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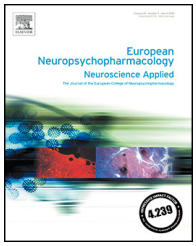

Psychopharmacological prescribing practices in pregnancy for women with severe mental illness: A multicentre study

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KEYWORDS
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Antipsychotics;
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Schizophrenia;
Bipolar disorder

Abstract
There is little known about real world psychopharmacological prescribing practices in managing pregnant women with severe mental illness (SMI). This study utilised a sample of 535 women with a SMI across two hospitals in Australia. This included women with psychotic disorders, bipolar disorder and a range of non-psychotic disorders. The majority of women with a SMI in pregnancy were prescribed psychotropic medication as part of their management. Furthermore, more than one class of agent was prescribed for 31% of women with psychotic disorders and 30% of women with bipolar disorder. Differences between sites were identified in prescribing practices across the mental disorders. This included the variation in rates of use of multiple agents and pattern of use across pregnancy. This study also identified that women with a SMI had elevated rates of gestational hypertension, gestational diabetes mellitus, smoking and obesity in pregnancy and neonates admitted following delivery compared with the Australian average. These findings suggest that studies that examine associated risks for severe mental disorders or their treatments on pregnancy and infant outcomes should take into account the prescribing practices including the likelihood of exposure to polypharmacy and a range of potential con-

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founding co-morbidities and exposures. The discrepancies in reported findings for pregnancy and infant outcomes following use of antipsychotic and mood stabiliser agents such as lithium may be at least partially accounted for by the complexity of multiple exposures that includes use of multiple psychopharmacological agents, co-exposures such as smoking and co-morbid conditions such as obesity.

Introduction

Managing severe mental illness (SMI) in pregnancy is a challenging area of psychiatry, where ensuring women remain well is balanced with minimising exposure to treatments and any associated harm for the fetus. Women with SMIs, including schizophrenia and other psychotic disorders, bipolar disorder and moderate to severe major depression often require long-term psychopharmacological treatments to remain well and prevent risks associated with relapse (Nilsson et al., 2008).

The development of new pharmacological treatments, an improved understanding of evidence-based management protocols and the findings of large clinical trials have all impacted positively on the effective treatment of adults with SMIs (Stroup et al., 2003). In recent years there has been an increase in the fertility rates and births to women with a SMI; whether this reflects effective treatment, the increase in focus on community management or other factors associated with the agents themselves is unclear (Vigod et al., 2012). There has also been a rise in the prescription of antipsychotic medications across the community with Australian prescribing rates increasing by over 200% over a decade with similar increases noted in the USA; including a rise in 'off label' usage (Alexander et al., 2011; Stephenson et al., 2013). This suggests it is highly likely that an increasing number of pregnancies will be exposed to psychotropic agents such as antipsychotics and mood stabilisers (Cooper et al., 2007; Finer and Henshaw, 2006). Therefore, research that examines the risks and benefits specifically in pregnancy has never been more needed to guide clinical practice (Galbally et al., 2018).

However, the focus of research on SMIs has typically been limited and either focused on examining a SMI diagnosis and pregnancy co-morbidities and outcomes or a specific psychotropic treatment agent and the association with pregnancy and infant outcomes. There has been little research, that has examined clinical practice in pregnancy, in an attempt to further our understanding of the contribution of disorder, treatment and relevant co-morbidities on maternal, pregnancy and infant outcomes. This is essential to make sense of any findings and appropriately attribute any adverse risks to disorder, treatment or indeed confounding co-morbidities. Understanding real life prescribing practices is crucial to this endeavour and to the interpretation and design of future research studies on psychopharmacological risks in pregnancy (Galbally et al., 2018).

This study examines prescribing practices, co-morbidities and pregnancy complications in women with severe mental illness attending two specialised antenatal clinics in two cities in Australia.

Experimental procedures

Sample

The sample comprised 535 women from two tertiary obstetric hospitals: Mercy Hospital for Women in Melbourne (MH), Victoria ($n = 122$) and King Edward Memorial Hospital (KEMH) in Perth, Western Australia ($n = 413$). Authors extracted data from the hospital records. Ethics approvals were acquired from each hospital's Human Research Ethics Committees.

This sample is drawn from two specialised antenatal clinics for women with severe mental illness where management includes specialist perinatal psychiatry, obstetrics, midwifery and allied health (Galbally et al., 2010; Nguyen et al., 2013). These clinics are located within tertiary, public funded, obstetric specialist women's hospitals.

