

## GENDER, PSYCHOSIS AND PSYCHOTROPIC DRUGS: DIFFERENCES AND SIMILARITIES

Urban Groleger & Virginija Novak-Grubič

University Psychiatric Hospital, Studenec 48, 1260 Ljubljana, Slovenia

### SUMMARY

*Acute psychosis is diagnosed by clearly defined operational criteria embedded into international classification systems. Many studies have tried to determine the role of gender in psychosis but mainly in terms of epidemiology and course of illness, most often schizophrenia. There are however also important gender-specific differences in clinical symptoms of acute psychosis. No guidelines or treatment recommendations suggest gender as an important factor in the choice of antipsychotic treatment, which is true for all treatment modalities (antipsychotic, dose, duration). We will review shortly available literature and present some of our own research data on gender differences in clinical presentations of acute psychosis. When the diagnosis of an illness depends almost entirely on symptoms and their presentations as in the case of acute psychosis, important gender specific differences might challenge the diagnostic process as well as treatment choice and course of psychosis. Our as well as other data confirm that acute psychosis manifest itself differently in males and females. To define further the impact of observed differences we need further research into gender specific clinical and not just epidemiological variables.*

**Key words:** psychosis – gender – symptoms - antipsychotics

\* \* \* \* \*

### INTRODUCTION

Psychosis regardless of its nosological entity (e.g. schizophrenia, delusional disorder, organic psychosis) or phase (e.g. acute, chronic) is diagnosed in the same way using the same criteria in males and females. Gender appears in various forms in connection to psychosis: (1) an epidemiological variable (e.g. male/female ratio in incidence or prevalence), (2) age of onset (e.g. in schizophrenia or mood disorders), (3) etiological factor (e.g. postpartum psychosis), (4) help-seeking behavior (e.g. in suicide prevention strategies), (5) social support or social systems (e.g. deficit syndrome in schizophrenia) or (6) special issues (e.g. pregnancy, birth, breast-feeding, menopause, motherhood) to mention only some of frequently addressed issues in research or publications. There are however other issues that influence clinical work with patients with acute psychosis, for example presentations of symptoms of acute psychosis that in our opinion influence various domains of clinical and therapeutic work with acutely psychotic patients and are related to gender differences. Since men and women are different in many biological, psychological, sociological and functional characteristics it seems logical to believe that illness which deeply changes many of these domains should express itself differently in both sexes. The article intends to summarize some international literature on gender differences in psychosis, mainly schizophrenia, especially in its acute forms. In addition the authors present local research data as well as parts of clinical cases on the issue of differences in symptoms, aggressive behavior as well as therapeutic response to antipsychotic medication. The aim of the article is to stress gender as clinically important topic in different

stages of treatment and care for the patients with psychosis.

### GENDER AND PSYCHOSIS – CASE VIGNETTES

We are presenting case vignettes from two acutely psychotic patients to illustrate differences in clinical symptoms (subjective) as well as their description by treating psychiatrist (objective).

**Case 1.** 28 years old female, hospitalized for the first time in acute psychiatric ward due to acute psychosis. Before admission she was reported to the police for harassment from a famous male singer that she frequently wrote to, spent nights in front of his house, followed him to clubs and concerts and at the end contacted his wife and threatened her revealing alleged intimate relationship with him. She was reported missing after a visit from the police at her home. She was found on the street without documents and due to odd behavior brought for a psychiatric evaluation. At admission she reported auditory hallucinations, erotic and paranoid delusions and thoughts broadcasting as well as thoughts inserting. She was excited, agitated and anxious. She denied any problems and both verbally and physically opposed to admission to the hospital. She changed in behavior half a year before admission when she ended partnership due to “a new boyfriend”. She frequently spoke about him to her parents but they never saw him and were not able to get to know any personal information about him. During this time she was seeking job after finishing university degree, but her functioning was low, everything was about her appearance and music, she spent a lot of money for

concerts and dresses. She lived with her mother, her father moved away and divorced a year ago.

