The Role of Estrogens in Schizophrenia Gender Differences

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Abstract

The male/female differences that have been described in schizophrenia are important because they may ultimately shed light on factors that mediate the expression of schizophrenic illness. The hypothesis of this article is that estrogens, either directly or indirectly, modify symptom expression and account for many of the observed gender differences. The role of sex hormones is divided into organizational and activational effects. Organizational effects take place during a critical period in fetal life and put a permanent stamp on the developing brain. Activational effects are the direct influences of circulating hormones that appear when hormonal levels rise, and wane when hormonal levels drop. Because levels of sex hormones in adult women fluctuate during the menstrual cycle, cyclic effects of high and low female hormones may induce specific responses by the adult female brain. All these effects have implications for genetic, environmental, pharmacological, neurocognitive, clinical, and epidemiological research in schizophrenia.

This article examines the organizational, activational, and cyclical role of estrogens as major determinants of the gender differences that have been described in schizophrenia. These differences include earlier onset in men (Lewine 1980; Seeman 1981; Bellodi et al. 1982; Loranger 1984), symptom variation (Lewine et al. 1984; Goldstein and Link 1988), family life variation (Seeman and Hauser 1984; Wattie and Kedward 1985; Goldstein and Kreisman 1988), superior treatment response in women (Young and Meltzer 1980; Kolakowska et al. 1985), superior outcome indices in women (Salokangas 1983; Seeman 1986; Goldstein 1988), and differences in aging effects (Seeman 1982; Flor-Henry 1985).

Prenatal Organizational Effects of Sex Hormones

The following is a summary of findings derived mainly from animal studies. The reader is referred to the original references for a comprehensive review of the subject.

Testosterone secretion begins in the male fetus with the development of Leydig cells in the testes. This occurs between fetal weeks 12 and 18 in the human (McEwen 1981) and marks the beginning of testosterone effects, both direct and indirect, on the male brain. Before then, male and female fetuses are hormonally identical, both bathed in maternal hormones to the extent that these gain passage through the placental membrane. The placenta itself converts maternal estradiol to estrone and selectively secretes estradiol back toward the maternal circulation. Consequently, much higher levels of estrone, an inactive metabolite, are found in the fetal bloodstream than in the mother's bloodstream (McEwen 1988a). Some mammalian species have a special mechanism (estrogen binding to alpha fetal protein) that precludes any circulating estrogens present in the fetal bloodstream from entering the brain during fetal life (Uriel et al. 1972). This mechanism is not thought to be operative in humans

(Uriel et al. 1972), but protection against circulating estrogens may be exerted through rapid metabolism to inactive conjugates such as estrone (Davidson et al. 1983). As in lower animals, much of the human male fetal testosterone is probably aromatized to estradiol in the brain (MacLusky et al. 1987) and hence-forth occupies estrogen receptors within specific brain cell nuclei. Some of it, however, occupies androgen receptors either directly or through conversion to dihydrotestosterone (Vito et al. 1985; Sholl and Pomerantz 1986). All the hormone receptors are similar in that they bind simultaneously to the hormone and to deoxyribonucleic acid (DNA) enhancer sequences within the cell nucleus (McEwen 1988a). The intranuclear hormone-receptor complex thus formed encodes genetic instructions that result in the production of specific enzymes which, in turn, catalyze structural and functional change. These changes are permanent for the organism, or "organizational." One example of a powerful sexually dimorphic organizational effect in rodents is the action of fetal androgens on the hypothalamus. The initial fetal testosterone surge in the male is thought to masculinize the hypothalamus for life, converting it into a tonic, rather than a cyclic releaser of anterior pituitary gonadotropins. In primates, including man, this same sex difference in the pattern of gonadotropin release (cyclicity in females, tonicity in males) appears to be the result of activational as opposed to organizational hormonal effects (MacLusky 1988). In other words, it is produced by adolescent hormone titers rather than being "programmed" from the first. Generally in man, hormone-dependent sex differences in central

nervous system (CNS) function are less "hard-wired" than in experimental animals (MacLusky 1988). They are less obligatory and more susceptible to developmental variation.

Sexually dimorphic brain nuclei, however, are known to exist in primate brains to the same extent that they do in lower animals (MacLusky and Naftolin 1981; Ayoub et al. 1983; Swaab and Fliers 1985). They are present in the hypothalamus, preoptic area, and central amygdala, brain areas that exert powerful effects on feeding, play, activity levels, aggression, certain kinds of learning, neurotransmitter secretion, and circadian rhythms, to say nothing about sexual and reproductive functions. In adult male and female brains, the density and distribution of androgen, estrogen, and progestin receptors in these sexually dimorphic areas do not, as might intuitively be anticipated, show sex differences (Brown et al. 1988). It is possible that the critical differentiating factors are sex-related receptor affinity states rather than receptor numbers (Seeman and Seeman 1986) or that crucial differences exist only during critical periods of fetal development. A review by McEwen (1988a) explores various possible ways in which male and female brains can develop dimorphically despite essentially identical numbers of the various sex hormone receptors.

