Background

- Previous research has shown that key reproductive life events are potential triggers of mood episodes in women with bipolar disorder.
- The association with childbirth has been studied in depth. In contrast, there is a paucity of research into mood episodes in women with bipolar disorder in relation to the menopause.
- Although limited by small sample sizes, studies published to date suggest the menopause is a period of increased risk of relapse for women with bipolar disorder and indicate potential association between perinatal and perimenopausal mood episodes (Blehar et al. 1998; Robertson-Blackmore et al. 2008; Marsh et al. 2009; Marsh et al. 2015).

Aim

To establish whether history of premenstrual mood change and postpartum episodes are associated with perimenopausal episodes in a large sample of women with bipolar disorder.

Methods

Participants

- Postmenopausal women with a lifetime DSM-IV diagnosis of bipolar disorder (n=339).
- All women were recruited to an ongoing UK programme of research into the genetic and non-genetic determinants of bipolar disorder (Bipolar Disorder Research Network, BDRN).

Clinical Assessment

- Lifetime psychiatric history: details of lifetime illness course were measured via semi-structured interview (Schedules for Clinical Assessment in Neuropsychiatry, SCAN, Wing et al. 1990) and review of medical case notes. Diagnoses and lifetime-ever clinical ratings, including history of postnatal mood episodes, were made using all available clinical data.
- Premenopausal illness episodes: postmenopausal women were asked via a postal questionnaire to report the presence or absence of any illness episode at the time of the menopause and provide details about the episode.
- Premenstrual syndrome: the self-report Premenstrual Symptoms Screening Tool (PSST, Steinert et al 2003) was used to measure lifetime diagnosis of premenstrual dysphoric disorder (present/absent) and a broader lifetime diagnosis of moderate/severe premenstrual syndrome (present/absent).

Statistical Analysis

- Demographic and lifetime clinical characteristics of women who reported presence (n=200, 59%) and absence (n=139, 41%) of a perimenopausal mood episode were compared. Chi squared tests were used to compare categorical data. Mann Whitney U tests were used to compare all continuous variables as none were normally distributed.
- Binary logistic regression was used to determine whether a history of postnatal mood episodes and premenstrual syndrome episodes could predict whether or not a woman experienced a mood episode in relation to the menopause after controlling for other significant differences between groups.

Results

- Presence of a perimenopausal episode was significantly associated with being younger at interview and at illness onset, and being less likely to work or have worked in a professional occupation (Table 1).

Table 1. Lifetime demographic and clinical characteristics of postmenopausal women with bipolar disorder with and without perimenopausal mood episodes.

<table>
<thead>
<tr>
<th></th>
<th>Absence of perimenopausal episode (n=139)</th>
<th>Presence of perimenopausal episode (n=200)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at interview in years, median (IQR)</td>
<td>58 (11)</td>
<td>56 (9)</td>
<td>0.040</td>
</tr>
<tr>
<td>Never married or lived as married, % (n)</td>
<td>9.4% (13)</td>
<td>6.5% (13)</td>
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<tr>
<td>Professional occupation, % (n)</td>
<td>79.9% (111)</td>
<td>68.5% (137)</td>
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<td>DSM-IV bipolar I disorder, % (n)</td>
<td>75.5% (105)</td>
<td>72.5% (145)</td>
<td>0.410</td>
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<td>Age of illness onset in years, median (IQR)</td>
<td>25 (14.5)</td>
<td>21 (12)</td>
<td>0.029</td>
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<tr>
<td>Average number of episodes per year of illness, median (IQR)</td>
<td>0.51 (0.59)</td>
<td>0.63 (0.63)</td>
<td>0.236</td>
</tr>
<tr>
<td>History of suicide attempt, % (n)</td>
<td>10.8% (15)</td>
<td>15.0% (30)</td>
<td>0.189</td>
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<td>History of rapid cycling, % (n)</td>
<td>25.2% (35)</td>
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- Presence of a perimenopausal episode was significantly associated with history of premenstrual dysphoric disorder (p<0.001) and the broader diagnosis of moderate/severe premenstrual syndrome (p<0.001) (Figure 1).
- There was a non-significant association between presence of a perimenopausal episode and history of postpartum mood episode (p=0.09) in the smaller sample of parous women only (Figure 1).

Figure 1. Proportions of postmenopausal women with bipolar disorder with and without perimenopausal mood episodes with history of postpartum mood episodes and premenstrual syndrome episodes.

- In multivariate regression models, controlling for differences between groups in age at interview, age at illness onset and occupation, the following significantly predicted presence of perimenopausal episode:
  - History of postpartum mood episode: odds ratio = 2.13 (95% CI 1.09 - 4.17; p=0.027).
  - History of premenstrual dysphoric disorder: odds ratio = 2.68 (95% CI 1.30 – 5.51; p=0.007).
  - History of moderate/severe premenstrual syndrome: odds ratio = 6.33 (95% CI 3.51 – 11.43; p<0.001).

Conclusions

- Some women who have bipolar disorder may be particularly sensitive to reproductive life events triggering mood episodes (menstruation, childbirth and menopause).
- Previous mood episodes in relation to the female reproductive life cycle may help clinicians predict individual risk of an episode for women with bipolar disorder approaching the menopause.
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Case Example

- 65 year old woman with bipolar I disorder.
- Age 14 years. Menarche: coincided with first mood episode.
- Age 25 years. Birth of first son: postpartum psychosis onset within 2 weeks of delivery, lasted 3 months.
- Age 27 years. Birth of second son: postpartum psychosis onset within a week of delivery lasted 8 weeks, followed by major depressive episode.
- Between ages 27-37 years. No major mood episodes.
- Age 37 years. Onset of menopause: episode of mania followed by severe depressive episode. Symptoms refractory to medication, responded to ECT.

Acknowledgements:
We would like to thank all the women who kindly participated in BDRN and all the mental healthcare professionals throughout the UK who helped in the recruitment of participants.

Supported by wellcome trust

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Future research

- Prospective longitudinal studies of women with bipolar disorder providing frequent contemporaneous ratings of mood and reproductive life events are required.