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REVIEW ARTICLE

# Does Gender Influence Outcome in Schizophrenia?

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## Abstract

Good outcome of schizophrenia has several meanings and most of these meanings carry both positive and negative undertones depending on perspective. Currently, a person's subjective sense that illness has been partly overcome and that life is meaningful has come to be viewed as the most valid signpost of a good outcome. A review of the literature shows that women have certain advantages over men in that their illness starts at a later age and that their symptoms respond more quickly and more completely to available treatments. These advantages serve women well at the outset of illness but benefits appear to dissipate over time. Gender differences in outcome thus vary depending on the age of the patient. They also vary with the social and cultural background of the study population. Neither sex, therefore, has a monopoly on good outcome. The hope is that studying gender differences will uncover critical elements of good outcome that lead to interventions that will benefit both women and men.

**Keywords** Schizophrenia · Outcome · Gender · Recovery · Response · Side effects

## Introduction

The answer to the question posed in the title of this article will vary depending on the meaning assigned to the term, 'outcome'. The concept of schizophrenia outcome has changed over the years. In the nineteenth century, when persons with psychotic illness spent whole lives in hospital, a 'good' outcome meant easy adaptation to institutional rules and routines. The therapeutic goal for schizophrenia patients was to achieve a state of calm and be able to work in a minor capacity within the institution [1]. Psychotic symptoms were not specifically targeted. The therapeutically challenging symptoms at that time were agitation, excitement, and aggression, and these were

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treated with a variety of sedatives and hydrotherapies [2]. As newer treatments emerged in the first half of the twentieth century – fever therapy [3], shock treatments [4], lobotomy [5], their merits were judged on the basis of two main factors: how rapidly and for how long they could calm agitated behavior. Lobotomies won this competition; this surgery was able, for the first time, to allow large numbers of patients to leave the asylum and return to live at home. Discharge from the institution became the standard definition of good outcome [6].

Once drugs that addressed specific psychotic symptoms were made available in the 1950s and psychiatric hospitals monumentally emptied, the definition of good outcome changed again. Rather than whether or not you were discharged home, the outcome criteria became: how short or long was your stay in hospital? Once out, how long before you were re-admitted [7]?

It was only with the advent of the Brief Psychiatric Rating Scale (BPRS) [8] in the early 1960s that a reduction in psychotic symptom became the gold standard for evaluating outcome. This is still the case today, although many other end points, beyond symptoms, are now also considered.

With patients no longer living in hospitals, consideration is now given to how well they are able to navigate life in the community. What is the quality of their housing? Are they gainfully employed? What is the extent of their social network? Do they have a family life? Are they abusing cigarettes, alcohol, or drugs? Are they in trouble with the law? Are they in good physical health? Are they adherent to their treatment regimens? Are they depressed or suicidal? Answers to these questions all contribute to the global current concept of outcome.

When taken individually, many measures of outcome have a mixed valence. They can be seen as good or bad depending on one's perspective. The old measure of calm and obedience, for instance, was seen as good from the standpoint of hospital nursing staff but would nowadays be critically appraised as passivity, counterproductive to life in the community. Working for the hospital was good from the perspective of the hospital's economy but is questionable from a human rights viewpoint, given that it was unpaid labor. Discharge from asylum to home was good in many ways but many patients were unhappy - they lost their social circle and familiar routines to be abruptly exposed to a very competitive and cruel world.

Current measures of outcome have similar good and bad facets. The removal of frightening delusions by antipsychotic medication is an excellent achievement but there are delusions, such as the false conviction of being loved or protected, which, when removed, lead to severe distress. So, too, faithful adherence to doctors' prescriptions is a wished-for goal, which may, in some instances, result in severe adverse drug effects. Substance use is unfortunate but may, for some, enhance friendship and social support. Depression and physical health problems, while both painful and stressful, may lead to increased attention and care, which, in the end, can prove beneficial. A global measure that balances positive and negative components of outcome and is subjectively evaluated by the patient has more recently been developed and is variously referred to as 'quality of life' or 'recovery'. The two terms are used somewhat differently but both encompass personal satisfaction, met versus unmet needs, fulfilled versus dashed hopes, attained versus failed goals, and quests for meaning.