However the sex differences occur, on a cellular level they may promote or delay cell death, enhance or eliminate synaptic connections, reorganize synaptic networks, affect dendritic length and branching, change nuclear or nucleolar size, or induce the formation of synaptic vesicles and terminals (MacLusky and Naftolin 1981; Hamburger and

Oppenheim 1982; Toran-Allerand 1984; DeVoogd 1987). Thus, the functioning of these dimorphic nuclei in later life may contrast markedly in the two sexes.

More recent studies in newborn rhesus monkeys have shown the presence of estrogen receptors not only in subcortical but also in cortical areas of the brain (MacLusky et al. 1987). Aromatase activity (conversion of androgens to estradiol) has been demonstrated in the hippocampus and neocortex of rodents and monkeys (MacLusky et al. 1987). Sex differences in the cerebral cortex may help to explain human cognitive differences between the sexes (Kimura and Harshman 1984) and sexually dimorphic responses to cortical lesions (Goldman et al. 1974; Lipsey and Robinson 1986).

Maturation and Birth Trauma. One of the ways in which male and female human cortical functions are known to differ is in the pace of early development. Female brains in general show earlier neuronal myelinization, earlier establishment of neuronal connections, and earlier lateralization of cerebral functions (Taylor 1969). This results in greater relative maturity of female brains at birth and subsequent lesser vulnerability to the potential trauma of the birth process (McMillen 1979).

Birth Trauma and Onset Age. It is possible that this protection from perinatal trauma determines the most salient difference between males and females in schizophrenia—the onset age of the disorder. Birth trauma may be the single most important factor that hastens the onset of schizophrenia in the genetically vulnerable (Green et al. 1987; Lewis and Murray 1987). The

greater prevalence of birth sequelae in boys, who, in general, suffer more hypoxia, more infection, more electrolyte imbalance, and lower Apgar scores than girls (Brothwood et al. 1986), may determine the age-of-onset disparity in those who go on to develop schizophrenia.

Onset Age and Outcome. The several year difference in age of onset, occurring as it does during the critical developmental stage of late adolescence, may explain most of the superior outcome seen in schizophrenic women. In other words, discrepancies in levels of gonadal steroids during critical time periods in fetal life may initiate a chain of events that results in gender differences in maturation which, in turn, may account for the greater vulnerability of the male brain at birth and may in this way determine the earlier age of onset in males who are genetically predisposed to schizophrenia. Early age of onset leads to interruption of cognitive and affective development, disruption of interpersonal processes, and insufficient integration of premorbid strengths, all of which result in poorer reintegration after an episode of psychosis and a more turbulent course of illness over time (Seeman 1983b).

Birth Trauma and Structural Abnormalities. Another potential effect of birth trauma may be subsequent abnormalities in brain structure (Weinberger et al. 1980; Andreasen et al. 1982) which have been associated with "defect" or "negative" symptoms, chronicity, and severity of the schizophrenic illness. "Negative" symptoms are much more frequent in schizophrenic males than females (Lewine 1985), and structural abnor-

malities are also more frequent in schizophrenic males (Andreasen et al. 1990).

Neuroleptic Response Effects. More general male/female differences, presumably also determined early via the organizational effects of prenatal hormones (Bardin and Catterall 1981), may assume significance in schizophrenia in that they determine neuroleptic response differences in the two sexes. Women, for instance, show slower gastric emptying times (Datz et al. 1987). This delays absorption and, in turn, may make for a more gradual onset of neuroleptic response. Slower absorption may help to explain why women suffer less from acute dystonias following neuroleptic initiation (Swett 1975) and why subsequent compliance with neuroleptic treatment is better in women (Zito et al. 1985). Cerebral blood flow is 15 percent higher in women than in men (Gur et al. 1982), which may result in more efficient neuroleptic distribution to the female brain. Body fat as a percentage of total body weight is about twice as high in women as in men (Frisch 1988). Since neuroleptics are lipophilic, the higher percentage of body fat leads to relatively more neuroleptic storage in women over longer periods of time. This, in turn, may protect women longer than men from schizophrenia relapse during drug-free periods (Seeman 1989). Dopamine receptors have been shown to deteriorate with age more rapidly in men than in women (Wong et al. 1984). This difference may explain the seemingly paradoxical trend toward a greater female/male ratio of neuroleptic need in older age (Seeman 1983a; D'Mello and McNeil 1990), since dopamine receptor density in schizophrenic

women may remain high for a decade after schizophrenic men no longer require receptor blockade.

Aging and Outcome. The differential rate of dopamine receptor decay may help to explain why short-term outcome favors schizophrenic women (Salokangas 1983; Seeman 1986; Goldstein 1988) while long-term outcome is indistinguishable between the two sexes (Harding et al. 1987).

Family Effects. The increased burden of families of schizophrenic males (Seeman and Hauser 1984; Goldstein and Kreisman 1988) is determined by multiple factors, and differential effects between the sexes are perhaps best explained by cultural pressures toward higher expectations of male offspring. Nevertheless, the earlier age of onset in males places extra stress on parents, particularly because they blame themselves for the development of their son's illness (Seeman 1983b). Daughters' schizophrenic illnesses most often begin after the young women have left the parental home, and this tends to extend illness attribution to causes other than familial. Men's greater aggressivity and suicidal impulsivity are probably hormonally determined and may be "built in" organizationally during the fetal period. Families of schizophrenic patients find these behaviors especially difficult to live with. They also find the "negative" symptoms of listlessness and affective withdrawal particularly troublesome (Goldstein and Kreisman 1988). As noted previously, these symptoms predominate in males (Lewine 1985) and may be a consequence of birth trauma.

