Sexual Dimorphisms in Psychosis:

Predicting Conversion and Implications for Personalized Medicine

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Abstract

The current paper explores the sexually dimorphic nature of psychosis risk, presentation, and treatment in the context of risk calculators. Predicting psychopathology is a novel and risky business, necessitating the consideration of a multitude of factors, including one's biological sex. Discussions surround the North American Prodrome Longitudinal Study (NAPLS) psychosis risk calculator and arguments for inclusion of sex as a predictor variable, as well as potential ethical implications pertaining to personalized psychiatry.

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Introduction

A relatively modern concept, the term "psychosis" is believed to have been coined in the early 19th century by Austrian physician Baron Ernst von Feuchtersleben. At the time, the condition was considered equivalent to psychopathy and insanity, purely a disease of the personality separated into four categories of melancholia, mania, dementia, and idiocy. With time came a shift in perspective within studies of psychosis and psychiatry as a whole: disorders such as these had organic pathology, they were diseases of the brain (Beer, 1996). As the gap between neurology and psychosis grew smaller, a more sophisticated classification system was developed to account for nuanced differences between disorders.

The most recent iteration of these systems, the DSM-5 (Diagnostic and Statistical Manual of Mental Disorders, 5th edition), developed the most comprehensive definition of psychosis to date, with considerations of its heterogeneous nature. Unlike previous editions of the DSM, the DSM-5 describes psychosis in dimensional, rather than categorical terms: "Schizophrenia Spectrum and Other Psychotic Disorders" is an umbrella term incorporating all clinical presentations of psychosis. Key features of psychotic disorders include positive symptoms such as delusions and hallucinations, negative symptoms such as anhedonia and social withdrawal, disorganized symptoms such as bizarre thinking and attentional difficulties, and motor symptoms such as catatonia (Bhati, 2013; Lange, Mueller, Leweke, & Bumb, 2017; Perkins et al., 2015). Psychotic disorders are arranged along a gradient of psychopathology in the DSM-5, with each one being defined by time constraints as well as etiology.

A number of etiological models of psychosis have been proposed, including the traumagenic neurodevelopmental model of psychosis, which attributes psychosis development to childhood adversity. Stress-induced changes to brain structures such as the frontal lobes, hippocampus, hypothalamic–adrenal–pituitary (HPA) axis, and ventricles massively increase vulnerability to environmental stressors later on which trigger psychosis onset (Read, Fosse, Moskowitz, & Perry, 2014). Understanding the causes of psychosis and risk factors that may contribute to its development is crucial for clinical treatment and possibly intervention. Psychosis risk research should allow clinicians to more quickly and accurately identify patients who are likely to develop psychosis and offer them appropriate care to lessen illness impact or, eventually, prevent onset altogether. Risk factors for psychosis include, but are not limited to, genetic risk (first- or second-degree relative with psychosis), drug abuse, social withdrawal/decline, previous psychiatric disease, odd beliefs/behavior, blunted/inappropriate affect, and cognitive deficits (Riecher-Rössler et al., 2009).

Interestingly, stark differences in clinical presentation of psychosis between genders has been thoroughly studied. Overall, men tend to display negative symptoms, poorer overall functioning, and cognitive symptoms whereas women are more prone to affective symptoms (anxiety, inappropriate affect, bizarre behavior) and positive symptoms (hallucinations, delusions) (Barajas, Ochoa, Obiols, & Lalucat-Jo, 2015; Groleger & Novak-Grubić, 2010; Willhite et al., 2008). Differential psychosis risk between genders is still a field in infancy, but some key features stand out. For instance, the estrogen hypothesis proposes a neuroprotective role of estrogen in psychosis development in women, who display a later age of onset than men (da Silva & Ravindran, 2015).

