

## Medicines Adverse Reactions Committee

Meeting date	11 March 2021	Agenda item	3.2.1
Title	<b>SSRI/SNRI antidepressants and the risk of postpartum haemorrhage</b>		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
<b>Active ingredient</b>	<b>Product name</b>	<b>Sponsor</b>	
<b>See Appendix 1 for full list.</b>			
PHARMAC funding	<b>PHARMAC fully funded brand(s) as of 28 January 2021:</b>		
	<b>Active ingredient</b>	<b>Funded brand (sponsor)</b>	
	<b>Citalopram</b>	Citalopram (PSM) (PSM Healthcare Ltd t/a API Consumer Brands)	
	<b>Escitalopram</b>	Escitalopram-Apotex (Ipca Pharma NZ Pty Ltd)	
	<b>Fluoxetine</b>	Fluox (Mylan NZ Ltd) Arrow-Fluoxetine (Teva Pharma NZ Ltd)	
	<b>Paroxetine</b>	Loxamine (Mylan NZ Ltd)	
	<b>Sertraline</b>	Arrow-Sertraline (Teva Pharma NZ Ltd)	
	<b>Venlafaxine</b>	Enlafax XR (Mylan NZ Ltd)	
	<b>Vortioxetine</b> is not funded by PHARMAC.		
Previous MARC meetings	<a href="#">124<sup>th</sup> meeting</a> : Selective serotonin reuptake inhibitors (SSRIs) and haemorrhage (December 2005). <a href="#">108<sup>th</sup> meeting</a> : SSRIs and haemorrhage (December 2001).		
International action	<a href="#">EMA</a> : PRAC recommendations for update of the product information (26 October 2020). <a href="#">MHRA</a> : SSRI/SNRI antidepressant medicines: small increased risk of postpartum haemorrhage when used in the month before delivery (7 January 2021).		
Prescriber Update	<a href="#">SSRIs – still associated with cases of bleeding</a> (December 2011) <a href="#">The use of antidepressants in pregnancy</a> (September 2010) <a href="#">Management of Postpartum haemorrhage</a> (December 1998)		
Classification	Prescription medicine		
Usage data	Number of people (including pregnant women) who received a dispensing of a PHARMAC funded medicine from a community pharmacy at least once during 2019: <ul style="list-style-type: none"> <li>• citalopram: 105,104</li> <li>• escitalopram: 65,250</li> <li>• fluoxetine: 81,019</li> <li>• paroxetine: 30,219</li> <li>• sertraline: 68,208</li> <li>• venlafaxine: 49,854</li> </ul>		

	<ul style="list-style-type: none"><li>• Vortioxetine – no data (not PHARMAC funded)</li></ul>
Advice sought	<p><b>The Committee is asked to advise whether:</b></p> <ul style="list-style-type: none"><li>• the current evidence supports an association of postpartum haemorrhage when SSRIs and SNRIs are used within the month prior/or close to delivery</li><li>• all data sheets for SSRIs, SNRIs and vortioxetine should be updated to include the risk of postpartum haemorrhage when used within the month prior/or close to delivery</li></ul>

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## 1 PURPOSE

On 28 September 2020, the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) reviewed the evidence on the risk of postpartum haemorrhage (PPH) with the use of selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenaline reuptake inhibitors (SNRIs), and other antidepressants [1]. The review of spontaneous data and the literature concluded a slightly increased risk of PPH with SSRIs, SNRIs and vortioxetine during the month before delivery [1]. Subsequently, the PRAC recommended that the product information for SSRIs, SNRIs and vortioxetine be updated to include the risk of PPH, particularly when exposed within the month prior to delivery [1].

Following PRAC's recommendation, the United Kingdom's Medicine and Healthcare products Regulatory Agency (MHRA) issued a Drug Safety Update alerting the same information in January 2021 [2].

The purpose of this report is to review the available evidence of postpartum haemorrhage (PPH) with the use of antidepressants, with focus on SSRI/SNRI and vortioxetine. This report also reviews the New Zealand data sheet for SSRIs, SNRIs, and vortioxetine to see if the risk of PPH is already stated or will be included in the next data sheet update as indicated by the sponsors.

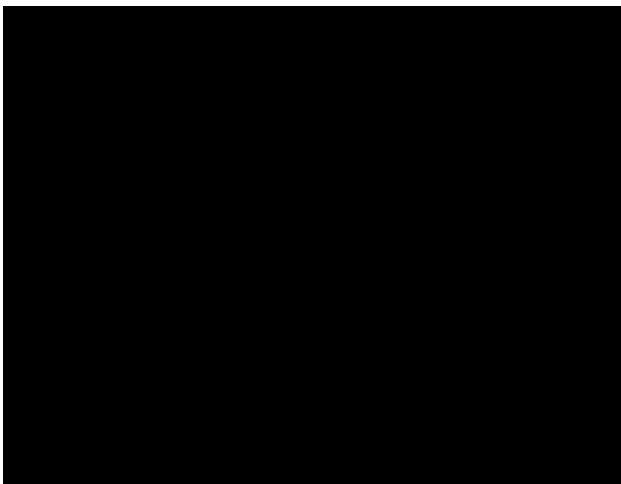
## 2 BACKGROUND

### 2.1 SSRI/SNRI and vortioxetine

#### 2.1.1 Selective serotonin reuptake inhibitors

SSRIs are used to treat mood disorders such as major depressive disorder. The mechanism of action is suggested to be through increasing serotonergic activity in the neurons by decreasing the function of presynaptic serotonin transporters by 60 to 80%. This increases the length of time the neurotransmitter serotonin is available in the synapse to occupy postsynaptic serotonin receptors [3] (see Figure 1)

**Figure 1: SSRI inhibits the reuptake of serotonin in the presynaptic cell by 'blocking' the serotonin reuptake transporter (labelled serotonin channel in the diagram)**



Source: <https://hopes.stanford.edu/ssris/> (accessed 19 February 2021)

The various SSRIs differ in chemical structure (Figure 2) and this affects their affinity to the serotonin transporter [4]. Citalopram consists of two stereoisomers, with one stereoisomer, S-citalopram (escitalopram) more potently inhibiting the serotonin transporter than its other stereoisomer [3].

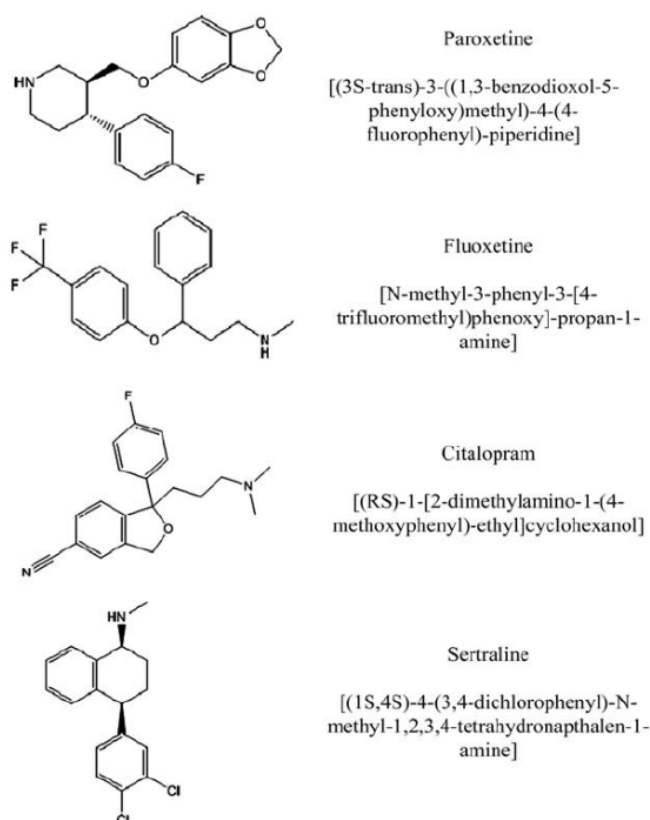


Figure 2: Chemical structures of SSRIs [5]

### 2.1.2 Serotonin and noradrenaline reuptake inhibitors

This report will only consider venlafaxine as this is the only approved SNRI in New Zealand. Venlafaxine is thought to treat various mood disorders by blocking the presynaptic serotonin and noradrenaline transporters. The dose of venlafaxine affects serotonin and noradrenaline reuptake. At low doses (75 mg per day) venlafaxine is essentially a SSRI. At higher doses (225-375 mg per day) venlafaxine has significant inhibitory effects on the noradrenaline transporter [6]. Venlafaxine may also increase blood pressure, especially at higher doses due to the noradrenaline effects [6].

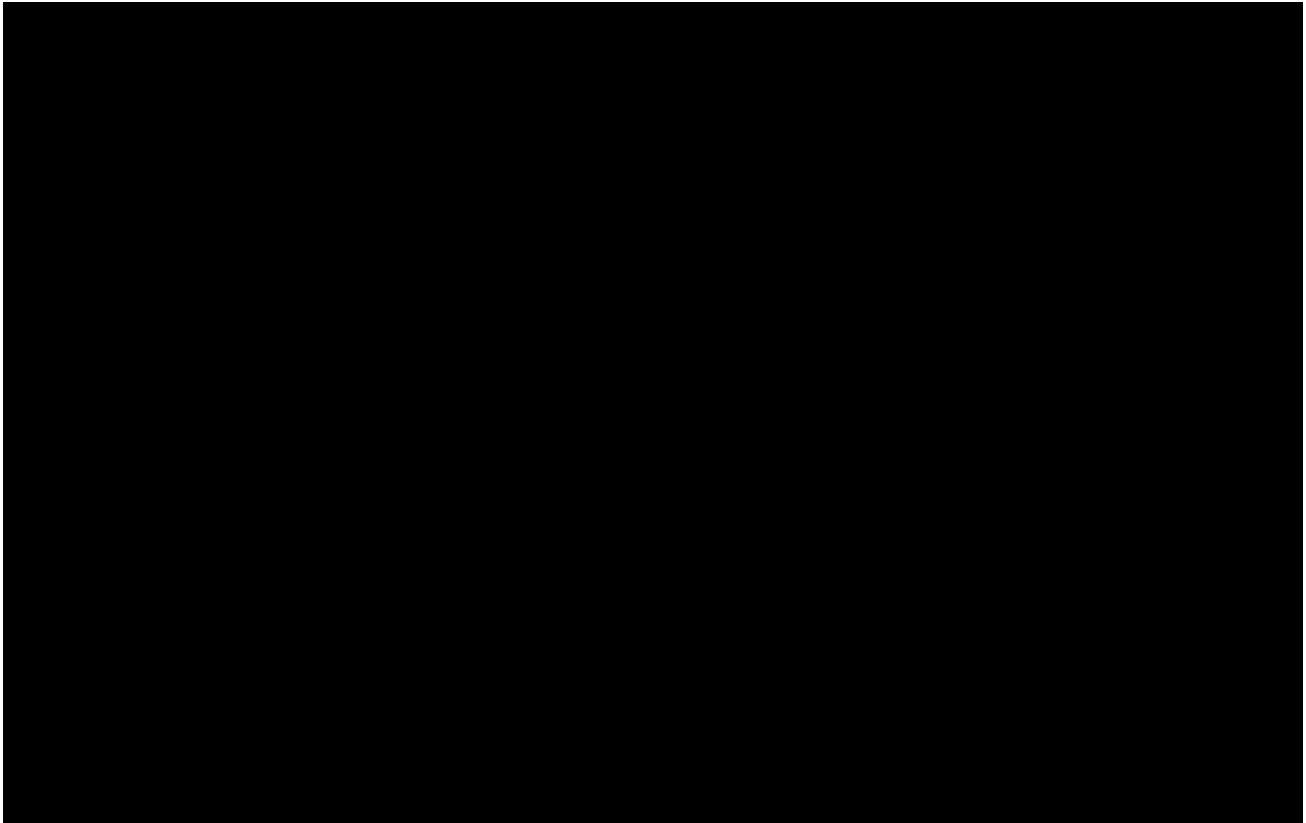
### 2.1.3 Vortioxetine

Vortioxetine is a serotonin modulator. It is a relatively new antidepressant approved by Medsafe in 2020 and currently not funded by PHARMAC. Its approved indication is for the treatment of major depressive disorder and to prevent its relapse [7]. Vortioxetine has “multimodal” action where it selectively inhibits the serotonin transporter and acts as an agonist or antagonist at various serotonin receptor subtypes [7]. It is hypothesised that these multimodal actions are responsible for its antidepressant effects [7].

