

Gender Differences in Pharmacokinetics and Side Effects of Second Generation Antipsychotic Drugs

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Abstract: Significant gender differences have been described for psychiatric disease prevalence and receipt of psychotropic medication. Second generation antipsychotic (SGAs) drugs are not a homogenous group as they differ in their receptor profiles, clinical efficacy and side effects. Gender differences in pharmacokinetics and side effects of second generation antipsychotic drugs have been investigated in several studies indicating that there is a distinct differences between men and women both for the SGAs as a whole group and for specific drugs in particular.

Nevertheless the influence of gender on efficacy and side effects of antipsychotic agents is still not well established. Even though higher rates of side effects are reported in women, recommended pharmacological dosage regimes do not differ between male and female patients.

For SGAs, the reasons for a higher risk in females may be multi-causal including gender-related differences in pharmacokinetics, pharmacodynamics, pharmacogenetics, immunological and hormonal factors as well as differences in the use of medications by women compared with men. In this review we give a brief overview of gender-specific pharmacokinetic factors leading probably to distinguished clinical outcome in both sexes.

Furthermore the implication of gender on common side effects of SGAs such as weight gain, glucose and lipid abnormalities, hyperprolactinemia, cardiac and sexual side effects is discussed with specific reference to studies done on schizophrenic patients.

Key Words: Antipsychotic agents, gender, side effects, weight gain, hyperprolactinemia.

I. INTRODUCTION

During the past decade, pharmacological research has greatly enhanced our understanding of several variables affecting the prescription of psychotropic medication. One variable of increasingly recognized importance is gender. Significant sex differences have been described for psychiatric disease prevalence, symptom presentation, treatment-seeking behaviour and receipt of psychotropic medication (for review see [78]). Also, several studies reported that women have a less severe course of schizophrenia than men. In general, female patients experience fewer negative symptoms, better social adaptation, a better response to lower doses of antipsychotic medication, fewer inpatient admissions and hospitalisations compared to men [5,71].

Up to 5% of all hospital admissions and up to 7000 deaths annually in the United States are the result of adverse drug reactions (ADRs) [70]. Identifying those

factors that may predispose to ADRs is essential for risk management. Amongst the known risk factors for adverse drug reactions are increasing age, polypharmacy, liver and renal disease as well as being female. However, the reasons for this increased risk in female patients are not entirely clear but include gender-related differences in pharmacokinetics, pharmacodynamics, pharmacogenetics, immunological and hormonal factors as well as differences in the use of medications by women compared with men.

In the past, women have been underrepresented in clinical trials of SGAs, which have caused a relative lack of data to evaluate possible sex differences in drug efficacy and side effects. A main reason for this underrepresentation is the fear of potential teratogenicity. As a result, major studies involving the efficacy of antipsychotic drugs did not include women. New registration guidelines require sex-specific analysis of efficacy and safety data. Due to these guidelines, an increasing number of studies are now available concerning differences in pharmacokinetic or pharmacodynamic between men and women. However, there

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are far more data on pharmacokinetics than on pharmacodynamic aspects.

The use of second generation antipsychotics (SGAs) is constantly increasing in recent years, because of their efficacy and favourable side effect profile compared to conventional antipsychotics. SGA's exert their action through a blockade of dopamine and serotonin receptors and each drug has a different set of pharmacologic characteristics [103]. Therefore, second-generation antipsychotics do not represent a homogeneous group. There are numerous preclinical studies illustrating differences in their mode of action, differences in gene expression and differences in their receptor profiles [12]. Additionally, clinical studies revealed that SGAs are also different in their efficacy, as well as in their side effect profiles [28,30].

Besides schizophrenic and bipolar patients these drugs are widely used for the treatment of a broad range of psychiatric symptoms and disorders (off-label use), such as dementia, depression, personality disorders, delirium, autism and developmental disorders [110]. Furthermore, antipsychotic drugs are frequently prescribed for untoward behaviour (e.g., aggressive behaviour) as much as for psychotic symptoms [91].