Measures

Sample characteristics: demographic, pregnancy, neonatal and mental health

Demographic data included maternal age and BMI at the first antenatal appointment. Maternal BMI score was used to produce a binary variable, where BMI < 25 was coded as 0 (Healthy Weight) and BMI ≥ 25 was coded 1 (Overweight or Obese). Women's current smoking status (0 = Non-smoker, 1 = Smoker), alcohol consumption (0 = No, 1 = Yes) and current substance abuse status (0 = No, 1 = Yes) was also extracted.

Pregnancy complications examined included gestational diabetes, hypertensive disorder of pregnancy and mode of delivery. Neonatal complications and outcomes included infant admission to special care nursery or neonatal intensive care, infant gestational age, weight, length and head circumference at birth, and Apgar at both 1 and 5 min after birth. Gestational Diabetes Mellitus (GDM) was coded from the hospital records as no GDM (coded 0) and GDM (coded 1). GDM in both centres is diagnosed at 28 weeks gestation using the full 75 g two-hour glucose tolerance test (GTT). Gestational Hypertension (GH) was coded from the hospital records as no hypertension (coded 0) and hypertension (coded 1). GH in both centres is diagnosed from 20 weeks gestation consistent with definitions outlined by the Society of Obstetric Medicine of Australia and New Zealand (Lowe et al., 2015). This includes any women meeting the criteria for pregnancy-induced hypertension and pre-eclampsia and is defined as a systolic blood pressure greater or equal to 140 mmHg, diastolic blood pressure greater or equal to 90 mmHg or without features diagnostic of pre-eclampsia (Lowe et al., 2015)

Severe mental illness (SMI) was coded on the primary mental health diagnosis recorded in womens' files. Both clinics have experienced perinatal psychiatrists who assign diagnoses using Diagnostic and Statistical Manual of Mental Disorder IV (DSM-IV) following a comprehensive assessment. From these recorded diagnoses women were assigned to one of three diagnostic groups: psychotic disorders (including schizophrenia, schizoaffective and related psychotic disorders), bipolar disorder, and non-psychotic SMIs. Non-psychotic SMIs included major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, anorexia and bulimia nervosa.

Psychotropic medication

Specific medications and dose were extracted from hospital records. For analysis, psychotropic exposure covered any exposure during pregnancy and then exposure separately during the first and third trimesters. Specific medications were reported individually and also grouped by number of agents prescribed. We summed each reported prescribed agent for each woman, resulting in three variables measuring total agents exposed to during pregnancy, exposed to during first trimester only, and exposed to during third trimester only. Atypical antipsychotics comprised quetiapine, olanzapine, risperidone, clozapine, aripiprazole, ziprasidone and asenapine. Typical antipsychotics comprised low-potency and high-potency groups. Mood stabilizers comprised lithium, sodium valproate, carbamazepine, lamotrigine, gabapentin. Antidepressants comprised selective-serotonin reuptake inhibitors (SSRIs), serotonin-norepinephrine reuptake inhibitors (SNRIs), mirtazapine, tricyclic antidepressants, and other antidepressants. Sedatives, psychostimulants and other psychotropic agents were also included as specific psychotropic classes.

Statistical analysis

Analyses were conducted using SPSS 24 (IBM Corp., 2016). We first presented descriptives for the two hospitals individually and then as a combined sample. Using a series of pairwise comparisons *z*-tests, we compared rates for the descriptive characteristics between hospitals. Further, using available data from the Australian 2014 National Perinatal Collection (Australian Intitute of Health and Welfare, 2016), we also compared these rates for both hospital samples individually and in the combined sample, with Australian population rates using Chi-square Tests of Independence.

Next, we presented the rates of use of multiple agents for women by hospital for any time during pregnancy and during first and third trimesters separately. We then compared the rates between hospitals using a series of logistic regressions to predict a binary transformation of the count variable at any time during pregnancy, and at first and third trimesters separately. Collapsed groups for the binary variables were *one prescribed agent or fewer* (0) and *two or more prescribed agents* (1). We present the odds ratio (*OR*) and the relative risk ratio (*RR*) both with their associated 95% confidence intervals, and the attributable risk (*AR*). The *AR* provides a percentage that quantifies the absolute risk of an event attributable specifically to the predictor of interest (i.e., the difference between prevalence rates in the group of interest versus the comparison group).

Finally, we present exposure rates to psychotropic drugs, for both class and specific agents within classes, by primary diagnosis and hospital, at any point in pregnancy. We presented the *OR* to compare the difference in odds for each class and agent within primary diagnosis and between hospitals. We did not compute an *OR* for comparisons where cell counts were either empty or comprised less than five women.