There is evidence from studies of childhood psychopathology that boys are more reactive than girls to stresses and conflicts in the family home (Rutter and Quinton 1984; Earls 1987; Rutter 1987). It is not yet known whether such differential sensitivities between the sexes might be prenatally determined. Whatever the case, they may shed light on the well-known enhanced sensitivity of schizophrenic males to the effect of familial emotionality (Vaughn et al. 1984).

In summary, the organizational effects of prenatal sex hormones create many permanent male/female differences that could influence onset age and outcome measures, symptom expression, family effects, and neuroleptic response in adult schizophrenia.

Activational Effects of Adolescent Sex Hormones

Since schizophrenia commonly begins in late adolescence (at least in males), the triggering effects of pubertal sex hormone surges have long been suspected as playing a part in the onset of schizophrenia (Tourney and Hatfield 1972). Gonadal hormones titers may, for instance, have a direct effect on synaptic structure (Olmos et al. 1987). There is, however, no clinical evidence for a direct relationship between hormonal levels and schizophrenia onset. Early puberty has not been associated with early onset in either sex. Estradiol, however, indirectly affects many neurotransmitter systems (Hruska 1986; McEwen 1988a, 1988b) so that the effect of a sudden surge of gonadal steroids in either sex may set off a chain of chemical events that may, in the genetically pre-

disposed, culminate in illness. The rapidity of chemical change (without time for homeostasis) may be the crucial factor in precipitating psychosis. This reflects current thinking about the trigger mechanism of post-partum psychosis (Kendell 1985) and may play a part in adolescent-onset schizophrenia. The hypothesis would thus be that puberty, a time of sudden, dramatic hormonal and neurochemical change, is a risk period for the development of schizophrenia which, in females, is made safer by the protective effects of estrogens.

Protective Effect of High Estrogen Levels. In experimental animals, estrogens enhance neuroleptic effects such as stereotypy and cataplexy and increase the density of dopamine type 2 (D_2) receptors (DiPaolo et al. 1982, 1984; Fields and Gordon 1982; Hruska 1986) as do neuroleptics. Although estradiol has multiple actions on striatal dopamine function in the rat (Hruska 1986; Van Hartesveldt and Joyce 1986), in the human the main effect seems to be neuroleptic-like. Psychosis, clinically, is linked to estrogen decline. One encounters premenstrual (low estrogen) exacerbations of schizophrenia (Endo et al. 1978; Glick and Steward 1980); relative freedom from relapse during pregnancy, a time of increasingly high estrogen levels (McNeil et al. 1984; Chang and Renshaw 1986); and increased vulnerability to psychosis post partum when estrogen levels have precipitously dropped (Mott 1982; Kendell et al. 1987; McNeil 1987) and after menopause when estrogens are low (Seeman 1983a). Together, these clinical observations suggest that high levels of estrogens serve a protective function in schizophrenia.

Through which mechanism such protection is conferred can be speculative only. Sampson and Kimura (1988) have recently reported that cognitive changes in the human female are a function of menstrual phase and sex hormone level. They noted fluctuations in fine motor skills and spatial ability which, in themselves, should have little import for schizophrenia. Nevertheless, other cognitive and affective processes may also be susceptible to the effects of levels of sex hormones mediated through neurotransmitter function.

Estrogens and Neuroleptic Response. With respect to neuroleptic responses, women appear to require lower doses than men in the acute stage of illness (Young and Meltzer 1980; Chouinard and Annable 1982; Nedopil et al. 1983; Chouinard et al. 1986) and in the maintenance stage (Seeman 1983a; Dworkin and Adams 1984). Women's lower dosage requirements may be due to the neuroleptic-enhancing properties of estrogen. The effect may be missed clinically because high doses of neuroleptics interfere with the hypothalamic-pituitary-ovarian axis and women given high neuroleptic doses may not be producing estrogens (Flint and Stewart 1983). It is therefore important to determine the endocrine status of women before male/female dose comparisons can be interpreted. In our study (Seeman 1983a), women over 40 required higher neuroleptic maintenance doses than age-matched men. Although their endocrine status was not determined, it is probable that estrogen levels were dropping in this age group.

Anecdotal reports occasionally claim higher neuroleptic dosage requirements in women than in men.

This may be especially true for nonovulating women. It is also possible that neuroleptic regimens that begin with relatively large doses interfere with estrogen secretion before they bring about symptom improvement; thus, women's potential response to low neuroleptic doses may be masked. This is an important research confound and an important clinical treatment issue.

Estrogens and Outcome. Improved neuroleptic response leads to relative freedom from unwanted effects, since most neuroleptic side effects are dose-related. When side effects are low, compliance with maintenance regimens is improved (Van Putten et al. 1981), and this may, to a large degree, explain women's better adherence to follow-up programs and subsequent superior middle-range outcome (Salokangas 1983; Watt et al. 1983; Seeman 1986; Goldstein 1988).

