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Review

Application of Antipsychotic Medication: Gender Differences in Tolerance and Medication Response

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Abstract: This paper covers the role of gender factor in the efficacy and tolerance of antipsychotic therapy in patients with schizophrenic spectrum disorders. The author describes phenomenology of definitions that characterizes differences between male and female sexes. The authors give the data on biological basis of gender differences, frequency of occurrence and clinical features of neuroendocrine dysfunctions (NED) in patients with schizophrenic spectrum disorders during the therapy by first and second generations antipsychotics. It is shown that female patients are more "vulnerable" for some NED. It is emphasized that the problem of tolerance is now more relevant and significant in comparison with the efficacy of antipsychotics, because intolerance or poor tolerance are one of the most common reasons for non-adherence to therapy up to the complete abandonment of it.

Keywords: *schizophrenic spectrum disorders, gender factor, antipsychotic therapy, neuroendocrine dysfunctions*

Introduction

In recent decades modern requirements to psychopharmacotherapy (PPT) and the appearance of the second-generation antipsychotics (SGAs) has changed the main parameters of the evaluation of the optimum results of the treatment. Nowadays efficacy is not the only parameter that is important, but more and more attention is paid to the tolerance. Be-sides, if you want to use PPT rationally, you need to consider the product-related factors on the one hand and the patient-specific approach (patients-related factors) on the other hand.

Experimental, biological and epidemiological studies showed two groups of factors that influence the efficacy and tolerance of antipsychotics in mentally ill patients. The authors say that the first and the main group includes factors associated with the antipsychotics that the patient is using: characteristics of pharmacodynamics (receptor preference spectrum), therapeutic margin (range between therapeutic and toxic doses), pharmacodynamic attributes, dose-related side effects (SE), polypragmasy, SE to the previous therapy and so on. The second group that is also very important includes the patients-related factors: age, gender, metabolism, eliminative, enzyme, allergic, immunological, morphofunctional (including antropometric) comorbid somatic diseases, information and so on [1 – 8].

In the recent years the paradigm of therapeutic approaches in psychiatry has changed. More and more attention paid to the second group of factors, in particular to the gender fac-tor that plays a certain role in the efficacy and tolerance of antipsychotics.

Phenomenology of definitions related to the differentiation between male and female gender is quite big (Fig.1). However, in most scientific sources the term "gender" is used not only to differentiate by sex character based on the social role offered by D. Mann, but more generally, implementing also the biological factor [9].

