Medicines Adverse Reactions Committee

Meeting date	12 September 2019	Agenda item	3.2.1
Title	**The use of topiramate during pregnancy for migraine prevention**		
Submitted by	Medsafe Pharmacovigilance Team	Paper type	For advice
Active ingredient	**Product name**		**Sponsor**
Topiramate	Topamax (film coated tablet, sprinkle capsule)		Janssen-Cilag
	Topiramate Actavis (film coated tablet)		Teva Pharma
PHARMAC funding	Topamax and Topiramate Actavis are fully funded		
Previous MARC meetings	14 June 2001: Anticonvulsants and teratogenicity 15 December 2005: Valproate and fetal abnormalities 8 March 2012: Safety of antiepileptic medicines in pregnancy 14 September 2017: Use of sodium valproate in pregnancy		
International action	US FDA 2011: Risk of oral clefts in children born to mothers taking Topamax (topiramate)		
Prescriber Update	February 2009: Anticonvulsants and congenital malformations December 2017: Spotlight on topiramate: Seize the day		
Classification	Prescription medicine		
Usage data	Approximately 8049 patients during 2018 (DataPharm). See also section 2.1.3.		
Advice sought	The Committee is asked to advise if there is sufficient evidence and/or need to restrict the use of topiramate during pregnancy and/or women of childbearing potential for the prevention of migraines.		

Table of Contents

1 PURPOSE

Migraine is a common condition with a higher prevalence in women than men [1]. It is also most common in those aged 30 to 39 years [1]. Migraine is not a fatal condition but is a major cause of disability [1]. During pregnancy most women (60–70%) with a history of migraine report improvement over their pregnancy course, while about 5% describe worsening, and the remainder report no change [2]. This is thought to be due to the changes in estrogen levels [2].

Topiramate is an antiepileptic medicine used in the treatment of epilepsy and prevention of migraines. The use of topiramate for migraine prevention in pregnant women is contraindicated in the United Kingdom (UK). However, in New Zealand there is no such contraindication, and topiramate can be used during pregnancy if the potential benefit justifies the potential risk to the fetus.

The purpose of this paper is to review information on the use of topiramate for the prophylaxis of migraine in pregnant women to determine the best course of action for New Zealand patients. Note that the use of topiramate in pregnant women for the treatment of epilepsy is not included in this review and is considered to be a risk benefit discussion for the woman and her doctor.

2 BACKGROUND

2.1 Topiramate [3, 4]

Indications:

Topiramate is an antiepileptic used in adults and children aged 2 years and over:

- as monotherapy in patients with newly diagnosed epilepsy
- for conversion to monotherapy in patients with epilepsy
- as add-on therapy in partial onset seizures, generalised tonic-clonic seizures or seizures associated with Lennox-Gastaut syndrome.

It is also indicated in adults for the prophylaxis of migraine headache.

Contraindications:

The only contraindication for use is hypersensitivity to any component of the product.

Dose and administration:

The doses used for epilepsy are shown in Table 1.

Table 1: Recommended doses for treatment of epilepsy in adults and children

		Monotherapy	Add-on therapy
Adults	**Starting dose**	25 mg as a single (nightly) dose for one week (or longer).	25 to 50 mg as a single (nightly) or divided dose for one week (or longer).
	Escalation dose	Increase by 25 to 50 mg/day at weekly or longer intervals.	Increase by 25 to 100 mg/day at weekly or longer intervals.
	Target dose	100 mg/day	200 to 400 mg/day
	Maximum dose	Up to 500 mg/day[1]	Up to 1000 mg/day
Children 2 years & over	**Starting dose**	0.5 to 1 mg/kg as a single (nightly) dose for the first week.	1 to 3 mg/kg/day up to 25 mg/day as a single (nightly) dose for the first week.
	Escalation dose	Increase by 0.5 to 1 mg/kg/day at weekly or longer intervals.	Increase by 1 to 3 mg/kg/day at weekly or longer intervals.
	Target dose	3 to 6 mg/kg/day	5 to 9 mg/kg/day
	Maximum dose	Up to 500 mg/day	Up to 30 mg/kg/day
Note: Daily doses greater or equal to 50 mg should be taken as two divided doses. [1] Some patients with refractory epilepsy have tolerated doses of 1000 mg/day.)			

Source: Topamax New Zealand data sheet [4]

For the prevention of migraine, titration should begin at 25 mg nightly for 1 week. The dose is then increased weekly in increments of 25 mg/day. The recommended daily dose for migraine prophylaxis is 100 mg/day in two divided doses. Some patients may experience a benefit at a total daily dose of 50 mg/day. Patients have received a total daily dose up to 200 mg/day.

Mechanism of action:

The precise mechanism by which topiramate exerts its anti-seizure effect is unknown. There are 3 properties that may contribute to its antiepileptic efficacy.

1. Action potentials elicited repetitively by a sustained depolarisation of the neurons were blocked by topiramate in a time-dependent manner suggestive of a state-dependent sodium channel blocking action.
2. Topiramate increased the frequency at which GABA activated $GABA_A$ receptors, and enhanced the ability of GABA to induce a flux of chloride ions into neurons, suggesting that topiramate potentiates the activity of this inhibitory neurotransmitter. Because the antiepileptic profile of topiramate differs markedly from that of benzodiazepines, it may modulate a benzodiazepine-insensitive subtype of $GABA_A$ receptor.
3. Topiramate also inhibits some isoenzymes of carbonic anhydrase. The pharmacologic effect is much weaker than that of acetazolamide and is not thought to be a major component of topiramate's antiepileptic activity.

Comments:

Information above on topiramate's mechanism of action is from the data sheet. Note that this relates to its action as an antiepileptic. However, its multiple molecular targets as listed above may account for its effects in migraine prevention, whereas other antiepileptics with more specific targets don't have a similar effect.

2.1.1 Approval history

New Zealand

Topamax (topiramate) was first approved by Medsafe in June 1998 as adjunctive therapy for adults and children aged 2 and above with partial onset seizures, seizures associated with Lennox-Gastaut syndrome, and generalised tonic-clonic seizures.

In 2003 an application was received to extend the indication to include prophylaxis of migraine headaches in adults. Medsafe's clinical evaluation of this application noted:

- Lack of information to support the use of topiramate as a first-line agent for prophylaxis of migraine as the benefit-risk ratio is less favourable than currently approved prophylactic regimes.
- Data supports to some extent the use of topiramate 100 mg in 2 divided doses as an agent for the prophylaxis of migraine in adults in whom beta-blockers or other prophylactic agents are contraindicated, or those non-responsive or intolerant to beta-blockers or other prophylactic agents.

Based on the information available at the time, it was recommended the application be deferred pending further data, particularly long-term efficacy and safety data in the proposed indication. The application to extend the indication to include prophylaxis of migraine headaches was subsequently approved in 2004.

The generic version of topiramate (Topiramate Actavis) was approved by Medsafe in 2009.

Comments:

The current indication for topiramate 'In adults for prophylaxis of migraine headache' does not restrict its use to second-line treatment.

United Kingdom

In the UK topiramate is contraindicated for migraine prophylaxis in pregnancy and in women of childbearing potential if not using a highly effective method of contraception. This contraindication came into effect with the approval of the indication for migraine prophylaxis which was approved in July 2005.

United States

In the United States (US) the use of topiramate for treatment of epilepsy was approved in 1996 and for migraine prophylaxis in 2004. Its use during pregnancy is not contraindicated. In March 2011 the FDA issued an alert informing that topiramate had been reclassified as pregnancy category D indicating there is positive evidence of human fetal risk on the basis of human data, but the potential benefits from use during pregnancy may be acceptable in certain situations despite its risks.

The FDA's alert in 2011 prompted the sponsor to update the pregnancy information in the New Zealand data sheet. Medsafe requested additional information be added to the data sheet, including pre-pregnancy counselling on the risk of fetal abnormalities, use of folate supplements before and during pregnancy, and whether any effects are expected in the neonate after birth. Medsafe also asked the sponsor to justify why they had not provided information on the benefits and risks of topiramate for migraine prevention.

Following this, in 2014 the FDA published a Pregnancy and Lactation Labeling Rule (PLLR). This rule moved away from using the pregnancy category letters (A, B, C, D, X). The updated content and format would assist healthcare providers in assessing benefit vs. risk and enable counselling and informed decisions to be made. In 2018 the FDA requested Janssen-Cilag (sponsor of Topamax) to conduct a review and submit information to comply with PLLR. The US data sheet for Topamax no longer contains information about it being in pregnancy category D.

