia patients. The exception is rheumatoid arthritis.[18] Altogether, schizophrenia has been associated with a nearly 50% higher lifetime prevalence of one or more autoimmune disorders,[19] but this is probably not a result of treatment because autoimmunity appears to *precede* the appearance of schizophrenia.[19]

Prolactin and Pregnancy

A recent study from Sweden found no evidence of increased risk of pregnancy complications or adverse pregnancy outcomes in women treated for hyperprolactinemia. However, the patients were older at their first pregnancy relative to comparison subjects and, over their lifetime, had fewer children,[20] attesting to the fertility impairment that results from high levels of prolactin.

In summary, although there is no evidence for the role of antipsychotic-induced hyperprolactinemia in osteoporosis, breast and prostate cancer, or autoimmunity, the secondary effects of high levels of prolactin manifest themselves as gynecomastia, galactorrhoea, sexual dysfunction, atrophic changes in the urethra and vaginal mucosa, reduced vaginal lubrication and dyspareunia, loss of libido, ovarian dysfunction, relative infertility, oligomenorrhoea and amenorrhoea, acne, and hirsutism, increasing the side effect burden for women.

Blood Dyscrasias

Clozapine-induced agranulocytosis is among the least understood adverse drug reactions in psychopharmacology, although female sex and polypharmacy are considered risk factors. In most studies, there is a trend association with female sex and a strong association with coprescription of other psychotropic drugs.[21,22]

No differences in age or gender distribution of blood dyscrasias (thrombocytopenia, pancytopenia, and neutrocytopenia) were found in a drug safety survey of 122 562 patients conducted between 1993 and 2000 in Germany.[23] Although blood dyscrasia in infants whose mothers take clozapine during pregnancy are theoretically possible, none have been reported.[24] In summary, there is no evidence that blood dyscrasias preferentially affect women.

Venous Thromboembolism

Despite the fact that oral contraceptives and postmenopausal hormone replacement therapy have been associated with venous thromboembolism (VTE) in women, the published data suggest no consistent differences in the general incidence of VTE among men and women.[25] From a baseline population of 29 952 recipients under 60 of conventional and atypical antipsychotic drugs, Zornberg and Jick identified 42 individuals with idiopathic VTE and matched them with 172 comparison subjects. They found that current exposure to conventional antipsychotic drugs was associated with a significantly increased risk of idiopathic VTE (adjusted OR compared with the general population = 7.1).[26] Elderly patients using atypical antipsychotics were at twice the risk compared with controls. Low-potency antipsychotic drugs that induce sedation, especially clozapine, were more strongly associated with venous thrombosis than high-potency drugs, the risk being highest during the initial months of treatment, probably because sedation was most prominent at that time. A case-control study of 62 cases of *fatal* pulmonary embolism demonstrated a 13-fold higher risk among users of antipsychotic medication.[27] The biological mechanisms responsible are unknown, but a number of hypotheses have been suggested: drug-induced sedation, obesity, hyperleptinemia, antiphospholipid antibodies, and/or increased coagulation. The association is strongest in smokers.[28,29]

In summary, sedative antipsychotics confer an increased risk of thromboembolic phenomena. Contraceptives, hormone replacement, pregnancy, and obstetrical complications are supplemental risk factors for women.[30]

Rate-Corrected QT Interval Prolongation

One of the best examples of a sex difference in the toxicity of pharmaceuticals is the drug-induced cardiac arrhythmia called torsades de pointes (TdP). TdP is a rare, life-threatening ventricular tachycardia associated with prolongation of the action potential of ventricular myocytes and, hence, prolongation of the QT interval, which measures the total time for activation and recovery of the ventricles. Prolongation of the rate-corrected QT interval (QTc) is a surrogate marker for the ability of a drug to cause TdP. In individual patients, an absolute QTc interval of >500 ms or an increase of 60 ms from baseline means increased risk of TdP. However, TdP can also occur with lower QTc values. Sudden unexpected deaths such as those associated with TdP have been reported in association with antipsychotic use since the early 1960s. Two-thirds of cases of drug-induced TdP occur in women. Clinical and experimental studies have shown sex differences in ventricular repolarization in humans and other animals—essentially a longer QTc interval at baseline in females. Reports of similar propensity toward drug-induced TdP in premenopausal and in postmenopausal women suggest that more than hormones are involved, although androgens are known to shorten the QT interval and blunt the QT response to drugs. Drugs that prolong cardiac repolarization include antiarrhythmics, gastrokinetics, antipsychotics, antihistamines, and antibacterials. The higher risk for women may be aggravated by gender-associated differences in drug exposure, in the number of drugs prescribed (polypharmacy), or in gender differences in pharmacokinetics and pharmacodynamics.[31,32]