Although second generation antipsychotics produce fewer extrapyramidal motor symptoms than traditional antipsychotics, clinicians must be aware of their property to cause a number of harmful side effects such as weight gain, glucose and lipid abnormalities, hyperprolaktinemia, cardiac and sexual side effects. The implication of gender on these side effects is focused in this review with a specific reference to studies done on schizophrenic patients.

II. GENDER DIFFERENCES IN THE COURSE OF SCHIZOPHRENIA AND IN TREATMENT RESPONSE TO ANTIPSYCHOTICS

For schizophrenia, the cumulative life time risk is identical for men and women, yet men fall ill earlier than women. On average, there is a 3-5 year difference in age of onset between the sexes, a difference that cannot be ascribed to gender differences in help seeking behaviour only [78]. Furthermore, men with schizophrenia show more negative symptoms and cognitive deficits, with greater structural brain and neurophysiologic abnormalities. On the other hand, schizophrenic women display more affective symptoms, auditory hallucinations and persecutory delusions with

a greater and more rapid response to antipsychotics in the premenopausal period but increased side effects. Additionally, the course of illness is more favourable in female schizophrenia patients in the short- and middle-term, with less smoking and substance abuse [78].

Neuroanatomic sexual dimorphism may be one reason for different clinical profiles in schizophrenic men and women. For example, several studies demonstrated temporolimbic abnormalities in male schizophrenia patients. Bryant *et al.* [19] reported that the left temporal lobe volume was significantly smaller in male schizophrenia patients than in male comparison subjects. In contrast, female patients with schizophrenia and female comparison subjects demonstrated no significant difference in temporal lobe volume. Additionally Gur *et al.* [46] reported that schizophrenic men had a reduction of the grey matter volume in temporolimbic structures, whereas women with schizophrenia showed decreased hippocampal volumes but increased amygdala volumes. Furthermore, in a volumetric MRI study corpus callosum volumes differed in men and women with schizophrenia [9].

Gender differences in response to antipsychotic agents have been well studied in both animals and humans, but most studies have focused on treatment with typical antipsychotics. In general, these studies showed that schizophrenic women had a higher degree of symptom improvement [97], but also an increased rate of extrapyramidal symptoms [98,102]. In a recent study, women on olanzapine had a significantly better treatment response than men, regardless of chronicity. Furthermore, premenopausal women had a significantly better treatment response than postmenopausal women, regardless of treatment and chronicity [43]. Research suggests that, both with respect to acute response and to maintenance, women with schizophrenia under 40 require lower antipsychotic doses than men, however with increased age this female advantage may disappear [97].

Differences in antipsychotic treatment response, clinical course and outcome of schizophrenia could be related to gender-specific cerebral differences. For example, the change in caudate nucleus volume over time with exposure to atypical antipsychotics may be sex dependent. Atypical antipsychotics exposure was associated with volume increase over time in males, and volume decrement over time in females [53].

In a very recent study, however, a lack of sex differences was found for striatal dopamine D2

receptor binding in drug-naive schizophrenic patients which does not support previous reports of left lateralized striatal asymmetry in male schizophrenic patients [90].

Several studies reported sex differences in cognitive functions in schizophrenic patients with male patients performing worse than female patients [99]. However, other groups showed either opposite findings [109] or no sex differences [88]. One explanation for these discrepancies between studies may be that the majority of studies were not designed to examine sex differences *per se*. Most studies on neurocognitive deficits provide strong evidence that atypical antipsychotic drugs are more effective in ameliorating neurocognitive deficits in schizophrenia patients than typical antipsychotic drugs (for review see [111]). Possibly, differences between schizophrenic men and women in the treatment response to SGAs are leading to sex differences in cognitive functions. Until now most studies were based on male patients only, and therefore are not able to examine sex differences in cognitive functions as a result of different treatment response. Thus, the question whether men or women have a better neurocognitive outcome or less cognitive side effects needs to be further examined.

Few studies have examined how sex and ethnicity interactions affect treatment of psychotic disorders. In a study by Arnold *et al.* African-American men and women with psychotic mood disorders were more likely to be discharged on high antipsychotic doses compared with white patients [7]. There were no ethnic or sex differences in the dosing of antipsychotics for the treatment of schizophrenia spectrum disorders or in the use of SGA's [7].

