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EDITORIAL

Treatment alliance and adherence in bipolar disorder

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Abstract

The clinician patient relationship lies at the core of psychiatric practice and delivery of mental health care services. The concept of treatment alliance in psychiatry has its origins in psychotherapy, but has also been influenced by several other constructs such as patient-centred care (PCC) and shared decision-making (SDM). Similarly, there has been a shift in conceptualization of treatment-adherence in psychiatric disorders including bipolar disorder (BD) from illness-centred and clinician-centred approaches to patient-centred ones. Moreover, the traditional compliance based models are being replaced by those based on concordance between clinicians and patients. Newer theories of adherence in BD place considerable emphasis on patient related factors and the clinician patient alliance is considered to be one of the principal determinants of treatment-adherence in BD. Likewise, current notions of treatment alliance in BD also stress the importance of equal and collaborative relationships, sensitivity to patients' viewpoints, sharing of knowledge, and mutual responsibility and agreement regarding decisions related to treatment. Accumulated evidence from quantitative research, descriptive accounts, qualitative studies and trials of psychosocial interventions indicates that efficacious treatment alliances have a positive influence on adherence in BD. Then again, research on the alliance-adherence link in BD lags behind the existing literature on the subject in other medical and psychiatric conditions in terms of the size and quality of the evidence, the consistency of its findings and clarity about underlying processes mediating this link. Nevertheless, the elements of an effective alliance which could have a positive impact on adherence in BD are reasonably clear and include PCC, collaborative relationships, SDM, open communication, trust, support, and stability and continuity of the relationship. Therefore, clinicians involved in the care of BD would do well to follow these principles and improve their interpersonal and communication skills in order to build productive alliances with their patients. This could go a long way in confronting the ubiquitous problem of non-adherence in BD. The role of future research in firmly establishing the alliance-adherence connection and uncovering the processes underlying this association will also be vital in devising effective ways to manage non-adherence in BD.

Key words: Treatment; Alliance; Adherence; Bipolar disorder; Components; Mediators

Core tip: A collaborative treatment alliance is central to tackling the ubiquitous problem of non-adherence in bipolar disorder (BD). Studies examining the link between alliance and adherence in BD have shown that an effective alliance positively impacts adherence. However, the existing literature is relatively limited, often of variable quality, and has not been able to clearly delineate the mediators of the alliance-adherence connection. Nevertheless, the key elements of productive alliances in BD which could positively influence treatment-adherence are reasonably clear. They can be readily implemented in clinical practice to enhance adherence in BD, till future research further clarifies the alliance-adherence association.

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INTRODUCTION

The changing face of mental health care

With the introduction of the concepts of patient-centred care (PCC) and shared decision-making (SDM) since the 1990s the face of health-care delivery has undergone a remarkable transformation. The preceding years had seen many clinical, economic and social changes such as the growing numbers of elderly patients and those with chronic conditions, the increasing complexity and cost of treatments, together with repeated calls for greater patient autonomy and choice by consumer advocacy groups. The PCC and SDM approaches were driven by the need to reorient and redesign an increasingly fragmented system of health-care in order to face these challenges[1-4].

PCC and SDM

The concept of PCC began attracting increasing attention from the 1990s as a result of two landmark publications by the Picker Institute and the United States Institute of Medicine[5,6]. PCC began to be acknowledged as a central component of health-care when the Institute of Medicine included it as one on the six components of high quality care[6]. The principle attributes of PCC include responsiveness (sensitivity to patients' values and preferences), respect (according dignity to patients), autonomy (acknowledging patients' rights of informed choice), empowerment (enabling patient and family participation in care), collaboration (equal and supportive partnerships), holism (bio-psychosocial approach), individualization (personalized care), communication (information sharing), access, coordination and continuity of care[1-3,7,8]. SDM is derived from the PCC paradigm and is based on the same guiding principles of patient autonomy, informed choice and collaborative alliances between with clinicians[9-14]. Additionally, it is an evidence based and patient-centred process of decision-making consisting of information sharing, elicitation of patients' preferences, mutual deliberation and agreement on the treatment decisions between patients and clinicians[9,15,16]. The traditional, paternalistic model of clinician-centred care, which was in vogue prior to these approaches, had been criticized for vesting power in the clinician to make all treatment decisions, often overlooking patients' preferences. In contrast, both the PCC[3,7,8,17] and SDM approaches[9,12,15,18] propagated power sharing and mutual responsibility for the treatment undertaken. Thus, they shifted the locus of care from the clinician to the patient and reduced the disparity between them. These attributes made these new approaches more ethical, more acceptable to patients, and enhanced their potential to improve health-care outcomes[3,4,18-20]. Not surprisingly, the notion of collaborative treatment alliances has constituted one of the chief components of PCC[1,3,7,21,22] as well as SDM[12,23-26]. Moreover, these constructs have led to a broader understanding of the concepts of treatment-adherence and engagement with services[2,8,26-28]. The principles of autonomy, holism and humanistic care espoused by the PCC[29-31] and SDM[18,19,26,32,33] models had always been a part of mental health care. In fact, a second report of the Institute of Medicine was devoted exclusively to the application of principles of PCC to mental and substance use disorders[29,34]. Nevertheless, implementation of both PCC and SDM in mainstream psychiatric practice has been poor and there is limited research regarding their impact on mental health outcomes[18,26,32,33,35].

TREATMENT ALLIANCE IN PSYCHIATRIC PRACTICE

The concept of treatment alliance in psychiatry has its origins in psychoanalysis and psychotherapy[36-39]. However, rather than the transference based psychoanalytic concepts of therapeutic relationships, psychiatry has found it easier to adopt the pan-theoretical construct of working alliance proposed by Bordin[40], which focuses on a "here and now" approach to alliance. The central characteristic of working alliance which determines its beneficial effects is therapist and client collaboration. Within this collaborative framework working alliance is composed of three elements: An affective bond between the client and the therapist, mutually shared goals, and agreement on treatment tasks. However, even this concept is not easily extrapolated to routine psychiatric

