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Consideration upon Antipsychotic Therapy in Women

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Most therapeutic guidelines do not dedicate a separate chapter to the peculiarities of antipsychotic therapy in women, despite a lot of fundamental (biological and genetic) data, as well as neuro-endocrinological, clinical and psychopharmacological data underlining the aforementioned etiological, pathogenic, clinical and prognostic peculiarities of antipsychotic therapy in women. According to data from literature, this approach based on gender differences can be an element for the background of a comprehensive view of the psychiatry, in all its fields, biological, psychological and social [1].

The different bio-psycho-social profile of each gender, and the way in which mental health disorders are clinically and therapeutically managed based on these differences could serve as a model for this complex picture of psychiatric approach, in which each of these three dimensions has its well determined role.

EPIDEMIOLOGICAL DATA AND CORRELATIONS WITH CLINICAL, BIOLOGICAL AND PHARMACOLOGICAL PARTICULARITIES FOR SCHIZOPHRENIC WOMEN

Epidemiologic studies show several aspects of female psychotic vulnerability:

- Classical studies considered the incidence and prevalence of schizophrenia as gender-neutral (equal at about 1% for both men and women). Studies during the last decade question this gender balance.
- Lewine (1984) [2] was the first researcher to hypothesize the existence of an increased incidence and prevalence in males. He assumed this discrepancy to be primarily due to a gender bias in diagnosis (skewed toward males).
- The meta-analysis by Ochoa et al (2012) [3] further suggested the clinical reality of a gender difference in incidence and prevalence. Aleman's meta-analysis (2003) had previously found an increased incidence in males (1.42 M to F ratio) while the prevalence was gender-neutral. It cannot be ignored that the risk of developing schizophrenia presents important gender differences [4].
- We hypothesize the differences in incidence may be related to the inherently greater vulnerability of males to neuro-developmental anomalies.
- Statistics confirm a younger age of onset for males (18-25 years of age) compared to females (25-35).
- The prodromal phase also sets in earlier in males (first symptoms around 22.5 years) compared to females (25.4 years). The mean delay between onset of symptoms and first inpatient admission is 6.3 years (28.2 years of age for males, 32.2 for females).
- Affective symptoms, depression and suicidal thoughts are more frequent in women, while negative symptoms are more prominent in males [5]. Depressive symptoms in schizophrenia are correlated with important neurobiological changes, which influence disease progression and prognosis:
- Diminished hippocampal volume, increasing the cognitive deficit;
- High cortisol – favors development of co-morbidities such as weight gain, diabetes mellitus, metabolic syndrome, cardiovascular disease and stroke;
- Diminished volume of amygdala – leading to disruptive behavior, hetero- and auto-aggressiveness including suicide. Lifetime suicide risk in schizophrenia is 10-15%, more frequent in men, but the gender disparity tends to disappear after menopause;
- Increased vulnerability of prefrontal cortex – leading to cognitive deterioration and social functioning issues.

Positive psychotic symptoms, as well as hetero- and auto-aggressiveness, increase in women in the pre-menstrual and menstrual periods [6]; the role of hormones is further emphasized by the risk of post-partum psychosis to present as debut of chronic schizophrenia. (1:1000) [7,8].

The risk factors for schizophrenia in women are:

- Family history of schizophrenia;
- Emotional and physical abuse in early life (childhood and adolescence);
- A history of premenstrual dysphoric syndrome;
- Structural brain abnormalities such as low volume of frontal cortex and large ventricles;
- Certain prenatal infections (immunology-detected high levels of antibodies) such as influenza, herpes zoster or toxoplasma gondii;
- Born in winter;
- Febrile seizures in the first year of life, with or without cerebral hypoxia, hypoperfusion, or hypoglycemia.

Risk factors for post-partum psychosis include high levels of stress, traumatic events and various physical conditions during pregnancy such as high blood pressure, anemia, (especially with iron deficit), diabetes mellitus, viral infections and interferon treatment. The onset is abrupt in 80% of cases, with acute symptomatology that could be recognizably assigned to ICD-10 criteria for psychotic illness, or it can have a subacute onset (20-25%), with prodromal signs and symptoms for at least the previous 2 weeks, e.g. hallucinations, delusions, loss of logical cohesion of thoughts, resistant insomnia, bulimia or anorexia with refusal of feeding, anxiety, psychomotor agitation, up to and including auto- and hetero-aggressiveness.

