GENDER ISSUES IN PSYCHIATRY

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ABSTRACT

During the past decade, the psychiatric literature has reflected a new level of interest in gender as a key variable in psychopathology research and psychiatric services delivery. Many of the advances in knowledge during the past decade are gender-related. It has long been known that chromosomal sex determination initiates sexually dimorphic developments that determine the later structure and function of the central nervous system in women and men. New information has substantially modified the ways in which basic scientists are thinking about these matters. There are also critical social influences that affect the trajectory of each human's development.

This brief overview of the major developments during the past 20 years attempts to highlight changing concepts during this time and to speculate what the next 10 years may bring.

INTRODUCTION

In the late 1980s, there was growing realisation, particularly in the USA, that medical research had not always served women well. It was noted that many drug trials excluded women, for example aspirin for coronary heart disease.[1] The General Auditing Office (GAO) report in 1990 criticised this practice, noting that even the National Institutes of Health had often not implemented their own guidelines. In 1993, USA Federal Drug Administration regulations revised recommendations, which suggested that:

- Drug development data should be analysed by gender
- Factors unique to women should be studied, including the effects of menstrual cycle and drug interactions with oral contraceptives and other hormone therapies.

Whilst these are recommendations only, they were considered likely to be effective in ensuring that both genders will more adequately benefit from health research. It is important to think about why women had been excluded so that future research can be more equitable. There were major and valid concerns about teratogenicity following the disasters with thalidomide and diethylstilbestrol used during pregnancy. Also, the menstrual cycle had been seen as a complex confounder, leading to a view that many research questions were too difficult to study sensibly in women. Both of these reasons are related to female reproductive function, signalling an inability of previous research to encompass the real parameters of women's lives. A paradigm shift seems to have occurred resulting in a different consideration of the menstrual cycle as a reasonably predictable biological rhythm changing at a pace that facilitates study. The menstrual cycle can provide a model for other biological rhythms which change either very much faster or much more slowly and which are genuinely difficult to follow.

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In addition, an international concern was developing that gender or race may determine unfairly the ways in which medical research is funded worldwide. The medical research agenda in each country is profoundly influenced by local political concerns and gender issues have not always been considered in a balanced and even-handed manner.

PSYCHIATRIC EPIDEMIOLOGY

Many key gender findings have emerged from large-scale psychiatric epidemiology research activities of the epidemiological catchment site study and National Comorbidity Survey of 1980-1999.[2-4] These replicated, in major measure, results from many previous studies that had used smaller scale methodologies. The latest epidemiological projects using different case finding instruments in the United Kingdom and Australia confirm these gender results.[5-8] Women have greater rates of depression, anxiety disorders, and somatisation disorders than men. Conversely, men have greater rates of substance abuse disorders and some personality disorders. There is a clear consensus about gender differences in mental illness. The key questions now to be asked are about how gender determines the development and experience of these common disorders.

There are also a number of important well-replicated negative gender findings. In the major mental illnesses such as schizophrenia and bipolar affective disorders, there are few if any female-male differences in prevalence. The one published exception to this, the higher female rates of schizophrenia reported by the Twelve Centers Epidemiology Study in China, may be explained by differences in case finding methods.[9] Women however have a later onset of schizophrenia and better outcome, and many observers have linked this to reproductive hormone levels, particularly oestrogens.[10-14]

These gender findings have finally settled a number of queries that were often heard in the days when we had data only from clinic studies. There had been a belief that women

more frequently attend general practitioners and outpatient clinics because they are more comfortable acknowledging psychological distress and disorder to themselves and seek help for it. Whilst this is almost certainly true, it is now clear that women also have higher base rates of the common mental disorders, regardless of whether they seek assessment and treatment or not.

