Medicines Adverse Reactions Committee

Meeting date	8/09/2022	Agenda item	3.2.3	
Title	**Quetiapine and gestational diabetes mellitus**			
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice	
Active ingredient	**Product name**	**Dose form: dose**	**Sponsor**	**TT50**
Quetiapine	Seroquel	Film coated tablet: 25, 100, 150, 200, 300 mg	CARSL Consulting	5799/1, a, c, b, d
	Quetapel	Film coated tablet: 25, 100, 200, 300 mg	Viatris Ltd	7757, a, c, d
	Quetiapine multichem	Film coated tablet: 25, 100, 150, 200, 300 mg	Multichem NZ Ltd	9408, a, b, c, d
	Quetiapine-DLRA	Film coated tablet: 25, 100, 150, 200, 300 mg	Dr Reddy's NZ Ltd	5799/1, a, c, b, d
PHARMAC funding	Quetapel is funded in the community and in hospitals			
Previous MARC meetings	n/a			
International action	The European Medicines Agency requested the sponsor [redacted] to provide a cumulative review of post-marketing, clinical trial and literature data. No regulatory action followed from this review.			
Prescriber Update	Diabetes and antipsychotic drugs (November 2004) Metabolic effects of antipsychotics (May 2009) Quetiapine – not without side effects (December 2016)			
Classification	Prescription medicine			
Usage data	See section 3.4			
Advice sought	**The Committee is asked to advise:** • whether there is evidence for an association between quetiapine and gestational diabetes mellitus • if there is evidence for an association, is the information in the quetiapine data sheet sufficient to mitigate this risk or is further regulatory activity is required • whether any communication is required, other than MARC's Remarks in *Prescriber Update*?			

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1 PURPOSE

On 22 January 2021, the sponsor [redacted] notified Medsafe of a safety signal for the risk of gestational diabetes mellitus (GDM) associated with the use of [redacted] (quetiapine). The signal was first identified by the European Medicines Agency (EMA) in April 2018, based on two literature articles by Gentile [1] and Kulkarni et al [2] which concluded that there might be an association between quetiapine and GDM. The EMA requested the sponsor to provide a cumulative review of post-marketing, clinical trial and literature data. [redacted]

This paper seeks the Committee's advice on whether quetiapine is associated with gestational diabetes mellitus, and if so, if any regulatory activity is required.

[redacted]

2 BACKGROUND

2.1 Schizophrenia and bipolar disorder

Quetiapine is indicated for treatment of schizophrenia and bipolar disorder (see section 3 of this report for information about quetiapine). Treatment of these conditions is usually long-term and complex, and involves pharmaceutical management, psychiatric care, physical assessment, lifestyle interventions and social support. Some patients may require hospitalisation to prevent self-harm or harm to others.

2.1.1 Schizophrenia [3]

The Royal Australian and New Zealand College of Psychiatrists *Clinical Practice Guidelines for the Management of Schizophrenia and Related Disorders* states the following: [3]

> ***What is schizophrenia?*** Schizophrenia is a complex disorder of brain function with wide variation in symptoms and signs, and in the course of the illness. The experiential '*core*' of schizophrenia has been described as a '*disturbance involving the most basic functions that give the normal person a feeling of individuality, uniqueness and self-direction*' (World Health Organization [WHO], 1992). The deficits in neurological, psychological and social function that manifest in the various syndromes of schizophrenia appear to have a number of genetic and environmental causes.

As many as 1 percent of people meet diagnostic criteria for the disorder over their lifetime. Schizophrenia ranks among the top 10 disorders worldwide for disease burden and disability. The incidence is higher in men than in women, with a ratio of 1.4 to 1. The prevalence is also thought to be higher among Māori.

There is no validated biological marker of schizophrenia and diagnosis is made by identifying the signs and symptoms, including delusional beliefs, hallucinations, disorganised thinking and speech, cognitive impairment, abnormal motor behaviour and negative symptoms.

Schizophrenia is associated with excess mortality, with a reduction in life expectancy of approximately 20 percent. The leading causes of premature death among people with schizophrenia are cardiometabolic diseases (see also section 2.1.3), suicide and accidents. The prevalence of tobacco smoking and substance use is also higher than the general population.

2.1.2 Bipolar disorder

Bipolar disorder can present with mania, hypomania or major depression. The mood episode at onset of bipolar disorder is usually major depression. Mania and bipolar major depression are often accompanied by psychotic features, such as delusions (false, fixed beliefs) and hallucinations (false sensory perceptions); by definition, psychosis does not occur in hypomania [4].

The pathogenesis of bipolar disorder is not known. However, family, twin, and adoption studies demonstrate that genetic factors are involved. In addition, altered brain structure and function are present in bipolar disorder; it is not clear whether these changes precede onset of bipolar disorder or represent its consequences [5].

Diagnosis of bipolar mood episodes and disorders is generally made according to the American Psychiatric Association's *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V) [4]. According to DSM-V, the subtypes of bipolar disorder include bipolar I and bipolar II. Patients with bipolar I disorder experience manic episodes and nearly always experience major depressive and hypomanic episodes. Bipolar II disorder is marked by at least one hypomanic episode, at least one major depressive episode, and the absence of manic episodes. Note that the Royal Australian and New Zealand College of Psychiatrists *Mood Disorders Clinical Practice Guidelines 2020* no longer differentiate between different subtypes of bipolar disorder [6].

Most patients with bipolar disorder have at least one comorbid psychiatric illness; common co-occurring disorders include anxiety disorders, substance use disorders, attention deficit hyperactivity disorder, eating disorders, intermittent explosive disorder, personality disorders and posttraumatic stress disorder. Approximately 10 to 15 percent of bipolar patients die by suicide, which is greater than the rate of suicide in the general population [4].

Table 1 summarises the prevalence statistics for bipolar disorder.

Table 1: Prevalence of bipolar disorder

Source: Malhi GS, Bell E, Bassett D, et al. 2021. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian and New Zealand Journal of Psychiatry* 55(1): 7-117. URL: https://www.ranzcp.org/files/resources/college_statements/clinician/cpg/mood-disorders-cpg-2020.aspx (accessed 17 March 2022).

2.1.3 Metabolic syndrome and obesity

Metabolic syndrome is a major public health issue that affects a diverse range of population groups. It is characterised by central obesity, dyslipidaemia, hypertension and insulin resistance. Compared to the general population, a person with metabolic syndrome has a two-fold increased risk of developing cardiovascular disease within the next 5–10 years and a five-fold increased the risk of developing type 2 diabetes mellitus [7].

People with severe mental health issues have an increased prevalence of metabolic syndrome and consequently cardiovascular disease and type 2 diabetes mellitus. The prevalence of metabolic syndrome within the population group is around two to three times higher than in the general population and even higher in people with schizophrenia [7].

In the second Australian National Survey of Psychosis, 53% of participants aged 18–64 years met criteria for metabolic syndrome, including at-risk levels of abdominal obesity (82%), high-density lipoproteins (50%), triglycerides (48%) and hypertension (49%). About one-quarter were at high risk of a cardiovascular event in the next 5 years. Less than half of those with known hypertension, hyperglycaemia or elevated cholesterol were receiving medication for these conditions [3].

2.1.4 Pregnancy

Ideally, plans for the treatment of a patient's psychiatric disorder during pregnancy should be in place before the woman becomes pregnant [8]. However, as many as 53% of pregnancies are unplanned in New Zealand, [9] so practitioners often need to make treatment decisions for patients who are already pregnant [8]. The patient's psychiatric history, severity of symptoms, response to medicines, and wishes regarding medicine use during pregnancy all play an important role in designing a course of clinical care during pregnancy [8]. There are two important goals: to ensure that the mother remains well during the pregnancy and the postnatal periods and to ensure that the developing baby does not suffer malformations or developmental problems [3].

About 10 percent of pregnant women have a psychiatric illness and 10-13% of fetuses are exposed to a psychotropic drug [8]. Women with psychiatric disorders can experience relapse during pregnancy, even when they are taking the appropriate medicine. The risk of relapse during pregnancy increases when medicines are discontinued. Chisholm [8] states that a relapse rate of 68% was reported in women with major depressive disorder (MDD) who discontinued their drugs during the first trimester. Bipolar disorder recurred in 81–85.5% of pregnant women who discontinued their mood stabilisers compared with 29–37% of those who did not. About 50% of patients with schizophrenia relapse if they stop taking their medicines. These high rates of relapse suggest that for many patients, treatment is needed during pregnancy to prevent recurrence.

2.1.5 Clinical guidelines

The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders (2021) [6]

These guidelines (also known as MDcpg^{2020}) provide up-to-date guidance regarding the management of mood disorders that is informed by evidence and clinical experience. The guideline is intended for clinical use by psychiatrists, psychologists, primary care physicians and others with an interest in mental health care. The MDcpg^{2020} builds on the previous 2015 guidelines and maintains its joint focus on both depressive and bipolar disorders. It provides up-to-date recommendations and guidance within an evidence-based framework, supplemented by expert clinical consensus.

Table 2 below shows the recommendations for managing mood disorders in pregnancy and post-partum.

Table 2: Managing mood disorders in pregnancy and post-partum

Source: Malhi GS, Bell E, Bassett D, et al. 2021. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian and New Zealand Journal of Psychiatry* 55(1): 7-117. URL: https://www.ranzcp.org/files/resources/college_statements/clinician/cpg/mood-disorders-cpg-2020.aspx (accessed 17 March 2022).

The MDcpg[2020] states that second-generation antipsychotics (SGAs), such as quetiapine or olanzapine, are used as alternatives in the treatment of bipolar disorder. They are generally considered to be safe in pregnancy; however, they may increase the risk for gestational diabetes and the likelihood of having a large baby.

Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders (2016) [3]

This guideline provides recommendations for the clinical management of schizophrenia and related disorders for health professionals working in Australia and New Zealand. It aims to encourage all clinicians to adopt best practice principles. The recommendations represent the consensus of a group of Australian and New Zealand experts in the management of schizophrenia and related disorders. This guideline includes the management of ultra-high risk syndromes, first-episode psychoses and prolonged psychoses, including psychoses associated with substance use. It takes a holistic approach, addressing all aspects of the care of people with schizophrenia and related disorders, not only correct diagnosis and symptom relief but also optimal recovery of social function.

With respect to pregnancy and schizophrenia, the guidelines state that good antenatal care and the safe delivery of a healthy baby are important outcomes. There are two important goals: to ensure that the mother

remains well during the pregnancy and the postnatal periods and to ensure that the developing baby does not suffer malformations or developmental problems. The guidelines also highlight the need for evidence-based information about the safety of antipsychotic medicines during pregnancy.

Tables 3–6 below provide information from the guidelines relevant to quetiapine, pregnancy and gestational diabetes.

Table 3: Approximate relative frequency of common side effects of antipsychotics

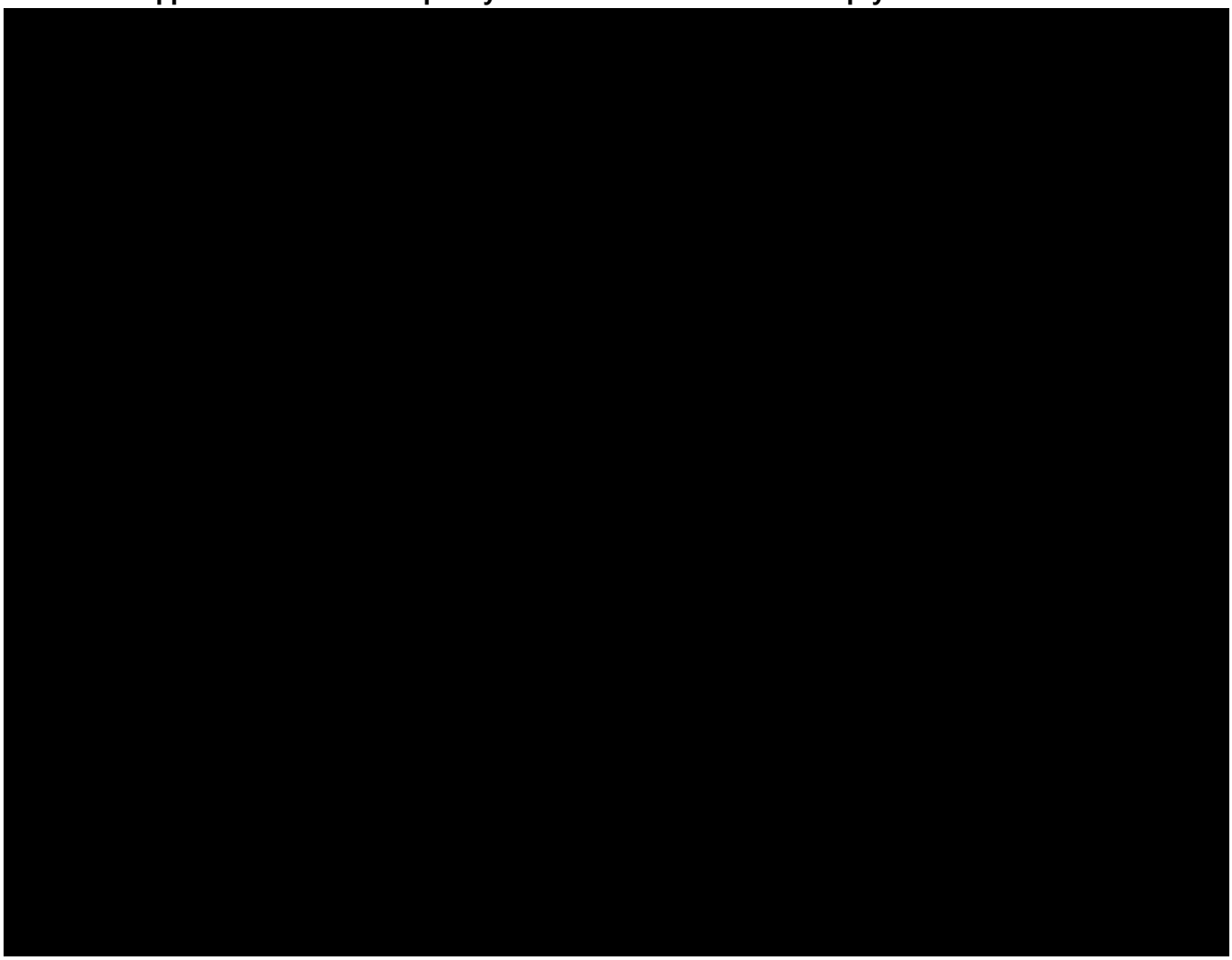


Table 4: Monitoring for people taking antipsychotic medication

Table 5: Management strategies for metabolic side effects of antipsychotic drugs

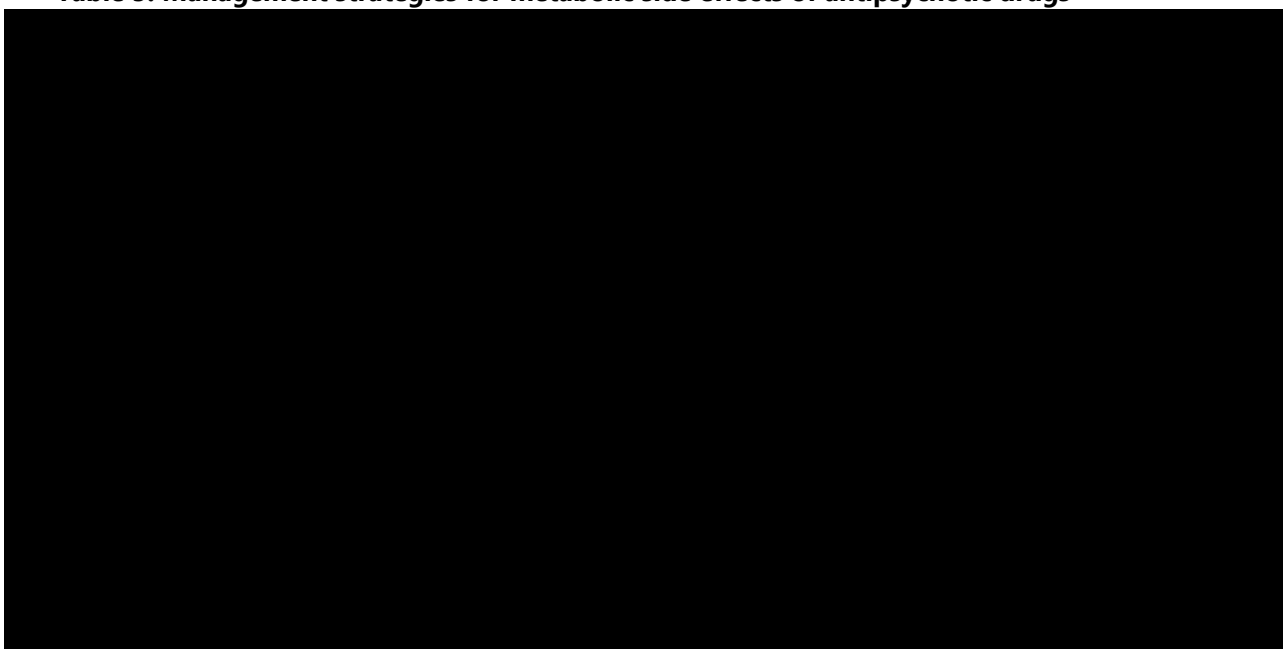


Table 6: Recommendations for the physical health of people with psychosis

[redacted]

bpac^{NZ} – Monitoring for metabolic disorders in patients taking antipsychotic drugs (2007) [10]

This article is a brief overview of recommended monitoring for metabolic disorders and other adverse effects associated with taking antipsychotics. bpac^{NZ} states that it is only a guide and intended to raise awareness of the potential for metabolic disorders so that appropriate monitoring can be considered in patients at risk. Local policies and practices should be referred to if available. GPs are an integral part of a multidisciplinary team involved in monitoring for metabolic disorders and the management of risk factors and lifestyle.

The monitoring recommendations are summarised in Table 7.

Table 7: Routine metabolic monitoring for people on antipsychotics

[redacted]

Weight gain

- Measure baseline weight and monthly weights for all patients prescribed atypical antipsychotics or phenothiazines including depot preparations.
- Offer dietary management for obese people (BMI > 30) or those gaining significant weight (≥ 7%) during treatment

Lipids

- Baseline fasting triglycerides and total cholesterol with any antipsychotic repeated three monthly with atypical agents for the first year of treatment.
- A full lipid profile performed annually as part of routine health monitoring with any antipsychotic

Glucose

- Consider screening all patients with schizophrenia for diabetes particularly those with risk factors for developing diabetes and those on higher risk drugs (clozapine and olanzapine). Educate those identified to be at risk about the symptoms of diabetes.
- In all patients measure baseline, at three months, and then annual fasting glucose. Repeat this pattern if the drug is changed. The frequency of monitoring may be increased if there are changes in fasting glucose or if risk factors change.
- In patients at high risk of developing diabetes consider monthly fasting blood glucose for the first three months and then check blood glucose three monthly for the first year followed by annually thereafter.