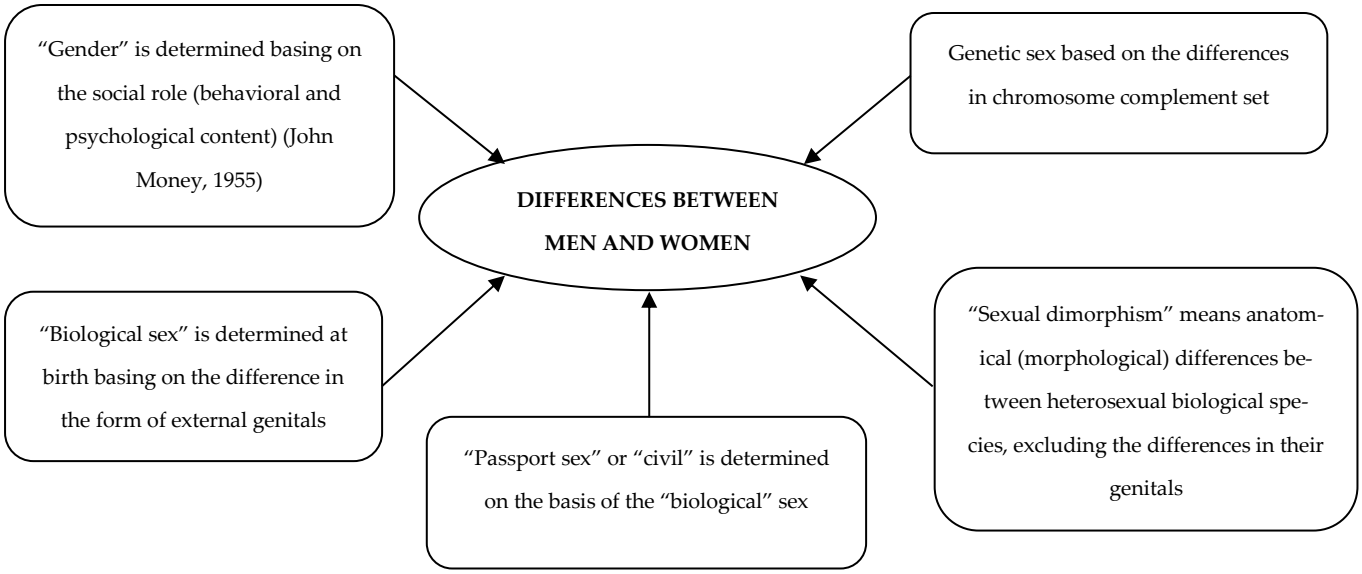

Figure 1. Phenomenology of definitions, concerning the differences between "male" and "female".

Though the gender factor is certainly very significant for the selection of psychopharmacotherapy to achieve the optimum efficacy and minimize the side effects, it is not well studied yet, that is shown by inconsistency and incoherence of the results obtained nowadays in the relevant studies.

Materials and Methods

We analyzed the literature review of PubMed since 1990 with the search terms: gender, anti-psychotics, schizophrenia, pharmacokinetics, pharmacodynamics, pharmacogenomics and also the publications taken from the literature lists to the original articles, that cover the gender-specific factors associated with the efficacy and side effects of antipsychotics. We found more than 200 publications that discuss different aspects of this problem.

Results

In most studies the gender is associated with such factors as age, onset of the disease, genetics and so on [10 – 14]. Some publications show the data related to the role of the gender factor in such neuroendocrine dysfunctions (NED), as weight gain, metabolic syndrome, neuroleptic hyperprolactinemia (NHP), and reproductive disfunctions, and they stress that women differ from men not only by the prevalence rate, but also by the manifestation of clinical symptoms associated with side effects of antipsychotics [15 – 17].

The role of gender in responding to antipsychotic therapy in schizophrenic patients is undeniable, however, it is believed that both "sex-specific" efficacy and gender differences in endocrine side effects present only in combination with other factors (Fig. 2) and

have a general etiopathogenetic basis associated with the peculiarities of the functioning of the endocrine system in men and women [15, 18 – 20].