Results

Table 1 displays the demographic, pregnancy, neonatal and mental health characteristics of the total sample, as well as a demographic breakdown between hospitals. KEMH women were younger than MH women were, and the rates of smoking, alcohol and illicit drug use during pregnancy were all higher in KEMH compared to MH women. Rates of smoking were significantly higher in women at both hospitals when compared to the total Australian women who birthed in 2014 (11%). Almost three-quarters of KEMH women had BMI scores in the overweight or obese ranges, which was a significantly higher rate compared to MH women with slightly more than half. The rates of women with a BMI in the overweight and obese range at KEMH were also significantly higher compared to all mothers who birthed in Australia in 2014 (46%). Interestingly, the rate of GDM was higher in MH women compared to KEMH women; however, both these rates were significantly higher than the rate for GDM in Australian women birthing in 2014 (8.3%). Rates of GH between the hospitals did not differ significantly; however, the rates were both significantly higher than the rate in Australian women who birthed in 2014 (3.4%).

The rates of primary diagnosis for psychoses between the hospitals were comparable at between one-quarter to one-third of the sample. However, rates of bipolar disorder and non-psychotic SMIs both differed significantly between the two hospitals, such that there were more women in the KEMH antenatal clinic diagnosed with bipolar disorder compared to MH women, and more women diagnosed with non-psychotic SMIs at the MH. At birth, there were no differences between the two hospitals in the obstetric outcomes (i.e. gestational age at birth, and birth weight, length and head circumference, and Apgar results). However, more infants at KEMH were admitted to a SCN or NICU after birth compared to infants at the MH. Despite this difference, both hospitals had significantly higher rates of SCN/NICU admission compared to all Australian births in 2014 (15%).

Psychotropic polypharmacy by primary diagnosis

Table 2 displays the rates of women not taking psychotropic medication, those taking only one psychotropic agent, and those taking a range of psychotropic agents at any point in pregnancy, and during first trimester only and third trimester only. We stratified these rates by both primary diagnosis and hospital centre. In general, across disorders and hospitals, rates of any psychotropic use reduced between the first and third trimesters. Across both sites and

Table 1 Demographic, pregnancy, neonatal and mental health statistics for sample by hospital ($N = 535$).

	Mercy Hospital ($n = 122$)		King Edward Memorial Hospital ($n = 413$)		Total sample	
	n	%	*n*	%	*n*	%
SMI diagnostic group						
Psychosis	29	23.8	125	30.3	154	28.8
Bipolar	39	32.0_a	179	43.3_b	218	40.7
Non-psychotic SMI	54	44.3_a	109	26.4_b	163	26.4
BMI $\geq$ 25 at booking	63	54.3_a	297	72.6_b[a]	360	68.6[a]
Smoking	36	28.3_a[a]	177	50.7_b[a]	213	44.7[a]
Alcohol use	5	3.9_a	65	16.4_b	70	13.4
Substance abuse	11	8.7_a	96	23.4_b	96	23.4
Gestational diabetes mellitus	25	19.7_a[a]	53	12.7_b[a]	78	14.3[a]
Gestational hypertension	13	10.2[a]	62	14.9[a]	70	12.9[a]
Delivery mode						
SVD	69	58.0_a	189	45.5_b	258	48.3
Assisted delivery	6	5.0_a	76	18.3_b	82	15.4
Elective cesarean	22	18.5	86	20.7	108	20.2
Emergency cesarean	22	18.5	64	15.4	86	16.1
Admission to SCN/NICU	26	20.5_a[a]	157	37.6_b[a]	183	34.1[a]
	M	*SD*	*M*	*SD*	*M*	*SD*
Maternal age at booking	31.43_a	5.20	29.19_b	5.80	29.71	5.74
Gestation at birth	38.14	2.49	38.27	2.45	38.24	2.46
Infant birth weight	3245.02	644.72	3251.76	666.21	3250.26	660.91
Infant birth length	49.68	3.23	49.21	3.68	49.32	3.59
Infant head circumference at birth	33.83	2.06	34.04	2.29	33.99	2.24
Apgar at 1 min	7.66	2.03	7.63	1.94	7.64	1.96
Apgar at 5 min	8.73	1.16	8.56	1.27	8.60	1.25

Note. Non-psychotic SMIs include major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, anorexia and bulimia nervosa, adjustment disorder. SCN: Special Care Nursery; NICU: Neonatal Intensive Care Unit.
Each subscript letter denotes significant differences ($p < .05$) in column proportions/means across each row between hospitals.
[a] Denotes sample rate differs significantly compared to Australian population rate reported in Australia's mothers and babies 2014—in brief, Perinatal statistics: BMI $\geq$ 25 at booking = 46%; Smoking = 11%; Gestational Diabetes Mellitus = 8.3%; Gestational Hypertension = 3.4%; Admission to SCN/NICU = 15% (Australian Intitute of Health and Welfare, 2016).