Long-range outcome is similar in the two sexes (Ciompi 1980; Harding et al. 1987) not only because of differential rates of dopamine (DA) receptor decay but perhaps also because female subjects in 20-year followup studies are postmenopausal and no longer hormonally advantaged over their male peers.

Estrogens and Drug Side Effects. With respect to the timing of neuroleptic-induced extrapyramidal symptoms, women are reported to suffer more parkinsonism and akathisia (Ayd 1961; Keepers et al. 1983) and more tardive dyskinesia (Chouinard et al. 1980; Glazer et al. 1981). The greater susceptibility to parkinsonism and akathisia may be a result of the additive effects of

estrogens and neuroleptics on DA blockade.

Tardive dyskinesia (TD), on the other hand, results from mechanisms not fully understood. The syndrome is known to appear clinically when neuroleptic doses are lowered after lengthy periods of dose maintenance. TD often becomes evident clinically in women at the time of menopause, even when neuroleptic doses are maintained. Estrogen drop at this time of life may induce the emergence of TD by relieving DA receptor blockade. The analogy to neuroleptic withdrawal makes this a likely explanation. Studies that report a greater prevalence of TD in women unfortunately do not report endocrine status, although ages are given (Smith and Dunn 1979; Kane and Smith 1982) and support the estrogen withdrawal mechanism.

In summary, the protective direct effects of female estrogens on the brain may help to explain the gender discrepancy in age of onset, superior outcome in women, and discrepant side-effect profiles in men and women. When more is known about direct cognitive and affective effects of sex hormones, symptom differences in men and women may also become attributable to the effects on the brain of diverse levels of distinctive circulating hormones.

Cyclical Effects of Sex Hormones

Cyclic effects are the marked changes in hormone levels that occur in the female menstrual cycle. The activational effects of hormones in women are consequently more labile than the corresponding effects in men.

Adult men maintain a tonic release of sex hormones, albeit with diurnal variation, from the testes; female hormones are released with an infradian cyclic pattern from the ovaries, by means of a complex feedback loop that includes the hypothalamus and the pituitary. The resultant fluctuation of female hormone levels may result in sensitized hormone receptors that underrespond or overrespond at different time periods. This may lead to affective lability, ego state fluctuations, and a predisposition to affective disturbance (Weissman and Klerman 1985) and certain personality disorders. When affective lability and ego disturbances are superimposed on schizophrenic illness, they lend a specific coloring to the expression of schizophrenic symptoms in women—more affective symptoms, more paranoid symptoms, and fewer deficit symptoms (Westermeyer and Harrow 1984; Goldstein and Link 1988).

Cyclicity and Neuroleptic Response. It is possible that neuroleptic response varies with the menstrual phase in women. Current work in our clinic is attempting to clarify the association of symptoms, menstrual phase, and neuroleptic response. Neuroleptic-induced side effects may also fluctuate over the menstrual cycle. Women's relative protection from acute dystonia (Ayd 1961; Swett 1975) may be explained not only by women's slower gastric emptying but also by homeostatic mechanisms induced by estrogen cyclicity. Acute dystonia is produced by the sudden disruption of the balance between acetylcholine (Ach) and DA that results from DA receptor blockade by neuroleptics. Homeostasis is reestablished over a period of days in men. In women,

dystonias rarely occur, perhaps because homeostatic mechanisms are already in place, required by the on and off DA receptor blockade occurring twice a month as a result of estrogen fluctuation.

In summary, symptom expression and variation in neuroleptic response in women may depend in part on changes induced by the cyclic release of female sex hormones.

Research Implications

What are the research implications of the putative protective effect of estrogens on the schizophrenic process?

Genetic Studies. Given the evidence that milder forms of schizophrenia exist among women than among men, one might expect that affected female relatives of probands would express mild forms. That expectation has implications for linkage studies, since the use of strict criteria to identify affected relatives may miss females with milder forms of illness. Thus, as has been shown in current linkage studies of schizophrenia (e.g., Sherrington et al. 1988), a definition of a broad spectrum of schizophrenia may be important in identifying cases of affected relatives. Age and menstrual status of female probands and female relatives need also to be taken into account in the construction of computerized linkage programs, given the evidence for the effects of estrogens on the expression and severity of psychosis.

Environmental Products. Certain chemicals (polychlorinated biphenyls [PCB's] and insecticides such as DDT) exhibit significant

estrogenic activity (MacLusky 1988). Cimetidine, an H_2 histamine antagonist, is antiandrogenic. Certain antimycotics inhibit aromatase, the enzyme responsible for the aromatization of testosterone to estradiol in the neuron. Similar chemicals are used in agriculture. A number of plants synthesize "phytoestrogens," substances that bear a structural resemblance to estrogens. They are found principally in soybeans, chickpeas, cherries, alfalfa, peas, and beans. They may also accumulate in the form of fungi on grain that has been poorly stored (MacLusky 1988). Whether such substances, which exert weak estrogenic effects, are synergistic or antagonistic to natural hormones is debatable, although some animal studies suggest a net synergistic effect (MacLusky 1988).