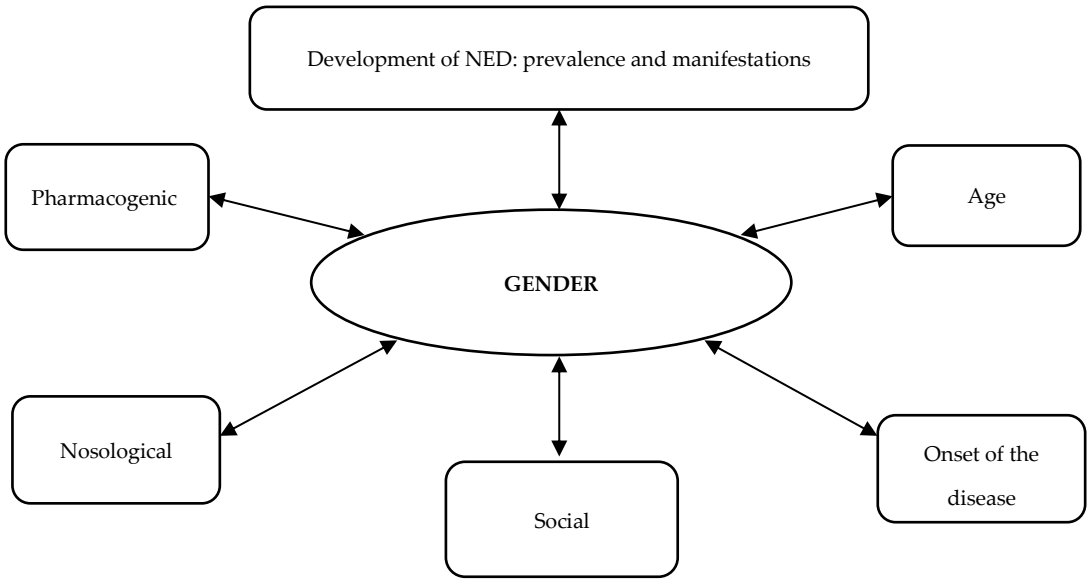

Figure 2. Gender-related efficacy and tolerance: main factors.

For example, when we consider functioning of the gonadal-pituitary hypothalamic axis, it is necessary to demonstrate the higher "vulnerability" of this part in women (for example, a high-er risk of the development of NHP). Such neuroendocrine abnormalities in patients with schizophrenia as chronical hyperprolactinemia (CH) can potentially be minimized with some second-generation antipsychotics (SGAs) that keep the optimum level of prolactin (PRL), Melkersson K. et al. say (1999) [21]. The studies of the influence of antipsychotics on the secretion of PRL, growth hormone, insulin-like growth factor-1, concentration of insulin and glucose showed that women require lower therapeutic doses of antipsychotics, however, the level of PRL was the same as in men who got higher doses of the products. The authors think that the gender-related differences in sensitivity to antipsychotics are caused by the gender differences in pituitary-hypothalamic regulation of the production of prolactin. Szymanski S. et al. [22] showed higher levels of PRL in women suffering from psychosis that correlated with the efficacy and tolerance of the therapy opposed to men.

Many authors demonstrated [15, 22, 23 – 29] that the level of PRL in the population in general does not have any significant gender differences, however, women respond to the therapy with antipsychotics with a more significant increase in its levels than men. The production of PRL is sup-pressed by dopamine, that is why a pronounced increase in the hormone in women implies higher sensitivity to the blockade of dopamine receptors with antipsychotics, that is probably associated with an antidopaminergic effect of the estrogen. These data are confirmed by the study held by Buckman M.T., Peake G.T. [30] who found out an increase in PRL level as a response to the administration of perfenazin in a group of psychologically healthy women who received exogeneous estrogen.

On the other hand, it is well known that the supporters of the "estrogen-protective" theory of the schizophrenia pathogenesis think that estrogen has a certain antipsychotic effect and can be protective for women with schizophrenia [18, 32 – 39]. The authors argue their case by saying that women in a reproductive period have a higher response to the therapy with antipsychotics and require smaller doses of these products to achieve a symptomatic remission than men or women after the menopause. Researchers think that

estrogens act as natural antipsychotics blocking or weakening the sensitivity of dopamine receptors or suppressing the synthesis of dopamine [33, 37, 40]. Besides the antipsychotic effect of estrogen, the authors show one more possible mechanisms of its actions associated with the activation of microsomal metabolism of antipsychotics in the liver that leads to a more expressed effect of antipsychotics. Kulkarni J. et al. [36] showed in their study that estradiol as an addition to the anti-psychotic therapy improves the values of PANSS scale. However, use of estrogens as an adjuvant to the antipsychotic therapy is limited by the side effects that provoke the development of breast and urologic cancer in women and feminization in men. Seeman M.V. and Lang M. [39] suppose that the use of selective modulators of estrogen receptors can help to avoid the development of such a side effect of estrogens.

Differences in the response to antipsychotics, the clinical course and the outcome of schizophrenia can be associated with gender-related peculiarities of the structure and functioning of the brain. For example, after the start of the use of SGAs change of the caudate of the striatum can be observed. Some authors think that the administration of these products is later associated with an increase in the volume of this formation in men and a decrease in women [41]. In their study Parellada E. et al. [42] did not find any gender-related differences in dopamine D2-linked receptors in drug-naïve patients with schizophrenia that did not correlate with the previous information about the left lateral striatal asymmetry in male patients.