Increased sympathetic tone, such as occurs in acute psychotic states, plays an important role in vulnerability to arrhythmia, but little is currently known regarding gender differences in the physiological response to sympathetic stimulation. In an experimental protocol, the QTc interval was initially prolonged and then shortened in both men and women during isoproterenol (a beta adrenoreceptor agonist) administration, but, on the whole, it was significantly longer in women than in men.[33]

A polymorphism of the CYP1A2 enzyme (CYP1A2-1F) appears to add to the risk of QT prolongation for drugs metabolized via that route.[34] Clozapine is metabolized via the CYP1A2 pathway, but a database and literature review conducted by the Novartis pharmaceutical company concludes that clozapine at therapeutic doses does not induce QTc prolongation whereas thioridazine, haloperidol, risperidone, olanzapine, sertindole, and ziprasidone all do. The review found that preclinical in vitro tests tend to overestimate the risk of clozapine, haloperidol, and risperidone with respect to QTc prolongation and underestimate it for sertindole and ziprasidone. The extrapolation of in vitro results to clinical events appears to be far from straightforward, however.[35]

The degree of QTc prolongation is dose dependent and varies among antipsychotics, reflecting their different capacity to block cardiac ion channels. Among currently available antipsychotic agents, thioridazine and ziprasidone are associated with the greatest QTc prolongation. Arrhythmias are more likely to occur if drug-induced QTc prolongation coexists with other risk factors, such as heart failure, electrolyte imbalance, overdose, use of physical restraints, old age, hepatic or renal impairment, and slow metaboliser status. In a PubMed search in September 2002 that used the search terms "antipsychotic drug" and "QT interval," 9 cases were found in which drug-induced QTc prolongation was associated

with second-generation antipsychotics drugs. There was no evidence of TdP in any of the cases.[36]

Currently available data do not support the occurrence of TdP with any of the available atypical antipsychotic drugs.[37] Nevertheless, drugs that prolong QTc should be used with caution, especially in women, and especially when other QTc prolonging drugs are also being administered.

Weight Gain

It is the weight-inducing properties of antipsychotics and the subsequent sequelae of obesity that are most problematic for women. In both sexes, being overweight is usually defined as a BMI of, or over, 25 kg/m^2. A BMI at or over 30 kg/m^2 represents obesity. Abdominal obesity, however, is differently defined in men and women. Generally, it means a waist measurement of over 88 cm for women and over 102 cm for men. Weight gain can be induced by many psychotropic medications, antidepressants, and mood stabilizers, as well as antipsychotics. The percentage of patients gaining weight during antipsychotic treatment can be as high as 80%, depending on the drug used, with approximately 30% developing obesity. Being overweight subsequently increases the risk for hypertension, coronary heart disease (CHD), ischemic stroke, impaired glucose tolerance, DM, dyslipidemia, respiratory problems, osteoarthritis, liver problems, and certain cancers, not to mention social opprobrium, physical discomfort, and lowered self-esteem. For women, extra weight also leads to reproductive problems and potential harm to the newborn.

Of the many antipsychotics in common use, it is generally acknowledged that clozapine and olanzapine result in the greatest frequency of weight gain, diabetes, and dyslipidemia. In short-term studies, a definite rank order of weight-gain potential among atypical antipsychotics has been established: clozapine, followed in decreasing order of magnitude by olanzapine, quetiapine, risperidone, amisulpride, aripiprazole, and ziprasidone. However, in long-term studies, while clozapine is the most likely and ziprasidone the least likely to increase weight, the rank order among the other drugs is less consistent.[38]

Few studies have examined gender differences in the likelihood of gaining weight while on antipsychotic treatment. Using survival and random regression models, Covell et al. compared the percentage of body weight gained over 2 years in patients assigned to clozapine versus first-generation antipsychotic medications, looking specifically for gender differences. At the end of 2 years, patients who were given clozapine gained more weight (7%) than those remaining on first-generation medications (4%) and weight gain was significantly greater among women than men.[39] Koga conducted a retrospective investigation of BMI in patients who had been treated with antipsychotic agents over extended periods. The OR for weight gain was significantly higher in women

than in men (4.94).[40] In a study (by the Lilly Research Laboratories) of a common combination treatment (olanzapine and fluoxetine), low baseline BMI, female gender, younger age, and increased fluoxetine dose were predictors of weight gain.[41] This suggests that women are at special risk from clozapine or olanzapine, perhaps especially so when in combination with other psychotropics.