Dietary or toxic contributions to schizophrenia severity are complicated variables to study but may be determining factors in, for instance, identical twins who are discordant for schizophrenia. Of significance as well may be the nature of maternal diet or drug ingestion during pregnancies that culminate in genetically at-risk children.

Drug Studies. Menstrual phase, fat distribution, and other male/female differences need to be taken into account in outcome studies of drug response (Hamilton and Parry 1983). This is especially true for drugs like neuroleptics which are lipophilic and exert hormonal effects.

The concomitant use of self-prescribed drugs such as alcohol, narcotics, nicotine, amphetamine, or tetrahydrocannabinol, which can alter hormonal output, is an important variable in the evaluation of drug efficacy and side effects.

Neurocognitive Studies. The study of cognitive strategies in schizophrenia needs to control for gender effects and for menstrual phase effects in women. This may be particularly important in laterality studies since left-right hemisphere sex differences in estrogen receptor levels have been found in rat cerebral cortex (Sandhu et al. 1986).

Clinical Studies. The effects of menstrual phase, contraceptive pills, anovulatory cycles, pregnancy, postpartum period, lactation, and menopause with or without replacement hormones on the severity of symptoms in schizophrenic women need to be documented and assessed. Family studies may need to take the sex of the schizophrenic relative into account when exploring issues of familial precipitants to relapse and family burden.

Epidemiology. The incidence of schizophrenia in children of mothers treated with diethylstilboestrol (DES) and in adults suffering from various hormonal anomalies may contribute to the understanding of gonadal hormone effects in schizophrenia.

It must be noted that research which includes the measurement of hormonal levels is very difficult to conduct. Measurements on saliva are less intrusive than frequent blood lettings, but methodological difficulties have not been overcome. Hormones are released in pulses, and it is difficult to compare levels from different time periods in the same individual or among individuals. Steady states are not long in duration and are affected by the time of day, food intake, fatigue, emotion, and other factors. Levels are altered by many drugs, notably

neuroleptic drugs. It is difficult to study drug-free patients, and most questions that need solutions require daily (at least) knowledge of hormonal levels over several months.

In summary, the organizational and activational (triggering as well as cyclic) effects of gonadal steroids on brain morphology, CNS development, and neurotransmitter systems, in conjunction with the interactional effects of environmental chemicals, open up new areas of research in studies of schizophrenia.

References

Andreasen, N.C.; Olsen, S.A.; Dennert, J.W.; and Smith, M.R. Ventricular enlargement in schizophrenia: Relationship to positive and negative symptoms. *American Journal of Psychiatry*, 139:297-302, 1982.

Andreasen, N.C.; Erhardt, J.C.; Swayze, V.W.; Alliger, R.J.; Yuh, W.T.C.; Cohen, G.; and Ziebell, I.E. Magnetic resonance imaging of the brain in schizophrenia. *Archives of General Psychiatry*, 47:35-44, 1990.

Ayd, F.J. A survey of drug-induced extrapyramidal reactions. *Journal of the American Medical Association*, 175:1054-1060, 1961.

Ayoub, D.M.; Greenough, W.T.; and Juraska, J.M. Sex differences in dendritic structure in the preoptic area of the juvenile macaque monkey brain. *Science*, 219:197-198, 1983.

Bardin, C., and Catterall, J. Testosterone: A major determinant of extragenital sexual dimorphism. *Science*, 211:1285-1294, 1981.

Bellodi, L.; Morabito, A.; Macciardi, F.; Gasperini, M.; Benvenuto, M.G.; Grassi, G.; Matzorati-Spairani, C.; and Smeraldi, E. Analytic considerations about observed distribution of

age of onset in schizophrenia. *Neuropsychobiology*, 8:93-101, 1982.

Brothwood, M.; Wolke, D.; Gamsu, H.; Benson, J.; and Cooper, D. Prognosis of the very low birthweight baby in relation to gender. *Archives of Disease in Childhood*, 61:559-564, 1986.

Brown, T.J.; Hochberg, R.B.; Zielinski, J.E.; and MacLusky, N.J. Regional sex differences in cell nuclear estrogen-binding capacity in the rat hypothalamus and preoptic area. *Endocrinology*, 123:1761-1770, 1988.

Chang, S.S., and Renshaw, D.C. Psychosis and pregnancy. *Comprehensive Therapy*, 12:36-41, 1986.

Chouinard, G., and Annable, L. Pimozide in the treatment of newly admitted schizophrenic patients. *Psychopharmacology*, 76:13-19, 1982.

Chouinard, G.; Annable, L.; Jones, B.D.; and Ross-Chouinard, A. Sex differences and tardive dyskinesia. (Letter to the Editor) *American Journal of Psychiatry*, 137:507, 1980.

Chouinard, G.; Annable, L.; and Steinberg, S. A controlled clinical trial of fluspirilene, a long-acting injectable neuroleptic, in schizophrenic patients with acute exacerbation. *Journal of Clinical Psychopharmacology*, 6:21-26, 1986.

Ciompi, L. The natural history of schizophrenia in the long term. *British Journal of Psychiatry*, 136:413-420, 1980.

Datz, F.L.; Christian, P.E.; and Moore, J. Gender-related differences in gastric emptying. *Journal of Nuclear Medicine*, 28:1204-1207, 1987.