practice because of several differences between psychotherapeutic and psychiatric settings[37,39,41-43]. These include a wider range of patients, professionals and settings; greater variability in treatment goals and interventions; and, differences in frequency and duration of contact in clinical practice. Patients with severe illnesses compromised awareness and increased risks of harm to self or others pose the greatest problems for establishing a working alliance. The necessity for use of coercive treatment measures in this group directly conflicts with the clinician's role as a therapist. Consequently, a number of other theoretical constructs have been utilized to establish the concept of alliance in psychiatry. Apart from the PCC and SDM models, these have included theories of health-behaviour, newer concepts of medication-taking such as concordance, and the use of recovery-orientated approaches to define the success of psychiatric treatment[41,44-46]. However, regardless of the conceptual framework it amply clear that collaborative partnerships, personal bonds and mutual agreement on tasks and goals between patients and clinicians lie at the heart of the treatment alliance in psychiatry. Moreover, these are the very same characteristics that determine the positive impact of effective alliances on several treatment outcomes including adherence to treatment. A systematic review by Thompson and McCabe[45] identified 10 studies, which had examined the association between treatment alliance and adherence. The majority of the studies had been conducted among patients with either depression or psychosis, while only three had included patients with bipolar disorder (BD). Eight of these 10 studies found a significant association between adherence and some component of the treatment alliance. A collaborative relationship, agreement on treatment tasks and stability of the alliance were the more salient determinants of adherence with treatment.

TREATMENT ALLIANCE AND ADHERENCE IN BD

The changing concepts of treatment-adherence

Newer approaches to medication-taking in chronic illnesses had also started to emerge around the 1990s. Much like PCC, a patient-centred view of treatment-adherence began to replace the earlier illness-centred orientations as it gradually became apparent that patients' views on medication-taking played a central role in determining adherence[47]. This change was driven by years of research on predictors of non-adherence, which revealed that demographic, clinical and treatment related determinants were not able to fully account for the extent of non-adherence. Simultaneously, the emergence of a number of health-behaviour models prompted a move away from biomedical to bio-psychosocial approaches to adherence[48]. This put the emphasis back on patients' perceptions, the clinician patient relationship, and on other influences in the patient's sociocultural environment. Eventually, traditional compliance-based approaches to medication-taking which were rooted in unequal and paternalistic clinician patient relationships, gave away to adherence and concordance based approaches[49]. The concepts of concordance, PCC and SDM are all based on the common principles of collaboration, responsiveness, open communication and mutual agreement on treatment between patients and clinicians[8,24,25,28]. It was therefore not surprising that psychiatry readily embraced these concepts in an effort to deal with the common and unrelenting problem of treatment non-adherence[50-53]. More pertinently, concordant and collaborative approaches to treatment have currently gained widespread recognition in the existing research on adherence in BD[44,54-57].

The association between treatment alliance and adherence in BD

Despite this recognition the evidence linking treatment alliance with adherence is still quite limited in BD, especially compared to other psychiatric and medical disorders. The table below summarizes this research.

The majority of studies included in the Table 1 have found a positive association between alliance and medication-adherence, while only five have failed to find such an association[58,59,67-69]. However, there was considerable variation in study designs. Measures of medication-adherence linked with alliance have varied from patient reports or clinician ratings, to persistence with treatment, dropout rates, missed medication days, and adherence with appointments or service engagement. Only about half of the studies have used validated scales of alliance; the rest have relied on self-designed questionnaires, treatment-attitude scales, or ratings of therapist interventions. Similar to studies of treatment alliance in other psychiatric disorders, the Working Alliance Inventory, based on Bordin's construct, was the most common scale used[45]. However, such overreliance on one instrument may have limited the scope of findings[37]. Though prospective studies are better indicators of the alliance-adherence link, three studies with longitudinal designs were unable to demonstrate an association between alliance and adherence on follow-up despite finding a positive association at baseline[69,72,76]. Finally, quite a few of the studies had small sample sizes and almost all included hospital attendees rather than community based patients, which meant that the results were not readily applicable to all patients with BD. Thus, the somewhat inevitable conclusion from these studies is that though there is definite evidence linking treatment alliance with adherence in BD, an unequivocal association between the two is still lacking.

Fortunately though, several other types of studies have endorsed the notion that effective treatment alliances have an important bearing on treatment-adherence in BD. Frank *et al*[78] provided their subjective impressions about "alliance building" among patients with mood disorders undergoing trials of acute and

