Abstract

Aim: Early intervention and prevention of serious mental disorders such as bipolar disorder has the promise of decreasing the burden associated with these disorders. With increasing early and preventive intervention efforts among cohorts such as those with a familial risk for bipolar disorder, there is a need to examine the the associated ethical concerns. The aim of this review was to examine the ethical issues underpinning the clinical research on pre-onset identification and preventive interventions for BD. **Methods:** We undertook a PubMed search updated to November 2014 incorporating search terms such as bipolar, mania, hypomania, ethic*(truncated), early intervention, prevention, genetic and family. **Results:** Fifty-six articles that were identified by this method as well as other relevant articles were examined within a framework of ethical principles including beneficence, non-maleficence, respect for autonomy and justice. The primary risks associated with research and clinical interventions include stigma and labelling, especially among familial high-risk youth. Side-effects from interventions is another concern. The benefits of preventive or early interventions were in the amelioration of symptoms as well as the possibility of minimising disability, cognitive impairment and progression of the illness. Supporting the autonomy of individuals and improving access to stigma-free care may help moderate the potential challenges associated with the risks of interventions. **Conclusions:** Concerns about the risks of early identification and pre-onset interventions should be balanced against the potential benefits, the individuals' right to choice and by improving availability of services that balance such dilemmas.

Key words: bipolar, depression, early intervention, prevention, ethics

Introduction

Bipolar Disorder (BD) is often a debilitating recurrent illness and a leading cause of medical morbidity across the world (1). The peak incidence is in the most developmentally significant and productive life years, thus contributing to a greater magnitude of this disability among youth (2). As for psychotic disorders (3), early intervention (EI) including preventive or at-risk interventions for persons with BD may help achieve better symptomatic, functional, and quality of life (QoL) outcomes (4). However, such preventive intervention efforts require identification and characterisation of at-risk states for BD.

Identification of at-risk states for BD: Identification of groups that predictably and reliably transition to BD has been the primary difficulty in early intervention for this disorder. As heritable factors are significant in the development of BD, familial HR groups have been the focus of EI efforts (5). Estimates of the risk of developing BD vary substantially between cross-sectional genetic epidemiologic studies and longitudinal examinations of children of bipolar parents. A meta-analysis of studies of the cross-sectional studies indicated a morbid risk of 8.7% for all first-degree family members compared with 0.7% for participants without a family history (6). However, recent studies where children of bipolar parents have been followed up from childhood till young adulthood, indicate that the prevalence of BD or BD spectrum disorders

varies between 7% and 22% (7-9). These latter studies may still be limited by the need for longer-term follow-up to cover the entire age of morbid risk, and thus these estimates may be lower than true estimates of prevalence.

Other approaches have borrowed from prevention efforts in psychosis and have attempted to combine family history along with measures of sub-threshold symptoms to identify individuals in pre-manic states (10, 11). Such individuals may be considered to be in the 'prodrome' of BD when a relatively high proportion of these individuals develop BD on prospective follow-up. The risk of prospective conversion to DSM-IV BD I or II among one such group of participants (12) with Bipolar-At-Risk (BAR) criteria was 11% over 12 months. To date, there have been no other prospective studies examining the predictive validity of at-risk criteria.

Apart from family history, separate focus has been on dimensions or profiles of symptoms being predictive of BD. In a recent systematic review (13), higher or discriminative scores on the General Behaviour Inventory (14), Hypomanic Personality Scale (15), Behavioural Activation Scale (16) and Child Behavior Checklist (pediatric bipolar disorder and mania subscales) (17) were identified to have a higher risk of conversion to BD in one prospective study each. However, the predictive abilities of these instruments have not been replicated, particularly in clinical help-seeking populations. The different risk states for BD have been conceptualized to be pre-illness 'stages' within a number of staging models (18-21), that has been reviewed elsewhere

(22). Within this report, we refer to the staging models proposed by Berk and McGorry (19) as well as by Duffy (21).

