Sex differences in schizophrenia

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Abstract
Evidence suggests sex differences in schizophrenia reflect differences in both neurodevelopmental processes and social
effects on disease risk and course. Male:female incidence approximates 1.4:1 but at older onset women predominate.
Prevalence differences appear smaller. Men have poorer premorbid adjustment and present with worse negative and less
depressive symptoms than women, which may explain their worse medium term outcome according to a range of measures.
Substance abuse is a predominantly male activity in this group, as elsewhere. Findings of sex differences in brain morphology
are inconsistent but occur in areas that normally show sexual dimorphism, implying that the same factors are important
drivers of sex differences in both normal neurodevelopmental processes and those associated with schizophrenia. There are
sex differences in antipsychotic responses but sex-specific endocrine effects on illness and response to antipsychotics are
potentially complex. Oestrogen’s role as an adjunctive medication is not yet clear due to methodological differences between
the few randomized controlled trials. Services that are sensitive to differences in gender can better meet their patients’
specific needs and potentially improve outcome.

Introduction
Sex differences in schizophrenia are one of the most
consistently reported aspects of the disease
(Goldstein et al., 2002a; Kraepelin, 1893;
Kretschmer, 1925; Leung & Chue, 2000). They
are described in almost all features of the illness from
prevalence, incidence, mean age at onset, clinical
presentation, course and in the response to treatment
(Castle, Abel, Takei, & Murray, 1995). Whether and
how women and men with schizophrenia differ is one
of the most interesting as well as clinically relevant
topics in schizophrenia research. Moldin (2000)
suggested that robust gender differences in major
disease variables ‘may have important implications
both in future research on the pathophysiology and
aetiology of schizophrenia and in clinical practice’. In
this review we consider further the notion that sex
and gender differences in schizophrenia are expressions
of sex differences in healthy brain development and
of gender differences in the social effects on
disease risk and course. In this respect, schizophrenia
is unlikely to differ from other neurodevelopmental
illness.

Several, but not all, domains of research into sex
and gender differences in schizophrenia are covered
in this review. These include: sex differences in
prevalence estimates and in incidence and its distri-
bution of onset over the life-cycle; differences in the
determinants of premorbid functioning and conse-
quences of the gender difference in age at onset;
gender-specific course and outcome; sex differences
in brain development and functioning, specifically as
they relate to sex differences in brain in schizophrenia
and sex differences in treatment response.

Sex differences in the incidence and
prevalence of schizophrenia

Disease incidence provides a measure of how many
new cases are expected to occur in a given population
over a given period of observation. This may be
particularly important in disorders such as schizo-
phrenia which are effectively groups of symptoms
making up syndromes where up to a third of new
cases do not develop into chronic illness (Jablensky
et al., 2000). Gradients in the incidence of a disorder
across time and place can provide powerful clues to
help unravel aetiology. However, variations in inci-
dence are also well described within or between
various populations. This implies that aetiological or
risk factors are not uniformly distributed. Sex differences in the incidence, or prevalence, presentation and outcome of illnesses represents an important boundary between risk groups (Jablensky, 2003).

Sex difference in incidence or prevalence of schizophrenia may depend on the stringency of the diagnostic criteria applied: the broader the criteria the less significant are the sex differences in incidence or prevalence (Castle, Abel, Takei, & Murray 1993; Castle et al. 1995; Goldstein, 1995; Morgan, Castle, & Jablensky, 2008). Recent meta-analysis identified a mean ratio of male:female schizophrenia incidence of 1.42 (95%CI 1.3, 1.56) and also found evidence of significantly lower estimates for less restrictive criteria (Aleman, Kahn, & Selten, 2003). However, all ratio estimates from different types of study (including for methodologically rigorous studies, those using DSM III-R/IV or ICD criteria, those before 1980) lay between 1.27 and 1.54 and significantly exceeded 1. McGrath, Saha, Chant, and Welham (2008) review found a median ratio of 1.4 (10th and 90th centiles 0.9, 2.4).