If diabetes develops switching to a less diabetogenic drug (risperidone, quetiapine, haloperidol) may be considered if clinically appropriate.

Updated bpac^{NZ} advice, via correspondence in 2013 [11]

This advice was published in 2013, following correspondence from a clinical pharmacist who questioned whether patients who have been prescribed atypical antipsychotics off-label still require metabolic monitoring. bpac^{NZ} stated that monitoring for metabolic adverse effects should occur in any patient prescribed an atypical antipsychotic medicine, regardless of dose or indication (Table 8).

Table 8: Recommended monitoring for patients taking atypical antipsychotics

New Zealand Formulary – Antipsychotic drugs [12]

The NZF has a general recommendation for use of antipsychotics during pregnancy, plus information about diabetes and weight gain, and monitoring recommendations.

2.1.5.1 Adherence to metabolic monitoring guidelines

Keenan et al. 2020. Metabolic screening in primary care for patients with schizophrenia or schizoaffective disorder and taking antipsychotic medication [13]

Keenan et al evaluated the metabolic screening in primary care for patients with schizoaffective disorders managed in primary care. They audited 8 general practices in the Waikato and Bay of Plenty regions. Patient monitoring was compared to the 2016 Royal Australian and New Zealand College of Psychiatrists (RANZCP) clinical practice guideline and the 2007 bpac^{NZ} guidelines (both are described above). None of the 117 patients included in the audit were fully monitored as per the RANZCP guidelines. Although two-thirds had been evaluated for glycosylated haemoglobin (HbA1c), lipids, blood pressure, complete blood count and weight, less than 10 percent of patients had had prolactin, waist circumference or electrocardiogram measurements recorded. The proportion of patients having a HbA1c measured was also significantly higher in younger patients and patients who were non-Māori or enrolled with an urban practice (all $P<0.05$). When using the simplified bpac^{NZ} guidelines, half of all patients were correctly monitored. The authors stated that their study highlights the fact that there is a need for either a more simplified monitoring policy or for improved GP education.

Huthwaite et al. 2018. Off label or on trend: a review of the use of quetiapine in New Zealand [14]

Huthwaite et al audited quetiapine prescribing in 57 general practices in the Compass Health Network (located in the lower North Island) from January 2015 to January 2016. Full metabolic monitoring was recorded as being done in only 2.3%, while partial monitoring occurred in 68% and no monitoring in 29.7%. Full monitoring comprised all the tests listed in the Capital and Coast District Health Board's antipsychotic metabolic monitoring guidelines. Partial monitoring included those with three or more of the recommended tests.

This study is discussed further in section 3.3.1.1 Unapproved (off-label) use.

Staveley et al. 2017. Metabolic monitoring in New Zealand district health board mental health services [7]

Staveley et al audited DHBs' metabolic monitoring practices in relation to consumers prescribed second-generation antipsychotic medicines, using a best practice standard developed following a review of the literature. They emailed each of the 20 DHBs and requested the policies and available information about the rates of monitoring. The definition of metabolic syndrome agreed by the researchers was the 2009 'harmonised' definition developed by international cardiac and metabolic health organisations, shown in Table 9. The harmonised definition includes five factors: waist circumference, blood pressure, fasting triglycerides, fasting HDL cholesterol and fasting plasma glucose. Abnormalities in three of the five factors must be present to meet the criteria for metabolic syndrome.

Table 9: Criteria for metabolic syndrome

Fourteen out of 20 DHBs had metabolic monitoring policies for consumers prescribed antipsychotic medication. Two of those policies are consistent with the literature-based guideline. Eight policies include actions to be taken when consumers meet criteria for metabolic syndrome. Four DHBs have systems for measuring their rates of metabolic monitoring. There is no consensus on who is clinically responsible for metabolic monitoring. The authors concluded that metabolic monitoring by mental health services in New Zealand reflects international experience that current levels of monitoring are low, and policies are not always in place. Collaboration across the mental health and primary care sectors together with the adoption of a consensus guideline is needed to improve rates of monitoring and reduce current rates of physical health morbidities.

Comments

These studies indicate that although metabolic monitoring guidelines exist, they are not routinely followed.

2.2 Antipsychotic-induced diabetes mellitus

There is a well-recognised association between treatment with some antipsychotic medicines and metabolic side effects, including weight gain and diabetes [15]. The prescribing information for these medicines in New Zealand and internationally contains recommendations for metabolic monitoring (see section 4.1.1 and section 4.1.2, respectively). Clinical guidelines also provide recommendations for metabolic monitoring of patients being treated with atypical antipsychotics – see section 2.1.5.

Antipsychotic-induced diabetes mellitus could be mediated by multiple mechanisms [16].

- Antipsychotics can inhibit the insulin signalling pathway in the target cells such as muscle cells, hepatocytes and adipocytes to cause insulin resistance.
- Antipsychotic-induced obesity can result in high levels of free fatty acids and inflammation, which can also cause insulin resistance.
- Antipsychotics can cause direct damage to pancreatic beta cells, leading to dysfunction and apoptosis of beta cells.

During pregnancy, high maternal blood glucose results in increased fetal insulin production. Because insulin is an anabolic hormone, increased production promotes fetal growth [17]. S-GAs cross the placenta and a direct effect on fetal insulin secretion is also possible . Even in the absence of maternal hyperglycaemia, fetal exposure to S-GAs could theoretically cause inhibition of insulin signalling, followed by insulin resistance and increased insulin secretion in the fetus.

2.3 Gestational diabetes mellitus

The World Health Organization (WHO) defines gestational diabetes mellitus (GDM) as 'carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy' [18].

In New Zealand, GDM refers to diagnosis of diabetes at 24 to 28 weeks of gestation. Diagnosis of diabetes in early pregnancy is more consistent with previously undiagnosed type 2 diabetes. The term "overt diabetes" is sometimes used to describe the diabetes status of these individuals until they are re-evaluated in the nonpregnant state and a formal diagnosis of type 2 diabetes can be made [18].

Pregnancy is accompanied by insulin resistance, mediated primarily by placental secretion of diabetogenic hormones including growth hormone, corticotropin-releasing hormone, placental lactogen (chorionic somatomammotropin), prolactin, and progesterone. These and other metabolic changes, which are generally most prominent in the third trimester, ensure that the fetus has an ample supply of nutrients [18].

Gestational diabetes mellitus (GDM) develops in pregnant people whose pancreatic function is insufficient to overcome the insulin resistance associated with the pregnant state. Among the main consequences of GDM are increased risks of preeclampsia, large for gestational age (LGA) newborns, and caesarean birth, and their associated morbidities. Patients with GDM are at high risk of developing type 2 diabetes later in life [18].

2.3.1 Prevalence

Gestational diabetes mellitus (GDM) is frequently described as the most common metabolic disorder of pregnancy with prevalence increasing at epidemic proportions [19]. However, reported prevalence worldwide varies between 1 and 45% of pregnancies. Different ethnicities have different susceptibility to GDM; therefore, differences in the ethnic make-up of the population studied as well as genetic variability will result in different prevalence rates of GDM. Similarly, the lack of consensus in which diagnostic threshold should be used to diagnose GDM results in variation in prevalence. Also, differences in the type of data used to calculate prevalence may lead to substantial differences in the reporting of GDM prevalence [19]. For example, Figure 1 below shows the prevalence of GDM in the Growing Up in New Zealand study according to data source. When combining data from all sources in the study, the prevalence of GDM cohort was 6.2%. Estimates varied from 3.8 to 6.9% depending on the data source.

Figure 1: Prevalence of GDM in the Growing Up in New Zealand study according to data source

Source: Lawrence R, Wall C and Bloomfield F. 2019. Prevalence of gestational diabetes according to commonly used data sources: An observational study. *BMC Pregnancy and Childbirth* 19(349): 1-9. DOI: https://doi.org/10.1186/s12884-019-2521-2 (accessed 23 February 2022).

The Ministry of Health reports that the number of pregnancies in New Zealand associated with gestational diabetes increased from 1.3% in 2001 to 2% in 2006 to 4.9% in 2012, equating to an annual increase of 13.9% ($p < 0.01$) (Figure 2). However, some of the increase may be a result of changes in local policy for GDM diagnosis [20].

Figure 2: Percentage of women with gestational diabetes in New Zealand, 2008–2012

Source: Ministry of Health. 2014. *Screening, Diagnosis, and Management of Gestational Diabetes in New Zealand: A Clinical Practice Guideline*. URL: https://www.health.govt.nz/system/files/documents/publications/screening-diagnosis-management-of-gestational-diabetes-in-nz-clinical-practive-guideline-dec14-v2.pdf (accessed 23 February 2022).

More recent data is shown in Figure 3. This figure shows the percentage of all deliveries with a GDM diagnosis via hospital discharge during the pregnancy. The overall percentages are lower than seen in Figure 2 above, but the increasing trend is similar.

Figure 3: Percentage of all deliveries with a gestational diabetes mellitus diagnosis via hospital discharge during the pregnancy, 2011–2020

Source: Ministry of Health, National Collections

Estimated rates of GDM in New Zealand vary by ethnicity. In 2012, the highest rates were in Asian (median 8.1%), Pacific (median 7.2%), and Middle Eastern, Latin American and African (median 7.5%) ethnicities (Table 10). Lower rates for Māori (median 3.3%) may reflect lower rates of screening attendance rather than lower rates of gestational diabetes [20].

Table 10: Percentage of women flagged with gestational diabetes by ethnicity in New Zealand, 2012

Source: Ministry of Health. 2014. *Screening, Diagnosis, and Management of Gestational Diabetes in New Zealand: A Clinical Practice Guideline*. URL: https://www.health.govt.nz/system/files/documents/publications/screening-diagnosis-management-of-gestational-diabetes-in-nz-clinical-practive-guideline-dec14-v2.pdf (accessed 23 February 2022).

2.3.2 Risk factors [20]

Risk factors for probable undiagnosed diabetes and GDM are shown in Table 11 below. It is likely that interactions between risk factors, rather than any single risk factor, predispose a woman to gestational diabetes.

Some women with no known risk factors may still be diagnosed with gestational diabetes. Risk factor screening would fail to identify these women. For women with probable undiagnosed diabetes, the risk of adverse outcomes for mother and infant from waiting until 24–28 weeks' gestation for screening and diagnosis for gestational diabetes (as currently recommended) is unknown. Identification of women with diabetes early in pregnancy allows preventive measures to be commenced earlier.

Table 11: Risk factors associated with probable undiagnosed diabetes and gestational diabetes

[redacted]

Source: Ministry of Health. 2014. *Screening, Diagnosis, and Management of Gestational Diabetes in New Zealand: A Clinical Practice Guideline*. URL: https://www.health.govt.nz/system/files/documents/publications/screening-diagnosis-management-of-gestational-diabetes-in-nz-clinical-practive-guideline-dec14-v2.pdf (accessed 23 February 2022).

Comments

Long-term use of an antipsychotic medicine is considered a risk factor for GDM.

2.3.3 Adverse outcomes

Maternal hyperglycaemia during pregnancy is associated with a number of adverse outcomes for both the mother and child [21]. These are summarised in Table 12.

Table 12: Adverse outcomes for mothers with hyperglycaemia during pregnancy and their children

Source: Durnwald C. 2021. *Gestational diabetes mellitus: Screening, diagnosis, and prevention*. In: *UpToDate* 30 November 2021. URL: https://www.uptodate.com/contents/gestational-diabetes-mellitus-screening-diagnosis-and-prevention (accessed 23 February 2022).

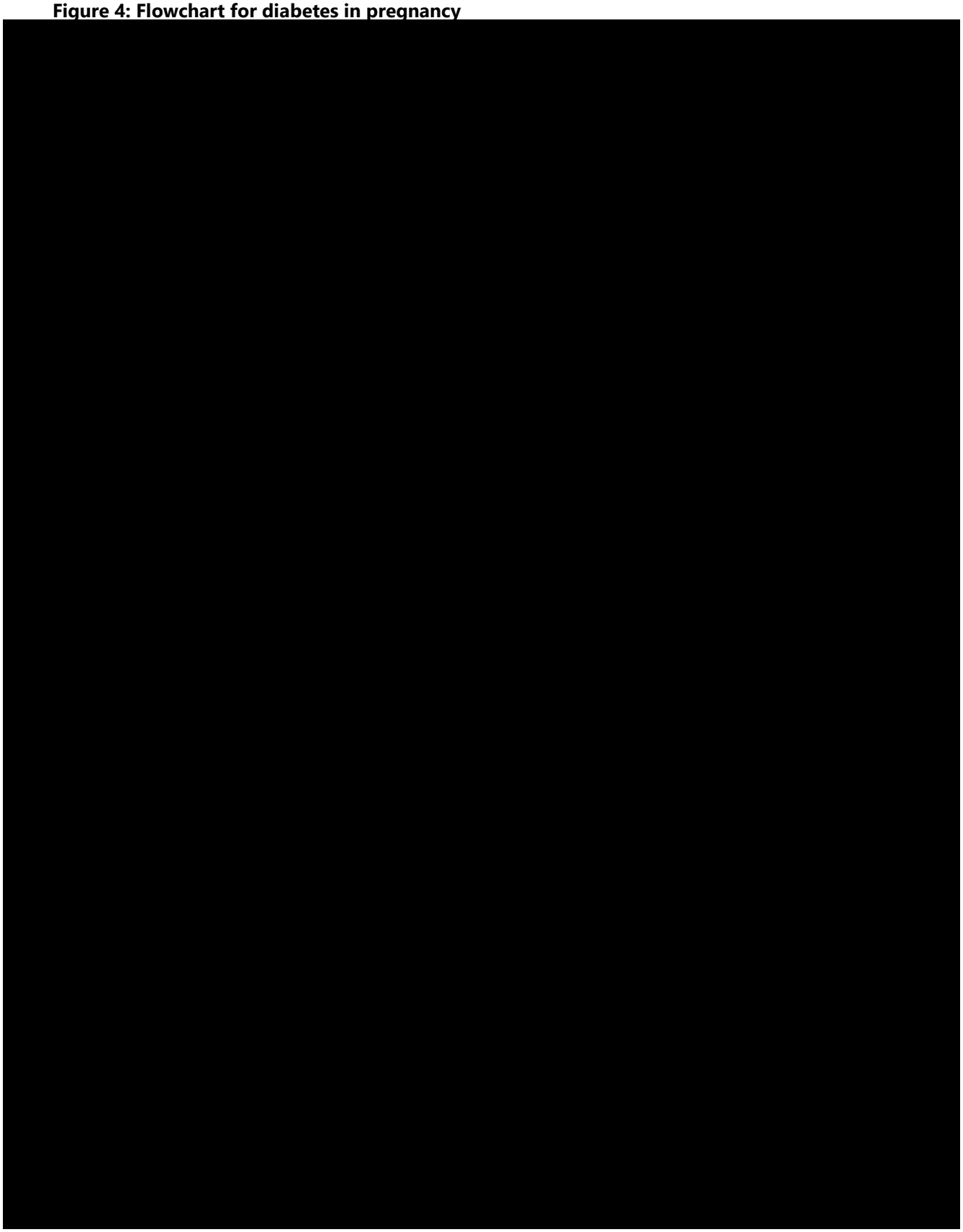
2.3.4 Screening for and management of GDM in New Zealand [20]

There is universal screening for GDM in New Zealand (Figure 4). During early pregnancy (< 20 weeks), glycated haemoglobin (HbA1c) levels will identify women with probable undiagnosed diabetes or prediabetes. All pregnant women without diabetes are offered glucose testing at 24–28 weeks' gestation to determine whether they have GDM.

If diabetes or GDM is identified, the pregnant woman should be referred to a specialist diabetes in pregnancy team and obstetric service for continuing care (DHB dependent). Treatment should include specialised dietary advice, lifestyle advice and pharmacological treatment as needed.

Following delivery, women with gestational diabetes should also be informed of their increased risk of having gestational diabetes in another pregnancy and of the lifelong risk of developing type 2 diabetes. Screening for diabetes and impaired glucose tolerance using HbA1c is recommended at three months postpartum. Unless symptomatic of diabetes, women should return annually for HbA1c screening with their primary care provider.

Figure 4: Flowchart for diabetes in pregnancy



Source: Ministry of Health. 2014. *Screening, Diagnosis, and Management of Gestational Diabetes in New Zealand: A Clinical Practice Guideline*. URL: https://www.health.govt.nz/system/files/documents/publications/screening-diagnosis-management-of-gestational-diabetes-in-nz-clinical-practive-guideline-dec14-v2.pdf (accessed 23 February 2022).

3 QUETIAPINE

3.1 Mechanism of action [22]

Quetiapine is an atypical antipsychotic agent. It's precise mechanism of action is unknown, but quetiapine and the active human plasma metabolite, norquetiapine interact with a broad range of neurotransmitter receptors. Quetiapine and norquetiapine exhibit affinity for brain serotonin (5HT2) and dopamine D1 and D2 receptors. The combination of receptor antagonism with a higher selectivity for 5HT2 relative to D2 receptors is believed to contribute to the clinical antipsychotic properties and low extrapyramidal side effects (EPS) liability of quetiapine compared to typical antipsychotics.

Quetiapine has no affinity for the norepinephrine transporter (NET) and low affinity for the serotonin 5HT1A receptor, whereas norquetiapine has high affinity for both. Inhibition of NET and partial agonist action at 5HT1A sites by norquetiapine may contribute to quetiapine's therapeutic efficacy as an antidepressant.

Quetiapine and norquetiapine have high affinity at histaminergic and adrenergic alpha1 receptors and moderate affinity at adrenergic alpha2 receptors. Quetiapine also has low or no affinity for muscarinic receptors, while norquetiapine has moderate to high affinity for several muscarinic receptor subtypes which may explain anti-cholinergic (muscarinic) effects.

3.2 Pregnancy

Changes in a woman's physiology during pregnancy mean that the pharmacokinetics of many medications, including antipsychotics, is impacted by dilution, hormonal, hepatic and renal factors throughout the perinatal and postnatal periods. Consequently, the dosages required for a woman to achieve optimal control of mental illness during pregnancy will likely change [2].

There is some evidence that the serum concentrations of quetiapine decrease during pregnancy, which may be clinically significant [23]. In a study in pregnant women treated with antipsychotics, in women receiving quetiapine 400 mg/day orally (33 women; 35 pregnancies) the serum concentration was significantly 76% lower during the third trimester (Table 13 and Figure 5) [23, 24].

Table 13: Serum antipsychotic concentrations during pregnancy

[redacted]

Source: Westin A, Brekke M, Molden E, et al. 2018. Treatment with antipsychotics in pregnancy: Changes in drug disposition. *Clinical Pharmacology and Therapeutics* 103(3): 477-84. DOI: 10.1002/cpt.770 (accessed 6 July 2022).