Gender differences have been replicated for child and adolescent psychiatric disorders. Boys are more likely to show disorder in childhood. There are important differences in the types of disorders found in each gender. Boys are more likely to display the so-called externalising disorders such as conduct disorder, whilst girls typically show the internalising disorders of depression and anxiety. Gender differences in neuro-physiological responses to trauma have been reported which may explain these findings.[15,16] Boys show hyperarousal — motor hyperactivity, impulsivity, and hypervigilance — a syndrome believed to be mediated through noradrenaline (NA) at the locus coruleus, the hypothalamic pituitary axis, and the adrenal glands (both the medulla and the cortex) in the classical 'fight-flight' enunciated by Cannon many years ago.[17]

In contrast, girls appear preferentially to show a dissociative response, characterised by avoidance, depression, and faint 'surrender', which is also brain stem-mediated by NA via the hypothalamic-pituitary axis. There is also an increase in vagal tone, leading to a decrease in blood pressure and heart rate. Involvement of dopamine (mesolimbic and mesocortical) activating the endogenous opiate mechanisms has been postulated.[16] By adolescence, the adult pattern of psychiatric disorders is emerging, raising speculation about the role of puberty, social changes, or both as causal.[16,18]

As others have done, Frank and Young focus on periods of withdrawal of ovarian hormones (both oestrogen and progesterone) in females at times of increased symptomatology.[19] Oestrogen is known to modulate the noradrenaline, serotonin, and dopamine systems, decreasing noradrenaline uptake from the synapse and increasing the number of serotonin receptors, both being similar to antidepressant effects.

USE OF PSYCHOTROPIC DRUGS

There are also important gender psychopharmacological considerations. Women are prescribed and take more drugs than men and probably experience more side effects than men. The ratio of lean body mass to adipose tissue, blood volume, cardiac output and organ size are all greater in men than in women. Given that women in general have more adipose tissue than men, drugs with a high fat affinity have a greater volume in which to be distributed in women. They therefore will be present in lower serum concentration but will show a great storage potential in women.

Further, several physiological functions responsible for drug pharmacodynamics and pharmacokinetics alter during the menstrual cycle. These include pulse rate, blood pressure, respiration rate, water retention, gastrointestinal transit time, urinary excretion, and arteriolar sensitivity to hormones, catecholamines, and oxytocin concentration. These factors need to be considered when prescribing psychotropic agents to women, particularly where the drug data may have come from mainly male populations. There are also sensitive and complex issues concerning the use of such drugs during each of the phases of pregnancy and during lactation — frequently the prescriber does not have adequate information to guide the decision and more research is required.

EXPLANATIONS FOR GENDER DIFFERENCES

Gender differences can be explained either psychosocially or biologically; it is likely that both groups of factors interact in complex ways.[20,21]

PSYCHOSOCIAL THEORIES

Psychosocial theories draw on the inferior social status of women in most societies. Issues to be considered are socio-economic status, which includes frank poverty, education, employment, social networks, abuse, and violent experiences. Poverty, both relative and absolute, adversely affects both physical and psychological health. Globally, poverty affects more women than men — it is estimated that 70% of the world's poor are women. Some contributing factors include the greater priority women give to the society's child-care and elder-care tasks. Women usually head single parent families. There are important gender differences in qualifications received and employment patterns. Women frequently face significant employment problems. In most countries, it is often difficult for women to find well-paid, safe work that fits in easily with their domestic responsibilities.

Lower socio-economic status has been repeatedly linked to psychiatric disorder and is probably operationalised through low income, poor-quality housing, nutrition, medical care, contraception, childcare, inadequate information to negotiate obscure welfare systems, and fragmented communities. In addition to this, low socio-economic status generates a sense of inferiority and low self-esteem, which predisposes people to psychiatric disorder. Social relationships both determine and result from psychiatric illness.[22-25] Social support is often closely linked to employment. A number of gender differences in social relationships have been reported. Women are usually more affiliative. The effects of marriage and widowhood differ for men and women. To give just one example amongst many, women are less likely to become depressed after being widowed than are men.[26]

INTERPERSONAL VIOLENCE

In general, interpersonal violence is a greater problem for women than for men. Only war zone violence and that perpetrated by strangers outside the home has more male than female victims; in all other violent situations, women are more frequently victims, often dramatically so. Much research into the prevalence of physical and sexual abuse and its consequences has been completed during the past decade. The reader is encouraged to read a sample of relevant literature which has recently been published.[27-32]

Physical, sexual, and emotional violence should now be seen as a non-specific risk factor for a wide range of medical, psychiatric, and psychological problems that women frequently experience. Elder abuse needs adequate public health attention in many countries. Violence and abuse is anchored in and transmitted through the family and implicitly condoned by societal institutions. Physicians, including psychiatrists, have a responsibility to work in concert with lawmakers, law providers, and welfare agencies to provide primary and secondary prevention of these problems.