There is also a combination product containing topiramate + phentermine (Qsymia) which is indicated as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with high BMI. Qsymia was approved by the FDA in 2012 and is contraindicated during pregnancy.

Comments:
The MARC reviewed the safety of antiepileptics during pregnancy in March 2012. This review excluded topiramate because negotiations with the sponsor following the FDA's 2011 alert was ongoing. This review also excluded valproate, but note the MARC discussed this more recently at the September 2017 meeting.

2.1.2 Use during pregnancy [3, 4]

Information below is included in Section 4.6 Fertility, Pregnancy and Lactation of the Topamax and Topiramate Actavis data sheets.

As with other antiepileptics, topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier. There are no adequate and well-controlled studies using topiramate in pregnant women.

Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate infants exposed to topiramate *in utero* have an increased risk of congenital malformations (eg, craniofacial defects such as cleft lip/palate, hypospadias and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.

Data from the North American Antiepileptic Drugs (NAAED) Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the 1st trimester of pregnancy. The prevalence of oral clefts was 1.4% compared to a prevalence of 0.38%–0.55% in infants exposed to other antiepileptics, and prevalence of 0.07% in infants of mothers without epilepsy or treatment with other antiepileptics. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral clefts in the United States and found a background rate of 0.17%. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED pregnancy registry was 21.3% (95%CI 7.9 to 57.1) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts of 3.2% among infants exposed to topiramate

monotherapy. The observed rate of oral clefts was 16 times higher than the background rate in the UK, which is about 0.2%.

In addition, data from other studies indicate that compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of antiepileptics in combination therapy. The risk has been observed in all doses and effects were reported to be dose-dependent. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate. There is an increased risk of pre-term labour and premature delivery associated with the use of antiepileptics, including topiramate.

Compared with a reference group not taking antiepileptics, registry data for topiramate monotherapy showed a higher prevalence of low birth weight (<2500 grams). One pregnancy registry reported an increased frequency of infants who were small for gestational age (SGA) among those exposed to topiramate monotherapy in utero. SGA has been observed in all doses and is dose-dependent. The prevalence of SGA is greater in women who received higher doses of topiramate during pregnancy. In addition, the prevalence of SGA for women who continued topiramate use later in pregnancy is higher compared to women who stopped its use before the 3rd trimester. The long-term consequences of the SGA findings could not be determined. A causal relationship for low birth weight and SGA has not been established.

Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In treating and counselling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

The risk of having an abnormal child as a result of antiepileptics is far outweighed by the danger to the mother and fetus of uncontrolled epilepsy.

It is recommended that:

- Women on antiepileptics receive pregnancy counselling on the risk of fetal abnormalities
- Antiepileptics should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication
- Folic acid supplementation (5 mg) should be commenced 4 weeks prior to and continue for 12 weeks after conception
- Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.

Comments:

There appears to be 2 main risks with the use of topiramate during pregnancy:

- increased risk for the development of oral clefts (estimates vary up to a 10-fold increase)
- increased frequency of infants who are small for gestational age (SGA).

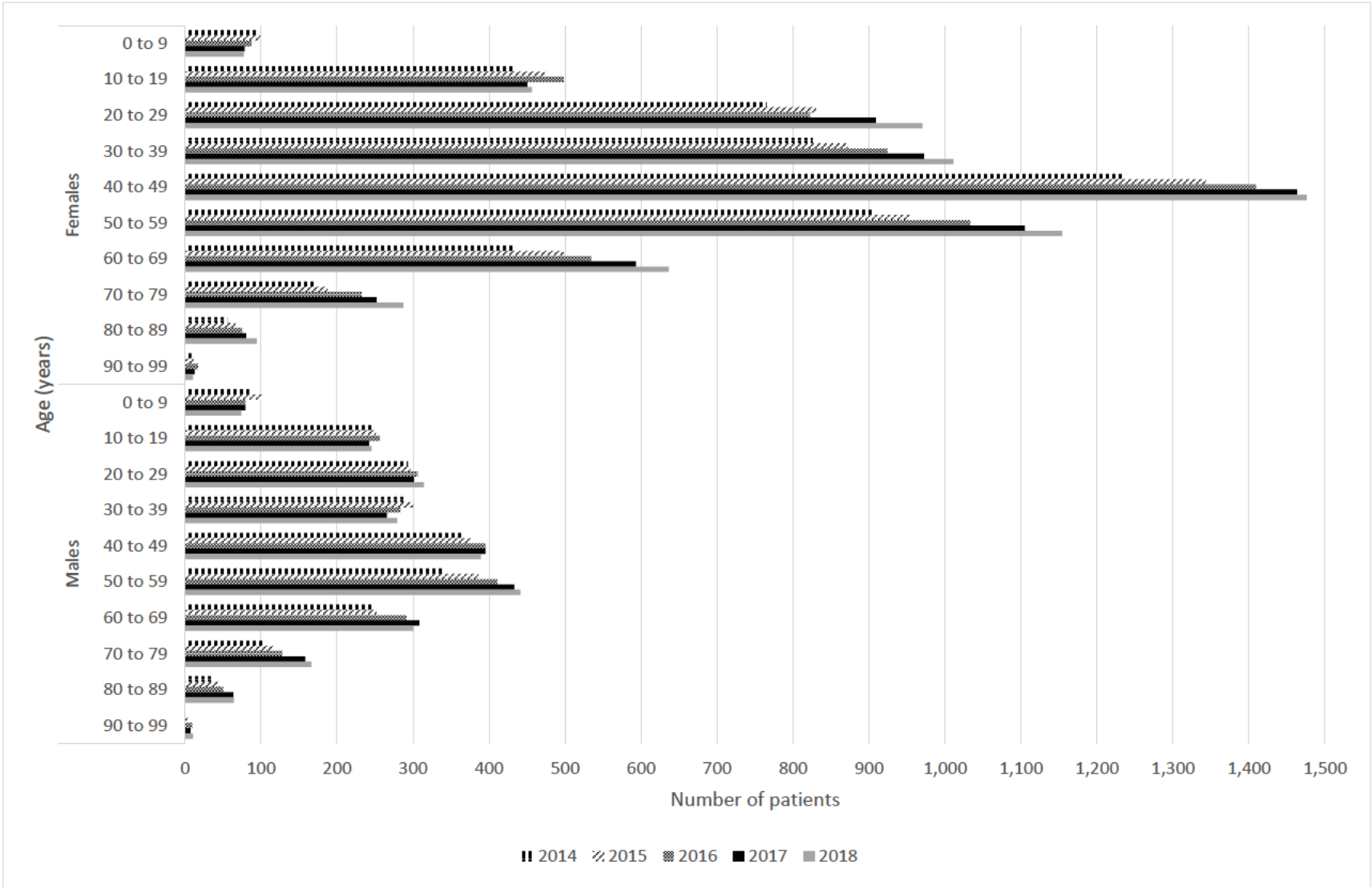
A 2016 study found the overall incidence of oral cleft in New Zealand over a 10 year period (from January 2000) was 1.79 per 1000 live births, higher than the norm for Western society (1.4 per 1000 live births) [5]. The major reason for this increased rate was an increased rate for Māori (2.37 per 1000 live births), especially the rate of cleft palate alone which was twice that of European (1.54 vs. 0.73 per 1000 live births). The rate of cleft lip alone was significantly lower in both Māori and Pacific populations. Importantly, oral clefts occur in the first trimester of pregnancy before many women know they are pregnant. According to data collected from the Growing Up in New Zealand study, around 40% of births were unplanned. The use of folic acid to prevent oral clefts remains controversial [6].

Small for gestational age (SGA) is defined as an infant with birth weight less than the 10th birth weight centile or a fetus with an estimated fetal weight on a customised growth chart less than the 10th customised centile for gestation [7].

2.1.3 Usage

Approximately 8049 patients received a community pharmacy dispensing of PHARMAC-funded topiramate for any indication during 2018 (extracted via DataPharm). Figure 1 shows analysis by gender, age and year of dispensing for 2014 to 2018 (extracted via Pharmaceutical Collections).

Figure 1: Number of patients dispensed PHARMAC-funded topiramate for any indication from a community pharmacy, 2014 to 2018



Source: Pharmaceutical Collections data, extracted 12 August 2019. This data is not a validated statistic and therefore considered unofficial. It is provided as an estimate only.

2.2 Migraine

2.2.1 Pathophysiology [1]

Current evidence suggests migraine results from a primary neuronal dysfunction leading to a sequence of changes intracranially and extracranially.