Figure 5: Quetiapine serum concentrations in pregnancy

Source: Westin A, Brekke M, Molden E, et al. 2018. Treatment with antipsychotics in pregnancy: Changes in drug disposition. *Clinical Pharmacology and Therapeutics* 103(3): 477-84. DOI: 10.1002/cpt.770 (accessed 6 July 2022).

Similarly, other studies have found that an increased dose of antipsychotic medicine is required to achieve the same serum concentration of the drug during pregnancy. Increased drug metabolism by CYP2D6, CYP3A4, CYP1A2 and CYP2C19 occurs during pregnancy. There is also an increase of around 5–8 litres in total body water in addition to an increased plasma volume of 30–50%, leading to an expansion of the volume of drug distribution. Increased renal blood flow and subsequent increased glomerular filtration also occur during pregnancy, leading to a faster rate of renal elimination of antipsychotic medicines [2].

Conversely, increasing sex steroids in the perinatal state may act directly on neurotransmitter receptors, balancing the reduction in plasma drug concentration so that higher drug concentrations may not be needed by some women to control symptoms. Changes to a woman's physiology also vary throughout the three trimesters of pregnancy with further changes occurring during labour. Some of the physiological changes affecting drug pharmacokinetics return to baseline 24 hours post-delivery; however, some have been shown to remain for 12 weeks [2].

3.3 Indications

Quetiapine is indicated in adults for the treatment of: [22]

- acute and chronic psychoses, including schizophrenia
- bipolar disorder including:
  - treatment of manic episodes satisfying DSM-IV criteria for mania associated with bipolar disorder
  - treatment of depressive episodes associated with bipolar disorder
  - maintenance treatment of bipolar I disorder, in combination with a mood stabiliser, for the prevention of recurrence of manic, depressive or mixed episodes.

3.3.1 Unapproved (off-label) use

Off-label use of antipsychotics, including quetiapine, is common in New Zealand and internationlly. Off-label indications include depression, anxiety and borderline personality disorder [2].

Huthwaite et al. 2018. Off label or on trend: a review of the use of quetiapine in New Zealand [14]

To aid the understanding of quetiapine prescribing in general practice in New Zealand, Huthwaite et al conducted a retrospective audit of the prescribing of quetiapine in 57 of the 59 practices in the Compass Health Primary Health Organisation (PHO). This was in response to a concern by the Clinical Quality Board of Compass Health that quetiapine was being prescribed off label.

The audit was conducted from January 2015 to January 2016. Data regarding the quetiapine prescriptions were extracted from the clinical records in the shared Practice Management Systems (PMS) and therefore represented prescribing data not dispensing data. Based on the quetiapine data sheet, the auditors made *a priori* decisions about what indications would be approved, and which would be considered 'off-label' (unapproved). The clinical notes and relevant correspondence were reviewed to determine the indication for use. Of the 2,161 patients prescribed quetiapine, only 460 (21.3%) were prescribed quetiapine for the licensed indication, with 1,556 (72%) receiving quetiapine for an off-label indication. Most patients (56.2%) were started on quetiapine in primary care, with 39% in secondary care. For the remaining 4.8%, it was unclear who initiated the prescribing. In the primary care-initiated group, full consent for the off-label prescribing was documented in 11% of the patient's records.

Table 14 lists the unapproved indications and Figure 6 shows the percentage for the groups of unapproved conditions for which quetiapine was prescribed. Sleep problems and anxiety were the most frequently prescribed non-approved conditions.

The dose range for unapproved prescribing was between 6.25 mg–800 mg, with 91% (1,416) being prescribed less than 100 mg daily (see Figure 7). Only 2.3% (36) of those prescribed quetiapine for an unapproved indication were prescribed more than 300 mg daily. A relatively wide dose range was noted in many cases, for example: 25 to 100 mg at night (or daily) as required, with the largest of these being 6.25 to 300 mg daily as required.

Table 14: Off-label prescribing of quetiapine: unapproved conditions for which quetiapine was prescribed

[redacted]

Figure 6: Unapproved conditions for which quetiapine was prescribed

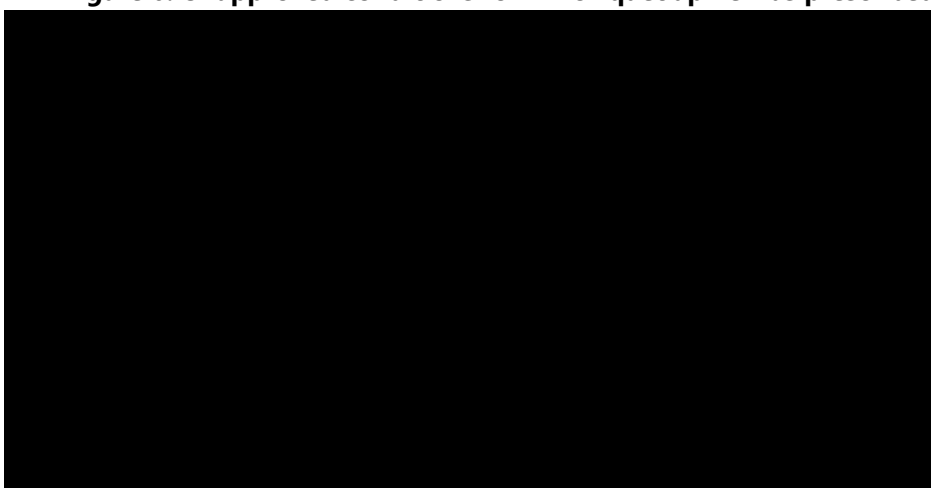


Figure 7: Dose range for non-approved prescribing

[redacted]

Comments

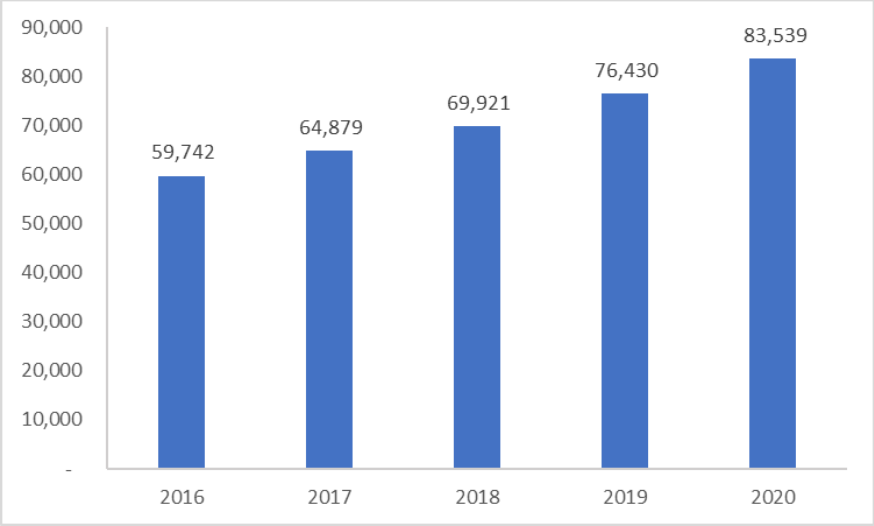
Although this was a regional rather than a nationwide study, the results suggest that quetiapine is widely prescribed in primary care for unapproved indications.

3.4 Quetiapine usage in New Zealand

3.4.1 Overall

The number of people being dispensed quetiapine (Figure 8) and the number of quetiapine dispensings (Figure 9) has increased from 2016 to 2020.

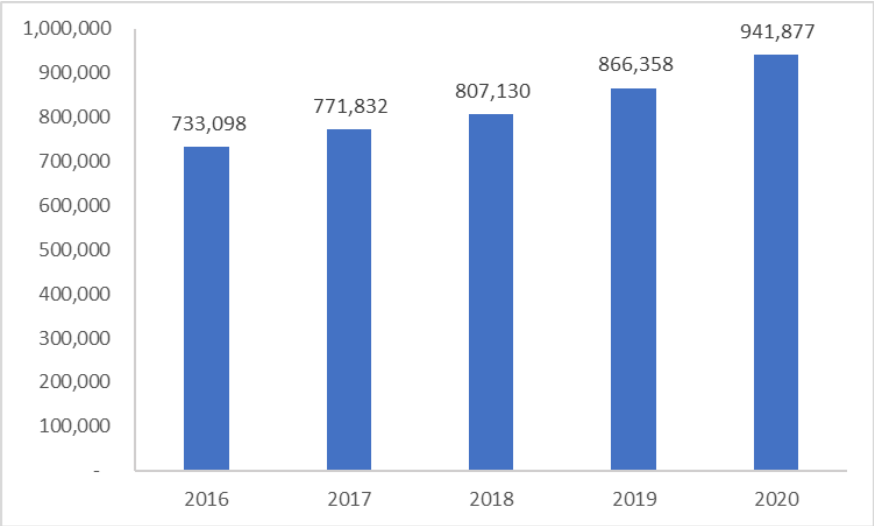
Figure 8: Number of people* dispensed quetiapine per year, 2016–2020



* Number of people who received at least one dispensing of the pharmaceutical product as a named person from the pharmacy during the year. Includes repeat dispensings.

Source: Ministry of Health. 2022. Pharmaceutical Data web tool version 13 January 2022 (data extracted from the Pharmaceutical Collection on 26 November 2021). URL: https://minhealthnz.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 20 June 2022).

Figure 9: Number of quetiapine dispensings* per year, 2016–2020



* Number of times a pharmaceutical product is dispensed to the named person from a pharmacy. Includes repeat dispensings.

Source: Ministry of Health. 2022. Pharmaceutical Data web tool version 13 January 2022 (data extracted from the Pharmaceutical Collection on 26 November 2021). URL: https://minhealthnz.shinyapps.io/pharmaceutical-data-web-tool/ (accessed 20 June 2022).

3.4.2 Pregnancy

[redacted]

[redacted]

[redacted]

[redacted]

Notes:

[redacted]

4 SCIENTIFIC INFORMATION

4.1 Prescribing information

4.1.1 New Zealand data sheet

The New Zealand Seroquel data sheet contains information about hyperglycaemia and diabetes [22].

4.4 Special warnings and precautions for use

Hyperglycaemia and Diabetes Mellitus

Increases in blood glucose and hyperglycaemia, and occasional reports of diabetes, have been observed in clinical trials with quetiapine. Although a causal relationship with diabetes has not been established, patients who are at risk for developing diabetes are advised to have appropriate clinical monitoring. Similarly, patients with existing diabetes should be monitored for possible exacerbation (see section 4.8 - Undesirable Effects). Patients with an established diagnosis of diabetes mellitus who are started on atypical antipsychotics should be monitored regularly for worsening of glucose control. Patients with risk factors for diabetes mellitus (e.g. obesity, family history of diabetes) who are starting treatment with atypical antipsychotics should undergo fasting blood glucose testing at baseline and periodically during treatment. Any patient treated with atypical antipsychotics should be monitored for symptoms of hyperglycaemia including polydipsia, polyuria, polyphagia and weakness. Patients who develop symptoms of hyperglycaemia during treatment with atypical antipsychotics should undergo fasting blood glucose testing. In some cases, hyperglycaemia has resolved when the atypical antipsychotic was discontinued; however, some patients required continuation of antidiabetic treatment despite discontinuation of the suspect drug.

Metabolic factors

In some patients, a worsening of more than one of the metabolic factors of weight, blood glucose and lipids was observed in clinical studies. Changes in these parameters should be managed as clinically appropriate.

4.6 Fertility, pregnancy and lactation

Pregnancy

Neonates exposed to antipsychotic medicines (including SEROQUEL) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring.

The safety and efficacy of quetiapine during human pregnancy have not been established. Following some pregnancies in which quetiapine was used, neonatal withdrawal symptoms have been reported. Therefore, quetiapine should only be used during pregnancy if the benefits justify the potential risks and the administered dose and duration of treatment should be as low and as short as possible.

Breastfeeding

There have been published reports of quetiapine excretion into human breast milk, however the degree of excretion was not consistent. Women who are breast-feeding should therefore be advised to avoid breast-feeding while taking quetiapine.

Fertility

The effects of quetiapine on human fertility have not been assessed. Effects related to elevated prolactin levels were seen in rats, although these are not directly relevant to humans because of species differences in hormonal control of reproduction (see section 5.3 Preclinical Safety Data).

4.8 Undesirable effects

Frequency	System Organ Class	Event
Common (≥1% to <10%)	Investigations	Blood glucose increased to hyperglycaemic level[1,8]

1. See 4.4 Special Warnings and Precautions for Use
8. Fasting blood glucose ≥ 126 mg/dL or a non fasting blood glucose ≥ 200 mg/dL on at least one occasion.

Diabetes Mellitus

Exacerbation of pre-existing diabetes mellitus, and diabetic ketoacidosis, have occurred very rarely with quetiapine therapy. The causal association with quetiapine has not been established (see section 4.4 Special Warnings and Precautions for Use).

Comments

Diabetes and hyperglycaemia are well-described in the NZ data sheet although there is no discussion of gestational diabetes.

There is limited data in pregnancy and quetiapine should only be used when the benefits outweigh the risks, and the dose and duration of treatment should be as low and as short as possible.

4.1.2 International prescribing information

Annex 1 shows the quetiapine prescribing information from Australia, the UK, EU (Ireland), the USA and Canada. Note that only text relevant to diabetes mellitus and blood glucose is included.

Comments

As in New Zealand, the quetiapine prescribing information in other countries contains text about diabetes mellitus, increased blood glucose and monitoring. None have information about gestational diabetes mellitus.

Compared to the NZ Seroquel data sheet, section 4.4 of the Australian product information has additional information about background rates of diabetes mellitus in patients with schizophrenia, and that epidemiological studies have identified an increased risk of treatment-emergent hyperglycaemia-related adverse events in patients treated with atypical antipsychotics. There is also information in section 4.8 about increases in blood glucose levels observed in clinical trials. We will be requesting updates to the New Zealand data sheet to align with the Australian product information.

4.2 Published literature

The studies below include those that stimulated the EMA's review, those included in the response from the sponsor and recent studies identified through a literature search.

4.2.1 Gentile. 2010. Antipsychotic therapy during early and late pregnancy. A systematic review [25]

Aim/Study type: This was a systematic review of studies focussed on investigating the safety of first- and second-generation antipsychotics (FGA and SGA, respectively) in pregnancy. The second aim was to attempt to identify the less harmful treatment option for the mother-infant pair.

Methods: Data was sourced from the medical literature since 1950 up to and including July 2008 (any language). Additional references were identified from reference lists of published articles. Manufacturers were contacted for unpublished data. Studies were selected by one reviewer (the author) based on their abstracts. Studies of any design were included if they reported primary data on the outcome of pregnancies exposed to antipsychotic medications. The review included 110 articles identified from electronic databases, 2 sets of manufacturer supplied data and 7 sources of information identified by hand searching. Many of the studies were case reports.

Results: Table 17 shows the studies identified by the author for quetiapine, including the sample size, daily dose, timing of exposure, major malformations and pregnancy and neonatal outcomes.

Table 17: Quetiapine studies identified by the author

Conclusions: The author concluded that the reviewed information was too limited to draw definite conclusions on structural teratogenicity of FGAs and SGAs. Both classes of drugs seem to be associated with an increased risk of neonatal complications. However, most SGAs appear to increase risk of gestational metabolic complications and babies large for gestational age and with mean birth weight significantly heavier as compared with those exposed to FGAs. These risks have been reported rarely with FGAs. Hence, the choice of the less harmful option in pregnancy should be limited to FGAs in drug-naive patients. When pregnancy occurs during antipsychotic treatment, the choice to continue the previous therapy should be preferred.

Comments

[redacted]

Of the included studies, none showed an increased risk of GDM associated with quetiapine use. The author was the only reviewer who performed selection and data extraction. Many of the studies were case reports (n=1), with limited information. Did not comment on potential biases, limitations for each of the included studies.

4.2.2 Gentile. 2014. Pregnancy exposure to second generation antipsychotics and the risk of gestational diabetes [1]

Aim/Study type: Review published data reporting on the incidence of gestational diabetes mellitus during second generation antipsychotic (SGA) treatment, and to establish whether or not this iatrogenic complication is a relevant concern in clinical practice.

Methods: Based on the author's previous search strategy (see Gentile 2010, above). Medical literature information published in any language since 1996 was identified using MEDLINE/PubMed, EMBASE, Scopus, and The Cochrane Library. All articles reporting metabolic complications in pregnancies exposed to single, specific SGAs were acquired, without methodological or language limitations.

Results: 1 study was identified for quetiapine (Wichman 2009 [26]) – this was a retrospective chart review of all pregnant women presenting at a US medical centre from 1993 to 2007. In total, 30,092 deliveries were identified, of which, 16 women were prescribed atypical antipsychotics at some point in their pregnancy. The medical charts of the infants exposed to atypical antipsychotics during pregnancy were reviewed to determine their outcomes, including gestational age, birth weight, and malformations. Of the 10 women treated with quetiapine, 2 cases of GDM were reported (Table 18). No fetal or neonatal complications were identified for the 2 cases.

Table 18: Main clinical findings of published cases of gestational diabetes mellitus (GDM) occurring in women treated with specific SGAs during pregnancy (quetiapine only)

[redacted]

Table 19 summarises data for SGAs as a group. Registry data from Sweden indicated an increased risk of GDM, even after adjusting for maternal factors (Bodén). When analysed as a class, antipsychotics (either typicals or atypicals) were associated with a nearly doubled risk for GDM (Reis). A prospective study of Canadian women exposed to SGAs with matched controls did not find an increased risk (Sadowsky).

Table 19: Studies investigating the risk of GDM associated with exposure to SGAs as a group

[redacted]

Limitations: Based on case reports, which are essentially qualitative and exploratory studies and are strongly subject to bias. The limited number of observations (a single patient), the lack of a control group and the subjectivity in interpreting outcomes minimise the validity of clinical inferences. Thus, both quality and number of available studies do not allow to estimate the prevalence of GDM induced by SGA treatment.

Conclusions: Among studies assessing the metabolic safety of specific SGAs, there are 18 cases of GDM overall: 5 cases involve clozapine (CLO), 9 olanzapine (OLA) - the SGA agent that shows the highest number of reported cases of pregnancy exposure - and 2 each for quetiapine and risperidone. Four of these cases, 2 involving CLO and 2 OLA, were complicated by serious fetal and/or neonatal consequences. Such reports of SGA-associated GDM, together with preliminary data coming from retrospective and prospective studies, may represent signals of a potential safety issue.

Comments

This was one of the studies that stimulated the safety signal review request from the EMA to the sponsor.

There was only one study in this review that had data for quetiapine. And only 1 of the 2 GDM cases continued quetiapine throughout pregnancy.

As with the 2010 Gentile review described above, this results of this review are limited by the quality of the included studies.