Table 1 Treatment alliance and adherence in bipolar disorder

Ref.	Details of the studies	Findings
Connelly *et al*[58], 1982	48 outpatients on lithium; cross-sectional study; adherence by serum levels; alliance by self-designed questionnaire based on the HBM	Satisfaction with the clinician and perception of continuity of alliance was not associated with medication adherence. Perception of continuity linked to appointment adherence
Connelly *et al*[59], 1984	75 outpatients on lithium; cross-sectional study; adherence by serum levels and SCQ; alliance by self-designed questionnaire	Satisfaction with the clinician and perception of continuity of alliance was not associated with medication adherence. Perception of continuity linked to appointment adherence
Cochran and Gitlin[60], 1988	48 outpatients on lithium; cross-sectional study; adherence by self-report questionnaire; alliance as a part of an "Attitude Questionnaire"	Treatment alliance and positive attitudes to treatment explained about half of the variance in adherence. Alliance mediated the relationship between attitudes and adherence
Ludwig *et al*[61], 1990	118 outpatients and inpatients; 37 with BD; cross sectional study; adherence by physician judgment; alliance by two attitude scales: COSS and KK Skala	Adherence was associated with "reliance on the physician" using the COSS scale, but not with the KK Skala scale
Lee *et al*[62], 1992	50 Chinese outpatients on lithium; cross-sectional study; adherence by serum levels, case-notes review and patient reports; knowledge by self-designed questionnaire	A high rate of adherence was found despite inadequate knowledge about lithium. Authors concluded that an effective treatment alliance was of greater importance in ensuring adherence than imparting information
Taylor *et al*[63], 2001	30 trial patients on maintenance lithium treatment and psychotherapy; cross-sectional study; adherence by RBC lithium levels; alliance by TATIS scale to assess therapists' techniques	TATIS scores were significantly associated with RBC lithium levels. Medication adherence improved with increased focus on collaborative relationship building, positive treatment-attitudes, acceptance of BD and necessity for long-term treatment
Kleindienst and Greil[64], 2004	171 trial patients on lithium or cabamazepine; 2.5 yr follow-up; adherence indexed by time to dropout; alliance by the ICS scale	Trust in medications, trust in clinicians and absence of negative treatment expectations were associated with longer time to dropoutin those on lithium, but not carbamazepine.
Patel *et al*[65], 2005	32 African-American and Caucasian adolescent outpatients; cross-sectional study; adherence by patient reports and from records; alliance by subjective perceptions of medications and mental health contact helpfulness	Medication adherence in African-American adolescents was significantly correlated with ratings of drug usefulness and helpfulness of mental health contacts. Helpfulness of mental health contacts was not associated with adherence among Caucasian adolescents
Guandiano and Miller[66], 2006	61 trial patients on medications and family intervention; 28 mo follow-up; adherence indexed by number of months in treatment; alliance by WAI - P and C versions	Alliance was associated with number of months in treatment, dropout rate, percentage of time depressed and expectations from treatment
Sajatovic *et al*[67], 2006	184 trial inpatients; cross-sectional study; adherence by patient interviews; alliance by WAI - P and C	Alliance scores did not differ between adherent and non-adherent groups
Lecomte *et al*[68], 2008	118 patients from early intervention services; 13 with BD; cross-sectional study; adherence by the MAS scale; alliance by WAI-P	Alliance scores were not associated with medication adherence but predicted poor service engagement
Sajatovic *et al*[69], 2008	302 trial patients; 3 yr follow-up; adherence by patient interviews; alliance by WAI - P and C	Alliance scores did not differ between adherent and non-adherent groups
Zeber *et al*[70,71], 2008 and 2011	435 inpatients and outpatients; cross-sectional study; adherence by patient-report of missed medication days and MMAS; alliance by HCCQ	Overall alliance scores were associated with self-report of missed medication days and individual items of the HCCQ were linked to MMAS and missed medication days
Perron *et al*[72], 2009	429 inpatients and outpatients; 1 year follow-up; adherence by MMAS; alliance by HCCQ	Treatment alliance demonstrated a small but significant association with medication at baseline, but not at follow-up
Cely *et al*[73], 2011	124 outpatients; cross-sectional study; adherence by MMAS; alliance by self-designed questionnaire	A negative perception of the treatment alliance among patients was significantly more common in the non-adherent group compared to the adherent group
Sylvia *et al*[74], 2013	3037 outpatients from the STEP-BD study; 1 yr follow-up; adherence by a clinical monitoring form; alliance by HAQ	Patients' perceptions of the strength of the treatment alliance were associated with adherence Perceptions of collaboration, empathy and accessibility were the elements of the alliance linked to adherence
Kassis *et al*[75], 2014	628 inpatients and outpatients; 76 with BD; cross-sectional study; adherence by patient-report and from records; alliance by PDRQ	Patients in the adherent group were more satisfied with their psychiatrists, including availability and accessibility of psychiatrists and agreement with them on symptoms
Kutzelnigg *et al*[76], 2014	891 outpatients on olanzapine and mood-stabilizers; 2 yr follow-up for 657 patients; adherence by clinician judgments; alliance by self-designed scale	Patients in the highly adherent group had a better treatment alliance than those in the non-adherent group at baseline but not during the follow-up period
Novick *et al*[77], 2015	903 outpatients on olanzapine; 291 with BD; 1 yr follow-up; adherence by MARS; alliance by WAI-C	Alliance scores were associated with medication-adherence both at baseline and after 1 yr of follow-up

COSS: Compliance self-rating scale; HAQ: Helping alliance questionnaire; HBM: Health belief model; HCCQ: Health care climate questionnaire; ICS: Illness concept scale; KK Skala: Krankheits konzept skala; MARS: Medication adherence rating scale; MAS: Medication adherence scale; MMAS: Morisky medication adherence scale; PDRQ: Patient doctor relationship questionnaire; SCQ: Standardized compliance questionnaire; STEP-BD: Systematic treatment enhancement program for bipolar disorder; TATIS: Treatment adherence training interventions scale; WAI - P and C: Working alliance inventory - patient and clinician versions.

maintenance treatment. They noted that information-exchange, active patient participation and collaborative decision-making all promoted alliance and led to very high rates of medication-adherence and low dropout rates. Havens and Ghaemi[79] stated that a sound treatment alliance could have inherent mood stabilizing effects and could supplement the benefits obtained by medication treatment of BD. Scott and Tacchi[80] have shown that psychosocial interventions promoting concordant relationships have the ability to enhance medication-adherence in BD. Finally, findings from qualitative studies have found that a successful clinician patient relationship is one of the most important determinants of adherence in BD[81-84]. However, many participants of these studies seem to have found such healthy relationships hard to come by, and mostly reported unhelpful and frustrating interactions with mental health professionals[85-87].

COMPONENTS OF AN EFFECTIVE TREATMENT ALLIANCE IN BD

Since treatment alliance is a multi-dimensional concept, an understanding of specific aspects of the alliance that influence medication-taking may inform efforts to prevent non-adherence[45]. Studies of BD have revealed the following as the principal components of an effective alliance, which have a bearing on adherence.

PCC

First and foremost a successful alliance in BD is built on the principles of PCC[44,88,89]. Studies of BD have shown that patients favour a patient-centred approach and may be less likely to engage in treatment when faced with paternalistic and authoritarian approaches based on the traditional medical model[90-92]. Awareness and sensitivity to views of patients is also crucial to a patient-centred approach[74]. A large number of studies of BD have shown considerable differences between views of patients and clinicians regarding medication-taking[81,93-96]. It is obvious that this clinician patient divide can only be overcome if clinicians are aware of patients' views and preferences and respond to them appropriately[44].

Collaboration

A collaborative clinician patient relationship appears to be one of the principal facets of treatment alliance that fosters adherence in BD[44,57,97]. Sylvia *et al*[74] found that more than any other aspect of alliance, patients' perceptions of collaboration in their relationships with clinicians was associated with adherence in BD. In another qualitative study, patients with BD felt that interactive relationships with their clinicians, based on equal participation and sharing of responsibilities were more likely to result in adherence[82]. Similar results have been obtained by several other studies of BD[75,78,84,96,98]. The most compelling evidence however, comes from the growing evidence of the efficacy of psychosocial interventions in augmenting treatment-adherence in BD[99,100]. It has been proposed that the efficacy of psychosocial treatments largely stems from their collaborative and patient-focused elements[44,57,101].