The vascular theory suggesting that migraine headache was caused by dilation of blood vessels while the aura of migraine resulted from vasoconstriction, is no longer considered viable. Vasodilation, if it occurs at all during spontaneous migraine attacks, is probably an epiphenomenon resulting from instability in the central neurovascular control mechanism.

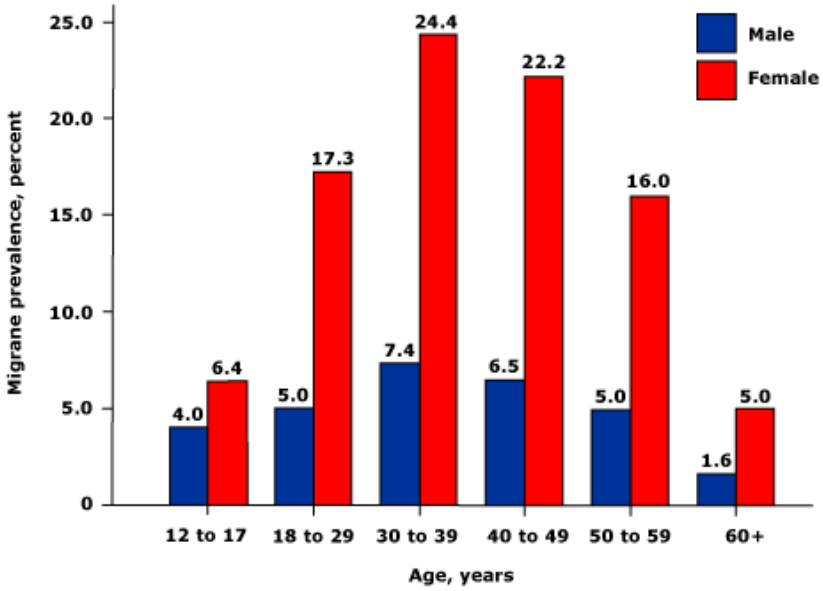
2.2.2 Epidemiology [1]

Migraine is a common disorder affecting up to 12% of the general population. It is more frequent in women than in men with attacks occurring in up to 17% of women and 6% of men each year. Migraine without aura is the most common type accounting for about 75% of cases.

Migraine is most common in those aged 30 to 39 years, an age span in which prevalence in men and women reaches 7% and 24%, respectively (Figure 2). Migraine also tends to run in families.

Although not fatal, migraine is a major cause of disability and ranked second worldwide in 2016 among all diseases with respect to years of life lived with disability.

Figure 2: Prevalence of migraine, by age and sex



Source: Lipton, RB, Bigal, ME, Diamond, M, et al. Migraine prevalence, disease burden, and the need for preventative therapy, Neurology 2007; 68:343 [8].

Comments:
The prevalence of migraine is higher in women than men, and peaks during childbearing years.

2.2.3 Clinical features [1]

Migraine is a disorder of recurrent attacks. The attacks unfold through a cascade of events that occur over several hours to days. A typical migraine attack progresses through 4 phases:

1. The **prodrome** consists of affective or vegetative symptoms that appear 24 to 48 hours prior to the onset of headache.

2. About 25% of people with migraines experience one or more focal neurologic symptoms in the second phase (migraine **aura**). Auras are most often visual but can also be sensory, verbal or motor disturbances.
3. The **headache** of migraine is often but not always unilateral and tends to have a throbbing or pulsatile quality. Accompanying features may include nausea, vomiting, photophobia, or phonophobia during attacks.
4. Once the headache resolves, the patient may experience a **postdromal** phase during which sudden head movement transiently causes pain in the location of the antecedent headache. Patients often feel drained or exhausted but some report a feeling of mild elation or euphoria.

Migraine trigger factors may include stress, menstruation, visual stimuli, weather changes, nitrates, fasting, wine, sleep disturbances and aspartame.

2.2.4 Prevention [9]

The goals of migraine prevention are to:

- Reduce attack frequency, severity, duration and disability
- Improve responsiveness to and avoid escalation in use of acute treatment
- Improve function and reduce disability
- Reduce reliance on poorly tolerated, ineffective or unwanted acute treatments
- Reduce overall cost associated with migraine treatment
- Enable patients to manage their own disease to enhance a sense of personal control
- Improve health-related quality of life
- Reduce headache-related distress and psychological symptoms.

None of the currently available oral preventive treatments were designed specifically for migraine and many of these medicines have limited to moderate efficacy, moderate to high rates of adverse events, contraindications, or interactions that limit use. These factors explain in part why few patients with migraine use preventive treatment (3–13%) even though it is believed that nearly 40% of those with episodic migraine and almost all of those with chronic migraine in the general population would benefit.

2.2.5 Migraine in pregnant women [2]

About 2% of women develop their first migraine during pregnancy usually in the 1st trimester.

The occurrence of migraine is modulated by fluctuations in estrogen levels. Most women (60–70%) with a history of migraine report improvement over the course of pregnancy, about 5% describe worsening, and the remainder report no change.

Review of studies evaluating pregnancy outcome in migraine sufferers generally conclude that migraine, treated or untreated, probably has no effect on most pregnancy outcomes, including risk of congenital anomalies. However, there may be an increased risk of developing preeclampsia-related hypertension which is associated with an increased risk of low birth weight.

Comments:
Although the prevalence of migraine is highest in women during their childbearing years, most women (60–70%) report an improvement in their migraine course during pregnancy.

2.3 Migraine prevention guidance

2.3.1 UpToDate [2]

Women with frequent migraine headaches often benefit from preventive therapy. The most common approach is daily use of beta blockers or calcium channel blockers at the lowest effective dose, and cognitive and behavioural therapy. Co-management with a neurologist is essential in these difficult cases.

First-line preventive therapies:

- Beta blockers (eg, propranolol, metoprolol, atenolol) are not teratogens but fetal/neonatal effects from beta blockade are possible with prolonged use and include mild fetal growth restriction and mild transient neonatal bradycardia, respiratory depression, hyperbilirubinemia, and/or hypoglycaemia. Growth restriction may be more of an issue with atenolol than with other beta blockers.
- Calcium channel blockers (short- and long-acting) are commonly used for treatment of hypertension and preterm labour without adverse fetal/pregnancy effects. An increase in congenital anomalies has not been reported in humans, although information is limited. Verapamil is the preferred agent because it is relatively safe and has good tolerability and ease of use.
- Cyproheptadine is an older antihistamine sometimes used as a preventative and does not appear to have adverse pregnancy effects.

Second-line preventive therapies:

- Low-dose antidepressants (eg, SNRI venlafaxine) or tricyclic antidepressants may be considered in refractory patients particularly those with suspected underlying chronic depressive illness or postpartum depression. Antidepressants have not been clearly associated with an increased risk of congenital anomalies, but can have neonatal effects when taken in the third trimester.
- Gabapentin is an option for refractory patients. Some antiepileptics particularly valproate are teratogenic and should be avoided.

Comments:

Antidepressants are included as a second-line preventive option in UpToDate stating they have not been clearly associated with an increased risk of congenital anomalies. In 2010, the MARC reviewed the association between SSRIs and SNRIs and congenital anomalies and concluded there is a small increased risk of congenital cardiac defects associated with fluoxetine similar to that seen with paroxetine. The MARC considered the possibility of a class effect for all SSRIs or a similar effect with SNRIs could not be excluded at the time of this review.

2.3.2 American Headache Society (AHS) [9]

The 2019 AHS position statement on integrating new migraine treatments into clinical practice includes guidance on the use of topiramate.

The following oral treatments have established efficacy and should be offered for migraine prevention based on the level of evidence and the American Academy of Neurology (AAN) scheme for classifying evidence (Table 2):

- antiepileptic medicines (divalproex sodium, sodium valproate, topiramate)
- beta-blockers (metoprolol, propranolol, timolol)
- frovatriptan (for short-term preventive treatment of menstrual migraine).

Importantly, sodium valproate and topiramate must not be prescribed to women of childbearing potential who are not using a reliable method of contraception due to the risk of birth defects.

The following treatments by prescription are probably effective and should be considered for migraine prevention:

- antidepressants (amitriptyline, venlafaxine)
- beta-blockers (atenolol, nadolol)
- angiotensin receptor blockers (candesartan).

Try to avoid preventive treatments (especially sodium valproate and topiramate) in pregnant or lactating women and those who are trying to conceive and discuss the potential for adverse effects on a pregnancy and developing fetus in women of childbearing age.