### 2.1.4 SSRIs/SNRIs and haemostasis

Serotonin plays a role in platelet aggregation (see Figure 3). In normal vascular injury, platelets release serotonin to promote vasoconstriction and activate other platelets to aggregate and adhere [8]. Serotonin is considered a relatively weak platelet activator in coagulation but can greatly potentiate the aggregation induced by other mediators such as adenosine diphosphate, ephedrine and collagen [8]. Because platelets are unable to synthesise serotonin themselves, the platelet serotonin reuptake transporter ensures intracellular stores of serotonin are not depleted. It is thought that the use of antidepressants, particularly serotonin reuptake inhibitors may increase the risk of bleeding events through serotonin reuptake inhibition which

subsequently depletes serotonin storage in platelets over time. Depletion of serotonin may result in disrupted platelet aggregation and adhesion, eventually prolonging bleeding time [9].



**Figure 3: The role of serotonin in platelet aggregation. Collagen exposed after endothelial damage stimulates platelet activation. The activated platelet releases intraplatelet granules containing serotonin. Serotonin released subsequently amplifies platelet aggregation. Serotonin is then recaptured by a specific serotonin reuptake transporter (5-HTT) back into the platelet. The use of SSRIs/SNRIs block the reuptake of serotonin via 5-HTT and leading to the depletion of serotonin stores within the platelet over time [10].**

Observational studies have shown major bleeds that do occur with the use of SSRIs tend to be upper gastrointestinal bleeding, stroke, PPH, and intraoperative bleeding. In addition, the risk of the bleeding is amplified with the use of non-steroidal anti-inflammatory drugs, antiplatelet medicines, or anticoagulants [3].

Comment:

Although there is biological plausibility for SSRIs/SNRIs to affect platelet aggregation, there is currently only low-quality evidence of these medicines causing bleeding in practice unless other medicines affecting haemostasis is taken concurrently.

## 2.2 Postpartum haemorrhage

### 2.2.1 PPH hospitalisation in New Zealand

For the 2019/2020 financial year, 486 women were hospitalised in New Zealand with PPH as the primary diagnosis in publicly and privately funded service. See Appendix 2 for more information on age, socioeconomic status, ethnicity and geographical location breakdown.

### 2.2.2 Definitions and diagnosis

Postpartum haemorrhage is defined as excessive bleeding after childbirth. The bleeding is greater than expected with signs and symptoms of hypovolaemia. PPH is an obstetric emergency and is one of the top five causes of maternal mortality [11].

PPH can be classified as [11]:

- primary: when the bleeding occurs in the first 24-hours after delivery
- secondary (also known as late or delayed): when bleeding occurs from 24-hours to 12 weeks after delivery

The criteria for diagnosis can vary considerably depending on the organisation [11], which is outlined in table 1:

**Table 1. Different organisations' definitions of PPH.**

Organisation	Definition of PPH
World Health Organization	<ul style="list-style-type: none"> <li>• Blood loss <math>\geq 500</math> mL within 24 hours after birth.</li> <li>• Severe PPH: Blood loss <math>\geq 1000</math> mL within the same time frame.</li> </ul>
American College of Obstetricians and Gynecologists	Cumulative blood loss $\geq 1000$ mL or blood loss accompanied by signs or symptoms of hypovolemia within 24 hours after the birth process (includes intrapartum loss) regardless of route of delivery.
Royal College of Obstetricians and Gynaecologists	Minor PPH (500 to 1000 mL) and major PPH ( $> 1000$ mL). Subdivisions of major PPH include moderate (1001 to 2000 mL) or severe ( $> 2000$ mL).
International expert panel	Active bleeding $> 1000$ mL within the 24 hours following birth that continues despite the use of initial measures, including first-line uterotonic agents and uterine massage.
Society of Obstetricians and Gynaecologists of Canada	Any amount of bleeding that threatens the patient's hemodynamic stability.
California Maternal Quality Care Collaborative	<ul style="list-style-type: none"> <li>• Stage 0: Every woman in labour/giving birth.</li> <li>• Stage 1: Blood loss <math>&gt; 500</math> mL after vaginal or <math>&gt; 1000</math> mL after caesarean delivery; or change in vital signs <math>&gt; 15\%</math> or heart rate <math>\geq 110</math> beats/minute, blood pressure <math>\leq 85/45</math> mmHg, O<sub>2</sub> saturation <math>&lt; 95\%</math>.</li> <li>• Stage 2: Continued bleeding with total blood loss <math>&lt; 1500</math> mL.</li> <li>• Stage 3: Total blood loss <math>&gt; 1500</math> mL or <math>&gt; 2</math> units packed red cells transfused; or unstable vital signs; or suspicion of disseminated intravascular coagulation.</li> </ul>

**Comment:**

The Royal Australasian and New Zealand College of Obstetrician and Gynaecologists (RANZCOG) follow the World Health Organization's definition of PPH [12].

The incidence of PPH varies considerably as this depends on the diagnosis definition as highlighted above and how blood loss is quantified. Quantitatively measuring blood loss shows rates of PPH to be as high as 10%, in contrast PPH diagnosed by estimated blood loss was 1-3% amongst women after delivery. In addition,



estimating the incidence of PPH is further complicated by the fact that bleeding cannot not always be seen externally (such as intra-abdominal bleeding), and that blood collection devices may be mixed with amniotic fluid resulting in more volume collected [11].

### 2.2.3 Risk factors

According to RANZCOG, many risk factors for PPH have been identified but only a small proportion of women with risk factors experience PPH. Despite this, it is recommended for women who have known risk factors to receive appropriate management in both the antenatal (before birth) and intrapartum (during the act of birth) period to mitigate the risk of PPH [12, 13]:

**Figure 4: Possible predisposing risk factors for PPH**

Antenatal risk factors	Intrapartum risk factors
<ul style="list-style-type: none"> <li>• History of previous PPH</li> <li>• Large for gestational age newborn (&gt;4 kg)</li> <li>• Placenta praevia/accreta</li> <li>• Hypertensive disorders (eg, preeclampsia, eclampsia, HELLP)</li> <li>• Obesity</li> <li>• High parity</li> <li>• Bleeding disorders</li> </ul>	<ul style="list-style-type: none"> <li>• Induction and/or augmentation</li> <li>• First stage labour &gt;24 hours</li> <li>• Delay in progress of second stage</li> <li>• Precipitate labour</li> <li>• Instrumental delivery</li> <li>• Caesarean section</li> <li>• Retained placenta</li> <li>• Lacerations</li> </ul>

### 2.2.4 Causes of PPH [11, 12]

- Uterine atony – there is lack of effective contraction of the uterus after delivery. This is the most common cause of PPH. Prolonged labour, increasing parity and uterine overdistension can cause the uterus to lose tone.
- Trauma – lacerations and ruptures from delivery or surgical incisions
- Retained products of conception – such as placenta, cotyledon or membranes.
- Bleeding disorders– eg, von Willebrand’s, disseminate intravascular coagulation, and thrombocytopenia

### 2.2.5 Management of primary PPH

The management of primary PPH requires timely identification and response to the bleeding. The overall management goals for PPH are to correct or maintain adequate blood volume, tissue oxygenation, reverse or correct the bleeding disorder and to eliminate the cause of PPH [11]. The RANZCOG outlines management of PPH based on the cause [12]:

- Correcting the uterine atony – through mechanical methods such as uterine massage and bimanual compression; pharmacological options may include: oxytocin, ergometrine, misoprostol and prostaglandin analogues.
- Trauma – thoroughly inspect for bleeding source in the genital tract. Once the bleeding source is found pressure should be applied to the area and repair attempted.
- Retained products of conception –the placenta should be removed if not already. The removed placenta should be examined for obvious missing tissue.
- Bleeding disorders – correct or manage the disorder eg, replace platelets and clotting factors, administer tranexamic acid

## 2.3 International Regulatory Action

### 2.3.1 European Medicines Agency – 28 September to 1 October 2020 [1]

The EMA's PRAC considered the issue of PPH with the use of SSRIs, SNRIs, vortioxetine and other antidepressants. The Committee considered seven published studies (see section 3.1.1 – 3.1.6). Based on the evidence reviewed, no updates were required for the product information for mirtazapine, trazodone, amitriptyline and bupropion at the current time. The innovator for amitriptyline was requested to monitor haemorrhage and PPH events in their next Periodic Safety Update Report single assessment.

The Committee requested that the sponsors for citalopram, desvenlafaxine, escitalopram, fluoxetine, fluvoxamine, milnacipran, paroxetine, sertraline and venlafaxine update their product information to:

#### Section 4.4 Special warnings and precautions for use

*SSRIs/SNRIs may increase the risk of postpartum haemorrhage (see sections 4.6, 4.8).*

#### Section 4.6 Fertility, pregnancy and lactation

*Observational data indicate an increased risk (less than 2-fold) of postpartum haemorrhage following SSRI/SNRI exposure within the month prior to birth (see sections 4.4, 4.8).*

#### Section 4.8 Undesirable effects

*SOC Reproductive system and breast disorders: postpartum haemorrhage\*; frequency not known  
Add a footnote under the Table that this event is a class effect: \* This event has been reported for the therapeutic class of SSRIs/SNRIs (see sections 4.4, 4.6).*

The PRAC also requested updates to the package leaflet (consumer medicine information).

The Committee also requested the sponsor for vortioxetine to update their product information:

#### Section 4.4 Special warnings and precautions for use

##### *Haemorrhage*

*Bleeding abnormalities, such as ecchymoses, purpura and other haemorrhagic events, such as gastrointestinal or gynaecological bleeding, have been reported rarely with the use of antidepressants with serotonergic effect, including vortioxetine. SSRIs/SNRIs may increase the risk of postpartum haemorrhage, and this risk could potentially apply also to vortioxetine (see section 4.6). Caution is advised in patients taking anticoagulants and/or medicinal products known to affect platelet function [e.g., atypical antipsychotics and phenothiazines, most tricyclic antidepressants, non-steroidal anti-inflammatory drugs (NSAIDs), acetylsalicylic acid (ASA)] (see section 4.5) and in patients with known bleeding*

#### Section 4.6 Fertility, pregnancy and lactation

*Observational data have provided evidence of an increased risk (less than 2-fold) of postpartum haemorrhage following exposure to an SSRI or SNRI within the month prior to birth. Although no studies have investigated an association between vortioxetine treatment and postpartum haemorrhage, there is a potential risk, taking into account the related mechanism of action (see section 4.4).*

The PRAC also requested updates to the package leaflet (consumer medicine information).

### **2.3.2 Medicines and Healthcare products Regulatory Agency – Drug Safety Update 7 January 2021 [2]**

In response to EMA's publication, the MHRA also highlighted this issue in their Drug Safety Update (DSU).