Thus, the data on the gender differences in the morphology of the brain in patients with schizophrenia are controversial, but there is information that gender differences in some areas of the brain are typical for the norm as well as for the pathology. This allows us to suppose that the same factors are important as gender-related differences during the normal processes of neuro-genesis and in patients with mental disorders [5, 37, 43]. Salem J.E. and Kring A.M. [38] were shown that if we want to better understand the gender differences in patients with schizophrenia, it may be useful to consider and study more the hypothesis that men are prone to a worse forecasted neurogenetic subtype of schizophrenia, and women are prone to a genetically "good" forecast and "affective subtype of schizophrenia" genetically related to the affective disorders.

By now there have been no certain recommendations or treatment regimens that imply also the role of gender differences as the main factor in the choice of this or that antipsychotic, that could work for all therapeutic modalities (antipsychotic, dose, duration of administration and so on), despite the active discussion of this problem [10].

In the 1990s women as a part of the population were unproportionally more than men represented in the clinical studies of antipsychotics. At the same time there was relatively little evidence that gives the significant evaluation of the possible gender differences in the efficacy and development of side effects [16].

However, the gender differences in the reaction to the therapy with the first-generation antipsychotics were quite well studied in animals as well as in people. In general, these studies showed that the stages of the positive reaction in female animals and improvement of symptomatic in women were higher [13], though the level of the expression of extrapyramidal symptoms was also higher [22, 39]. As some authors say [17, 22, 27, 32, 34, 35], young women with schizophrenia require less doses of the first-generation antipsychotics than men. Authors think that it can be explained either by a smaller body mass in women (younger than 40 years old), or by the fact that after the menopause women more often require even higher doses of antipsychotics than men. The study of outpatients with schizophrenia [17] showed that the average supporting doses of chlorpromazine (262 mg) in women were equivalent to 431 mg in men. At the same time Salokangas R.K. [44] showed that only middle-aged women require lower doses of antipsychotics than men in general, and also women after the menopause who got too high doses of the products. Other authors showed in their studies [3, 12, 25, 45, 46] a faster and better improvement in the condition of women as a response to the therapy with the first-generation antipsychotics than in the condition of men in case of the first psychotic episode (FPE) as well as

in case of chronical schizophrenia. After 20 weeks of the antipsychotic therapy 87% of women had a full symptomatic remission in comparison with only 55% of men. Besides, the cumulative percent of women achieving the remission after 45 weeks of the therapy was 95.4%, and only 70.7% of men had a remission even after 56 weeks of the treatment. Vilyanov V.B. [47] showed in his study that the efficacy of the first-generation antipsychotics has significantly ($p<0.01$) decreased in men for the last 30 years. The author points out the influence of the gender factor as one of the signs of pathomorphosis of schizophrenia that can be neutralized with the help of SGAs.

On the contrary some other papers [48, 49] did not find the absence of the influence of doses of the first-generation antipsychotics on the development of neuroleptic hyperprolactinemia (NHP) in women and the absence of gender differences in the selection of the doses and reaction to the therapy taking into account the age in which the disease started. However, analyzing these variants it is still unclear if the results of such studies can be applicable for the whole population of patients with schizophrenia, men and women in general. The relative slowdown of cerebral blood flow with age [50], the slow decline in D2-receptor activity with age [14, 51] and the de-crease in estrogen levels after menopause may be an explanation why older women need higher doses of antipsychotics. The researchers think that in terms of both severity of reaction and personal and social safety, women with schizophrenia who are more than 40 years old need fewer antipsychotic doses than men, though at older age these benefits for women may disappear [13, 35].