Interventions among at-risk states for BD: Within such high-risk groups, intervention studies have been limited to familial HR individuals, as descriptive studies on the 'prodrome' of BD have been relatively recent. Among youth with a family history of BD and mood symptoms, lithium (target S lithium levels 0.9-1.3meq/L) (23) was not superior to placebo in alleviating depressive and manic symptoms respectively in a post-hoc analysis of a double-blind placebo-controlled trial. The negative finding may be related to low power (n= 30) to detect significant differences in this study. Four participants out of 17 withdrew from the active study arm and three of these participants reported cognitive impairments. In another adequately powered, long-term double blind placebo controlled study, divalproex (15mg/kg body weight) (24) was not significantly different from placebo in delaying time to discontinuation due to any mood event. Though there were no statistically significant differences in side-effects among the two groups, possibly related to the lack of statistical power for non-primary outcomes, 34.5% of the participants in the divalproex arm reported sedation while only 14.8% of the placebo treated participants reported the same adverse event. The negative primary outcomes raise concern about the true efficacy profiles in this population as well as potential issues with the diagnosis of prodromal or subsyndromal diagnoses among children and adolescents, particularly those with pre-pubertal BD. In addition, side effects including those related to cognition and arousal may be significant in this

population. In an observational study of 9-20 year old children of Bipolar I parents, 57% of the 25 who received an antidepressant ceased the medication due to an adverse reaction; such reactions were more prevalent in younger participants, indicating the possibility differential anti-depressant related efficacy and adverse event outcomes among youth with a family history (25). Similarly, in a small randomised open label study of paroxetine with or without divalproex among 9 children or adolescents with MDD and with a familial risk of developing BD, 50% developed new onset of manic symptoms and or emergent suicidality (26). Among pediatric populations with major depression, large database studies (27) as well as reviews (28) have identified a significant association with antidepressant use and emergent manic symptoms.

In a single-blind trial, quetiapine in doses between 300 and 600mg was significantly superior to placebo among 20 adolescents with non-manic mood symptoms and a first-degree family history of mania (29). However, the body-mass index of the young persons receiving quetiapine increased significantly during the 12-week study period and more than half experienced somnolence.

Given these risks with medications, psychological interventions may have a safer role among youth at risk of developing BD. In a randomised controlled study of 40 youth aged 9 to 18 years, with at least one parent with BD and having active manic or depressive symptoms, family-focused therapy delivered over four months resulted in earlier improvement and more time in remission over one year follow-up (30). Another study of Cognitive Behavioral Therapy (CBT) is underway in Germany among

participants with a family history of affective or schizoaffective disorder aged 15 to 30 years and with a recent onset of depressive or manic symptomatology (31).

In summary, there is some evidence that mood symptoms in people with family history of BD can improve with treatment, though there is no evidence as yet that BD can be prevented. However, within these emerging interventions, ethical concerns such as the extent of possible benefits or harms require careful consideration. This may also guide further research and improve the awareness of clinicians and researchers of the complexities in this field. Thus, the specific aims of this review are to examine the benefits and risks of preventive interventions for BD.

Methods

A PubMed search performed in November 2014 incorporating search terms such as bipolar, mania, hypomania, ethic*(truncated), early intervention, prevention, genetic, family was used to identify 76 articles. Fifty-six relevant articles were included in the current review based on their discussion of aspects relating to prevention of BD (universal, selective or indicative, rather than secondary prevention). In discussing these studies, we used the model suggested by Beauchamp and Childress (32). This model incorporates the four main ethical principles of (a) respect for autonomy, (b) non-maleficence, (c) beneficence, and (d) justice. These ethical principles are widely used in discussing medical ethics and were chosen for this report for its relative ease of comprehensibility by clinicians.

Among the four ethical principles, respect for autonomy is often considered the most central. Autonomy indicates "freedom from external constraint and the presence of critical mental capacities such as understanding, intending and voluntary decision-making capacity" (33). Non-maleficence refers to the idea of abstaining from harm. However, given that most aspects of care are associated with some harm, these must be balanced against the benefits of interventions or 'beneficence'. The principle of beneficence refers to the duty to help others often by preventing or removing potential harm. A hierarchical ordering of these principles is not supported by ethical theory or morality (33). Lastly, the principle of justice refers to the distribution of limited resources for the care and prevention of mental disorders. This particular model was chosen due to its simplicity and ease of use by clinicians.