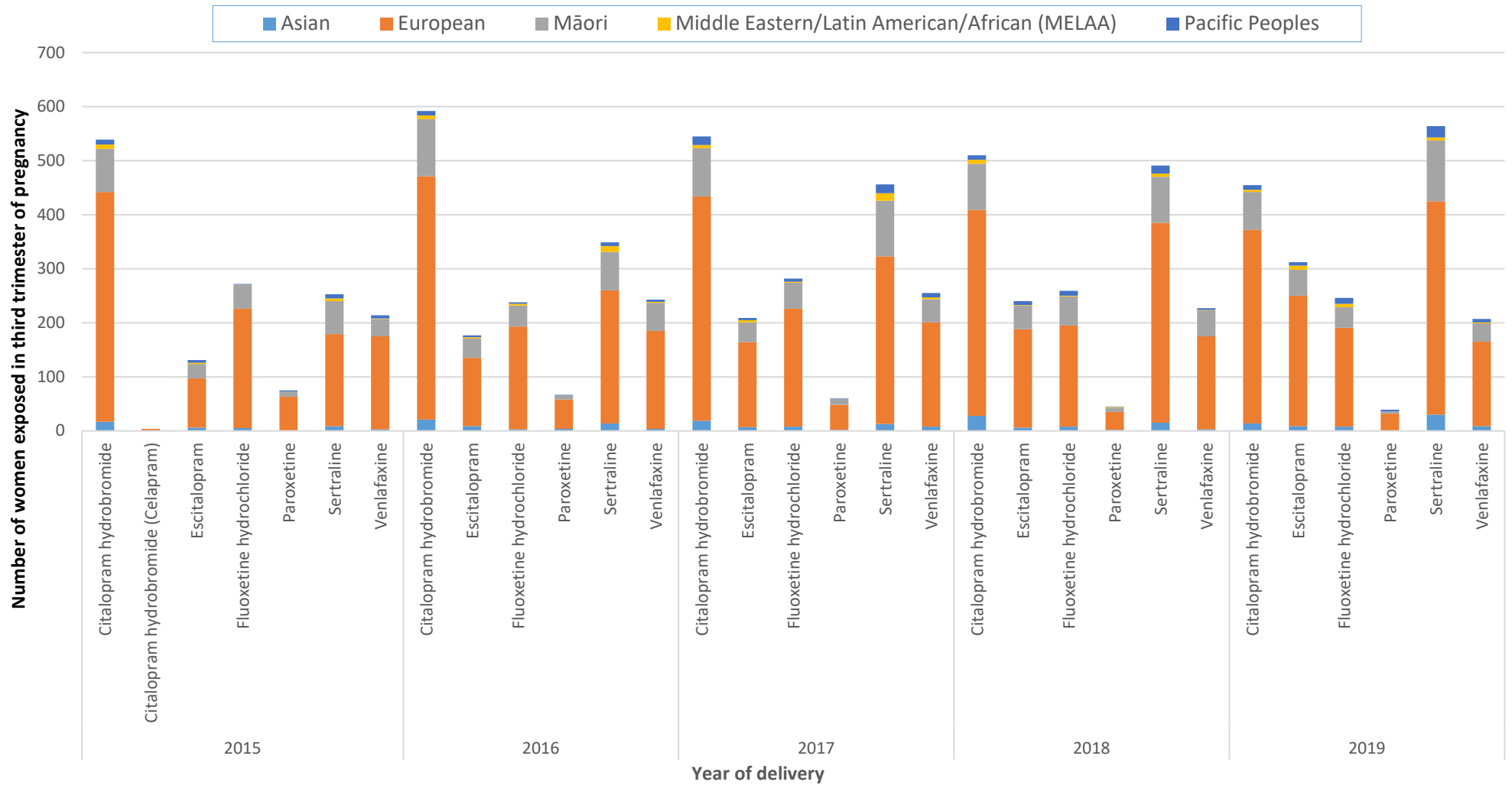
The MHRA highlighted to prescribers that although the risk of PPH is small (less than 2-fold), it may be significant for individual patients with other high-risk factors for PPH (such as a person on anticoagulants or have bleeding disorders). The update reminded prescribers to assess the benefits and risks for use of antidepressants during pregnancy, and the risk of untreated depression during pregnancy.

### **2.4 Usage data in New Zealand**

The Ministry of Health's Qlik Sense data analysis tool was used to query the National Collections data for third trimester pregnancy exposure to SSRIs and venlafaxine. Exposure to these medicines comes from the Pharmaceutical Collection (PHARMS) and only reflect community dispensed, PHARMAC subsidised medicines during pregnancy. It does not capture whether or not these medicines were actually taken during pregnancy as prescribed, nor does it capture antidepressants dispensed in hospital pharmacies.

Figure 5 captures the exposure of SSRIs and venlafaxine in the third trimester of pregnancy. The overall trend over the years 2015 to 2019 in the context of third trimester of pregnancy shows that exposure to paroxetine and citalopram has gradually decreased over the last five years, whereas exposure to sertraline has increased.

**Figure 5: Exposure to SSRIs and venlafaxine in third trimester of pregnancy between the delivery years 2015 to 2019.**



## 2.5 New Zealand data sheet review (as at 2 February 2021)

A review was conducted on 2 February 2021 to see if the SSRIs, venlafaxine and vortioxetine data sheets contained information on PPH risk when used within one month prior/or close to delivery. The data sheets were retrieved using the Medsafe Data Sheets and Consumer Information Search:

<https://www.medsafe.govt.nz/Medicines/infoSearch.asp>

**Table 2. Selective serotonin inhibitors approved in New Zealand**

Product name, form and strength	Sponsor	Wording on PPH risk included or has the sponsor communicated with Medsafe?
<b>Citalopram</b>		
Citalopram PSM Healthcare film-coated tablets, 20mg	PSM Healthcare Ltd trading as API Consumer Brands	No. [REDACTED]
Cipramil film-coated tablets, 20mg	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	No. [REDACTED]
<b>Escitalopram</b>		
Lexapro film-coated tablets, 10mg, 20mg	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	No. [REDACTED]
Loxalate film-coated tablets, 10mg, 20mg	Mylan New Zealand Ltd	No. [REDACTED]
Escitalopram–Apotex film-coated tablets, 10mg, 20mg	Apotex NZ Ltd	No. [REDACTED]
<b>Fluoxetine</b>		
Arrow-Fluoxetine dispersible tablets, 20mg	Teva Pharma (New Zealand) Ltd	No. [REDACTED]
Arrow-Fluoxetine capsules, 20mg	Teva Pharma (New Zealand) Ltd	No. [REDACTED]
Fluox capsules, 20mg	Mylan New Zealand Ltd	No. [REDACTED]
Fluox dispersible tablets, 20mg	Mylan New Zealand Ltd	No. [REDACTED]
Fluoxetine-AFT oral solution, 20mg/5ml	AFT Pharmaceuticals Ltd	No. [REDACTED]
Prozac 20 capsules, 20mg	Eli Lilly and Company (NZ) Ltd	No. [REDACTED]
<b>Paroxetine</b>		

Aropax film-coated tablets, 20mg	GlaxoSmithKline (NZ) Ltd	No. [REDACTED]
Loxamine film-coated tablets, 20mg	Mylan New Zealand Ltd	No. [REDACTED]
<b>Sertraline</b>		
Arrow-Sertraline film-coated tablets, 50mg, 100mg	Teva Pharma (New Zealand) Ltd	No. [REDACTED]
Setrona film-coated tablets, 50mg, 100mg	Douglas Pharmaceuticals Ltd	No. [REDACTED]
Zoloft film-coated tablets, 50mg, 100mg	Reckitt Benckiser (New Zealand) Limited	No. [REDACTED]

**Table 3. Serotonin and noradrenaline reuptake inhibitors approved in New Zealand**

Product name, form and strength	Sponsor	Has wording on PPH risk when SSRIs used within one month prior to delivery?
<b>Venlafaxine</b>		
Efexor-XR modified-release capsules, 37.5mg, 75mg, 150mg	Upjohn New Zealand ULC	Yes. In section 4.6.
Enlafax XR modified-release capsules, 37.5mg, 75mg, 150mg	Mylan New Zealand Ltd	Yes. In section 4.6

**Table 4. Vortioxetine**

Product name, form and strength	Sponsor	Has wording on PPH risk when SSRIs used within one month prior to delivery?
<b>Vortioxetine</b>		
Brintellix film-coated tablets, 5mg, 10mg, 15mg, 20mg	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	No. [REDACTED]
[REDACTED]		

### 3 SCIENTIFIC INFORMATION

#### 3.1 Published literature

A summary of published literature is provided in this section with the full articles attached as annexes. There are seven studies in total: five observational studies, one systematic review, and one systematic review with meta-analysis. Huybrechts et al. 2020 was excluded in this report because the study focused on duloxetine, which is not available in New Zealand.

##### 3.1.1 A cohort study on low income women in the United States – Palmsten et al 2013 [14]

Title: Use of antidepressants near delivery and risk of postpartum haemorrhage: cohort study of low-income women in the United States.

Objective: to determine whether use of serotonin or non-serotonin reuptake inhibitors near delivery was associated with PPH

Comment:

From appendix 1 of the study:

Serotonin reuptake inhibitors (defined as high affinity to the serotonin transporter with a dissociation constant,  $K_d$  0-0.99 nM):

**Paroxetine, clomipramine, sertraline, duloxetine, fluoxetine, escitalopram, citalopram, imipramine, fluvoxamine, amitriptyline, venlafaxine**

Non-serotonin reuptake inhibitors (defined as low affinity to the serotonin transporter with a dissociation constant,  $K_d \geq 10$  nM):

Desipramine, **nortriptyline**, amoxapine, **doxepin**, trimipramine, trazodone, nefazodone, **maprotiline, bupropion, mirtazapine**

Study population: pregnant women aged 15 to 55 with a diagnosis of mood or anxiety disorder who had live births between the years 2000 to 2009. Data was extracted from the Medicaid database.

Exposure: four mutually exclusive exposure groups based on dispensing date and days supplied relative to the delivery date:

- current exposure: women with a supply of antidepressants that overlapped with the delivery date
- recent exposure: women with a supply of antidepressant on at least one day in the month before the delivery date but not on the delivery date
- past exposure: women with a supply of antidepressants ending between five to one month before delivery
- unexposed: no supply of antidepressants in the five months before delivery (reference group)

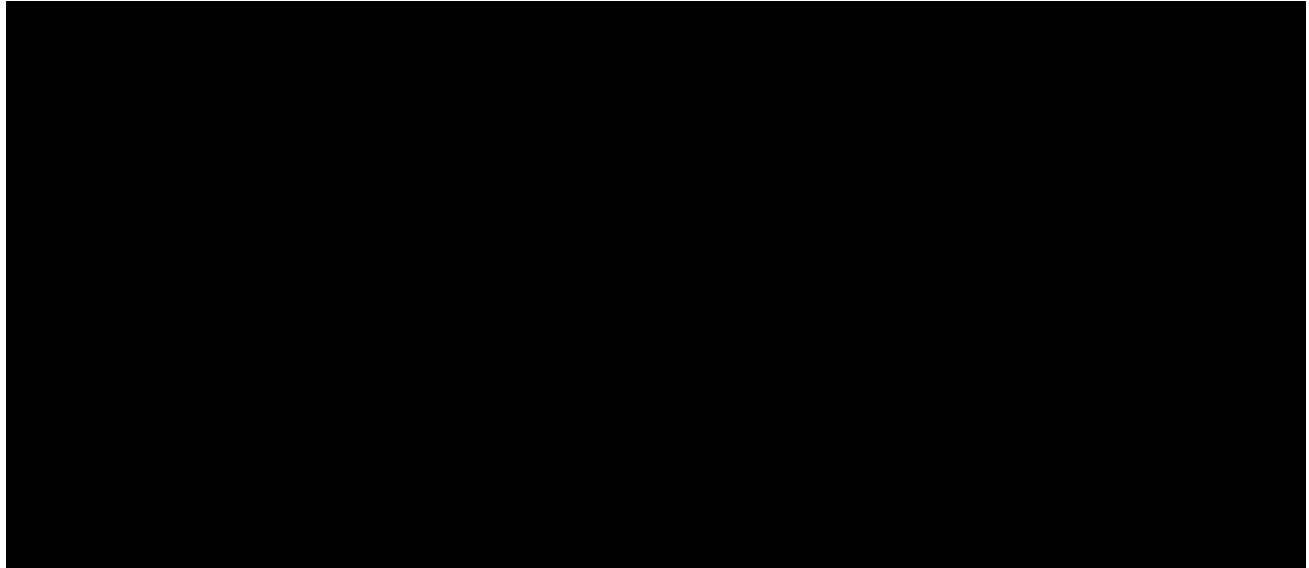
Exposures were further analysed based on serotonin reuptake inhibitors vs non-serotonin reuptake inhibitors; current, recent and past exposure to specific antidepressant drug classes; and exposure to certain antidepressant medication if at least 100 women with mood/anxiety disorder were taking them.

Outcome: women with ICD-9 code for 666.x (postpartum haemorrhage) during the admission to hospital for delivery, or within three days after delivery in outpatient delivery setting.

Methods: baseline information on comorbidities and healthcare use was obtained from Medicaid between one to five months before delivery. Potential confounders (see † in Table 5 below) were adjusted for. The risk for PPH was compared between women with exposure to antidepressants and women unexposed using relative risk (RR) with 95% confidence interval (95% CI). Models were adjusted for potential confounders and high-dimensional propensity score was used to empirically identify and adjust for additional factors that might have been surrogates for unmeasured confounders in the database.

Results: 12,710 (12%) women had current exposure to serotonin reuptake inhibitor monotherapy, and 1,495 (1.4%) women had current exposure to non-serotonin reuptake inhibitor monotherapy. Compared to pregnant women with mood or anxiety disorder unexposed to antidepressants, women with current exposure to serotonin reuptake inhibitors had a 1.47-fold increased risk of postpartum haemorrhage (95%CI 1.33 to 1.62) and women with current non-serotonin reuptake inhibitor exposure had a 1.39-fold increased risk (95%CI 1.07 to 1.81) (see Table 5).