The effects of multiple disadvantages take their additive toll on the psychological and physical health of women. Consider the low socio-economic status black woman, who is poorly educated, does low paid and potentially dangerous work, with a psychiatric illness, who fears the effect of poverty on her children and experiences bigotry and racism on a daily basis.

BIOLOGICAL THEORIES

There have been considerable advances in our understanding of the basic biological central nervous system (CNS) differences between females and males during the past 20 years, which have altered key concepts about prenatal development and the way in which gonadal steroids influence adult mental functioning. It has been known for many years that gender, determined at conception by the chromosomal complement, sets in train certain processes that result in dimorphic brain structure and function.

The role of key hormones is now seen as more complicated than was previously thought and the brain is viewed as more plastic. Sex steroids should be viewed as neurosteroids, both neuro-receptors and modulators.[33,34] Neurosteroids are those steroids synthesised in the brain. They may be neuro-active or neuro-inactive; when active they regulate the synthesis and activity of enzymes and receptors and modulate neuronal excitability. Recently, receptors for sex steroid hormones in the brain have been clearly identified. Oestrogen receptors are involved in neuronal growth, leading to the conclusion that sex hormones and receptors may profoundly influence mood, thought, and behaviour.

This research has lead to new concepts about prenatal development and how the dimorphic CNS develops. The earlier view held that the default state in mammals was female and the developing foetus became a male individual only if androgens were added early in prenatal life. Such a model cannot encompass easily the oestrogen receptors in the developing brains of males. The more sophisticated view is that the developing brain is exposed to both testosterone and ovarian hormones, which act in association with adrenal hormones, growth factors, and neurotransmitters. Together these produce the permanent male-female differences in brain structure and subsequent behaviours, including cognitive functions.

In mammals, females have larger brains in proportion to body size than males and larger corpora collosa and anterior commissures relative to brain size. The female brain shows less hemispheric asymmetry, lacking the greater right-sided hemispheric volume typically seen in male brains. In animal studies, some of these lateralisation effects can be cancelled by exposure to stress or oestrogen at certain critical periods prenatally and perinatally. There are also sexual differences in the limbic lobe, including greater hippocampal plasticity (sprouting of dendrites in an enriched environment) in female brains; testosterone may suppress this plasticity. Some hypothalamic nuclei are larger in males and are thought to regulate male sexual behaviour. Positron emission tomography studies have suggested greater global cerebral blood flow and glucose metabolism in women than men. The patterns of brain synapses and dendritic spines vary in relation to oestrogen levels in the oestrus cycle of the rodent.

Oestrogen increases the sensitivity to serotonin agonists. Oestrogen has an anti-dopamine action post-pubertally,[35-37] stimulating prolactin secretion by down-regulating dopamine receptors in the anterior pituitary. Oestrogen also affects the immune system through an effect on lymphocyte concentrations, for example during pregnancy. Oestrogen up-regulates γ-aminobutyric acid. Progesterone and one of its metabolites acts as a sedative, anxiolytic, and anticonvulsant. Thus, it is more than possible that fluctuations of gonadal hormones and their metabolites during the menstrual cycle may contribute to alterations in mood and cognition.

A number of fascinating clinical studies have examined the use of sex hormones in the treatment of depression and puerperal disorders such as psychosis in women.[38-41] It appears that women who experience marked dysphoria premenstrually are more liable to develop post-natal and post-menopausal syndromes at phases of her life when her sex hormones are low or falling rapidly. Some women with puerperal psychosis experience the subsequent return of their psychotic symptoms premenstrually.[42] The variable results of these studies collectively can be seen as supporting an hypothesis that some women are vulnerable to either low levels of oestrogen, or possibly progesterones, or to the rate of change of these hormones. These changes in what Frank and Young have recently dubbed "the neuroendocrine soup in which our brains reside" determine susceptibility to psychiatric conditions.[19] These ideas have been brought together in the concept of the 'hypoestrogenic brain' as outlined by Arpels, who reductionistically sees a women's brain as an 'oestrogen end organ'.[43]

In summary, recent research has established unequivocally that there are major gender CNS differences in brain structure and function. Changes in reproductive (and other) hormones can reversibly alter brain structure and function.

