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Second-Generation Antipsychotics

Is There Evidence for Sex Differences in Pharmacokinetic and Adverse Effect Profiles?

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Abstract

Six second-generation antipsychotics (SGAs), aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone, are currently US FDA approved. The aim of this review is to investigate whether sex differences exist for efficacy and adverse effects of these drugs.

Sex-related differences have been shown in the pharmacokinetics of cytochrome P450 (CYP), with a higher activity in females for CYP3A4 and CYP2D6. However, even if there are pharmacokinetic differences between females and males, significantly higher plasma concentrations in women have been demonstrated only for olanzapine and clozapine.

To date, sex differences in adverse effects have not been well studied, but some adverse effects such as weight gain, hyperprolactinaemia and cardiac effects are reported to be particularly problematic for women. Most of the studies reviewed indicate that clozapine and olanzapine are associated with greater bodyweight gain than the other atypical antipsychotics, and that serious adverse effects such as metabolic syndrome, which includes increased visceral adiposity, hyperglycaemia, hypertension and dyslipidaemia induced by SGAs, are more frequent in females. According to most studies, the risk for cardiac adverse effects induced by SGAs is the same in male and female patients. Although women are at a lower risk of sudden cardiac death, they have a higher risk of induced long QT syndrome from antiarrhythmic and, probably, antipsychotic drugs. The propensity of sexual dysfunctions is higher with conventional antipsychotics than with SGAs. Addi-

tionally, there is some evidence that female sexual dysfunction is associated with high prolactin levels; however, whether the degree of prolactin level elevation is different between female and male patients remains controversial. There is no evidence for sex differences for any of the SGAs to cause a higher rate of extrapyramidal symptoms, acute dystonia or any other movement disturbance. Knowledge of the risks and benefits associated with the use of SGAs during pregnancy and lactation is limited, although the direction of dose adjustments during pregnancy depends on the drug and the enzyme that is responsible for its metabolism.

In general, data on sex differences were mostly obtained by *post hoc* analysis and, therefore, the conclusions that can be drawn are limited. For a better understanding of the basic mechanisms of sex differences, future studies with a primary focus on this topic are required. Data that are more specific will help determine the extent to which these differences will have implications for clinical management.

During the past decade, pharmacological research has greatly enhanced our understanding of several variables affecting the prescription of psychotropic medication. The US FDA stated that it would refuse to file a new drug application that did not include a breakdown of results by sex.[1] From 2000, the FDA has been allowed by the US National Institutes of Health (NIH) to use a 'clinical hold' on drug trials that did not enroll enough women for analysis by sex.[2] New registration guidelines require sex-specific analysis of efficacy and safety data and have led to an increasing number of studies concerning differences in pharmacokinetic and, to some extent, pharmacodynamic differences in men and women.[3] Significant gender differences have been described for psychiatric disease prevalence, symptom presentation, treatment-seeking behaviour and prescription of psychotropic medication.[4]

In this review of second-generation antipsychotics (SGAs), we focus exclusively on biological differences between men and women, and therefore refer to 'sex differences' rather than 'gender differences', which would imply an understanding of the social and cultural components of sex differences, as discussed in the agenda for research on women's health for the 21st century published by the NIH.[5]

Sex-related differences in pharmacokinetics have been identified for some drugs,[6] including theophylline, several benzodiazepines and lidocaine (lignocaine), since the 1980s. There are various examples of drugs, e.g. diazepam, vancomycin, ofloxacin and cefotaxime, with differences in pharmacokinetics related to general sex differences, such as bodyweight, organ size or body composition.[6-8] Probably the best established sex differences are those in response to medications that can affect heart rhythm, including some antihistamines, antibacterials, antiarrhythmics and antipsychotics. Woosley et al.[9] showed that these drugs share the ability to block potassium channels in the heart, which in turn can affect the rhythm of the heart. The Digitalis Investigation Group trial reported that digoxin therapy was associated with a significantly increased risk of death in women but not in men.[10] However, this finding should be interpreted with caution, as the analysis according to sex was not pre-specified and women comprised only a small proportion (up to 22%) of the study population.

There is a general lack of comparative studies investigating sex differences in the efficacy and adverse effect profile of SGAs. Women are still under-represented in clinical trials, mainly because of fear of potential teratogenicity. As a result, major studies involving the efficacy of antipsychotic drugs have not included women of childbearing potential.