Most psychiatrists believe that women have a later onset of schizophrenia and a better course of illness than men and that these two phenomena are related to one another, i.e. a worse illness subtype occurs earlier and therefore accounts for the worse prognosis in men; or, later illness onset in women represents a less aggressive illness and allows for better outcome. To a great extent the epidemiological literature encourages such views. Incidence rate ratios tell of rates of disease within specified time frames. They do not reflect the interactions seen in some studies between disease age of onset and gender. Whilst the rate ratio curve for incidence is normally distributed, the curves for age at onset are not. Men show a modal incidence in their early twenties and perhaps a second peak around middle age. Women also show modal onset in their early twenties, but this is a lower frequency, somewhat broader mode and is followed by a more pronounced peak in middle age than men (Drake, Addington, Viswanathan, Lewis, & Abel in submission; Höhner, Maurer, Loffler, & Riecher-Rössler, 1993; Hambrecht, Maurer, Hafner, & Sartorius, 1992; Leung & Chue, 2000). Thus, there is a switch from male predominance in incidence during the early twenties to female predominance in incidence at older ages. Using admixture analysis of a relatively small case register sample of non-incident cases, Castle et al. (1993) suggested that the early modal onset of non-affective psychosis lies at 21–22 years in both women and men, whereas there are secondary underlying curves with modes at ~36 years in men and ~39 years in women; and women alone have a third mode of onset in their early 60s.

Sex and age at onset differences in the clinical presentation and course of non-affective psychosis are key biomarkers and may provide important clues to the aetiology of the disorder. However, conclusions from this literature have been unclear because of small sample sizes, lack of follow up or the bias inherent in non-incident samples (Castle et al., 1993; Goldstein & Link, 1988; Roy, Maziade, Labbé, & Mérette, 2001; Thara & Rajkumar, 1992; Vazquez-Barquero et al., 1996). More recently, one of the largest samples to date (n = 537) of first episode schizophrenia (i.e. two incident samples combined (J. Addington & D. Addington, 2001; J. Addington, van Mastigrt, & D. Addington, 2003; Lewis et al., 2002)) aged 10–65 was examined for differences in presentation and course of disorder over a 12–18 month follow up period (Drake et al., in submission). Admixture analysis suggested underlying distributions with modes in the early 20s and mid 40s for each sex. Men predominated under 43 years and women over 43 (Figure 1).

Using the 10 countries WHO cohort, Susser and Wanderling (1994) have further distinguished sex differences in incidence of schizophrenia with that of non-affective remitting psychosis or NARP. They also looked at variation in sex differences by setting, i.e. developing versus developed country and rural versus urban settings. They reported that the annual incidence of NARP per 10,000 people in women was approximately double that in men in the developing country setting, 0.878 versus 0.486, respectively.
Sex differences in presentation and course of illness

Sex differences in symptom expression have important implications for a number of reasons. For example, symptom presentation and course likely play an important role in determining treatment regimens and understanding sex differences in treatment response. Gender differences in clinical presentation and course have been reported as broadly consistent in different countries and cultures (Goldstein, 1997; Hambrecht et al., 1992; Harrison et al., 2001). One of the largest and most comprehensive epidemiological, population-based samples is from the National ‘Low Prevalence’ study from Australia (Morgan et al., 2008). This is an incident sample which includes 1090 new cases of psychotic disorder. At presentation, this study reported that women were more likely to have depressive symptoms and less likely to show negative symptoms. Women may also have higher levels of depressive symptoms than men throughout disease progression (Castle et al., 1993; Goldstein & Link, 1988). The prominence of affective symptoms in mentally ill women overall may represent the likelihood that women are more likely to express affective symptoms than men overall, and therefore sex differences in symptom expression in schizophrenia may be related to gender differences (in illness expression) rather than schizophrenia per se (Flor-Henry, 1983).