Table 2: Treatments with evidence of efficacy in migraine prevention

Established efficacy[†]	Probably effective[‡]	Possibly effective[§]
Antiepileptic drugs[‖]	Antidepressants	ACE inhibitors: Lisinopril
Divalproex sodium[‖]	Amitriptyline	Alpha-agonists
Valproate sodium[‖]	Venlafaxine	Clonidine
Topiramate[‖]	Beta-blockers	Guanfacine
Beta-blockers	Atenolol	Antiepileptic drugs: Carbamazepine
Metoprolol	Nadolol	Beta-blockers
Propranolol		Nebivolol
Timolol		Pindolol
Triptans: Frovatriptan[¶]		Antihistamines: Cyproheptadine
OnabotulinumtoxinA[32]		Angiotensin receptor blockers: Candesartan

ACE, angiotensin-converting enzyme.
[†]More than 2 Class I trials based on AAN Scheme for Classification of Evidence.[33]
[‡]One Class I or 2 Class II studies based on AAN Scheme for Classification of Evidence.[33]
[§]One Class II study based on AAN Scheme for Classification of Evidence.[33]
[‖]Not for use in women of childbearing potential who are not using an appropriate method of birth control.[34,35]
[¶]Short-term prevention of menstrual migraine.
[‡‡]For prevention of chronic migraine.
Source: Adapted from Silberstein et al [10]

2.3.3 National Institute for Health and Care Excellence (NICE) [11]

Guidance for diagnosis and management of headaches in those aged 12 years and over includes a section on prophylactic treatment for migraine with or without aura.

The recommendation is to offer topiramate or propranolol for the prophylactic treatment of migraine according to the person's preference, comorbidities and risk of adverse events. Advise women and girls of childbearing potential that topiramate is associated with a risk of fetal malformations and can impair the effectiveness of hormonal contraceptives. Ensure they are offered suitable contraception if needed.

2.3.4 Best Practice Advocacy Centre (bpac^{nz}) [12]

Migraine prophylaxis should be considered for patients when:

- they find acute treatment to be inadequate
- they have more than 3 attacks per month despite optimal management
- they are at risk of medicine overuse headache.

In general, prophylaxis treatment is considered effective if the frequency of migraine is reduced by half. Prophylactic medicines often need to be titrated to avoid adverse effects and it may take 4 to 8 weeks of daily treatment until the medicine is effective – warning patients in advance may improve treatment adherence.

Treatment reviews

Migraine prophylaxis over long periods is rarely appropriate as the frequency of migraine attacks often varies with time. Titrate the dose downwards over 2 to 3 weeks to determine if a patient has an ongoing need. Monitor and record the patient's symptoms during this time. Guidelines recommend considering withdrawal

after 4 to 6 months of successful treatment. However, the timing of treatment withdrawal should be discussed on a case-by-case basis with patients.

Prophylaxis

First-line medicines:

- Beta-blockers are generally first-line in patients without asthma or peripheral vascular disease. Nadolol and metoprolol are recommended and approved in New Zealand for this indication. Propranolol is also prescribed for migraine prophylaxis as an unapproved indication, however, the concurrent use of rizatriptan may result in elevated plasma concentrations of rizatriptan.
- Amitriptyline is an alternative first-line medicine (unapproved indication) for those with comorbid chronic pain, disturbed sleep or depression. A low starting dose (eg 5–10 mg one to two hours before bedtime is initially recommended and can slowly titrate up to a maintenance of no more than 50–75 mg).

Second-line medicines:

- Topiramate and sodium valproate (unapproved indication) are effective in the prophylaxis of migraine. However, they are second-line medicines due to the risk of serious adverse effects. Sodium valproate and topiramate should be avoided in women of childbearing potential. The use of sodium valproate during pregnancy is associated with an increased risk of neural tube defects. Topiramate should not be prescribed to patients with liver disease or angle-closure glaucoma. Patients should be monitored for psychological and behavioural changes, including depression and suicidal ideation.

2.3.5 New Zealand Formulary (NZF) [13]

Provoking factors such as stress, irregular lifestyle (eg, lack of sleep) or chemical triggers (eg, alcohol, nitrates) should be explored when migraine attacks are frequent. Preventive treatment for migraine should be considered for patients who:

- suffer at least 2 attacks a month
- suffer an increasing frequency of headaches
- suffer significant disability despite suitable treatment for migraine attacks
- cannot take suitable treatment for migraine attacks.

Prophylaxis is also necessary in some rare migraine subtypes and those at risk of migrainous infarction.

The beta-blockers propranolol, atenolol (unapproved indication), metoprolol, nadolol and timolol are all effective.

Tricyclic antidepressants (unapproved indication), topiramate, sodium valproate (unapproved indication) and gabapentin (unapproved indication) are also effective for preventing migraine. Sodium valproate is contraindicated in female children and females of childbearing potential for the prophylaxis of migraine and other unapproved indications.

Pizotifen is an antihistamine and a serotonin-receptor antagonist structurally related to tricyclic antidepressants. It is of limited value and may cause weight gain.

Botulinum toxin type A is used for prophylaxis of headaches in adults with chronic migraine.

Clonidine is not recommended. It can aggravate depression and cause insomnia.

Comments:
In general, beta-blockers appear to be recommended first-line for migraine prophylaxis in various clinical guidelines. Beta-blockers are listed as Category C medicines in the NZ data sheets. Side effects of beta-blockers in the fetus are similar to other antihypertensives and include bradycardia. As with other medicines, beta-blockers should be used during pregnancy only if the benefits outweigh the risks.

2.4 Data sheets

Information relating to the use of topiramate during pregnancy and women of childbearing potential is provided in Table 3. Please note this information is not presented in full; refer to the data sheet through the links provided to access the full information.

In general, the New Zealand and Australian data sheets are very similar. However, there are some differences compared with the UK, such as:

- Contraindicated in the UK for migraine prophylaxis in pregnancy and women of childbearing potential if not using a highly effective method of contraception.
- Information in section 4.6 pregnancy and breastfeeding is more concise in the UK and there are subsections describing the risks for AEDs vs. topiramate, and use in epilepsy vs. migraine.

Table 3: Comparison of information relating to pregnancy and women of childbearing potential in topiramate data sheets in New Zealand, Australia and the United Kingdom

	New Zealand (Topamax data sheet)	**Australia (Topamax PI)**	**United Kingdom (Topamax SmPC)**
4.1 Indications	In adults for prophylaxis of migraine headache.	In adults for prophylaxis of migraine headache.	In adults for prophylaxis of migraine headache after careful evaluation of possible alternative treatment options.
4.3 Contraindications	-	-	Contraindicated for migraine prophylaxis in pregnancy and in women of childbearing potential if not using a highly effective method of contraception.
4.4 Warnings and precautions	Women of childbearing potential Topiramate may cause fetal harm when administered to a pregnant woman. There is an increased risk of pre-term labour and premature delivery associated with the use of AEDs, including topiramate. Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see pregnancy and breastfeeding).	Women of childbearing potential Topiramate may cause fetal harm when administered to a pregnant woman. There is an increased risk of pre-term labour and premature delivery associated with the use of AEDs, including topiramate. Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus (see section 4.6 fertility, pregnancy and lactation).	Women of childbearing potential Topiramate may cause fetal harm and fetal growth restriction (small for gestational age and low birth weight) when administered to a pregnant woman. The North American Antiepileptic Drug pregnancy registry data for topiramate monotherapy showed an approximate 3-fold higher prevalence of major congenital malformations (4.3%) compared with a reference group not taking AEDs (1.4%). In addition, data from

			other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of AEDs in combination therapy. Before the initiation of treatment with topiramate in a woman of childbearing potential, pregnancy testing should be performed and a highly effective contraceptive method advised (see section 4.5). The patient should be fully informed of the risks related to the use of topiramate during pregnancy (see section 4.3 and 4.6).
4.6 Fertility, pregnancy and lactation	Pregnancy As with other antiepileptics, topiramate was teratogenic in mice, rats and rabbits. In rats, topiramate crosses the placental barrier. There are no adequate and well-controlled studies using topiramate in pregnant women. Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate infants exposed to topiramate *in utero* have an increased risk of congenital malformations (eg, craniofacial defects such as cleft lip/palate, hypospadias and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen.	Use in pregnancy Category D. When administered orally during organogenesis, topiramate was teratogenic in mice, rats and rabbits at maternal exposures (plasma AUC) less than clinical exposure at the maximal recommended dose. In mice, the numbers of fetal malformations (primarily craniofacial abnormalities) were increased at all dose levels tested. The malformations in rats (limb reduction defects) and rabbits (axial and costal skeletal defects) were similar to those seen with carbonic anhydrase inhibitors in these species. Carbonic anhydrase inhibitors have not been associated with malformations in human beings. There are no studies using topiramate in pregnant women. In postmarketing experience,	Pregnancy *Risk related to AEDs in general* Specialist advice should be given to women who are of childbearing potential. The need for treatment with AEDs should be reviewed when a woman is planning to become pregnant. Monotherapy should be preferred whenever possible because therapy with multiple AEDs could be associated with a higher risk of congenital malformations than monotherapy, depending on the associated antiepileptics. *Risk related to topiramate* Topiramate was teratogenic in mice, rats and rabbits (see section 5.3). In rats, topiramate crosses the placental barrier.