III. GENDER DIFFERENCES IN PHARMACOKINETICS OF SGAs

The identification and quantification of pharmacokinetic variability is more and more realized as a key requirement for safe and effective drug treatment. Sex-related differences in pharmacokinetics have been considered as potentially important determinants for clinical effectiveness and frequency of ADRs [6,50,64]. In this chapter we give an overview of underlying gender-specific pharmacokinetic factors leading probably to distinguished clinical outcome in both sexes.

Physiological factors that may contribute to gender-related differences in pharmacokinetics of drugs are

absorption (e.g. gastric acid secretion and gastrointestinal blood flow are lower and gastric emptying time is longer in women), distribution (e.g. women typically weigh less and tend to have a higher percentage of body fat), metabolism (e.g. drug metabolizing enzyme activity differs with sex) and excretion (e.g. women have a lower glomerular filtration rate and a lower creatinine clearance compared with men) [13,50].

Several cytochrome P450 (CYP) isoenzymes, including CYP3A4, CYP2D6, CYP1A2 and CYP2C19, are identified as major enzymes responsible for the metabolism of many drugs.

Only few and inconsistent data are available describing potential gender based differences in CYP2D6 and CYP3A4 activity. Some data suggest higher CYP3A4 activity in women [38,50,54,57], other data show increased CYP2D6 activity in pregnant [108] and premenopausal women. Recently McCune [82] could not detect any gender-based differences in CYP3A4 and CYP2D6 activity. However Tamminga *et al.* [104] examined a large database of 4301 phenotyped Dutch volunteers and found a 20% increase in CYP2D6 activity and a reduced CYP2C19 activity in females compared to men. Hagg *et al.* [48] confirmed these findings on CYP2D6 and also observed a negative influence of exogenous estrogen on CYP2C19 activity.

Men seem to have a higher activity relative to women for CYP1A2 and potentially CYP2E1, and there is some evidence of higher glucuronosyltransferases activity in men compared to women [83]. Nevertheless so far there are no studies showing any relevance of gender specific differences of phase II metabolism of SGAs.

For the old antipsychotic agent haloperidol a wide interindividual variation in serum concentrations is shown and caused to some extent by ethnicity and gender [120]. Caucasian males have significantly lower plasma haloperidol levels than Asian males while no ethnic differences in haloperidol levels were found among females. In addition, body weight and smoking had significant effects on haloperidol kinetics, whereas age, gender, and comedication showed only slight effects [17].

Gender-related differences in pharmacokinetics for SGAs are demonstrated for clozapine, olanzapine and sertindole. CYP1A2 is a major determinant for

clozapine elimination with slight differences between men and women [58]. Results suggest that women have higher plasma levels than men for clozapine and its metabolite norclozapine. These gender specific differences are not detected for the metabolite N-oxide-clozapine [73]. Plasma levels of clozapine and N-desmethylclozapine may be affected by treatment duration. In a study by Fabrazzo *et al.* clozapine and its metabolite were significantly higher in females than in males after 4 and 6 weeks, but not after 24 weeks of treatment [36].

Pharmacokinetic differences may result in gender differences in plasma concentrations. For clozapine and olanzapine, there is good evidence for such differences [95]. In a study by Skogh *et al.* women had a significantly higher median concentration to dose (C/D) ratio for olanzapine than men [100]. Furthermore, higher plasma concentrations of olanzapine were associated with female gender in two more studies [40,66].

For sertindole, the mean peak plasma concentration values for young and elderly female subjects were 20% and 31% higher than those observed for male subjects. Age did not affect sertindole plasma levels since no differences were observed between young and elderly subjects in the absorption and elimination of sertindole [118]. Likewise, there was no significant influence of age and gender on the pharmacokinetics of ziprasidone [114], when the pharmacokinetics of ziprasidone were studied in healthy young men and women, and healthy elderly (> or = 65 years) men and women. Again for quetiapine there was no significant correlation between C/D ratio and age and gender in a recent study [52].