Recently, Drake et al. (in submission) addressed the relationship between sex, age at onset and symptom presentation and course in a large first episode sample. Consistent with previous studies, early onset cases (women and men) showed worse overall Positive And Negative Symptom Scale (PANSS) score, negative and cognitive symptoms and worse depression-anxiety scores in women. Overall, independent of age at onset, men presented with more negative symptoms and women with more mood symptoms. The association of older age at onset with fewer negative and cognitive symptoms at presentation among women was also consistent with other findings (Grossman, Harrow, Rosen, Faull, & Strauss, 2008; Morgan et al., 2008; Sartorius et al., 1986). Sex differences in presentation may be important in determining outcomes but in themselves may be determined by the age at presentation or age at onset. Paranoid symptoms may be more severe in women with older onset than men with older onset (Castle et al., 1993; Hafner et al., 1993).

In many studies, women have a better prognosis than men over 2–10 years for many measures (Angermayer, Kühn, & Goldstein, 1990; Hafner et al., 1993; Jablensky et al., 1992; Robinson et al., 1999) though some studies, often smaller ones, find no differences (Angermayer et al., 1990; McCreadie et al., 1989; Rajkumar & Thara, 1989) and studies that control for premorbid adjustment and baseline
Sex-specific effects on brain development and sex differences in schizophrenia brain

Animal and human studies clearly demonstrate that normal development of the brain differs in females and males, in large part this is mediated by the regulatory effects of sex steroid hormones and genes on normal sexual differentiation (Allen & Gorski, 1986; Arnold, van Nas, & Lusis, 2009; Gorski, 2000; Handa, Condon, Whitmoyer, & Gorski 1986a; Handa, Hines, Schoonmaker, Shryne, & Gorski, 1986b; Handa, Burgess, Kerr, & O’Keeffe, 1994a; Handa, Burgess, Kerr, & O’Keeffe 1994b; MacLusky, Clark, Naftolin, & Goldman-Rakic, 1987; McEwen, 1983; Park, Baum, Paredes, & Tobet, 1996; Pilgrim & Hutchison, 1994; Tobet, 2002; Tobet, Basham, & Baum, 1993; Tobet, Henderson, Whiting, & Sieghart, 1999). The consequences of early insults to, or genetically determined disruption of, brain development are likely to be influenced by such sex-specific developmental effects (Goldstein, 2006; Goldstein & Walder, 2006; Goldstein et al., 2002a). In addition to understanding the influence of differences in the healthy female and male brain in the face of disease, an understanding of sex-specific brain abnormalities in schizophrenia may also provide important aetiological clues (Goldstein et al., 2002a).

Sex differences in the healthy brain

Although the effects of sex hormones on brain development have mainly been demonstrated in animals, recent work suggests that the spatial organization of oestrogen receptors in human adults is similar to homologous regions in several mammalian species (Donahue et al., 2000). Early work in rodents demonstrated that the male brain becomes ‘masculinized’ by oestrogen beginning in the second trimester when the testes begin to secrete testosterone, which is in part converted to oestrogen by aromatase. Oestrogen has an impact at every level of neuronal growth and death, i.e. neuronal differentiation, migration, synaptogenesis, and apoptosis, and even neurogenesis. Such studies have also highlighted the relationship between differential localization of androgen and oestrogen receptors during critical periods of development and sex differentiated brain morphology and behaviour, (Fernández-Guasti, Kruijver, Fodor, & Swaab, 2000; McEwen, 1983; Sandhu, Cook, & Diamond, 1986). More recently, studies in monkeys and humans demonstrated that androgens have direct effects on sexual differentiation of the brain (Herman, Zehr, & Wallen, 2006; Thornton, Zehr, & Loose, 2009). Further, ‘activational effects’ of circulating hormones, occurring later in development (e.g. during puberty), can potentiate neural circuits laid down during early development (Kawata, 1995; Pilgrim & Hutchison, 1994; Schulz, Molenda-Figueira, & Sisk, 2009). The last decade has revealed the importance of sex-specific genetic programmes in early brain development prior to gonadal differentiation (Arnold, 2009; Dewing et al., 2006; Wade & Arnold, 1996). Later in development these sex-specific genetic effects can be enhanced or modified by gonadal steroids during puberty (Schulz et al., 2009). In addition, the co-localization of gonadal hormone receptors with neurotransmitters, such as the monoamines and γ-aminobutyric acid (GABA), and growth factors, such as insulin and nerve growth factors, were found to mediate the relationships between receptor density and dimorphisms (Kawata, 1995; Tobet et al., 1999; Toran-Allerand, 1996).