4.2.3 Kulkarni et al. 2015. Antipsychotic use in pregnancy [2]

Aim: To review published data regarding the safety of antipsychotic medications in pregnancy with a focus on the most commonly used atypical antipsychotics. Also presents data from the Australian National Register of Antipsychotic Medication in Pregnancy (NRAMP), an Australian prospective cohort study that investigates the effect of antipsychotic medications in pregnancy on mother and baby. NRAMP was set up by the authors to address the knowledge gap. A major gap in the literature is the prospective collection of clinical data from a cohort of women taking antipsychotics in pregnancy and studying the impact of medications on their babies.

Table 20 summarises the key points from the review paper (using the paper's headings and subheadings).

Table 20: Key points from Kuklarni et al's review paper

[redacted]

[redacted]

Expert opinion: Given the potential harm of not treating severe psychiatric illnesses during pregnancy, careful administration of antipsychotics is recommended for pregnant women who suffer from severe mental disorders. The most frequently used antipsychotics in pregnancy are olanzapine, risperidone and quetiapine, and do not appear to cause consistent, congenital harm to the fetus. No specific patterns of fetal limb or organ malformation related to these drugs have been reported. There is some evidence suggesting an association between antipsychotic use in pregnancy and the development of gestational diabetes. Also there appears to be an association between antipsychotic medication use in pregnancy and increased neonatal respiratory distress and withdrawal symptoms. Further studies are needed for clinicians to balance good maternal mental health, healthy pregnancies and good infant health outcomes.

Comments

This was one of the studies that stimulated the safety signal review request from the EMA to the sponsor.

This article is an expert opinion of the data rather than full a systematic review.

4.2.4 Vigod et al. 2015. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study [27]

Aim/study type: High dimensional propensity score (HDPS) matched cohort study to evaluate maternal medical and perinatal outcomes associated with antipsychotic drug use in pregnancy.

Methods: Multiple linked population health administrative databases in the entire province of Ontario, Canada. Among women who delivered a singleton infant between 1 April 2003 and 31 December 2012, and who were eligible for provincially funded drug coverage (eligibility for drug coverage includes unemployment, disability, high prescription drug costs relative to net household income, receipt of home care services), those with ≥2 consecutive prescriptions for an antipsychotic medication during pregnancy, at least one of which was filled in the first or second trimester, were selected. Of these antipsychotic drug users, 1021 were matched 1:1 with 1021 non-users by means of a HDPS algorithm.

The study design was chosen to account for observed and unobserved confounding factors that might explain the association between antipsychotic drug use in pregnancy and important maternal and perinatal outcomes. The HDPS algorithm attempts to further minimise residual confounding by indication by also incorporating proxy (or surrogate) variables—healthcare diagnoses, procedures, and drug claims—which, when combined, collectively behave as a good overall proxy for important unobserved confounders. In typical pharmaco-epidemiological studies, HPDS methods result in less biased estimates of treatment effects when benchmarked against those from randomised controlled trials.

The main maternal medical outcomes were gestational diabetes, hypertensive disorders of pregnancy and venous thromboembolism. The main perinatal outcomes were preterm birth (<37 weeks) and a birth weight <3rd or >97th centile. Conditional Poisson regression analysis was used to generate rate ratios and 95% confidence intervals, adjusting for additionally prescribed non-antipsychotic psychotropic medications.

Results: Out of 1209 antipsychotic users in the overall cohort, 1021 (84%) were successfully matched using the HDPS algorithm (Table 21). About 90% of matched antipsychotic users were exclusively prescribed an atypical antipsychotic medication, and, of these, 556 were exclusively prescribed quetiapine, 166 olanzapine, and 112 risperidone.

Unmatched antipsychotic users were older and had higher baseline medical morbidity than unmatched non-users (Table 21). They also had more prenatal visits and were less likely to receive antenatal care from an obstetrician. There were substantial differences between unmatched users and non-users for all mental health measures. After matching, there was marked attenuation in the standardised differences for all baseline characteristics. Although reduced by the matching process, notable standardised differences persisted between matched users and non-users for psychotic and major mood disorders, as well as for pre-scribed antidepressant drugs, mood stabilisers, and benzodiazepines. Nearly 88% of antipsychotic users, compared with 27% of matched non-users, were prescribed an antipsychotic medication within one year before the estimated date of conception.

Table 21: Characteristics of 41,253 women who were categorised by whether they were prescribed an antipsychotic drug during pregnancy. Values are numbers (percentages) unless otherwise stated

[redacted]

Table 22 shows that compared with non-users, women prescribed an antipsychotic medication in pregnancy did not seem to be at higher risk of gestational diabetes (rate ratio 1.10 [95% CI 0.77 to 1.57]), hypertensive disorders of pregnancy (1.12 [0.70 to 1.78]), or venous thromboembolism (0.95 [0.40 to 2.27]). When the analysis was restricted to atypical antipsychotics and specific drugs, the results were unchanged (Figure 13).

Table 22 also shows that the preterm birth rate, though high among antipsychotic users (14.5%) and matched non-users (14.3%), was not relatively different (rate ratio 0.99 [0.78 to 1.26]). Neither birth weight <3rd centile or >97th centile was associated with antipsychotic drug use in pregnancy (rate ratios 1.21 [0.81 to 1.82] and 1.26 [0.69 to 2.29] respectively). When the analysis was restricted to atypical antipsychotics and specific drugs, the results were unchanged (Figure 14).

Table 22: Main maternal and perinatal outcomes

[redacted]

Figure 13: Main maternal outcomes, restricted to use of any atypical antipsychotic or a specific antipsychotic

[redacted]

Figure 14: Perinatal outcomes, restricted to use of any atypical antipsychotics or a specific antipsychotic

Limitations: The study included only women for whom information on prescription medicines was available through a provincially covered drug plan. Individuals eligible for this drug plan tend to have worse health states, greater disability, and are of lower socioeconomic status compared with individuals who pay privately for their medication. Therefore, these results may not be entirely generalisable to antipsychotic users who are healthier and of higher socioeconomic status.

HDPS matching is meant to minimise residual confounding and to approximate relative risk estimates observed in a randomised clinical trial. However, a balanced match was not achieved on some characteristics. Most notably, the groups differed after matching on additionally prescribed non-antipsychotic psychotropic medication – although they were adjusted for. Residual confounding may have persisted due to inadequate capture of variables such as smoking and obesity or due to unmeasured factors such as psychiatric symptoms.

Conclusions: The authors concluded that antipsychotic drug use in pregnancy had minimal evident impact on important maternal medical and short term perinatal outcomes. However, the rate of adverse outcomes is high enough to warrant careful assessment of maternal and fetal wellbeing among women prescribed an antipsychotic drug in pregnancy.

Comments

This study did not find an increase in the risk of gestational diabetes for any antipsychotic and when quetiapine was used alone. Although the study compared antipsychotic users with non-users, the use of matching may have reduced residual confounding between the two groups. However, they were not able to capture (and therefore match) smoking or obesity data, both of which are risk factors for GDM.

Only included women who were eligible for access to healthcare, physician services and medicines. These women may be different from those in New Zealand, where access to healthcare is publicly funded for all women.

4.2.5 Park et al. 2018. Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes [15]

Aim/study type: This was a cohort study of non-diabetic pregnant women which examined the risk of gestational diabetes associated with continuation during pregnancy compared to discontinuation of aripiprazole, ziprasidone, quetiapine, risperidone, or olanzapine.

Methods: To create the cohort, the authors used the Medicaid Analytic eXtract (MAX), which is a person-level nationwide claims database and contains information on demographics, hospitalisations, outpatient visits, and pharmacy dispensing records. Non-diabetic pregnant women with a live-born infant in Medicaid (2000–2010) who had ≥ 1 antipsychotic dispensing during the 3 months (140 days) before pregnancy were included. For each antipsychotic, women with ≥ 2 dispensings (continuers) were compared to women with no dispensing during the first half of pregnancy (discontinuers).

Gestational diabetes cases were classified as those women who (1) had two or more diagnosis codes for any diabetes between 141 days after last menstrual period (LMP) and delivery; and (2) who had a glucose tolerance test or a gestational diabetes diagnosis in the same time frame.

A generalised linear model and propensity score stratification was used to obtain absolute and relative risks of gestational diabetes, adjusting for confounders. Covariates were selected based on clinical plausibility as confounders or proxies of confounders for the association between antipsychotic continuation and gestational diabetes, and included demographics, psychiatric diagnoses, comorbidity, other medication use, history of GDM, and the duration of antipsychotic treatment received in the 3 months before the LMP. The propensity score was the predicted probability of continuing the treatment as opposed to discontinuing after last menstrual period, estimated by logistic regression with all covariates.

In dose-response analyses, they included women with only one dispensing during the first 140 days to estimate the relationship at lower doses. They also combined the users of individual drugs to form three 'risk-stratified groups', based on the drugs' weight gain potential and risk of diabetes outside of pregnancy: Low risk = aripiprazole and ziprasidone; Medium-risk = quetiapine and risperidone; High-risk = olanzapine.

They also conducted a bias analysis to examine the extent to which adjustment for confounding by unmeasured or poorly measured obesity would change the observed associations. The prevalence estimate of obesity was obtained from the Massachusetts General Hospital registry for pregnant women with psychiatric illness. They assumed that overweight or obese women have 4 times the risk of gestational diabetes compared to non-obese women and examined the potential bias over a range of obesity prevalence differences (0 to 25%) between continuers and discontinuers.

Results: Among 1,543,334 pregnancies, the number of baseline antipsychotic users was 1,924 for aripiprazole, 673 for ziprasidone, 4,533 for quetiapine, 1,824 for risperidone, and 1,425 for olanzapine. Continuers generally had higher comorbidity and longer baseline antipsychotic use. After propensity score weighting, most patient characteristics were well balanced between continuers and discontinuers, except for a few important covariates such as obesity and bipolar disorders which remained slightly unbalanced between the olanzapine continuers and discontinuers (Table 23).

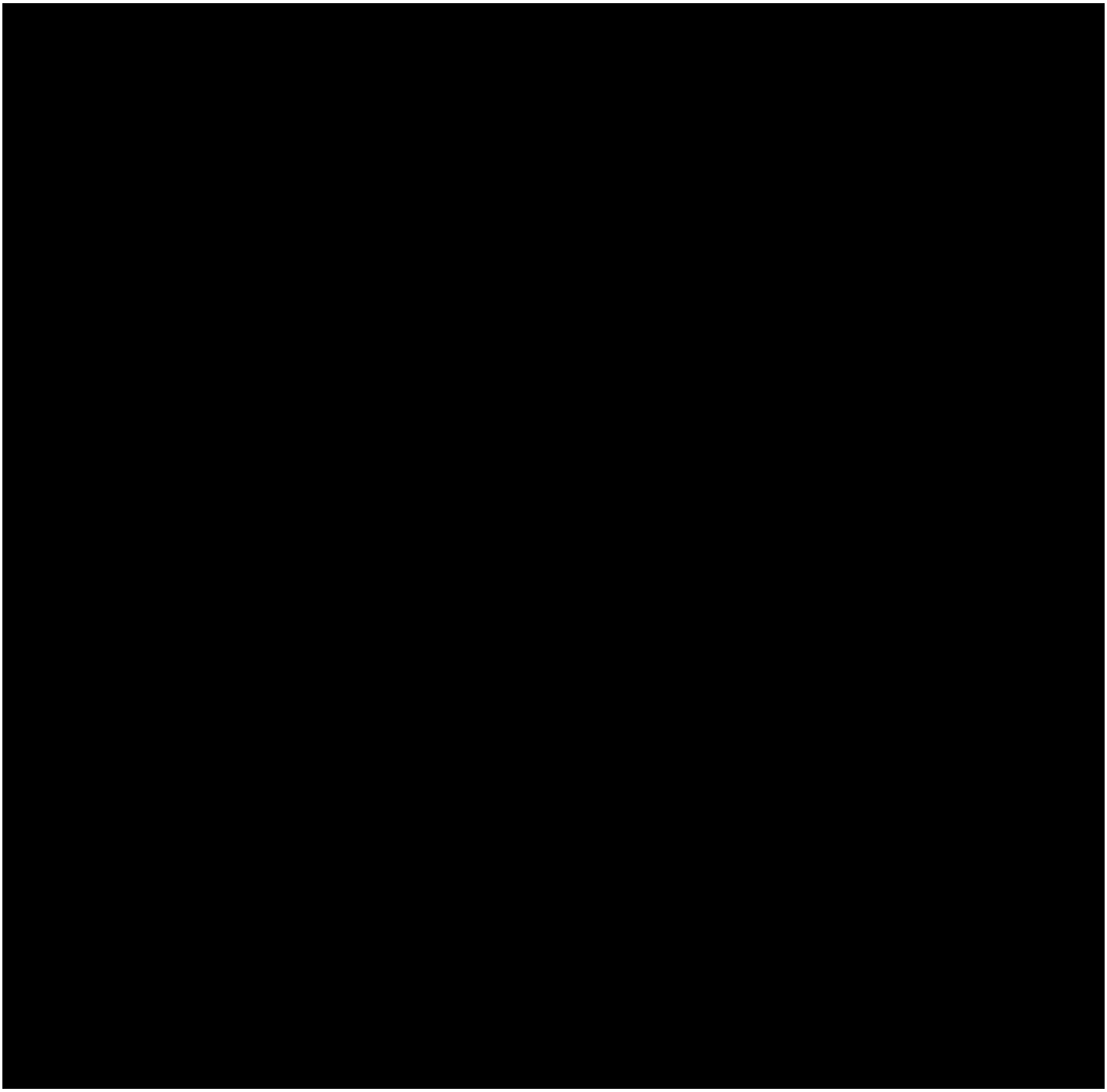
Table 23: Selected patient characteristics comparing continuers to discontinuers of each atypical antipsychotic medication, weighted by propensity score

Table 24 shows the unadjusted and adjusted risk of GDM for each group. For quetiapine, the crude risk of gestational diabetes for continuers vs. discontinuers was 7.1% vs. 4.1%, and the adjusted relative risk was 1.28 (1.01–1.62). The adjusted relative risks in the low-(aripiprazole, ziprasidone), medium-(risperidone, quetiapine), and high-risk (olanzapine) group were 0.91 (0.60–1.39), 1.37 (1.12–1.69), and 1.61 (1.13–2.29), respectively.

Table 24: Unadjusted and adjusted risk of gestational diabetes, comparing continuers to discontinuers of each antipsychotic medication or group

In dose-response analysis, the risk increased with increasing cumulative dose of olanzapine until about 700 mg and plateaued thereafter (Figure 15). No clear trend was seen for other antipsychotics considering the width of the confidence band.

Figure 15: Dose-response analyses between the cumulative dose of antipsychotic exposure during the first 20 weeks of pregnancy and the risk of gestational diabetes



The bias analyses illustrated that with an overall obesity prevalence of 62% among atypical antipsychotic users observed in the Massachusetts General Hospital registry, the absolute difference in the prevalence of obesity between continuers and discontinuers would have to be more than 25% for the observed relative risk of 1.61 in olanzapine users to be completely attributable to residual confounding. To put this into context, a 25% difference would mean that 80% of continuers and 55% of discontinuers would be obese patients, with all other covariates balanced between the two groups. In quetiapine users, the difference would have to be greater than 20%.

Limitations: Residual confounding due to unmeasured or poorly measured factors such as lifestyle factors. The authors could not fully adjust for the duration of antipsychotic exposure, which may have extended many

years before recording in the database. They do not have information on the reasons for discontinuation, which may be associated with the disease severity or indication for antipsychotic use not recorded in the data. Use of low-dose quetiapine for insomnia is well known, and women without psychiatric disorder who used quetiapine for insomnia before the start of pregnancy may be more likely to discontinue after becoming pregnant. A pharmacy dispensing record does not guarantee the actual intake of the drug.

Conclusions: Compared to women who discontinued before the start of pregnancy, those who continued olanzapine or quetiapine during the first 20 weeks of pregnancy had an increased risk of gestational diabetes that may be explained by the metabolic effects associated with the treatment. Further studies are needed to understand the potential effect on gestational diabetes risk of switching antipsychotic agents during pregnancy. Such information would aid treatment decisions in women for whom treatment discontinuation is not an option. In conclusion, while the risk of gestational diabetes is an important consideration in selection of a drug, other dimensions of antipsychotic treatment including the benefit of continuing a specific treatment and the risk of efficacy loss due to changes in treatment should be taken into account in decision making for pregnant women.

Comments

[redacted]

Medsafe reviewed this paper and the potential safety signal of GDM with atypical antipsychotics in 2019. At that time, Medsafe considered no action was warranted and routine monitoring should continue. This was because there is detailed information in the data sheets on hyperglycaemia and diabetes (see section 4.1.1), and there have been no reported cases in New Zealand.

Medicaid captures 50% of pregnancies and 80% of antipsychotic prescriptions in the US. It is possible that the characteristics of the women not covered by Medicaid are different from those that are covered, and different again from New Zealand women. The results may not be generalisable to NZ.