There are strong commonalities in the mechanism of action of each of the SGAs. Nevertheless, each drug has a unique set of receptor affinities,

which are biochemical properties that result in different adverse effect profiles. A recent comparative study revealed that, with the exception of clozapine which was the most effective treatment for negative symptoms, the overall efficacy of SGAs was roughly equal.[11] To date, six SGAs, aripiprazole, clozapine, olanzapine, quetiapine, risperidone and ziprasidone, are FDA approved. This approval was initially only for the treatment of schizophrenia but has recently been extended to the treatment of patients with bipolar mania (except clozapine), either as monotherapy (aripiprazole, olanzapine, risperidone, quetiapine and ziprasidone) or as combination therapy with lithium or valproic acid (olanzapine, risperidone and quetiapine). Finally, olanzapine is also FDA approved for maintenance treatment of bipolar disorder and, in a combination formula with fluoxetine, for treatment of patients with depressive episodes associated with bipolar disorder.

In this review, we discuss whether sex differences should be considered when using SGAs. We have selected reports dealing with sex difference in efficacy as well as in the adverse effect profiles for the six FDA-approved SGA drugs. We conducted a MEDLINE search for each drug using terms such as 'sex differences' in combination with 'neuroleptic', 'antipsychotic', 'second generation antipsychotics', 'pharmacokinetics' and some specific adverse effects for the years 1966 to December 2005. Additionally, we have examined reference lists from relevant articles to make sure that the review is comprehensive. Table I summarises the evidence for biological sex differences.

Table I. Evidence for female sex differences (vs males)

Higher clozapine[12] and olanzapine[13,14] plasma concentrations
Higher prolactin levels[15-18]
Higher prevalence of osteoporosis[19]
Larger increase in bodyweight[20,21]
Higher prevalence of metabolic syndrome[22]
Greater corrected QT interval prolongation and higher incidence of torsades de pointes[23-26]

1. Second-Generation Antipsychotics (SGAs) and Drug Response

The prevalence of psychiatric diseases differs between the sexes. Men and women may also exhibit a different presentation of symptoms. With schizophrenia in particular, research has revealed a difference in the general disease course between men and women that may have an impact on treatment outcome.

There are some data indicating a different response to medication in the two sexes but studies comparing clinical response in men and women are rare. For example, the difference in age at onset of schizophrenia between males and females is smaller in antipsychotic-resistant patients than in antipsychotic-responsive patients.[27] The response to clozapine in the treatment of severely ill, treatment-resistant patients with schizophrenia yielded better results for men, probably influenced by a selection bias.[28] For risperidone, no significant sex differences were evident either in treatment response or in neurological adverse effects.[29] This absence of sex differences in response to risperidone treatment may obviate the need for a sex-based differential dose administration in schizophrenia management. Again, none of these studies was designed to address the question of sex differences *a priori*.

To our knowledge, there are no studies reporting significant sex differences in treatment response for any SGA in acute bipolar mania.

2. Pharmacokinetics in Women

Women experience adverse effects more frequently than men for numerous drugs; however, it is often not clear if this is due to sex differences in the pharmacokinetics or pharmacodynamics of these drugs. Pharmacokinetic variables may play a major role in efficacy and safety of drug treatment in women. In women, absorption, protein binding, volume of distribution and metabolism of drugs may differ because of hormonal influences on physiological functions. Sex-related differences have been shown for phase I (cytochrome P450 [CYP]) as well as phase II (especially glucuronidation) reactions. In general, women have lower gastric acid secretion,

lower gastrointestinal blood flow and a longer gastric emptying time. Furthermore, women have larger lipid compartments, which leads to prolonged half-lives and, probably, accumulation of lipophilic antipsychotics. This would suggest the need for longer dosing intervals, particularly during pregnancy.[30,31] Moreover, differences in the distribution of drugs between men and women can be attributed to differences in body size. To investigate genuine sex effects on the plasma concentrations of antipsychotics, concentration values have to be weight-corrected before comparison.[32]

Hepatic clearance of drugs is a function of liver blood flow and hepatic enzyme activity. Although cardiac output and hepatic blood flow are lower in women than in men, differences in hepatic enzyme activity seem to play the major role in determining pharmacokinetic variability by sex. CYP3A4, CYP2D6 and CYP1A2 are the most important enzymes for the hepatic metabolism of antipsychotic agents.[33] Data on potential sex-based differences in CYP activity support higher activity in females for CYP3A4 and CYP2D6, especially in pregnant and premenopausal women,[8,34-37] and lower activity in females for CYP1A2, CYP2C19, CYP2E1 and phase II glucuronosyltransferases.[8,34-36]