Marked gender differences have been noted in many, but not all, current elements of outcome in schizophrenia. This paper is a review of such differences as published in the last 10 years, in English, and retrieved from Google Scholar.

## Gender Differences in Elements of Schizophrenia Outcome

### Hospitalization

Women with schizophrenia have shorter hospital stays than men and are less frequently readmitted [9]. They are in hospital for less time over the course of their life than men are. This may not always, however, represent a better outcome. For some, living in the community may not be an improvement over life in hospital [10]. Throughout the world, many patients with schizophrenia currently live on the street or in prison. They suffer from poverty, stigma, loneliness and isolation, violence and sexual exploitation, obesity, and undertreated health problems; they have a high suicide rate and, on average, die earlier than the general population by almost 20 years. Because of shorter stays, women more than men escape the downside of modern hospitalization (coercive treatment, exposure to violence, shame and helplessness), but they are more exposed than men to the hazards of life outside the institution.

### Homelessness

Rootlessness and lack of a permanent place to live is the fate of many individuals diagnosed with schizophrenia today. The prevalence of homelessness in this condition is variously reported to range from 1 to 45%, a very wide range, artificially expanded because definitions of homelessness vary widely [11]. Approximately 11% of all homeless people are reportedly diagnosed with schizophrenia, four males to every female [12, 13]. When the definition of homelessness is residence in a shelter, however, the gender ratio becomes roughly equal, meaning that homeless women are less rejecting of shelters than are homeless men (who prefer to live independently on the street). It also means that women are less often than men rejected from shelters because of shelter rules such as no alcohol or drugs on the premises, and no antisocial behavior. Women are usually homeless because they lack family support [12] whereas men may be homeless by choice – families may want them at home but they prefer to be on their own, as shown in a 5-year follow up study of a first episode schizophrenia cohort [14]. Homelessness by choice can thus be viewed as a positive event, tied to independence, even though it can lead to negative endpoints - victimization, substance abuse, infection, and poor health.

### Employment

Reportedly, only 11% to 37% of individuals diagnosed with schizophrenia in North America and Europe hold paid jobs (this percentage includes sheltered employment) [15] although specific employment figures, of course, vary with place, time period, and regional economics. In the 5-year follow up of 1st episode psychosis patients, mentioned earlier [14], more women than men were either in school or working; more men were without occupation. There is, however, no overall consistency in reports of sex differences in employment rates [16, 17]. Novick et al. in their study of regional differences in schizophrenia outcome, found that paid employment was generally higher in males, especially in East Asia, North Africa, and the Middle East [18].

Employment for people with schizophrenia more often than not means entry-level jobs that do not pay well, that lead nowhere, that are often perceived as personally demeaning, and that offer no opportunity for learning a new skill. Those who are not employed may, in a variety of

ways, see themselves as better off than those who are – able to pursue their interests in the creative arts or to spend time in leisure activities while financially supported by disability pensions that pay nearly as much as entry level jobs [19]. Meaningful occupation is universally seen as a positive, but not when it is narrowly defined as paid employment.

## Marriage and Parenting

More women than men with schizophrenia are partnered or married [20], perhaps because negative symptoms (more prevalent in men) stand as barriers to intimacy, but also because women, whose illness begins later, often marry before their illness begins. Whether one marries or not is mainly determined by social and cultural factors, however, and not by how free of illness one is. For example, arranged marriages in many parts of the world are less affected by the mental health of the two partners than marriages in the West where a substantial degree of social skills is necessary to navigate the demands of courtship [21]. In some cultures, there is a pervasive belief that marriage cures mental illness as a result of which families try to arrange such marriages while keeping secret the fact of illness.

A stable household and strong family bonds are an undeniable source of stability [22, 23] but marriages in the context of schizophrenia can lead to domestic abuse [24–27], with women usually on the receiving end of that abuse. Because opportunities to meet prospective spouses are sometimes confined to psychiatric clinics or group homes or sheltered work shops, both partners may have a history of psychotic disorder; more than half the husbands of women with schizophrenia have been described as alcohol and drug users [26, 28]. Marriage between two unstable partners are not likely to be durable [21, 29] and the married state may, for some, cause more unhappiness than remaining single. This is attested to by the fact that marriage is reported to be a risk factor for suicide in both men and women in the context of schizophrenic illness [30]. Thus, using marriage statistics as an index of good outcome is problematic.

