Clinical characteristics and management of bipolar disorder in women across the life span

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Though prevalent in both genders, specific consideration needs to be given when treating a woman suffering from bipolar disorder over her lifetime. Bipolar disorder is a serious and incapacitating illness affecting an estimated 5% of women. The first episode of illness in women is usually a depressive episode. Female gender has been associated with greater axis-one comorbidity, more depressive episodes, rapid cycling and mixed affective states. Special consideration is required for the treatment of bipolar disorder during reproductive events. More studies are required to better understand the course, outcome and gender-specific treatment strategies of this disorder.

Keywords: bipolar disorder, depression, gender, lithium, mania, mood-stabilisers, old age, pregnancy, women

future medicine

Bipolar disorder is a serious and debilitating illness. There are significant differences in the presentation of this illness between the sexes. Furthermore, there are unique problems in the managment of women with bipolar disorder. Most research conducted on bipolar disorder is not gender specific, except for studies of bipolar disorder in women during reproductive events; however, specific knowledge regarding bipolar disorder in women comes from comparing data from male and female subgroups. There are many gaps in our gender-specific knowledge of the management of bipolar disorder. Given that current best practice suggests that physicians should tailor treatments to suit the individual, there is a clear need to fill any such gaps. The optimum management of patients with bipolar disorder requires acknowledegment that gender can potentially alter management decisions. Childbearing, other reproductive issues (e.g., menstruation and menopause), differences in phenomenology, disease course and differing sexual side effects of medications need to be duly considered [1].

Previously known as manic depression and characterized by episodic mood swings between mania and depression, bipolar illness is now understood to be a much more complex spectrum disorder than previously believed [2]. Current diagnostic criteria divide the bipolar spectrum into bipolar I disorder, characterized by full manic and depressive episodes; bipolar II disorder, characterized by depressive and hypomanic episodes; cyclothymic disorder and bipolar disorder not otherwise specified [3]. There are other bipolar categories including rapid cycling and mixed episodes.

Epidemiology of bipolar disorder

In 1994, the US National Comorbidity Survey estimated the lifetime prevalence of bipolar disorder to be 1.6% [4]. A recent estimate has put the lifetime prevalence of bipolar spectrum disorders at 4% [5]. Elsewhere, the prevalence of bipolar II disorder has been estimated to be between 3–5% and the total prevalence of bipolar spectrum disorders may be greater than 5% [6].

Regarding gender differences, bipolar I disorder is equally common in men and women, whereas unipolar depression is more common in women than in men [7]. Bipolar II disorder is suggested to be intermediate [6]. Rapid cycling bipolar disorder, a condition which affects 15% of bipolar disorder patients, has been shown to be more prevalent in women than in men. In a meta-analysis of ten studies including 2057 patients with bipolar disorder, Tondo and Baldessarini found that 72% of cases of rapid cycling were in women [8].

Onset

The average age of onset of bipolar disorder was reported as 21 years in the National Comorbidity Survey [9]. Kawa and colleagues, in a study of 90 males and 121 females with bipolar disorder, found the median age of onset not to be significantly different between genders: 19.5 years in males and 18 years in females ($p = 0.26$) [10]. Elsewhere, significant differences have been demonstrated in age of onset, with women having a later onset than men [11,12]. Significant gender differences were demonstrated in the type of episode at onset. A first episode of mania or hypomania was reported for 43 and 27% of males and females, respectively; and a

first episode of depression was reported for 57 and 73% of males and females, respectively ($p = 0.05$).

If onset in women coincides with pregnancy and childbirth, accurate diagnosis and treatment is essential for good outcomes for both mother and child.

Gender differences in presentation of bipolar disorder

Several important gender differences in the clinical features and course of bipolar disorder have been reported.

Bipolar disorder has been postulated to be equally prevalent in men and women; however, certain subtypes are thought to be unequally distributed. Bipolar I disorder, manic type, is thought to be more prevalent in men [13] and bipolar II disorder, depressive type, is thought to be more common in women [14]. Manic episodes are more common in men, while rapid cycling is seen more frequently in women [14–16]. The mood of patients with the rapid cycling variant tends to be depressive rather than manic and this pattern seems to be more common in bipolar II disorder [17]. The depressive episodes experienced by women may also be more resistant to treatment and may be of longer duration than those seen in men [18]. Women may have a greater seasonal pattern of mood disturbance [19].