SDM

Similar to PCC, SDM is not only one of key components of an efficacious treatment alliance in BD, but also the one most likely to influence adherence[56,88,102,103]. However, literature on SDM in BD is sparse. A recent systematic review found only 13 studies on the subject[89]. Nevertheless, these studies have shed light on several important aspects of SDM in BD. This review found that most treatment related decisions in BD involved those pertaining to adherence. The greater part of patients with BD preferred a SDM approach and wanted information about treatment choices, but many relied on their clinicians to take the final treatment related decisions. Certain demographic factors such as age, gender, educational level and ethnicity had some bearing on preferred involvement in SDM, though the findings were not always consistent. Similarly, it was not clear whether patients with BD sought greater involvement in decision-making than patients with other psychiatric disorders. Symptom severity, rather than diagnosis appeared to have a greater impact on patient involvement in SDM. However, regardless of the preferred level of involvement, almost all patients reported that SDM was not as commonly practiced in actual clinical settings as they had wanted. Though the implementation of SDM was low in routine care, collaborative decision-making was more likely if decisions were of complex nature and when patients initiated the process. Patients also wanted clinicians to pay attention to both interpersonal and affective elements of SDM. A sound alliance based on SDM was associated with a number of positive outcomes, mostly greater patient satisfaction, while the association with treatment-adherence was found in only two studies[74,104]. These findings were remarkably similar to what has been found among patients with medical illnesses[8,18,105,106], as well as those with other psychiatric disorders[23,25,33,107,108]. Moreover, a similar profile of patient preferences, patient and clinician involvement in SDM, and low implementation of SDM in clinical practice has been found in a number of other quantitative[109-112] and qualitative studies of BD[82-84,92,98], as well as surveys of patients with BD[96,113]. Another aspect that deserves mention is the use of decision-aids to further the process of SDM in BD. Decision-aids are tools based on updated evidence, which help patients compare different treatment options and provide them structured assistance through all steps of SDM[34,114]. Though decision-aids have been used for other psychiatric disorders[23,25,34,107], they have not yet been developed for BD[115]. A particular concern about the use

of SDM among patients with psychiatric disorders has been the problem of decisional incapacity. When acutely ill, patients might not have the capacity of making proper decisions; this may represent a significant barrier to application of SDM to psychiatric disorders. Advance directives have been proposed as a solution to this dilemma. They are documents completed by patients while still in possession of decisional capacity, regarding treatment decisions that could be made on their behalf in the event they lose the ability to make proper decisions when they are acutely ill. Some efforts have been made to implement advance directives among patients with schizophrenia[25,108], but research on such directives in BD is still at a very preliminary stage[116].

Communication

Constructive communication practices, referred to as collaborative or participatory styles of communication are based on the PCC and SDM approaches[8,45,117,118]. A participatory style of communication not only helps in building a strong alliance, but also has a positive effect on treatment-adherence by promoting positive attitudes to treatment among patients[44,45]. A meta-analysis among patients with various medical conditions found that communication practices of physicians were significantly associated with adherence and poor communication led to a 19% increase in non-adherence[119]. The review by Thompson and McCabe[45] found treatment-adherence to be associated with some or the other aspect of communication practices in eight of the 12 studies of patients with psychiatric disorders. Collaborative communication has a significant impact on adherence among patients with BD as well[44,97,120]. A two-way communication between the patients and clinicians allowing open discussions and free expression of patients' concerns appear to be the main constituents of a beneficial communication pattern in BD[78,89,98,121]. Exchange of information, particularly about medications is also accorded high priority by patients[83,96,98,113,122]. Other clinician attributes considered important by patients with BD include clinicians' ability to listen to, understand and value their views on medication-taking, along with flexibility regarding treatment options and devoting sufficient time to treatment related discussions[75,82,89,96,121].

Trust and support

Trust in the clinician is considered an important aspect of a successful alliance in BD[101,103]. Kleindienst and Greil[64] found that trust in the clinician was associated with lower dropout rates among patients on maintenance lithium treatment. Trusting and collaborative clinician-patient relationships can enhance adherence by fostering improved treatment-attitudes and aiding effective decision-making[75,82,84,86,123]. Both emotional and practical support are also essential components of a healthy alliance in BD. Strauss and Johnson[124] found that productive treatment alliances were associated with greater levels of social support among patients with BD. Similarly, the importance of a supportive relationship with the clinician in alliance building has formed a major theme in several qualitative studies of BD[83,98,125].

Stability and continuity

Continuity of care, ideally by a single treatment-team, frequent follow-ups and longer sessions with patients have all been emphasized as crucial elements of a alliance in BD[56,57,120]. Zeber *et al*[70] found that treatment-adherence was better when clinicians remained in constant contact with their patients and regularly monitored their patients' progress. Patient perceptions regarding continuity of care were found to be associated with attendance rates in other studies of BD[58,59]. Patients with BD also consider stability, consistency and continuity of treatment alliances as critical influences on their medication-taking behaviour[83,85,92,98].

Self-management

The recovery-orientated approach to care is currently being promoted as an key element of care in psychiatric disorders including BD. One aspect of recovery-orientated care is its emphasis on self-management or self-directed care[126]. Self-management strategies are adopted by many patients with BD and are also essential components of psychosocial treatments for BD[44,127]. Promoting self-management has thus been advocated as a necessary component of effective alliances in BD[88,89].

MEDIATORS OF THE ALLIANCE-ADHERENCE LINK IN BD

The positive association between treatment alliance and adherence in BD could be attributed to a number of intervening variables or mechanisms. An effective alliance results in less negative attitudes, a greater acceptance of illness, and the ability to tolerate medication side effects eventually leading to improved adherence[44,60,61,123,124]. Other potential mediators, which have demonstrated a positive association with treatment alliance in BD include reduction of symptom severity[66,72,77,124,128], enhancement of insight[77], and improvement in patient functioning or quality of life[72,77,129]. Certain psychosocial processes could also mediate the association between alliance and adherence. An efficacious treatment alliance has been linked with increased patient satisfaction[74,83,123,128,129], positive treatment expectancies[64,66], reduced stigma[124], improved self-efficacy[128], higher levels of perceived support[124,125], and some aspects of locus of control among patients with BD[130]. However, the association between all these variables and alliance in BD has often been inconsistent and largely correlational than causal. Therefore, there is still considerable uncertainty about the mechanisms underlying the beneficial effects of a successful alliance on adherence in BD.

