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Research paper

Psychopharmacological drug utilization patterns in pregnant women with bipolar disorder – A nationwide register-based study

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ABSTRACT

Background: Bipolar disorder is often associated with a lifetime indication for treatment with psychotropic drugs, thus pregnant women face the dilemma whether to continue treatment or not. This study describes the psychopharmacological drug utilization patterns among women with bipolar disorder from 12 months preconception to 12 months postpartum.

Methods: We conducted a register-based cohort study among all Danish women aged 15–55 with a diagnosis of bipolar disorder, who gave birth to their first and singleton child between January 1997 and December 2012. Psychotropic drug use was determined by prescriptions obtained from the Danish National Prescription Registry.

Results: We identified 336 women. The proportion of women redeeming prescriptions for any psychotropic drug decreased during pregnancy, from 54.8% in the 3 months preconception to 36.6% in the third trimester ($p < 0.001$). Lithium dosing increased significantly during pregnancy. A total of 35 (41.2%) of the women on psychotropic monotherapy and 37 (50.0%) of the women on psychotropic polypharmacy used an antidepressant without concomitant use of a mood-stabilizer at some time during pregnancy.

Limitations: Only redemption of prescriptions was assessable, thus we were not able to assess compliance and discontinuation of treatment before the end of the treatment duration. There was no information on drug use during hospitalizations.

Conclusions: We found a decrease in the proportion of women redeeming prescriptions during pregnancy. There was a high prevalence of antidepressant use without a mood-stabilizer, potentially putting women at risk for a switch to mania – although this is still debated. This calls for further investigation.

1. Introduction

Bipolar disorder is a brain disorder characterized by extreme recurrent mood shifts, including manic and depressive episodes. The lifetime prevalence is more than 1%, with no distinction between different ethnic and socioeconomic groups (Grande et al., 2015). The age of onset is usually in late adolescence or early 20 s, putting women at risk during their reproductive years (Emilien et al., 2007; Müller-Oerlinghausen et al., 2002; Yonkers et al., 2004). Bipolar disorder is often associated with a lifetime indication for psychotropic drugs (Anderson et al., 2012; Grunze et al., 2013; Müller-Oerlinghausen et al., 2002). Therefore, pregnant women and women planning pregnancy face the dilemma whether to continue treatment or not. Both continuation and discontinuation of treatment have their risks (Epstein et al., 2014), and the best therapeutic strategy to handle these risks has not been established.

The first-choice drugs for treating bipolar disorder are mood-stabilizers, like lithium, anticonvulsants and most atypical antipsychotics. If needed, multiple mood-stabilizers can be combined. Antidepressants are often used (Bjørklund et al., 2015), but the effects are much debated in both acute and long-term treatment (Frye, 2011; Grunze et al., 2013). Current guidelines discourage antidepressant monotherapy and recommend concomitant use of a mood-stabilizer because of the potential risk for treatment-emergent affective switches. (Grunze et al., 2013; Müller-Oerlinghausen et al., 2002).

The reproductive safety profile for most psychotropic drugs is not perfectly clear, although significant attempts have been made to specify the risks (McKnight et al., 2012; Vigod et al., 2015). It is known that both carbamazepine and valproate can cause congenital abnormalities and use of these drugs should thus be avoided during pregnancy (Iqbal et al., 2001). Use of lithium has been associated with cardiotoxicity and Ebstein's anomaly in newborns, but there are indications that these

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risks have been overestimated in the past (Bergink and Kushner, 2014). Studies on the teratogenicity of selective serotonin reuptake inhibitors (SSRIs) showed conflicting results in the past, but a large and recent study did not find SSRIs to be associated with congenital heart anomalies (Petersen et al., 2016). Possible teratogenic drug effects mostly occur in the first trimester (Grande et al., 2015; Yonkers et al., 2004).

The advantages of avoiding potential teratogenic drug effects by discontinuation of treatment need to be weighed against the possible disadvantages for the woman's mental well-being. Discontinuation of treatment, especially when done abruptly, can lead to a two-fold increase in risk of relapses (Viguera et al., 2007). Since bipolar episodes are associated with an increased risk in alcohol abuse, illicit drug use, smoking, poor nutrition and suicide (Goodwin and Jameson, 2007), a relapse during pregnancy may lead to serious adverse effects affecting the fetus as well. Therefore, discontinuation of treatment during pregnancy may be considered more harmful than continuation in individual cases.

All this underscores the complexity of the psychopharmacological treatment of pregnant women with bipolar disorder. Physicians should encourage women to carefully plan their pregnancy, thus creating time for thoughtfully considered treatment choices. The therapeutic strategy must be determined based on an individual risk-benefit analysis, balancing the potential teratogenic effects of the psychotropic drugs against the possible harm to both mother and fetus caused by the underlying bipolar disorder if not treated (Goodwin and Consensus Group of the British Association for Psychopharmacology, 2009; Cohen, 2007). Since often these risks are uncertain, physicians are clinically challenged to define the optimal therapeutic strategy (Jones et al., 2014).