These differences in enzyme activity lead to a high interindividual variability in plasma concentrations of certain SGAs, which is most likely responsible for distinct clinical outcome in both sexes.[38-40] In several studies, higher plasma concentrations of clozapine and olanzapine have been found in females, probably caused by lower CYP1A2 activity.[12,13,41-44] The limited information available suggests that an average female nonsmoker requires low clozapine doses to reach therapeutic concentrations.[42,45] For olanzapine, individual factors with the largest impact on olanzapine pharmacokinetics are sex and smoking status.[46] According to the manufacturer, the dose and dose range of olanzapine do not need to be routinely adjusted for female patients relative to male patients.[47] However, a dose adjustment may be necessary only when several factors co-exist that alter the metabolism of olanzapine. For example, a young male patient who is a smoker may need a 3- to 4-fold higher dose of olanzapine to reach the same plasma concentration as a non-smoking elderly female patient.[13,14]

No sex-related differences in plasma concentrations have been detected for risperidone, ziprasidone, quetiapine and aripiprazole so far.[32,48,49] In a recent pharmacokinetic study, we found 35% higher quetiapine plasma concentrations in females, but significance was lost after weight correction.[50] No specific pharmacokinetic study has been conducted to investigate sex effects for risperidone long-acting injection (Risperdal Consta®),[1] which is a combination of extended-release microspheres for injection.

Renal clearance of drugs that are not actively secreted or reabsorbed is dependent on the glomerular filtration rate, which is directly proportional to bodyweight and, consequently, higher on average in men than in women. Hence, sex differences in rates of renal excretion for most drugs are most likely attributable to simple weight differences.[51,52]

3. Adverse Effects of SGAs in Women

Most drugs that have been withdrawn in recent years had greater health risks for women.[53] In general, women have an increased likelihood of comorbid illnesses, resulting in higher prescription rates and the possibility of more frequent drug interactions.[54] Therefore, dosing and safety studies need to consider these differences carefully and produce recommendations that are appropriate to both sexes. Recommendations have been recently established for SGAs, including regular monitoring of body mass index, the plasma glucose level, lipid profiles and signs of elevation of prolactin level or sexual dysfunction.[55]

In a retrospective cohort study of 52 819 women, Wang et al.[56] found some evidence that dopamine antagonists may confer a small but significant risk of breast cancer. The question of breast cancer being induced by elevated prolactin levels was recently clarified by Oksbjerg Dalton et al.[57] The overall

1 The use of trade names is for product identification purposes only and does not imply endorsement.

relative risk for breast cancer adjusted for age, age at first birth and number of births was not increased in schizophrenic women.[57]

3.1 Hyperprolactinaemia and Osteoporosis

The prevalence of osteoporosis is about 3- to 4-fold higher in females, and the percentage of patients with osteoporosis increases progressively with age.[19] The question arises whether there is a causal relationship between hyperprolactinaemia and osteoporosis. Conventional antipsychotics and certain SGAs such as amisulpride[58] and risperidone[58,59] cause significant elevations in prolactin levels. For risperidone, increases in prolactin levels are dose-related.[60] On the other hand, other SGAs such as clozapine, olanzapine, quetiapine and ziprasidone have minimal effects on prolactin levels in adults.[60] These antipsychotic agents appear to spare dopamine blockade within the brain's tuberoinfundibular tract, a dopamine pathway that also controls prolactin secretion.[61-64] The recently approved antipsychotic aripiprazole has a prolactin-lowering effect and a more salutary impact on sexual function compared with other antipsychotics.[65] In general, the relationship between the degree of prolactin level elevation and specific adverse effects remains controversial.[66,67]

Some studies have reported that women have significantly greater elevations in prolactin levels than men during long-term antipsychotic treatment with equivalent doses.[15,16] Studies showing an association between prolactin-raising antipsychotics and higher rates of bone pathology in premenopausal women argue that these are the result of a hypogonadism secondary to hyperprolactinaemia.[68] Conversely, a long-term study found no sex differences, as both male and female patients had high rates of hyperprolactinaemia and a range of osteopenic and osteoporotic measures that fell outside the normal age-related values.[69]

In premenopausal women, high prolactin levels will lower estrogen levels, which may contribute to the development of reduced bone mineral density, although a causal association between antipsychotics and osteoporosis has not been established.[70] Nevertheless, the reduced bone mineral density in patients with schizophrenia could be caused by reasons others than hyperprolactinaemia, such as lifestyle factors.[71]

Another group could find lower bone mineral density only in males compared with controls and found no relation to prolactin-increasing antipsychotics.[72] Before further data can clarify the situation, it might be advisable to control bone mineral density in schizophrenia patients and consider the prolactin-raising profile when choosing an antipsychotic.

