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Guest Editorial

Intervening early across the lifespan: going beyond youth-focused psychosis care to meet the needs of women

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Psychotic disorders have sex-specific differences in their onset, symptoms and course. The early intervention in psychosis model represented the first step toward personalised psychosis care, recognising stage-specific care needs. Incorporating knowledge about sex-specific differences in care programmes should be the next evolution of personalised psychosis care.

Keywords
Sex-specific differences; service development; personalised care; early intervention in psychosis; first-episode psychosis.

Early intervention in psychosis: the first step toward personalised psychosis care

Psychiatry has always aspired toward the kind of personalised care that is increasingly embedded in specialities such as oncology and cardiology. Personalised medicine is not novel, indeed William Osler's view was that 'it's much more important to know what sort of a patient has a disease then what sort of disease a patient has'. Other specialities have operationalised this philosophy through the development of personalised risk scores and tailored treatment plans, reflecting an accumulation of knowledge regarding interindividual differences. Psychiatry has some way to go in this regard, with clinical treatment remaining, in the main, a homogeneous offering.

Yet progress has begun. The developmental of specialised services for the treatment of psychosis, the early intervention in psychosis (EIP) model, represented one of the first large-scale attempts to deliver a personalised approach to treatment. It was recognised that those with early-stage psychotic illnesses had different care needs to those with a more established course. This focused service delivery on rapid detection, a low threshold for assessment and phase-specific psychosocial interventions, making a distinction from the focus of adult mental health services on 'chronic and enduring' mental illness. The first EIP service built on these principles was founded in Melbourne, Australia, in the 1990s.[1] The model has since been adopted across the world. There is robust evidence of superior outcomes with this approach,[1] which is the goal of any personalised treatment programme.

Focusing care on the incident peak of the first episode of psychosis (FEP) centred these services on late adolescence and early adulthood. Many retained an upper age limit of 35 years. Psychosocial interventions reflected the developmental challenges of this phase of life: individuation from family, engagement in tertiary education or career building, establishing and maintaining intimate relationships and friendships, building agency and self-efficacy. The life-building that can be so thoroughly derailed by a psychotic illness. This had the effect of characterising these services as youth mental health services. More recently, there have been specific calls for EIP services to be further integrated with and reformulated as broad youth mental health services.[2]

Nevertheless, it is worth questioning whether focusing exclusively on a single determinant of illness outcome, early-life onset, and structuring EIP services ever more closely around this factor is the optimal approach to improve outcomes for all experiencing a FEP. The success of the EIP model prompts the consideration of other well-replicated, illness-modifying factors that could enhance this framework further. Among the most consistently observed findings in the epidemiology of psychosis are sex-related differences in onset, symptoms and course. Although this was recognised at the inception of the EIP model, the subsequent three decades have yielded a more nuanced understanding of sex-specific differences from aetiology to outcome. This begs the question: is it time for the next evolution in personalised psychosis care, one that is predicated on a sex-specific approach?

Biological determinants: the ovarian hormone rollercoaster in psychosis

Sex-specific differences in the onset and progression of psychosis have been extensively documented, with a differential age at onset being one of the most consistently reported. Women tend to develop psychosis later than men, with a distinct bimodal incidence curve, peaking in early adulthood and again in the fourth to fifth decade.[3] The alignment of these risk periods with key transitions in the reproductive life cycle has drawn attention to the role of gonadal hormones in modulating psychosis risk.

Although oestradiol is a broadly protective hormone against neuronal oxidative stress and inflammation, it confers a particular protection for psychosis vulnerability. This is evident early on, with earlier menarche associated with a delayed onset of schizophrenia. For individuals with an established psychotic disorder, elevated levels of circulating oestrogen are correlated with improvements in both negative and cognitive symptoms. Oestradiol-mediated sensitisation of dopamine D_2 and D_3 receptors in the ventral tegmental area modulates psychotic symptoms.[4,5] Overall, symptom profiles tend toward greater affective comorbidity in women, and more pronounced negative and cognitive symptoms in men.

However, although oestradiol is protective, its level is not constant. During reproductive years, hormone levels fluctuate cyclically over a much larger range in women than in men. Psychiatric admissions increase during the perimenstrual phase of the cycle, with an improvement in psychotic symptomatology as oestradiol builds again.[4] The point of one of the most acute drops in oestradiol levels, the puerperium, coincides with a dramatic increase in psychosis risk. Post-menopause, hospital admission rates for existing psychotic disorders equilibrate between men and women, and women experience the second 'peak' of FEP. Protection during periods of oestrogen peaks and vulnerability during hypoestrogenic troughs and eventual withdrawal are two sides of the same coin, and are essential to understanding stage-specific psychosis risk in women.

Other hormonal mediators, including non-oestrogen sex hormones and the hypothalamic-pituitary-gonadal axis, are also likely

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to influence psychosis vulnerability. However oestrogenic protection has resulted in an assumed 'female advantage' in psychotic disorders. This view has paradoxically disadvantaged women with psychosis, who, by presenting later and with a more cyclical course, do not fit the early and intensive approach of current EIP services.