GENDER DIFFERENCES IN CLINICAL PSYCHO-PHARMACOLOGY OF ANTIPSYCHOTICS

Genetic studies have not shown a significant sex difference in the risk for developing schizophrenia (i.e., no gender bias in genetic vulnerability – [9]. Latest pharmaco-genomic studies have revealed, however, gender differences in response to antipsychotics and experience of adverse effects that could be genetically determined [10].

A. There is a different response to antipsychotics in males and females.

- This is significantly influenced by sex hormones themselves as well as neurotransmitters which may be affected by the sex hormones.
- Women achieve a higher plasma level than men after administration of a similar dose of antipsychotic. The therapeutic response is faster in women [11,12].

Some adverse effects are 50-75% more frequent in women, a valuable observation to keep in

mind when using strategies to increase treatment adherence, including social and psychological support [13]. Side effects of antipsychotic therapy are greater in women than men [14].

Sex differences in specific side effects associated with antipsychotic drugs:

- Prevalence of weight gain and metabolic syndrome has been reported to be higher in women than in men, but cardiovascular risk is higher in males [10] and increases in the female population after menopause. Metabolic syndrome may lead to vascular damage that could compromise cerebral function and structure, further compounded by diabetes, high blood pressure, dyslipidemia etc. Organic brain changes lead, in turn, to increasing cognitive deficit, social dysfunction and even antisocial behavior.

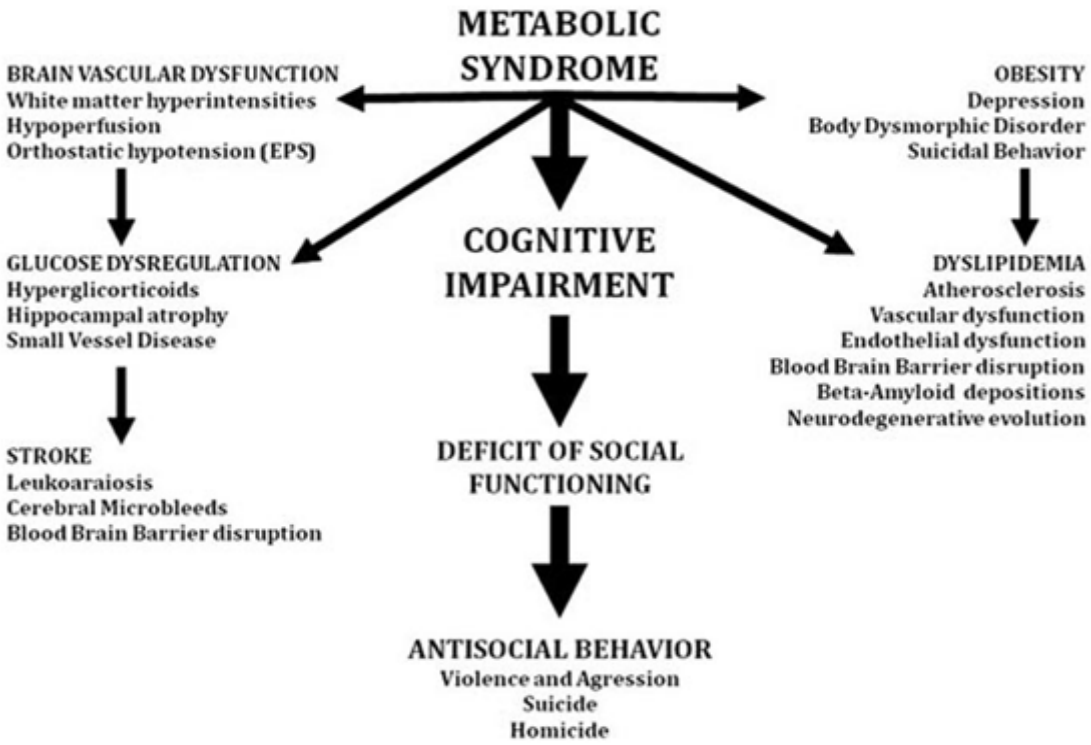

Figure 1: The multifaceted mechanisms of metabolic syndrome increasing cognitive deficit in women with schizophrenia.