using the binary grouping for psychotropic polypharmacy, women with bipolar disorder were two times more likely to be prescribed two or more psychotropic agents at any point during pregnancy compared to all other women (60.6% versus 43.5%; *OR* = 2.01 [95% CIs: 1.33, 3.04], $p = .001$, *RR* = 1.39 [95% CIs: 1.18, 1.64], *AR* = 17.1%). There were no differences in the odds of being prescribed two or more classes of psychotropic agents at any point during pregnancy between women with psychotic disorders compared to all other women (45.5% versus 52.5%), and between women with non-psychotic SMI diagnoses compared to all other women (54.3% versus 41.4%).

During first trimester only exposure, this pattern was the same as psychotropic polypharmacy at any point during pregnancy. Women diagnosed with bipolar disorders were twice as likely to be prescribed two or more classes of psychotropic agent compared to all other women (57.8% versus 41.6%; *OR* = 2.01 [95% CIs: 1.33, 3.04], $p = .001$, *RR* = 1.39 [95% CIs: 1.17, 1.65], *AR* = 16.2%). There were no differences in the odds of being prescribed two or more classes of psychotropic agents at any point during pregnancy during the first trimester of pregnancy women with psychotic disorders compared to all other women (42.9% versus 50.4%), and between women with non-psychotic SMI diagnoses compared to all other women (40.5% versus 51.6%). During third trimester, the pattern remained the same as at any point in pregnancy and the first trimester, although the significant effect for bipolar disorders was weaker. Women with bipolar were over one and a half times more likely to be prescribed two or more classes of psychotropic agent compared to all other women (47.2% versus 35.3%; *OR* = 1.71 [95% CIs: 1.13, 2.60], $p = .012$, *RR* = 1.33 [95% CIs: 1.09, 1.64], *AR* = 11.9%). There were no significant effects of the other two groups for the remaining dummy contrasts (psychosis [36.5%] compared to all other women [41.7%]; and, non-psychotic SMI diagnoses [34.4%] compared to all other women [42.7%]).

Across all primary diagnosis groups, women at KEMH were nearly four times more likely than MH women to be taking two or more psychotropic agents of different classes at any point during pregnancy (57.1% versus 25.2%; *OR* = 3.95 [95% CIs: 2.53, 6.16, $p < .001$, *RR* = 2.66 [95% CIs: 1.66, 3.01], *AR* = 31.9%). During first trimester only, this pattern was the same as for any point during pregnancy (KEMH: 54.2% versus MH: 25.2%; *OR* = 3.51 [95% CIs: 2.25, 5.48], $p < .001$, *RR* = 2.15 [95% CIs: 1.57, 2.94], *AR* = 29.0%). Although the size of the effect weakened during the third trimester compared to the first trimester, KEMH women remained more

Table 2 Psychotropic prescribing in antenatal women across pregnancy, first trimester and third trimester by primary diagnosis and hospital ($N = 535$).