Differential outcomes: the interaction of biological and environmental determinants

Although sex refers to biological differences, gender encompasses social and societal differences. They interact bidirectionally, and within this interface are important insights about how differential outcomes are generated. A later onset of psychosis affords more time to attain the developmental milestones of adulthood. At the onset of illness, women are more likely to be employed, have left the parental home, be married and have children.[6] This is another component of the assumed female advantage, the superior social attainment of women with a FEP. However, most of these advantages are present pre-morbidly, because of later illness onset and because women in the general population attain these milestones on average earlier than men. It would be misleading to assume that the presence of a family system, for instance, equates to effective functioning within that system. Longitudinal studies indicate that superior functional outcomes for women are mediated by these favourable premorbid characteristics, but diminish over time, converging with those of men after an average of 10 years.[6]

Women also carry less advantaged social differences into illness. Women with psychosis are significantly more likely than their non-psychotic counterparts to have experienced physical and sexual abuse. Childhood adversity, a known risk factor for earlier onset in both sexes, has a stronger impact on women,[7] effectively negating any late-onset advantage. Illness-mediating variables, even where less common in women, may confer a greater relative risk. For instance, the association between substance use and earlier onset of psychosis is stronger in women than men, compared with their non-substance-using counterparts.[7]

As a psychotic illness develops, the interaction between biological determinants and treatment continues to play a role. Women are generally more responsive to lower doses of antipsychotic medications. As oestradiol modulates this effect, it becomes more pronounced at certain points of the menstrual cycle and is affected by hormonal contraception.[8] Women are also more susceptible to the side-effects of antipsychotic medication, including metabolic dysregulation, cardiac issues and cancer risk mediated by antipsychotic-induced hyperprolactinaemia.[9] Dimorphic treatment strategies are not part of routine care, despite the fact that EIP services are increasingly focused on mitigating the physical health consequences of treatment.

Psychosis care with a sex-specific focus: the next step in personalised care

Personalised care can be a double-edged sword if wrongly implemented. Focusing on a single illness model can tailor services for a particular subgroup so specifically that others may end up underserved. Rather, a more inclusive approach would involve considering multiple factors that influence the course of illness, thereby creating a more comprehensive and effective personalised treatment strategy. This is also more likely to affect psychosis outcomes on a whole-population level. The sex-specific care needs outlined represent a way forward for the evolution of EIP services, beyond youth-focused care.

To achieve this evolution, it is imperative to enhance and support competencies in women's health among EIP clinicians. This need extends beyond those with medical training to include all professionals within EIP services. Clinicians must be equipped to recognise hormonal change and understand the implications of current hormonal status, reproductive history and the use of hormonal contraception or replacement therapy. This knowledge is essential for identifying the consequent psychological and social needs of female patients, and integrating this information from the point of assessment through to treatment planning. These competencies should not be assumed, particularly in youth-orientated services.

Once in treatment, the 'head start' of women must not blind us to those who may be drowning when appearing to be swimming. Female patients, who are disproportionately older, often face additional challenges, including caregiving responsibilities for both children and elderly dependents, the need to return to established careers, financial hardship, bereavement and deteriorating health. Women are disproportionally likely to have experienced major traumas, which will have a direct bearing on their recovery. Apart from being vigilant against ceding a head start, we must also address sex-specific treatment risks. This would be much aided by the development of dimorphic treatment guidelines, addressing relative dosage, affective comorbidities and metabolic sensitivity, an unjustifiably neglected endeavour.

Peer support, a critical component of recovery, relies on the solidarity of shared experiences. This could be enhanced by the inclusion of female-specific groups or groups focused on a particular shared experience, such as parenting. Family education, support and therapy must be tailored to address the needs of children and partners of women experiencing an FEP, as their experiences will differ markedly from those of families where the patient is a dependent.

How EIP services are conceptualised is reflected in how they are integrated within the broader health service. Increasing integration with more general youth services represents one route to facilitate early detection. Another, not necessarily mutually antagonist view, is to integrate EIP in areas where women receive care during intervals of heightened vulnerability to psychosis. Understanding hormonal determinants of risk can guide this integration, linking EIP services with obstetric and maternal healthcare during the reproductive years and with general practice and women's primary healthcare in later life. Whether care is delivered collaboratively or directly in these settings, equality of access can be maintained by providing follow-up care within an EIP service. Closer integration with child support services would ensure that caregiving arrangements are adequately supported during periods of active illness.

Removing the age criterion, where this bisects adulthood, renders these service changes accessible to all women. In the UK, the National Institute for Health and Care Excellence recommended broadening the age criterion of EIP services to 65 years. Where this has been implemented, the newly admitted cohort are predominantly female, with a distinct illness profile compared with those aged <35 years.[8] Consideration could also be given to the duration of treatment within EIP services once admitted. There are already calls to extend the tenure of EIP care to maintain the gains achieved. Protecting the 'head start' of women, insofar as it is present, may be addressed by the same recommendation.

Women have historically been excluded from healthcare studies, contributing to ongoing research gaps. For example, there is a paucity of studies examining the subjective experiences of women having their sex-specific care needs addressed within treatment settings. Larger and more diverse studies are required to elucidate how biological factors interact with environmental variables, to influence illness outcomes. Indeed, understanding the interaction of sex and gender should ultimately yield more personalised and responsive care for all, including transgender and nonbinary individuals. Yet, the absence of complete knowledge should not justify contemporary inertia. Personalised care is not revolution but evolution, which will continue to adapt as our understanding deepens.

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We should not conflate the 'early' of early intervention in psychosis with early life. It is possible to intervene early in an illness that has its onset at any age. Although this applies to psychosis care, it is relevant to any personalised approach to mental illness. Robust findings support a review of clinical programmes to address women's care needs, moving us ever closer to more tailored, personalised, efficacious care.

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Author contributions

S.N. and M.C. conceived the idea for the article. S.N. drafted the first version of the manuscript. S.N., G.M., N.D., D.M., J.C. and M.C. critically revised and contributed to the final article. S.N., G.M., N.D., D.M., J.C. and M.C. have read and approved the final version for submission.

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Declaration of interest

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