**Table 5: Different 'exposure' levels to SRI and non-SRI antidepressants and the relative risks for PPH with 95% confidence intervals**





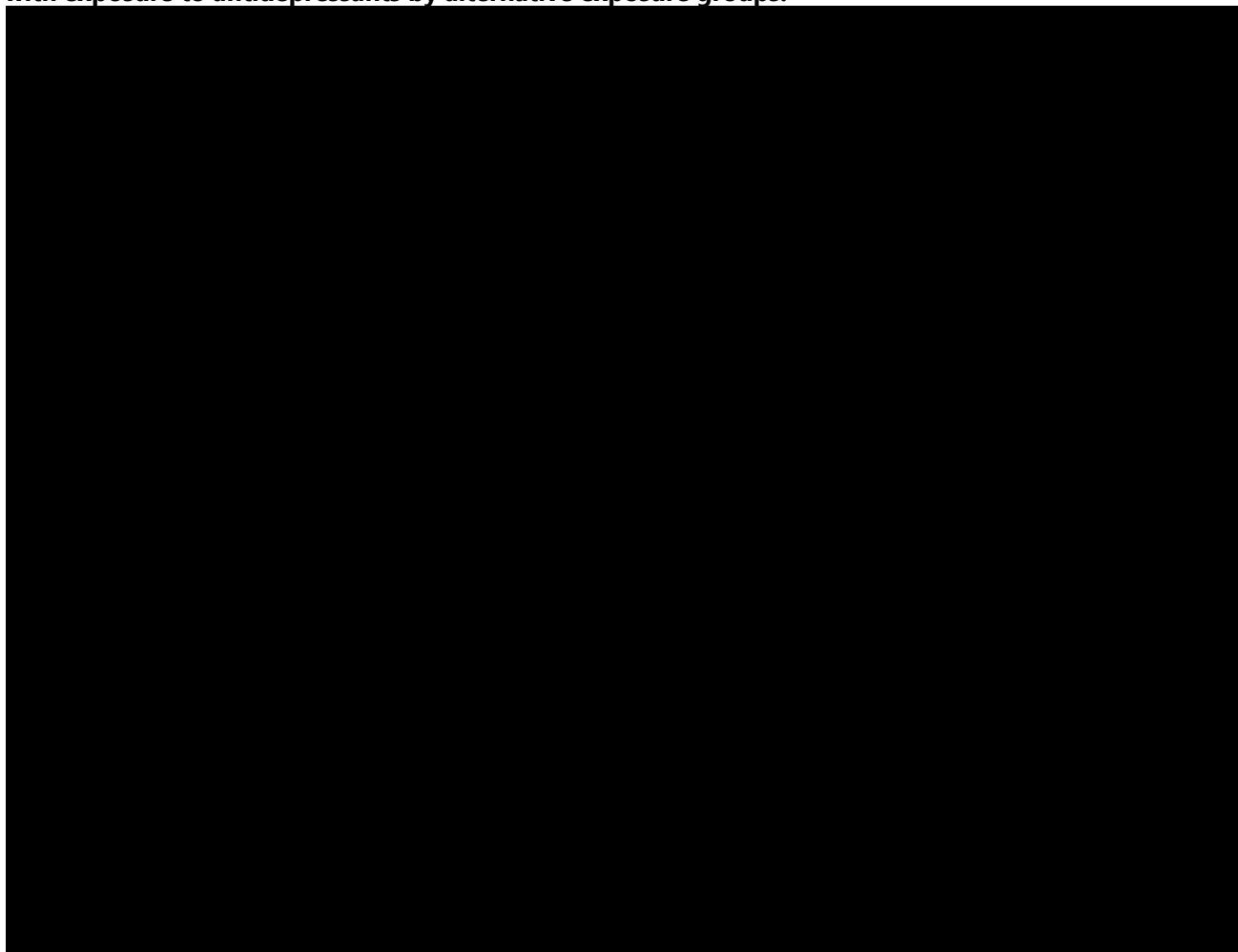
The risk of PPH was associated with current exposure to serotonin reuptake antidepressants (see Table 6 for a list of specific serotonin reuptake inhibitors). The highest association was with current use of venlafaxine (RR= 2.24, 95%CI 1.69 to 2.97). However, not all serotonin reuptake inhibitor continued to show statistical significance with recent use, and there was no associated risk with past use.

**Table 6: Fully-adjusted RR and 95% confidence interval comparing risk of PPH by specific antidepressants; restricted to women with serotonin reuptake inhibitor or monotherapy.**



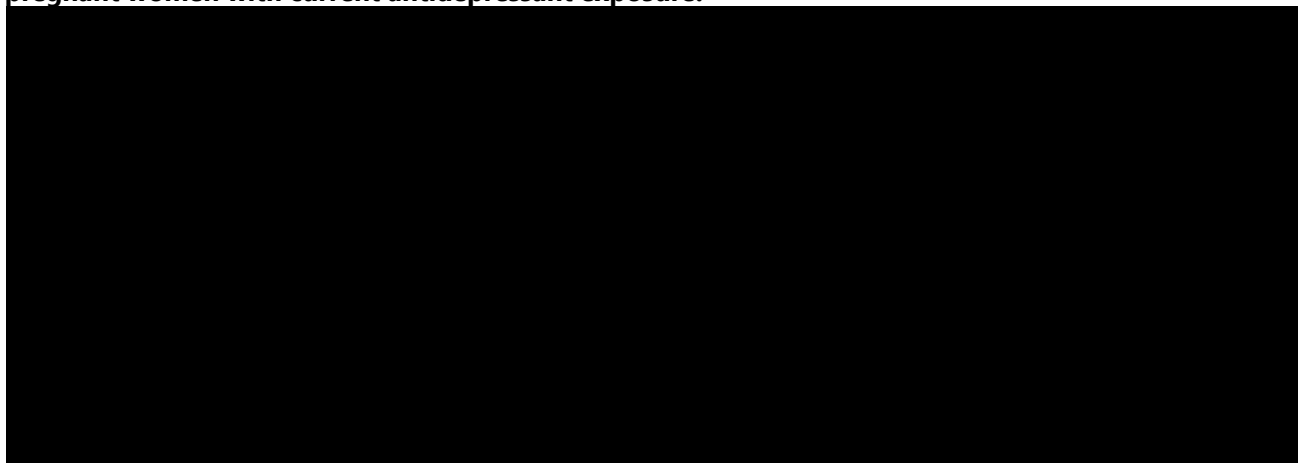
When the analysis was grouped in alternative exposure groups (Table 7), current exposure to any antidepressant was associated with an increased risk of PPH with a RR=1.44 (95%CI 1.32 to 1.58). This risk was also seen in the current and recent SSRI monotherapy exposure; and current, recent and past SNRI monotherapy exposure groups.

**Table 7: Fully adjusted RR and 95% confidence interval comparing the risk of PPH in pregnant women with exposure to antidepressants by alternative exposure groups.**

A large black rectangular redaction box covers the entire content of Table 7.

The results from high-dimensional propensity score adjustment for additional potential confounders (see Table 8) yielded an odds ratio (OR) of 1.52 (95%CI 1.35 to 1.71) for current exposure to serotonin reuptake inhibitors, and OR of 1.39 (95%CI 1.03 to 1.89) for current use of non-serotonin reuptake inhibitors.

**Table 8: High-dimensional propensity score analysis. Figures are odds ratio with 95% confidence intervals adjusted for 10<sup>th</sup> of propensity score, comparing risk for postpartum haemorrhage in pregnant women with current antidepressant exposure.**

A large black rectangular redaction box covers the entire content of Table 8.

Authors' conclusions: all classes of antidepressants were associated with an increased risk of PPH. The positive association seen between non-serotonin reuptake inhibitors and PPH was unexpected and could indicate that all antidepressants carry the risk of PPH close to the delivery date. The study could not rule out confounding by unmeasured factors associated with the underlying disorders and the severity of the disorder.

Comment:

This study found an increased risk of PPH for women with recent exposure to serotonin reuptake inhibitors and non-serotonin reuptake inhibitors compared to unexposed women.

### 3.1.2 Matched cohort study – Heller et al 2017 [9]

Title: Increased postpartum haemorrhage, the possible relation with serotonergic and other psychopharmacological drugs: a matched cohort study.

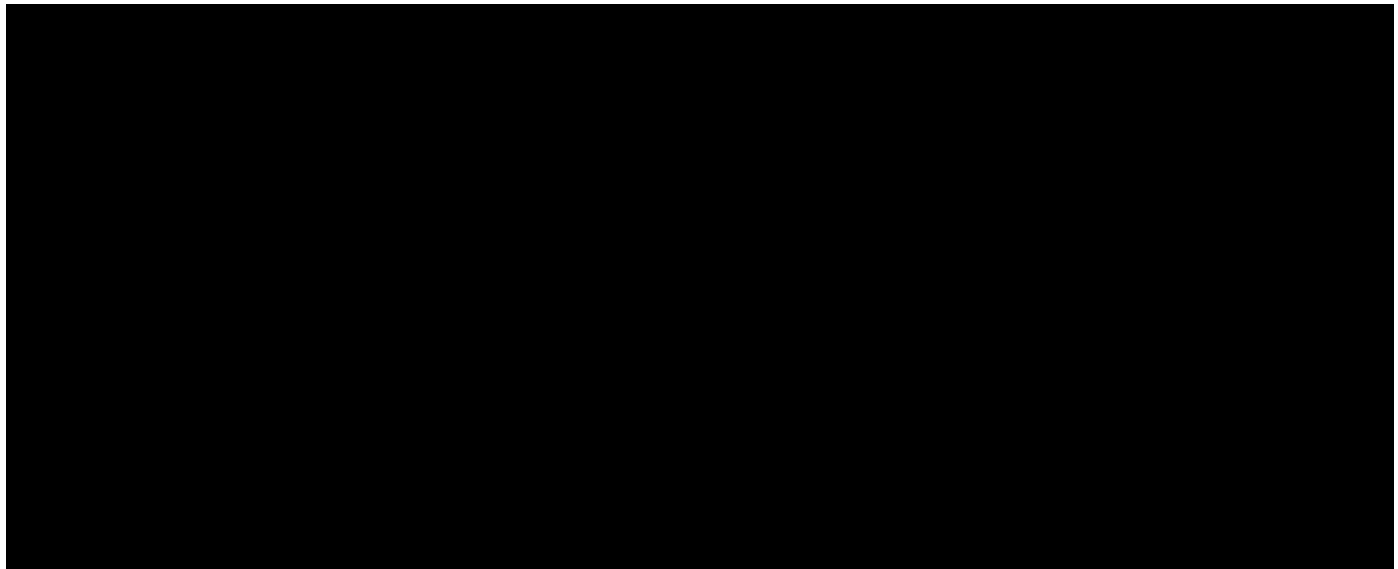
Setting: a matched cohort observational study was performed that included all pregnant women using serotonergic medications or other psychopharmacological medication and visiting one of the two teaching hospitals in Amsterdam between 2010 to 2014.

Outcome: Cases of PPH, during the admission to hospital for delivery, or within three days after the delivery date for outpatient deliveries. PPH defined as blood loss >1000 mL.

Cohort and control definitions: *cohort* was defined as women with single pregnancies who used psychopharmacological medicines in the third trimester of pregnancy. This cohort was further split into two sub-cohorts. Cohort 1 being women who used serotonergic antidepressants (SSRIs, TCAs or SNRIs) with or without other psychopharmacological drugs. Cohort 2 used *only* psychopharmacological drugs but no antidepressants. (NOTE: for the purpose of this summary, serotonergic medicines will only be reviewed eg, cohort 1 since the focus of this paper is on antidepressants and PPH). The cohort was matched with *controls* for parity, ethnicity, socioeconomic status, macrosomia, gestational duration, history of PPH, induction of labour, hypertensive disorder. pregnancies of women without documented psychiatric problems and measured the outcome of PPH. Five controls were matched for each cohort member.

Results: there were 578 pregnancies in cohort 1 (women taking serotonergic medication). After matching, the differences in the baseline characteristics disappeared between the cohort and control (see Table 9). Prior to matching, the adjusted odds ratio (aOR) was 1.6 (95%CI 1.2 to 2.1) and after matching aOR was 1.5 (95%CI 1.1 to 2.1).

**Table 9: baseline characteristics and the outcomes of 578 women using serotonergic medicines and the controls before and after matching.**



Authors' conclusions: there was a 1.5-fold higher risk of PPH in women taking serotonergic medication in the third trimester of pregnancy compared to the control group. However, the authors mentioned that it could be plausible that this could be a result of the underlying condition itself, rather than the medication.