*Psychiatric status:* Conscious, oriented, active in interview, spontaneous in speech and attitude, tense, frightened, becoming agitated during interview, describing auditory hallucinations, thoughts broadcasting of a nice and inviting content, flattened affect, erotic and paranoid delusions without any formal thought disorder, deny suicidal or aggressive thoughts, opposing hospitalization without insight into problems, complications or events leading to psychiatric interview.

**Case 2.** 28 years old male, hospitalized for the first time in acute psychiatric ward due to acute psychosis. He actively came for help due to auditory hallucinations that lasted for four days. Voices direct him, talk about him and wanted him to attack other people. These words are “evil” and related to feelings of burning in the chest. He was afraid to lose control over him but never thought about suicide. He didn’t eat or sleep. He thought to be connected with an unknown force that manipulates with him, maybe because of bad things he allegedly did in the past. He was not able to work, his concentration was poor, and he could not focus on work. He lives alone, regularly employed as a traffic engineer at a railway company. He agreed to hospitalization. Before described changes in perception, thoughts and behavior no changes were noticed. He is single now for two years, before he had several brief heterosexual relationships.

*Psychiatric status:* Conscious, oriented, active in interview, taciturn, somewhat tense, quite, with psychomotor retardation, hypomimic, occasionally frightened, auditory hallucinations with imperative content, paranoid delusions, intrusive thoughts, thought eco, depressive mood, affect is lowered, without suicidal ideation or intent, confirms aggressive thoughts with insight and behavioral control, wishes to be admitted.

**Case comments.** Both patients were diagnosed with acute schizophrenia like psychosis (first-episode psychosis). In both patients no family data suggested psychotic or mood disorders’ loading. There was no alcohol or drug abuse in either of both patients. Psychotic episode was shorter in male (one month) than in female patient (2 and a half months). Both were treated with antipsychotic in monotherapy, female with olanzapin 20 mg daily and male with amisulpride 800 mg daily. Both patients fulfill criteria for acute psychotic disorder, both have psychopathological symptoms in various domains of behavior, mood, thought form and content, will, social activities and function as well as impulses. There is however difference in the “color” of mood and thoughts, behavior and impact on functioning as well as regulation of impulse control, and insight. According to two cases it seems that psychosis in male patient impacted more internal brain and psychological

functions (mood, social activities) and in female patient more external (behavior, impulse control).

We cannot generalize observed differences following two short cases. There is however a notion that there is more to the content of psychosis in terms of gender than just diagnostic criteria. Our question is whether these differences could impact the choice of antipsychotic medications as well as psychotic episode outcome.

## GENDER AND PSYCHOSIS – LITERATURE REVIEW

It is surprising that given the clinical heterogeneity in psychotic disorders, the majority of data concerning gender exists for schizophrenia. One of the challenging statements suggests that schizophrenia equally affects both gender (lifetime risk) but other epidemiological data found prevalence male/female ratio from 1.4 (McGrath, 2007) to 2 (Myles-Worsley et al, 1999) across the world. Systematic review from Saha and colleagues (2005) did not confirm these alleged differences. There is however strong evidence that onset of schizophrenia in men precedes that in women by 3.5 – 6 years (Riecher-Rossler and Hafner, 2000). Given the data of equal lifetime prevalence we therefore might expect a raise in incidence later in life in females. Howard and coworkers (2000) have indeed found that a subgroup of patients with late onset of schizophrenia (after 45 years of age) is composed mainly of women. Rosenthal (1970) have reviewed epidemiological data from United States on first admissions for schizophrenia and calculated proportions of males and females by age. At the age of 25 years 70% were males and 30% females, at the age of 35 years the proportion was equal, at the age of 50 years the proportion reversed to 2-3 female for every male (Rosenthal 1970).

The data on the later onset of psychosis in women and data on lower social functioning, education and occupational level in men compared to woman have been interpreted in many ways mainly in terms of time difference in both gender to build-up proper social network and to achieve higher level of education and occupation, including family (partners and children). Earlier onset of illness for males is supposed to contribute to more negative and non-affective symptoms and poorer outcome (Preston et al. 2002).