Thus, further studies focusing on gender differences in plasma concentration of novel antipsychotics are still needed since the reported studies are done with a rather small number of patients. Because of high interindividual variations significant gender related differences might be detected in a sample size higher than 1000 individuals. One important variable yielding higher plasma levels in women is body weight. Therefore we have to claim: plasma levels as well as C/D ratios have to be corrected for body weight in studies performed to detect gender differences as women tend to have a lower body weight on average. For example, we found in a recent study significantly higher plasma levels of risperidone and its active metabolite 9-OH-risperidone only for the uncorrected C/D ratio, which was apparently due to weight differences between men and women. The weight-

corrected C/D ratio did not present any distinctive sex differences [1].

IV. GENDER DIFFERENCES IN SIDE EFFECTS OF SGAs

Side effects of antipsychotic drugs are an important factor in a patient's decision to discontinue medication [37]. Due to the side effect profiles of SGAs, consensus recommendations have been recently established which include regular monitoring of body mass index, plasma glucose level, lipid profiles, and signs of prolactin elevation or sexual dysfunction [79]. Frequent side effects of SGAs such as cardiac side effects, hyperprolactinemia, sexual side effects, and weight gain and to lower extent extrapyramidal symptoms are evaluated for gender differences in the last years. Despite gender differences in side effects induced by SGAs, there are no recommendations to prescribe antipsychotic drugs different for men and women.

When SGA's are investigated for their side effects profiles, a study design has to be set up that allows to distinguish between gender specific phenomenon related to schizophrenia and side effects induced by intervention with SGAs.

CARDIAC SIDE EFFECTS

Female gender is associated with an increased risk of torsades de pointes in the setting of drugs that can prolong the QT interval [117]. These drugs are all potassium channel blocking agents and include many frequently used antiarrhythmic drugs, as well as a variety of noncardiac medications [117]. SGA's are thought to prolong QT intervals to some degree by reducing the flow of repolarizing K⁺ currents, ultimately making the myocardium more excitable [105]. The potassium channel most often involved in drug-induced QT syndromes is the potassium rectifier (I_{Kr}) channel [33].

A prolonged QT interval on the electrocardiogram is associated with the occurrence of torsades de pointes and related ventricular arrhythmias. Although there is no specific threshold above which torsades de pointes will occur, it appears there is no significant risk of developing arrhythmias below a QT interval of 500 msec [89]. Women are at lower risk of sudden cardiac death overall, but they have a higher risk of acquired long QT syndrome from antiarrhythmic drugs [10]. Sex hormones may be a major factor in the differential

presentation of arrhythmias in men and women [93]. There is good evidence that estrogens facilitate bradycardia-induced prolongation of the QT interval [51]. The potential to block cardiac voltage-gated potassium channels is increasingly important to be aware of during the development of new antipsychotic drugs [32].

The clinical development of atypical antipsychotics has coincided with increased interest among regulatory authorities and clinicians in the effects of non-cardiac medications on the electrical activity of the heart, particularly the QT interval. All of the currently available atypical antipsychotics have been found to block cardiac voltage-gated potassium channels, an activity that may predict QTc prolongation *in vivo* [32].

The effects of haloperidol, thioridazine, ziprasidone, quetiapine, olanzapine and risperidone on the QTc interval at and around the time of estimated peak plasma concentrations were characterized in a prospective, randomized study [49]. Mean QTc intervals did not exceed 500 milliseconds in any patient taking any of the antipsychotics studied. The mean QTc interval change was greatest in the thioridazine group, both in the presence and absence of metabolic inhibition [49]. Ziprasidone prolongs QTc to a moderate degree, though to a greater extent than quetiapine, risperidone, olanzapine and haloperidol [44,47,67].