Overall, the studies identified through the search strategy covered the domains of non-maleficence and autonomy. The data on beneficence or benefits of preventive interventions were identified using reviews on prevention of BD (34) supplemented with an additional search on Pubmed using the search terms: 'benefits', 'prevention' and 'mania'. Though few studies have examined the issue of distributive justice in preventive interventions, a narrative effort is made to describe the issues pertaining to the same.

Results and discussion

The ethical issues in prevention of BD will be considered within the framework of the benefits, risks, autonomy and justice of such prevention efforts.

Benefits of preventive interventions

Approximately one third of adults with BD have reported long delays of over 10–12 years before receiving a correct diagnosis (35, 36). The diagnosis may be missed in the absence of a carefully taken history or corroborating information in a proportion of the patients with BD (18-37%) (37, 38). Such delayed or missed diagnoses may be associated with poorer outcomes. In a 4-year prospective study of adult outpatients with BD, the length of delay to first treatment was associated with spending more time depressed, greater numbers of episodes, greater severity of depression, fewer euthymic days and more days of ultradian cycling (39). While the effects of delay in first treatment could be mediated by the effects of age of onset (40), the abovementioned prospective study (39) identified an independent relationship between delay in treatment and poor outcomes.

In addition to the effects of time to first treatment, greater number of prior episodes or duration of illness is also associated with greater cognitive dysfunction, treatment resistance, more frequent medical comorbidity and more neurobiological abnormalities in recurrent unipolar disorder and BD (41). A review of cognition among participants with BD identified that cognitive functions may be average or greater than average prior to illness onset, and impaired after the onset of the illness (42). Among patients with

BDI, the number of manic episodes was found to be associated with greater impairments in attention and executive functions, after controlling for depression, disease chronicity and concurrent medication treatment (43). In another study of first and multi-episode manic inpatients, those with multiple episodes had poorer verbal fluency than those in their first episode (44). However, longitudinal studies examining cognition and brain imaging from before the onset of illness till later stages of illness are needed to clarify whether there is such 'neuroprogression' among persons with BD (45, 46). Another argument for the possibility of such a progressive course of illness is differential treatment response in various stages of the illness. A higher number of episodes has been associated with a poorer acute and maintenance treatment response (47), as well as with poorer longitudinal symptomatic and functional outcome among persons with BD (48). The response to psychological interventions (49, 50) and lithium (51, 52) was better in persons with earlier initiation of treatment or fewer episodes.

These findings emphasize the benefits of earlier intervention among persons with BD using the principles of beneficence and justice. The strongest argument for the benefits of at-risk interventions may be the improvement seen with therapeutic interventions such as quetiapine (29) or family-focused therapy (30) among symptomatic at-risk participants. With respect to research design, such benefits add to the merit of future intervention studies and may offset the risks of prevention efforts to some degree.

Risks of identifying at-risk individuals

The primary concern with prevention efforts is that of identification of at-risk individuals. With previously described literature on the probability of developing BD among familial high risk individuals, 77%–91% of offspring of BD probands do not develop BD, although they are at increased risk of other problems, including substance abuse and unipolar depression. This raises the concern that identification of risk based on family history may have a high false positive rate, which may be associated with ethical concerns if all offspring of BD parents are labelled to be at risk. This may relate to the associated loss of autonomy and exposure to harmful effects of interventions. The attitudes of young persons with respect to being identified a genetic high-risk have not been fully studied. In an exploratory study, when participants with a high family loading for BD were asked if they would take a predictive test for BD they were more likely to report in the affirmative if the test answer was definitive but were likely to prefer to not take the same test if the answer was probable (53). This raises questions about whether individuals would chose to be identified as being at-risk of BD if family history alone were to be used as a marker of risk. However, other studies have supported positive attitudes of parents towards early identification and intervention, even when the probabilities of risk of developing these disorders among their children were lower. In a survey among self-selected participants, 46.2% of parents when asked about hypothetical early intervention options for children at 20-30% risk of developing affective illnesses, reported they would agree for early identification and monitoring (54). Forty-six percent of those parents also agreed for psychological interventions at the onset of mild symptoms among such children. In another recent survey, the majority

(51%) of parents with depressive and bipolar disorders reported that they would agree to take a genetic test for mood disorders for their children even if the positive predictive validity of the test was modest (20%) (55). However, this interest was related to their desire to change their parenting behaviours and did not extend to letting their children know about their risk for BD. Another concern about identification of being at-risk may be the limits of medical insurance coverage in certain health care systems. When asked about genetic testing for BD among participants with BD in the US Bipolar Genome study, 63% expressed this concern (56). Thus, special care must be taken in identifying at-risk individuals especially those under the age of consent due to concerns about labelling and stigma.