	Data from the North American Antiepileptic Drugs (NAAED) Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the 1st trimester of pregnancy. The prevalence of oral clefts was 1.4% compared to a prevalence of 0.38%–0.55% in infants exposed to other antiepileptics, and prevalence of 0.07% in infants of mothers without epilepsy or treatment with other antiepileptics. For comparison, the Centers for Disease Control and Prevention (CDC) reviewed available data on oral clefts in the United States and found a background rate of 0.17%. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED pregnancy registry was 21.3% (95%CI 7.9 to 57.1) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts of 3.2% among infants exposed to topiramate monotherapy. The observed rate of oral clefts was 16 times higher than the background rate in the UK, which is about 0.2%. In addition, data from other studies indicate that compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of antiepileptics in combination	cases of hypospadias have been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants. A causal relationship with topiramate has not been established. There are no adequate and well-controlled studies using topiramate in pregnant women. Topiramate can cause fetal harm when administered to a pregnant woman. Data from pregnancy registries indicate that infants exposed to topiramate in utero have an increased risk of congenital malformations (e.g., craniofacial defects, such as cleft lip/palate, hypospadias, and anomalies involving various body systems). This has been reported with topiramate monotherapy and topiramate as part of a polytherapy regimen. Data from the North American AED (NAAED) Pregnancy Registry indicate an increased risk of oral clefts in infants exposed to topiramate monotherapy during the first trimester of pregnancy. The prevalence of oral clefts was 1.4% compared to a prevalence of 0.38% - 0.55% in infants exposed to other AEDs, and a prevalence of 0.07 % in infants of mothers without epilepsy or treatment with other AEDs. The relative risk of oral clefts in topiramate-exposed pregnancies in the NAAED Pregnancy Registry was	In humans, topiramate crosses the placenta and similar concentrations have been reported in the umbilical cord and maternal blood. Clinical data from pregnancy registries indicate that infants exposed to topiramate monotherapy have: • An increased risk of congenital malformations (particularly cleft lip/palate, hypospadias, and anomalies involving various body systems) following exposure during the first trimester. • A higher prevalence of low birth weight (<2500 grams) compared with a reference group. • An increased prevalence of being small for gestational age. Long term consequences could not be determined. *Indication migraine prophylaxis* Topiramate is contraindicated in pregnancy and in women of childbearing potential if a highly effective method of contraception is not used (see sections 4.3 and 4.5).

	therapy. The risk has been observed in all doses and effects were reported to be dose-dependent. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate. There is an increased risk of pre-term labour and premature delivery associated with the use of antiepileptics, including topiramate. Compared with a reference group not taking antiepileptics, registry data for topiramate monotherapy showed a higher prevalence of low birth weight (<2500 grams). One pregnancy registry reported an increased frequency of infants who were small for gestational age (SGA) among those exposed to topiramate monotherapy in utero. SGA has been observed in all doses and is dose-dependent. The prevalence of SGA is greater in women who received higher doses of topiramate during pregnancy. In addition, the prevalence of SGA for women who continued topiramate use later in pregnancy is higher compared to women who stopped its use before the 3rd trimester. The long-term consequences of the SGA findings could not be determined. A causal relationship	21.3 (95% Confidence Interval 7.9–57.1) as compared to the risk in a background population of untreated women. The UK Epilepsy and Pregnancy Register reported a similarly increased prevalence of oral clefts of 3.2% among infants exposed to topiramate monotherapy. The observed rate of oral clefts was 16 times higher than the background rate in the UK, which is approximately 0.2%. In addition, data from other studies indicate that, compared with monotherapy, there is an increased risk of teratogenic effects associated with the use of anti-epileptic drugs in combination therapy. The risk has been observed in all doses and effects were reported to be dose-dependent. In women treated with topiramate who have had a child with a congenital malformation, there appears to be an increased risk of malformations in subsequent pregnancies when exposed to topiramate. There is an increased risk of pre-term labour and premature delivery associated with the use of AEDs, including topiramate. Compared with a reference group not taking antiepileptic drugs, registry data for topiramate monotherapy showed a higher prevalence of low birth weight (<2500 grams). One pregnancy registry reported an increased frequency of	

	for low birth weight and SGA has not been established. Topiramate should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. In treating and counselling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks, particularly when topiramate is considered for a condition not usually associated with permanent injury or death. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. The risk of having an abnormal child as a result of antiepileptics is far outweighed by the danger to the mother and fetus of uncontrolled epilepsy. It is recommended that: • Women on antiepileptics receive pregnancy counselling on the risk of fetal abnormalities • Antiepileptics should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication • Folic acid supplementation (5 mg) should be commenced 4 weeks prior	infants who were small for gestational age (SGA; defined as birth weight below the 10th percentile corrected for their gestational age, stratified by sex) among those exposed to topiramate monotherapy in utero. SGA has been observed in all doses and is dose-dependent. The prevalence of SGA is greater in women who received higher doses of topiramate during pregnancy. In addition, the prevalence of SGA for women who continued topiramate use later in pregnancy is higher compared to women who stopped its use before the third trimester. The long-term consequences of the SGA findings could not be determined. A causal relationship for low birth weight and SGA has not been established. Topiramate should be used during pregnancy only if potential benefit justifies the potential risk to the fetus. In treating and counselling women of childbearing potential, the prescribing physician should weigh the benefits of therapy against the risks. If this drug is used during pregnancy or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus. The risk of having an abnormal child as a result of antiepileptic medication is far	

	to and continue for 12 weeks after conception • Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.	outweighed by the danger to the mother and foetus of uncontrolled epilepsy. It is recommended that: • Women on antiepileptic drugs (AEDs) receive pregnancy counselling with regard to the risk of foetal abnormalities • AEDs should be continued during pregnancy and monotherapy should be used if possible at the lowest effective dose as risk of abnormality is greater in women taking combined medication • Folic acid supplementation (5mg) should be commenced four weeks prior to and continue for twelve weeks after conception • Specialist prenatal diagnosis including detailed mid-trimester ultrasound should be offered.	

3 SCIENTIFIC INFORMATION

3.1 Published literature

Some articles from the literature are summarised below. The meta-analysis by Alsaad et al (section 3.1.8) includes all the studies presented in sections 3.1.1 to 3.1.7. See also section 3.2.1 for the company's literature review.

3.1.1 Hunt et al 2008 – Topiramate in pregnancy: Preliminary experience from the UK epilepsy and pregnancy register [14]

The UK epilepsy and pregnancy register is a prospective pregnancy register set up to determine the relative safety of all antiepileptics taken in pregnancy. The authors report results for first-trimester exposures to topiramate through 31 August 2007. Women were included if they had epilepsy and became pregnant while taking topiramate either alone or with other antiepileptics, and were referred before outcome of the pregnancy was known.

Full outcome data were available on 203 pregnancies. 178 of the 203 pregnancies (87.7%) resulted in live birth. Of these, 31 pregnancies had an abnormality of some kind (17.4%, 95% CI 12.5% to 23.7%) with 16 of these being a major congenital malformation (9.0%, 95% CI 5.6% to 14.1%). Four major congenital malformations were oral clefts (2.2%, 95% CI 0.9% to 5.6%) with three infants having both cleft lip and cleft palate. Four cases of hypospadias were reported (5.1%, 95% CI 0.2% to 10.1%) among 78 known live male births of which two were classified as major malformations.

Three major congenital malformations were observed in 70 monotherapy exposures (4.8%, 95% CI 1.7% to 13.3%) (Table 4). Of the 56 monotherapy outcomes for which there were full data on gestational age and birth weight, 8 (14.3%) were small for gestational age. The mean total daily dose for those who were small for gestational age (346 mg) was not significantly different from those who were not small for gestational age (239 mg).