Little is known about the actual treatment patterns in pregnant women with bipolar disorder. Previous studies on drug utilization during pregnancy mainly focused on the prevalence of use of one drug or classes of drugs, and did not make a distinction between the different indications (Jiminez-Solem et al., 2013; McCrea et al., 2015; Munk-Olsen et al., 2012).

1.1. Aim of the study

The aim of this study was to investigate the psychopharmacological drug utilization patterns from 12 months preconception to 12 months postpartum among women with bipolar disorder who gave birth between 1997 and 2012.

2. Methods

2.1. Setting

Denmark has a tax-funded health care system ensuring easy and equal access to health care for all its citizens, and all contacts with the system are recorded in administrative and medical registers. The records carry a unique personal identification number, called the CPR-number, assigned to every Danish citizen. Linkage between registers at an individual level is possible because this CPR-number is used in all Danish registers (Pedersen, 2011).

2.2. Design and study population

We conducted a register-based retrospective cohort study among pregnant women with bipolar disorder. We identified all women born between 1942 and 1997 who received a diagnosis of a single manic episode or bipolar disorder (International Classification of Diseases (ICD)-10: F30-F31, ICD-8: 296.19, 296.39, 298.19) in the Danish Psychiatric Central Research Register (DPCRR) (Mors et al., 2011). Among these women, we used the Danish Medical Birth Registry (DMBR) (Knudsen and Olsen, 1998) to identify those who gave birth at ages 15–55 between January 1, 1997 and December 31, 2012. To obtain a homogenous sample, we only included women with a bipolar disorder or hypomania/mania diagnosis ever before pregnancy, and only pregnancies of first-borns and singletons. For the same reason, all patients with a diagnosis of schizophrenia (ICD-10: F20, ICD-8: 295.x9, excl. 295.79) ever before or during our observation period were excluded.

2.3. Descriptive variables

We assessed age, civil status and education status at the date of conception, smoking during pregnancy, any psychiatric contacts (both in- and outpatient, subdiagnoses and number of inpatient days) in the year preconception, and any history of alcohol abuse, illicit drug use, epilepsy, and suicide attempts (Pedersen et al., 2012; Webb et al., 2015) ever before pregnancy.

Civil status was obtained from the Danish Civil Registration System (Pedersen, 2011). Information on education status was identified from the education registers, providing information on the highest completed education level (Jensen and Rasmussen, 2011), where we classified our study population into 3 groups: primary school (lowest), secondary school and a combined group of higher education level.

Age at conception, as well as information on smoking during pregnancy was obtained from the DMBR. Diagnoses with epilepsy (ICD-8 293.2 and ICD-10 G40-41), alcohol abuse (ICD-8 291.x9, 303.x9, 303.20, 303.28, 303.90, ICD-10 F10), illicit drug use (ICD-8 294.39, 304.x9, ICD-10 F11-16, F18-19) and prior suicide attempts/self-harm (Reuter Morthorst et al., 2016) were identified from the DPCRR and the National Patient Register (NPR), the latter containing information on somatic diagnoses from in-and outpatient and emergency room contacts at somatic hospitals (Lynge et al., 2011). Information on age at first psychiatric hospital contact with bipolar disorder and prior psychiatric contacts were also obtained from the DPCRR (Mors et al., 2011).

Finally, we identified all hospital admissions in the DPCRR and NPR from 12 month preconception to 12 months postpartum including pregnancy-related admissions (ICD-10 O).

2.4. Psychotropic drug use

From the Danish National Prescription Registry (DNPR) (Kildemoes et al., 2011) we identified all prescriptions for psychotropic drugs (Anatomical Therapeutic Chemical (ATC) code N), including amount in Defined Daily Doses (DDDs), that were redeemed from 12 months preconception to 12 months postpartum. We assumed intake of the drugs prescribed. We defined 7 psychotropic drug groups: lithium, anticonvulsants, atypical antipsychotics, typical antipsychotics, antidepressants, benzodiazepines/sedatives and other psychotropic drugs, where the latter contained all the nervous system drugs that could not be placed in one of the other groups. The psychotropic drug groups are listed in Appendix 1.

We calculated the total number of DDDs prescribed as the number of packages prescribed multiplied by the number of DDDs per package. The DDD of a drug is defined as the average daily dose for an adult, when used for its primary indication (WHO, 2015). For each 3-month interval (consisting of 90 days), we assessed the average number of DDDs per women per day through dividing the total number of DDDs prescribed in that period by the number of women that redeemed prescriptions, divided by 90 days. The treatment duration of the prescriptions was calculated from the prescribed number of DDDs. We assumed the use of 1 DDD per day with a grace period of 28 days, with the dispensing date being the first day of treatment. Polypharmacy was defined as overlapping treatment periods for at least 90 days (Leckman-Westin et al., 2014), with every change in treatment being counted as a different polypharmacy episode.