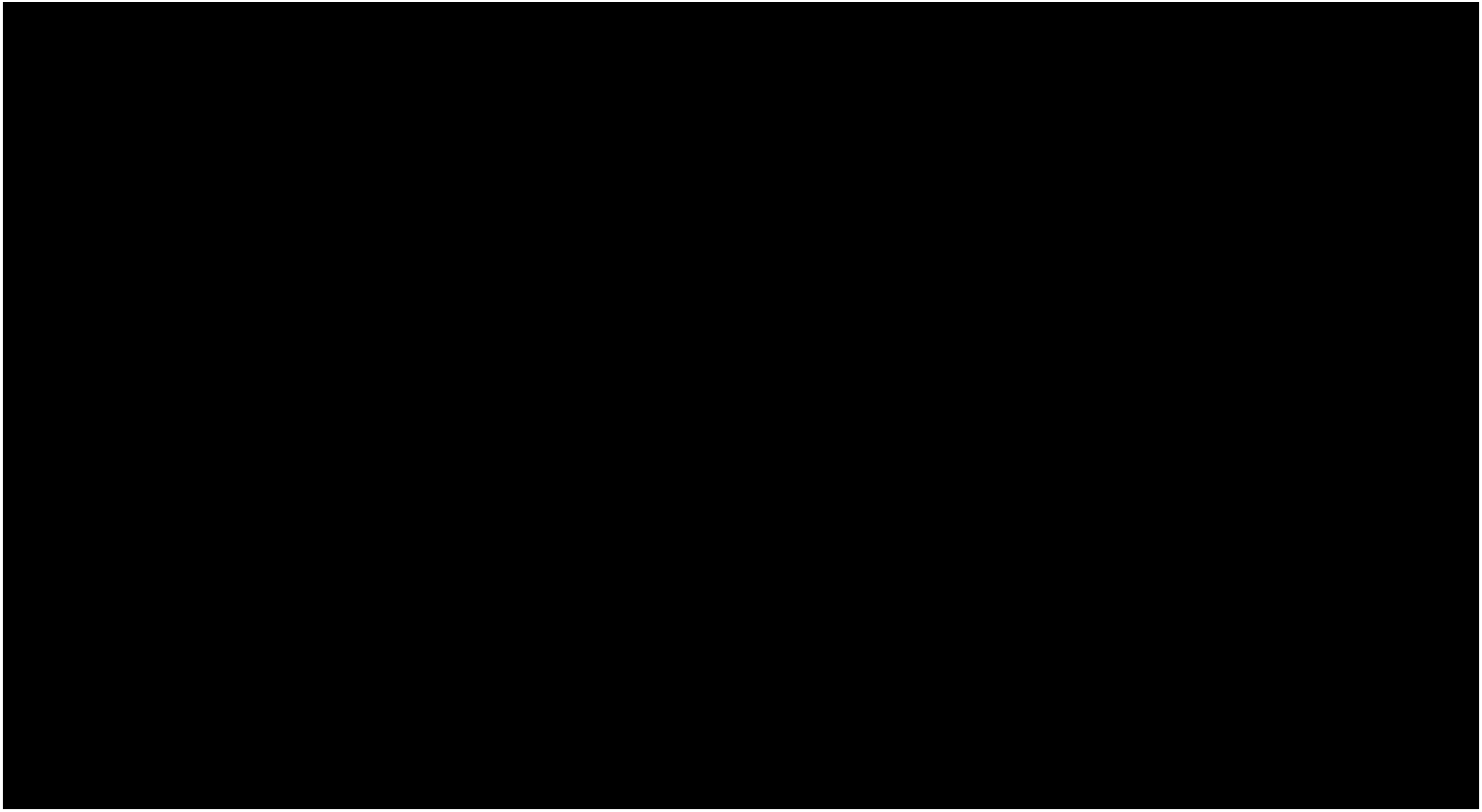
4.2.6 Uguz. 2019. Antipsychotic use during pregnancy and the risk of gestational diabetes mellitus: A systematic review [28]

Aim/study type: A systemic review of the literature that aimed to discuss the potential relationship between the use of antipsychotic drugs during pregnancy and GDM.

Methods: The author searched PubMed for English language reports between 1 January 1996, and 31 March 2018, using a combinations of key words (including quetiapine). Reports that met the following criteria were included in the review: (1) published in English language in a peer-reviewed journal; (2) clearly reported the diagnosis of GDM; and (3) clearly reported the maternal use of antipsychotics during pregnancy. Experimental studies involving animals, reviews, case reports, editorials, and comments on the reports were excluded from the review. The author selected studies using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines and checklist.

Results: 10 studies met the selection criteria: 3 population-based cohort studies, 1 population-based matched cohort, 1 retrospective cohort, 3 prospective, 2 retrospective review studies (Table 25). Most of the studies had significant limitations, as described in Table 25. This systematic review suggests that although some authors reported that the prevalence rate of GDM in pregnant women using antipsychotic drugs seems to be higher compared with pregnant women who are not exposed to these drugs, results of most studies do not support a significant connection between antipsychotic treatment and the development of GDM when confounding variables were taken into account. Limited data suggest similar risk of GDM in FGA and SGA users during pregnancy. Relatively well-designed comparative studies suggest that even if an association between antipsychotic drugs and increased risk of GDM, this association is not independent of underlying maternal diagnoses such as psychotic disorders or bipolar disorder.

Table 25: Characteristics of studies included in the review



Limitations: Most studies had a retrospective design or were based on electronic medical registry data. None of the prospective studies were randomised controlled comparative clinical trials. Most of the data were unclear on the duration of actual use and daily dosage of antipsychotic drugs. Also, electronic databases in some studies were limited in suggesting compliance and dropout problems. Most studies lacked data on concomitant medications, did not provide data on psychiatric diagnoses, nor data on the severity and comorbidity among the psychiatric diagnoses.

Conclusions: The available studies are both few in number and have many methodological limitations. When results and limitations of the studies included in this review were considered, it may be concluded that there is no adequate scientific evidence indicating a causal association between the use of antipsychotic drugs during pregnancy and the development of GDM. In addition, the available studies imply that presence of schizophrenia and related psychotic disorders and bipolar disorder in pregnant women rather than the use of antipsychotic drugs are important factors in the possible risk of GDM. Further randomised-controlled clinical studies that exclude the limitations of the available studies are required to reach definitive conclusions on this topic.

Comments

[redacted]

4.2.7 Galbally et al. 2020. The association between gestational diabetes mellitus, antipsychotics and severe mental illness in pregnancy: A multicentre study [29]

Aim/Study type: This retrospective study examined the risk of developing GDM in relation to mental disorder, psychotropic treatment and comorbid risk factors.

Methods: 539 women with severe mental illness (SMI) disorders from two Australian tertiary obstetric hospitals. The authors extracted data from the hospital records. Measures included:

- GDM diagnosis – from hospital records. Both hospitals diagnose GDM at 28 weeks' gestation using the full 75 g 2-hour glucose tolerance test as part of a universal screening policy for pregnant women (the criteria for GDM in Australia changed during the study period, and very few women in the sample were tested for GDM after this change).
- Mental health diagnosis, based on primary mental health diagnosis and grouped into three diagnostic groups: psychotic disorders (includes schizophrenia, schizoaffective and related psychotic disorders), bipolar disorder, and non-psychotic severe mental illness (includes major depressive disorder, obsessive compulsive disorder, post-traumatic stress disorder, panic disorder, and anorexia nervosa)
- Psychotropic medication extracted from hospital records. Grouped into atypical antipsychotics (quetiapine, olanzapine, risperidone, clozapine, aripiprazole, ziprasidone and asenapine), typical antipsychotics (low potency and high potency) and mood stabilisers (lithium, sodium valproate, lamotrigine, carbamazepine and gabapentin). Some analyses used individual agents. Other psychotropic agents were recorded, including antidepressants, hypnotics and anxiolytics.
- Other measures: body mass index, age, smoking, alcohol and illicit substance use. Five women were excluded from the analysis due to having co-morbid diagnoses associated with GDM (pre-existing diabetes and bulimia nervosa).

Results: Table 26 shows the demographic information by SMI groups. Using the whole sample, there were no associations between GDM and smoking (GDM 42.9% vs no GDM 44.8%, P = 0.796), alcohol consumption (GDM 6.8% vs no GDM 14.6%, P = 0.096), and illicit drug use (GDM 17.3% vs no GDM 20.5%, P = 0.541). Table 27 shows the frequencies for specific antipsychotic and mood stabilisers. There was no significant association found in the sample for parity and GDM.

Table 26: Demographic statistics by severe mental illnesses group

[redacted]

[redacted]

Women in the psychotic disorders group demonstrated a higher attributable risk of having GDM compared with women in the non-psychotic SMI groups (RR 1.86, 95% CI 1.09‑3.17, AR 8.9%). There was no difference in the attributable GDM risk between women with bipolar disorder and women in the non-psychotic SMI groups (RR 1.07, 95% CI 0.61‑1.87, AR 0.7%).

Psychotropic medication and GDM

There was no increased risk of GDM for women exposed to typical antipsychotics versus women not exposed (RR 0.49, 95% CI 0.13–1.88, AR −7.6%), and for women exposed to mood stabilizers versus no exposure (RR 1.44, 95% CI 0.92–2.25, AR 5.7%). The rate of GDM was significantly higher in women exposed to atypical antipsychotics (17.3%) compared with women not exposed (10.7%; RR 1.62, 95% CI 1.04–2.52, AR 6.6%).

Table 28 shows the dose for specific psychotropic agents by GDM groups, and the rates of GDM by psychotropic agent exposures, attributable risk and unadjusted relative risk of GDM for each psychotropic agent compared with the comparison group. Exposure to quetiapine was not associated with an increased GDM rate. 91.4% of women taking quetiapine continued on the agent throughout pregnancy. One patient commenced quetiapine in the third trimester.

Low-dose quetiapine is typically used (off-label) to treat anxiety and sleep disorders rather than psychotic or bipolar disorders, so the authors investigated the quetiapine dose on GDM rates compared with the control group. The authors split the quetiapine sample into low dose (<300mg, n=75) and those within the therapeutic range (≥300mg, n=21) to test if GDM rates are related to quetiapine dose. Although lower-dose quetiapine was not associated with increased GDM rates compared with the control group, women taking higher-dose quetiapine were at significantly higher relative risk of having GDM (Table 28). In addition, women taking a higher dose range of quetiapine (23.8%) had a significantly greater risk of having GDM compared with women in the lower dose group (6.7%; RR 3.57, 95% CI 1.14–11.18, AR 17.1%). Throughout pregnancy, 93.1% of women continued taking lower-dose quetiapine and 85.7% continued taking higher-dose quetiapine.

Table 28: Median and interquartile range for agent dose by gestational diabetes mellitus group, and the rates, attributable risk and unadjusted relative risk estimates with 95% confidence intervals of gestational diabetes mellitus for women exposed to specific psychotropic agents compared with a no exposure group

[redacted]

Smoking, alcohol consumption and illicit drug use were not associated with elevated GDM rate in women with mental disorders.

SMI, GDM and birth outcomes

Women with bipolar disorder and GDM had babies born with significantly smaller head circumference, and those with GDM, regardless of disorder, had babies born earlier compared to those without GDM (Table 29).

Table 29: Univariate birth outcome descriptive statistics (main effects and interactions) by severe mental illnesses and GDM for the factorial multivariate analysis of variance

[redacted]

No differences were identified when the analyses were re-run to omit the 75 women whose ethnic backgrounds are associated with GDM (Aboriginal and Torres Strait Islander, Chinese, South-East Asian, Pacific Islander, Middle Eastern, South American and African).

Limitations

Lack of a standardised mental health diagnostic measure; past history of GDM and family history of either type 2 diabetes or GDM were not recorded; and ethnicity was not recorded across the whole sample. There was no control group of untreated women without a mental disorder.

Conclusions: The authors concluded that the study findings support the need for early screening (eg, 16–18 weeks rather than routine 28 weeks) and closer surveillance of metabolic risk in pregnancy for women with psychotic disorders and those taking specific atypical antipsychotic agents.

Comments

[redacted]

4.2.8 Ellfolk et al. 2020. Second-generation antipsychotics and pregnancy complications [17]

Aim/Study type: This population-based cohort study investigated whether the use of second generation antipsychotics (S-GA) during pregnancy is associated with an increased risk of pregnancy and neonatal complications.

Methods: A population-based birth cohort study using national register data extracted from the "Drugs and Pregnancy" database in Finland, years 1996–2016. The database uses data from the Medical Birth Register, the Abortion Register, The National Register of Congenital Malformations, and the Prescription Register. The sampling frame included 1,181,090 pregnant women and their singleton births. Women were categorised into groups:

- Exposed to S-GAs: purchased olanzapine, quetiapine, risperidone, aripiprazole, clozapine, ziprasidone, sertindole, or asenapine during pregnancy or 1 month before pregnancy (n=4,225)
- Continuous use of S-GAs: women who purchased S-GAs in at least 2 trimesters (n=2,135)
- Exposed to F-GAs during pregnancy but did not purchase S-GAs during the same period (2,126); however pregnancies that were only exposed to prochlorperazine were excluded (550) leaving 1,576 women in the F-GA group
- Continuous use of F-GAs: women who purchased F-GAs in at least 2 trimesters (722)
- Unexposed controls: pregnant women with no purchases of S-GAs or F-GAs during pregnancy or 1 month before pregnancy. Controls were matched for year of birth of the child (± 1 month) and were randomly selected as 5 controls for 1 exposed (n=21,125).

Pregnancy outcomes in S-GA users were compared with those in the two comparison groups using multiple logistic regression models. Covariates included maternal demographic, social and medical characteristics, and use of other drugs.

Results: The prevalence of any antipsychotic use in 1,181,090 singleton births was 0.5% during pregnancy or 30 days before it. S-GAs have basically replaced the use of F-GAs among pregnant women during the last 20 years. S-GA and F-GA users were two or three times more frequently smokers than women not using antipsychotics. Overweight was also more prevalent in S-GA users than in unexposed women (45.5% vs. 32.8%).

Pregnancy and delivery diagnoses by exposure status are shown in Table 30. Comparing S-GA users with unexposed ones, the risk was increased for GDM (adjusted odds ratio, OR 1.43; 95% CI 1.25–1.65), caesarean section (OR 1.35; 95% CI 1.18–1.53), being born large for gestational age (LGA) (OR 1.57; 95% CI 1.14–2.16), and preterm birth (OR 1.29; 95% CI 1.03–1.62). Comparing SGA users with the F-GA group, the risk of caesarean section and LGA was higher (OR 1.25, 95%CI 1.03–1.51; and OR 1.89, 95% CI 1.20–2.99, respectively).

Table 30: Pregnancy complications among S-GA users, F-GA users and unexposed mothers

Table 31: Number of pregnancies with S-GA purchases and GDM recorded during pregnancy, by drug

The risk of GDM, caesarean section, LGA and preterm birth increased further with continuous S-GA use (Table 32). Infants in the S-GA group were also more likely to suffer from neonatal complications.

Table 32: Pregnancy complications among S-GA users, F-GA users and unexposed mothers during at least 2 trimesters

[redacted]

- Missing data – only insulin-treated diabetes was recorded in MBR before 2004. Recording of glucose tolerance test and GDM diagnoses started only in 2004, as did recording of maternal height and weight for BMI. This coincides with a change in pattern of S-GA and F-GA use (F-GA prior to 2004 and S-GA from 2004) and reflects the large number (almost 60%) of missing BMI data in the F-GA group.
- Data on pre-pregnancy BMI were only available from 2004. Alcohol use is not routinely collected and could not be included in analyses.
- Drug compliance cannot be confirmed, however the authors included analyses of women purchasing S-GAs in at least 2 trimesters, suggesting compliance.
- No information the severity of maternal illness and the possibility of residual confounding by behavioural factors such as alcohol and illicit drug use.

Conclusions: Prenatal exposure to S-GAs is associated with an increased risk of pregnancy complications related to impaired glucose metabolism. Neonatal problems are common and occur similarly in S-GA and F-GA users.

Comments

[redacted]

For the risk calculations, quetiapine was grouped with other antipsychotics in this study – there was no quetiapine-specific data. There was an increased risk of GDM when SGAs were compared with unexposed controls. However, this may be due to confounding by indication.

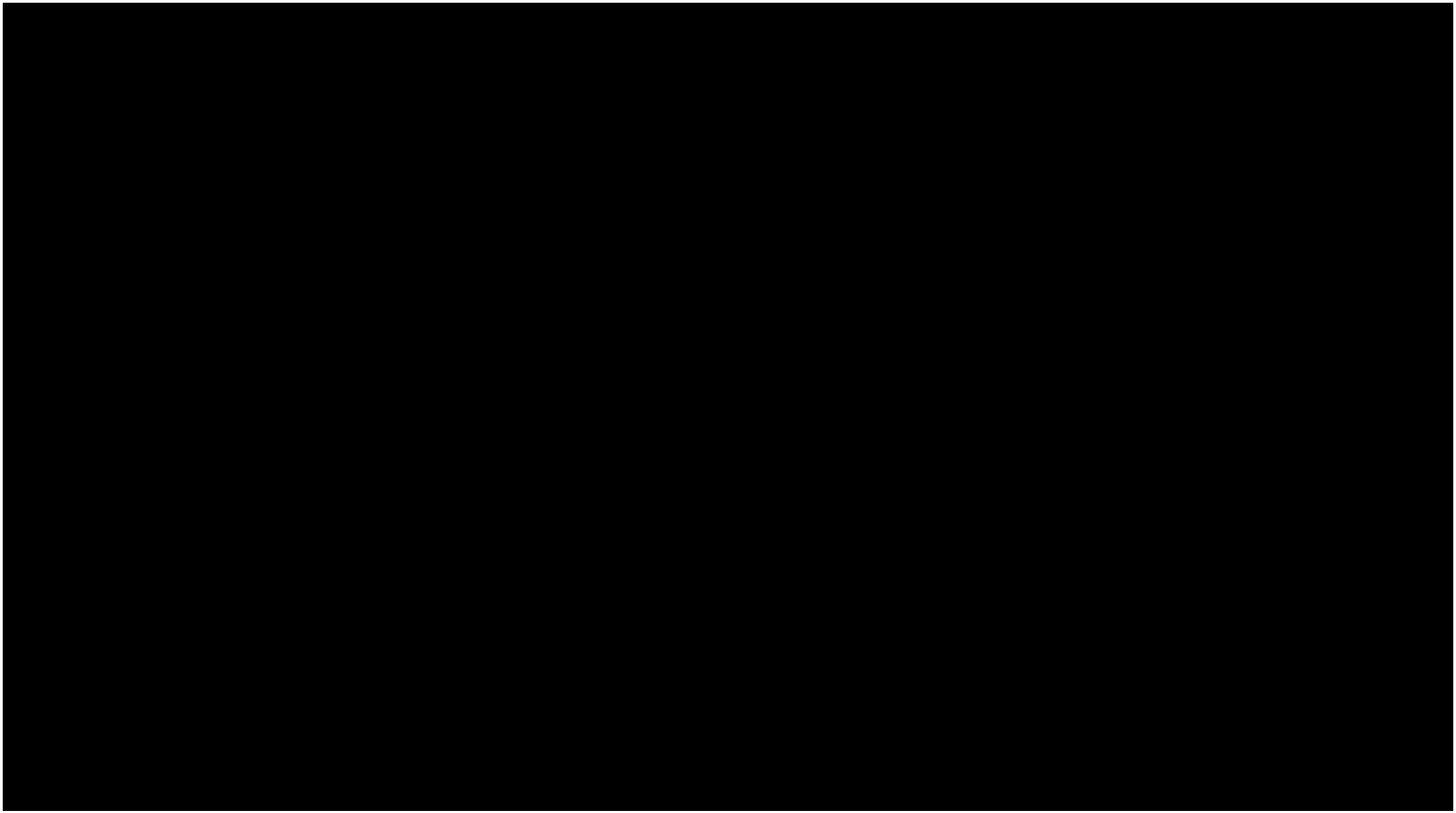
4.2.9 Kucukgoncu et al. 2020. Antipsychotic exposure in pregnancy and the risk of gestational diabetes: A systematic review and meta-analysis [30]

Aim/Study type: A systematic review and meta-analysis to assess GDM risk associated with antipsychotic exposure in pregnancy.