Comorbidity

Comorbid psychiatric disorders may be more common in women than in men [20]. It is also reported that women with bipolar disorder more frequently suffer from thyroid disease and migraine headaches [21]. Comorbid substance abuse is reported in women with bipolar disorder more often than in the general population [20]. Gender-specific patterns of substance abuse have been reported, with the risk for alcoholism higher among female patients with bipolar disorder than males.

Treatment & treatment choices in women with bipolar disorder

The rates at which people with bipolar disorders seek treatment are low. Kessler and colleagues, in a clinical reappraisal study of bipolar I disorder patients ($n = 59$), reported that although 93% had received some treatment, only 45% had been treated in the previous year [22]. Of this group, only half were treated by a mental health specialist, with the remainder treated within the human-services and/or self-help sector.

The use of antidepressants in bipolar disorder is controversial. It is postulated that inadequate mood stabilization and the use of antidepressants may increase the risk of rapid cycling [8], may contribute to the development of mania and may increase cycle frequency [12]. Women may be at increased risk of rapid cycling compared with men. Therefore, it has been suggested that, for women in particular, it is important to maximize the use of mood stabilizers and use antidepressants with caution.

Lithium has been associated with inadequate response in rapid cycling patients [18]. There are no clear differences in response to lithium between genders [23], although whether there are significant gender differences in response to other medications remains to be clarified. There are some data on the response of rapid cycling patients to treatment with carbamazepine [24]. The use of valproate and atypical antipsychotics has been reported [12]. Female patients also need advice regarding the fact that mood stabilizer medications, including carbamazepine and topiramate, may be associated with drug interactions which can increase the clearance of the oral contraceptive pill [25].

A poorer response by women than men was observed in an open-label study of 42 patients with bipolar disorder treated with oxcarbazepine. Response, defined as a moderate or marked improvement in the clinical global impressions – improvement scale, was noted in ten of ten men and 14 of 32 women ($p = 0.006$) [26].

There is also evidence that women suffer from more mixed affective states than men. Given that patients with mixed states appear to respond poorly to lithium, this again presents a dilemma in treating women with bipolar disorder [17].

There are clinically significant data in gender-specific side-effect profiles. Long-term use of valproate for epilepsy has been associated with polycystic ovary syndrome and hyperandrogenism [27]. Studies with bipolar patients receiving valproate have revealed similar findings [28]. Typical antipsychotic medication and atypical agents such as risperidone, which have been shown to be effective in treating some episodes of bipolar illness, have been associated with hyperprolactinemia within the therapeutic dose range [29]. This increases the risk of infertility and sexual dysfunction in women. There is also a suggestion that increased prolactin may lead to decreased bone mineral density and osteoporosis, impacting on another substantial women's health issue [30]. Atypical antipsychotics have

been shown to be effective for the treatment of acute manic episodes and there is substantial evidence to suggest that they may be useful for the treatment of other phases of bipolar illness. They also have the advantage of not being associated with teratogenic outcomes which are problematic with conventional mood stabilizers [31,32].

Gender differences in prognosis of bipolar disorder

Regarding prognosis, there is only limited knowledge of sex differences. Most patients suffer many episodes of illness (on average 0.4–0.7 episodes/year), each typically lasting 3–6 months [4]. The prognosis for someone suffering a bipolar illness frequently involves a number of poor outcomes. The divorce rate is twice that of the general population [33]. Many patients experience difficulties in employment [21].

The suicide rate in bipolar disorder has been estimated at 10–19% [18], which is approximately 15 times the rate in the general population. A total of 80% of completed suicides occur during the depressive phase of illness [34]. As female patients are at a greater risk of depressive episodes [7] and patients can spend up to a third of their lives in the depressive phase of illness, women are at particular risk of suicide.

Reproduction

Managing bipolar illness is more complex during the reproductive phase of a woman's life. The treating physician must consider the consequences if medications are reduced or withdrawn, compared with the risk of harm to the fetus or breast-fed infant if exposed to pharmacologic agents used to treat the mother. A treatment plan needs to be agreed upon in frank and open discussions between the patient and her treating physician, which balances risks and benefits and is tailored to the individual needs of the patient.