Of 103 live births exposed to topiramate as part of a polytherapy regimen and for which there were data regarding birth weight and gestational age, 20 infants (19.4%) were small for gestational age. The mean total daily dose for infants who were small for gestational age (405 mg) was significantly different from those who were not small for gestational age (260 mg). 13 exposed to topiramate polytherapy reported a major congenital malformation (Table 5).

The rates of oral clefts (2.2%) and hypospadias (5.1%) was much higher than that reported in the United Kingdom. For oral clefts, which occur in 1 in 500 live births in the United Kingdom, the observed rate was 11 times higher than the background rate. For hypospadias, which is estimated to occur in 1 in 300 live births, the observed rate was approximately 14 times the background rate.

The authors conclude the number of outcomes of human pregnancies exposed to topiramate is low, but the major congenital malformation rate for topiramate polytherapy raises some concerns. Overall, the rate of oral clefts observed was 11 times the background rate.

Table 4: Major congenital malformations with topiramate monotherapy

No.	Dose TPM during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Major congenital malformation
1	200	29	G3P2	Partial	NR	41	3,850	F	Cleft lip and bilateral cleft palate
2	400	34	G3P2	NR	No	37	2,355	M	Hypospadias
3	600	27	G1P1	NR	Yes	39	3,289	NR	Cleft lip and palate

TPM = topiramate; GTC = generalized tonic- clonic seizure; NR = not recorded.

Table 5: Major congenital malformations with topiramate polytherapy

No.	Dose TPM during pregnancy/d, mg	Other AED doses during pregnancy/d, mg	Maternal age, y	Parity	Seizure type	GTC seizure in pregnancy	Gestational age, wk	Weight, g	Sex	Major congenital malformation
1	800	Clobazam 20; lamotrigine 550; vigabatrin 1,000	29	G2P1	Partial	No	40	2,381	M	Left hydronephrosis, dysmorphic
2	75	Ethosuximide 1,000; sodium valproate 1,000	39	G3P2	Partial	No	38	3,160	M	Pyloric stenosis
3	250	Lamotrigine 200	19	NR	NR	NR	NR	NR	F	Hernia and hydrocele
4	175	Lamotrigine 125	24	NR	Partial	No	38	2,530	F	Anal atresia
5	150	Sodium valproate 1,500	32	G2P1	GTC	Yes	42	3,660	M	Pyloric stenosis
6	150	Sodium valproate 200	24	G4P3	GTC	No	34	NR	F	Tracheoesophageal fistula
7	50	Sodium valproate 2,500	26	G3P2	GTC	Yes	41	3,400	M	Hypospadias
8	500	Sodium valproate 500	24	G1P0	NR	NR	40	2,455	F	Cleft palate, crossed toes
9	400	Lamotrigine 400	24	G1P0	GTC	NR	40	3,280	F	Bilateral dislocated hips
10	350	Lamotrigine 50	27	G2P1	JME	No	40	2,960	M	Harold type II Talipes, plagiocephaly
11	500	Carbamazepine 1,200; clobazam 10	28	G1P0	NR	Yes	38	NR	M	Congenital dislocated hip
12	800	Levetiracetam 500; lamotrigine 800	21	G1P0	Partial	Yes	33	2,460	M	Pyloric stenosis
13	250	Lamotrigine 300; phenobarbitone 60	37	G3P2	GTC	No	40	3,560	M	Left cleft lip and palate

TPM = topiramate; AED = antiepileptic drug; GTC = generalized tonic–clonic seizure; NR = not recorded; JME = juvenile myoclonic epilepsy.

Comments:

The major congenital malformations seen in this study have been described with other antiepileptics. There was no apparent dose response relationship for either topiramate used in monotherapy or polytherapy. These results are only relevant to women using topiramate for treatment of epilepsy as this was the population studied (ie, women using topiramate for migraine prophylaxis were not included). Note there was no control group in this study.

3.1.2 Mølgaard-Nielsen & Hviid 2011 – Newer-generation antiepileptic drugs and the risk of major birth defects [15]

This population-based Danish cohort study looked at the association between fetal exposure to newer-generation antiepileptics during the first trimester of pregnancy and the risk of major birth defects. Enrolment in the registry is voluntary and based on referral by a clinician or by the woman herself. 837,795 live-born infants in Denmark from 1 January 1996 to 30 September 2008 were included, of which 19,960 were diagnosed with a major birth defect (2.4%) during the first year of life.

1532 infants were exposed to a newer-generation antiepileptic during the first trimester. The majority reported a maternal disease diagnosed before the second trimester of epilepsy (n=1164) with the remainder diagnosed with migraine (n=34) and any mood affective disorder (n=28). Of the 1532 infants exposed to lamotrigine, oxcarbazepine, topiramate, gabapentin or levetiracetam during the first trimester, 49 were diagnosed with a major birth defect (3.2%) compared with 19,911 infants (2.4%) of the 836,263 unexposed pregnancies (adjusted prevalence odds ratio (POR) 0.99, 95% CI 0.72 to 1.36). As shown in Table 6, a major birth defect was diagnosed in 5 of 108 infants (4.6%) exposed to topiramate (adjusted POR 1.44, 95% CI 0.58 to 3.58). There were a limited number of topiramate-exposed cases but the authors state results indicate it is not a major human teratogen.

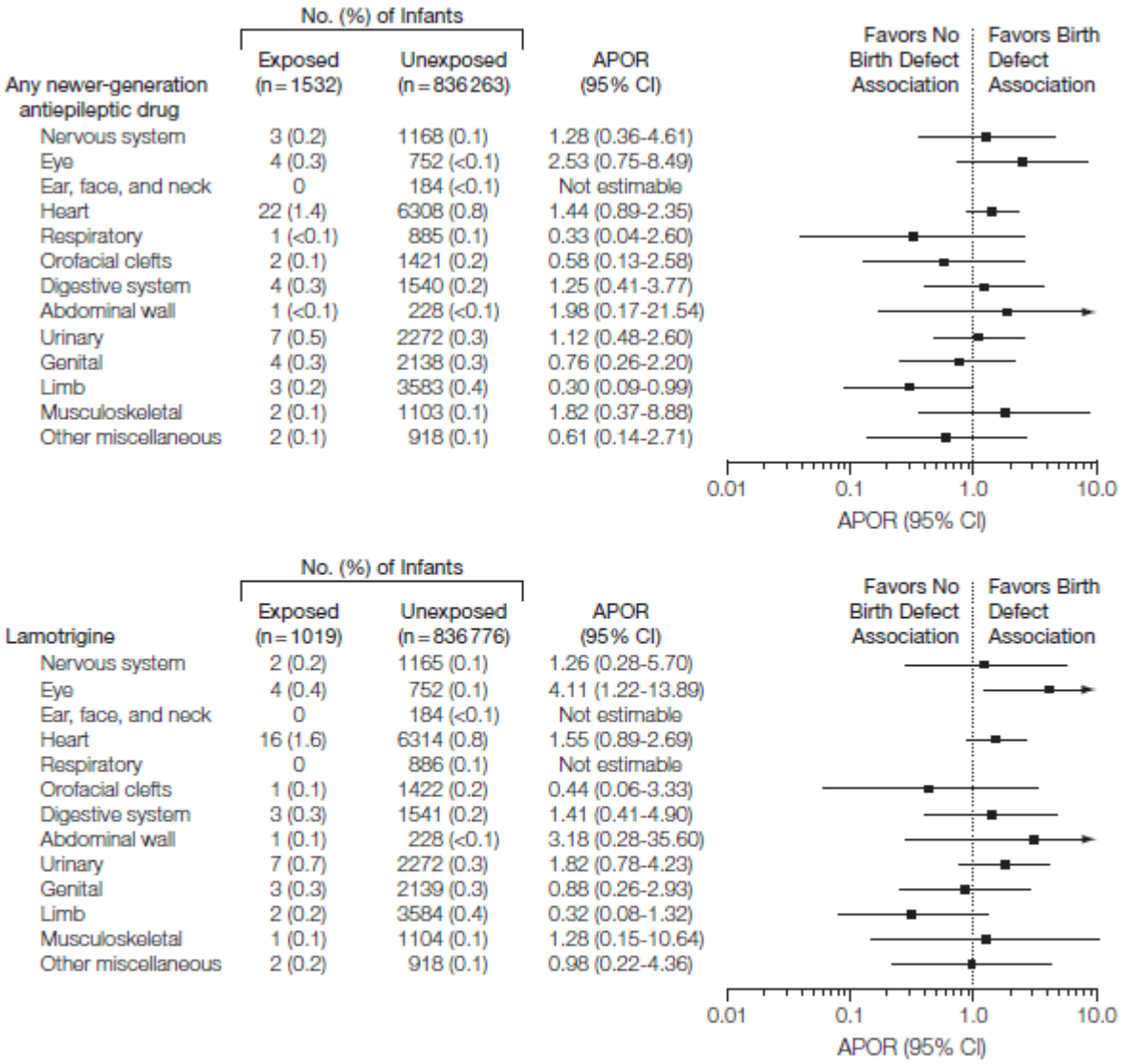
Figure 3 shows exploratory analyses of associations between first trimester use of newer-generation antiepileptics and major birth defect subgroups categorised by organ system. There was no significant increased risk of any major birth defect subgroup in infants exposed to any antiepileptic during the first

trimester. However, these exploratory analyses were based on small numbers of cases and should be interpreted with caution.