There is a growing body of evidence from human imaging and postmortem research demonstrating...
they reported that these regions were significantly
auditory cortex, insula, basal forebrain, cingulate
frontal cortices, posterior parietal cortex, primary
hippocampus, orbital, dorsolateral and medial pre-
frontal cortices, posterior parietal cortex, primary
auditory cortex, insula, basal forebrain, cingulate
gyrus, medial dorsal thalamus, and basal ganglia).

They reported that these regions were significantly
more likely to retain sexual dimorphisms (of adult
human cerebral volumes) than brain regions that,
according to the animal literature, did not have a
high density of sex steroid receptors early in
development.

Sex differences in the brain in schizophrenia

It is increasingly recognized that normal sex diffé-
tiated brain development has important implica-
tions for understanding sex differences in
neurodevelopmental and psychiatric disorder.
Schizophrenia is a neurodevelopmental disorder
with foetal and early postnatal origins and therefore
it is likely that sex differences in brain abnormalities
in schizophrenia are initiated at the time of the early
sexual differentiation of the brain, that is, during
foetal and early postnatal development (Goldstein &
Walder, 2006). This premise has support from
animal studies demonstrating differential brain
abnormalities and behavioural consequences,
depending on the timing of the insult during foetal
and early postnatal brain development, for female
compared with male animals (Goldman, Crawford,
Stokes, Galkin, & Rosvold, 1974; Grimm & Frieder,
1985) and human studies (Rantakallio & vonWendt,
1985) and is consistent with studies demonstrating
significant differential risks for schizophrenia in
women and men, given exposure to particular
obstetric factors (Goldstein & Walder, 2006). Early
studies of sex differences in structural brain abnor-
malities in schizophrenia generally found greater
abnormalities among men (Nopoulos, Flaum, &
Andreasen, 1997). In men with schizophrenia, MRI
and postmortem studies reported larger lateral and
third ventricles, and anterior temporal horn; smaller
medial temporal volumes, e.g. hippocampus and
amygdala, Herschel’s gyrus, superior temporal gyrus,
and overall smaller frontal and temporal lobe vol-
umes, although findings were not wholly consistent
(Flaum et al., 1995; Lauriello et al., 1997). In addition,
more left-lateralized abnormalities were
reported among men (Bogerts et al., 1990;
Goldstein et al., 2002a; Gur et al., 2000a, b;
Hirayasu et al., 2000). Other abnormalities more
likely to be found in men than women with schizo-
phrenia included greater sulcal volume and smaller
thalamic size which together suggested somewhat
more pervasive brain damage in men than women
(Nopoulos et al., 1997).

Recently, work has reported region-specific struc-
tural brain abnormalities in women dependent on
the region assessed. Some have reported smaller volumes
of heteromodal association areas among women with
schizophrenia than men (e.g. dorsolateral prefrontal
cortex and superior temporal gyrus (STG) and
orbital prefrontal cortex. Others found smaller vol-
umes of STG in men, and similar abnormalities in

Sex differences in schizophrenia
women and men in dorsolateral prefrontal cortex (Gur et al. 2000a). Studies have demonstrated different differences between women and men with schizophrenia compared with their healthy controls, depending on the prefrontal region assessed (Goldstein et al., 2002a; Gur et al., 2000a, b). The inconsistencies across studies may be in part due to methodological and sample size differences and to a relative dearth of conceptual models tested in studies of sex differences.