Comment:

The study was able to minimise possible observed measured differences in characteristics by matching the cohort and the controls with nine confounding variables. However, they acknowledged that they could not rule out unmeasured and unknown factors eg, smoking and BMI.

### 3.1.3 Retrospective cohort study with trajectory models – Palmsten et al 2020 [15]

Title: Patterns of prenatal antidepressant exposure and risk of pre-eclampsia and postpartum haemorrhage

Objective: to estimate the risk of pre-eclampsia and PPH associated with patterns of prenatal antidepressant exposure.

Exposure to antidepressants was extracted from pharmacy dispensing information. The dispensing date plus the number of days supplied of the antidepressant was used to determine dates with antidepressant exposure between last menstrual period (LMP) and 35 gestational weeks. The dose on each day was expressed as fluoxetine-equivalent dose.

Methods: 'k-means longitudinal (kml, allowing for k=2 to k=8 clusters)' was used to cluster women into groups with similar antidepressant exposure, so called trajectories. This model can be used to define a pattern of antidepressant exposure over time). See Figure 6 below for definitions of the five trajectories from the LMP to 35 weeks of gestation (8 months of pregnancy).

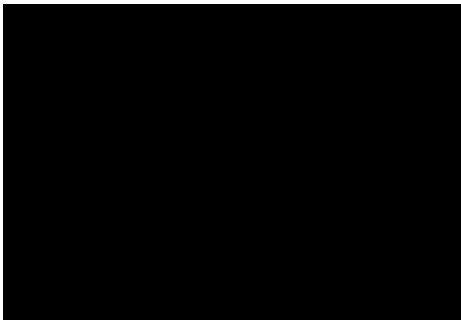
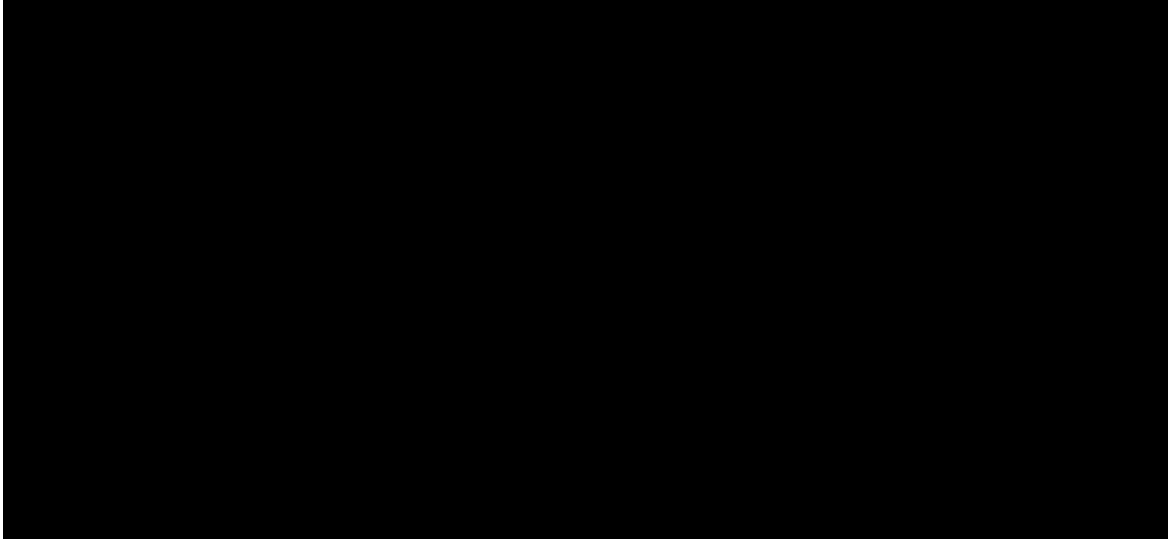
The RR (relative risk) and 95% confidence intervals were estimated for each trajectory exposure group and the outcome of PPH. The primary reference group was an active comparator with the least exposure to antidepressant (trajectory A – low antidepressant exposure with reduction/discontinuation) to reduce confounding by disease severity. Additional confounders were minimised as well as unmeasured confounders: smoking and obesity.

Secondary comparators included women with a depression or anxiety diagnosis without antidepressant dispensing as reference group. A sensitivity analysis was applied, restricting to pregnancies exposed to SSRIs only.

Outcomes: PPH was based on diagnosis codes within 14 days after delivery. PPH was defined based on ICD-9/10.

Results: among the 15,041 pregnancies exposed to an antidepressant, there were five trajectory models that best described the exposure of antidepressants from the LMP through to 35 weeks gestation (see Figure 6). The five trajectories are labelled A, B, C, D and E below.

**Figure 6: Average daily fluoxetine equivalent dose per week by gestational week for 35-week antidepressant (AD) trajectory groups**

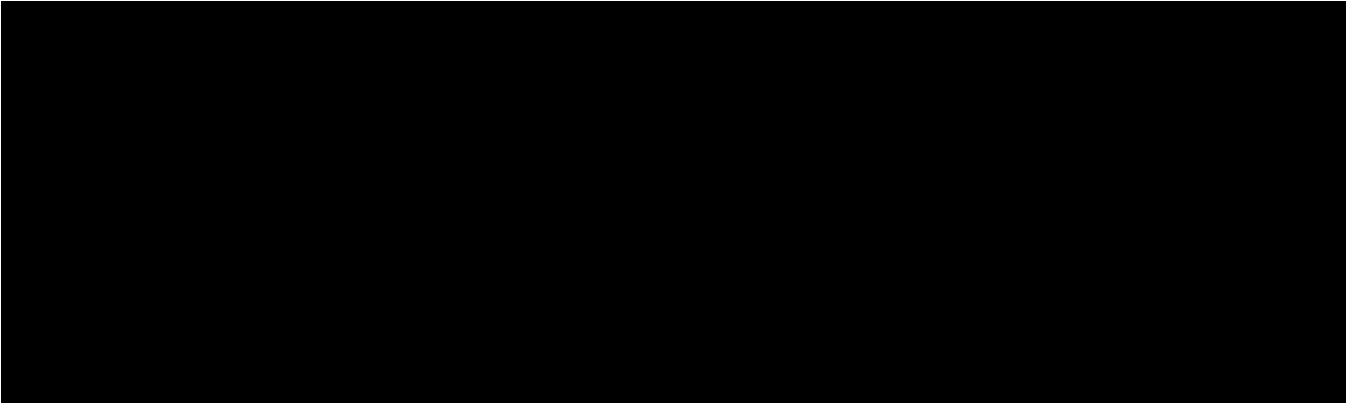


Compared to the lowest trajectory group (A), low-sustained exposure (B), moderate-sustained exposure (D), and high-sustained exposure (E) were associated with increased risk of PPH (see Table 6). Trajectory (C) was not associated with an increased risk of PPH.

The secondary comparators (Table 10) showed that women on trajectory E had an aRR of 2.09 when women with depression but not on antidepressant treatment was used as the reference group (95%CI 1.41 to 3.08) and an aRR of 2.62 when compared to women with anxiety but not on antidepressant treatment was used as the reference group (95%CI 1.78 to 3.85). These aRRs were higher compared to trajectory E using trajectory A as the primary comparator.

The association for trajectory B, D and E were similar between the primary reference group (trajectory A) and when the reference group was women who suffered from anxiety but were not taking antidepressants.

**Table 10: Associations between antidepressant 35-weeks trajectory groups and risk of PPH with: women in trajectory group A as reference (primary comparison), and women with depression or anxiety with no antidepressant (as secondary comparisons)**



In the sensitivity analysis (Table 11), restricting to SSRI use, the RR for PPH tended to be lower when comparing to all antidepressant use, particularly at high doses. Low sustained SSRI exposure (trajectory B) had a higher aRR (1.69, 95%CI 1.31 to 2.18) compared to all antidepressants (aRR 1.32, 95%CI 1.05 to 1.66).

**Table 11: Associations between antidepressant 35-week trajectory groups and risk of PPH with women in trajectory A as comparison, restricting to SSRIs**



Comments:

Excerpt from their supplementary table:

**'Antidepressants' defined in this study:**

**"SSRI:** Citalopram, Escitalopram, Fluoxetine, Fluvoxamine, Paroxetine, Sertraline; **SNRI:** Levomilnacipran, Venlafaxine, Duloxetine, Desvenlafaxine; **Bupropion:** Bupropion; **Other:** Vilazodone, Vortioxetine, Reboxetine, Mirtazapine, Nefazodone, Selegiline, Mianserin, Reboxetine, Trazodone, Amoxapine, Maprotiline, Isocarboxazid, Phenelzine, Tranylcypromine, Moclobemide, Amytryptiline, Clomipramine, Desipramine, Dothiepin, Doxepin, Imipramine, Nortriptyline, Protriptyline, Trimipramine"

Authors' conclusions: compared with first trimester reduction/discontinuation of antidepressant dose, sustained antidepressant exposure during gestation was associated with an increased risk of PPH, especially for women with high sustained antidepressant exposure. However, the risk of PPH was somewhat similar between women with depression without antidepressant exposure and most antidepressant exposure trajectories, with the exception of the high-sustained exposure group.

Comments:

Unlike the other studies that looked at antidepressant exposure in the later stages of pregnancy, this study focused on antidepressant exposure from the LMP to 35 weeks of gestation.

### 3.1.4 National register-based cohort study in Sweden – Skalkidou et al 2020 [16]

**Title:** SSRI use during pregnancy and risk for postpartum haemorrhage: a national register-based cohort study in Sweden.

**Objective:** to evaluate whether SSRI use during pregnancy, as well as prior or current untreated psychiatric illness is associated with PPH.

**Study population:** data for this national register-based retrospective cohort study were retrieved from the Swedish Pregnancy Registry. This Registry collects information on pregnancies and deliveries in Sweden from the first antenatal visit until post-delivery follow-up. The study included all deliveries in the Registry that occurred after 22<sup>+0</sup> gestational weeks between January 2013 to July 2017. Women with high risk factors for PPH were excluded (such as severe placental abnormalities, multiple pregnancies or treatment with anticoagulants).

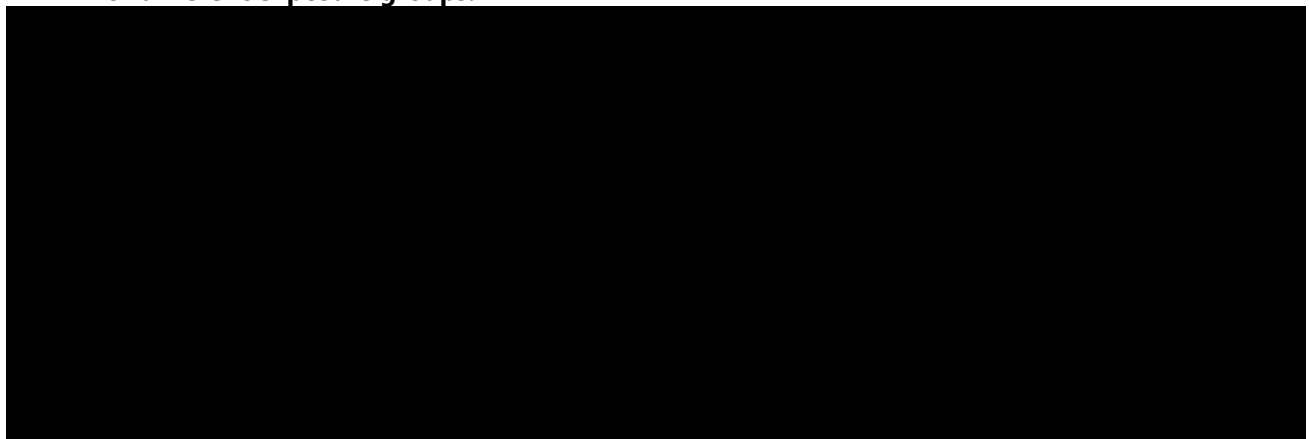
**Exposures:** primary exposure was defined as self-reported SSRI use during a part of or the entire pregnancy. Information on self-reported SSRI use in pregnancy was gathered through the 12 scheduled antenatal visits before delivery and entered by the caregiver. Secondary exposure was self-reported history of or current psychiatric illness which was manually entered by the midwife.

**Outcome measure:** PPH defined as blood loss > 1000 mL during the first two hours postpartum reported by the delivering midwife or obstetrician.