Davidson, I.; Stott, J.; Longstaff, A.; Abramovich, D.; and Pearson, C. Oestrogen concentration in midtrimester human fetal brain: A possible role in its sexual differentiation.

Journal of Steroid Biochemistry, 18:525-529, 1983.

DeVoogd, T.J. Androgens can affect the morphology of mammalian CNS neurons in adulthood. *Trends in Neuroscience*, 10:341-342, 1987.

DiPaolo, T.; Daigle, M.; and Labrie, F. Effect of estradiol and haloperidol on hypophysectomized rat brain dopamine receptors. *Psychoneuroendocrinology*, 9:399-404, 1984.

DiPaolo, T.; Payet, P.; and Labrie, F. Effect of prolactin and estradiol on rat striated dopamine receptors. *Life Sciences*, 31:2921-2929, 1982.

D'Mello, D.A., and McNeil, J.A. Sex differences in bipolar affective disorder: Neuroleptic dosage variance. *Comprehensive Psychiatry*, 31:80-83, 1990.

Dworkin, R.J., and Adams, G.L. Pharmacotherapy of the chronic patient: Gender and diagnostic factors. *Community Mental Health Journal*, 20:253-261, 1984.

Earls, F. Sex differences in psychiatric disorders: Origins and developmental influences. *Psychiatric Development*, 1:1-23, 1987.

Endo, M.; Asano, Y.; Yamashita, I.; Daiguji, M.; and Takahashi, S. Periodic psychosis recurring in association with menstrual cycle. *Journal of Clinical Psychiatry*, 39:456-461; 465-466, 1978.

Fields, J.Z., and Gordon, J.H. Estrogen inhibits the dopaminergic supersensitivity induced by neuroleptics. *Life Sciences*, 30:229-234, 1982.

Flint, N., and Stewart R. Amenorrhea in psychiatric patients. *Archives of General Psychiatry*, 40:589, 1983.

Flor-Henry, P. Schizophrenia: Sex differences. *Canadian Journal of Psychiatry*, 30:319-322, 1985.

Frisch, R. Fatness and fertility. *Scientific American*, 258:88-95, 1988.

Glazer, W.M.; Naftolin, F.; Moore, D.C.; Bowers, M.; and MacLusky, N.J. The relationship of circulating estradiol to tardive dyskinesia in men and post-menopausal women. *Psychoendocrinology*, 9:429–434, 1981.

Glick, J., and Steward, D. A new drug treatment for premenstrual exacerbation of schizophrenia. *Comprehensive Psychiatry*, 21:281–287, 1980.

Goldman, P.; Crawford, H.; Stokes, L.; Galkin, T.; and Rosvold, H. Sex dependent behavioral effects of cerebral cortical lesions in the developing rhesus monkey. *Science*, 186:540–542, 1974.

Goldstein, J.M. Gender differences in the course of schizophrenia. *American Journal of Psychiatry*, 145:684–689, 1988.

Goldstein, J.M., and Kreisman, D. Gender, family environment, and schizophrenia. *Psychological Medicine*, 18:861–872, 1988.

Goldstein, J.M., and Link, B. Gender differences in the clinical expression of schizophrenia. *Journal of Psychiatric Research*, 22:141–155, 1988.

Green, M.F.; Satz, P.; Soper, H.V.; and Kharabi, F. Relationship between physical anomalies and age at onset of schizophrenia. *American Journal of Psychiatry*, 144:666–667, 1987.

Gur, R.C.; Gur, R.E.; Obrist, W.D.; Hungerbuhler, J.P.; Younkin, D.; Rosen, A.D.; Skolnick, B.E.; and Reivich, M. Sex and handedness differences in cerebral blood flow during rest and cognitive activity. *Science*, 217:659–661, 1982.

Hamburger, V., and Oppenheim, R.W. Naturally occurring neuronal death in vertebrates. *Neuroscience Commentaries*, 1:39–55, 1982.

Hamilton, J., and Parry B. Sex-related differences in clinical drug response: Implications for women's health. *Journal of the American Medical Women's Association*, 38:126–132, 1983.

Harding, C.M.; Brooks, G.W.; Ashikaga, T.; Strauss, J.S.; and Breier, A. The Vermont longitudinal study of persons with severe mental illness: II. Long-term outcome of subjects who retrospectively met *DSM-III* criteria for schizophrenia. *American Journal of Psychiatry*, 144:727–735, 1987.

Hruska, R.E. Elevation of striatal dopamine receptors by estrogen: Dose and time studies. *Journal of Neurochemistry*, 47:1908–1915, 1986.

Kane, J.M., and Smith, J.M. Tardive dyskinesia: Prevalence and risk factors, 1959–1979. *Archives of General Psychiatry*, 39:473–481, 1982.

Keepers, G.A.; Clappison, V.J.; and Casey, D.E. Initial anticholinergic prophylaxis for neuroleptic-induced extrapyramidal syndromes. *Archives of General Psychiatry*, 40:1113–1117, 1983.

Kendell, R.E. Emotional and physical factors in the genesis of puerperal mental disorder. *Journal of Psychology*, 1:3–11, 1985.