There are contrasting views as to whether pregnancy may be protective against mood fluctuations in bipolar patients. A retrospective study of 28 pregnant women with bipolar I disorder, treated for acute episodes but not receiving maintenance treatment, concluded that there was a marked improvement in the clinical course of their bipolar illness [35]. However, in a study of 42 pregnant women with bipolar disorder, age matched with nonpregnant women (n = 59), illness recurrence risk after discontinuing lithium maintenance was the same between pregnant and nonpregnant women [36]. In the same study, the risk of postpartum recurrences increased to 2.9 times the frequency of recurrences in the nonpregnant group.

Pharmacologic management of bipolar disorder during pregnancy

Pharmacologic management of bipolar disorder during reproduction is associated with dangers to the fetus and breast-fed infant, and also with the difficulties of changed pharmacokinetics due to physiologic changes in a woman's body during pregnancy. In counterpoint, disruption to stable pharmacotherapy poses clear risks of destabilizing the mother's mental state, which may itself impact on the safety, wellbeing and life of the child.

Pharmacokinetics during pregnancy

The pharmacokinetics of the mood stabilizers lithium and lamotrigine are altered during pregnancy to a clinically significant extent. Glomerular filtration rate (GFR) increases by 50% and is maintained at that high level throughout pregnancy. Renal perfusion increases in early pregnancy by 75% and declines in the late third trimester [37]. Lithium is eliminated from plasma by renal clearance and lithium plasma levels will fall if the prepregnancy dose is maintained. A dose adjustment proportional to the change in GFR may be required. If the dose of lithium is reduced during pregnancy, lithium plasma levels may drop considerably. The GFR quickly returns to prepregnancy levels postpartum and the dose of lithium needs to be adjusted accordingly. Lamotrigine clearance from plasma is variable during pregnancy, steadily increasing to peak at an average of over 350% of prepregnancy clearance at 32 weeks gestational age, then declining and rapidly returning to prepregnancy values postpartum [38].

Teratogenicity & toxicity

A significant risk of fetal malformations and toxicity has been associated with the most commonly used mood stabilizing agents. There is insufficient experience with the newer agents to characterize their safety profile.

The greatest risk of exposure of the fetus to mood stabilizers occurs during the first trimester of pregnancy, the period of organogenesis and neural tube closure. Lithium use in pregnancy has been associated with an increased risk of cardiac malformations of Ebstein type [39,40]; however, these malformations remain uncommon. The risk of congenital abnormalities due to lithium use is estimated as 1 in 1000 (0.1% risk) [41].

Treatment with valproate during the first trimester of pregnancy has been associated with neural tube defects including hydrocephalus and meningomyelocele [42,43] and spina bifida [44]. An effect of increasing teratogenicity with increasing dose has been established in a primate model [45]. Other severe malformations have been reported including skeletal abnormalities and microcephaly [46], septo-optic dysplasia [47] and congenital heart defects [48]. Congenital limb defects of different types have been reported. The risk of limb deficiencies due to valproate exposure is calculated as approximately 0.42% [49]. Fetal valproate syndrome, a consistent facial phenotype of neonates and infants exposed *in utero* to valproate, has been described in over 40 cases. This syndrome consists of minor abnormalities which include epicanthic folds, a small nose with a flat nasal bridge and anteverted nostrils, a long thin upper lip and thickened lower lip and low set posteriorly angulated ears [46,50–52].

Treatment with carbamazepine during the first trimester of pregnancy has also been associated with defects of neural-tube closure. A study documented nine cases of spina bifida among 984 fetal exposures to carbamazepine, estimating the risk of spina bifida as 1% [53]. Carbamazepine exposure was associated with minor craniofacial defects and fingernail hypoplasia in a study of 56 births. Developmental delays occurred in five of 25 infants studied [54].

Nutritional supplementation with folate and selenium prior to and during pregnancy has been demonstrated to reduce the risk of defects of neural tube closure in the general population. The use of folate and selenium is recommended for women taking valproate or carbamazepine who are considering pregnancy; however, no data are available to confirm that the risk of neural tube defects is reduced by nutritional supplementation in this specific population [55].