In response to risk research, risk calculators have been developed for a quite a few medical conditions – risk calculators[1] for cancer, bronchitis, diabetes, emphysema, heart disease, osteoporosis, and stroke are already being used by clinicians for disease prevention and management. Essentially, these algorithms determine the likelihood of developing a given disease within a specific period of time, typically one to two years. The calculators take factors such as gender, age, height, weight, medical history, physical activity, smoking history, family history, diet, reproductive history, and environment into account to personalize results to the greatest degree of certainty (albeit not 100%) possible. Only recently, a similar model has been applied to psychiatry, psychosis in particular. The North American Prodrome Longitudinal Study (NAPLS) constructed a risk calculator to determine the likelihood of a patient developing a full-blown psychotic disorder over the course of one to two years. Given the previous discussion of gender considerations in psychosis, it is surprising that the NAPLS algorithm does not use gender as a predictor. The current paper explores the NAPLS calculator along with sexually dimorphic presentations and etiology of psychosis to determine whether the predictive power of the calculator can be strengthened by inclusion of gender as a predictor. Further discussion considers implications of risk calculators in psychiatry and medicine at large, weighing ethical concerns against potential clinical benefits.

[1] Risk calculators for cancer, bronchitis, diabetes, emphysema, heart disease, osteoporosis, and stroke can be found at http://www.yourdiseaserisk.wustl.edu

Constructing a Risk Calculator: NAPLS and EDIPPP

The North American Prodrome Longitudinal Study (NAPLS) is the largest collaborative, multisite longitudinal inquiry into the early stages of psychosis to date (Addington et al., 2007). First and foremost, integrating eight different investigative sites into a single, focused research project rectified small sample sizes that limited previous prodromal studies: single sites were averaging 18 at risk subjects per year, hardly enough to test hypotheses related to psychosis onset and trajectory. Sites were located at the National Institute of Mental Health, Zucker Hillside Hospital, University of California San Diego, Emory University, University California Los Angeles, University of North Carolina, Yale University, University of Toronto, and Harvard University. The overarching goal of NAPLS was the aggregation of a federated, longitudinal database to characterize important variables in at risk individuals and in those who eventually convert to a full-blown psychotic disorder. Original studies at each site were developed for different purposes; once repurposed for NAPLS, steps were taken to ensure methodological similarity across all studies. All sites used the Structured Interview for Prodromal Syndromes (SIPS) to evaluate prodromal state, and baseline and longitudinal variables were equalized across the board. Once subjects were categorized by psychosis vulnerability, the largest and most relevant group included those at clinical high risk (CHR). The second phase of the NAPLS study, or NAPLS-2 (Addington et al., 2012), utilized datasets generated by the initial phase of the study to determine factors contributing to psychosis development.

Findings from NAPLS revealed key factors that characterize CHR subjects as well as those that distinguish subjects who progressed to psychosis compared to those whose prodromal symptoms remitted. Most notably, CHR subjects reported more subjective stress in response to stressful life events (LE) and daily hassles (DH) relative to healthy controls (HC). In addition,

CHR subjects who progressed to psychosis reported more stress as well as a greater frequency of LE compared to those who did not progress to full blown psychosis (Trotman et al., 2014). These results align with the well-known diathesis-stress neural model of schizophrenia, which proposes the neural dopamine abnormalities underlying schizophrenia makes victims more susceptible to stress (Walker & Diforio, 1997). In other words, it is both a biological propensity and a vulnerability to stress that triggers the cascading decline of neural, cognitive, and social functioning into full-blown psychosis. A second notable finding of NAPLS involves thought disorder; severity of thought disorder, including unusual thought content and suspiciousness, informed psychosis risk prediction (Perkins et al., 2015). Of the symptom domains examined (positive, negative, disorganized, and general), both positive and disorganized symptoms – thought disorder and difficulty focusing, respectively - appeared to have predictive power.

One of the primary aims of NAPLS was to follow study participants over time and track conversion rate; collected data could then be used to predict conversion likelihood in CHR subjects. Accordingly, an algorithm[2] was developed with predictive power comparable to similar algorithms used in other areas of preventative medicine, such as in early detection of cardiovascular disease or cancer (Cannon, Cadenhead, Cornblatt, & Woods, 2008). Improved upon with a cohort from NAPLS-2, the multivariate risk calculator (Cannon et al., 2016) was intended to predict likelihood of conversion to psychosis over the course of two years. Typically, onset of psychosis is preceded by subtle cognitive changes (Cannon et al., 2016) that are well documented by a wealth of literature and discussed above. The NAPLS risk calculator combined several factors intended to assess these changes and determine likelihood of prediction based on

[2] Psychosis risk calculator now available at http://riskcalc.org/napls/

the given prodromal profile. Included factors were: (1) modified SIPS (Structured Interview of Psychosis-risk Syndromes) items P1 and P2 (measuring unusual thought content and suspiciousness) (2) decline in social functioning over the past year (3) the Hopkins Verbal Learning Test (measuring verbal learning and memory) (4) BACS (Brief Assessment of Cognition in Schizophrenia) raw score (measuring processing speed) (5) age (6) stressful life events (7) family history of psychosis and (8) trauma.