3.2 Sexual Adverse Effects

When considering antipsychotic treatment, it should be noted that schizophrenia affects sexuality, pregnancy, the puerperium, parenting and family planning in female patients. While women with schizophrenia have higher rates of coerced sex, sexual risk behaviour and unwanted pregnancies,[54] men with schizophrenia frequently lose their sexual drive early in the course of illness. Sexual adverse effects seem to be associated with both novel and conventional antipsychotic medications.[73]

The propensity of sexual dysfunctions is higher with conventional antipsychotics than atypical antipsychotics.[74] However, sexual dysfunctions including decreased libido, impaired arousal and erectile orgasmic dysfunction are also common among patients receiving atypical antipsychotics.[75] These effects may be caused by anticholinergic activity, α-1 adrenoceptor inhibition or by hyperprolactinaemia.[76] When sexual dysfunction was assessed in 101 patients receiving conventional antipsychotic medication, there was a relationship between prolactin level and sexual dysfunction in females.[74] In the same study, it was found that if a man becomes hyperprolactinaemic following antipsychotic treatment, the raised prolactin level is likely to be the main cause of any sexual dysfunction seen.[74] In contrast to other atypicals, treatment with risperidone can result in a sustained elevated prolactin level.[77] One study reported that sexual dysfunctions are significantly more frequent with risperidone than olanzapine,[78] suggesting a relationship

between increased prolactin levels and sexual dysfunction. Olanzapine reversed hyperprolactinaemia in risperidone-treated female schizophrenic patients and switching to olanzapine reduced sexual and/or reproductive dysfunction.[79] Sexual functioning was also different in patients treated with quetiapine compared with risperidone, with less frequent sexual adverse effects in the quetiapine group.[80]

3.3 Weight Gain, Metabolic Syndrome and Diabetes Mellitus

As suggest by several authors, antipsychotic-induced weight gain seems to be more prevalent in women.[20,21] Most studies reviewed indicate that clozapine and olanzapine are associated with more bodyweight gain than the other atypical antipsychotics,[21,81] and there are potential factors that place certain patients at greater risk for bodyweight gain, including low pre-treatment body mass index, young age and female sex.[82,83] The association of weight gain with plasma concentrations during treatment with olanzapine may support the use of plasma drug concentration as a marker for antipsychotic-induced weight gain in the treatment of schizophrenia.[84]

Compared with clozapine or olanzapine, weight gain during treatment with risperidone[85] and quetiapine[86] is less pronounced. Recently, it has been suggested that ziprasidone may be largely free of weight gain.[87,88] Limited controlled studies support the hypothesis that clozapine and olanzapine may have a direct effect on glucose regulation independent of adiposity.[89] There are data showing that olanzapine- and clozapine-treated patients had a significantly higher serum insulin level than patients treated with classical antipsychotics, despite having a similar body mass index.[90-92] Leptin level has also been associated with antipsychotic-induced weight gain.[93] In a comparative study, clozapine and olanzapine caused a marked increase in weight and serum triglyceride and leptin levels.[94] These increases were modest in patients treated with quetiapine and minimal in those receiving risperidone.[95] The influence on both insulin and leptin levels may be associated with the weight gain-inducing ability of these agents. Bobes et al.[96] performed a cross-sectional study of outpatients receiving a single antipsychotic medication. They identified female sex, higher initial body mass index and duration of treatment of <1 year as risk factors of weight gain for olanzapine, and female sex alone as a risk factor for risperidone. These findings are in contrast to two 6-week controlled studies reported by Basson et al.[97] that compared olanzapine versus haloperidol and olanzapine versus risperidone during acute treatment. They stated that males had a significantly higher weight increase than females receiving olanzapine. Part of this conflicting data may be explained by differences in study duration and in baseline body mass indices.