Thorup and coworkers (2008) have investigated these differences in a group of 578 young adults with first-episode schizophrenia spectrum disorder. They found no differences in age at first-onset of symptoms, age at first contact and duration of untreated psychosis. Men had more severe negative symptoms, poorer premorbid functioning and poorer social networks, were more often unemployed, lived alone and were more often substance abusers. Women had more hallucinations and lower self-esteem. Women also made more suicide attempts. On the other hand woman

showed significantly better social functioning. The authors concluded that differences in psychosis by gender couldn't be explained by older age of onset for women.

Tang and colleagues (2007) reported on gender differences in 542 Chinese inpatients with schizophrenia. Men had an earlier onset (lower age than 45), they had less paranoid schizophrenia, they required higher medication daily doses, they were prescribed with less atypical antipsychotics, they were more likely to be smokers, and more likely to be single. Women, on the other hand were more likely to have persistent positive symptoms, had more severe positive and affective symptoms, and more frequently attempted suicide. The authors concluded with the notion that observed gender differences should be considered in the assessment and management of patients with schizophrenia.

Preston and coworkers (2002) investigated 38 male and 20 female patients with schizophrenia on gender related differences and found significantly poorer premorbid adjustment at the late adolescent stage and higher level of negative symptoms in males compared to females.

Muller (2007) gathered clinical routine structured data on 119 inpatients with acute episode of schizophrenia and analyzed gender-specific relationships of depression with other psychopathological and clinical variables. Mean depression and PANSS scores were not statistically different in both sexes. However in women high scores of depression were associated with higher negative symptom scores and younger age whereas in men depression correlated with positive symptoms and short hospitalization.

Reeves and colleagues (2002) found more involuntary hospitalization and more patients lost to follow-up in males with late-onset schizophrenia (over the age of 60 years) than in females.

Pruessner and coworkers (2008) investigated HPA axis regulation in men and women with recent onset psychosis compared to healthy controls. Measuring cortisol response to awakening the authors found significantly blunted cortisol response in psychotic males compared to females but no differences between psychotic group and healthy controls. HPA axis dysregulation was proposed by the authors to be related with observed unfavorable course of psychosis in men.

Szymanski and coworkers (1995) found higher HVA and prolactin levels in women with psychosis, which was correlated with better treatment response than in men. Comparing both patients with acute and chronic schizophrenia authors found the same and stable gender differences at the beginning and later on in the course of the illness.

Krakowski and Czobor (2004) reported on gender differences in suicide and violence in patients with psychiatric disorders. In spite of different diagnostic

profile of men and women included in the study no overall differences in aggressive and violent behaviors were noted. Women demonstrated more aggression at the beginning of the hospitalization and were more often suicidal. Men on the other hand experienced more academic and substance abuse problems.

Among 665 acute psychiatric inpatients studied in our centre in Slovenia (Tavcar et al, 2005), 139 were subject to physical measures against their will (FVU), majority were men (61.8%). Confusion and police involvement were main reasons for measures in men, and suicidality and non-compliance in women.

Hafner and colleagues (1998) reported on clinical symptoms in schizophrenia patients by gender. In women, they found more restlessness, anxiety and depression related symptoms with preserved adaptability (and function even with pronounced acute illness). In men, they found more neglect, withdrawal, loss of interests and substance abuse with lower functioning and early loss of functioning even in milder forms of acute psychosis. According to the authors, gender differences are not stable in the course of schizophrenia but change differently in men and women. They also found developmental gender differences in boys and girls who would later on develop schizophrenia in terms of more externalization in males and internalizations in females. Authors' conclusions were that these differences influence expression of emotions and affect as well as emotional content as well as expression of other psychotic symptoms.

Recently, Cotton and coworkers (2009) published data on 661 first-episode psychosis patients. In their sample females were more likely to have a history of suicide attempts and depression. Males were more likely to have substance abuse problems, more severe psychopathology, and lower levels of functioning as well as poorer compliance with treatment. The authors did not report on the treatments used in their sample.