IMPLICATIONS FOR RESEARCH AND PRACTICE

Despite the sizeable body of literature on treatment alliance and related concepts such as PCC and SDM, there is still considerable scepticism in the field of mental health regarding these approaches because of the lack of conceptual uniformity and clarity, uncertainty regarding their impact on salient patient outcomes such as treatment-adherence and barriers to their optimum implementation in routine psychiatric settings[15,44,89,108]. Doubts have also been raised about the cross-cultural validity of these concepts[89,131-133]. This is especially true for BD, where research lags behind other medical and psychiatric disorders in all these aspects. Nevertheless, several implications of the existing evidence are reasonably clear for clinicians as well as researchers. It has to be acknowledged that the locus of health-care has irrevocably shifted from the clinician to the patient. Therefore, professionals would do well to be aware of the essentials of alliance building and follow these principles in order to build productive alliances with their patients. Not only is this the right approach, but it is probably the most effective one while confronting the ubiquitous problem of non-adherence in BD. Priorities for further research are reaching a consensus on what constitutes an effective alliance in BD, establishing the connection between alliance and adherence more firmly, and working out the processes underlying this link. The success of such research endeavours will hold the key to developing successful alliances and effective treatments, both of which may reduce the burden of non-adherence in BD.

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REVIEW

Women who suffer from schizophrenia: Critical issues

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Abstract

Many brain diseases, including schizophrenia, affect men and women unequally - either more or less frequently, or at different times in the life cycle, or to varied degrees of severity. With updates from recent findings, this paper reviews the work of my research group over the last 40 years and underscores issues that remain critical to the optimal care of women with schizophrenia, issues that overlap with, but are not identical to, the cares and concerns of men with the same diagnosis. Clinicians need to be alert not only to the overarching needs of diagnostic groups, but also to the often unique needs of women and men.

Key words: Schizophrenia; Women; Gender differences; Unmet needs

Core tip: Schizophrenia and related disorders are expressed differently in men and women. Causative factors may differ, as can the expression, timing and severity of symptoms. Prevention, course of illness, and treatment response are all intimately linked to gender.

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INTRODUCTION

This review focuses on my experience dealing with clinical issues critical to women with schizophrenia. My work in this field began many years ago, and results are being continually updated as new information emerges. The paper is divided into the following main sections: Potential prevention strategies for women, the need for early and accurate diagnosis, the troubling complexities of the mental health system, effective treatment of schizophrenia and avoidance of adverse effects, the provision of access to vocational and avocational opportunities, attention to stigma, self-harm and suicide, the need for maintenance of physical, reproductive, and

emotional health. Many of these issues are not specific to schizophrenia, nor are they all specific to women. But, directly or indirectly, they all bear on the health and well being of women with schizophrenia.

In each of the sections listed above, I reference my own work plus recent key papers from the PubMed database. Most of these topic areas continue to be the focus of intense research, and many questions await resolution. The paper ends by broadly outlining future directions for the field.

POTENTIAL PREVENTION STRATEGIES

Schizophrenia is defined by its symptoms, which are thought to arise from the interaction of inherited or *de novo* genetic polymorphisms with exposure to environmental stressors at critical periods of a person's life. The details of specific gene mutations, the severity and identity of stressors, and critical chronology remain largely unknown. The strongest contributor to identifiable disease risk is a history of schizophrenia in close family members[1]. Knowledge of family history can now be combined with genetic risk scores from whole genome scans, which together, provide valuable information about a person's vulnerability to schizophrenia[2]. Nevertheless, when it comes to prevention, even in the era of Clustered Regularly Interspaced Short Palindromic Repeats (commonly known as CRISPR)[3], it is not possible to edit out the hundreds of genes that potentially contribute to schizophrenia in any one individual. Even if in the future all suspicious genes could be eliminated, profound ethical concerns make this form of prevention doubtful[4,5].

Some investigators believe that prevention strategies for men and women need to differ. The genetic predisposition to schizophrenia may, for instance, be sexually dimorphic[6-8], although evidence for this is sparse. On the other hand, because male and female DNA is so often exposed to somewhat dissimilar environmental inputs, it may well transpire that the turning off and on of genes in particular sets of cells - the domain of epigenetics - is relatively sex-specific. Therefore, developments in epigenetics may one day enable the prevention of sex-specific expression of schizophrenia-inducing genes[9,10]. However, for the time being, genetic counseling for women and men[11] and individual contraception counseling[12] are the best ways to try to prevent the transmission of schizophrenia at the gene level.

Women with schizophrenia planning to be mothers and wanting to prevent schizophrenia in their offspring can be counseled (although this is, of course, impractical) to choose relatively young - but not too young - mates with no family history of psychosis[13] and to strategically plan the conception in order to avoid giving birth during late winter or early spring[14]. There is no direct evidence that this will work to prevent schizophrenia in the next generation, but there is an association (which does not imply causation) between season of birth and schizophrenia in offspring. The potential connection has been attributed either to fetal and/or neonatal exposure to infectious/immune factors or to the lack of sunlight and low levels of vitamin D. Associated preventive measures include adequate nutrition during pregnancy, and Vitamin D and folic acid supplements[15]. Other suggestions for mothers with schizophrenia to boost the health of their infants are: limits on maternal weight gain during pregnancy, appropriate immunization, low doses of antipsychotic (AP) drugs during pregnancy and lactation, abstention from tobacco, alcohol and other substances[16-18], and rapid treatment of infection and inflammation[19-21]. Nutritional deficiency, stress, and toxic substances in pregnant women have long been recognized to increase the risk for schizophrenia in offspring[22-24]. Infection, inflammation and immune reactivity have more recently been considered serious contributors to schizophrenia susceptibility[21,25].

Obstetric complications pose a potential risk to the infant brain. They are more common in the birth history of those who go on to develop schizophrenia than in their psychiatrically well peers, but it is not known whether obstetric complications arise from prior fetal problems or whether they result from substandard obstetric care[26,27]. Regardless, women with schizophrenia require exemplary care during pregnancy, labor, and delivery. The quality of maternal care of young children is also critical, as early physical and psychological trauma have been associated (again, this is an association that may not be contributory) with the later development of schizophrenia[26,28,29]. Such trauma is theoretically preventable through parent support and parent training groups, family health education, and child welfare monitoring, but interventions such as these require intensive collaborative work at the level of whole communities.

Further theoretical possibilities for prevention (based entirely on studies of association) are keeping children in their country of birth, since migration is a risk factor for schizophrenia[30,31], residing in rural rather than urban parts of the country[32,33], keeping children and adolescents away from alcohol and drugs[34] and teaching them emotion-regulating strategies (reappraising, accepting, and refocusing[35]) to prevent adversities such as discrimination and social defeat from culminating in paranoid delusions[36].