One approach to mitigate these risks may be in the use of developmentally appropriate explanations for both children and parents, informing them about the risks and benefits within the consent process for research studies and clinical interventions. Another approach to the 'false positive' problem may be to have a broader trans-diagnostic approach in early intervention. A trans-diagnostic approach to prevention in early stages is consistent with the principle of developmental multi-finality (57) where psychopathological manifestations of the underlying vulnerability for an illness may be dependent on the systems in which they exist. This has been elaborated into a developmentally informed staging approach for BD (20, 21) that considers sleep disorders, anxiety and episodic and recurrent major depressive states to be on the developmental continuity for those who later develop BD. Among familial high-risk

participants within Dutch (9) and Canadian (8) offspring studies, the risk of developing depressive disorders was 30% and 41% respectively. In addition, a majority of participants had one or more DSM-IV diagnoses. This higher risk of development of major depression among those thoughts to be at genetic risk for BD is also highlighted in genetic association studies of probands with BD (6, 58). One follow-up study of individuals with a genetic vulnerability for either depressive or bipolar disorders among their mothers (n = 97) (59) identified that a greater number of participants developed depression (n= 22) than bipolar disorders (n =9). Interestingly, 57% developed at least one psychiatric disorder. Thus, within familial high-risk cohorts, if intervention targets included depressive, bipolar and other psychiatric disorders, the risk of false positives was outweighed by the likelihood of true positives. This indicates that a broad approach to identifying multiple psychiatric outcomes may decrease the risk of false positives inherent in at-risk approaches for any single disorder.

Identification of 'pluripotential' at-risk states with multiple diagnostic outcomes may be a potential solution to this statistical and ethical dilemma. Such pluripotential states that combine a number of risk factors that may be related to age, clinical characteristics, family history or biological characteristics may identify a pool of participants that have a high risk of transition to one or more of major psychiatric disorders. Among such a population, the risk of transition to multiple outcomes decreases the low likelihood of false positives associated with transition to any one disorder.

Apart from familial high-risk strategies, sub-threshold manic symptoms have been used as a 'state marker' for pre-illness stages of BD (12, 60). One ethical challenge with this approach is the risk of 'medicalizing' symptoms that may be seen to be an extension of normal human emotions. In a community-based epidemiological sample of young adults, 23 individuals with 'pure hypomania' had experienced periods of hypomania in the absence of depressive episodes (61). These individuals were married more often than controls, had higher monthly incomes and experienced little distress about their hypomanic symptoms. For this subgroup, interventions may be unnecessary, or even potentially harmful. One approach to improving the risk-benefit approach in the use of sub-threshold manic symptoms has been to include major or minor depressive episodes within the criteria for at-risk states for BD (10). This may exclude the possibly higher-functioning and non-distressed hypomanic individuals from preventive intervention strategies.

Assessment of subthreshold manic symptoms may be particularly problematic among young children. Some authors (62) have raised concerns about the downward extrapolation of the primary symptoms of mania, namely 'euphoria' and 'irritability' to children. It is unclear if young children easily understand cognitively complicated notions such as euphoria especially when suffering from comorbid attention and anxiety difficulties noted among pre-pubertal children with manic symptoms. Moreover, when parents or other caregivers have described children to be 'euphoric', children have been then able to provide a developmentally appropriate and reasonable explanation for that

description (63). While bragging about their abilities or reporting an unrealistic positive view of their popularity, children may also appear to be ‘grandiose’, especially when associated with difficulties in global or social cognition. An erroneous label of pre-manic or subthreshold manic states among children may then contribute to further risks of harm through labelling, stigma or from interventions where the risks of harm outweigh potential benefits. This is of particular significance given the concerns about misdiagnosis of BD itself among pre-pubertal children (64). Delaying disclosure of any identified putative risk to children who are unable to understand the complexities of the risk as well as avoiding potentially risky interventions among younger children may be appropriate to reduce such risks. Apart from the use of subthreshold symptoms and family history, the use of predictive genetic tests may be associated with substantial harms (55), but these are not described in this review, as these are not current avenues of research or clinical practice in early intervention for BD.