Fat distribution patterns differ between women and men. Premenopausal women usually develop peripheral (gluteal) obesity with accumulation of subcutaneous fat, whereas men and postmenopausal women tend toward central or abdominal obesity, which is associated with increased cardiovascular mortality and the development of type 2 diabetes.[42] Visceral fat cells differ from peripheral ones in their lipolytic activity and in their response to insulin, adrenergic and angiotensin stimulation, and density of sex hormone receptors. The weight threshold before metabolic disturbances begin to set in is, in fact, higher for women than it is for men, but once diabetes occurs, women incur more cardiovascular risk than men.[42] This is an important point that will be returned to later.

In addition to calorie excess, genetic variables play a major role in the development of obesity. As of October 2005, 176 human instances of obesity had been linked to single-gene mutations in 11 different genes; 50 loci related to Mendelian syndromes relevant to human obesity had been mapped to a genomic region, and causal genes or strong candidates had been identified.[43] Some of these genes are expressed in a sex-specific manner.[44]

The weight-gain liability of antipsychotic drugs has been attributed to histamine (H1) receptor binding. Working with mice, Kim et al.[45] have recently shown that olanzapine and clozapine selectively activate hypothalamic AMP-kinase and that this activation is abolished when the histamine H1 receptor (HIR) is deleted in H1R knockout mice. It is known that, in rodents, central histaminergic activity affects feeding differently in the 2 sexes.[46] Gender influences both the diurnal rhythm of feeding and the response of H1 receptors to feeding, crucial factors in the development of obesity in rodents.[47,48]

Obesity and Cancer

An obesity-cancer link has been hypothesized. The genesis and progression of malignancy relies on diverse mechanisms, including changes in the synthesis and bio-availability of sex hormones, insulin resistance, release of growth factors, and/or proinflammatory cytokines and abnormal expenditure of energy. Irigaray et al. have shown that adipose tissue acts as a reservoir for lipophilic, liposoluble environmental carcinogens. Carcinogens are stored in adipose tissue and then released into the general circulation, instigating mutagenesis.[49] Of 6 common cancers (breast, colon, rectal, gastroesophageal,

prostate, and respiratory), persons with schizophrenia are reported to have a significantly higher risk (compared with the general population and to patients with bipolar disorder) only of colon cancer. In a recent study, patients with schizophrenia taking antipsychotics had a 308% increased colon cancer risk (adjusted OR = 4.08).[50] Two meta-analyses of the literature show that waist circumference correlates better with the risk for colorectal cancer than BMI and that, as a consequence, obesity in men is more closely associated with these cancers than is obesity in women.[51,52] However, postmenopausal women who are not taking hormone replacement therapy and who show abdominal obesity are also at increased risk for colon cancer.[53]

Women face other theoretical cancer risks from the added weight. Existing data suggest that weight gain during adult life, specifically after menopause, increases the risk of breast cancer among postmenopausal women,[54,55] but women with schizophrenia show only a marginally increased breast cancer risk (adjusted OR, 1.52) over women with bipolar disorder or women in the general population.[55] As discussed in the section on prolactin elevation, more weight means more estrogen, a potential risk factor for breast cancer, but more prolactin means less estrogen, so that these 2 side effects of antipsychotics may, when balanced, prevent an increase in risk not only for osteoporosis but also for breast cancer.

With respect to endometrial cancer, obesity, abdominal adiposity, and adult weight gain were all 3 strongly associated with risk in a recent study. Once again, the associations were strongest in postmenopausal women not on hormone replacement therapy.[56]

With respect to cancer, the weight-gain potential of antipsychotic medication puts men at increased risk for colon cancer and postmenopausal women at risk for both colon and endometrial cancer.