Taking into consideration the risk of iatrogenic metabolic syndrome associated with pharmacotherapy of schizophrenia in women, we believe practicing clinicians should be well aware of the diagnostic criteria for metabolic syndrome, according to IDF (2014) – see table 1.

Table 1: IDF Criteria for Metabolic Syndrome.

According to the new IDF definition, for a person to be defined as having the metabolic syndrome they must have: Central obesity (defined as waist circumference* with ethnicity specific values) plus any two of the following four factors:	
Raised triglycerides	≥ 150 mg/dL (1.7 mmol/L) or specific treatment for this lipid abnormality
Reduced HDL cholesterol	< 40 mg/dL (1.03 mmol/L) in males < 50 mg/dL (1.29 mmol/L) in females or specific treatment for this lipid abnormality
Raised blood pressure	systolic BP ≥ 130 or diastolic BP ≥ 85 mm Hg or treatment of previously diagnosed hypertension
Raised fasting plasma glucose	(FPG) ≥ 100 mg/dL (5.6 mmol/L), or previously diagnosed type 2 diabetes If above 5.6 mmol/L or 100 mg/dL, OGTT is strongly recommended but is not necessary to define presence of the syndrome.

* If BMI is >30kg/m^2, central obesity can be assumed and waist circumference does not need to be measured.

- Antipsychotic-induced Hyperprolactinemia is more frequent in women and leads directly to galactorrhea (”false lactation”) but also to dysmenorrhea and amenorrhea, as well as osteoporosis - consequences of prolactin-induced hypogonadism [15,16].

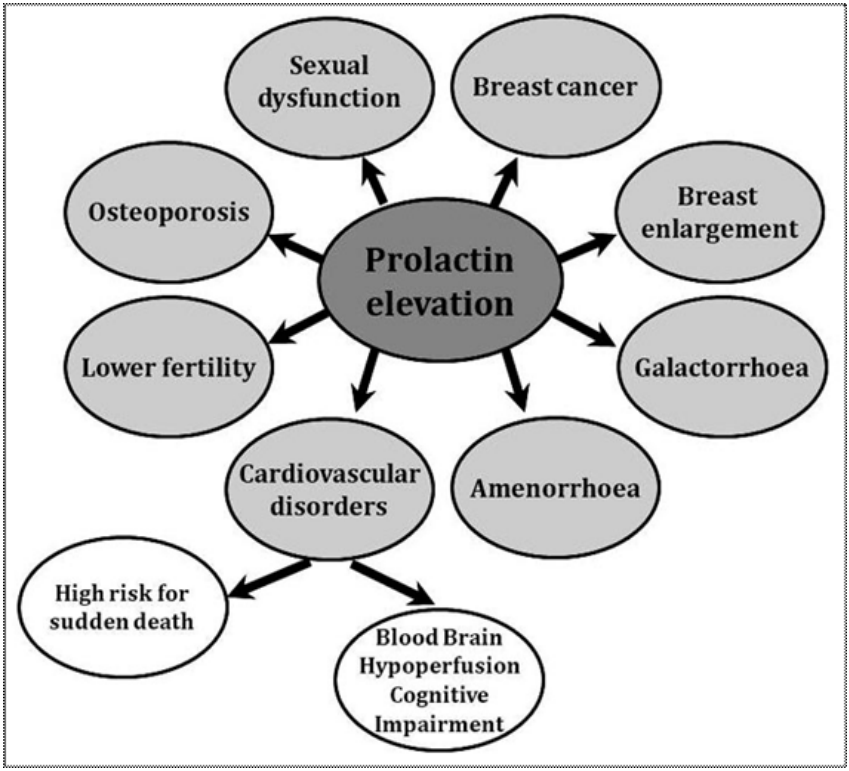

Figure 2: Adverse effects of prolactin elevation in women with schizophrenia (adapted after [17]).

Elevation of prolactin levels is correlated with the antipsychotics properties to block D2 receptors in the tubero-infundibular area. The intensity with which various antipsychotics do this is listed here:

- High (potential to elevate prolactin): haloperidol, ziprasidone, amisulpride;
- Medium: risperidone, paliperidone, sertindol, olanzapine;
- Minimal: quetiapine, aripiprazole, clozapine.