Methods: The authors performed a systematic literature search using PubMed, Science Direct, Scopus, and Web of Science databases up to 22 August 2018. No restrictions to language or date were applied. Randomised controlled trials, case–control or cohort studies reporting GDM risk in antipsychotic-exposed, healthy controls or antipsychotic-ceased patients were included in the meta-analysis. The primary outcomes were study-defined GDM, including number of events, odds ratios, and/or risk ratios (RR) with confidence intervals (CI). The time of antipsychotic exposure in the included studies was defined as either at least one exposure during first trimester, or at least one exposure during first or second trimester, or exposure any time during pregnancy. They examined the differences on GDM outcomes between antipsychotic-exposed and healthy controls, and antipsychotic-exposed and antipsychotic-ceased groups by calculating unadjusted and adjusted RR estimates. Statistical heterogeneity was assessed using Q and I^2 tests, in which $I^2 \geq 50\%$ was considered to indicate heterogeneity. When heterogeneity was present between studies, the antipsychotic-exposure period was examined. They performed meta-regression analyses to examine the relationship between study quality (Newcastle-Ottawa Scale; NOS), smoking and alcohol use rates, gestational age, and unadjusted GDM outcomes.

Results: Ten studies were included in the analysis: 6 were retrospective database investigations and 4 were prospective cohort investigations (Table 33). 8/10 studies compared antipsychotic-exposed group with healthy controls, 3/10 had an antipsychotic-ceased group as a control group. There were 6,213 subjects in the antipsychotic-exposed group, 6,836 in the antipsychotic-ceased control group, and 1,677,087 for the healthy control group. The authors stated that overall study quality was high, with NOS scores between 6 and 9.

Table 33: Summary of studies included in the meta-analysis



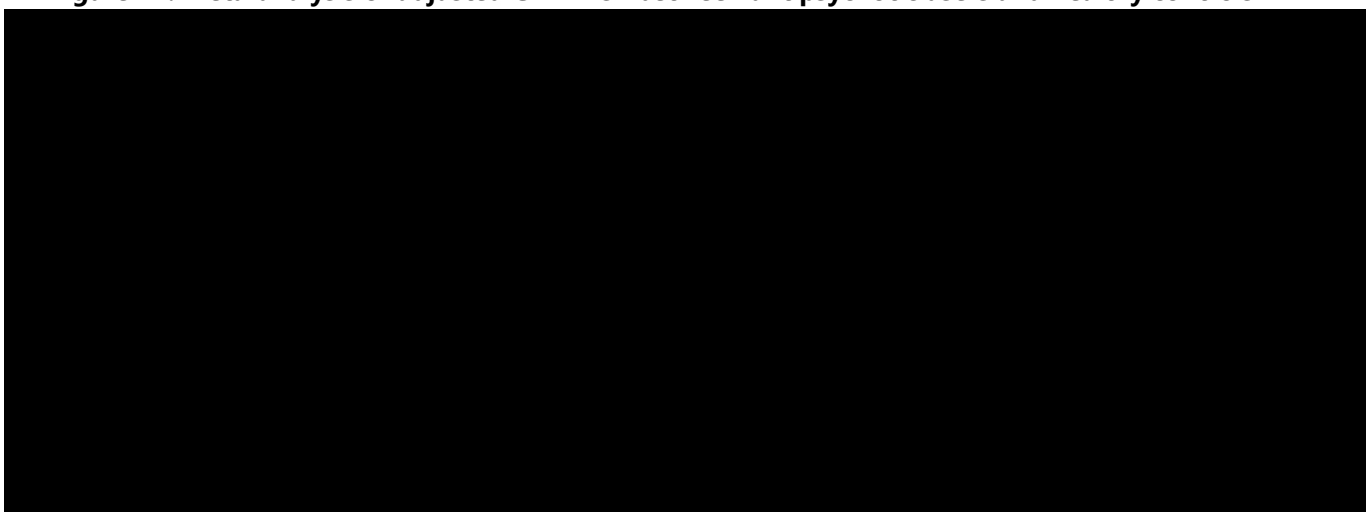
GDM in antipsychotic-exposed group versus healthy controls

In the overall meta-analysis, the crude risk for developing GDM in the antipsychotic exposure group was significantly higher than in healthy controls. Compared with the healthy controls, the unadjusted cumulative RR for GDM associated with antipsychotic use was 1.63 (95% CI = 1.20 to 2.22, P = 0.02) (Figure 16). No evidence of publication bias was found for antipsychotic-exposed and healthy control comparison (Egger's test = 0.805, CI = −1.75 to 3.36). There was significant heterogeneity on the unadjusted risk for GDM outcomes across the studies included in this analysis (I^2 = 59.64, df = 7, P = 0.01).

Figure 16: Meta-analysis of unadjusted GDM risk between antipsychotic users and healthy controls

Four studies reported adjusted differences between antipsychotic-exposed individuals and healthy controls (Figure 17). The adjusted risk for GDM was significantly higher in the antipsychotic-exposed group than in healthy controls (estimated RR = 1.30, 95% CI = 1.023–1.660, P=0.032). There was no significant heterogeneity in RRs across 3 studies (I^2 = 14.37, df =3, P=0.32).

Figure 17: Meta-analysis of adjusted GDM risk between antipsychotic users and healthy controls



Six studies reported outcomes from patients who had been exposed to antipsychotics during early pregnancy (at least once in the first and/ or second trimester). The antipsychotic-exposure period in the remaining 2 studies was specified as anytime during pregnancy. Compared with the healthy controls, the unadjusted RR estimate for GDM in patients with early antipsychotic exposure (estimated RR = 1.42, 95% CI = 1.07 to 1.89, P = .015) and anytime antipsychotic exposure (estimated RR = 2.533, 95% CI = 1.73 to 3.71, P < .001) was significantly higher (Figure 18). There was no significant heterogeneity in RR estimates of GDM risk in early antipsychotic exposure and anytime antipsychotic-exposure groups.

Figure 18: Random effects model of RR estimates of GDM risk

GDM in antipsychotic-exposed group versus antipsychotic-ceased group

The unadjusted RR estimate for GDM was significantly higher in the antipsychotic-exposed group compared with the antipsychotic-ceased group (estimated RR = 1.55, 95% CI = 1.187 to 2.034, P = .001) (Figure 19).

Figure 19: Meta-analysis of unadjusted GDM risk between antipsychotic exposed and ceased groups

Only 2 studies reported adjusted risk of GDM in the antipsychotic-exposed group and the antipsychotic-ceased patients (Figure 20). The adjusted RR estimate for GDM was similar between the antipsychotic exposed group and the antipsychotic-ceased group (estimated RR = 0.78, 95% CI = 0.28 to 2.16, P = .633). Significant heterogeneity was detected on RRs across outcomes (I_2 = 85.43, df = 1, P = .009).

Figure 20: Meta-analysis of adjusted risk of GDM between antipsychotic exposed and ceased groups

Meta-regression

In meta-regression analyses, no significant association was found between study quality (measured with NOS), smoking and alcohol use rates, gestational age, and cumulative crude GDM risk.

Limitations: Significant heterogeneity across studies evaluating the unadjusted risk of GDM between antipsychotic-exposed and healthy pregnant women. Lack of antipsychotic-specific data. Limited information on concurrent medications that may independently increase the risk of GDM. Diversity of psychiatric diagnoses, and comorbid illnesses may increase the risk of GDM. The meta-analysis only included a small number of studies, some with small sample sizes. The unadjusted RR reported in the meta-analysis may reflect effects of other confounding variables on GDM.

Conclusions: The results indicate an increased risk of GDM with antipsychotic exposure in pregnant women, who may benefit from close pregnancy monitoring, early testing for GDM (during first trimester rather than between 24 and 28 weeks), targeting modifiable risk factors, and lifestyle modifications.

Comments

The authors stated that the overall quality of the studies was high (using the Newcastle-Ottawa Scale). Some of these studies were also reviewed by Uguz – for which he identified significant methodological limitations. Very few of the studies were specific for quetiapine. Only 2 studies reported an adjusted risk in continuers versus discontinuers.

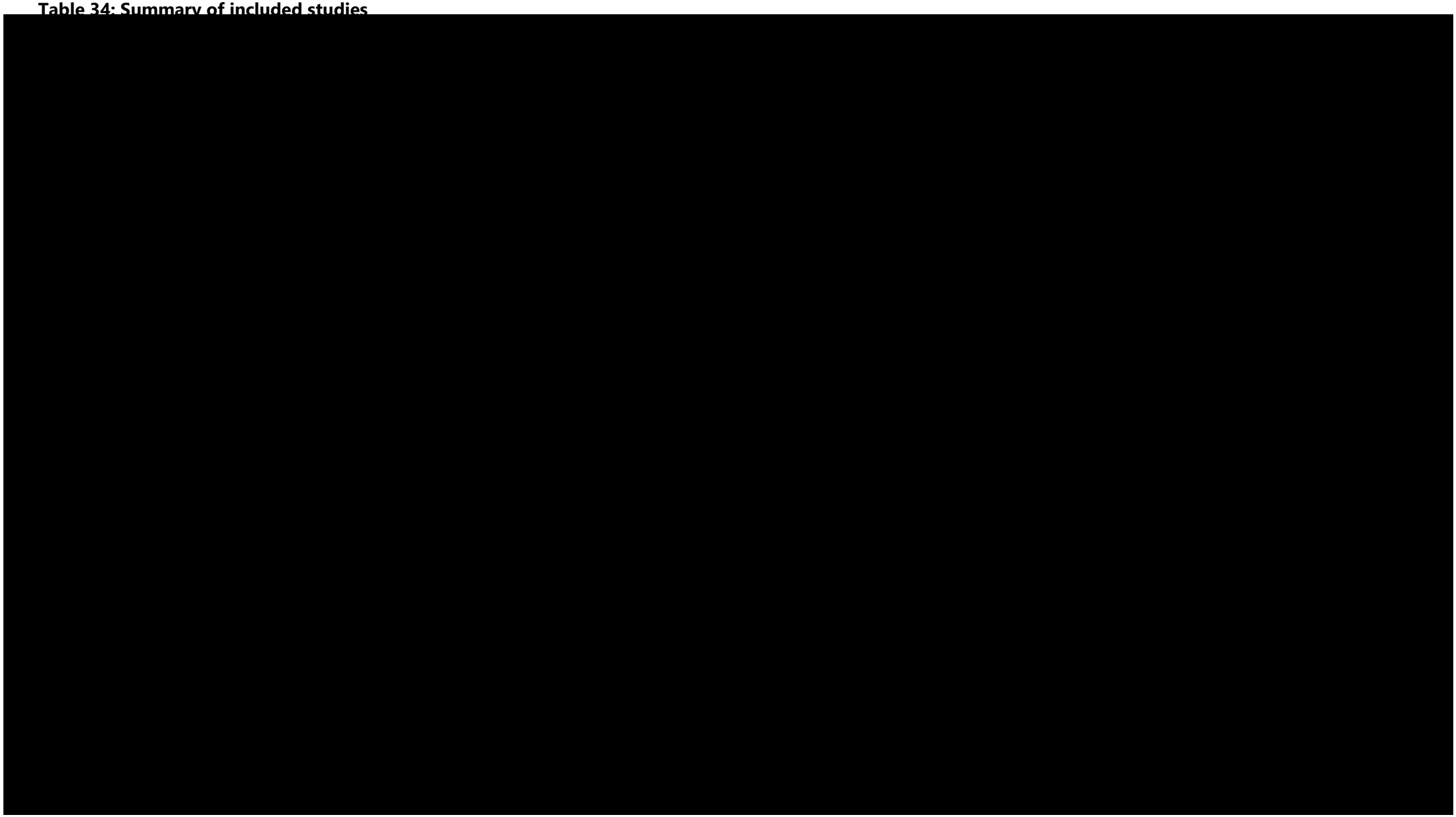
4.2.10 Wang et al. 2021a. The use of antipsychotic agents during pregnancy and the risk of gestational diabetes mellitus: a systematic review and meta-analysis [31]

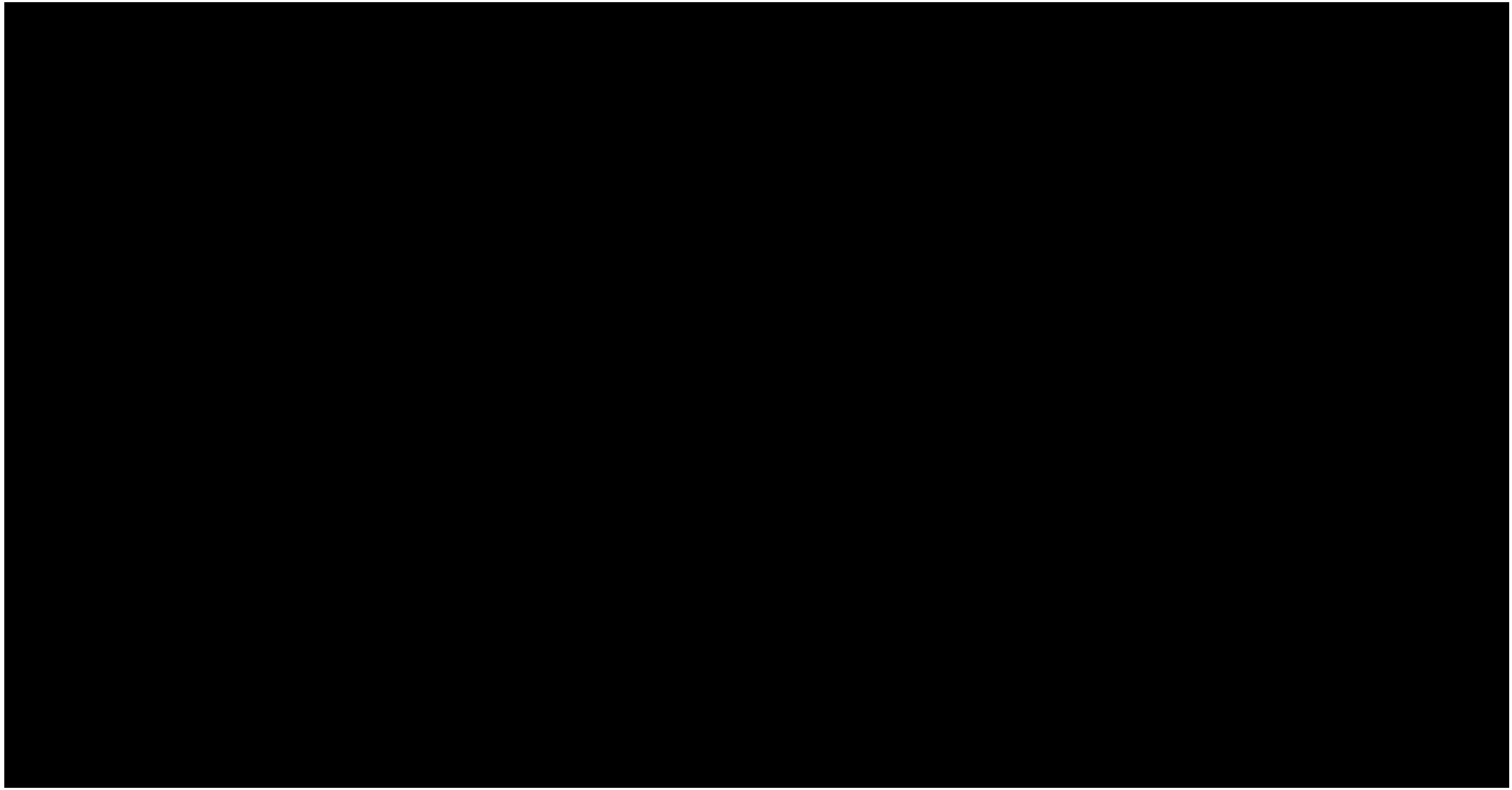
Aim/Study type: Systematic review and meta-analysis to evaluate the association between antipsychotic use in pregnancy and GDM.

Methods: The authors conducted a systematic literature search in PubMed, EMBASE, PsycINFO and Cochrane Library databases up to March 2019, for data from observational studies assessing the association between gestational antipsychotic use and GDM. Articles that met the following criteria were included in this review: (1) cohort or case-control design; (2) reported the association between gestational antipsychotic use and the risk of GDM; and (3) published in the English language. Other study types, including animal studies, case reports, conference abstracts, book chapters, reviews and summaries or articles written in other languages were excluded. The primary outcome was GDM. The Newcastle-Ottawa Scale (NOS) was used to assess the methodological quality of observational studies. Separate NOS criteria were used for case-control and cohort studies. Estimates were pooled using a random effect model, with the I^2 statistic used to estimate heterogeneity of results.

Results: 10 studies met the systematic review inclusion criteria (Table 34) with 6,642 exposed and 1,860,290 unexposed pregnancies.

Table 34: Summary of included studies





Of the 10 studies:

- 4 were prospective cohort and 6 were retrospective cohort studies
- 5 were administrative database or registry studies, 4 used ad hoc disease registries, 1 used an ad hoc clinical sample
- exposure data was collected via prescription data, questionnaires, interviews, or medical staff
- 5 studies evaluated any antipsychotic exposure in mothers, 5 focussed on second generation antipsychotics only, 3 reported on specific drugs
- 2 studies reported the impact of dosage on the risk of GDM
- 6 studies dealt with confounding by multivariable adjustments in the regression model, restriction in the control group selection or with propensity score methods
- 4 studies used further control groups to address confounding by indication, of which 3 addressed maternal psychiatric diagnosis as a confounding factor
- all ascertained GDM in either a database, a physician's diagnosis report or by structured questionnaire and selected adequate follow-up time for their outcome of interest.

Six studies were considered of good quality according to the NOS assessment and were included in the meta-analysis. The pooled adjusted relative risk was 1.24 overall [95% CI: 1.09–1.42] (Figure 21). The I^2 result suggested low heterogeneity between studies (I^2 = 6.7%, p = 0.373). For the 4 studies focussing on any antipsychotic exposure (FGAs+SGAs), the pooled adjusted RR was 1.30 (95% CI: 1.06–1.60). For the 2 SGA studies, the pooled RR was 1.12 (95% CI: 0.79–1.60).

Figure 21: Forest plot of the meta-analysis for gestational diabetes mellitus

Limitations: Methodological differences in study designs, the selection of the exposure and control groups, duration of follow-up, exposure and outcome definitions, may influence the accuracy of the risk estimates. Studies using administrative databases/registries may be more representative of the general population but may not comprehensively cover all potential confounders such as diet, alcohol and tobacco use. Antipsychotics are often prescribed by specialist care providers rather than primary care providers, and most administrative databases/ registries do not contain specialist information which may cause underestimation of

exposure duration or overall exposure episodes. Disease registries are prone to selection bias and have no untreated control group, which may affect the actual drug effect. Poor antipsychotic adherence among patients with schizophrenia is common and the authors recommend to only include women who are in receipt of at least two prescriptions or with continuous usage for a set period of time.

Conclusion: The authors concluded that the use of antipsychotic medications during pregnancy is associated with an increased risk of GDM in mothers. However, the evidence is still insufficient, especially for specific drug classes. They recommended more studies to investigate this association for specific drug classes, dosages and comorbidities to help clinicians to manage the risk of GDM if initiation or continuation of antipsychotic prescriptions during pregnancy is needed.