THE FUTURE

Where are we likely to go from here? We are likely to see further academic appointments in women's mental health, the development of more gender health journals similar to the Archives of Women's Mental Health, further faculties dedicated to gender and mental health such as the Women's Mental Health Section of the World Psychiatric Association, and ongoing psychiatric studies in which gender is researched in a sophisticated manner. There will be the publication of

more books focused on gender and mental health.[24,44-46] These findings from good quality gender mental health research will inevitably flow through to greater concern about acceptability of services to women; are they welcoming, safe, free from sexual harassment, and subtle sexism, and do they cater for women's multiple social roles as worker, mother, wife, social support, and carer, many of which are undervalued but essential to the smooth running of society.

REFERENCES

1. Jensvold MF, Halbreich U, Hamilton JA. Psychopharmacology and women; sex, gender and hormones. Washington, DC: American Psychiatric Press; 1996.
2. Regier D, Boyd JH, Burke JD, et al. One-month prevalence of mental disorders in the United States: based on five epidemiological catchment (ECA) sites. Arch Gen Psychiatry 1988;45:977-986.
3. Kessler R, McGonagle K, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States; results from the National Comorbidity Survey. Arch Gen Psychiatry 1994;51:8-19.
4. Kessler RC, Nelson CB, McGonagie KA, et al. The epidemiology of co-occurring addictive and mental disorders: implications for prevention and service utilization. Am J Orthopsychiat 1996; 66:17-31.
5. Mason P, Wilkinson G. The prevalence of psychiatric morbidity: OPCS survey of psychiatric morbidity in Great Britain. Br J Psychiatry 1996;168:1-3.
6. Meltzer H, Gill B, Pettigrew M, et al. The prevalence of psychiatric morbidity among adults living in private households; OPCS surveys of psychiatric morbidity in Great Britain. Report 1. London: HMSO Publications Centre; 1995.
7. Henderson S, Andrews G, Hall W. Australia's mental health: an overview of the general population survey. Aust NZ J Psychiatry 2000;34:197-205.
8. Tesson M, Hall W, Lynskey M, et al. Alcohol- and drug-use disorders in Australia: implications of the National Survey of Mental Health and Wellbeing. Aust NZ J Psychiatry 2000;34:206-213.
9. Pearson V. The mental health of women in China. HK J Psychiatry 1998;8:3-8.
10. Szymanski S. Sex differences in schizophrenia. In: Jensvold MF, Halbreich U, Hamilton JA, eds. Psychopharmacology and women. Washington DC: American Psychiatric Press; 1996: 287-297.
11. Szymanski S, Lieberman JA, Alvir JM, et al. Gender differences in onset of illness, treatment response, course, and biologic indexes in first-episode schizophrenic patients. Am J Psychiatry 1995; 152:698-703.
12. Seeman MV. Gender differences in treatment response in schizophrenia. In: Seeman MV, ed. Gender and psychopathology. Washington DC: American Psychiatric Press; 1995.
13. Seeman MV. Schizophrenia, gender and affect. Can J Psychiatry, 1996;41:263-264.
14. Seeman MV, Lang M. The role of estrogens in schizophrenia gender differences. Schizophren Bull, 1990;16:185-194.
15. Perry BD, Pollard R. Homeostasis, stress, trauma, and adaptation. A neurodevelopmental view of childhood trauma. Child Adolescent Psychiatr Clin North Am 1998;7:33-51.
16. Perry BD, Azad I. Posttraumatic stress disorders in children and adolescents. Curr Opin Pediatr 1999;11:310-316.
17. Cannon WB. Bodily changes in pain, hunger, fear and rage: an account of recent researches into the function of emotional excitement. 2nd ed. New York: Appleton-Century; 1936.
18. Angold A, Worthman CW. Puberty onset of gender differences in rates of depression; a developmental, epidemiologic and neuroendocrine perspective. J Aff Disorders 1993;29:145-158.
19. Frank E, Young E. Pubertal changes and adolescent challenges: why do rates of depression rise precipitously for girls between ages 10 and 15 years? In: Frank E, ed. Gender and its effects on psychopathology. Washington DC: American Psychiatric Association Inc; 2000.