Kendell, R.E.; Chalmers, J.C.; and Platz, C. Epidemiology of puerperal psychoses. *British Journal of Psychiatry*, 150:662–673, 1987.

Kimura, D., and Harshman, R. Sex differences in brain organization for verbal and non verbal functions. *Progress in Brain Research*, 61:423–441, 1984.

Kolakowska, T.; Williams, A.O.; Ardern, M.; Reveley, M.A.; Jambor, K.; Gelder, M.G.; and Mandelbrote, B.M. Schizophrenia with good and poor outcome: I. Early clinical

features, response to neuroleptics and signs of organic dysfunction. *British Journal of Psychiatry*, 146:229–239, 1985.

Lewine, R.R.J. Sex differences in age of symptom onset and first hospitalization in schizophrenia. *American Journal of Orthopsychiatry*, 50:316–322, 1980.

Lewine, R.R.J. Schizophrenia: An amotivational syndrome in men. *Canadian Journal of Psychiatry*, 30:316–318, 1985.

Lewine, R.R.J.; Brubach, D.; and Meltzer, H.Y. Effect of diagnostic criteria on the ratio of male to female schizophrenic patients. *American Journal of Psychiatry*, 141:84–87, 1984.

Lewis, S.W., and Murray, R.M. Obstetric complications, neurodevelopmental deviance, and risk of schizophrenia. *Journal of Psychiatric Research*, 21:413–421, 1987.

Lipsey, J., and Robinson, R. Sex dependent behavioral response to frontal cortical suction lesions in the rat. *Life Sciences*, 38:2185–2192, 1986.

Loranger, A.W. Sex differences in age at onset of schizophrenia. *Archives of General Psychiatry*, 41:157–161, 1984.

MacLusky, N.J. Developmental actions of gonadal steroids. *Progress in Clinical Biological Research*, 281:243–263, 1988.

MacLusky, N.; Clark, A.S.; Naftolin, F.; and Goldman-Rakic, P.S. Estrogen formation in the mammalian brain: Possible role of aromatase in sexual differentiation of the hippocampus and neocortex. *Steroids*, 50:459–474, 1987.

MacLusky, N.J., and Naftolin, F. Sexual differentiation of the central nervous system. *Science*, 211:1294–1303, 1981.

McEwen, B.S. Neural gonadal steroid actions. *Science*, 211:1303-1311, 1981.

McEwen, B.S. Actions of sex hormones on the brain: "Organization" and "activation" in relation to functional teratology. *Progress in Brain Research*, 73:121-134, 1988a.

McEwen, B.S. Genomic regulation of sexual behavior. *Journal of Steroid Biochemistry*, 30:179-183, 1988b.

McMillen, M.M. Differential mortality by sex in fetal and neonatal deaths. *Science*, 204:89-91, 1979.

McNeil, T.F. A prospective study of postpartum psychoses in a high-risk group: 2. Relationships to demographic and psychiatric history characteristics. *Acta Psychiatrica Scandinavica*, 75:35-43, 1987.

McNeil, T.F.; Kaij, L.; and Malmquist-Larsson, A. Women with non-organic psychosis: Pregnancy's effect on mental health during pregnancy. *Acta Psychiatrica Scandinavica*, 70:140-148, 1984.

Mott, P.N. Psychiatric illness following childbirth in Southampton: A case register study. *Psychological Medicine*, 12:557-561, 1982.

Nedopil, N.; Pflieger, R.; and Ruther, E. The prediction of acute response, remission and general outcome of neuroleptic treatment in schizophrenic patients. *Pharmacopsychiatry*, 16:201-205, 1983.

Olmos, G.; Aquilera, P.; Tranque, P.; Naftolin, F.; and Garcia-Sequra, L.M. Estrogen-induced synaptic remodelling in adult rat brain is accompanied by the reorganization of neuronal membranes. *Brain Research*, 425:57-64, 1987.

Rutter, M. Psychosocial resilience and protective mechanisms. *American Journal of Orthopsychiatry*, 57:316-331, 1987.

Rutter, M., and Quinton, D. Parental psychiatric disorder: Effects on children. *Psychological Medicine*, 14:853-880, 1984.

Salokangas, R.K.R. Prognostic implications of the sex of schizophrenic patients. *British Journal of Psychiatry*, 142:145-151, 1983.

Sampson, E., and Kimura, D. Reciprocal effects of hormonal fluctuations on human motor and perceptual-spatial skills. *Behavioral Neuroscience*, 102:456-459, 1988.

Sandhu, S.; Cook, P.; and Diamond, M. Rat cerebral cortical estrogen receptors, male-female, right-left. *Experientia Neurologica*, 92:186-196, 1986.

Seeman, M.V. Gender and the onset of schizophrenia: Neurohumoral influences. *Psychiatric Journal of the University of Ottawa*, 6:136-138, 1981.

Seeman, M.V. Gender differences in schizophrenia. *Canadian Journal of Psychiatry*, 27:107-112, 1982.

Seeman, M.V. Interaction of sex, age, and neuroleptic dose. *Comprehensive Psychiatry*, 24:125-128, 1983a.