Being a parent has also been used as a marker of good function. Parenting is more common among women with schizophrenia than it is among the men [31]. Thorup et al. [14] found that 17.5% percent of women compared to less than 5% of men were living with children 5 years after a first episode of schizophrenia. This comparison may not be meaningful, however, because most men are significantly younger than most women 5 years after a first episode, thus having had less opportunity to bear children.

Many parents with schizophrenia, because of health-related problems, lose custody of their children [31, 32] and consequently suffer from the extra trauma of loss and separation. Parenting itself is inherently difficult and stressful and can be especially challenging for parents struggling with psychotic symptoms [33]. Its status as a sign of positive outcome is, for all these reasons, debatable.

## Substance Abuse

Substance abuse is frequently considered a marker of poor outcome. It is significantly more prevalent among men with schizophrenia than among women, the sex differential already evident as early as the first few years following a first episode [14]. Substance abuse correlates with violence, unemployment, homelessness, non-adherence to treatment, poor relationships and poor health. Despite this, some studies have shown that a majority of those with a diagnosis of schizophrenia who drink alcohol and use drugs of abuse show better symptomatic

and functional outcomes than those who abstain [34]. A prospective 7 year study of patients with a dual diagnosis (schizophrenia and substance use disorder) found that most such patients (though not all) showed substantial improvement over time in symptoms, employment, maintenance of independent housing, and life satisfaction [35]. Contrary to expectation, in many cases, cognitive functions in dual diagnosis patients have been found to be less impaired than in patients with schizophrenia alone [36, 37]. There are several hypotheses for these counterintuitive findings that bear testing. One is that those diagnosed with a co-morbid substance use disorder frequently become abstinent after experiencing a psychotic episode and are more inclined to subsequently remain abstinent than individuals with schizophrenia who drink or use drugs only sporadically. Another hypothesis is that an initial high level of cognitive functioning and social skill is required in order to develop and maintain an addiction. It is also possible that those whose brains succumb to psychosis only after exposure to toxic substances may have been born with a greater cognitive reserve than those who become psychotic in the absence of such a powerful trigger.

Various other co-morbidities, in the same way as co-morbid substance abuse, seem to bode well for relatively intact cognitive function in the context of schizophrenia [38]. It may be that, under the weight of comorbidity, the threshold for developing schizophrenia is crossed even when cognition is relatively intact so that, when the co-morbid condition is successfully treated, the original intact functioning is able to re-assert itself.

With respect to comorbid substance abuse, a person who is 'high' is perceived by others to be 'a lush' or 'a junkie', less degrading terms than 'psycho', so that alcohol and drug use may paradoxically lessen stigma. This is important because poor social and cognitive outcomes can result from biased public attitudes toward illness as much as from the illness itself [39]. These are all speculations that have not been tested. Neither is it known whether substance abuse affects outcomes differently in men and women with schizophrenia. The telescoping effect usually reported in women (a relatively quick route to adverse outcomes for substance use) [40] is no longer seen in recent cohorts of alcohol-using women in the United States [41]. It is possible, however, that, while more men than women with schizophrenia use drugs and alcohol, the negative effects take a greater toll on women.

## Violence

Men with schizophrenia are reported to commit severe acts of violence more frequently than women [42]. However, less severe aggressive behaviors, such as verbal insults and threats, are seen more frequently among women. In a study by Fazel et al., almost 11% of men with schizophrenia in this sample and 3% of women were ever convicted of a violent offence [43]. Violence in the context of psychosis is linked to substance abuse, and can lead to legal problems, imprisonment, and coercive treatment measures such as physical restraints and isolation rooms, involuntary treatment and community treatment orders. Not all of these sequelae, however, show higher male than female prevalence. Physical restraint measures are used more often with male patients [44], but forced medication and seclusion may be more frequent with female patients. Studies disagree widely on sex difference in the application of coercive treatment because practices vary from hospital to hospital and from one time period to another [45–47]. It is possible that, in popular discourse, violence is more frequently associated with males than with females in the schizophrenia population, not necessarily because it is more frequent among males but, rather, because men, when violent, do more damage than violent women.