20. Engel G. The clinical application of the biopsychosocial model. Am J Psychiatry 1980;137:535-547.
21. Eisenberg L. Is psychiatry more mindful or brainier than it was a decade ago? Br J Psychiatry 2000;176,1-5.
22. Romans S, Walton V, McNoe B, et al. Otago women's health survey 30-months follow-up. I: onset patterns of non-psychotic psychiatric disorder. Br J Psychiatry 1993;163:733-738.
23. Romans S, Walton V, McNoe B, et al. Otago Women's Health survey 30-month follow-up. II: remission patterns of non-psychotic psychiatric disorder. Br J Psychiatry 1993;163:739-746.
24. Romans SE. Folding back the shadows: a perspective on women's mental health. Dunedin: University of Otago Press; 1998.
25. Romans SE. Women and social relatedness. In Romans SE, ed. Folding back the shadows: a perspective on women's mental health. Dunedin: University of Otago Press; 1998.
26. van Grootheest DS, Beckman ATF, van Groenooou, MIB, et al. Sex differences in depression after widowhood. Do men suffer more? Soc Psychiatry Psychiatr Epidemiol 1999;34:391-398.
27. Higenbottam T. Women victims of domestic violence. Br Med J 1989;299:995-996.
28. McLeer SV, Anwar RA, Herman S, et al. Education is not enough: a systems failure in protecting battered women. Ann Emerg Med 1989;18:651-653.
29. Randall T. Domestic violence begets other problems of which the physicians must be aware to be effective. JAMA 1990;264:943-944.
30. Mazza D, Dennerstein L, Ryan V. Physical, sexual and emotional violence against women: a general practice-based prevalence study. Med J Aust 1996;164:14-17.
31. Mullen PE, Martin JL, Anderson JC, et al. The long-term impact of the physical, emotional and sexual abuse of children: a community study. Child Abuse Neglect 1995;20:7-21.
32. Richardson J, Feder G. Domestic violence: a hidden problem for general practice. Br J Gen Pract 1996;46:239-242.
33. Mellon SH. Neurosteroids: biochemistry, modes of action and clinical relevance. J Clin Endocrinol Metab 1994;78:1003-1008.
34. Bicknell RJ. Sex-steroid actions on neurotransmission. Curr Opin Neurol 1998;11:667-671.
35. Hafner H, Behrens S, De Vry J, et al. An animal model for the effects of estradiol on dopamine-mediated behavior: implications for sex differences in schizophrenia. Psychiatry Res 1991;38:125-134.
36. Hafner H, Behrens S, De Vry J, et al. Oestradiol enhances the vulnerability threshold for schizophrenia in women by an early effect on dopaminergic neurotransmission. Evidence from an epidemiological study and from animal experiments. Eur Arch Psychiatr Clin Neurosci 1991;241:65-68.
37. Riecher-Rossler A, Hafner H, Stumbaum M, et al. Can estradiol modulate schizophrenic symptomatology? Schizophr Bull 1994; 20:203-14.
38. Klaiber EL, Broverman DM, Vogel W, et al. Estrogen therapy for severe persistent depressions in women. Arch Gen Psychiatry 1979;36:550-554.
39. Gregoire AJ, Kumar R, Everitt B, et al. Transdermal oestrogen for treatment of severe postnatal depression [see comments]. Lancet 1996;347:930-933.
40. Zweifel JE, O'Brien WH. A meta-analysis of the effect of hormone replacement therapy upon depressed mood. Psychoneuroendocrinology 1997;22:189-212.
41. Ahokas AJ, Turtiainen S, Aito M. Sublingual oestrogen treatment of postnatal depression [letter]. Lancet 1998;351:109.
42. Brockington IF, Kelly A, Hall P, et al. Premenstrual relapse of

puerperal psychosis. J Aff Disorders 1988;14:287-292.
43. Arpels JC. The female brain hypoestrogenic continuum from the premenstrual syndrome to menopause. A hypothesis and review of supporting data. J Reprod Med 1996;41:633-639.
44. Seeman MV. Gender and psychopathology. Washington DC: American Psychiatric Press; 1995.
45. Wallis LA, Kasper AS, Reader GG, et al. Textbook of women's Health. Philadelphia: Lippincott-Raven; 1998.
46. Frank E. Gender and its effects on psychopathology. Washington DC: American Psychiatric Association Inc; 2000.

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