	Schizophrenia/psychosis			Bipolar disorders			Non-psychotic SMI		
	Mercy ($n = 29$)	KEMH ($n = 125$)	Total ($n = 154$)	Mercy ($n = 39$)	KEMH ($n = 179$)	Total ($n = 218$)	Mercy ($n = 54$)	KEMH ($n = 109$)	Total ($n = 163$)
	n (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)	*n* (%)
Across pregnancy									
None	1 (3.4%)	15 (12.0%)	16 (10.4%)	10 (25.6%)	22 (12.3%)	32 (14.7%)	29 (53.7%)	15 (13.8%)	44 (27.0%)
One	20 (69.0%)	48 (38.4%)	68 (44.2%)	13 (33.3%)	41 (22.9%)	54 (24.8%)	17 (31.5%)	34 (31.2%)	51 (31.3%)
Two	7 (24.1%)	41 (32.8%)	48 (31.2%)	10 (25.6%)	55 (30.7%)	65 (29.8%)	5 (9.3%)	38 (34.9%)	43 (26.4%)
Three	1 (3.4%)	14 (11.2%)	15 (9.7%)	6 (15.4%)	46 (25.7%)	52 (23.9%)	3 (5.6%)	19 (17.4%)	22 (13.5%)
Four	0 (0%)	7 (5.6%)	7 (4.5%)	0 (0%)	13 (7.2%)	12 (5.5%)	0 (0%)	2 (1.8%)	2 (1.2%)
Five	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.05%)	0 (0%)	1 (0.9%)	1 (0.6%)
Six	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)
First trimester									
None	1 (3.4%)	17 (13.6%)	18 (11.7%)	10 (25.6%)	22 (12.3%)	32 (14.7%)	29 (53.7%)	16 (14.7%)	45 (27.6%)
One	20 (69.0%)	50 (40.0%)	70 (45.5)	13 (33.3%)	47 (26.3%)	60 (27.5%)	17 (31.5%)	35 (32.1%)	52 (31.9%)
Two	7 (24.1%)	40 (32%)	47 (30.5%)	10 (25.6%)	51 (28.5%)	61 (28.0%)	5 (9.3%)	37 (33.9%)	42 (25.8%)
Three	1 (3.4%)	12 (9.6%)	13 (8.4%)	6 (15.4%)	44 (24.6%)	50 (22.9%)	3 (5.6%)	18 (16.5%)	21 (12.9%)
Four	0 (0%)	6 (4.7%)	6 (3.9%)	0 (0%)	14 (7.8%)	14 (6.4%)	0 (0%)	3 (2.8%)	3 (1.8%)
Five	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Six	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.6%)	1 (0.5%)	0 (0%)	0 (0%)	0 (0%)
Third trimester									
None	1 (3.4%)	26 (20.8%)	27 (17.5%)	10 (25.6%)	34 (19.0%)	44 (20.2%)	29 (53.7%)	23 (27.1%)	52 (31.9%)
One	20 (69.0%)	51 (40.8%)	71 (46.1%)	13 (33.3%)	58 (32.4%)	71 (32.6%)	17 (31.5%)	38 (34.9%)	55 (33.7%)
Two	7 (24.1%)	35 (28.0%)	42 (27.3%)	10 (25.6%)	50 (27.9%)	60 (27.5%)	5 (9.3%)	39 (35.8%)	44 (27.0%)
Three	1 (3.4%)	11 (8.8%)	12 (7.8%)	6 (15.4%)	30 (16.8%)	36 (16.5%)	3 (5.6%)	7 (6.4%)	10 (6.1%)
Four	0 (0%)	2 (1.6%)	2 (1.3%)	0 (0%)	5 (2.8%)	5 (2.3%)	0 (0%)	1 (0.9%)	1 (0.6%)
Five	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	1 (0.9%)	1 (0.6%)
Six	0 (0%)	0 (0%)	0 (0%)	0 (0%)	2 (1.1%)	2 (0.9%)	0 (0%)	0 (0%)	0 (0%)

Note. Non-psychotic SMI group comprises diagnoses of major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, anorexia and bulimia nervosa, adjustment disorder.

likely than Mercy Hospital women were to be taking two or more psychotropic agents of different classes (43.9% versus 25.2%; $OR = 2.32$ [95% CIs: 1.49, 3.62], $p < .001$, $RR = 1.74$ [95% CIs: 1.27, 2.40], $AR = 18.7\%$).

Psychotropic class and agent by primary diagnosis and hospital

Table 3 displays psychotropic drug use, both class and specific agents within each class, by primary diagnosis and hospital centre at any point in pregnancy. MH women with non-psychotic SMI primary diagnoses were more likely to be not taking any medication during pregnancy, compared to KEMH women with non-psychotic SMI. More KEMH women with bipolar disorder used atypical antipsychotics than the MH women. Specifically, KEMH women were more likely to be taking quetiapine and less likely to be taking aripiprazole compared to the MH women. Rates for both typical antipsychotic use and mood stabilizers did not differ between the two hospitals; this includes rates for the general class and the specific agents within both classes.

Rates of antidepressant use were significantly higher at the KEMH compared to the MH for women in all three primary diagnoses groups. For specific types of antidepressants, the rates of SSRI and SNRI antidepressant agents were both significantly higher for non-psychotic SMI women at the KEMH compared to the MH. Although numbers in each cell were not sufficient to conduct inferential analyses, there were some interesting patterns of sedative and psychostimulant use by hospital. Sedatives were used by 11% ($n = 14$) of women with psychotic disorders, 11% ($n = 12$) of women with bipolar disorders and 22% ($n = 24$) of women with non-psychotic SMI at the KEMH, compared to only one woman (2%) with non-psychotic SMI at the MH. In addition, at the KEMH women in each of the three primary diagnoses categories were using stimulants, with the highest rate of use by women with bipolar disorders; in comparison, no woman at the MH was taking stimulants.

Discussion

This study reports the real-life picture of managing women with severe mental illnesses in pregnancy including the complexity of co-morbidities and the prescription of multiple agents across pregnancy. For psychiatric and obstetric services managing severe mental illness in pregnancy this highlights the complexity and inherent risks with elevated rates of obesity, smoking, and pregnancy complications than

Table 3 Prescription drugs use by primary diagnosis and hospital ($N = 535$).