Obesity and Pregnancy

Obesity also carries reproductive risks. Increased maternal weight is associated with infant neural tube defect, heart defects, anorectal atresia, hypospadias, limb reduction defects, diaphragmatic hernia, and omphalocele. In total, 7 of 16 categories of birth defects have been attributed to overweight mothers. The mechanisms underlying these associations are not yet understood, but it has been hypothesized that they may relate to undiagnosed diabetes in the mother.[57,58] This is important even though there is currently no direct evidence that the use of weight-inducing antipsychotics during pregnancy increases the risk for major congenital malformations.[59]

Mechanism of Weight Gain and Sex Differences in Dieting Outcome

Clozapine-induced adiposity in rats reflects a direct drug effect on adipocyte function that is independent of drug-induced hyperphagia. If true in humans, this means that eating less may not be the answer to antipsychotic weight gain.[60] Even if it were, when on the same restricted diet, men mobilize intra-abdominal fat, whereas women preferentially lose subcutaneous fat. The greater reduction in intra-abdominal fat seen in men improves their metabolic risk profile, but dieting may not have the same beneficial effect in women.[61]

Metabolic Hormones and Gender

Leptin, adiponectin, and resistin are metabolic hormones secreted by adipose tissue and are involved in the central control of food intake. Leptin conveys information to the hypothalamus on how much energy is stored in fat and, thereby, controls appetite and energy expenditure. Receptors for leptin have been found in hypothalamic neurons. Adiponectin decreases blood glucose and insulin resistance. Resistin increases insulin resistance in rodents, but its role in humans has not been fully established. Ghrelin, another metabolic hormone, is secreted in the mucosa of the stomach; it increases gastric motility and acid secretion, stimulates appetite, and also conveys information to the hypothalamus. Gender differences in these hormones are only beginning to be understood.

Leptin levels generally correlate with the extent of body fat, but females have markedly higher leptin concentrations than males for any given degree of fat mass.[62] This is even true in childhood.[63] During pregnancy, leptin concentration in maternal plasma correlates not only with mother's body mass but also with sex of the fetus, being higher in women carrying female fetuses. Umbilical cord leptin correlates with both the baby's birth weight and the baby's gender.[64] Higher pretreatment circulating leptin levels appear to predict lesser weight gain following olanzapine treatment,[65] which suggests that doing a leptin level before initiating therapy could help determine the safety of olanzapine for a particular person. But, paradoxically, obese people generally have a high circulating leptin concentration. This is probably due to desensitization and resistance to the effects of leptin, in much the same way as individuals with type 2 diabetes become resistant to insulin.[65]

Atmaca et al. have investigated the effects of quetiapine, olanzapine, risperidone, and clozapine on leptin and triglyceride levels, as well as on weight. At 6 weeks, olanzapine and clozapine induced a marked increase in weight, serum triglyceride, and leptin levels; increases were modest in patients receiving quetiapine and minimal in those receiving risperidone. Serum leptin levels, BMI, and triglyceride levels correlated positively with each other.[66] However, in more recent studies, the impact of olanzapine on leptin appears to be small.[67]

Gender differences may account for discrepancies among studies. Variation in the leptin gene, for instance, may be a risk factor for weight gain following long-term

clozapine treatment in males only.[68] With respect to resistin, male homozygotes of a polymorphism of the human resistin gene (g-420 G) had less visceral fat than carriers of the C allele, and this was independent of age and total adiposity. This association was not present in women.[69] Gender differences in ghrelin have not, thus far, been investigated.

In summary, leptin, ghrelin, adiponectin, and resistin play important roles in energy homeostasis, glucose and lipid metabolism, reproduction, cardiovascular function, and immunity and are significantly regulated not only by the adiposity that can be a byproduct of antipsychotic treatment but also by gender-specific strategies used to regulate energy expenditure.[70]

Leptin, Pregnancy, and Labor

Leptin is produced by the placenta so that leptin levels rise during pregnancy and fall after childbirth. Leptin is also expressed in uterine tissue, inhibiting uterine muscle contractions.[71] This physiologic inhibitory effect of leptin on uterine contractility may play a role in the difficult labors and high caesarian rates associated with both maternal obesity[72] and maternal schizophrenia.[73]

Leptin and CHD

Prospective studies have shown a positive association between leptin concentrations and CHD in men, but the significance in women is unclear. With adjustment for age, social class, smoking, and physical activity, Lawlor et al. found that leptin level was positively associated with BMI in women, as well as with fasting insulin, total cholesterol, low-density lipoprotein (LDL)-cholesterol, triglycerides, and hypertension. However, leptin was not associated with CHD risk in this British study.[74] A comparable study in the United States, on the other hand, found increased leptin concentrations to be significantly associated with myocardial infarction (MI) or stroke in both men and women, independently of traditional cardiovascular risk factors such as obesity.[75]

In summary, metabolic hormones may prove to be important predictors of risk for persons on antipsychotic medication, perhaps in sexually dimorphic ways.