One important risk factor for cardiovascular disease is metabolic syndrome, which is defined by a cluster of clinical features including increased visceral adiposity (as measured by waist circumference), hyperglycaemia, hypertension and dyslipidaemia.[22] As recently shown in the CATIE (Clinical Antipsychotic Trials of Intervention Effectiveness) schizophrenia trial, prevalence of metabolic syndrome was significantly higher for females than for males.[98]

Several retrospective papers have recently studied the incidence of newly diagnosed diabetes mellitus secondary to the use of SGAs and reached different conclusions. In 2004, Ollendorf et al.[99] found an increased risk of developing secondary diabetes with SGAs compared with conventional antipsychotics. Several authors reported an increased risk among patients who received more than one SGA or clozapine or quetiapine compared with patients on first-generation antipsychotics alone.[100,101] Only one study reported higher incidence rates for diabetes for male patients.[102] The differential risk among SGAs has not yet been adequately established. Other risk factors for diabetes, such as advanced age, non-White ethnicity, family history, obesity, lack of physical activity and the diagnosis of schizophrenia, probably contribute more to the risk than exposure to any single antipsychotic drug.[103]

The American Diabetes Association recently published the outcomes of a consensus development conference on antipsychotic drugs, obesity and diabetes.[104] The conference recognised that SGAs are associated with adverse effects including obesity, diabetes and dyslipidaemia. The conference recommended baseline screening and ongoing monitoring for the development of significant weight gain, dyslipidaemia and diabetes.

3.4 Cardiac Adverse Effects

Women have often been excluded from large cardiovascular trials, but recent efforts to address sex-specific health issues have dramatically improved the amount of data available to optimise the cardiovascular health of female patients.[105] Animal and human studies demonstrated that QT interval prolongation increases the risk of developing torsades de pointes – a polymorphic ventricular arrhythmia that can progress to ventricular fibrillation and sudden death.[62,106,107] Makkar et al.[23] found in a meta-analysis that women made up 70% of the 332 cases of torsades de pointes but their proportional use of these cardiovascular drugs was only 44%. A greater than expected female prevalence of torsades de pointes was consistently observed with all of the cardiovascular drugs analysed.[24-26] Even so, women appear to have a lower incidence of atrial fibrillation, a difference in the age distribution of supraventricular tachycardia and a lower incidence of arrhythmia-induced sudden death than men.[24]

Clinical and experimental studies further show that female sex is associated with a longer corrected QT (QTc) interval at baseline and a greater response to drugs that block cardiac voltage-gated potassium channels, both of which facilitate the emergence of arrhythmia.[108] The paradox of a longer QTc interval and higher incidence of torsades de pointes but lower population-based incidence of sudden death in women has not been resolved.

Sex hormones may be a major factor affecting the QT interval and there is evidence that estrogens influence bradycardia-induced prolongation of the QT interval. Potassium channel-blocking agents, including many frequently used antiarrhythmic drugs, as well as a variety of noncardiac medications such as all currently available atypical antipsychotics, are linked to QTc prolongation *in vivo*.[26] Overall, women are at a lower risk of sudden cardiac death but they have a higher risk of induced long QT syndrome from antiarrhythmic and probably antipsychotic drugs.[109] However, androgens protect against torsades de pointes by shortening the QT interval in men.[110] Sex hormones prolong the QT interval and downregulate potassium channel expression in the rabbit heart.[111]

In a study published in 2004,[112] the mean QTc intervals did not exceed 500ms in any patient taking thioridazine (300 mg/day), ziprasidone (160 mg/day), quetiapine (750 mg/day), risperidone (6–8 mg/day increased to 16 mg/day), olanzapine (20 mg/day) or haloperidol (15 mg/day). Each of the antipsychotics studied was associated with measurable QTc prolongation at steady-state peak plasma concentrations. The mean QTc interval change was greatest in the thioridazine group.[112] Although female sex is already a risk factor for drug-induced torsades de pointes, women are more likely to be concomitantly taking other QT-prolonging drugs.[113]