When the NAPLS-2 risk calculator was internally validated, it achieved a C-index of 0.71; a C-index of 1 would indicate an ability for unerring prediction. This is well within the range of other clinically applicable calculators (Cannon et al., 2016) and can be considered functionally accurate albeit imperfect in prediction power. The calculator has been externally validated as well, with the EDIPPP (Early Detection, Intervention, and Prevention of Psychosis Program) Project (Carrión et al., 2016). Initially created as a platform for community outreach and education in the treatment and prevention of psychotic disorders, EDIPPP amassed a sample of 210 adolescents and young adults at high risk for or in the early stages of psychosis to assess NAPLS-2 algorithm predictive power in practice. The goal of their project was two-fold: assess individual algorithm predictors to form a risk calculator independent from NAPLS and determine whether the NAPLS-2 calculator can be applied to samples outside of the initial sample. In the sample validated by EDIPPP, a few predictors were not significant, including having a first-degree relative with psychosis and a decline in social functioning. However, there was significant correlation between predicted risk and conversion outcome, indicating an overall strong predictive power. Although the NAPLS calculator was successfully validated with an external sample, results will be more reliable with additional samples, ideally taken from outside of North America and from demographically diverse groups. Interestingly, a patient cohort at the

PACE clinic was evaluated for the predictive validity of variables used in the initial NAPLS calculator. Of the five variables, high unusual thought content scores, low functioning, and genetic risk with functional decline were significantly correlated with conversion to psychosis (Thompson, Nelson, & Yung, 2011). However, we are still left with questions about clinical application and practice – whether successful prediction of conversion can positively impact patient outcome is unknown. It is also unclear whether risk and conversion is influenced by gender; the remainder of this paper will grapple with the interaction of gender with psychosis risk and evaluate related predictors that may improve both predictive power and clinical application.

Gender as a Predictor

Within each NAPLS risk algorithm, sex was not a considered predictor for conversion despite well documented sex differences in both prodromal symptom (Barajas et al., 2015) and illness trajectory (Häfner, Heiden, & Behrens, 1998). Differences have been attributed to differential neurodevelopmental susceptibilities among males and females; males tend to have more typical schizophrenic trajectories in terms of symptom presentation and age of onset due to perinatal sensitivities and propensities (Castle & Murray, 1991). More recent hypotheses have focused on the role of gonadal hormones in modulating neurotransmitter action. More specifically, an estrogen hypothesis proposes neuroprotective effects of estrogen, partly through conversion of testosterone, which may prove to have clinical benefit with further research and testing (da Silva & Ravindran, 2015).

Regardless of mechanism, gender differences are apparent in both prodromal and active psychosis yet inconclusive in terms of conversion risk. For example, being female is a significant predictor of affective psychosis (Amminger et al., 2006) whereas overall, being male is a

significant risk factor for conversion to psychosis (Aleman, Kahn, & Selten, 2003; Nordentoft et al., 2006). To date, investigators have not been able to clearly delineate rates of transition to psychosis by gender but analysis of sex dimorphisms during prodromal phases prior to conversion may offer insight into differential development of illness. Additionally, a more comprehensive understanding of how sex tends to map onto the psychosis continuum will ideally inform education, treatment, and early intervention practices.

In high-risk patients, males are noted as exhibiting more significant negative symptoms and poorer overall functioning compared to concordantly examined female cohorts, possibly reflecting the influence of sex on developing certain psychotic subtypes (Willhite et al., 2008). Females, on the other hand, outperform males in overall neurocognitive performance, but display heightened anxiety, inappropriate affect, and bizarre behavior compared to male counterparts (Barajas et al., 2015). These findings map well onto established sex--differentiated clinical presentation of acute psychosis where women are prone to positive, emotional and affective symptoms whereas men display more negative, cognitive and functional symptoms (Groleger & Novak-Grubić, 2010).