Diabetes, Antipsychotics, and Gender

Since the introduction of atypical antipsychotics, there has been a yearly increase in type II DM in patients with schizophrenia, due, for the most part, to weight gain[76] but also to the development of insulin resistance. Women appear to be intrinsically more insulin resistant than men, possibly as a result of specific sex-linked gene expression.[77] Multiple sex-linked genes are thought to regulate the susceptibility to type 2 diabetes.[78] Androgens may increase risk for diabetes in women while decreasing it in men. A meta-analysis of cross-sectional studies indicates that testosterone level is significantly lower in men but higher in women with type 2 diabetes when compared with controls. Prospective studies show that men with high testosterone levels have a 42% *lower* risk of type 2 diabetes compared with controls while high testosterone seems to *increase* the risk for women.[79]

Consequences of Diabetes

There are several differences between the genders with respect to the consequences of diabetes. Women with type 2 DM experience more symptoms of hyperglycemia than their male counterparts. Women with diabetes have an increased risk of hypertension compared with men with diabetes. Women have a more severe type of dyslipidemia than do men (low levels of high-density lipoprotein [HDL]-cholesterol, small particle size of LDL-cholesterol, and high levels of triglycerides), and these predict coronary disease in women more strongly than they do in men.[80] Diabetes is also associated with polycystic ovary syndrome in women.[81]

Insulin resistance, usually linked to obesity, is associated with certain antipsychotics more than with others. Comparing olanzapine and risperidone with respect to their relative risk for diabetes, 6 studies have demonstrated significantly greater risk with olanzapine. In 2 of these studies, the risk was reported as higher in women. No conclusions could be reached for clozapine and quetiapine in this data set.[82] A review of the topic concludes that, in general, the rank order of hyperglycemia risk for second-generation antipsychotics correlates with their weight-gain liability.[83]

Diabetes and Pregnancy

Women with diabetes pose a risk for their children as well as for themselves. In studies in experimental animals, excess glucose metabolism by embryos of mothers with hyperglycemia was found to interfere with several biochemical pathways and result in oxidative stress. Oxidative stress inhibits the expression of genes essential to neural tube development and other forms of diabetic embryopathy.[84] Reviewing 7 cohort studies between 1985 and 2006, the risk of a congenital malformation was increased by an OR of 1.2 for each 1 SD unit increase in glycosylated hemoglobin (GHb). One hundred and seventeen anomalies were found among 1977 pregnancies. At normal GHb concentrations, the absolute risk of congenital anomaly was approximately 2%. At 2 SD above normal, the risk was 3% and at 8 SD it was 10%. The pattern was similar for measures of HbA1c. Several factors in addition to maternal glycemic control (maternal age, weight, and use of periconception folic acid supplements) were also relevant to the risk of congenital anomaly.[85]

Diabetes and Women's Reproductive Cancers

Evidence suggests that women with type 2 diabetes may be at increased risk of breast cancer, possibly due to chronic exposure to insulin resistance and/or hyperinsulinemia.[86,87] Breast cancer risk may already be increased in the pre-diabetes phase. Lipscombe et al.[88] found that having diabetes was associated with an almost 40% increase in mortality within the first 5 years following breast cancer.