	Schizophrenia/psychosis ($n = 154$)			Bipolar disorders($n = 218$)			Non-psychotic SMI($n = 163$)		
	Mercy ($n = 29$)	KEMH ($n = 125$)	OR[a] [95% CI]	Mercy ($n = 39$)	KEMH ($n = 179$)	OR[a] [95% CI]	Mercy ($n = 54$)	KEMH ($n = 109$)	OR[a] [95% CI]
	n (%)	*n* (%)		*n* (%)	*n* (%)		*n* (%)	*n* (%)	
No medication	**1 (3.4%)**	**16 (12.8%)**	**4.11 [0.52, 32.33]**	**8 (20.5)**	**20 (11.2%)**	**0.49 [0.20, 1.21]**	**27 (50.0%)**	**16 (14.7%)**	**0.17* [0.08, 0.37]**
Atypical antipsychotics	**25 (86.2%)**	**98 (79.7%)**	**0.51 [0.19, 1.81]**	**15 (38.5%)**	**118 (65.9%)**	**3.01* [1.51, 6.33]**	**13 (24.1%)**	**38 (34.9%)**	**1.69 [0.81, 3.53]**
Quetiapine	7 (24.1%)	33 (26.4%)	1.13 [0.44, 2.88]	6 (15.4%)	95 (53.1%)	6.22* [2.48, 15.58]	7 (13.0%)	28 (25.7%)	2.32[0.94, 5.73]
Olanzapine	6 (20.7%)	43 (34.4%)	2.01[0.76, 5.31]	7 (17.9%)	24 (13.4%)	0.71[0.28, 1.78]	5 (9.3%)	12 (11.0%)	1.21[0.40, 3.64]
Clozapine	4 (13.8%)	8 (6.4%)	0.43[0.12, 1.53]	0 (0%)	1 (0.6%)	-	0 (0%)	0 (0%)	-
Risperidone	2 (6.9%)	18 (14.4%)	[b]	0 (0%)	4 (2.2%)	-	0 (0%)	1 (0.9%)	-
Aripiprazole	7 (24.1%)	12 (9.6%)	.33*[0.12, 0.94]	2 (5.1%)	4 (2.2%)	[b]	0 (0%)	1 (0.9%)	-
Ziprasidone	1 (3.4%)	1 (0.8%)	[b]	0 (0%)	0 (0%)	-	1 (1.9%)	0 (0%)	-
Asenapine	0 (0%)	1 (0.8%)	-	0 (0%)	1 (0.6%)	-	0 (0%)	0 (0%)	-
Typical antipsychotics	**3 (10.3%)**	**21 (16.8%)**	**1.75[0.49, 6.32]**	**0 (0%)**	**4 (2.2%)**	-	**1 (1.9%)**	**0 (0%)**	**-**
Typical antipsychotics - low potency	0 (0%)	7 (5.6%)	-	0 (0%)	3 (1.7%)	-	1 (1.9%)	0 (0%)	-
Typical antipsychotics - high potency	3 (10.3%)	20 (16.0%)	1.65[0.46, 5.98]	0 (0%)	3 (1.7%)	-	0 (0%)	0 (0%)	-
Mood stabilizers and antiepileptics	**2 (6.9%)**	**6 (4.8%)**	**0.68 [0.13, 3.56]**	**20 (51.3%)**	**80 (44.7%)**	**0.78 [0.38, 1.54]**	**5 (9.3%)**	**9 (8.3%)**	**0.88 [0.28, 2.77]**
Lithium	2 (6.9%)	1 (0.8%)	[b]	11 (28.2%)	32 (17.9%)	0.55[0.25, 1.23]	2 (3.7%)	2 (1.8%)	[b]
Sodium valproate	0 (0%)	2 (1.6%)	-	2 (5.1%)	11 (6.1%)	[b]	1 (1.9%)	3 (2.8%)	[b]
Carbamazepine	0 (0%)	2 (1.6%)	-	1 (2.6%)	6 (3.4%)	[b]	0 (0%)	1 (0.9%)	-
Lamotrigine	1 (3.4%)	1 (0.8%)	[b]	8 (20.5%)	35 (19.6%)	0.94[0.40, 2.23]	2 (3.7%)	1 (0.9%)	[b]
Gabapentin	0 (0%)	0 (0%)	-	1 (2.6%)	0 (0%)	-	0 (0%)	2 (1.8%)	-
Other antiepileptics	0 (0%)	0 (0%)	-	0 (0%)	1 (0.6%)	-	0 (0%)	0 (0%)	-
Antidepressants	**3 (10.3%)**	**39 (31.2%)**	**3.93*[1.12, 13.77]**	**13 (33.3%)**	**94 (52.5%)**	**2.21*[1.07, 4.58]**	**16 (29.6%)**	**18 (74.3%)**	**6.87*[3.33, 14.19]**
SSRI	3 (10.3%)	21 (16.8%)	1.75 [0.49, 6.32]	7 (17.9%)	58 (32.4%)	2.19[0.91, 5.26]	13 (24.1%)	45 (41.3%)	2.22*[1.07, 4.61]
SNRI	0 (0%)	16 (12.8%)	-	5 (12.8)	35 (19.6%)	1.65[0.60, 4.53]	2 (3.7%)	37 (33.9%)	13.36*[3.08, 57.93]
Mirtazapine	0 (0%)	5 (4.0%)	-	1 (2.6%)	15 (8.4%)	[b]	1 (1.9%)	20 (18.3%)	[b]
Tricyclic antidepressants	0 (0%)	2 (1.6%)	-	0 (0%)	2 (1.1%)	-	0 (0%)	2 (1.8%)	[b]
Other antidepressants	0 (0%)	1 (1.8%)	-	0 (0%)	3 (1.7%)	-	0 (0%)	3 (2.8%)	-
Sedatives	**0 (0%)**	**14 (11.2%)**	**-**	**0 (0%)**	**12 (11.2%)**	**-**	**1 (1.9%)**	**24 (22.0%)**	[b]
Psychostimulants	**0 (0%)**	**1 (0.8%)**	**-**	**0 (0%)**	**10 (5.6%)**	**-**	**0 (0%)**	**4 (3.7%)**	**-**
Other	**0 (0%)**	**0 (0%)**	**-**	**0 (0%)**	**1 (0.6%)**	**-**	**0 (0%)**	**2 (1.8%)**	**-**