Comments

The adjusted risk of GDM in users of FGA + SGA compared to nonusers (RR = 1.30, 95% CI: 1.06–1.60; p = 0.336; Figure 21) is very similar to that calculated by Kucukgoncu, using the same four studies (RR = 1.30, 95% CI = 1.023–1.660, p=0.032, Figure 17).

4.2.11 Wang et al. 2021b. Association between antipsychotic use in pregnancy and the risk of gestational diabetes: population-based cohort studies from the United Kingdom and Hong Kong and an updated meta-analysis [32]

Aim/Study type: Two retrospective population-based cohort studies in the United Kingdom and Hong Kong investigating whether exposure to antipsychotic medications during pregnancy is associated with gestational diabetes mellitus.

Methods: Data was extracted from the UK The Health Improvement Network (THIN) and HK Clinical Data Analysis and Reporting System (CDARS). The study population was the entire pregnancy population of THIN and CDARS aged between 15 and 50 years old from 1 Jan 1990 to 9 Jan 2017 in THIN and 1 Jan 2001 to 31 Dec 2015 in CDARS.

Nondiabetic women who received any type of antipsychotic medicine before their first pregnancy were included in the cohorts. The exposed group (continuers) included women who continued using antipsychotics from the start of pregnancy to delivery, while the comparison group (discontinuers) included women who were prescribed antipsychotics before the start of pregnancy but stopped during pregnancy. Exclusions: pregnancies ending in miscarriage or abortion, women with pre-existing diabetes before pregnancy or who had been prescribed teratogenic medicines during pregnancy. GDM was identified using GDM diagnosis and/or clinician-reported GDM.

Calculated odds ratios to assess the association between antipsychotic use during pregnancy and GDM. Used propensity score fine-stratification weighting to adjust for potential confounding factors. Conducted subgroup analyses for users of first generation antipsychotics (FGAs) and second generation antipsychotics (SGAs) and for different periods (trimester) of exposure. Covariates in both databases were maternal age and calendar year at the start of pregnancy, maternal underlying medical conditions, time from the first prescription of any antipsychotics to start date of study and use of other psychotropic drugs. Additionally, the THIN database also included BMI, smoking status, alcohol consumption status and family history of diabetes. CDARS included household income status.

The authors also did a post hoc meta-analysis to synthesise the results of THIN and CDARS and also added them to their previous meta-analysis (Wang et al, 2021a [31]– described in section 4.2.10 above)

Results: 3,114 women with registered first pregnancies (2,351 in THIN and 763 in CDARS) were included. In both populations, continuers were more often diagnosed with underlying medical conditions compared to discontinuers. Also, continuers were more likely to have a BMI of over 30 kg/m2 (21.83% vs 15.85%) and more likely to be prescribed antidepressants (THIN: 53.88% vs 30.82%; CDARS: 30.73% vs 15.00%, respectively) and lithium (THIN: 2.33% vs 0.57%; CDARS: 2.60% vs 0, respectively). Most of included women (58.41 %) had their

first prescription more than two years before pregnancy and were registered as current smoker (50.74%) and/or drinker (57.64%).

In total, 171 women (5.49%; 2.55% in THIN and 14.55% in CDARS) were diagnosed with GDM in both databases. Of these 171 women with GDM, 91 (53.22%) had received continued treatment with antipsychotics into pregnancy.

For continuers, the incidence of GDM was 16.78% (n=71) in CDARS and 2.58% (n=20) in THIN (Table 35). The crude OR of antipsychotic use during pregnancy and GDM was 1.02 (95% CI: 0.60-1.76) in THIN and 1.51 (95% CI: 0.99-2.30) in CDARS when continuers were compared with discontinuers. The adjusted OR of GDM in continuers was 0.73 (95% CI: 0.43-1.25) in THIN and 1.16 (95% CI: 0.78-1.73) in CDARS compared with discontinuers, and showed no evidence of an association between continued use of antipsychotic medication during pregnancy and the onset of GDM.

349 mothers in THIN were continually prescribed SGAs in pregnancy of whom 14 (4.01%) were diagnosed with GDM, while 149 women received SGAs only of whom 22 (14.77%) developed GDM in CDARS (Table 35). There was no evidence that SGAs were associated with an increased risk of GDM (THIN: SGAs: aOR: 0.98, 95% CI: 0.51-1.88; CDARS: SGAs: aOR: 1.04, 95% CI: 0.58-1.85).

Table 35: Results from analysis comparing continuers with discontinuers

[redacted]

The most commonly used antipsychotic agents in THIN were quetiapine (n=571), chlorpromazine (n=450) and olanzapine (n=450), while haloperidol (n=443), risperidone (n=353) and trifluoperazine (n=317) were the most common in CDARS. Numbers of GDM in each specific drug exposure were very limited and no statistically significant association was found in either THIN or CDARS. There was no evidence of an association between antipsychotic exposure and GDM by stratifying trimesters in both populations.

When the results were combined together in a meta-analysis, there was no statistically significant association between prenatal continued exposure to antipsychotics and the risk of GDM (aOR: 0.95, 95% CI: 0.61-1.49, I2=46.2%, p=0.173) (Figure 22). Additionally, there was no evidence for an increased or a decreased risk of GDM in women who had continued treatment with FGAs or SGAs only during pregnancy (FGAs: aOR: 0.95, 95% CI: 0.52-1.75, I2=28.9%, p=0.236; SGAs: aOR: 1.01, 95% CI: 0.66-1.56, I2=0.0%, p=0.894).

Figure 22: Forest plots of fully adjusted results from analysis for continuers compared with discontinuers

There was no evidence of a change in risk of GDM and prenatal exposure to haloperidol, quetiapine, chlorpromazine, or olanzapine (Figure 23).

Figure 23: Forest plots of fully adjusted results from analysis for individual antipsychotics

Adjusted results showed no statistically significant association between prenatal antipsychotic exposure in any trimester and the risk of GDM.

When added to the previous meta-analysis using a random effects model (Wang et al 2021a [31], the pooled RR reduced from 1.24 (95% CI: 1.09-1.42) to 1.19 (95% CI: 1.02-1.37; I^2 = 22.4%) for any antipsychotic prescriptions (Figure 24). The pooled RR of studies comparing continuers to discontinuers was 1.11 (95% CI: 0.91-1.35, I^2=21.6%) (Figure 25).

Figure 24: Forest plots for updated meta-analysis, any antipsychotics

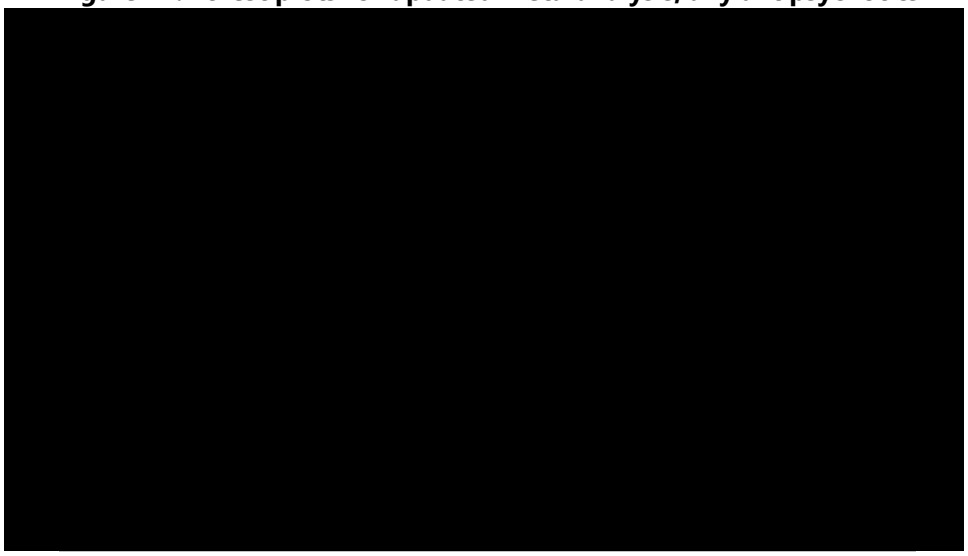


Figure 25: Forest plots for updated meta-analysis, particularly compared continuers with discontinuers

Limitations: Using administrative databases may have led to underestimation of exposure, as antipsychotics are often initially prescribed by specialist care providers rather than primary care providers. The overall sample size was small. Data in the THIN and CDARS databases are not collected for research purposes so does not collect potential confounding factors. There may be non-differential misclassification of undiagnosed or wrongfully diagnosed GDM as different diagnostic criteria for GDM have been used over time. Decisions to continue or discontinue medication during pregnancy may depend on other risk factors, and continuers and discontinuers may receive different metabolic monitoring and prenatal care during pregnancy, leading to bias.

Conclusions: The authors concluded that their results do not suggest an increased risk of GDM in women who continued using antipsychotics during pregnancy compared to women who stopped. Based on these results, women should not stop their regular antipsychotics prescriptions in pregnancy due to the fear of GDM.

Comments

The authors found no association between GDM and antipsychotics in the studied populations. When the results were added to their previous meta-analysis, the RR was lowered. Note that the CDARS data is for pregnant women in Hong Kong, who may differ from pregnant women in the UK-based THIN data set and pregnant women in New Zealand.

4.2.12 Heinonen et al. 2022. Antipsychotic use during pregnancy and risk for gestational diabetes: A national register-based cohort study in Sweden [33]

Aim/Study type: Register-based cohort study that aimed to determine whether antipsychotic use during pregnancy is associated with GDM.

Methods: Linked data from the Medical Birth Register and the Prescribed Drug Register including all 1,307,487 singleton births between July 2006 and December 2017. Pregnancies with pre-pregnancy diabetes and women using valproic acid were excluded. Antipsychotics were divided into first-generation antipsychotics (n = 728), high-risk metabolic second-generation antipsychotics including olanzapine, clozapine and quetiapine (n = 1710), and other second-generation antipsychotics (n = 541). Medicine exposure was allocated into any use (dispensed at any time during pregnancy including 1 month before pregnancy), late use (dispensed during the last 90 days of pregnancy with or without earlier dispensing), and early use only (dispensed 1 month before and during pregnancy but not during the last 90 days). The risks for gestational diabetes, fetal growth disturbances, pre-eclampsia, caesarean section and preterm labour were assessed. Women treated during pregnancy were compared to women not treated during pregnancy and to women who used antipsychotics before/after but not during pregnancy. Risk ratios were calculated using modified Poisson regression in multivariate regression models. Adjustments were made for maternal factors (age, parity, smoking, BMI).

Results: There were 2677 individual pregnancies during which the women were treated with an antipsychotic. In 302 pregnancies, the women were treated with more than one category of antipsychotics.

The crude risk ratio for gestational diabetes for women treated with high-risk metabolic second-generation antipsychotics during pregnancy was 2.2 (95% confidence interval [CI] 1.6–2.9) compared to untreated pregnant women (n = 1,296,539) and 1.8 (95% CI 1.4–2.5) compared to women treated before/after pregnancy (n = 34,492) (Table 36). After adjustment for maternal factors, including body mass index, the risk ratios were 1.8 (95% CI 1.3–2.4) and 1.6 (95% CI 1.2–2.1).

Table 36: Risk ratios for GDM and disturbances in fetal growth after treatment with F-GAs, the high metabolic risk S-GAs (olanzapine, clozapine and quetiapine), and other S-GAs (risperidone, aripiprazole, sertrindole, paliperidone, ziprasidone)

[redacted]

Exposed infants had an increased risk of being large for gestational age: adjusted risk ratios 1.6 (95% CI 1.3–1.9) and 1.3 (95% CI 1.1–1.6) compared to no maternal antipsychotic use during pregnancy and maternal use before/after the pregnancy (Table 37). Other antipsychotics were not associated with metabolic risks.

Table 37: Frequencies of GDM and fetal growth disturbances after treatment with F-GAs, high-risk S-GAs and other S-GAs

[redacted]

Limitations: Register-based study using prescription data cannot confirm actual medicine intake, and excludes medicines prescribed in hospital. Likewise, there was no access to information on duration of treatment or dose. Confounding by indication and disease severity.

Conclusions: Olanzapine, clozapine and quetiapine used during pregnancy were associated with increased risks for gestational diabetes and the infant being large for gestational age. The authors recommend screening for GDM in women treated with quetiapine, olanzapine or clozapine, but not discontinuation of treatment. In the case of starting a new antipsychotic treatment in pregnancy or, preferably, before a planned pregnancy, some other antipsychotic might be considered to avoid these metabolic risks.

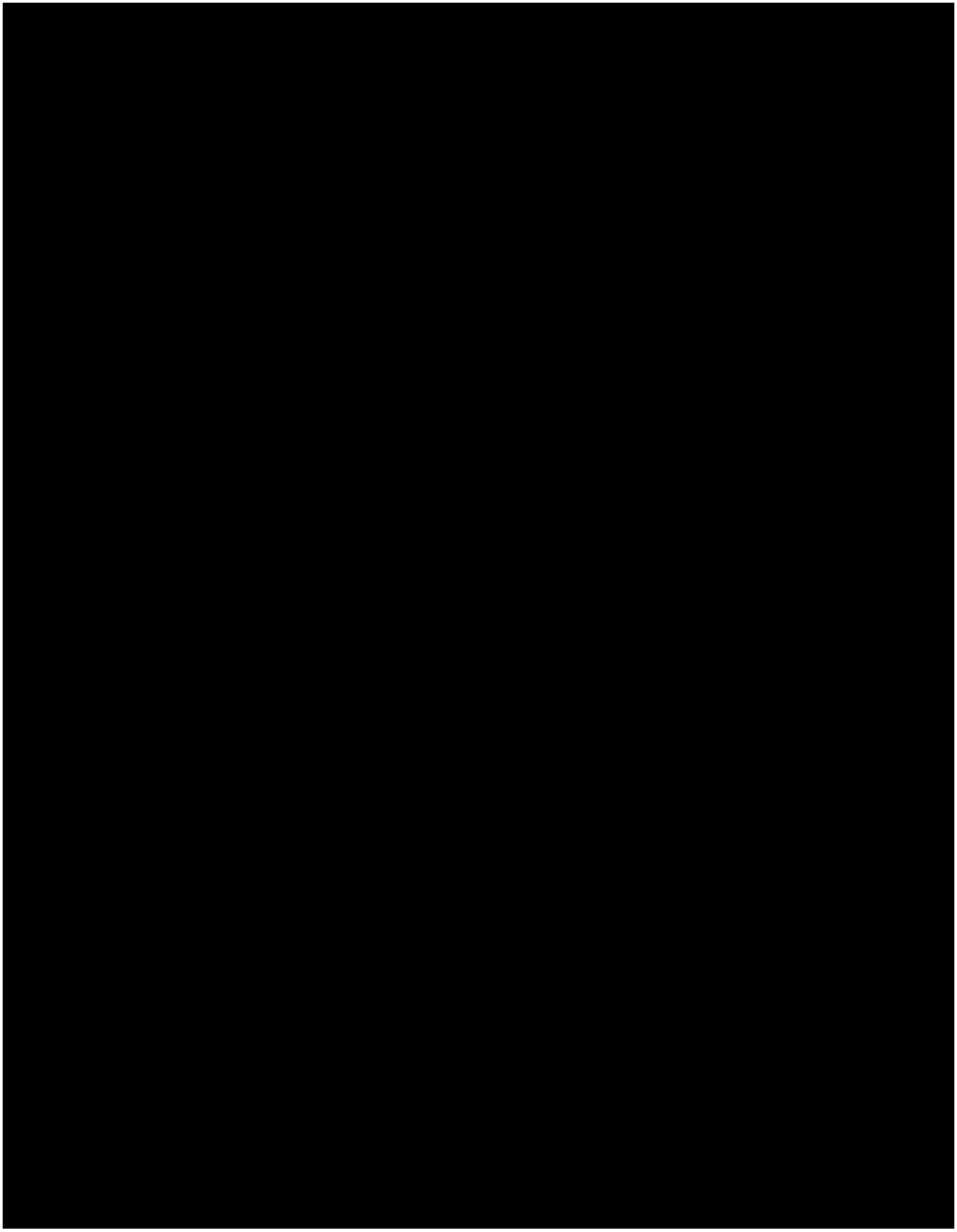
Comments

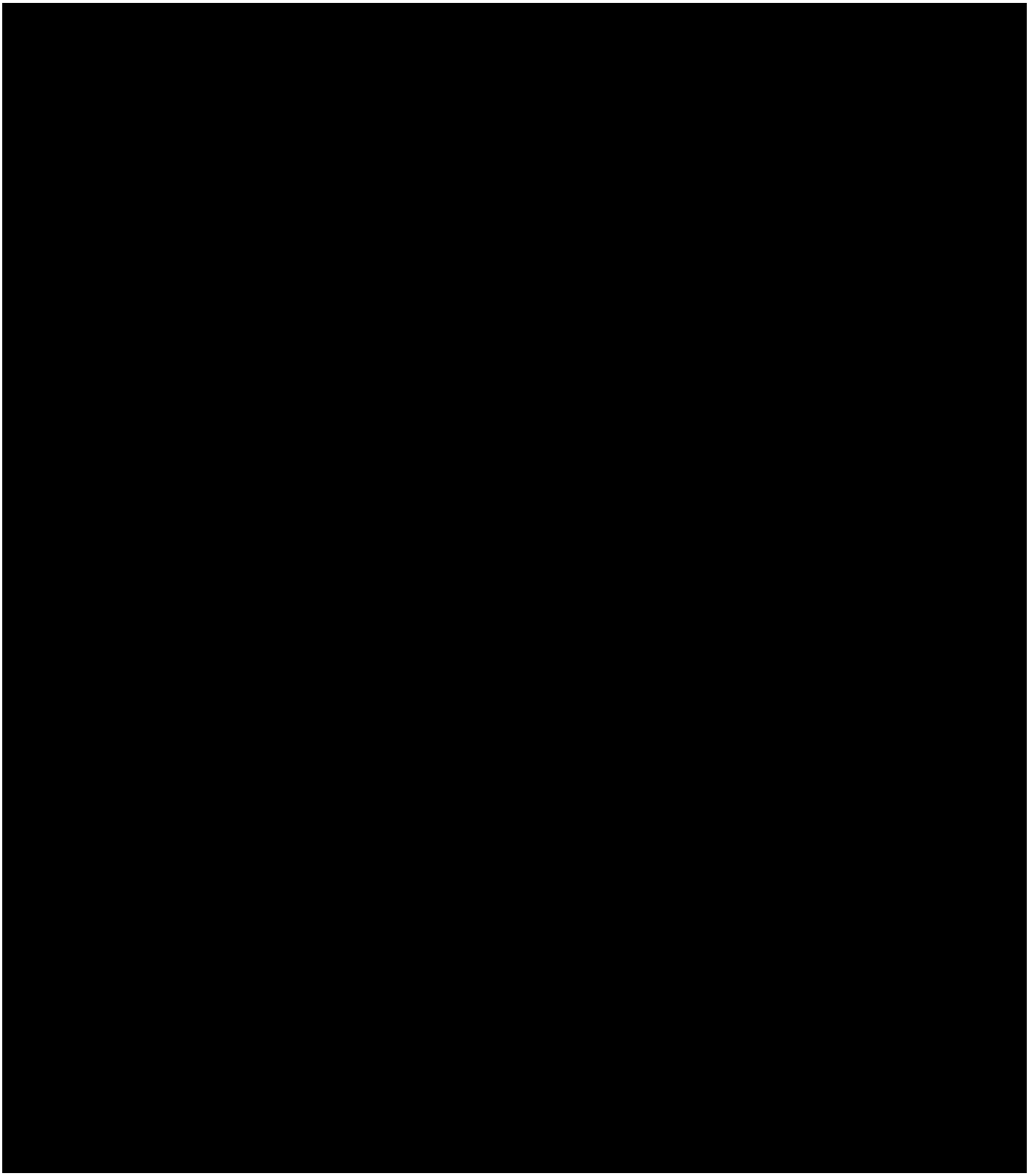
This study grouped quetiapine with olanzapine and clozapine. There were no quetiapine-only calculations.