3.5 Extrapyramidal Symptoms

Antipsychotic drug-induced acute extrapyramidal symptoms such as acute dystonic reactions, parkinsonism, akathisia and late-onset tardive dyskinesia are the major adverse effects associated with typical antipsychotics. Extrapyramidal symptoms occur in up to 75% of patients treated with typical antipsychotics and significantly contribute to medication noncompliance.[114-116] At equivalent doses, acute dystonia, long thought to be more prevalent among men, has been shown in a first-episode, fixed-dose, 10-week study to occur more often in women.[117] Earlier clinical studies had not taken into account the fact that young male patients were commonly given higher doses than women. In contrast, SGAs have a lower potential for producing extrapyramidal symptoms than conventional antipsychotics.[115] Risperidone has the highest (dose-related) risk of the SGAs of inducing extrapyramidal

symptoms, followed by olanzapine.[118] Clozapine and quetiapine carry a low risk of extrapyramidal symptoms. They bind more loosely than dopamine to the dopamine D_2 receptor, with dissociation constants that are higher than those for dopamine, thus minimising extrapyramidal signs.[119,120] This has been attributed to their fast dissociation from the D_2 receptor, which results in lower D_2 occupancy over time.[118,121]

In a *post hoc* analysis, sex differences were determined in treatment response and the incidence and severity of extrapyramidal symptoms among outpatients who received risperidone in an 8-week open-label trial. No significant sex differences in treatment response and in the incidence or severity of extrapyramidal symptoms were found in this study.[29] To our knowledge, there are no further studies that have investigated the influence of sex on the prevalence and severity of acute extrapyramidal symptoms for SGAs. For conventional antipsychotics, it was shown in a cross-sectional study that the prevalence of tardive dyskinesia is approximately 5% higher in women than in men.[122] However, a 5% difference may not be clinically significant. Detection of sex differences may also depend upon the study design, as tardive dyskinesia has been shown to be more of a risk factor for elderly men in a cohort study,[117] whereas the severity of tardive dyskinesia may be relatively greater in women in their later years.[122] However, spontaneous dyskinesia was also found to be more common in women.[122] The observation that SGAs in general have a reduced risk for tardive dyskinesia compared with conventional antipsychotics is also supported by a systematic review of studies involving open or controlled treatment with any SGA.[123]

4. SGAs in Pregnancy and Lactation

Until recently, knowledge about the risks and benefits associated with the use of SGAs during pregnancy and lactation was limited. Each mother-infant dyad has to be evaluated individually, weighting the risk of untreated maternal illness against the risk of toxic effects on mother and child. A recent study reported that opposing changes in drug metabolism occur during pregnancy, with CYP1A2 activity being decreased and CYP2D6 and CYP3A activities increased. The direction of dose adjustments during pregnancy will depend on the drug and the enzyme that is responsible for its metabolism.[37]

Atypical antipsychotics in pregnancy and breast-feeding do not show evident advantages in safety when compared with typical antipsychotic agents.[124] Olanzapine, risperidone, quetiapine and clozapine do not seem to increase fetal teratogenic risk,[125] whereas data on aripiprazole, amisulpride and ziprasidone are currently not yet available. An increased risk for pregnant women treated with clozapine or olanzapine developing gestational diabetes has been described by several case reports.[126] Clozapine cannot be recommended for use during pregnancy because of an increased risk of floppy infant syndrome, neonatal seizures,[127] gestational diabetes associated with shoulder dystocia of the neonate,[128,129] and the potential for agranulocytosis[130] making white blood counts in newborns necessary.

For lactation, it is generally agreed upon that infants should be exposed to <10% of the maternal dose. In several case series and case reports it could be shown that plasma concentrations in infants were very low and sometimes even below detection limits for olanzapine[131,132] and risperidone.[133-135] One case report of quetiapine demonstrates the ingestion of an extremely low dose of 0.09% of the weight-adjusted maternal dose.[136] Clozapine should again be avoided because of its tendency to accumulate in infant serum and its relatively high concentrations in breast milk.[137]

5. Conclusions

Including women in clinical trials and analysing data by sex will further advance our understanding of drug efficacy and safety in women by providing information on drug dose, pharmacokinetics and pharmacodynamics. Although sex differences are found for pharmacokinetic factors, significantly higher plasma concentrations for women could be demonstrated only for olanzapine and clozapine. There is good evidence that women have a higher

prevalence of longer QTc interval and incidence of torsades de pointes, as well as higher bodyweight increases, rates of metabolic syndrome and of hyperprolactinaemia.

Future studies with a primary focus on sex-specific topics are required. These data will help us to determine to what extent sex differences in pharmacokinetics and pharmacodynamics will have an impact on the clinical management of men and women.

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