The relative risk for endometrial cancer among women with diabetes compared with nondiabetic women was 1.94 in a Swedish prospective cohort of 36 773 women. When diabetes was associated with obesity and low physical activity, the risk increased further.[89]

Diabetes, Cardiovascular Risk, and Sex

Women with DM, regardless of menopausal status, have a 4- to 6-fold increase in the risk of developing coronary artery disease (CAD), whereas, in men, diabetes raises the risk 2- to 3-fold.[42,90] A 13-year follow-up study of 1296 nondiabetic subjects and 835 type 2 diabetic subjects aged 45–64 years with no cardiovascular disease found that the CHD event rate per 1000 person-years was 11.6 in nondiabetic men, 1.8 in nondiabetic women, 36.3 in diabetic men, and 31.6 in diabetic women. In other words, men in general are at greater risk for coronary disease than women; this is well known. But the diabetes-related hazard ratio for a major CHD event is much higher in women. In this study, the OR for a CHD event (after adjustment for age, socioeconomic status, and other cardiovascular risk factors) was 2.8 in diabetic men and 9.5 in diabetic women compared with nondiabetic peers.[91]

Diabetes, Mortality, and Sex

Women with DM have a poorer prognosis after MI and a generally higher risk of death from cardiovascular disease. A comparison of 3 consecutive US nationally representative cohorts shows that, among diabetic men, the all-cause mortality rate and the cardiovascular disease mortality decreased between 1971 to 1986 and 1988 to 2000, in line with decreases in the nondiabetic population. Among women with diabetes, however, neither all-cause nor cardiovascular disease mortality declined during those years and the all-cause mortality rate difference between diabetic and nondiabetic women more than doubled (from a difference of 8.3 to 18.2 annual deaths per 1000 persons). As a result, all-cause mortality in diabetes was essentially similar in the 2 sexes by 2000 and was declining only in men, not in women.[92]

In summary, diabetes, for which antipsychotics increase the risk, is more of a health hazard for women than it is for men.

Table 1. Optimal Lipids and Lipoproteins in Women

LDL-C	<100 mg/dl
HDL-C	>50 mg/dl
Triglycerides	<150 mg/dl
Non–HDL-C	<130 mg/dl

Note: LDL, low-density lipoprotein; HDL, high-density lipoprotein.

Lipids

Over one-third of patients treated with a second-generation antipsychotic develop clinically meaningful triglyceride elevations. This is most pronounced with clozapine and olanzapine[93]; it varies among drugs and between sexes.[94] Substantial male-female differences in lipid levels already exist pretreatment (table 1).

The transport of fat in the blood stream is approximately twice as fast in women as in men and this may help explain why obesity and diabetes are associated with greater lipoprotein abnormalities and cardiovascular disease in women compared with men. Women show a greater change in triglyceride level and a lesser change in LDL than men after high-carbohydrate or high-fat feeding. HDL, HDL(2), and apolipoprotein A-I levels are the ones that change more in women.[95]

LDL may be a less important risk factor in women than in men, perhaps because estrogen protects the arterial wall against LDL deposition. HDL is a better predictor of risk in women, and triglycerides are an independent predictor of CAD risk in postmenopausal women. Diet, weight loss, and exercise are less effective in altering lipoprotein levels in women than in men for reasons that are not totally clear, but endogenous gonadal hormones probably play a role.[96]

Metabolic Syndrome

The metabolic syndrome is characterized by hyperglycemia, hyperlipidemia, hypertension, and abdominal obesity (table 2) and is a strong determinant of cardiovascular disease, aggravated, if not induced, by antipsychotic medication.[97–99] In the presence of metabolic syndrome, the rate for cardiovascular events rises in women, becoming identical in the 2 sexes.[100,101] Reasons for this are unclear but gonadal hormones may play a role. Estrogen receptor alpha in the neurons of the ventromedial nucleus of the hypothalamus has been shown to play an essential role in the control of energy balance and the maintenance of normal body weight.[102] There is also strong evidence for gene by sex interaction in the etiology of body mass, insulin resistance and possibly also dyslipidemia, all of which play important roles in the metabolic syndrome and in CHD.[103]

The metabolic syndrome may also directly influence the QT interval of the electrocardiogram via hypertension

Table 2. Metabolic Syndrome = Presence of 3 of the Following Abnormalities

Criterion	Males	Females
Waist circumference	>102 cm	>88 cm
High-density lipoprotein (HDL)	<40 mg/dl	<50 mg/dl
Diastolic blood pressure	≥85 mm Hg	≥85 mm Hg
Systolic blood pressure	≥130 mm Hg	≥130 mm Hg
Fasting triglycerides	≥150 mg/dl	≥150 mg/dl
Fasting plasma glucose	≥110 mg/dl	≥110 mg/dl

and insulin resistance. In the Salzburg-Atherosclerosis-Prevention-program-in-subjects-at-High-Individual-Risk study, the presence of metabolic syndrome significantly lengthened the QTc, but only in men.[104]