## Suicide

The lifetime mortality from suicide in schizophrenia is 4–6% [48]. As in the general population, most studies report higher suicide rates in male than in female patients [49–51]. The preponderance of males committing suicide can already be seen in the 1st episode population [16, 52] where 2·3% of men and 1·5% of women die by suicide within 5 years of their first diagnosis. Significantly more women than men, however, attempt suicide [53].

More suicide attempts by women is to be expected because more women than men with schizophrenia suffer from comorbid depression [54], the main trigger to suicide. In addition, there is the relatively greater male access to lethal means of suicide such as guns, the greater male tendency, in the context of schizophrenia, to social withdrawal and isolation, to the absence of emotional and instrumental support and to aggressive urges that can be turned inwards towards the self. Importantly, however, the male/female difference in suicide rate in schizophrenia is not as marked as in the general population. In a meta-analysis of published studies of psychiatric in-patients, Large et al. [55] found no gender-related suicide difference, suggesting that women who are ill enough to be hospitalized are as likely as men to find the lethal means they need to end lives that have become subjectively intolerable. Suicide and early death are acknowledged as the two worst possible outcomes of schizophrenia.

## Mortality

Because of poverty, life style, medication, stigma, and disparities in the provision of health care, the schizophrenia population also suffers disproportionally from a number of serious diseases [56]. Cardiovascular disease is a prominent cause of mortality, accounting for half of the deaths from natural causes in schizophrenia in the United States. Cardiovascular death is more common in men than in women, as it is in the general population, but the ratio of death from heart disease in women with schizophrenia relative to other women is higher than the analogous ratio for men [57].

There are specific cardiovascular risk factors for women in this population, namely comorbid polycystic ovarian syndrome, early menopause, gestational hypertension and gestational diabetes, and susceptibility to drug-related prolongation of cardiac depolarization. Chronic smoking, very prevalent among people with schizophrenia, is more of a risk for heart disease in women than in men [58]. Diabetes and metabolic disease pose potentially fatal risks to both men and women in this population [59]. Lethal accidents such as poisoning or dangerous falls account for twice as many deaths as suicide in schizophrenia patients [57, 60], even in 1st episode samples [61].

Overall, life expectancy is lower than the national standard by over 18.7 years in men with schizophrenia and by 16 years in women [62]. Premature death from any cause occurs in this population in 3·3% of men and 2·0% of women [43]. What is most troubling is that the survival gap between those with schizophrenia and the rest of the population appears to be widening rather than narrowing with time [63]. A critical question is the role in premature death of antipsychotic medication, a question that remains unresolved [64, 65].

## Symptom Response to Drugs

Response to antipsychotic drugs is a critical component of outcome, not only because of its effect on symptoms of schizophrenia, but also because these drugs produce side effects

that may, to some degree, contribute to mortality. Men and women differ in very many aspects of antipsychotic drug response. To begin with, differences between the sexes have been reported in the quality of the relationship between patient and prescriber, an important factor in subsequent adherence to prescribed drug regimens [66]. There are also fundamental, gender-based attitudinal differences towards therapeutic drugs in general, men more than women starting off with a negative attitude toward all medication [66]. Once the drug enters the body, there are important sex differences in absorption, distribution, metabolism, and elimination (pharmacokinetics) and in the action of the drug at target brain sites (pharmacodynamics) [67, 68]. Because women, more than men, take a variety of different kinds of drugs, they are more exposed to drug interactions [69]. These differences lead to gender disparities in both the clinical effectiveness of antipsychotics and in the extent and severity of side-effects.

In general, women's psychotic symptoms appear to respond more rapidly and more thoroughly than men's to antipsychotic medication, perhaps because a) women are more likely to take their pills as prescribed b) the metabolism of these drugs results in higher blood levels in women than in men c) estrogens at brain receptor sites enhance dopamine blockade and/or d) women have more of the symptoms that are responsive to drugs (delusions and hallucinations) and fewer of those that are not (negative symptoms and cognitive symptoms) [70]. Important to keep in mind is the observation that women with schizophrenia tend to improve to a greater degree than men even in the absence of drugs. A 10 year follow up from the Danish Opus trial found that 30% of schizophrenia patients on no medication had achieved a remission of symptoms at 10 years, women significantly more so than men [71]. What this means is that women's relative success in achieving remission cannot be attributed solely to a superior drug response. Nevertheless, a portion of women's symptom outcome is likely to result from relatively high blood levels of antipsychotic medication given that women also report more side-effects than men [72].