**Method:** pregnant women with self-reported SSRI use at any time point during pregnancy were compared with non-SSRI-treated women with prior or current psychiatric illness, as well as with healthy women with no psychiatric illness or reporting SSRI use. Exposed women (pregnant women on SSRI at some time point during pregnancy) were compared with non-SSRI treated women with self-reported history of or current psychiatric illness, and with healthy women who were not on SSRI and no psychiatric history (reference group). Confounders were adjusted using Model B and C. The difference between Model B and C is that Model C had six additional confounders that were controlled for (see Table 12 for confounders adjusted for in Model B and C). As there were high numbers of missing values, so called multivariate imputation by chain equation was performed to impute variables with missing values

**Results:** the overall prevalence of PPH was 7.0% (18520/265080) in healthy women, 7.6% (2150/28390) among women with prior or current psychiatric illness without SSRI use, and 9.1% (781/8851) among women treated with SSRI at any time-point during pregnancy. There were statistically significant ORs in the two groups studied: PPH in women with SSRI use during pregnancy, and PPH in women with prior or current psychiatric illness without SSRI use. These associations remained and stayed relatively similar after adjusting for confounders in Model B and C, as well as after imputation the missing data (see Table 12).

**Table 12: Logistic regression models, estimating OR and 95% confidence intervals regarding risk for PPH\* with different exposure groups.**



Authors' conclusions: SSRI treatment at any point during pregnancy was associated with increased odds for PPH compared with both healthy women (no prior psychiatric illness or SSRI use) and women with a history of or current psychiatric disorder but not taking SSRIs. Women with a history of or current psychiatric disorder but not taking SSRIs were also at an increased risk of PPH but to a lesser degree.

Comments:

This study was based on self-reporting of SSRI use in pregnancy and psychiatric illness which were entered by caregivers. The authors acknowledged it was unclear how accurate the recorded data was. Furthermore, duration and compliance with SSRI treatment, and the SSRI treatment period in relation to date of delivery was not collected in this Registry.

From the information gathered, only SSRI antidepressants were studied. Information on specific SSRIs was not collected in the Registry.

### 3.1.5 A systematic review by Bruning et al 2015 [17]

Title: Antidepressants during pregnancy and postpartum haemorrhage: a systematic review.

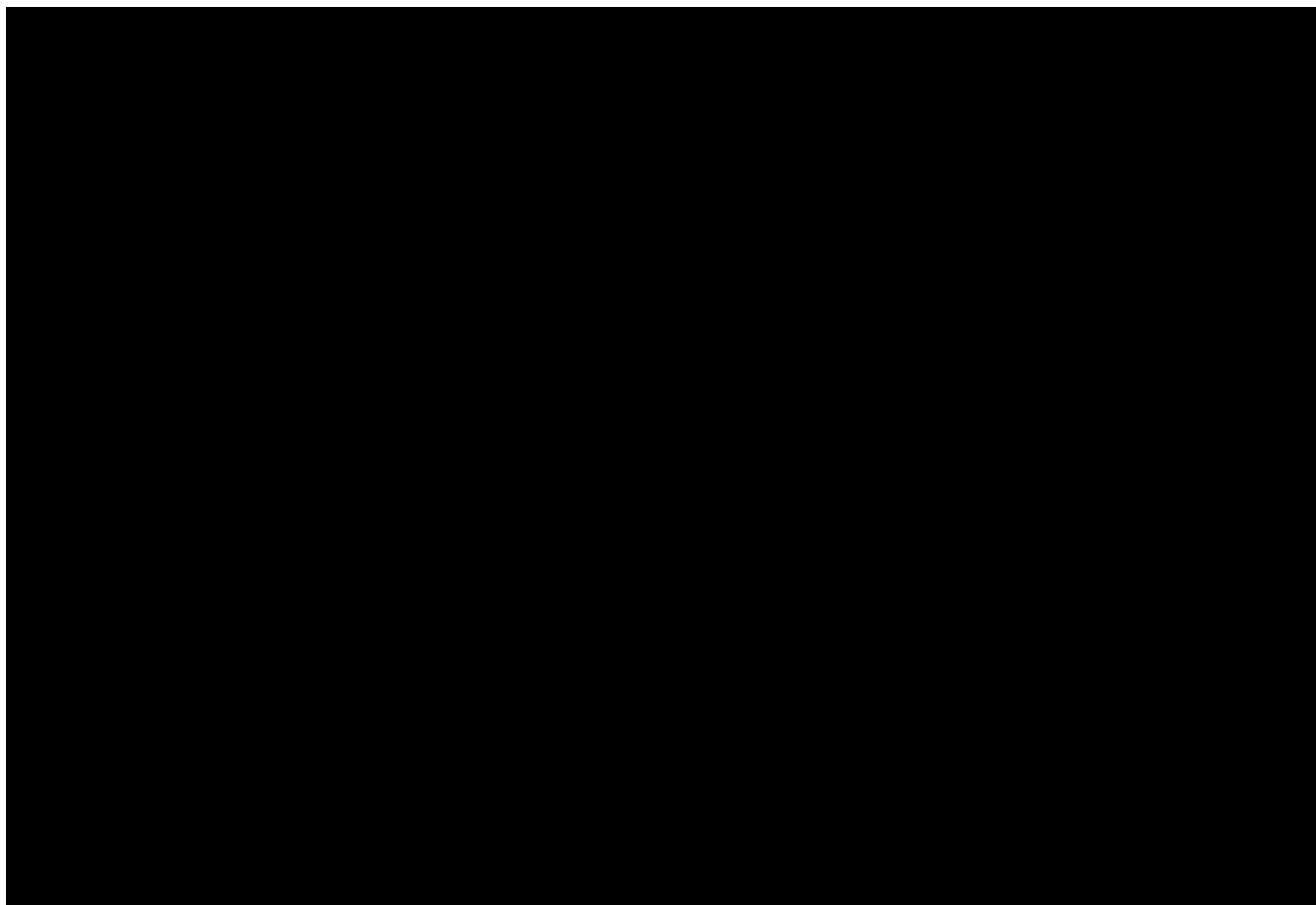
Systematic review approach: PubMed and Embase were used to search published studies related to antidepressants in pregnancy and the risk of PPH on 28 May 2014. Studies were included if they were: published in English or Dutch and bleeding that occurred during or after delivery associated to any type of antidepressant medication during pregnancy. The Newcastle-Ottawa Assessment Scale (NOS) was used to assess the quality of the studies. The Royal College of Obstetricians and Gynaecologists contained a list of risk factors for PPH and this list was used to see whether the studies had controlled for confounders.

Results: four studies met the criteria (see Table 13 for a summary of the studies). None of the four studies were considered to be of very good quality. Three were considered good quality (NOS 6-7), and one study was of satisfactory quality (NOS 4). The studies had different designs, adjusted confounders, outcomes and definitions for PPH. Due to this, heterogeneity pooling of the study results were not used to perform a meta-analysis.

- Salkeld et al. 2008 did not find a statistically significant increase in PPH when women were exposed to either SSRIs or non-SSRIs in late pregnancy.
- The main outcome of the study by Reis and Kallen et al. 2010 was not PPH but the authors did mention that there was a slightly increased risk of bleeding after delivery when antidepressants were used early between ten to 12 weeks of pregnancy (OR 1.11, 95%CI 1.03 to 1.19) but no association was found when used in late pregnancy.
- Palmsten et al. 2013 was discussed in Section 3.1.1.
- Lupattelli et al. 2014 found no risk of PPH when exposed to SSRIs/non-SSRIs during late pregnancy, but a 3.75-fold increase when exposed to TCAs, and other antidepressant medicines from 30 weeks of gestation (95%CI 1.09 to 12.94). The definition of PPH in this study was blood loss > 500 mL.



**Table 13: Characteristics of the four studies included in the review**



Authors' Conclusions: four studies met the inclusion criteria. Of them, two studies (Reis and Kallen 2010, and Palmsten 2013) reported a slight increase in incidence of PPH in women who used antidepressants (SSRI and non-SSRIs) during pregnancy. The other two studies identified no overall increased risk of PPH among pregnant women exposed to antidepressants. Although the four studies reviewed had large patient size, the number of women taking antidepressants in pregnancy is small and the incidence of PPH is low. This may have led to insufficient sample sizes in order to detect a significant difference in the incidence of PPH.

### **3.1.6 A Systematic review and meta-analysis by Jiang et al 2016 [18]**

Title: Antidepressant use during pregnancy and risk of postpartum haemorrhage: a systematic review and meta-analysis.

Background: Since the systematic review conducted by Bruning et al. 2015, there have been more studies published allowing for a more detailed analysis of the association between antidepressant use in pregnancy and the risk of PPH.

Systematic review and meta-analysis approach: PubMed and Embase were searched from inception to August 2016. Observational studies that met the following criteria were included in the systematic review:

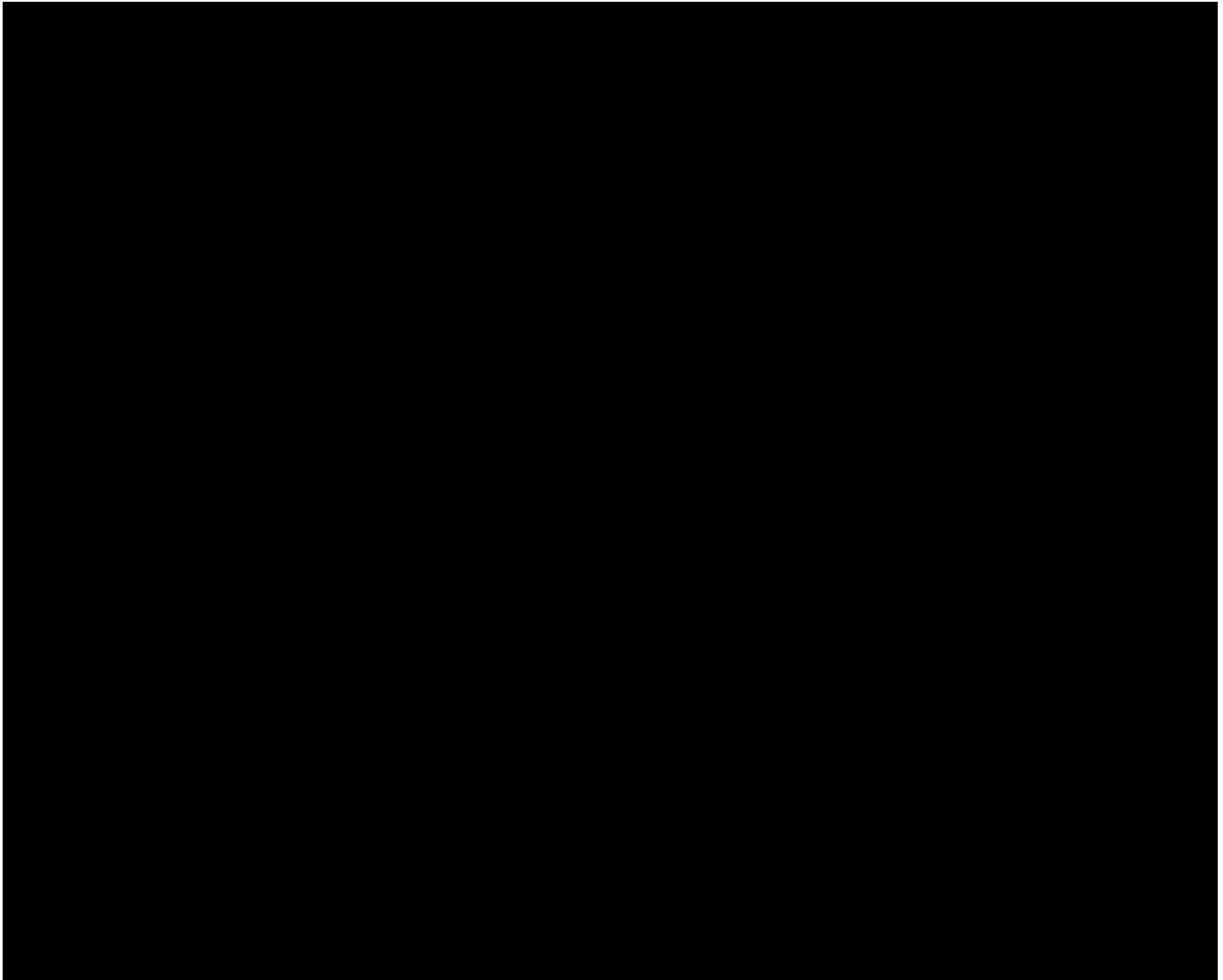
- case-control or cohort studies
- using non-antidepressant users as the reference group
- the association between antidepressant use and PPH risk was investigated
- adequate data provided to extract risk estimates.