Taking into consideration women's increased vulnerability to these particular side-effects, strict monitoring of prolactin levels is recommended. A thorough assessment and differential diagnosis also needs to rule out other conditions that could lead to increased prolactin [18]:

- **Physiological:** Pregnancy, Breast-feeding, Stress (causes temporary increase in prolactin secretion), Physical activity: intensive effort (causes temporary increase in prolactin secretion), Sexual activity, Sleep (causes temporary increase in prolactin secretion)
- **Pathological:** Pituitary disorders, Prolactinomas, Mixed pituitary adenomas, Cushing's disease, Acromegaly, Not secreting adenomas, Empty sella syndrome, Pituitary stalk section or tumors, Lymphoid hypophysitis, CNS disorders, Tumors, Craniopharyngioma, Sarcoidosis, Spinal cord lesions, Granulomatous diseases, Vascular disorders, Autoimmune disorders, Hypothalamic tumors or metastasis, Cranial irradiation, Seizures, Systemic diseases, Severe hypothyroidism, Empathic cirrhosis, Chronic renal insufficiency, Polycystic ovary syndrome, Estrogen-secreting tumors, Pseudocyesis, Chest trauma following an operation, accident, herpes zoster (shingles), Stage immediately following an epileptic fit
- **Pharmacological:**

  Psychotropic drugs
- **D2 receptor antagonists:**

  First-generation antipsychotics, (Phenothiazines, Thioxanthenes, Butyrophenones);

  Second-generation antipsychotics (Paliperidone, Risperidone, Quetiapine, Olanzapine), Benzamides (amisulpride);

  Other dopamine (D2) antagonists (Amoxapine, Metoclopramide),
- Antidepressants

  Tricyclic – Amitriptyline, Desipramine, Clomipramine, Amoxapine;

  Tetracyclic;
- Mono-Amine Oxidase Inhibitors – Pargyline, Clorgyline;
- Selective Serotonin Reuptake Inhibitors – Paroxetine, citalopram and fluvoxamine).

Other drugs:

- Opiates and cocaine;
- Antihypertensives (Methyldopa, Verapamil, Reserpine, Labetalol);
- Gastrointestinal medication (D2 receptor antagonists – Metoclopramide, Domperidone, H2 receptor antagonists – Ranitidine, Cimetidine);
- Hormone preparations (Estrogens, Oral contraceptive pills, Antiandrogens);
- Protease inhibitors;
- Benzodiazepines (occasionally – Alprazolam)
- Fenfluramine
- Alcohol

NB. Prolactin increases were not routinely observed with the long-term use of nefazodone, bupropion or trazodone.

When considering schizophrenia treatment in women, pharmacological decisions are made on an individual basis, taking into account response and tolerability; it is, however, recommended to try and avoid antipsychotics with high prolactin-inducing potential whenever possible. This aspect also needs to be thoughtfully weighed in cases requiring a polypharmacy approach.

Risk of Motor Side Effects and EPS (Extra-Pyramidal Symptoms)

- Dystonic reactions are more frequent in young males.
- Akathisia is also more frequent in young males [19]
- Tardive Dyskinesia **(TD)** – it is commonly held that risk of developing TD with prolonged exposure to antipsychotics may be bigger in elderly women (compared to men over 65), while in younger age groups, men may still be at a higher risk [20,21].
- Medication-induced Parkinsonism presents no gender difference [22]

Hematological side effects - Women are at higher risk for:

- Leucopenia and/or agranulocytosis in the context of polypharmacy with antipsychotics (clozapine) and mood stabilizers (valproic acid, carbamazepine);
- Thrombo-embolism consecutively to treatment with sedative antipsychotics and oral contraceptives, favored by decreased mobility and physical activity, dehydration [23]

There are certain side effects of antipsychotics that may alter the patient's body image, self-esteem and perceived attractiveness, occasionally severe enough to lead to depressive episodes:

- Weight gain;
- Acne and other skin-related side effects (e.g., hyperpigmentation);
- Hirsutism or excessive hair growth (face and body);
- Hair loss;
- Alterations in gait gaze or voice;
- Prolactin-related side effects (mentioned earlier);
- Sexual dysfunction (lack of desire).