HYPERPROLACTINEMIA AND SEXUAL SIDE EFFECTS

Prolactin elevations in patients treated with older antipsychotics like butyrophenone and phenothiazine derivatives may be associated with hyperprolactinemia and sexual dysfunction - a common cause of drug non-compliance, particularly in men [41]. Also in some of the currently marketed SGAs prolactin elevation occurs frequently and is a persistent phenomenon [24,45]. Increased prolactin plasma levels cause galactorrhoea, amenorrhoea, sexual dysfunction, breast engorgement and as a long-term consequence osteoporosis [113]. During SGAs treatment prolactin concentrations can rise up to ten times of normal levels and existing data indicate that 17-78% of female patients have amenorrhoea with or without galactorrhoea. In males, prolactin elevations have been linked specifically to diminished libido, impotence, and sterility.

Kleinberg *et al.* designed an analysis of compiled data from randomized, double-blind studies of

risperidone in patients with chronic schizophrenia to describe the relation between risperidone, serum prolactin levels, and possible adverse events [68]. It was shown that the incidence of adverse events was positively correlated with risperidone dose in men, but adverse events in men were unrelated to plasma prolactin levels [68]. Among women, the risperidone dose was not correlated with adverse events, nor were the adverse events correlated with endpoint prolactin levels [68]. Although elevated serum prolactin has been associated with such side effects as galactorrhoea, and perhaps sexual dysfunction, attempts to develop a relationship between degree of prolactin elevation and specific side effects have not been successful [25,68].

For olanzapine, the rates of prolactin elevation were approximately of those observed with haloperidol and were more transient. Olanzapine, even at the highest doses (15 +/- 2.5 mg/day), was not associated with persistent elevations of prolactin [27]. David *et al.* [29] examined the comparative effects of olanzapine, risperidone, and haloperidol on prolactin levels based on data from 3 multicenter, double-blind, randomized clinical trials. Magnitude of response, dose dependency, time course, effects of sex and age were assessed. A significant effect of sex was observed across all studies, with haloperidol- and risperidone-treated women experiencing a greater mean change in prolactin levels than men. These effects remained after adjusting for the higher baseline prolactin levels of women. Kearns *et al.* [65] compared the prolactogenic effects of risperidone, clozapine and typical antipsychotic agents in an outpatient community-based psychiatric population. The percentage of women with elevated prolactin concentrations exceeded the percentage of men in all groups observed.

The recently approved antipsychotic aripiprazole differs from the second generation antipsychotics by being a partial agonist at the D2 receptor. Aripiprazole has shown a profound prolactin lowering effect, superior subjective tolerability, and a more salutary impact on sexual function, compared with other antipsychotics [80]. Some more prolactin-sparing properties are probably seen for clozapine and quetiapine [15,16,101].

Neuroendocrine abnormalities in patients with schizophrenia, such as chronic hyperprolactinemia, may now potentially be minimized by the use of newer prolactin-sparing antipsychotic drugs. Melkersson *et al.* [85] studied the effects of antipsychotics on the prolactin (PRL) secretion, the growth hormone (GH)-

insulin-like growth factor I (IGF-I) axis and the glucose-insulin homeostasis. They detected a slight to moderate degree of hyperprolactinemia in one third of patients on long-term treatment with classical antipsychotics. Despite lower dosages of antipsychotics in women, hyperprolactinemia was more common in women compared to men, indicating a sex-related difference in the sensitivity to antipsychotics in the hypothalamic-pituitary PRL-regulation.

Furthermore, a negative relationship between age and prolactin levels of premenopausal women was reported [18]. However, the interpretation of changes in prolactin plasma levels during menstrual cycle, has to consider that prolactin and beta-endorphin may have peaks in the periovulatory phase [75]. Additional data described an association between the frequency of prolactin and LH pulses [81]. These data suggest a menstrual-related rhythm in women for prolactin concentrations.

Last but not least, a relationship between estrogen and prolactin could be demonstrated. A rise in estrogen levels probably stimulates an increase in prolactin during pregnancy. Increased prolactin levels are also found in women taking estrogen-containing oral contraceptives, although this effect is very small with low-estrogen formulations. Functions of the pituitary lactotrophs regulated by estrogen include prolactin gene expression, release, storage, and cellular expression [92]. Estradiol inhibition of dopamine synthesis in the tuberoinfundibular dopaminergic neurons may also contribute to some gender differences in neurocognitive function and to psychiatric conditions clinical features.