Seeman, M.V. Schizophrenic men and women require different treatment programs. *Journal of Psychiatric Treatment and Evaluation*, 5:143-148, 1983b.

Seeman, M.V. Current outcome in schizophrenia: Women vs. men. *Acta Psychiatrica Scandinavica*, 73:609-617, 1986.

Seeman, M.V. Neuroleptic prescription for men and women. *Social Pharmacology*, 3:219-236, 1989.

Seeman, M.V., and Hauser, P. Schizophrenia: The influence of gender on family environment. *International Journal of Family Psychiatry*, 5:227-232, 1984.

Seeman, M.V., and Seeman, P. Molecular psychiatry, receptor density, and receptor sensitivity states. *Integrative Psychiatry*, 4:41-43, 1986.

Sherrington, R.; Brynjolfsson, J.; Petursson, H.; Potter, M.; Dudleston, K.; Barraclough, B.; Wasmuth, J.; Dobbs, M.; and Gurling, H. Localization of a susceptibility locus for schizophrenia on chromosome 5. *Nature*, 336:164-166, 1988.

Sholl, S., and Pomerantz, S. Androgen receptors in the cerebral cortex of fetal rhesus monkeys. *Endocrinology*, 119:1625-1631, 1986.

Smith, J., and Dunn, D. Sexual differences in the prevalence of severe tardive dyskinesia. *American Journal of Psychiatry*, 136:1080-1082, 1979.

Swaab, D.F., and Fliers, E. A sexually dimorphic nucleus in the human brain. *Science*, 228:1112-1115, 1985.

Swett, C. Drug-induced dystonia. *American Journal of Psychiatry*, 132:532-534, 1975.

Taylor, D.C. Differential rates of cerebral maturation between sexes and between hemispheres. *Lancet*, II:140-142, 1969.

Toran-Allerand, C. On the genesis of sexual differentiation of the central nervous system: Morphogenetic consequences of steroidal exposure and possible role of alpha-fetoprotein. *Progress in Brain Research*, 61:63-98, 1984.

Tourney, G., and Hatfield, L. Plasma androgens in male schizophrenics. *Archives of General Psychiatry*, 27:753-755, 1972.

Uriel, J.; DeNechaud, B.; and Dupiers, M. Estrogen binding properties of rat, mouse, man fetospecific serum proteins. Demonstration by immuno-autoradiographic methods. *Biochemistry and Biophysics Research*

Communications, 45:1175-1180, 1972.

Van Hartesveldt, C., and Joyce, J. Effects of estrogen on the basal ganglia. Neuroscience and Biobehavior Review, 10:1-14, 1986.

Van Putten, T.; May, P.R.A.; Marder, S.R.; and Wiltmann, L.A. Subjective response to antipsychotic drugs. Archives of General Psychiatry, 38:187-190, 1981.

Vaughn, C.E.; Snyder, K.S.; Jones, S.; Freeman, W.B.; and Falloon, I.R.H. Family factors in schizophrenic relapse. Archives of General Psychiatry, 41:1169-1177, 1984.

Vito, C.; Baum, M.; Bloom, C.; and Fox, T. Androgen and estrogen receptors in perinatal ferret brain. Journal of Neuroscience, 5:268-274, 1985.

Watt, D.C.; Katz, K.; and Shepherd, M. The natural history of schizophrenia: A 5-year prospective follow-up of a representative sample of schizophrenics by means of a standardized clinical and social assessment. Psychological Medicine, 13:663-670, 1983.

Wattie, B.J.S., and Kedward, H.B. Gender differences in living conditions found among male and female schizophrenic patients on a follow-

up study. International Journal of Social Psychiatry, 31:205-216, 1985.

Weinberger, D.R.; Bigelow, L.B.; Kleinman, J.E.; Klein, S.T.; Rosenblatt, J.E.; and Wyatt, R.J. Cerebral ventricular enlargement in schizophrenia. An association with poor response to treatment. Archives of General Psychiatry, 37:11-13, 1980.

Weissman, M.M., and Klerman, G.L. Gender and depression. Trends in Neurosciences, 8:416-420, 1985.

Westermeyer, J.F., and Harrow, M. Prognosis and outcome using broad (DSM-II) and narrow (DSM-III) concepts of schizophrenia. Schizophrenia Bulletin, 10:624-637, 1984.

Wong, D.F.; Wagner, H.N., Jr.; Dannals, R.F.; Links, J.M.; Frost, J.J.; Ravert, H.T.; Wilson, A.A.; Rosenbaum, A.E.; Gjedde, A.; Douglass, K.H.; Petronis, J.D.; Folstein, M.F.; Toung, J.K.T.; Burns, H.D.; and Kuhar, M.J. Effects of age on dopamine and serotonin receptors measured by positron tomography in the living human brain. Science, 226:1393-1396, 1984.

Young, M.A., and Meltzer, H.Y. The relationship of demographic, clinical, and outcome variables to neuroleptic treatment requirements. Schizophrenia Bulletin, 6:88-101, 1980.

Zito, J.M.; Routt, W.W.; Mitchell, J.E.; and Roerig, J.L. Clinical characteristics of hospitalized psychotic patients who refuse antipsychotic drug therapy. American Journal of Psychiatry, 142:822-826, 1985.

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