While teratogeny originates only during the first trimester of pregnancy, toxicity can occur at any stage during pregnancy and breastfeeding. Toxicity can manifest as a less active baby or 'floppy-baby syndrome'. Specific symptoms can range from rash to life-threatening hepatic complications. Toxicity during the perinatal period is associated with the greatest concern. Breastfeeding is also associated with some concern, although the benefits of breastfeeding, which include the nutritional benefits of human milk as well as mother–baby bonding, are generally considered to outweigh the risks, even if the breastfeeding mother is receiving mood stabilizing medications.

Treatment plan

If a mood stabilizer is required during the first trimester, then counseling should be offered, ideally prior to conception. The ideal situation is to have a planned pregnancy, with a treatment strategy planned prior to pregnancy, tailored to the individual and negotiated between the woman considering pregnancy, the treating physician and, if desired, the woman's partner. Many options should be considered in a treatment plan. The frequency of visits to the physician treating the woman's mood disorder should increase and the treatment plan should be reviewed regularly. Risks and benefits of treatments should be clearly explained by the physician. Decisions should be made on a basis of informed and mutual agreement between all parties.

Women should be aware of the benefits of pharmacotherapy as well as the risks associated with drug exposure to the fetus. Procedures to monitor fetal development need to be planned and scheduled. The planning may require sensitivity towards the parents' attitude towards therapeutic abortion. Counseling regarding termination of pregnancy should be provided when serious teratogenic drug effects are detected. Monitoring procedures according to local guidelines are generally preferred. The availability and legal status of therapeutic abortion varies with location.

The clinician carrying out the monitoring procedure should be advised that the fetus has been exposed to mood stabilizing medications that increase the risk of abnormal findings. A transabdominal ultrasound may be conducted at 10–12 weeks. If the investigation is inconclusive it should be repeated near the end of the first trimester of pregnancy. Ultrasound has a high degree of diagnostic accuracy for identifying malformations; however, the diagnostic accuracy of monitoring procedures may vary with gestational age and specific abnormality. In some hospitals, ultrasonography at 18–20 weeks is recommended. The number and timing of ultrasound procedures may vary with local guidelines, affordability, confidence in the accuracy of the ultrasound investigation and the preferences of the patient and her treating physician.

Raised levels of maternal serum α-fetoprotein suggest an increased risk of neural tube defects. Maternal serum screening is a routine procedure useful in detecting several fetal abnormalities. There is some variation in procedure between locations and the use of local guidelines is preferred.

The option of discontinuing mood-stabilizing treatment prior to conception may be considered. The imperative to discontinue mood stabilizers is greater with valproate and carbamazepine than lithium due to their greater teratogenicity. This is not a suitable option for many patients, whose risk of relapse is considered too high or who are not willing to risk a possible relapse. It is also a problematic strategy for couples who experience a delay in conception. If mood stabilizer treatment is discontinued, a decision should be made whether an alternative treatment, such as psychotherapy, should be initiated. If there is a relapse, or an increased likelihood of relapse, mood stabilizer treatment should be resumed, taking into account the current trimester of pregnancy. Women who remain episode-free during the first trimester may be reluctant to resume mood stabilizer treatment for the remainder of the pregnancy.

Physicians are often confronted with unplanned pregnancies among women receiving treatment with mood stabilizers. A decision needs to be made whether to continue, taper off, or abruptly discontinue the medications. There is a paucity of data in the published literature that can assist physicians and their patients to make these decisions. The decision to continue mood-stabilizing treatment is a common one. Abrupt discontinuation of mood stabilizers is associated with a high risk of relapse. The nature of the current treatment and the phase of pregnancy are key in the decision-making process.

Discontinuation of medications for parturition can also be considered, but again this is not a suitable option for many women. Medications are tapered off from week 36–38. This strategy has been criticized due to risk of relapse and also due to suggestions that it may be associated with a high number of induced labors. The utility of lithium discontinuation for parturition is supported by the finding of reduced lithium clearance in the neonate [56].

Postpartum

The risk of relapse or exacerbation of bipolar illness increases substantially in the postpartum period. Indeed, this is the phase of life with the highest risk of a new episode of bipolar disorder. This risk is highest within 90 days of parturition and is associated with more severe episodes of illness. A history of a postpartum mood episode after a first pregnancy significantly increases the risk of a mood episode with a subsequent delivery [57]. Where a postpartum mood episode is not experienced after a first delivery, the risk of a mood episode in subsequent deliveries remains unchanged [58].