In the last few years studies of the gender differences have been published that analyzed patients who use SGAs. Some papers covered the efficacy of this group of products in men in comparison with women, however, the gender-related benefits were less significant here than in a similar study of the features of some SGAs. In some studies [46, 53] the authors did not find out any gender differences in the efficacy of the therapy with clozapine. In other publications [6, 52] there is evidence that the female gender is a predictor of a weaker stage of the reaction to the treatment. Haring C., Meise U., Humpel C. et al. [54] showed that male plasma contains only 69.3% of the level that women have. Like the first-generation antipsychotics, clozapine does not increase significantly the level of PRL in plasma, though it can increase its level for a short time [55, 56]. A higher level of suppression of the PRL secretion as a response to oxytocin challenge test during the treatment with clozapine correlates with a better clinical reaction to the administration of the medication [57]. Goldstein, J. M., Cohen, L. S., Horton, N. J. et al. [58] showed in their study that women who take olanzapine significantly better respond to the therapy indpendently of the duration of the treatment and the length of the disease.

In their review Aichhorn W. et al. (2005) [16] give the data regarding the study of gender pharmacokinetic differences and side effects in case of the use of six SGAs – aripiprazole, clozapine, olanzapine, quetiapine, risperidone, ziprasidone. Gender-related differences were demonstrated in pharmacokinetic of the cytochrome P450 (CYP) with a higher activity in women for CYP3A4 and CYP2D6. However, even if there are pharmacokinetic differences between men and women, women had only olanzapine and clozapine in a higher concentration in their plasma.

It is necessary to stress that many studies prove the influence of the gender factor not only on the efficacy of the therapy, but also on the tolerance, namely on the profile of side effects of antipsychotics. Nowadays researchers actively study a wide spectrum of neuroendocrine and metabolic disorders during the therapy with SGAs. These studies have shown the influence of the gender on the frequency of the development of different side effects.

The results of the studies held in the department of psychiatric endocrinology of Moscow Research Institute of Psychiatry in 2002 – 2007 showed that the frequency of NED during a long (18 months) monotherapy with SGAs (olanzapine, risperidone, clozapine, quetiapine, amisulpride) in women is significantly ($p<0.01$) higher than it is in men (43.6% and 18.2% respectively). The frequency analysis of NED during monotherapy with one

medication showed that women have NED statistically ($p<0.01$) more often during the treatment with all medications mentioned above, except for quetiapine. Men have NED with almost the same frequency during the therapy with risperidone, clozapine, quetiapine. Men have NED more often during the therapy with olanzapine (differences are not significant). During the therapy with amisulpride they have NED significantly ($p<0.01$) more rarely in comparison with patients who get clozapine, risperidone, quetiapine. Women have NED significantly ($p<0.01$) more rarely during the therapy with quetiapine (intergroup comparisons with a respect to the gender factor). Besides, women have a wider spectrum of clinical manifestations of NED in comparison with men [2, 15].

Now we know that NHP is a frequent and stable disorder that women of a reproductive age have in 48 – 93% of the cases and men have in 42-47% of the cases [59]. During the treatment with antipsychotics the level of PRL can increase by more than 10 times in comparison with the norm. 48 – 93% of women have menstrual disorder with galactorhea, or without it and decrease in libido. In case of men an increase in PRL is associated with a decrease in libido, impotence and sterility. At the same time the data regarding the connection of these clinical manifestations with the level of PRL and also the influence of gender on sexual disfunctions are still inconsistent.

Kleinberg D.L., Davis J.M., De Coster R. [60] showed in their study that risperidone causes dose-related increase in PRL in both genders, but the side effects associated with HP did not correlate with the level of this hormone. 10% of women who took risperidone had amenorrhea and galactorhea independently of the dose. Men had erectile and ejaculatory dysfunction only if they had high doses.