## **GENDER AND PSYCHOSIS – OUR RESEARCH DATA**

We present partial data from two prospective one-month studies conducted in Psychiatric intensive care unit of University Psychiatric Clinic in Ljubljana, Slovenia in 1999 (n=198) and 2006 (n=161) (unpublished data). We included samples of all patients admitted to acute psychiatric ward in two one-month periods. We present data from part of used measures (CGI, GAS, BPRS and PANSS) as well as dosages of antipsychotics used in CPZ mg daily equivalents to treat patients with acute psychosis regardless of its nosological entity. The purpose of presented data is to illustrate the existence of gender differences in acute psychosis. The data have been presented in international meetings and will be published as the whole data set elsewhere.

In both samples the male/female ratio was 1.15. We found no differences in CGI or GAS at admission and at discharge from the acute ward. However we were able to confirm more deficit symptoms in males (BPRS-deficit subscale, 4.9 vs. 3.3 in females;  $p=0.000$ ) as well as higher score on BPRS-schizophrenia subscale (22.2 vs. 18.3 in females;  $p=0.043$ ). On the other hand higher score on BPRS-anxiety depression subscale (7.3 vs. 6.1 in males;  $p=0.011$ ) was found in females with acute psychosis. PANSS was done in 41 males and 51 females with acute psychosis. Four items were significantly more pronounced in women: suspiciousness, grandiosity, hostility and impulse control disturbances. Men with acute psychosis scored significantly higher on items of blunted affect, emotional withdrawal, poor rapport, social withdrawal, difficulty in abstract thinking, stereotyped thinking, mannerism, poor attention, disturbances of volition, preoccupation and active social avoidance. In summary, females in our sample scored higher in positive and behavioral symptoms but males in negative, cognitive symptoms and functional decline measured by PANSS.

We were also able to confirm differences in dosages of antipsychotics used to treat psychosis in our sample. Males received higher doses of antipsychotics (1096 vs. 882 cpz mg equivalent daily), higher doses of FGAs (1736 vs. 371 cpz mg equivalent daily) and lower doses of SGAs (340 vs. 691 cpz mg equivalent daily) but the differences were not statistically significant due to large variability of doses used and relatively small samples.

## DISCUSSION

We were able to link literature review data, our clinical case vignettes as well as our own research data to suggest that the gender might play an important role in the management of acute psychosis. The level of evidence is however still low and sometimes conflicting due to different methodologies, samples and the use of term "acute psychosis". The most solid evidence on gender differences (Tang et al. 2007, Thorup et al. 2008, Muller 2007, Haffner et al. 1998, Cotton et al. 2009) agree on different clinical presentations of acute psychosis, premorbid adaptation, functioning and to a minor extent treatment differences (Tang et al. 2007). Our own data confirm reports on significant differences in clinical symptoms of acute psychosis in males and females. In females mood symptoms (depression and anxiety) were observed more often which contrasts deficit and cognitive symptoms in males with acute psychosis. Functioning is disrupted in males sooner and to a greater extent. More positive symptoms have been confirmed in females along with more impulsivity, suicidal and aggressive behavior. On the other hand psychoactive substance abuse and poorer compliance have been confirmed in males. Clinical symptoms and related behaviors are most often leading clues to the choice of antipsychotics. There is however very few objective evidence on the impact of these variables on

the choice of treatment. Recent meta-analysis of Leucht and coworkers (2009) suggests different subgroups of psychotic patients matching different antipsychotics as first-choice treatment. However gender has not been included as a discriminatory variable.

Gender is a complex variable that includes all aspects of brain activities, psychological functioning, and social network, development, roles and learned behaviors and is difficult to interpret in terms of research. In plethora of psychotic symptoms each one of them could be different in males or females. We suggest that these differences might be attributed to the effect of gender and might be relatively uniformly distributed in both genders in acute psychosis.

The presented evidence suggest that management of acute psychosis might be gender-specific, which should influence both diagnostic criteria as well as treatment in all its modalities (choice of antipsychotics, side-effect profile and doses used).