Given that fewer women than men are reported to develop schizophrenia (2/1 male/female ratio in the under-20 age bracket, although the discrepancy tends to even out with increasing age)[37], that the "female" hormone estrogen is known to be neuroprotective[38,39], and that women are especially vulnerable to psychosis during the postpartum period when estrogen levels precipitously drop[40], my research group predicted in the 1990s that, among women with schizophrenia, girls with early menarche (early pubertal rise in estrogen levels) would show a later onset of schizophrenia than girls who enter puberty at older ages[41]. This is precisely what we found in our clinic population, and this finding has been replicated by some groups, but not by all[42-44].

If accurate, this observation could lead to weight gain strategies[45] that bring menarche forward. This would, of course, not prevent schizophrenia, but might delay its onset in vulnerable women.

Knowing that low estrogen periods are times of special risk for psychotic episodes is especially useful for secondary prevention (prevention of recurrent episodes of psychosis) in women diagnosed with schizophrenia. Relapse can be prevented by increasing the dose of AP medication at low estrogen times in the menstrual month[46,47], during the postpartum period[48], after menopause[49,50], whenever therapeutic estrogen is stopped[51,52], or during therapy with anti-estrogen drugs[53,54]. These theoretical examples suggest that effective prevention of schizophrenia may, in the future, be possible in a sex-specific manner[55,56], though this is not the case presently.

EARLY ACCURATE DIAGNOSIS

It is well-established that delay in seeking treatment once psychotic symptoms have emerged is associated with impaired treatment response and a relatively poor prognosis[57]. Our group found that, on retrospective interview, the first sign of behavioral disturbance eventually leading to a diagnosis of schizophrenia occurred at approximately the same age in women and men, but that the pre-psychotic prodrome was almost twice as long for women[58]. The duration of untreated psychosis did not differ between the two sexes, but the interval between first behavioral sign and first treatment did - the lag was six years for men and nine years for women[58]. The corollary to this finding is that factors other than early diagnosis must determine prognosis because women's outcome relative to men's, despite a longer untreated interval, is generally superior, at least over the reproductive years[59,60]. Potential factors that favor women, besides estrogen levels, are premorbid functioning generally superior to that of premorbid men, more friendships, closer family relations, greater academic success, and a relative absence of substance abuse[61-63].

As important as the speed of diagnosis is its accuracy. Diagnosis leads, at least in theory, to disease-specific treatment, although this is not always true in psychiatry where illness categories often overlap and the same treatments are used for different diagnostic entities. Nevertheless, it is my clinical experience that women's diagnoses frequently changes from depression to posttraumatic stress syndrome to eating disorder to schizophrenia to bipolar disorder (not necessarily in that order). This may be because it is more difficult to apply textbook schizophrenia criteria to women than to men. Women do not always exhibit the characteristic symptoms; they show few "negative" symptoms, few cognitive symptoms, and they rarely show flattened affect[64-66]. Prior to being diagnosed with a schizophrenia-related disorder, women with psychosis are often considered to be suffering from a mood disorder whereas, in men, a first tentative diagnosis is frequently alcohol or drug-induced psychosis[67]. Differential diagnoses sometimes missed in women include thyroid disease, autoimmune disorder, corticosteroid treatment, and anorexia-related starvation. All these conditions are much more prevalent in women than in men[68,69] and need to be ruled out before a diagnosis of schizophrenia is made.

COMPLEXITY OF THE MENTAL HEALTH SYSTEM

The mental health system in most countries is very complex and leaves individuals who experience mental distress not knowing whether to turn to physicians or social workers or psychologists or spiritual counselors. Family doctors may or may not recognize symptoms of early psychosis and, even when they do, may not know where to refer their patients. Waiting lists for the various mental health professionals are often long. Visits may or may not be covered by available insurance. Navigation services that help patients identify financial, linguistic, cultural, logistical and educational barriers to mental health care and provide guidance to access are badly needed by both women and men[70]. The routes to care differ in the two sexes, obstetricians and midwives sometimes serving as intermediaries for women, and guidance counselors and police more often paving care routes for men.

EFFECTIVE TREATMENT

Treatment is known to be most effective when it is individualized to meet the specific needs of the person being treated. Gender, age, family situation, place of residence, state of health, and personal preferences all play a part in determining optimal intervention. One example is the decision-making process around drug dosing. In women of reproductive age, effective drug doses can usually be lower than doses recommended for men[71-75]. Women's ability to respond at lower doses has been attributed to the effects of female hormones on the absorption and metabolism of AP drugs and also to women's relatively increased blood flow to the brain, carrying with it more drug to cell receptor targets[76]. The presence of estrogen at the dopamine receptor site helps to slow the transmission of dopamine[77], an excess of which is thought responsible for psychotic symptoms.

In addition, because AP drugs are lipophilic and women's reserves of adipose tissue are on average larger than men's, women store these drugs in their bodies for comparatively longer periods. This means that psychotic relapse after drug discontinuation is not as rapid in women[78-80]. It also means that, in theory, the intervals between women's intramuscular depot AP injections can be longer than those in men, but the sex-specific spacing of AP depot drugs has not yet been researched.

Another reason why AP drug doses can generally be

Table 1 Side effects of antipsychotics that negatively affect appearance[124]

Weight gain
Bad teeth
Hirsutism
Acne
Hair loss
Salivation
Slurred speech
Blepharospasm
Parkinsonian gait
Dyskinesias
Urinary incontinence

lower in women than in men is because many women take more concomitant drugs than men do, notably antidepressants, mood stabilizers, analgesics, and contraceptives or hormone replacements, all of which can interact with and influence the blood level of AP medication[78,81].

An important aspect of pharmacotherapy for women is that levels of female hormones change over the course of a monthly cycle and also over reproductive phases such as pregnancy, lactation, and menopause. This affects the dosage requirement of AP medication, *i.e.*, there will be a need for higher doses during low estrogen phases[47-50,82,83]. Adjunctive estrogen or selective estrogen receptor modulators can make treatment more effective and can reduce AP doses and, thus, help to prevent side effects. This applies to both sexes, but is especially applicable to women[84-90].

Besides pharmacotherapy, other aspects of schizophrenia treatment need to be differentiated according to the patient's gender, *e.g.*, substance abuse treatment, cancer screening (breast, prostate, cervix)[91-96], interventions for sexual dysfunction[97-99], contraceptive prescribing[12], treatment of comorbidities (osteoporosis and cardiovascular care for instance[100,101]), safeguards against domestic abuse and victimization[102-108], screening for proclivity to violence[109], provision of parenting support and child custody issues[110-112].