Therefore the question arises, if dose regimens should be altered in women during menstrual cycles, pregnancy, the postpartum period and menopause [47,59,96].

Patients taking antipsychotics often complain - spontaneously or after focused questioning - of sexual side effects. Assessing antipsychotic-induced sexual dysfunction may be confounded by the psychoses being treated, patient compliance and sexuality's complexities.

Antipsychotic treatment has to take into account that schizophrenia affects sexuality, pregnancy, the puerperium, parenting and family planning in female patients. While women with schizophrenia have high rates of coerced sex, sexual risk behaviour and unwanted pregnancies [87], men with schizophrenia frequently lose their sexual drive early in the course

of illness. In case of a severe course they stop to be sexually active as opposed to women. Antipsychotics are generally believed to reduce desire, cause orgasmic dysfunction, and lead to difficulties during sexual performance.

It is uncertain whether the SGAs have a more favourable sexual side effect profile since sexual side effects seem to be adverse effects associated with both novel and conventional antipsychotic medications [116].

In a comparative study, no statistically significant difference was shown between haloperidol and clozapine with regard to their propensity to induce sexual side effects [56]. Sexual functioning was different in patients treated with quetiapine compared to risperidone, showing the quetiapine group with less frequent sexual side effects [69].

Sexual dysfunction including decreased libido, impaired arousal, and erectile orgasmic dysfunction is common among patients receiving atypical antipsychotics [2]. These effects may be caused by anticholinergic activity, alpha-1 inhibition, and hypogonadism due to hyperprolactinemia [31].

However, one has to keep in mind, that medication is not the only reason for sexual dysfunction since patients with schizophrenia experience more frequent sexual dysfunction, with or without medications [3].

WEIGHT GAIN

Weight gain has always been an issue related to antipsychotic treatment, but as a side effect, it has historically been overshadowed by the risk of extrapyramidal symptoms (EPS). SGAs carry a much lower risk of EPS but an increased risk of weight gain.

Weight gain, seems to be particularly problematic in olanzapine and clozapine [4]. For example, in clozapine-treated patients, lower baseline body weight was indicated to be related with maximum weight gain [107,112]. Compared to clozapine or olanzapine weight gain during treatment with risperidone [23] and quetiapine [101] is less pronounced. Lately it has been suggested that ziprasidone may be largely free of weight gain [42,106].

Mechanisms underlying drug-induced weight gain are not entirely known. Both serotonin 5-HT_{2c} and histamine H₁-blocking activities of these drugs have

been implicated [115] and it has been demonstrated that 5-HT_{2c}-receptor-deficient mice become overweight as a result of abnormal control of feeding behaviour. Blocking of central H₁-receptors also increases food intake in rats fed a low protein diet [86].

Weight increase is significantly higher in patients treated with clozapine than in patients treated with haloperidol [55]. Sex, severity of illness, comedication, mean clozapine dose and degree of improvement did not show an influence on weight [55]. Both female and male patients treated with clozapine gain body mass which may place them at greater risk for cardiovascular morbidity [39]. Olanzapine-treated patients had a significantly higher serum insulin level compared to patients treated with classical antipsychotics, despite similar body mass index, pointing to a probable influence of olanzapine on insulin [34,84]. In clozapine-treated patients, the insulin levels correlated to plasma concentrations, indicating a likely influence of clozapine on insulin [84].

Leptin has been reported to be associated with antipsychotic-induced weight gain [35]. In a comparative study, clozapine and olanzapine caused a marked increase in weight, serum triglyceride and leptin levels. These increases were modest in patients treated with quetiapine and minimal in those receiving risperidone [8]. The influence of clozapine and olanzapine on both insulin and leptin levels may be associated with these agents weight-gain inducing ability. Bobes *et al.* [14] performed a cross-sectional study with outpatients receiving a single antipsychotic medication. They identified gender, initial body mass index and duration of treatment as factors modifying the effect of treatment with olanzapine. The risk of weight gain was higher in women than in men, higher in overweight patients than in low or normal weight patients and much higher in patients with less than one year of treatment than in patients with more than one-year treatment. An increased risk of weight gain in women compared to men was also seen with risperidone.