Gorobets L.N. [15] say that women with paranoid schizophrenia with continuous and episodic course with a growing defect significantly ($p<0.01$) more often have menstrual disorder and de-crease in libido independently of the medication. When the women are treated with a rescue antipsychotic therapy, they have menstrual disorders significantly ($p<0.01$) more often during the treatment with risperidone and amisulpride (65.2% and 61%, respectively). Women have a statistically significant ($p<0.01$) increase in the frequency and severeness of the decrease in libido during the therapy with risperidone, olanzapine, clozapine and haloperidol (56.2%, 56%, 52% and 72% respectively), and of galactorhea during the therapy with risperidone, amisulpride, haloperidol, and olanzapine (69.6%, 57.4%, 72% and 46,5% respectively). On the contrary, in case of men rescue antipsychotic therapy does not influence significantly sexual functions and the development of galactorhea. David S.R., Taylor C.C., Kinon B. J. et al. [61] also showed a more significant prolactogenic effect in women in comparison with men during the therapy with haloperidol, risperidone, and clozapine. On the contrary Basson B.R. et al. (2001) [62] think that men more often have neuroendocrine disorders, when they take antipsychotics, especially HP and sexual disfunctions. Grunder G. et al. [63] got similar results.

Most of the studies mentioned above demonstrate that clozapine and olanzapine are associated with more weight gain than other SGAs, and women have more often such significant side effects as a metabolic syndrome including increased visceral adiposity, hyperglycemia, hypertension and dislipidemy caused by SGAs. Some papers [15, 64] showed that gender, the initial body mass and the duration of the treatment are factors that influence the increase in BMI. Women are at a higher risk of weight gain than men, patients with initially low weight are also at a higher risk. The highest risk is for those who get the therapy for less than one year, than for those who are treated longer than this. The risk of the increase in BMI for women was also higher than for men during the treatment with risperidone [62]. So, most studies confirm that women can more easily than men have an increase in BMI during the treatment with SGAs.

However, Basson B.R. et al. [62] got opposite results in their study. They compared olanzapine with haloperidol and olanzapine with risperidone in two controlled double-blind trials. The authors made a conclusion that the gender had a significant influence on the increase in body mass, but only in those cases, when patients take olanzapine, and this

increase is higher for men than for women. It is interesting that patients who got the highest doses of the medication did not gain more weight than those who got low doses.

There is much less information regarding the gender differences in the development of dysthyroidism in mentally ill patients. Reiser L.W. [65] (1984) says that women have dysthyroidism caused by antipsychotics 7 times more often than men. Women notably have a dysfunction of the thyroid gland before they have the mental disorder, but men in most cases get it after the manifestation of the schizophrenic process. Gorobets L.N. [15] showed in his work that SGAs influence the functional state of hypothalamus-pituitary-thyroid axis at the central (hypothalamus-pituitary) as well as at the peripheral (pituitary-thyroid gland) levels. TRH-test shows the safety of the secretory reserve of the pituitary gland in women during the treatment with olanzapine and haloperidol and the suppression of the secretory function of the pituitary gland during the treatment with clozapine (in 75% of the cases) and quetiapine (in 33.3% of the cases).

Conclusions

Thus, the data regarding the role of gender factor in the efficacy and tolerance of the antipsychotics show that it is necessary to consider these parameters during antipsychotic therapy. It is also necessary to stress that the problem of tolerance is nowadays more relevant and significant in comparison with the efficacy of antipsychotics, because the intolerance, or poor tolerance are one of the most common reasons of not following the treatment program up to the full abandoning of it. All this clearly requires further comprehensive studies of this problem to clarify the role of the gender factor in pathobiologic mechanisms of schizophrenia and in the development of clinical, diagnostic and therapeutic indications for antipsychotic therapy, that include these parameters. The promising area for further studies is the creation of a big database of gender-related differences in pharmacokinetics and pharmacodynamics. Women require less antipsychotic medication than men to achieve a better symptom response, but this is at the expense of a higher side effect burden, in particular hormonal and metabolic side effects. In order to optimize outcome in women with psychosis, prescribers should ensure that gender differences are taken into account. For these reasons, there is a pressing need to intro-duce ‘gender-sensitive’ psychosocial therapy in order to improve both the monitoring and management of the physical health in patients with schizophrenia as a part of their overall care. Further studies in this area can help to systemize the information in order to create the therapeutic recommendations and algorithms to improve the quality of treatment of the patients with schizophrenia spectrum disorders.

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