Models of service provision may also assist in decreasing stigma among those identified to be at-risk of psychiatric disorders (65). Across the world, youth-friendly, holistic, stigma-free programs are being developed that seek to provide EI (66). ‘headspace’ services in Australia, the Headstrong program in Ireland and the Youthspace program in the UK are examples of youth access initiatives that have succeeded in engaging young people and providing care for early-stage mental health difficulties (66). In addition, surveillance or intervention programs based on clinical or familial high risk may offer parents and youth an opportunity to access supports in a stigma-free environment. The

innovative Flourish program established across three sites in Canada offers such services for parents and youth where familial high-risk identification has been well accepted. The program offers a stage-specific approach to interventions where low risk interventions are prioritised for those with less serious concerns, and primarily at parent's request. As with 'headspace' centres, parent and youth advisory groups at the Flourish program help facilitate engagement and reduce stigma.

Risks of preventive interventions

The potential harms from interventions such as antipsychotics or mood stabilizers may be considerable among at-risk individuals. In the previously mentioned study of quetiapine for non-bipolar mood disorders among HR youth, most had experienced somnolence and weight gain (29). Antidepressants have been noted to have poor efficacy and greater risk of negative outcomes including manic symptoms and suicidality as outlined above. A review of stage-specific treatment options recommends avoiding antidepressants or mood stabilizers for those without clear major mood episodes (67). The treatment of established depressive episodes among those with high familial risk is more complicated. For persons with particularly severe depressive episodes or those that are not responsive to psychological interventions, a short trial of an antidepressant may be warranted with an informed discussion on the benefits and risks of such medications. Psychosocial interventions such as family-focused therapy (FFT) (30) may have a much lower risk. The use of these agents as first line approaches may be associated with a better risk-benefit ratio than traditional agents for established

BD. Furthermore, the data on neurological effects of such agents such as antidepressants and lithium in animal models are equivocal in that there are studies indicating both positive (68, 69) and negative effects (70, 71). Until the longer-term effects of such agents are better known, these agents should be used with care, especially among youth. Another approach to managing the risks of interventions may be in including participants and family members in the process of consent based on an evaluation of risks and benefits for the individual participants. Thus the process of informed consent and the inherent respect for autonomy may help moderate the balance of risks and benefits.

Respect for autonomy

The process of informed consent allows participants to evaluate the balance of risks and benefits and participate in research when the risks are considered less than the perceived benefits to themselves or to the community as a whole. A particular issue in consenting process relates to the need to have informed consent from guardians, often parents, when the research involves young people. As has been demonstrated with mothers of children with serious mental illnesses (72), parents may carry a sense of responsibility and guilt that may be higher for mental illnesses than for other medical conditions. These emotions may influence their decision making for allowing children to receive interventions for prevention of BD- especially among familial risk groups. In addition, if the parents suffer from BD or related disorders, cognitive difficulties, sub-threshold symptoms, and the fear of the illness may also affect the parents' informed consent for

their children. In these situations, particular care must be taken in the consent process using steps such as obtaining informed consent over multiple sessions, assessing factors that may affect the consent process and a detailed assessment of the capacity to consent. In addition, seeking assent from children themselves (30) improves their autonomy and is consistent with recommendations on research involving children (73). The ethical difficulties associated with research and clinical care of at-risk individuals should not detract from these efforts, especially if there is a reasonable likelihood that they stand to benefit from the results of the research. This is also the case if the research is "responsive to the health needs and priorities of these populations"- consistent with the Declaration of Helsinki (74).

In clinical practice, though the process of consent is less formal than that in research, every attempt should be made to discuss a balance of risks and benefits of proposed interventions or early identification. In clinical care, the process of help-seeking may also be an exercise of individual autonomy. For these individuals, potential risks and benefits may be moderated by the autonomy inherent in help seeking and in the process of consent. The previously described pharmacological (29) and psychotherapeutic interventions (30) included participants whose parents sought help for symptomatic conditions for their children, including major depression, BD not otherwise specified (NOS) or other non-bipolar psychiatric diagnoses.