Overall, findings suggest that factors contributing to the normal sexual dimorphisms of developing and adult brain (i.e. early developmental effects of hormones and genes on sexual differentiation) are the same factors that result in sex-specific brain abnormalities in schizophrenia (Goldstein et al., 2002a). This is consistent with the timing of premorbid developmental effects implicated in schizophrenia and is supported by some preliminary evidence. Szczesko et al. (2002) also provide evidence for differential sex effects in brain abnormalities during the premorbid period using MRI and neuro-psychological stimuli in first episode patients. This study reported an association between anterior hippocampal volume and executive and motor functioning in male patients, which was not present in women. Moreover, anterior hippocampal volume was more strongly associated with motor functioning among male than female patients. First episode studies are important to allow accurate adjustment for differing age at onset in women and men with schizophrenia (Drake et al., in submission) and to minimize the effect of sex differences in treatment.

Sex differences in treatment

Biological and environmental factors are likely to contribute to the well recognized sex differences in the response of women and men to treatment (see Smith, this issue, pp. 472–484). Brain sexual dimorphism and function are associated with sex differentiated distribution of gonadal hormones and their receptors (McEwen, 1983; MacLusky et al., 1987; Ostlund, Keller, & Hurd, 2003) and these include brain regions implicated in the metabolic pathways of psychotropic drugs (Goldstein et al., 2001). However, factors more difficult to measure are also likely to have an important effect on sex differentiated treatment outcomes in schizophrenia. For example, worse outcomes in men may be related to substance abuse, which is more common in men in general, and in men with schizophrenia in particular. The Australian Low Prevalence Study (Jablensky et al., 2000) reported that 36% of men with a psychotic disorder had a history of illicit substance abuse or dependence compared to 16% of women. Comparison rates for the general population were 3% and 1% for men and women, respectively, and these rates are likely underestimated. It is well known that substance abuse has a profound negative effect on illness course; affecting relapse rates and hospitalizations, and being associated with poor social outcomes including housing, criminality and vulnerability to physical diseases such as hepatitis C and HIV. However, the worst outcomes for men have been recorded in the literature antedating the widespread use of illicit substances in the community. It is unlikely, therefore, that substance abuse is the sole explanation of gender difference in outcomes. Poorer premorbid and social functioning in men with schizophrenia (Goldstein & Link, 1988) may exacerbate illness course by making engagement with treatments and services more difficult and by worsening social isolation, which in itself promotes poor functioning.

Sex differences in response to antipsychotic medications may also reflect differential effects of treatment on particular kinds of symptoms and cognitive dysfunctions. For example, recent studies reported superior cognitive improvement in women than men treated with olanzapine, risperidone and clozapine (Howard et al., 2001). Alternatively, some atypical antipsychotics, such as clozapine may work better than typical agents on negative symptoms, which are more likely found in men, or on affective symptoms, which are more likely found in women (Goldstein & Link, 1988). Examining sex differences in treatment response to particular symptoms and particular cognitive functions may be more informative than assessing overall change in symptom severity.