NOS (Newcastle-Ottawa scale) was used to assess the quality of the studies that met the inclusion criteria. Data were pooled using a random-effects model. The primary outcome assessed was the risk of PPH with antidepressant use compared with no treatment. The risks of PPH were expressed as OR with 95% CI for case-control studies, and RR with 95% CI for cohort studies. Subgroup analysis was performed to attempt to explain possible heterogeneity between studies. These subgroups were based on the definition of PPH, type of antidepressant and the risk windows defined by the studies. ORs were used as approximations of RR as PPH was rare in all populations and subgroups reviewed.  $I^2$  statistic was used to assess heterogeneity between studies with  $I^2 > 50\%$  being considered indicative of substantial heterogeneity

Results: eight studies met the systematic review criteria. These studies ranged from 2008 to 2016, sample size from 367 to 318,840 with the pooled total of 572,686. The number of PPH events ranged from 23 to 22,509 with the pooled total of 48,784 PPH cases. Of the eight studies, six of them were of high quality based on the NOS scoring system ( $\geq 7$ ).

The meta-analysis of eight studies covering 17 estimates (see Figure 7) showed that the use of antidepressants during pregnancy significantly increased the risk of PPH (RR=1.32, 95%CI 1.17-1.48,  $p < 0.001$ ) however there was considerable heterogeneity across studies ( $I^2 = 85.2\%$ ) (see also Table 14).

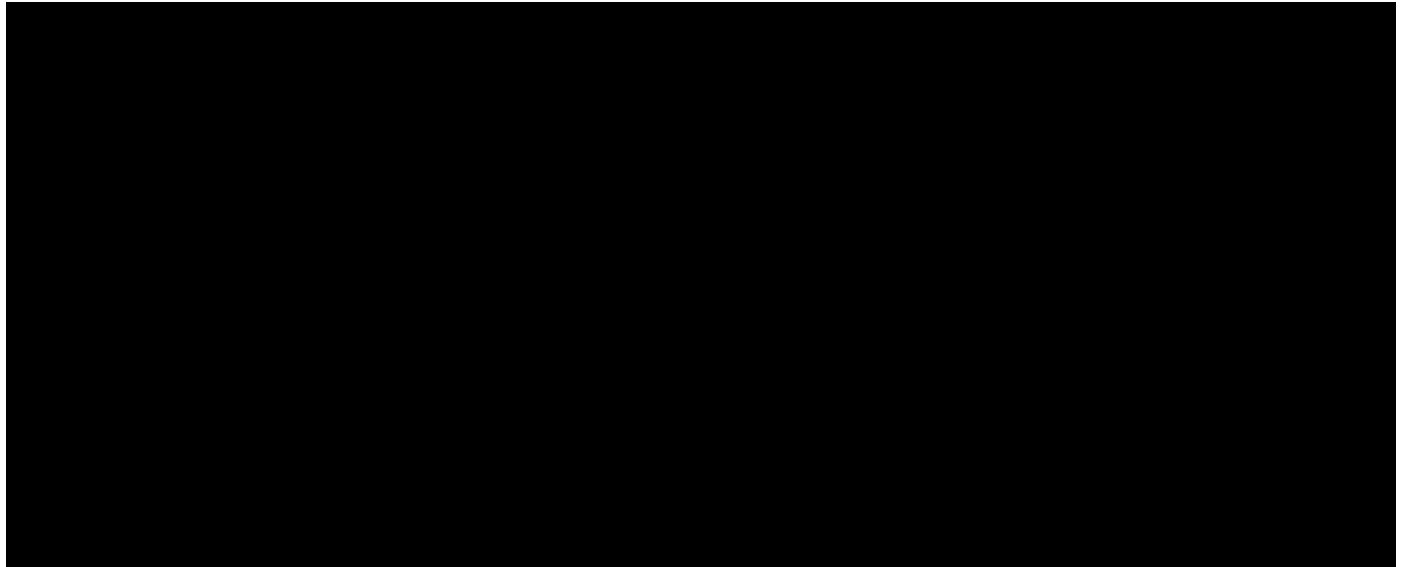
**Figure 7: Relative risk of PPH in antidepressant users during pregnancy. The eight studies yielded 17 estimates**



In the subgroup analysis (Table 14), significant associations were observed for certain types of antidepressants: non-SRIs (RR=1.31, 95%CI 1.10 to 1.56), SRIs (RR=1.23, 95%CI 1.06 to 1.44) and SSRIs (RR=1.20, 95%CI 1.04 to 1.38). A more pronounced risk was found among SNRI users (RR=1.62, 95%CI 1.41 to 1.85). When the studies were grouped by antidepressant exposure window, significant associations were observed among current and recent users. There was no association with past users of antidepressants and PPH. Within the current users of antidepressants, the risk further increased among the current SSRI and SNRI users.

**Table 14: Subgroup analysis with pooled OR and heterogeneity statistic I<sup>2</sup>.**

*Current use: overlapped with the delivery date; recent use: within 30 days before delivery date; past use: antidepressant discontinued 30 days before delivery date.*



Authors' conclusions: the findings of the meta-analysis support an increased risk of PPH in women exposed to antidepressant during late gestation. The positive association between SRI use in pregnancy and PPH support the hypothesis that serotonin plays a role in platelet aggregation. The stronger association with PPH seen with SNRI use in pregnancy compared to SSRI may be due to the added effects of SNRI at higher doses increasing blood pressure with the noradrenaline pathway. Elevated blood pressure is a risk factor for PPH. Finally, non-SRI antidepressants in pregnancy also showed a positive association with the risk of PPH which could suggest that the risk of bleeding may not be restricted to just SRIs.

Comments:

This published study from Jiang et al. is the most recent (and only) meta-analysis on the potential association of antidepressant use in pregnancy and PPH.

### 3.2 CARM data

Up to 31 December 2020, CARM has received two reports of vaginal haemorrhage with SSRI use. There were no reports related to venlafaxine or vortioxetine. The CARM report is provided in Annex 7.

- CARM ID: 64675: a 25-year-old female was on citalopram (suspect) and zopiclone. She experienced abnormal bleeding such as vaginal haemorrhage, haematuria, haemoptysis and gingival bleeding.
- CARM ID: 107889: a 22-year-old female was on fluoxetine [REDACTED] and experienced a panic reaction, increased sweating, palpitation, vomiting and vaginal haemorrhage.

Note that these reactions are coded as vaginal haemorrhage and does not necessarily mean postpartum haemorrhage.

## 4 DISCUSSION AND CONCLUSIONS

This report reviews the use of serotonergic antidepressants (SSRIs and SNRIs) prior to delivery and the risk of PPH. The four observational studies examined (Palmsten 2013 and 2020, Heller 2017, and Skalkidou 2020) showed an association of PPH with the use of serotonin reuptake inhibitors, and this is reflected in the meta-analysis by Jiang 2016 with a pooled OR for SRI (1.23, 95%CI 1.06 to 1.44), SSRI (1.20, 95%CI 1.04 to 1.38), and SNRIs (1.62, 95%CI 1.41 to 1.85). Although these studies showed the risk was increased with the use of

serotonin reuptake inhibitor, it also revealed that the use of non-serotonin reuptake inhibitors can increase the risk of PPH. This was reflected in the meta-analysis from Jiang 2016 showing non-SRI had a pooled OR 1.31 (95%CI 1.10 to 1.56).

Interestingly, the results from Skalkidou 2020 showed women not any taking antidepressants but had a current or a history of psychiatric illness had an increased risk of PPH as well.

Two observational studies examined the association between the timing of antidepressant medicine use prior to delivery and the risk of PPH. Palmsten 2013 showed that SSRIs and SNRIs use close to delivery was associated with an increased risk of PPH while Heller 2017 showed that serotonergic antidepressants (SSRIs, SNRIs, and TCAs) were associated with PPH risk when taken in the third trimester of pregnancy. The meta-analysis from Jiang 2016 showed statistically significant pooled ORs with recent (within 30 days before delivery) and current (overlap with delivery date) users of SSRIs and SNRIs.

The limitation to these associations, as outlined by Bruning 2015 is that the number of people in this group taking antidepressant medicine is small and the incidence of PPH low. This may have led to insufficient sample sizes in order to detect a significant difference in the incidence of PPH. Bruning also commented that studies that were reviewed differed in study designs, definition/diagnosis of PPH and exposure.

The severity of depression is an unmeasured confounder that could overestimate the risk of PPH in pregnant women taking antidepressants according to Jiang 2016 and Palmsten 2013. There are unmeasured behavioural factors associated with the severity of depression and antidepressants use such as poor diet, alcoholism, smoking and illicit drug use which are associated with a higher risk of PPH. Heller 2017 commented that the severity of depression rather than antidepressant use could be a risk factor related to PPH since women with stress due to psychiatric illness may be more prone to prolonged labour, delivery by emergency caesarean section and operative vaginal delivery.

At the time of writing this report, two products (venlafaxine) contain the risk of PPH when taken near delivery in section 4.6 of the data sheet. Five products are intending to include this wording, while the remaining products do not contain the wording and have not yet advised Medsafe of their intention to do so.

## 5 ADVICE SOUGHT

The Committee is asked to advise whether:

- the current evidence supports an association of postpartum haemorrhage when SSRIs and SNRIs are used within the month prior/or close to delivery
- all data sheets for SSRIs, SNRIs and vortioxetine should be updated to include the risk of postpartum haemorrhage when used within the month prior/or close to delivery

## 6 APPENDICES

### 6.1 Appendix 1 – Approved SSRIs/SNRIs/vortioxetine in New Zealand (as at 21 January 2021)

Sources: Medsafe Product/Application Search (<https://www.medsafe.govt.nz/regulatory/DbSearch.asp>)

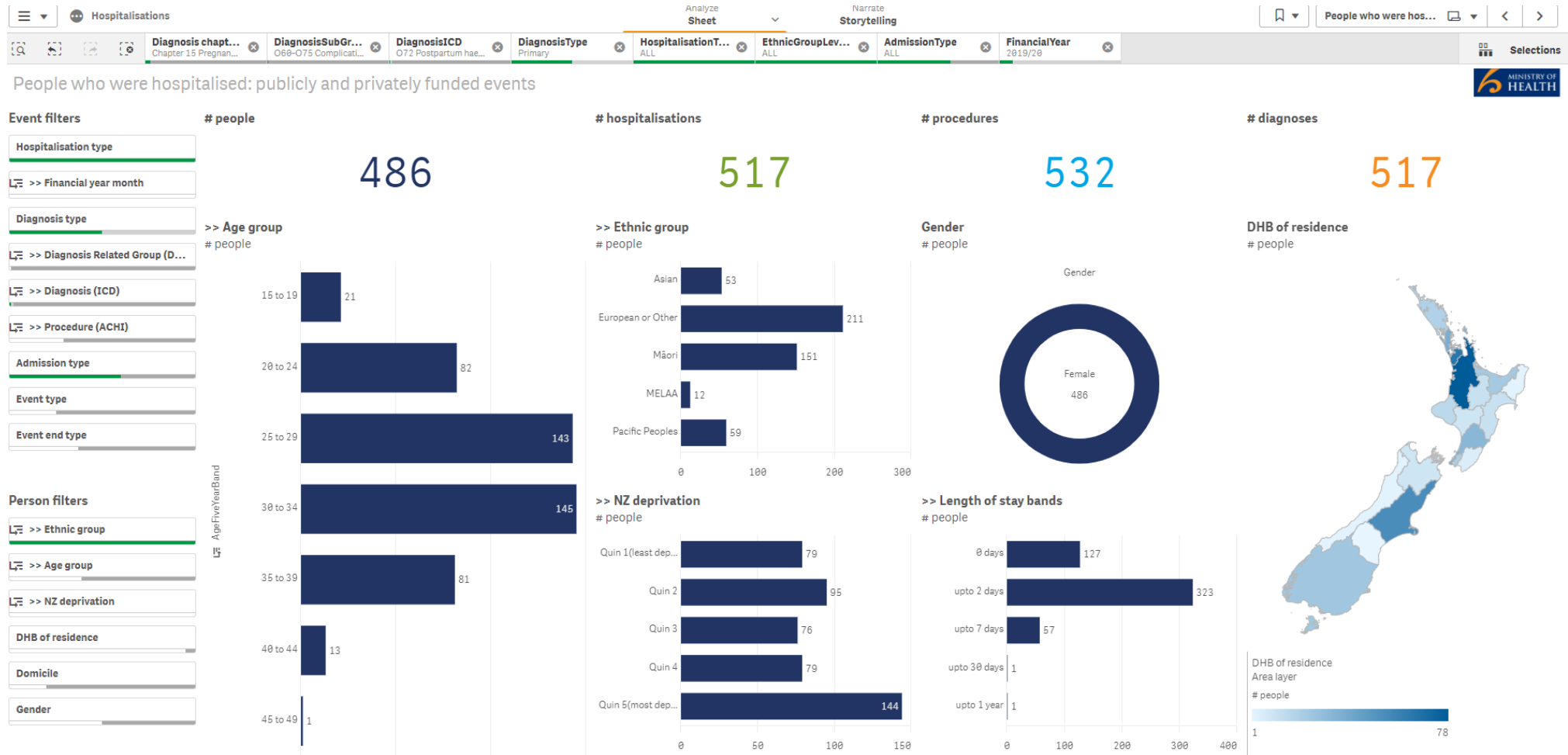
Product name, form and strength	Sponsor	Reference Product	Approval date
<b>Citalopram</b>			
Citalopram PSM Healthcare film-coated tablets, 20mg	PSM Healthcare Ltd trading as API Consumer Brands	Cipramil	19/02/2009
Cipramil film-coated tablets, 20mg	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	-	11/12/1997
<b>Escitalopram</b>			
Lexapro film-coated tablets, 10mg, 20mg	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	Cipralext	28/11/2002
Loxalate film-coated tablets, 10mg, 20mg	Mylan New Zealand Ltd	Lexapro	06/06/2010
Escitalopram–Apotex film-coated tablets, 10mg, 20mg	Apotex NZ Ltd	Lexapro	30/06/2016
<b>Fluoxetine</b>			
Arrow-Fluoxetine dispersible tablets, 20mg	Teva Pharma (New Zealand) Ltd	Prozac	08/03/2012
Arrow-Fluoxetine capsules, 20mg	Teva Pharma (New Zealand) Ltd	Prozac	17/10/2013
Fluox capsules, 20mg	Mylan New Zealand Ltd	Prozac	18/11/1999
Fluox dispersible tablets, 20mg	Mylan New Zealand Ltd	Prozac	18/07.2002
Fluoxetine-AFT oral solution, 20mg/5ml	AFT Pharmaceuticals Ltd	Prozac	07/10/2010
Prozac 20 capsules, 20mg	Eli Lilly and Company (NZ) Ltd	Innovator	04/02/1988