Note that the olanzapine and clozapine data sheets contain warnings about hyperglycaemia and diabetes mellitus, including recommendations for monitoring.

4.3 Company information

[redacted]





4.4 Case reports

4.4.1 New Zealand

Up to 31 March 2022 there have been 189 reports to CARM with quetiapine as the suspect medicine. Of these 189 reports, there was 1 report of diabetes mellitus and 1 of hyperglycaemia – see Table 38. Neither were reported as serious. There were no reports of GDM.

Table 38: CARM reports of diabetes and hyperglycaemia

CARM ID Reported	Gender Age	Medicines:	Reported terms	
080345 Aug 2008	Female 58 years	**Quetiapine:**	Hyperglycaemia Brand switch Sleep disturbed	
080917 Sep 2008	Female 43 years	**Quetiapine:** Ziprasidone: Venlafaxine:	Diabetes mellitus Hepatic enzymes increased Weight increase	

Note: Suspect medicines are in bold.

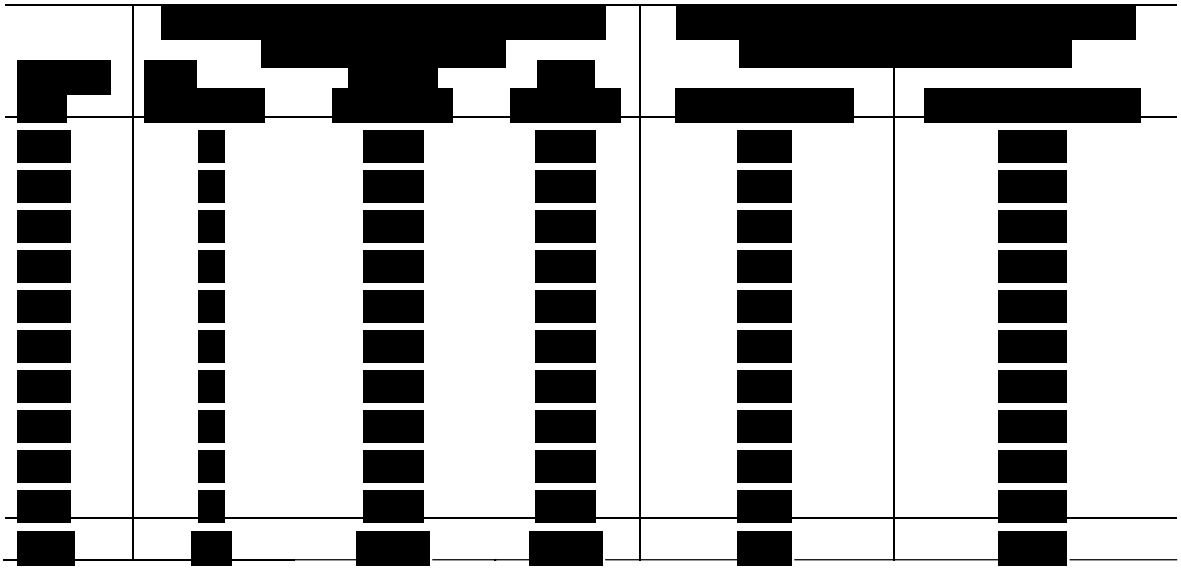
4.4.2 International

4.5 GDM and quetiapine: National Collections data

- [redacted]

[redacted]

[redacted]



[redacted]

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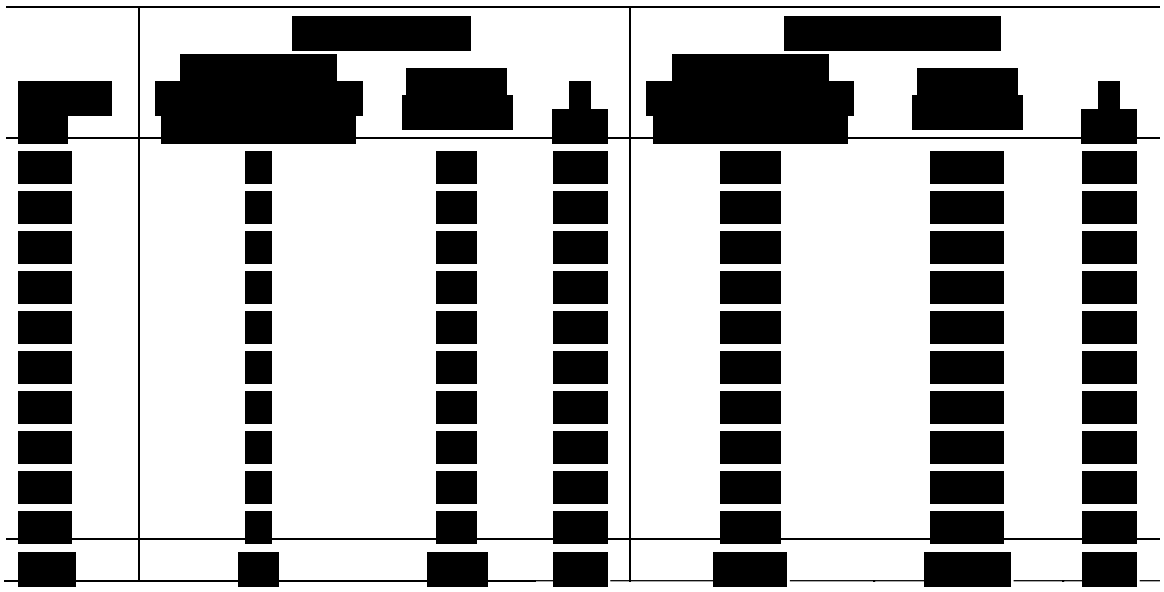

[redacted]

5 DISCUSSION AND CONCLUSIONS

Gestational diabetes mellitus (GDM) is defined as carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy. Many risk factors for GDM are similar to those for type 2 diabetes, including older age, non-white race and obesity. NZ screening guidelines state that long-term use of antipsychotic medicines is also risk factor for GDM.

GDM can lead to adverse pregnancy outcomes such as preeclampsia, caesarean delivery, neonatal hypoglycaemia and macrosomia. Patients with GDM are at high risk of developing type 2 diabetes later in life. The prevalence of GDM is increasing in New Zealand and worldwide.

There is universal screening for GDM in New Zealand. During early pregnancy (< 20 weeks), HbA1c levels will identify women with probable undiagnosed diabetes or prediabetes. All pregnant women without diabetes are offered glucose testing at 24–28 weeks' gestation to determine whether they have GDM.

Quetiapine is a second generation antipsychotic, indicated for schizophrenia and bipolar disorder. Quetiapine use in New Zealand is increasing, both in the general population and during pregnancy. There is also evidence of off-label prescribing.

Quetiapine is associated with metabolic side effects including weight gain and diabetes mellitus. These metabolic effects are known to occur in the general population, but how this relates to pregnant women is not fully understood, especially because pregnant women are already predisposed to insulin resistance. Clinical guidelines recommend routine metabolic monitoring of patients taking antipsychotics. However, there is evidence that these guidelines are not routinely followed.

The prescribing information for quetiapine in New Zealand and internationally recommends monitoring for hyperglycaemia and diabetes mellitus during treatment. However there is no information regarding GDM or monitoring during pregnancy.

There are inconsistent results in the literature as to whether quetiapine is associated with GDM. Many of the studies are small, with significant limitations. Larger, register-based studies may cover more of the population but generally are not able to cover all potential confounders such as alcohol use, diet and smoking. Also, antipsychotics are often prescribed by secondary care providers and most administrative databases/registries do not capture secondary care information. This may underestimate exposure duration or overall exposure. Quetiapine is often grouped in with other antipsychotics in these studies. Most studies compared women who were prescribed antipsychotics during pregnancy with those who were not (eg, women without mental health considerations). This is likely to have resulted in confounding by indication, as women using antipsychotics tend to smoke more frequently, have a higher pre-pregnancy BMI and have lower socioeconomic status than non-users – all of which are risk factors for GDM.

There are no NZ adverse event case reports of GDM in association with quetiapine. [redacted]

6 ADVICE SOUGHT

The Committee is asked to advise:

- whether there is evidence for an association between quetiapine and gestational diabetes mellitus
- if there is evidence for an association, is the information in the quetiapine data sheet sufficient to mitigate this risk or is further regulatory activity is required
- whether any communication is required, other than MARC's Remarks in *Prescriber Update*?

7 ANNEXES

- Annex 1: International prescribing information for quetiapine
- [redacted]

8 REFERENCES

[1] Gentile S. 2014. Pregnancy exposure to second generation antipsychotics and the risk of gestational diabetes. *Expert Opinion on Drug Safety* 13(12): 1583-90. DOI: 10.1517/14740338.2014.931368 (accessed 14 March 2022).

[2] Kulkarni J, Storch A, Baraniuk A, et al. 2015. Antipsychotic use in pregnancy. *Expert Opinion on Pharmacotherapy* 16(9): 1335-45. DOI: 10.1517/14656566.2015.1041501 (accessed 14 March 2022).

[3] Galletly C, Castle D, Dark F, et al. 2016. Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for the management of schizophrenia and related disorders. *Australian and New Zealand Journal of Psychiatry* 50(5): 1-117. URL: https://www.ranzcp.org/files/resources/college_statements/clinician/cpg/schizophrenia-disorders-cpg.aspx(accessed 17 March 2022).

[4] Suppes T. 2022. Bipolar disorder in adults: clinical features. In: *UpToDate* 11 April 2022. URL: https://www.uptodate.com/contents/bipolar-disorder-in-adults-clinical-features (accessed 11 August 2022).

[5] Stovall J. 2021. Bipolar disorder in adults: epidemiology and pathogenesis. In: *UpToDate* 9 August 2021. URL: https://www.uptodate.com/contents/bipolar-disorder-in-adults-epidemiology-and-pathogenesis (accessed 11 August 2022)..

[6] Malhi GS, Bell E, Bassett D, et al. 2021. The 2020 Royal Australian and New Zealand College of Psychiatrists clinical practice guidelines for mood disorders. *Australian and New Zealand Journal of Psychiatry* 55(1): 7-117. URL: https://www.ranzcp.org/files/resources/college_statements/clinician/cpg/mood-disorders-cpg-2020.aspx (accessed 17 March 2022).

[7] Staveley A, Soosay I and O'Brien AJ. 2017. Metabolic monitoring in New Zealand district health board mental health services. *New Zealand Medical Journal* 130(1465): 44-52. URL: https://journal.nzma.org.nz/journal-articles/metabolic-monitoring-in-new-zealand-district-health-board-mental-health-services (accessed 17 March 2022).

[8] Chisolm MS and Payne JL. 2016. Managment of psychotropic drugs during pregnancy. *BMJ* 532(Jan 20): h5918. DOI: 10.1136/bmj.h5918 (accessed 30 June 2022).

[9] Hohmann-Marriott B. 2018. Unplanned pregnancies in New Zealand. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 58(2): 247–50. DOI: 10.1111/ajo.12732 (accessed 1 August 2022).

[10] bpac NZ. 2007. Monitoring for metabolic disorders. *Best Practice Journal* Issue 3: 28-31. URL: https://bpac.org.nz/magazine/2007/february/antipsychotics.asp(accessed 1 August 2022).

[11] bpac NZ. 2013. Correspondence: Metabolic monitoring with antipsychotics. *Best Practice Journal* 51: 44-5. URL: https://bpac.org.nz/BPJ/2013/March/correspondence.aspx#2.

[12] New Zealand Formulary (NZF). 2022. *NZF v122: Antipsychotic drugs* 1 August 2022. URL: https://nzf.org.nz/nzf_2098 (accessed 14 August 2022).

[13] Keenan R, Chepulis L, Ly J, et al. 2020. Metabolic screening in primary care for patients with schizophrenia or schizoaffective disorder and taking antipsychotic medication. *Journal of Primary Health Care* 12(1): 29034. DOI: https://doi.org/10.1071/HC19023 (accessed 17 March 2022).

[14] Huthwaite M, Tucker M, McBain L, et al. 2018. Off label or on trend: a review of the use of quetiapine in New Zealand. *New Zealand Medical Journal* 131(1474): 45-50. URL: https://journal.nzma.org.nz/journal-articles/off-label-or-on-trend-a-review-of-the-use-of-quetiapine-in-new-zealand (accessed 17 March 2022).

[15] Park Y, Hernandez S, Bateman B, et al. 2018. Continuation of atypical antipsychotic medication during early pregnancy and the risk of gestational diabetes. *American Journal of Psychiatry* 175(6): 564-74. DOI: 10.1176/appi.ajp.2018.17040393 (accessed 14 March 2022).
[16] Chen J, Huan X-F, Shao R, et al. 2017. Molecular mechanisms of anti-psychotic drug-induced diabetes. *Frontiers in Neuroscience* 11: 643. DOI: https://doi.org/10.3389/fnins.2017.00643 (accessed 12 August 2022).
[17] Ellfolk M, Leinonen M, Gissler M, et al. 2020. Second-generation antipsychotics and pregnancy complications. *European Journal of Clinical Pharmacology* 76(1): 107-115. DOI: 10.1007/s00228-019-02769-z (accessed 14 March 2022).
[18] Durnwald C. 2021. Gestational diabetes mellitus: Screening, diagnosis, and prevention. In: *UpToDate* 30 November 2021. URL: https://www.uptodate.com/contents/gestational-diabetes-mellitus-screening-diagnosis-and-prevention (accessed 23 February 2022).
[19] Lawrence R, Wall C and Bloomfield F. 2019. Prevalence of gestational diabetes according to commonly used data sources: An observational study. *BMC Pregnancy and Childbirth* 19(349): 1-9. DOI: https://doi.org/10.1186/s12884-019-2521-2 (accessed 23 February 2022).
[20] Ministry of Health. 2014. *Screening, Diagnosis, and Management of Gestational Diabetes in New Zealand: A Clinical Practice Guideline*. URL: https://www.health.govt.nz/system/files/documents/publications/screening-diagnosis-management-of-gestational-diabetes-in-nz-clinical-practive-guideline-dec14-v2.pdf (accessed 23 February 2022).
[21] bpac NZ. 2015. Monitoring diabetes before, during and after pregnancy. *Best Tests* July(2015): 1-11. URL: https://bpac.org.nz/BT/2015/July/diabetes.aspx(accessed 23 February 2022).
[22] AstraZeneca Limited. 2021. *Seroquel New Zealand Data Sheet* 12 April 2021. URL: https://www.medsafe.govt.nz/profs/Datasheet/s/seroqueltab.pdf (accessed 22 February 2022).
[23] IBM Micromedex. 2022. *Quetiapine fumarate* June 2022. URL: https://www.micromedexsolutions.com/ (accessed 6 July 2022).
[24] Westin A, Brekke M, Molden E, et al. 2018. Treatment with antipsychotics in pregnancy: Changes in drug disposition. *Clinical Pharmacology and Therapeutics* 103(3): 477-84. DOI: 10.1002/cpt.770 (accessed 6 July 2022).
[25] Gentile S. 2010. Antipsychotic therapy during early and late pregnancy. A systematic review. *Schizophrenia Bulletin* 36(3): 518-44. DOI: 10.1093/schbul/sbn107 (accessed 14 March 2022).
[26] Wichman CL. 2009. Atypical antipsychotic use in pregnancy: a retrospective review. *Archives of Women's Mental Health* 12(1): 53-7 (abstract only). DOI: 10.1007/s00737-008-0044-3 (accessed 25 March 2022).
[27] Vigod S, Gomes T, Wilton A, et al. 2015. Antipsychotic drug use in pregnancy: high dimensional, propensity matched, population based cohort study. *BMJ* 350: h2298. DOI: 10.1136/bmj.h2298 (accessed 14 March 2022).
[28] Uguz F. 2019. Antipsychotic use during pregnancy and the risk of gestational diabetes mellitus: A systematic review. *Journal of Clinical Psychopharmacology* 39(2): 162-7. DOI: 10.1097/JCP.0000000000001002 (accessed 14 March 2022).
[29] Galbally M, Frayne J, Watson S, et al. 2020. The association between gestational diabetes mellitus, antipsychotics and severe mental illness in pregnancy: A multicentre study. *Australian and New Zealand Journal of Obstetrics and Gynaecology* 60(1): 63-9. DOI: https://doi.org/10.1111/ajo.12986 (accessed 14 March 2022).
[30] Kucukgoncu S, Guloksuz S, Celik K, et al. 2020. Antipsychotic exposure in pregnancy and the risk of gestational diabetes: A systematic review and meta-analysis. *Schizophrenia Bulletin* 46(2): 311-18. DOI: 10.1093/schbul/sbz058 (accessed 30 March 2022).
[31] Wang Z, Wong ICK, Man KK, et al. 2021a. The use of antipsychotic agents during pregnancy and the risk of gestational diabetes mellitus: a systematic review and meta-analysis. *Psychological Medicine* 51(6): 1028-37. DOI: 10.1017/S003329171900401X (accessed 11 April 2022).
[32] Wang Z, Man KK, Ma T, et al. 2021b. Association between antipsychotic use in pregnancy and the risk of gestational diabetes: Population-based cohort studies from the United Kingdom and Hong Kong

and an updated meta-analysis. *Schizophrenia Research* 229(March): 55-62. DOI: 10.1016/j.schres.2020.11.021 (accessed 15 August 202.

[33] Heinonen E, Forsberg L, Nörby U, et al. 2022. Antipsychotic use during pregnancy and risk for gestational diabetes: A national register-based cohort study in Sweden. *CNS Drugs* Feb(online ahead of print): DOI: 10.1007/s40263-022-00908-2 (accessed 30 March 2022).