Hypertension

Although antipsychotics usually *lower* blood pressure, drug-induced obesity, low-socioeconomic status, a sedentary life style, and high alcohol consumption can add to the risk of hypertension. In a Norwegian study, high BMI at baseline predicted hypertension for women, as did BMI increase over an 8-year period. For a given increase in BMI, initially obese women had a greater increase in blood pressure than did lean women and a rise in BMI in obese women increased systolic blood pressure more than it did in men. In men, baseline weight had no effect, but weight increase over the 8 years of the study predicted subsequent hyertension.[105] With respect to stroke risk, young (under 45) schizophrenia patients show a two-fold increased risk of developing stroke during the 5-year period following their hospitalization compared with age-matched controls. In a recent study, the risk of stroke was much higher for female than for male patients.[106]

Coronary Heart Disease

When 3 risk factors for MI (hyperlipidemia, DM, hypertension) are combined, the relative risk of MI is higher in women than men.[107] In the clinical antipsychotic trials of intervention effectiveness trial, the 10-year CHD risk for schizophrenia patients was relatively higher in women and significantly elevated over controls in both males (9.4% vs 7.0%) and females (6.3% vs 4.2%), even after controlling for BMI.[108] Women with schizophrenia are disadvantaged with respect to cardiovascular risk even without the addition of antipsychotic medication. Social factors such as a single parenthood, for instance, are linked to greater cardiovascular risk for women. In the National Health and Nutrition Examination Survey III, single mothers were more likely than partnered mothers to smoke and be overweight or obese. Those with clinical risks for cardiovascular disease, including diabetes, elevated C-reactive protein, hypercholesterolemia, or hypertension were more likely to be unpartnered. After adjusting for age, mothers who had experienced a MI, heart failure, or stroke were 3 times more likely to be without a partner than those without prior cardiovascular events.[109] Data from the same survey showed that education and income were independently and negatively associated with cumulative health risks (diastolic and systolic blood pressure, pulse, HDL and total cholesterol, GHb, c-reactive protein, albumin, and waist-to-hip ratio). Those with relatively poor education and low income (characteristics of most individuals suffering from schizophrenia) had a greater prevalence of high-risk values for each of the 9 biological risk factors listed above.[110]

Antipsychotic Blood Levels and Sex

Some of the adverse effects of antipsychotics in women may come about because blood levels of drug are higher in women than men, even when the dose is identical. This is true when the drug is risperidone,[111–113] quetiapine (especially with valproate c-medication),[114] olanzapine, or clozapine.[115,116]

It is probable that women's susceptibility to specific side effects is partly caused by high circulating plasma levels of drug and partly by genetic susceptibilities, hormonal effects, and vulnerabilities associated with reproductive functions.

Conclusion

Women are more susceptible than men to the weight gain induced by antipsychotics and dieting is less successful for them in reversing the subsequent metabolic, lipemic, cardiovascular risks. Cardiovascular death, to which men in the general population are more vulnerable than women, is disproportionately increased in women by the use of antipsychotics. Even in childhood and adolescence, the bulk of serious antipsychotic side effects (obesity/excessive weight gain, type II diabetes and dyslipidemia, digestive/urogenital problems, and neurological/sensory symptoms) is borne by girls.[117] Prolactin-elevating drugs produce a variety of distressing symptoms, more in women than in men, reduce gonadic hormone secretion, and interfere with fertility. Sedating antipsychotics lower the threshold for embolic phenomena during pregnancy, and postpartum and antipschotic-induced weight gain increases the potential for obstetric complications.

Fears have also been raised about an increased risk of breast cancer and of osteoporosis, but there is as yet no evidence for either.

It is not possible to state unequivocally which antipsychotic is the best option for women, but it is known that ziprasidone and aripiprazole are least likely to cause the 2

main serious side effects: prolactin elevation and weight gain (with its sequelae). Ziprasidone, however, carries the risk of QTc prolongation, so aripiprazole emerges, all things being equal, as the least harmful at this time. It is too early, however, to be able to assess its safety with respect to pregnancy and breast-feeding. The safest course is to keep doses especially low in women and to avoid polypharmacy whenever possible.

Acknowledgments

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