Unadjusted estimates showed a significant association between exposure to any newer-generation antiepileptic or lamotrigine alone during the first trimester and the risk of major birth defects. However after adjustment for older-generation antiepileptic use and epilepsy, no associations remained. Some of the mothers in the cohort were treated with both older and newer generation antiepileptics or switched from older to newer generation antiepileptics when pregnancy status was determined, explaining the reduction in risk after adjustment.

The authors conclude among live-born infants in Denmark, first trimester exposure to lamotrigine, oxcarbazepine, topiramate, gabapentin or levetiracetam compared with no exposure was not associated with an increased risk of major birth defects.

Figure 3: Associations between first trimester exposures of newer-generation antiepileptics and subgroups of major birth defects by organ system



The adjusted prevalence odds ratios (APORs) were adjusted for maternal use of older-generation antiepileptic drugs during the first trimester and maternal diagnosis of epilepsy before the second trimester. The sum of birth defects from the subgroups is larger than the number of birth defects in the overall analyses in which only the first birth defect was counted because some participants had birth defects from more than 1 subgroup. CI indicates confidence interval.

Table 6: Associations between newer-generation antiepileptic use during pregnancy and major birth defects in a cohort of 837,795 live births in Denmark

	Exposure During First Trimester			
			POR (95% CI)	
	No. of Women[a]	Birth Defects, No. (%)	Crude	Adjusted[b]
Newer-generation antiepileptic drugs				
Exposed	1532	49 (3.2)	1.35 (1.02-1.80)	0.99 (0.72-1.36)
Unexposed	836 263	19 911 (2.4)	1 [Reference]	1 [Reference]
Lamotrigine, mg/d	1019	38 (3.7)	1.59 (1.15-2.2)	1.18 (0.83-1.68)
≤250	766	31 (4.0)	1.73 (1.21-2.48)	1.29 (0.88-1.90)
>250	253	7 (2.8)	1.17 (0.55-2.47)	0.84 (0.39-1.82)
Oxcarbazepine	393	11 (2.8)	1.18 (0.65-2.15)	0.86 (0.46-1.59)
Topiramate	108	5 (4.6)	1.99 (0.81-4.88)	1.44 (0.58-3.58)
Gabapentin	59	1 (1.7)	0.71 (0.10-5.10)	0.53 (0.07-3.85)
Levetiracetam	58	0	Not estimable	Not estimable

Abbreviations: CI, confidence interval; POR, prevalence odds ratio.
[a] The numbers of women exposed to each individual antiepileptic drug sums to more than 1532 because some of them took more than 1 drug.
[b] Adjusted for use of older-generation antiepileptic drugs during the first trimester and diagnosis of epilepsy before the second trimester.

Comments:

There was no association found between the use of newer antiepileptics during the first trimester and risk of major birth defects in this large Danish study. However, the number of topiramate-exposed cases was low. There was no exploratory analysis by indication for use (ie, treatment of epilepsy vs. migraine prevention).

The overall prevalence of major birth defects was 2.4% which is in accordance with the prevalence found in a study population in Atlanta, Georgia of 2.17% for defects diagnosed at birth and 3.15% for defects diagnosed at any age, and with EUROCAT data from Europe of 2.04%.

3.1.3 Green et al 2012 – Utilization of topiramate during pregnancy and risk of birth defects [16]

This retrospective cohort study was conducted using the Wolters Kluwer Pharma Solutions database in the United States. The authors evaluated the risk of oral cleft and major congenital malformation in infants born to women exposed to topiramate in their first trimester of pregnancy compared with women who used other antiepileptics or those with disease states in which topiramate may have been used. All women with a diagnosis or procedure code for pregnancy, delivery or birth who were dispensed topiramate, any other antiepileptic or who had an ICD-9 code for diagnosis of migraine, epilepsy, or diabetes were identified.

870 infants born to mothers exposed to topiramate in the first trimester and 3615 infants born to mothers exposed to other antiepileptics in the first trimester were identified from 2002 through 2010. First trimester exposure was based on prescription dispensing dates and days supplied relative to infant birth date, accounting for premature delivery. Infants born to women with migraine without epilepsy (n=26,865), women with epilepsy (n=2607) and women with diabetes mellitus (n=13,062), as well as randomly sampled women (n=99,761) were used for comparison.

For all cohorts except the random sample, topiramate and valproate exposure were excluded as well as exposure to known non-antiepileptic teratogens. For the topiramate and antiepileptic exposure cohorts, non-antiepileptic teratogens except valproate were excluded only in the first trimester. In the antiepileptic cohort, topiramate was excluded only in the first trimester. Because of the small number of mother-infant pairs overall, polytherapy with multiple antiepileptics was permitted in all cohorts.

The frequency of oral clefts in infants exposed to topiramate or other antiepileptics in the first trimester was 0.23% (2 of 870) and 0.17% (6 of 3615), respectively (Table 7). The relative risk (RR) of oral clefts was increased

but not significantly for infants exposed to topiramate compared with other antiepileptics (RR 1.39, 95% CI 0.28 to 6.85). For infants of mothers in disease-state cohorts, the frequency of OC occurrence was 0.16% for migraine (42 of 26,865), 0.31% for epilepsy (8 of 2607) and 0.26% for diabetes (34 of 13,062). The RR of oral clefts in infants exposed to topiramate were 1.47 (95% CI 0.36 to 6.06), 0.75 (95% CI 0.16 to 3.52) and 0.88 (95% CI 0.21 to 3.67) for the migraine, epilepsy and diabetes cohorts, respectively, compared with the individual disease-state cohorts.

The rate of a major congenital malformation diagnosis for infants exposed to topiramate in the first trimester was 4.25% (37 of 870) and 3.21% (116 of 3615) for other antiepileptics (Table 8). The RR was not significantly increased in infants exposed to topiramate compared with other antiepileptics (RR 1.33, 95% CI 0.92 to 1.90). The RR of major congenital malformation occurrence for infants exposed to topiramate compared with those in disease-state cohorts were 1.12 (95% CI 0.81 to 1.55), 0.98 (95% CI 0.68 to 1.41) and 0.65 (95% CI 0.47 to 0.89) for migraine, epilepsy and diabetes cohorts, respectively.

Table 7: Frequency of oral clefts

Cohort	Patients, n	Oral Clefts, n (%)	RR Topiramate vs Comparator (95% CI)
Topiramate in first trimester	870	2 (0.23)	—
Anti-epileptic drug in first trimester	3615	6 (0.17)	1.39 (0.28-6.85)
Migraine	26,865	42 (0.16)	1.47 (0.36-6.06)
Epilepsy	2607	8 (0.31)	0.75 (0.16-3.52)
Diabetes†	13,062	34 (0.26)	0.88 (0.21-3.67)
Random sample	99,761	159 (0.16)	1.44 (0.36-5.81)

†Excludes individuals diagnosed with only gestational diabetes.
CI = confidence interval; RR = relative risk; — = not applicable.

Table 8: Frequency of major congenital malformations

Cohort	Patients, n	Major Congenital Malformations, n (%)	RR Topiramate vs Comparator (95% CI)
Topiramate in first trimester	870	37 (4.25)	—
Anti-epileptic drug in first trimester	3615	116 (3.21)	1.33 (0.92-1.90)
Migraine	26,865	1017 (3.79)	1.12 (0.81-1.55)
Epilepsy	2607	113 (4.33)	0.98 (0.68-1.41)
Diabetes†	13,062	859 (6.58)	0.65 (0.47-0.89)
Random sample	99,761	3758 (3.77)	1.13 (0.82-1.55)

†Excludes individuals diagnosed with only gestational diabetes.
CI = confidence interval; RR = relative risk; — = not applicable.

The authors conclude the results suggest little or no increase in risk for oral cleft or major congenital malformations when topiramate is used during pregnancy compared with exposure to other antiepileptics or to disease states such as migraine, epilepsy or diabetes. However, small numbers of events limit the strength of inferences.