## CONCLUSIONS

Acute psychosis can differ substantially in various domains and symptom presentations in males and females. Using different approaches (case analysis, review of publications and our own data) similar differences in symptoms have been confirmed. In males more negative, cognitive and functional symptoms dominate in clinical presentation of acute psychosis whereas in females more positive, emotional and affective as well as impulse control, behavioral and suicidal symptoms dominate. The differences in psychosis do not exist only in symptoms but are prominent throughout the course of psychotic, mainly schizophrenia spectrum illness. The presented data urge to more research in the topic of gender differences, types of psychosis and gender-specific use of antipsychotics.

## REFERENCES

1. Cotton SM, Lambert M, Schimmelmann BG, et al. Gender differences in premorbid, entry, treatment, and outcome characteristics in a treated epidemiological sample of 661 patients with first episode psychosis. *Schizophr Res*, 2009; 114: 17-24.
2. Hafner H, an der Heiden W, Behrens S, et al. Causes and consequences of the gender difference in age at onset of schizophrenia. *Schizophr Bull*, 1998; 24: 99-113.
3. Howard R, Rabins PV, Seeman MV, et al. Late-onset schizophrenia and very-late-onset schizophrenia-like psychosis: an international consensus. *Am J Psychiatry*, 2000; 157: 172-8.
4. Krakowski M, Czobor P. Suicide and violence in patients with major psychiatric disorders. *J Psychiatr Pract*, 2004; 10: 233-8.
5. Leucht S, Corves C, Arbter D, et al. Second-generation versus first-generation antipsychotic drugs for schizophrenia: a meta-analysis. *Lancet*, 2009; 373: 31-41.

6. McGrath JJ. The surprisingly rich contours of schizophrenia epidemiology. *Arch Gen Psychiatry*, 2007; 64: 14-6.
7. Muller MJ. Gender-specific associations of depression with positive and negative symptoms in acute schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry*, 2007; 31: 1095-100.
8. Myles-Worsley M, Coon H, Tiobech J, et al. Genetic epidemiological study of schizophrenia in Palau, Micronesia: prevalence and familiarity. *Am J Med Genet*, 1999; 88: 4-10.
9. Preston NJ, Orr KG, Date R, et al. Gender differences in premorbid adjustment of patients with first-episode psychosis. *Schizophr Res*, 2002; 55: 285-90.
10. Pruessner M, Boekestyn L, Bechara-Evans L, et al. Sex differences in the cortisol response to awakening in recent onset psychosis. *Psychoneuroendocrinology*, 2008; 33:1151-4.
11. Reeves S, Stewart R, Howard R. Service contact and psychopathology in very-late-onset schizophrenia-like psychosis: the effects of gender and ethnicity. *Int J Geriatr Psychiatry*, 2002; 17: 473-9.
12. Riecher-Rossler A, Hafner H. Gender aspects in schizophrenia: bridging the border between social and biological psychiatry. *Acta Psychiatr Scand*, 2000; 102(Suppl 407): 58-62.
13. Rosenthal D. *Genetic theory and abnormal behavior*. New York: McGraw-Hill, 1970.
14. Saha S, Chant D, Welham J, et al. A systematic review of the prevalence of schizophrenia. *PLoS Med*, 2005; 2(5): 0413-0433.
15. Szymanski S, Lieberman JA, Alvir JM, et al. Gender differences in onset of illness, treatment response, course, and biological indexes in first-episode schizophrenia patients. *Am J Psychiatry*, 1995; 152: 698-703.
16. Tang YL, Gillespie CF, Epstein MP, et al. Gender differences in 542 Chinese inpatients with schizophrenia. *Schizophr Res*, 2007; 97: 88-96.
17. Tavcar R, Dernovsek MZ, Grubic VN. Use of coercive measures in psychiatric intensive care unit in Slovenia. *Psychiatr Serv*, 2005; 56: 491-2.
18. Thorup A, Petersen L, Jeppesen P, et al. Gender differences in young adults with first-episode schizophrenia spectrum disorders at baseline in the Danish OPUS study. *J Nerv Ment Dis*, 2007; 195(5): 396-405.

Correspondence:

Urban Groleger, M.D., MSc  
University Psychiatric Clinic  
Studenec 48, 1260 Ljubljana  
E-mail: urban.groleger@psih-klinika.si