Weaving these findings together with predictor variables incorporated into the NAPLS-2 calculator may offer further insight into the predictive value or shortcomings of the algorithm. As aforementioned, the current calculator does not consider sex as a variable in predicting psychosis conversion; although predictive ability is high, there is room for improvement, possibly in incorporating considerations of gender in the pathogenesis of psychosis. Most notably, the first item considered in the calculator are modified SIPS (Structured Interview of Psychosis-risk Syndromes) scores for items P1 and P2, measuring unusual thought content and suspiciousness. Recent studies have indicated that positive prodromal symptoms such as these have a higher

predictive value for males than for females (Walder et al., 2013). Similar findings align with the second considered variable, decline in social functioning over the past year: there is a significantly stronger relationship between social functioning and prediction of conversion among high-risk male youth than females (Walder et al., 2013). As for the measure incorporating results from the Hopkins Verbal Learning Test (HVLT), which assesses verbal learning and memory abilities, there are general sex differences favoring females that are retained through development of psychotic symptoms, but deficits are not more pronounced in either sex (Bozikas et al., 2010). The fourth variable, an assessment of processing speed as measured by the BACS (Brief Assessment of Cognition in Schizophrenia), shows no sex difference in prodromal and psychotic cohorts, although it has been found that processing speed predicts social functioning over the following year (Bachman et al., 2012). As aforementioned, social functioning declines predict conversion in males more accurately than females; analysis of implications on processing speed as a sexually differential predictor has yet to be done.

Interactions between sex and the fifth NAPLS-2 predictive variable, age, have long been established as significant. More specifically, women tend to first present with psychotic symptoms at a later age than men, possibly due to the neuroprotective effects of estrogen which raise susceptibility thresholds in women until menopause (Häfner et al., 1998). Age, therefore, does not differentially predict the likelihood of conversion in men and women, but it may be helpful in predicting expected illness trajectory and time of conversion where applicable. Estrogen's role in delaying psychosis onset in women may be partly due to its mediation of stress tolerance. The sixth variable, stressful life events, may have sex-specific implications in terms of conversion prediction as men and women tend to tolerate and experience stress differently. Relevant to the risk calculator are findings indicating that women "need more exposure to

stressful life events than males to trigger a psychotic disorder" (Ochoa, Usall, Cobo, Labad, & Kulkarni, 2012). Alternately, studies have indicated higher susceptibility to stress-related pathology among women due to different stress-processing strategies modulated by estrogen (Ter Horst, Wichmann, Gerrits, Westenbroek, & Lin, 2009). Simply experiencing stressful life events is not predictive of conversion; exposure to stressful life events is differentially predictive of conversion between men and women. Whether greater exposure to stressful life events is more or less predictive of conversion in females remains unclear given contradictory findings.

Overall, the seventh considered variable, a family history of psychosis (specifically, having a first-degree relative with a psychosis) combined with functional decline in premorbid individuals is highly predictive of eventual transition to psychosis (Yung, Phillips, Yuen, & McGorry, 2004). However, the predictive value of family history depends upon the interaction between parent and offspring sex: male offspring of a mother with psychosis are more likely to develop psychosis than their sisters whereas female offspring of an affected father are more likely to develop psychosis that their brothers (Goldstein et al., 2011). The NAPLS-2 calculator does not take this interaction into account and could therefore be inaccurately predicting conversion without considering the sex of affected parents and the relationship between affected individuals and their prodromal relatives. The eighth and final predictor, trauma, may be differentially predictive between sexes as well. As aforementioned, there is debate as to whether stress sensitivities in women increase or decrease liability in developing psychosis. However, stress sensitivity has been documented as a mediator between trauma and attenuated positive symptoms solely in females (Gibson et al., 2014). In other words, regardless of stress thresholds, the effects of trauma on psychosis development depend on perception of stress in females. It is the interaction between stress sensitivities and experience of trauma that determines psychosis

development; each variable is unlikely to have significant predictive value on its own, and their interaction only becomes significant for female subjects.

Looking Toward the Future: Personalized Psychiatry, Sex Considerations, and Ethical Concerns

Assessing each predictor for potential sex effects validates the incorporation of sex into the NAPLS risk calculator. Take the sex of affected family members and patients for instance: male offspring of an affected mother are more likely to develop psychosis than their female siblings. The NAPLS-2 cohort consisted of more males (344) than females (252) and neither their relationship with their affected family member nor the family member's sex were identified. Data could have possibly been skewed toward predicting conversion of either males or females, depending on these two variables. Therefore, incorporating sex – as well as family member relationship and sex – into the algorithm will likely raise its predictive ability. Further examples can be extrapolated from the preceding discussion, but conclusions remain well-defined: without the addition of sex as a predictor, the NAPLS calculator cannot run at its full potential, running the risk of over- or under-estimating conversion probabilities due to a gender-neutral approach.