DRUG SIDE EFFECTS

Effective treatment means the removal of symptoms and improvement of function; ideally, it also means freedom from adverse side effects. Side effects cause distress, stop patients from regularly taking the medicines they need, and often cause serious harm to health, perhaps even contributing to the high mortality rate among individuals with schizophrenia[113]. Unfortunately, AP medications have many side effects[114] and on average, women suffer more negative effects than men[115,116]. Women may be more vulnerable than men to adverse drug reactions because the doses recommended when a drug goes on the market are calculated on the basis of a 70 kg man.

There are well-known gender differences in drug reactions. In a recent study of over a thousand patients with psychosis, twice as many women as men described their side effect burden as severe. In this study[117], the effects that women complained of (more than men) included: Concentration difficulties, sedation, blurred vision, nausea, constipation, dizziness on rising, heart palpitations, pruritus, photosensitivity, increased pigmentation, weight change, galactorrhoea and headache.

Women have unique risk factors for some adverse effects of APs, such as Torsade de Pointes[118], which is a form of ventricular tachycardia that occurs in patients whose QT interval is relatively long. The QT interval is a measure of the time between the start of the Q wave and the end of the T wave on the electrocardiogram; it is the time it takes for the heart to come back to normal after depolarization, which, on average, is longer in postpubertal women than it is in men. For this reason, two-thirds of Torsade de Pointes occur in women[118]. That being said, more men with schizophrenia than women die of heart disease. Much remains unknown about gender differences in cardiovascular function and cardiac response to therapeutic drugs.

The hypercoagulability state induced by APs raises the risk for venous thromboembolism, pulmonary embolism, and cerebrovascular accident. The use of oral contraceptives, as well as hormone replacement therapies, pregnancy, the immediate postpartum state, and obstetrical complications are all risk factors for these complications[119]. There are many such factors, however, including ethnicity[120]. Despite the many contributing factors, pregnant women on APs have been shown to be at significantly higher risk for venous thromboembolism than pregnant women in the general population[121,122].

With respect to the potential for AP to heighten the risk of breast cancer *via* weight gain and prolactinemia, the jury is still out[94] on this important concern. What is known, however, is that the cancer death rate of women with schizophrenia is high relative to women in the general population[95], although this cannot be attributed to AP drugs. Many side effects of APs, *e.g.*, weight gain, skin blemishes, and hair loss[123], negatively affect appearance (Table 1)[124]. Women are more sensitive to such effects than men are.

APs also have negative reproductive effects. They can disrupt menstrual cycles[125], interfere with a woman's ability to conceive[126], increase the risk for gestational diabetes[127], increase the risk of premature labor[127] and, by entering breast milk, can make breastfeeding a risk for infants of mothers with schizophrenia[128]. The secondary effect of hyperprolactinemia can lead to hirsutism, amenorrhea, galactorrhea, pseudocyesis[129], and osteoporosis[125].

In addition, older women may be more susceptible than older men to tardive dyskinesia (TD)[114]. It is known that TD prevalence is influenced not only by age and sex, but also by many confounding factors, such as individual genetics[130], the specific AP used, its dose, treatment duration, alcohol, tobacco, and marijuana usage, ethnicity, the precise definition of TD, the rating

scale used to assess TD, the predominant symptoms (positive or negative) and the presence or absence of prior brain damage. Because estrogen modulates dopamine-mediated behaviors and protects against oxidative stress-induced cell damage caused by long-term exposure to AP medication, one hypothesis is that when all the confounding factors are controlled, TD prevalence is equal in women and men prior to menopause and becomes subsequently higher in women[131].

Because of sex differences in immunity, women are also more susceptible to the agranulocytosis inducible by clozapine[132]. In general, older individuals, men as well as women, are at relatively increased risk of adverse effects of all drugs[133].

VOCATIONAL AND AVOCATIONAL OPPORTUNITIES

Women with schizophrenia want meaning in their lives, as do men. Meaning comes in several forms: hope in the future, the belief that one is needed, interest in what one is doing, earning money, engaging in artistic endeavors, pursuing a goal. In our study of clinic members with longstanding schizophrenia, more women than men were working outside the home[134], probably because "women's" jobs were more plentiful at the time in our region. Job availability always depends on time, place, and economic conditions. When homeless, or living in room and board homes or with parents, the housewife role is not readily available to women with schizophrenia. Many prefer self-employment opportunities[135] and appreciate assistance in the form of supported employment, individual placement, and job buddies. They welcome opportunities to learn, to volunteer and to be of help to others. Like men, women need creative channels to enable self-expression as they seek ways to be meaningfully occupied[136].

FREEDOM FROM STIGMA

Stigma (being devalued and discriminated against, with consequent loss of self-respect) is a significant problem in schizophrenia[137]. The diagnostic label of schizophrenia is itself frightening to many people, conjuring up fears of dangerousness, unprovoked and uncontrollable violence, irrationality, and incurability. The population at large does not always appreciate the fact that those who suffer from schizophrenia, and this is especially true for women, are more often victims than perpetrators of violence[138]. Different studies have used different definitions of both violence and of victimization, making these terms difficult to quantify across studies. Within a one-year period, it has been estimated that between 11% and 52% of persons with serious mental illness (SMI) exhibit violence at a 2-8 higher rate than that found in the general population[139]. The same study found rates of victimization in persons with SMI to be between 20% and 42%, 23 times that of the general population. Perpetration of violence and victimization are risk factors for each other and often overlap in the same person. Interestingly, Desmarais *et al*[139] reported higher rates of perpetration of violence among women with SMI than among men. They speculate that this is due to the fact that violence in this population most often occurs in the context of close relatives, and women with SMI are more likely than men to be living with family; consequently, they have more opportunity to vent their rage at domestic targets such as husbands and parents.

Women with schizophrenia are too often victims of sexual exploitation, domestic abuse, and random violence[106-108]. Risk factors are age, place of residence, and degree of psychopathology, in addition to personality and behavioral factors[140]. The factors that contribute to the perpetration of violence have been described by the same research team as substance abuse, young age, homelessness, unemployment, low educational attainment, low socioeconomic status, membership in an ethnic minority, past hospitalization for psychosis, past conviction for violent crime, personality factors, and residence in disorganized neighborhoods[140]. These are risk factors for both women and men, but they occur more frequently in men.