Basson *et al.* [11] compared olanzapine versus haloperidol and olanzapine versus risperidone in two controlled double-blind studies. They emphasize that gender has a significant effect on weight change but only among patients taking olanzapine. Males receiving olanzapine gained significantly more weight than females on olanzapine. Interestingly patients receiving high doses did not gain more weight than patients receiving low doses.

In a prospective, open label, and repeated-measures study with risperidone, no significant differences were detected between male and female patients [74].

EXTRAPYRAMIDAL SYMPTOMS

Extrapyramidal symptoms, including acute dystonic reactions, drug-induced parkinsonism, and akathisia are the most troublesome side effects associated with typical antipsychotic drugs. Extrapyramidal symptoms occur in up to 75% of patients treated with typical antipsychotics and significantly contribute to medication non-compliance [20,21,61,76].

The newer atypical antipsychotics have a lower potential for producing EPS than conventional antipsychotics [61,77] which is the clearest advantage of SGAs compared with conventional compounds [94]. The association of atypical antipsychotic drugs with fewer drug-induced movement disorders may be based on different pathophysiological processes [22].

These side effects are very distressing, especially uncontrollable restlessness and tremors. High potency antipsychotic agents, as haloperidol or fluphenazine, induce more EPS than low potency drugs. In contrast to the effect on EPS, low potency antipsychotic drugs cause more sedation and hypotension than high potency drugs [60].

However, these findings might have been biased by the use of the high-potency antipsychotic haloperidol as a comparator in most of the trials [77]. A meta-analysis of 31 studies revealed that a optimum doses of low-potency conventional antipsychotics might not induce more EPS than new generation drugs [77]. Additionally, risperidone's risk of inducing EPS is dose-related, as is olanzapine's, although the latter seems to carry a comparatively lower risk to overt EPS, perhaps related to its inherent antimuscarinic activity [63]. Clozapine and quetiapine carry a very low risk of EPS. This has been attributed to their very fast dissociation from the D₂ receptor, which results in lower D₂ occupancy across time [62].

In a posthoc analysis sex differences were determined in treatment response among outpatients who received risperidone in an 8-week, open label, clinical trial. Both male and female patients showed improvements over baselines in the incidence and severity of parkinsonism, dystonia, and dyskinesia. No significant sex differences in treatment response were observed for

any of the efficacy outcomes or in the incidence and severity of extrapyramidal symptoms [72]. To our knowledge, there are no further studies for SGAs which have investigated the influence of gender on the prevalence and severity of acute EPS. The prevalence of tardive dyskinesia is significantly higher in women (26.6%) than in men (21.6%) [119]. Overall, prevalence of tardive dyskinesia seems to reach its peak in the 50 to 70-year-old age group in men and continues to rise after age of 70 in women.

Therefore, women tend to have more severe tardive dyskinesia than men. Again spontaneous dyskinesia was found to be more common in women as well [119]. A systematic review supports the observation that SGA's agents have a reduced risk for tardive dyskinesia, compared with conventional antipsychotics [26].

OUTLOOK

The conducted studies on antipsychotic drugs suggest that sex-related differences are likely to be a multifactorial phenomenon. Differences may be caused by differences in pharmacokinetics of SGAs between male and female patients. Especially the distinguished activity of CYP P450 enzymes might be essential for gender related differences in plasma concentrations of SGAs as shown for olanzapine and clozapine. Consequently, clinicians have to be aware of a substantial implication of gender on efficacy and side effect profile of antipsychotics. Ongoing research will provide more information on genetically determined gender differences in response to drug therapy. To our opinion, pharmacogenetic studies will advance substantially the research dealing with gender-related effects on therapeutic outcome and side effect profile.

Gender differences in side effects of SGAs, as discussed for QTc-prolongation, hyperprolactinemia or weight gain should lead to a deliberate prescription of SGAs for women. In conclusion, a major effort should be undertaken to build up a greater database for gender-specific differences in pharmacokinetics and pharmacodynamics. Future studies have also to focus on distinguished outcome for efficacy and side effects for male and female patients.

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