At their core, the NAPLS research goals overlap with those fundamental to personalized (or precision) medicine (PM): prevention and early intervention. Results would ideally allow clinicians the opportunity to manipulate intervention strength according to a patient's calculated level of risk. However, the realm of PM extends far beyond prevention; assessing likelihood of pathology is a crucial yet early step in pursuing individualized treatment. In fact, PM is simply a more integrated approach to medicine at large (Wald & Morris, 2012). The intent of medicine

has always been to provide optimal care to patients with considerations of their unique clinical presentations, fine-tuning the process as years and knowledge accumulate. The advent of PM marks a fundamental shift in medical perspectives, introducing an emphasis on fine-tuning tailored treatments according to disease etiology and paying specific attention to genomic effects on risk and drug metabolism (Personalized Medicine Coalition, 2014).

Most relevant to the above discussions is the interaction of biological sex with drug metabolism, particularly antipsychotics. Women tend to have a greater bioavailability and slower elimination of drugs, as well as more side-effects, which suggests that women should be dosed differently and at different intervals than men. Treatment response has also been shown to be greater in women than men, but this may be attributed to medication compliance (which tends to be lower in men) and symptomatology differences (where women are more prone to affective and positive symptoms and men tend to display cognitive and negative symptoms) which further emphasizes the need for individualized treatment (Lange et al., 2017).

Personalized medicine has been proven effective in managing a variety of conditions, including certain cancer types and blood clots. Large-scale genomic databases provide evidence based treatment for individuals with particular genetic makeups. For example, Warfarin, Pertuzumab (or Herceptin), and Imatinib (or Gleevec) are only used for specific patients: Warfarin prescription is dependent on which genetic variants of VKORCl and CYP 2C9 a patient has, Pertuzumab is only given to patients with HER-2 positive tumors, and Imatinib targets only patients who are CML positive for the Philadelphia chromosome (Stahl, 2008). Like psychosis, breast cancer is a heterogeneous disease and therefore particularly in need of personalized treatment due to the massive variation in clinical presentation and pathogenesis. In psychiatric research, a number of SNPs (single nucleotide polymorphisms) have been identified as

potentially predictors of drug response. For example, the D2 receptor may play a role in antipsychotic response and the 5-HT2A receptor may predict antidepressant side effects (Stahl, 2008). While these results are only preliminary, they offer hope to the future of personalized psychiatry once empirical links between these genetic variations and treatment response have been established.

As personalized psychiatry grows from infancy to widespread practice, there are a number of considerations the scientific and healthcare communities must take into account to ensure ethical and targeted success. While the efforts of NAPLS are critical in developing firm ground for eventual clinical implementation, providers should not only be aware of pathology risk but of predisposed presentation as well. Psychosis subtypes depend on etiology which, in turn, depend partially on sex. As aforementioned, women are more susceptible to affective psychosis whereas men tend to display negative symptoms and more severe psychopathology, placing them at polar ends of the psychosis continuum (Barajas et al., 2015). As more precise diagnostic descriptions, these subtypes may better inform treatment and early intervention in ways that have yet to be clarified. For instance, antipsychotics tend to target positive symptoms, which may not be as beneficial to men who tend to present with negative symptoms more often.

Perhaps a more ethically significant consideration is the potential impact this may have on patients. Ultimately, knowledge of potential conversion risk or pathology risk in other circumstances may impact patient-provider relationships in ways that are difficult to anticipate, potentially leading to over-treatment of false positives or reduced treatment motivation in patients who perceive the prodromal label as a so-called psychiatric death sentence (Corcoran, Malaspina, & Hercher, 2005). Prognostic information may lead to fatalistic rather than optimistic attitudes; whether this would be a practical and realistic response is debatable. After all, the