The functional impairment and burden of disease therefore requires serious consideration in women, especially when treating mothers of infants and children, given evidence of affect dysregulation, attachment disorder and other emotional disorders in the offspring of mothers with bipolar illness [59–61].

Menopause

Onset of bipolar disorder during the fifth decade of life is more common in women than in men [12]. This coincides temporally with menopause. An association between mood episodes and changes in sex hormones, particularly estrogen, has been postulated but is poorly understood.

Old age

Bipolar disorder in old age is associated with late-onset mania, comorbid neurologic disorders and increased morbidity. However, very few gender-specific data are available. Shulman and Post identified 67 patients aged 60 years and over who had been admitted to the Bethlem Royal and Maudsley Hospitals (London, UK) over a 10-year period and met research criteria for bipolar affective disorder [62]. There was a strong female preponderance for bipolar disorder in this study of 49 females and 18 males. Of these patients, there was a male preponderance for comorbid cerebral–organic or neurologic abnormalities (11 of 18 males and 5 of 49 females). The average age of onset of the first affective episode was 50.4 years for females and 44.8 years for males, but this difference was not statistically significant. The first manic episode occurred at 61.9 years in females and 53.2 years in males ($p < 0.05$ Mann-Whitney U-test). In a different study of 50 elderly patients admitted with an index episode of mania, Shulman and colleagues again observed that women experienced their first manic episode at a greater age than men [63]. The mean age of first manic episode was 68.7 years for women and 58.7 years for men ($p = 0.04$).

It is interesting to note that, although the age of onset for bipolar disorder measured from epidemiologic studies is generally found to be in the late teens or early twenties, in the two studies of bipolar disorder in old age cited above, admissions of patients with acute episodes of mania were often found in patients whose first bipolar episode was at a much later age. Reasons for this are unclear.

Conclusion

While there are specific considerations when treating bipolar disorder in women, they are inadequately researched. This review has focused largely on reproductive events. While the treatment of bipolar disorder during pregnancy and breastfeeding is clearly important, other topics, such as whether there are gender differences in the efficacy of various treatment strategies, remain largely unaddressed. Gaps still exist in our understanding of the role of sex hormones in mood disorders and with treatments. Very few gender-specific data are available on bipolar disorder in postmenopausal women at any age, or in elderly women.

Future perspective

Much work remains to be carried out before the course and outcome of bipolar disorder in women is thoroughly understood. It can be expected that over the next 5–10 years, significant advances will be made in this field, not due to the importance of gender being specifically addressed as a research question, but more likely since there is a trend for longitudinal studies and clinical trials to recruit larger numbers of participants. As numbers increase, reaching significance in gender-based subgroup analyses becomes a realistic possibility. These substudy findings will increase our understanding of gender differences in bipolar disorder.

Bipolar disorder investigated specifically in women tends to focus primarily on reproduction. It is likely that existing guidelines for pharmacologic treatment of bipolar disorder during pregnancy and breastfeeding will be revised and that new guidelines will be developed [55]. Guidelines can be expected to change to reflect increased knowledge of the safety of the many medications available during reproduction, especially as more is discovered about the safety of newer agents such as lamotrigine and as the role of antipsychotics in the treatment of bipolar disorder becomes more clearly defined.

Executive summary

- The onset of bipolar disorder is usually in the late teens or early twenties, with a depressive phase of the disorder being most common in women.
- An estimated 5% of women will suffer from bipolar disorder at some stage during their life.
- Female gender is associated with a greater likelihood of rapid cycling and mixed affective states.
- Women with bipolar disorder who are considering having a baby should consult their physician and establish a medication plan, ideally prior to conception.
- There are no mood-stabilizing agents available for the treatment of bipolar disorder that have been shown to have no risk to the fetus when used during pregnancy. Treatment decisions need to be made by balancing the risks with the benefits of treatment with these agents.
- A link between menopause and onset of bipolar disorder requires further investigation.
- The role of sex hormones, such as estrogen, in psychiatric illness is still to be fully defined.

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