Notwithstanding important social considerations, much evidence has accumulated that women and men differ in their response to antipsychotic medication. Pinals, Malhotra, Missar, Pickar, and Breier (1996) argued that many studies are methodologically flawed, citing a lack of double-blindness, inadequate drug-free washout periods, little control for dose and subject’s weight, and lack of adequate matching of women and men as reasons for reported differences. Their own study took these factors into account and found no significant sex differences in response to typical antipsychotics. Two studies in the last decade have compared treatment response to typical and atypical agents in women and men. Goldstein et al. (2002b) reanalysed a large international clinical trial of olanzapine compared with haloperidol controlling for illness chronicity and menopausal status. Seven hundred female and 1295 male inpatients were randomised to receive a 6-week trial of olanzapine versus haloperidol. Women on olanzapine had a greater drop in overall symptomatology by week 4 than any other group,
and their level of symptomatology remained lower throughout the 6-week trial. The sex differences in treatment response in haloperidol compared with olanzapine were in part dependent on chronicity, and in women, menopausal status. That is, first episode women on haloperidol exhibited an increase in symptomatology over the 6-week trial compared to their male counterparts, while multiply-hospitalized women had a better treatment response on haloperidol than their male counterparts. Women on olanzapine had a significantly better treatment response than men, regardless of chronicity. Finally, premenopausal women had a significantly better treatment response than postmenopausal women, regardless of treatment and chronicity. Women required lower average doses than men but drug plasma levels were not available. Although the sex differences in overall symptomatology on olanzapine were clinically small, women on olanzapine showed a larger drop in symptomatology over a 6-week period than any other group (Goldstein et al., 2002b). Sex differences in the pharmacokinetics of typical and atypical antipsychotics may explain much of the sex difference in treatment response. For example, recent data found that men clear olanzapine nearly 40% faster than women. This is further influenced by ethnicity and smoking status, such that African American men who smoked had the highest clearance rate (Bigos et al., 2008). Pharmacokinetic differences may be especially relevant in studies reporting sex differences in short duration follow up.

Recent awareness of sex differences in the adverse side effect profiles of drugs such as olanzapine in long-term use moderate the clinical implications from reports of sex differences in short-term treatment response. Women have a greater risk of serious weight gain and obesity, as well as metabolic syndrome (MetS) and its cardiovascular outcomes with some of the atypical agents such as olanzapine. For example, in the Clinical antipsychotic trials of intervention effectiveness (CATIE) trial, 36% of men developed MetS compared to 51% of women with schizophrenia ($p = 0.0002$). Compared to healthy women and men, women treated with antipsychotic drugs were 251% more likely to develop MetS as opposed to men treated with antipsychotic drugs who were 138% more likely to develop MetS than controls. Even when body mass index was taken into account, treated men were 85% more likely, and treated women 137% more likely than controls to have MetS (independent of age and ethnicity) (Enger, Weatherby, Reynolds, Glasser, & Walker, 2004; Goff et al., 2005).

Relatively recent studies examining the gold standard atypical agent, clozapine, also report that women show significantly higher plasma levels of clozapine than men treated with the same dose per kg and independent of smoking or menopausal status (< or > 40 years of age) (Tang et al., 2007). Earlier studies showing that men with schizophrenia have a better treatment response to clozapine than women (Lieberman et al., 1994; Szymanski et al., 1996) may need reinterpretation in light of these data. However, selection bias may also partly explain such sex differentiated responses. That is, samples were selected for treatment-resistant cases and treatment-resistant women represent a more severely ill sample than women with schizophrenia in general.

Some (Seeman, 1982), but not all (Tang et al., 2007) studies suggest that menopausal status may determine response to antipsychotic agents. One popular biological notion invoked to explain this is the effect of gonadal steroids. Women with severe mental illness, including schizophrenia, are more likely to have low oestrogen levels and irregular menstrual cycles (Riecher-Rössler, 2002; Smith, 2003; Smith, O'Keane, & Murray, 2002; Taherianfard & Shariaty, 2004) independent of medication. Not all women become hyperprolactinemic with prolactin-inducing antipsychotics – but most do (75% versus 34% men) (Smith et al., 2002). Much of this endocrine disruption is likely to be non-specific and related to higher levels of stress (accompanied by overactivity of the stress axis and high cortisol levels), poor physical health and chaotic, unhealthy lifestyles in people with chronic mental illness.

There is also some evidence that psychotic symptomatology varies with menstrual phase, with higher symptom levels associated with lower oestrogen levels (Endo, Daiguji, Asano, Yamashita, & Takahashi, 1978; Mahe & Dumaine, 2001; Huber, Borsutzky, Schneider, & Emrich, 2004; Bergemann et al., 2002). In addition, low oestrogen phases of the menstrual cycle have been associated with higher rates of hospital admission (Huber et al., 2004) and with poorer cognitive performance, in particular verbal and spatial memory, and perceptual-motor speed (Hoff et al., 2001). Disruptions in a number of endocrine axes, whatever the cause, are unlikely to be specific to either the mechanisms behind the development of schizophrenia or to the disorder itself, but they may have important consequences for the nature and course of cognitive and other functional deficits in the disease process.