eventual goal of personalized medicine is to lower mortality rates and improve treatment outcome. The true measure of the clinical significance of obtaining this type of information is whether these goals can be met as a direct result. Whether this information will be beneficial in practice is yet to be determined, but it is reasonable to assume its roles in psychotropic prescription practices. With the above considerations in mind, there is a long-standing debate on whether to include a psychosis prodrome diagnosis in the DSM. Early recognition of psychiatric disorders may not be as beneficial as similar practices across other medical disciplines. Whereas early detection of illnesses such as cancer may improve prognosis, recognizing prodromal psychotic characteristics in symptomatic patients presents significant risks to treatment trajectory. Psychiatric illness carries stigma; early intervention efforts may be compromised by psychosocial and intrapersonal anxieties regarding perception of the patient as a fragile, sick individual. Furthermore, patients and their families may unknowingly blur the distinction between vulnerability and disease, altering their perception of the patient's wellbeing and status. They may also hinder the intervention process by projecting their own perceptions of wellness onto treatment protocol and compliance. Other concerns regarding a prodromal diagnosis include confidentiality measures to ensure protection from discrimination on a personal and institutional level, potential risks to both false positive (e.g. over-treatment) and true positive patients (e.g. efficacy of early intervention weighed against psychosocial consequences of diagnosis), and compromised patient autonomy due to misinformation and younger age of prodromal patients (Corcoran et al., 2005).

Oftentimes, determining appropriate treatment for optimal response in individual psychiatric patients is a trial-and-error process, taking months to years of fiddling with dosages and medication type before patients experience symptom remission or even reduction. With

continued research into personalized psychiatry and genomic effects on pharmacokinetics and pharmacodynamics, psychiatrists should expect to see quicker and more effective responses to psychotropic medication. More precise risk evaluations may resolve some abovementioned concerns regarding false positives and over-treatment. Furthermore, a thorough understanding of individual pathology should allow clinicians to better educate their patients and allow for shared decision making regarding treatment trajectory (Drake, Cimpean, & Torrey, 2009). Not only will this offer patients a sense of agency in their own recovery process, but it may improve compliance with their chosen protocol.

Conclusion

Historically, neuroscience and other biomedical research has focused heavily on male subjects (Beery & Zucker, 2011), significantly compromising our comprehensive understanding of disease models that are potentially sexually dimorphic. Investigators tend to assume results can be generalized to larger populations from male subsets or are concerned that menstrual fluctuations in ovarian hormone levels reduce the homogeneity of studied populations and confound results (Wizemann & Pardue, 2001). Other researchers simply find the estrus cycles of research subjects to complicate experimental design even though there are relatively straightforward models and approaches recently proposed to assess and/or manipulate female endocrine profiles within the context of a given research question (Clayton, 2016).

Perhaps more important than working around differences in hormone fluctuations between male and female subjects is acknowledging the interaction of disease state and treatment response with endocrine status. Gender gaps exist in a number of illnesses, including depression, anxiety, and other trauma- and stress-related disorders; proposed explanations for the gaps surround monthly and lifetime fluctuations in estrogen and progesterone in women, which may

increase vulnerability to these disorders (Riecher-Rössler, 2017). Most notably, major depression affects twice as more women than men, though available antidepressants do not address sexually dimorphic distribution of illness. In accordance with the aforementioned proposal, women are more likely to experience depression and anxiety during periods of low estrogen and progesterone. Although ketamine – historically used as an anesthetic and pain reliever - has recently been established as a quick-acting antidepressant, its effects had only been assessed on male subjects; it was eventually discovered that estrogen and progesterone mediate the antidepressant action of ketamine and therefore women require significantly lower doses than men to experience the benefits of ketamine (Carrier & Kabbaj, 2013).

The sexually dimorphic antidepressant action of ketamine is but one of many instances illustrating the importance of incorporating an understanding of sex differences into our medical and scientific knowledge base. Without the pivotal study highlighting amplified effects of ketamine in typical female endocrine environments, female patients would have continued to receive potentially harmful amounts of a potent substance with unknown side effects. The intention of this paper is to highlight sex differences in risk factors for psychosis with an eye toward personalized medicine. As was the case with ketamine, antipsychotics or other treatments for psychosis may not be optimized for sexually differential treatment and one or both sexes may not be receiving sufficient treatment as a result. Research directed toward understanding the sex-specific causes and treatment of psychiatric conditions is essential; a gender-neutral approach may end up doing more harm than good (Howard, Ehrlich, Gamlen, & Oram, 2017).

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