GENDER DIFFERENCES IN NEUROBIOLOGY OF SCHIZOPHRENIA

There are several structural differences between the healthy male and female brain that are maintained during the course of schizophrenia, which may partly correlate with gender differences in clinical presentation:

- Amygdala is bigger in males;
- Fronto-medial cortex is bigger in males;
- Hypothalamic dimorphism;
- Inverse correlation between testosterone levels and neuroprotective abilities;
- Historically, males are considered to have a lower vulnerability to psychological trauma;
- Hypothalamic – Pituitary – Adrenal **(APA)** axis has a lower activity in males compared to females.

In turn, females have larger:

- Hippocampus;
- Corpus callosum;
- Para-limbic and orbito-frontal areas;
- Neuroprotection abilities, positively correlated with estrogen levels;
- Vulnerability to psychological trauma;
- Hyperactive HPA axis.

Hyperactivity of HPA axis is influenced by vulnerability to acute and chronic social stress may lead to different models for women and men in dependence with primary and secondary vulnerability to stress [24].

MALE		FEMALE
	PRIMARY VULNERABILITY OF STRESS	
• Increased risks of neurodevelopmental disorders and brain abnormalities • Neurological vulnerability • Hypoxic encephalopathy	**PRE- AND PERINATAL PERIOD**	• Increased level of cortisol • Hippocampal vulnerability • Cognitive dysfunction • Cognitive and somatic vulnerability
	SECONDARY VULNERABILITY OF STRESS	
• Autist spectrum disorder • ADHD • Addiction • Cloninger I alcoholism • Aggressive behavior • Early onset psychosis / Schizophrenia • EPS	**ADOLESCENCE**	• Depression • Anxiety • Suicidal thoughts and behavior • Early atypical depression • Body dysmorphic disorder • Metabolic syndrome
• Schizophrenia > Depression • Dual pathology • Antisocial behavior	**ADULTS**	• Depression > Schizophrenia • Dual pathology • Pregnancy • Suicidal thoughts
• Affective disorders > Schizophrenia • Parkinson Disease	**AGING**	• Tardive schizophrenia • Alzheimer's Disease • Lewy bodies dementia

Figure 3: Gender Differences and Stress across the Lifespan of Individuals with Schizophrenia [24].

Diminished neuroprotection as an effect of menopause increased the excitatory effect of glutamatergic activity and apoptotic risk, leading to greater prefrontal cortex grey matter loss in women. Functional connectivity is significantly more reduced in women with chronic schizophrenia, associated with the reduction of the power of Gamma synchronicity, EEG marker which usually increases in women with schizophrenia during menstrual period. High power of Gamma synchronicity is an indicator of a more pronounced cognitive impairment [25].

ROLE OF ESTROGEN IN THE CLINICAL NEUROBIOLOGY OF WOMEN WITH SCHIZOPHRENIA

Estrogen – Neurotransmitters Connections

- Estrogen deprivation in primates [26] for 30 days leads to a 30% loss in the dopaminergic cells of substantia nigra [27].
- In castrated female rats (oophorectomy), substitution therapy with exogenous estrogens leads to recovery of dopaminergic transmission in the striatum [28].
- Estrogens' neuroprotective effect has also been shown in the PD animal model [29].
- In humans, the level of D2 receptors in the frontal cortex and basal ganglia decreases with age, more so in women than in men [30].
- Estrogens may reduce the dopaminergic-mediated cognitive decline [31].

Fluctuations in Estrogen-Mediated Neuroprotection and the Vulnerability to Antipsychotic-Induced Extra-Pyramidal Symptoms (EPS) and Cognitive Decline

It is well known that psychotic symptomatology may vary with the menstrual cycle in some patients, as estrogens may sometimes attenuate psychotic symptoms. A decrease in estrogens leads to increased serotoninergic and cholinergic transmission, while major estrogen deficit may occasionally lead to psychotic symptoms (with or without significant cholinergic input). Consequently, high serotonin levels in post-menopausal women (especially in cases with more dramatic menopause onset and associated symptoms, e.g. 'hot flashes' etc.) increase the risk of developing serotonin syndrome when SSRI are added for depressive symptoms [32].

Mechanisms Underlying Serotoninergic Hyperactivity Caused By Estrogen Deficit

The experimental pharmacological model is very similar to psychosis induced by MDMA (3,4-methylenediox-N-methylamphetamine or "Ecstasy"):

- Central hyperactivity of serotoninergic neurons;
- Block of serotonin transporters (increasing neurotransmitter availability);
- Long-term neurotoxic effects via down regulation and selective synaptic pruning of serotoninergic neurons, which lose more and more connections;
- Ultimately, degeneration of serotoninergic neurons.