Product name, form and strength	Sponsor	Reference Product	Approval date
<b>Paroxetine</b>			
Aropax film-coated tablets, 20mg	GlaxoSmithKline (NZ) Ltd	Innovator	30/04/1992
Loxamine film-coated tablets, 20mg	Mylan New Zealand Ltd	Aropax	24/11/2005
<b>Sertraline</b>			
Arrow-Sertraline film-coated tablets, 50mg, 100mg	Teva Pharma (New Zealand) Ltd	Zoloft	27/02/2009
Setrona film-coated tablets, 50mg, 100mg	Douglas Pharmaceuticals Ltd	Zoloft	16/12/2009
Zoloft film-coated tablets, 50mg, 100mg	Reckitt Benckiser (New Zealand) Limited	Innovator	09/07/1992

Product name, form and strength	Sponsor	Reference Product	Approval date
<b>Venlafaxine</b>			
Efexor-XR modified-release capsules, 37.5mg, 75mg, 150mg	Upjohn New Zealand ULC	Innovator	01/03/2007
Enlifax XR modified-release capsules, 37.5mg, 75mg, 150mg	Mylan New Zealand Ltd	Efexor	12/03/2009

Product name, form and strength	Sponsor	Reference Product	Approval date
<b>Vortioxetine</b>			
Vortioxetine film-coated tablets, 5mg, 10mg, 15mg, 20mg	Pharmacy Retailing (NZ) Ltd t/a Healthcare Logistics	-	05/03/2020

## 6.2 Appendix 2 – Qlik data graphic showing PPH hospitalisation (primary diagnosis) in New Zealand for the financial year 2019/2020





## 7 ANNEXES

- Annex 1 - Palmsten K H-DS, Huybrechts KF, Williams PL, Michels KB, Achtyes ED, Mogun H, Setoguchi S,. 2013. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *British Medical Journal* 21(347): DOI: 10.1136/bmj.f4877
- Annex 2 – Heller H RA, Bruning A, et al., . 2017. Increased postpartum haemorrhage, the possible relation with serotonergic and other psychopharmacological drugs: a matched cohort study. *BMC Pregnancy and Childbirth* 17(166): DOI: 10.1186/s12884-017-1334-4
- Annex 3 – Palmsten K CC. 2020. Patterns of prenatal antidepressant exposure and risk of preeclampsia and postpartum haemorrhage. *Paediatric and Perinatal Epidemiology* 34(194): DOI:10.1111/ppe.12660
- Annex 4 – Skalkidou A S-PI, Wikman A, Hesselman S, Wikström AK, Elenis E,. 2020. SSRI use during pregnancy and risk for postpartum haemorrhage: a national register-based cohort study in Sweden. *BJOG* 127(11): e1366-1373. DOI: 10.1111/1471-0528.16210
- Annex 5 – Bruning AH HH, Kieviet N, Bakker PC, de Groot CJ, Dolman KM, Honig A,. 2015. Antidepressants during pregnancy and postpartum hemorrhage: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 189(e38-47). DOI: 10.1016/j.ejogrb.2015.03.022
- Annex 6 – Jiang HY XL, Li YC, Deng M, Peng CT, Ruan B,. 2016. Antidepressant use during pregnancy and risk of postpartum hemorrhage: A systematic review and meta-analysis. *J Psychiatr Res* 83(e160-167). DOI: 10.1016/j.jpsychires.2016.09.001
- Annex 7 – CARM report

## 8 REFERENCES

1. European Medicines Agency. 2020. *PRAC recommendations on signals* 26 October 2020. URL: [https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-28-september-1-october-2020-prac-meeting\\_en.pdf](https://www.ema.europa.eu/en/documents/prac-recommendation/prac-recommendations-signals-adopted-28-september-1-october-2020-prac-meeting_en.pdf) (accessed 30 January 2021).
2. Medicines and Healthcare products Regulatory Agency. 2021. *Drug Safety Update: SSRI/SNRI antidepressant medicines: small increased risk of postpartum haemorrhage when used in the month before delivery* 7 January 2021. URL: <https://www.gov.uk/drug-safety-update/ssri-slash-snri-antidepressant-medicines-small-increased-risk-of-postpartum-haemorrhage-when-used-in-the-month-before-delivery> (accessed 30 January 2021).
3. Hirsch M BR. 2020. In *UpToDate: Selective serotonin reuptake inhibitors: Pharmacology, administration, and side effects* 16 March 2020. URL: [https://www.uptodate.com/contents/selective-serotonin-reuptake-inhibitors-pharmacology-administration-and-side-effects?search=ssri&source=search\\_result&selectedTitle=2~136&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/selective-serotonin-reuptake-inhibitors-pharmacology-administration-and-side-effects?search=ssri&source=search_result&selectedTitle=2~136&usage_type=default&display_rank=1) (accessed 30 January 2021).
4. Coleman JA GE. 2018. Structural basis for recognition of diverse antidepressants by the human serotonin transporter. *Nat Struct Mol Biol* 25(2): e170-175. doi: 10.1038/s41594-018-0026-8 (accessed 31 January 2021).
5. Das RS AY. 2012. Simultaneous Monitoring of Selective Serotonin Reuptake Inhibitors in Human Urine, Plasma and Oral Fluid by Reverse-Phase High Performance Liquid Chromatography. *Journal of Chromatographic Science* 00(e1-9). doi: 10.1093/chromsci/bms119 (accessed 31 January 2021).
6. Nelson C. 2020. *Serotonin-norepinephrine reuptake inhibitors (SNRIs): Pharmacology, administration, and side effects* 2 October 2020. URL: [https://www.uptodate.com/contents/serotonin-norepinephrine-reuptake-inhibitors-snr-is-pharmacology-administration-and-side-effects?search=snri&source=search\\_result&selectedTitle=2~139&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/serotonin-norepinephrine-reuptake-inhibitors-snr-is-pharmacology-administration-and-side-effects?search=snri&source=search_result&selectedTitle=2~139&usage_type=default&display_rank=1) (accessed 31 January 2021).
7. Pharmacy Retailing t/a Healthcare Logistics. 2020. *Brintellix tablets New Zealand data sheet* URL: <https://www.medsafe.govt.nz/profs/Datasheet/b/brintellixtab.pdf>
8. Paton C. 2005. SSRIs and gastrointestinal bleeding. *British Medical Journal* 331(7516): e529-530. DOI: 10.1136/bmj.331.7516.529 (accessed 12 February 2021).

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9. Heller H RA, Bruning A, et al., . 2017. Increased postpartum haemorrhage, the possible relation with serotonergic and other psychopharmacological drugs: a matched cohort study. *BMC Pregnancy and Childbirth* 17(166): DOI: 10.1186/s12884-017-1334-4 (accessed 12 February 2021).
10. Abajo F. 2011. Effects of Selective Serotonin Reuptake Inhibitors on Platelet Function Mechanisms, Clinical Outcomes and Implications for Use in Elderly Patients. *Drugs & aging* 28(5): e345-67. DOI: 10.2165/11589340-000000000-00000 (accessed 12 February 2021).
11. Belfort M. 2021. *In UpToDate: Overview of postpartum hemorrhage* 10 February 2021. URL: [https://www.uptodate.com/contents/overview-of-postpartum-hemorrhage?search=postpartum%20hemorrhage&source=search\\_result&selectedTitle=1~150&usage\\_type=default&display\\_rank=1](https://www.uptodate.com/contents/overview-of-postpartum-hemorrhage?search=postpartum%20hemorrhage&source=search_result&selectedTitle=1~150&usage_type=default&display_rank=1) (accessed 12 February 2021).
12. The Royal Australian and New Zealand College of Obstetricians and Gynaecologists. 2017. *Management of Postpartum Haemorrhage (PPH)* July 2017. URL: [https://ranzocg.edu.au/RANZCOG\\_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Management-of-Postpartum-Haemorrhage-\(C-Obs-43\)-Review-July-2017.pdf?ext=.pdf](https://ranzocg.edu.au/RANZCOG_SITE/media/RANZCOG-MEDIA/Women%27s%20Health/Statement%20and%20guidelines/Clinical-Obstetrics/Management-of-Postpartum-Haemorrhage-(C-Obs-43)-Review-July-2017.pdf?ext=.pdf) (accessed 12 February 2021).
13. Canterbury District Health Board. 2020. *POSTPARTUM HAEMORRHAGE (PPH)* November 2020. URL: <https://edu.cdhb.health.nz/Hospitals-Services/Health-Professionals/maternity-care-guidelines/Documents/GLM0021-Postpartum-Haemorrhage.pdf> (accessed 12 February 2021).
14. Palmsten K H-DS, Huybrechts KF, Williams PL, Michels KB, Achtyes ED, Mogun H, Setoguchi S., 2013. Use of antidepressants near delivery and risk of postpartum hemorrhage: cohort study of low income women in the United States. *British Medical Journal* 21(347): DOI: 10.1136/bmj.f4877 (accessed 12 February 2021).
15. Palmsten K CC. 2020. Patterns of prenatal antidepressant exposure and risk of preeclampsia and postpartum haemorrhage. *Paediatric and Perinatal Epidemiology* 34(194): DOI: - 10.1111/ppe.12660 (accessed 12 February 2021).
16. Skalkidou A S-PI, Wikman A, Hesselman S, Wikström AK, Elenis E., 2020. SSRI use during pregnancy and risk for postpartum haemorrhage: a national register-based cohort study in Sweden. *BJOG* 127(11): e1366-1373. DOI: 10.1111/1471-0528.16210 (accessed 12 February 2021).
17. Bruning AH HH, Kieviet N, Bakker PC, de Groot CJ, Dolman KM, Honig A., 2015. Antidepressants during pregnancy and postpartum hemorrhage: a systematic review. *Eur J Obstet Gynecol Reprod Biol* 189(e38-47). DOI: 10.1016/j.ejogrb.2015.03.022 (accessed 12 February 2021).
18. Jiang HY XL, Li YC, Deng M, Peng CT, Ruan B., 2016. Antidepressant use during pregnancy and risk of postpartum hemorrhage: A systematic review and meta-analysis. *J Psychiatr Res* 83(e160-167). DOI: 10.1016/j.jpsychires.2016.09.001 (accessed 12 February 2021).