Note. Non-psychotic SMI group comprises diagnoses of major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, anorexia and bulimia nervosa, adjustment disorder.

—Binary regression not conducted due to one or both cells being constant.

[a] Within each Primary Diagnosis group, the odds ratio (OR) that a KEMH woman (0), versus a Mercy Hospital woman (1), will be using an agent belonging to the prescription drug class at any point during pregnancy.

[b] OR unstable and not reported: large standard error due to small cell count.

* $p < .05$.

would be expected for women delivering a baby in Australia (Australian Intitute of Health and Welfare, 2016). For instance, 11% of women across Australia smoked in pregnancy yet for this study 45% smoked in pregnancy. Smoking in pregnancy is associated with increased rates of preterm delivery and placental complications (Shah and Bracken, 2000). In Australia, around 46% of women in pregnancy are either overweight or obese and this study suggests the rate for women with a SMI is 69%. Obesity has been linked with a number of pregnancy and postpartum complications including an increased risk of malformation; a highly relevant association when considering any association between pharmacological exposure in pregnancy and malformation outcomes (Cheney et al., 2018; Galbally et al., 2018; Persson et al., 2017). However, this study also found that most women with a SMI in pregnancy, particularly those with psychotic disorders and bipolar disorder, are managed with psychotropic treatments as part of antenatal care.

The prescribing practices across the two sites within this study showed some differences despite both sites being public funded tertiary obstetric hospitals and both having a consultant psychiatrist with perinatal mental health expertise leading each clinic. This study also highlighted that across both sites the majority of women with a SMI did require at least one psychotropic medication in pregnancy as part of their management and for some more than one class and agent. At KEMH, women were four times more likely to be on two or more psychotropic agents in pregnancy across pregnancy and across the diagnostic groups than those attending MH. Overall, this suggests that studies examining either the risk of severe mental disorders on pregnancy outcomes also need to include detailed information on psychotropic agent use to produce meaningful findings.

Differences across the sites were evident in both the pharmacological management of psychotic disorders and bipolar disorder as well as the range of mental disorders included in the non-psychotic SMIs. KEMH had 12% of women with psychotic illnesses on no medication throughout pregnancy in contrast to 3% of women attending the MH. Yet no woman with a psychotic disorder was managed with more than three agents at the MH and 69% were managed with a single agent. In contrast, 11% of the KEMH women with psychotic disorders had three or more agents in pregnancy. The latest Australian clinical practice guidelines for the management of schizophrenia and related disorders recommends against the use of more than one agent and where possible adhering to monotherapy for the management of psychotic disorders (Galletly et al., 2016). These recommendations are supported in a range of international guidelines where monotherapy, where possible, is advised (Fleischhacker and Uchida, 2014). Recent Australian perinatal mental health guidelines that include the management of psychotic disorders in pregnancy are silent on the use of antipsychotic monotherapy or polytherapy for the management of psychotic disorders, but make the general recommendation to consider the use of antipsychotics for treating psychotic symptoms in pregnancy (Austin et al., 2017).