This is especially important to consider in order understanding how the co-morbidity of schizophrenia and MDMA (Ecstasy) addiction compromises cortical integrity.

The Serotoninergic Hyperactivity Caused By Estrogen Deficit Has Important Pharmacological Consequences:

- First-generation antipsychotics ('neuroleptics') may paradoxically exacerbate psychotic phenomena;
- Treatment with SSRIs, as well as some second-generation ('atypical') antipsychotics that interfere with serotonin transporters (ziprasidone), may also induce or exacerbate psychotic symptoms;
- Therapeutic response is obtained with serotonergic second-generation ('atypical') antipsychotics (quetiapine, loxapine).

The phenomenon of "serotoninergic disconnection' may adversely affect cognitive abilities, while excess serotonin, or rapid fluctuations in serotonin levels, may lead to psychomotor agitation, anxiety and aggressiveness.

Risk Factors for Psychomotor Agitation and Aggressiveness in Women

- A history of premenstrual dysphoric syndrome, which may exacerbate psychotic symptoms and antisocial behavior;
- A history of childhood abuse (emotional, physical or and/or sexual);
- Birth trauma associated with hypoxia and hypoxic encephalopathy;
- Vulnerability of orbito-frontal cortex, further increased by therapy with haloperidol (and possibly other first-generation antipsychotics).

Aggressive behavior (to self and/or others) at onset of schizophrenia is usually an argument for long-term antipsychotic use and is associated with a higher incidence of depot use.

The Cholinergic Hyperactivity Caused By Estrogen Deficit Also Presents Important Pharmacological Consequences

- There is both central and peripheral cholinergic hyperactivity, as muscarinic as well as nicotinic receptors are over-stimulated;
- Psychopathologically, the cholinergic syndrome is characterized by psychomotor agitation, psychosis, confusion, seizures, and – untreated - coma;
- There is an important autonomous imbalance with deregulation of the sympathetic - parasympathetic physiological equilibrium, which is especially dramatic in the cardiovascular system (tachycardia or bradycardia, labile blood pressure with hypo- or hypertension, cardiac arrhythmia);
- The aforementioned imbalance amplifies the risk of sudden death in the context of antidepressant and/or antipsychotic medication.

N.B. An abrupt discontinuation or 'therapeutic switch' of a psychoactive substance that has muscarinic receptor-blocker properties may lead to a cholinergic syndrome, with important CNS (central nervous system) hyperactivity.

It is important to keep in mind that women also present a greater risk to have congenital QT interval prolongation; as such, they have a greater propensity toward cardiac arrhythmias in the context of antipsychotic and/or antidepressant medications that prolong the QT interval (e.g. quetiapine, citalopram, most tricyclic antidepressants). This becomes especially problematic when associated with electrolyte imbalances (e.g. hypomagnesaemia, hypocalcaemia, hypokalemia) and/or autonomic instability, leading to torsade's des pointes and sudden death.

DRUG INTERACTIONS

- Women have a higher risk of co-morbidities and a higher risk of clinically significant drug interactions.
- The increased vulnerability to drug interactions is partly linked to the female predisposition toward certain aspects of liver metabolism, such as a dysfunctional P450 enzyme within cytochrome CYP2D6, with consequences on antipsychotics clearance, plasma level, and clinical response.
- Smoking and oral contraceptives increase the risk of thrombo-embolism, partly by interfering with the P450 CYP1A2 system.
- Antipsychotics devoid of major interference with the dopaminergic D2 receptors may be a preferred alternative for schizophrenia treatment in women.
- Depot antipsychotics usually have less side effects of this type compared to oral medication.

Despite a lack of consensus within the neuroscientific and neuropsychiatric communities about the practical role of gender differences in therapeutic approach of schizophrenia, it is commonly held that women present less severe forms of the illness, but with more frequent depressive symptoms than men. Social impact of schizophrenia in women is more powerful because of the stronger influence on family life, through women social role, while pregnancy and motherhood in women with poorly controlled chronic schizophrenia presents difficult ethical issues and choices.

Although antipsychotic prescribing guidelines do not commonly differentiate between men and women [33], we share the view of many other clinicians that the patients gender needs to be stronger considered in order achieving optimal prescribing of antipsychotics.

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