In general, schizophrenia is a heavily stigmatized illness, men perhaps suffering more than women because of the perception that they are prone to act out violently and indiscriminately. Women, however, suffer from a specific form of stigma - the frequent conviction of health workers that individuals with schizophrenia should not bear children, and, in the event of pregnancy, should seek abortion. Women with this illness are widely considered incapable of being good mothers, making prenatal care more problematic, as women fear disclosing that they are pregnant, afraid that their infants will be apprehended at birth[141,142]. Healthcare professionals may not be aware of their own discriminatory attitudes, often communicated inadvertently by words and gestures[143]. Finding effective ways of combating biased attitudes both in oneself and in others is a critical issue for all care providers treating patients with stigmatized illnesses.

RELIEF FROM THOUGHTS OF SELF-HARM AND SUICIDE

In the context of schizophrenia, triggers for male suicidal activity (ideation, attempts, and completed suicide) have been described as being: (1) psychotic symptoms and (2) the prospect of chronic disability, while triggers for suicidal activity in women have been mainly attributed to depression. Male suicides in this population decline with age, whereas this is not the case for women. In a longitudinal study, a 10.5% rate of suicide in the first two years after hospital discharge in men dropped to 0% twenty years later, while women's rate of suicide (6%) was spread more evenly over the twenty years[144].

Table 2 Existential concerns[179,180]

Meaning
Fear
Justice
Mortality
Identity
Relatedness
Freedom of choice

Suicide in women with schizophrenia is not as rare (relative to men) as it is in the general population[145]. The clinical implications are that both depression and substance abuse need to be vigorously treated in patients with schizophrenia because both contribute to impulsive acts of self-harm. In treatment settings, suicidal ideas are often "contagious"[146], with one completed suicide sometimes sparking a series of further self-harm attempts[147]. The index of suspicion needs to be high and suicidal ideation needs to be taken seriously[148].

PHYSICAL HEALTH

The life expectancy of individuals with schizophrenia is significantly shorter than that of the general population, with 90% of deaths attributable to physical illness. The assumption is that early mortality in schizophrenia is secondary, if not to suicide, then to lifestyle factors such as heavy smoking, alcohol abuse, and lack of physical activity[149-151]. More recently, a new understanding of the brain-gut connection[152] has implicated nutritional factors. In addition, there is the probability of shared susceptibility genes between schizophrenia and physical diseases that can decrease health-related quality of life and hasten death, auto-immune disease (*e.g.*, Crohn's disease, multiple sclerosis, systemic lupus erythematosus, type 1 diabetes, and ulcerative colitis) being one such category of illness[153].

Social precipitants of early death are critical in this population: Poverty[154], homelessness[155], social isolation[156], poor hygiene[157], malnourishment[158], exposure to toxic substances[159] and adverse treatment effects[114]. High mortality from diabetes, cardiovascular disease and malignancies can, in part, be due to a relative lack of screening, delays in diagnosis, and suboptimal treatment[94,95,160-162]. Javatilleke *et al*[163] conclude their list of causes of lost life expectancy in severe mental illness by pointing out that the range of causes is very broad, with many putative causes varying according to gender.

REPRODUCTIVE HEALTH

Reproductive health includes sexual health (libido, sexual function, the ability to establish and maintain sexual relationships)[99,164,165], menstrual health[47,125,166], the preservation of fertility[167,168], contraception[12], prenatal care[122], pregnancy[18,169], postpartum care[170] and lactation support[171], parenting support and training groups, home visiting, peer support, respite care[111,112,172,173], and menopausal care[49,50,83,174].

Clinicians may not realize that during pregnancy, physiological changes such as delay in gastric emptying and increase in gastric pH prolong the time it takes for AP drugs to reach peak levels. Increased cardiac output steps up blood flow to the liver and may boost the speed of drug elimination. There is an overall increase in body water, which only affects hydrophilic drugs such as lithium, and there is also an increase in the lipid compartment, which provides extra storage space for lipophilic drugs (including APs). The blood flow to the kidneys is increased, as is the glomerular filtration rate, which means a greater degree of renal clearance. The plasma albumin concentration is reduced so that more free drug is available to the brain. Enzyme activity is affected by the increase in pregnancy hormones; some enzymes are affected more than others. For most APs, the net serum concentration in the third trimester is significantly decreased from what it was at the beginning of pregnancy. The exceptions are olanzapine and clozapine, both of which are inactivated by Cytochrome P450 enzyme 1A2, whose activity decreases during the 2nd and 3rd trimester of pregnancy because of rising estrogen levels. This enzyme is also highly inducible by smoking and, since women tend to reduce their cigarette smoking during pregnancy, the activity of this enzyme is further reduced. Therefore, the serum levels of olanzapine and clozapine rise during pregnancy[175-177].

FURTHER AREAS OF CONCERN

There are other areas of concern to women with schizophrenia. Some of these are the availability of crisis support[178], the achievement of nightmare-free restorative sleep[179-182], the safety of treatment settings[104,183], the safety and affordability of housing[184], access to skills training in new technologies[185] and assistance with existential concerns[186,187]. Whereas existential issues such as free will, personal identity, fears for the future, contemplation of mortality, justice concerns, finding meaning in life, and relating to others are all similar in men and women, as women age, they express more security fears, while aging men are more likely to report not being valued and fearing that they are a burden to others. Physical appearance may be more central to identity for women than for men[188] (Table 2).

FUTURE DIRECTIONS

Many of the issues that are critical to the care provision of women diagnosed with schizophrenia stem from a failure to recognize male/female differences in this illness. Sex differences are based in dimorphic brain structure and function, particularly evident in the dopaminergic system that is so crucial to the development of schizophrenia[189]. They are driven by sex hormones, but also depend, to an extent not yet fully understood, on non-gonadal functions of the X and

Y chromosomes because genes on sex chromosomes influence brain development disproportionally to their relatively small number. The number of sex chromosomes, X chromosome inactivation patterns, X-linked imprinting effects, and the indirect effects of sex chromosomes on the expression of autosomal genes all contribute to sex differences in neuropsychiatric disease[190].

Future research into sex differences in brain disorders such as schizophrenia will benefit from a fuller understanding of the causes of sex differences and their effects not only on brain and behavior but also on metabolic, cardiovascular, inflammatory and immune parameters. The field also needs to better understand the timing of the emergence of sex differences. Longitudinal studies that track developmental processes over time are needed. The effect of puberty with its influx of sex-specific hormones on brain maturation needs to be better understood. Biological sex differences need to be disentangled from environmental influences, an important issue for all psychiatric diseases. Sex differences in the brain, whether innate or secondary to exposure and learning, confer differential risk or resilience that fosters or inhibits the expression of specific symptoms, psychiatric diagnoses, and their outcomes.

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