Another ethical dilemma for at-risk intervention for BD is its onset during a period when individuals often develop the ability to consent. In admixture analyses of large samples of persons with BD, the highest risk of onset was prior to a mean age of 21.3 years (75). Hence the age of consent, which varies between 16 and 21 years in many jurisdictions across the world, becomes important in the consent process. In certain countries, children under the age of 16 may also be considered to be competent (76) to make decisions regarding their medical treatment. Special care must be taken in the process of consent involving such young people in research and clinical practice.

The informed consent process including both parents and children, which may be considered to be one of procedural fairness or justice leads to a broader community-based issue of distribution of resources as another ethical concern in the care for persons at risk of BD.

Distributive justice

Principles of justice may help clinicians navigate the transition from contemplating the ethics of providing interventions for individuals with risks for psychiatric disorders to those of prevention of such disorders among the population. Indeed, in many countries, physicians are more oriented towards the treatment of the individual patient, rather than that of resource distribution among the population (77). The notion of distributive justice refers to “fair, equitable and appropriate distribution in society, determined by justified norms of distribution, and based on the terms of social cooperation” (33). This

includes the burdens such as costs of healthcare or insurance as well as the benefits including improvements in clinical states and functioning. Such a balance between the relative benefits and costs may be explored using economic analyses for interventions. As preventive interventions in BD are yet to have cost-effectiveness or utility studies, some may apply the principles of distributive justice to suggest that finite resources could be better spent elsewhere. However, a strong argument towards investment in further research in the area would be the high economic burden of BD, which was ranked to be among the leading causes of loss of life years to disability (1) among the economically productive 15–44 year age group.

Within economic analyses, comparisons of costs per Quality-Adjusted Life Years lost to illness or the incremental cost-effectiveness ratios compared with other interventions controlling for the potential confounders may help policy makers decide across funding for different health programs. A recent study on specialised EI for persons with BD demonstrated a significant cost saving over time for the EI approach compared with usual mental health care (78). The intervention included evidence based pharmacological interventions as well as at least 3 sessions of group psychoeducation within a specialized mood disorders clinic with regular follow-up for 2 years. The participants randomised to the specialized mood disorders program had fewer hospitalizations, were prescribed mood-stabilizers and antipsychotics more often and reported greater levels of satisfaction with their care.

To date, there have been no economic analyses on preventive efforts for BD. Apart from the limitations in research in the area of at-risk states for BD, research on cost utility in mental health in general has lagged behind other areas of medicine. In an analysis of studies published until 2001 (79), the number of cost-utility analyses (CUAs) registered for depression and BD amounted to 2% of the total while these disorders contributed to the greatest disability adjusted life years (DALYs; 12% of total) in the US. On the other hand, despite contributing to only 2% of total DALYs, osteoarthritis had a similar proportion of CUAs (1.5%). In addition, psychological and behavioural interventions had fewer CUAs than those for pharmaceutical and surgical products (79) pointing to the need for greater economic evaluations for these interventions where the risk-benefit analysis may be more favourable for at-risk individuals.

Apart from the economic data, the process of help-seeking and arguing for resources may drive the provision of services. Those at high risk for serious mental illnesses may face barriers including those of stigma or pre-existent difficulties which may impair their ability to argue for and access health care. Advocacy by mental health clinicians and researchers are thus important for resource distribution consistent with needs.

Conclusions

Within the context of prevention research for BD, the risks of stigma and side-effects of interventions may need to be balanced against the immense potential for benefit in

economic, emotional and social terms. In individual clinical and research situations, the balance of the risks and benefits may vary and may be moderated by the role of autonomy and consent. Investment in preventive research for BD and other serious mental illnesses, including cost-effectiveness research may assist in arguing for equitable clinical funding for preventive and therapeutic interventions for these disorders. Current data indicates that earlier stages of BD may be able to be identified and interventions improve the pre-bipolar symptoms. It is possible that with safe and stage-specific interventions, cognitive and emotional sequelae of these disorders may be ameliorated.

Conflicts of Interest

The authors have no conflicts to declare in relation to the current manuscript.

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Ethical considerations in preventive interventions for Bipolar Disorder

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