In managing bipolar disorder, there were also differences between the sites with a higher rate of antipsychotic use at the KEMH and mood stabilizers at the MH. In particular, the rate of use of quetiapine was 53% at the KEMH and only 15% at the MH, whereas 28% of women at the MH with bipolar disorder were on lithium in contrast to 18% of KEMH women suggesting different clinical preferences for agents in the management of bipolar disorder in pregnancy. The recent concerns about a possible increased risk of GDM with specific antipsychotic medications may be a factor in different prescribing practices across the two sites (Gentile, 2014; Park et al., 2018). Both sites had the majority of women managed on one to three agents of medication, and there was a higher rate of more than one class of agent for these women potentially indicating the complexity of management of bipolar disorder generally and in pregnancy. While the number of agents used to manage bipolar disorder at the MH remained stable from the 1st to 3rd trimesters, at the KEMH there was a drop in the number of agents from 12% being managed on no agents in the 1st trimester to 19% by the 3rd trimester with fewer on multiple agents as pregnancy progressed.

The early postpartum is a high risk period for significant relapses for bipolar disorder and while not reported in this study it would be interesting to examine the management patterns after delivery and its relationship to relapse risk. Certainly previous studies have linked remaining on medications, such as lithium, to a reduced risk of postpartum relapse for women with bipolar disorder (Bergink et al., 2012; Viguera et al., 2000).

The use of psychostimulants in pregnancy also varied across the two sites. For 4% of all women attending KEMH they were also prescribed a psychostimulant while at the MH there were no women in pregnancy prescribed psychostimulants across any of the diagnostic groups. Previously Western Australia, where the KEMH is located, had the highest rate of psychostimulant prescription for children in Australia and higher than many reported rates outside of Australia (Preen et al., 2007). However, this is the first study that we are aware of, to report Australian data on usage of psychostimulants in pregnancy and highlights a potential difference in prescription rates between a sample of pregnant women from Victoria and Western Australia. This may be useful for further exploration using a community sample of pregnant women across states in Australia.

This study was only able to utilise reported prescription and usage data from medical files, confirmation of compliance through blood levels was not possible for medications other than lithium and some of the anti-epileptics. However, as this data reports on specific antenatal clinics for women with SMIs non-compliance is regularly assessed and reported in files. This study also relies on retrospective data gathered through file audit on all aspects reported and cannot quantify exposures such as alcohol and smoking use. These women attended specific antenatal clinics for severe mental illness located in tertiary hospitals. These clinics were located within tertiary hospitals in recognition of the complexity and complications of antenatal care for women with SMI. Therefore, women with SMI attending secondary or community services for antenatal care were not able to be included. Furthermore, while experienced consultant psychiatrists assessed the reported diagnosis, these diagnoses were not confirmed with a structured diagnostic measure.

Improving the care of women with severe mental illness in pregnancy is important if we are to improve maternal morbidity and mortality across the perinatal period

and equally to improving the lifelong health and wellbeing of their children (Galbally et al., 2017; Jones et al., 2014; Nguyen et al., 2013). However, unless we can understand and account for the complexity of common comorbidities and real-life management in our research, we cannot progress our understanding and recommendations to women and clinicians as to how best to manage SMIs in pregnancy. Ensuring we develop comprehensive and clinically relevant guidelines for management of severe mental disorders in pregnancy is important to improve consistency of care equally within specialist perinatal mental health services as well as outside of these services where many women are managed.

These findings suggest at a minimum that research in pregnancy that examines the risks for adverse pregnancy and offspring outcomes, for severe mental illness or the treatments used for these conditions, should include confounders such as smoking, alcohol and substance use, and obesity as well as accounting for any polypharmacy. The lack of inclusion of confounders and polypharmacy may also explain why we continue to have conflicting findings for risks associated with psychotropic treatments and mental disorders in pregnancy no matter the volume of research published. Ensuring future research engages with the complexity of this clinical area rather than a focus on power alone is likely to progress our understanding and result in clinical care associated with improved outcomes for women and infants.

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Contributors

MG proposed the original study. MG, JF, MS designed the overall study, data collection and undertook the ethics application on each site. SW undertook the statistical analysis and all authors contributed to the interpretation of findings. MG and SW prepared the draft of the paper and all authors critically reviewed and revised for content and gave approval to the final to be published version of the manuscript.

Conflict of interest

MG has previously received honorarium for speaking from Lundbeck. MS has previously received honorariums for speaking from Lundbeck, Astra Zeneca, and Eli Lilly. The other authors declare that they have no competing interests.

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