## Side-Effects

Despite such reports, systematic reviews of adverse effects of antipsychotics find no clear objective differences in side effect prevalence by gender [73, 74]. However, it is interesting that for all drug categories (not only for psychiatric drugs) women *report* more adverse effects than men do. The explanation may be that women report all adverse effects they experience, even when they are minor, whereas men tend only to report the more serious effects [75].

Women have a particularly low tolerance for specific side-effects, such as those that they perceive as undermining their appearance (weight gain, muscle movement, negative effects on skin and hair) [76]. Moreover, certain side effects *are* objectively more prevalent in women (prolongation of the QT interval, and prolactin-induced side effects [77]. All statements about the prevalence and severity of side effects, however, must be tempered by contributory factors such as age, reproductive status and, to a lesser extent, the phase of the menstrual cycle [78, 79]. Pregnancy is a very important variable with respect to side effects because two individuals instead of one are potentially affected. As an example, antipsychotics are known to predispose to gestational diabetes and raise the specter of potential harm not only to the mother, but also to the child [80–83].

Even though women's psychotic symptoms on the whole appear to respond better to antipsychotic medications than men's do [84], taking side effects into consideration, it is questionable as to which sex benefits most.

### Functional Outcomes

When focusing on functional rather than symptomatic outcomes of schizophrenia, numerous studies agree that women outperform men [85, 86]. Functional outcome refers to educational achievement, occupational functioning and interpersonal functioning and its meaning overlaps with concepts such as quality of life and recovery.

### Quality of Life/Recovery

'Recovery' in the context of schizophrenia has been variously defined. It usually refers to a patient's subjective sense of mastery over the illness whether or not symptoms remain and whether or not objective function has been fully restored. In this sense of the term, Thorup et al. [14] as well as others [87, 88] found that women achieve better recovery when examined during the early and medium term of illness; longer term differences are, however, less clear cut [89]. Jääskeläinen and colleagues [90] conducted a meta-analysis of gender and recovery and found no significant difference between men and women. These investigators defined recovery as improvement in both clinical and social domains for a minimum period of 2 years.

Finding a gender difference in recovery may well depend on the age of the sample at the time of evaluation, with women initially doing better but men catching up in later years [91–93]. It may also depend on the region of the world that is sampled [18]. Regional differences suggest that male/female differences in schizophrenia outcomes are not based on biological factors but, rather, on experiential features that depend on gender-determined societal pressures and expectations. Medical approaches to men and women also differ depending on culture and tradition and economics. For instance, there are parts of the world where women have relatively poor access to health care and, therefore, are not identified as suffering from schizophrenia unless their illness becomes very severe.

**Fig. 1** Variety of outcomes

## Conclusion (Fig. 1)

Over the years, the meaning of a positive outcome of schizophrenia has changed. While several diverse components of outcome are generally acknowledged, a person's subjective sense that illness has been partly overcome and that life is meaningful despite symptoms and despite treatment side effects has currently come to be viewed as the most valid signpost of a good outcome. Because subjective measures are always problematic to assess, it is, therefore, difficult to make definitive statements about the extent or even the direction of gender differences. Women have certain advantages in that their illnesses start later than men's and that, on the whole, their symptoms respond better to available treatments. These advantages serve them well at the outset of illness but appear to dissipate over time. Gender differences in various aspects of outcome, therefore, vary depending on the age of the patient. They also vary with the social and cultural background of the study population. There are, thus, few definitive answers. The hope is that studying gender differences will uncover critical elements of good outcome that can subsequently lead to effective intervention in both women and men.

### Compliance with Ethical Standards

**Conflict of Interest** There is no conflict of interest. The author has nothing to disclose.

**Ethical Approval** This is a review paper. No ethical approval was sought.

**Informed Consent** This is a review paper. There was no need for consent.

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