**Adjunct treatment with gonadal steroids**

Disruption of the HPG and HPA axes is likely to be associated with non-specific effects of either chronic or severe mental illness. Treatment trials have been developed using gonadal steroids as adjunct
therapy for women and men with schizophrenia. Kulkarni et al., (1996) reported symptom improvement for short-term outcome in a small open-label pilot study of women with schizophrenia. In a subsequent randomized 28-day trial of 102 women with schizophrenia on typical and atypical antipsychotic medications, they compared an adjunctive 100 g estradiol transdermal patch with a 50 g patch and reported a significant improvement in acute psychotic symptomatology using the 100 g patch, but no effect on negative symptomatology (Kulkarni et al., 2002). A systematic Cochrane review (Chua, Izquierdo de Santiago, Kulkarni, & Mortimer, 2009) recently assessed all the clinical trials of adjunctive oestrogen with or without progesterone in schizophrenia since 2003. They concluded that the effectiveness of adjunctive oestrogen treatment is still in question. Even the five studies they were able to include from a possible 19 (Bergemann et al., 2005; Good et al., 1999; Kulkarni et al., 2002; Louza et al., 2004) varied and included pre- and postmenopausal women, different types of adjunctive oestrogen and different routes of administration, as well as a mix of acute phase and chronic phase women. All had very small sample sizes (12–36 subjects) and sample selection and bias may be very important in the outcomes of such studies. Bergmann and colleagues found no effect of 17-beta estradiol in a study which included pre- and postmenopausal. By contrast, a recent study in Iran, Akhondzadeh et al. (2003) used 0.05 mg of ethinyl estradiol in an 8-week trial with haloperidol and demonstrated significant improvement in psychotic symptomatology in 32 premenopausal women with schizophrenia who had regular menstrual cycles. In order to assess fully the effect of adjunctive oestrogen (with or without progesterone) in combination with antipsychotic medications and other psychosocial interventions, attention must be paid to a range of study design factors. These include controlling for age of the women and age at onset, as well as phase of the illness (e.g. acute or chronically ill), menstrual status and functioning, smoking status, use of illicit drugs, ethnicity, type of antipsychotic medication (e.g. typical or atypical), any changes in plasma levels of antipsychotic medication across the adjunct treatment (oestrogen can alter plasma levels of some drugs), preparation of oestrogen and route of administration, domain of the outcome (e.g. positive and/or negative symptomatology, relapse, hospitalizations, cognition), and attention to differential drop-out rates. Further work is also needed to assess the impact of these hormones on the long-term effects of gender differences in illness course.

Conclusions

There is now clear evidence that women and men show differences in the incidence of schizophrenia and, despite the fact that the modal onset for both women and men is the same (~22 years of age), the age at onset distributions of this disease are also distinct. Prevalence estimates appear to show no, or at least less distinct, sex differences. It is also likely that normal differences in sexual differentiation of the brain inform sex-differentiated brain abnormalities in schizophrenia. These may be initiated during foetal and early postnatal development, but are also likely to be influenced by gender differences in psychosocial experience and exposures that occur throughout life. Such differences are likely to be non-specific to schizophrenia and may pertain to other mental illness. The differences described are relevant to a number of clinical outcomes including the responses to treatment of women and men with schizophrenia and the sex-differentiated distribution of adverse events. Government health policy in the UK has embraced gender as a key determinant of health, service need and therefore of service planning (DoH, 2002). Recognizing ways in which the needs of people with schizophrenia differ as a result of their gender provides an important opportunity to deliver high quality, patient-centred care and the prospect of better outcomes for this devastating illness.

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References


MacLusky, N.J., Clark, A.S., Naftolin, F., & Goldman-Rakic, P.S. (1987). Estrogen formation in the mammalian brain: Possible...