Comments:

No significant differences were seen between topiramate and comparison antiepileptic or disease-based cohorts in the frequencies of oral clefts or major congenital malformation occurrences. This study included women taking topiramate for epilepsy and migraine prevention. There was no increased risk of oral cleft or major congenital malformation events for mothers exposed to topiramate as compared with mothers with these disease states. In the antiepileptic exposure group, it is unknown which antiepileptics were included and how many women were on each (eg, was valproate included and how many women were taking it).

3.1.4 Margulis et al 2012 – Use of topiramate in pregnancy and risk of oral clefts [17]

This US case-control study evaluated the association between monotherapy topiramate use in pregnancy and cleft lip with or without cleft palate (CL/P) in the offspring. Data from the Slone Epidemiology Center Birth Defects Study (BDS) from 1997–2009 and the National Birth Defects Prevention Study (NBDPS) from 1997–2007 were analysed. Both studies include infants with major congenital malformations as cases and infants with no malformations as controls.

Conditional logistic regression was used to compare first trimester use of topiramate monotherapy to no antiepileptic use during the periconceptional period between mothers of infants with CL/P and mothers of controls for each study separately, and in pooled data.

BDS contained 785 CL/P cases and 6986 controls; NBDPS contained 2283 CL/P cases and 8494 controls. The odds ratios for the association between topiramate use and CL/P were 10.1 (95% CI 1.1 to 129.2) in BDS, 3.6 (95% CI 0.7 to 200) in NBDPS and 5.4 (95% CI 1.5 to 20.1) in pooled data.

The authors concluded first trimester use of topiramate may be associated with CL/P.

Comments:
Results of this pooled analysis are consistent with earlier reports of an increased risk of CL/P associated with the use of topiramate in the first trimester of pregnancy.

3.1.5 Hernandez-Diaz et al 2012 – Comparative safety of antiepileptic drugs during pregnancy [18]

The authors reported on the population of women who enrolled in the North American AED Pregnancy Registry between 1997 and 2011. Data on antiepileptic use and maternal characteristics were collected through phone interviews at enrolment, 7 months' gestation and postpartum. Malformations were confirmed by medical records. The risk of major malformations was calculated among infants exposed to specific antiepileptics in monotherapy during the first trimester of pregnancy and among an unexposed group.

The risk of major malformations was 9.3% (30 of 323) for valproate, 5.5% (11 of 199) for phenobarbital, 4.2% (15 of 359) for topiramate, 3.0% (31 of 1033) for carbamazepine, 2.9% (12 of 416 for phenytoin, 2.4% (11 of 450) for levetiracetam, and 2.0% (31 of 1562) for lamotrigine. Compared with lamotrigine, the risk ratio (RR) was 5.1 (95% CI 3.0 to 8.5) for valproate, 2.9 (1.4 to 5.8) for phenobarbital, and 2.2 (1.2 to 4.0) for topiramate. 5 infants exposed to topiramate (1.4%) had a cleft lip.

The authors conclude antiepileptics such as valproate and phenobarbital were associated with a higher risk of major malformations than new antiepileptics such as lamotrigine and levetiracetam. Topiramate was associated with an increased risk of cleft lip compared with that of a reference population.

Comments:
See section 3.2.3 for an updated review of data from this registry.

3.1.6 Vajda et al 2013 – Associations between particular types of fetal malformation and antiepileptic drug exposure *in utero* [19]

The authors analysed data from the Australian Register of Antiepileptic Drugs in Pregnancy looking for information to indicate whether valproate or other antiepileptics may be associated with specific teratogenic patterns. Recruitment into the registry is completely voluntary.

Multiple variable logistic regression and other statistical analyses of data relating to 1733 fetuses from 1703 pregnancies. Almost all (about 98%) of the pregnancies were in women with epileptic seizure disorders, but 147 had taken no antiepileptics in at least the first trimester of pregnancy. Fetal malformations occurred in 109 of the 1733 pregnancy offspring (6.3%). Malformations were present in 5 of the 147 offspring not exposed to antiepileptics in at least the first trimester of pregnancy (3.4%), with malformations in 104 of the remaining 1586 (6.6%) first trimester antiepileptic exposed pregnancies: odds ratio (OR) 0.50 (95% CI 0.2 to 1.25). Further details of malformation rates are shown in Table 9.

Table 9: Exposure to individual antiepileptics occurring in >10 pregnancies, and associated malformation rates for those used in monotherapy

AED	AED total exposures	AED in monotherapy	Malformations	% Malformed
CBZ	519	361	18	5.0
LTG	542	315	13	4.1
VPA	447	271	37	13.7
LEV	151	63	1	1.6
TPM	117	44	1	2.3
PHT	84	44	2	4.5
CZP	108	26	0	0
GPT	31	14	0	0
OxCBZ	19	12	0	0
PB/PMD	15	5	0	0
ETHO	16	4	0	0
VGT	12	1	0	0
No AEDs	147	147	5	3.4

AED, antiepileptic drug; CBZ, carbamazepine; CZP, clonazepam; ETHO, ethosuximide; GPT, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OxCBZ, oxcarbazepine; PB/PMD, phenobarbitone, primidone; PHT, phenytoin; TPM, topiramate; VGT, vigabatrin; VPA, valproate.

The recorded malformations in the 104 malformed fetuses among the 1586 exposed to antiepileptics during pregnancy and in the 147 not exposed are shown in Table 10. Because multiple malformations can be present in the same fetus, the total individual malformations exceeds the total number of fetuses. There appeared to be a statistically significant association between topiramate and hypospadias and various abnormalities of the brain, but there are too few data to warrant undue confidence in accepting the association between topiramate and brain malformations. The 4 instances of hypospadias among the 60 male infants exposed to topiramate during pregnancy (6.67%) and 10 in the 681 males exposed to antiepileptics apart from topiramate (1.47%, OR 4.79, 95% CI 1.46 to 15.77). The rates of occurrence of hypospadias in topiramate-exposed fetuses (6.67%) were not statistically significantly higher than those in males not exposed to antiepileptics (4.62%, OR 1.48, 95% CI 0.32 to 6.89).

Table 10: Fetal malformations and the associated AEDs

Malformation	All AEDS	CBZ	LTG	VPA	LEV	TPM	PHT	No AED
Total exposed	1586	519	542	447	151	117	84	147
Total with malformations	104	28	27	54	5	11	5	5
Spina bifida	10	2	1	8	0	1	0	0
Sacral groove	4	2	0	2	0	0	0	0
Heart/great vessels	26	3	9	15	1	2	1	1
Hypospadias	14	3	3	6	1	4	1	3
Urinary tract	11	8	1	3	2	2	0	0
Digits	14	1	1	12	1	0	0	1
Palate/lip	6	0	1	5	0	0	0	0
Skull	15	4	6	8	1	1	0	0
Face	4	1	3	2	0	0	0	0
Legs	5	1	1	4	0	0	0	0
Mouth	6	0	1	5	0	0	1	1
Brain	16	4	4	10	1	3	0	1

AED, antiepileptic drug; CBZ, carbamazepine; CZP, clonazepam; ETHO, ethosuximide; GPT, gabapentin; LEV, levetiracetam; LTG, lamotrigine; OxCBZ, oxcarbazepine; PB/PMD, phenobarbitone, primidone; PHT, phenytoin; TPM, topiramate; VGT, vigabatrin; VPA, valproate.

The authors conclude this study suggests topiramate is a human teratogen with a possible tendency to produce hypospadias, but larger-scale investigations are needed.

Comments:

The association found in this study between topiramate exposure and hypospadias is based on small numbers of occurrences and should therefore be interpreted with care.

3.1.7 Mines et al 2014 – Topiramate use in pregnancy and the birth prevalence of oral clefts [20]

This was a multi-centre retrospective cohort study evaluating the association between topiramate use in early pregnancy and risk of oral clefts. It was funded by the marketing authorisation holder for Qsymia (phentermine + topiramate). Automated data from four US sources were used from 1997 to 2011. The authors compared the prevalence of oral clefts in infants of women exposed to topiramate in the first trimester (topiramate cohort) with the prevalence in infants of women formerly exposed to topiramate or other antiepileptics (formerly exposed (FE) cohort) and infants of women with similar medical profiles (SMPs) to the topiramate cohort that were not exposed to topiramate (SMP cohort).

Across all centres, 1945 TPM-exposed dyads, 13,512 FE dyads, and 13,614 SMP dyads were identified. There were a total of 36 cases qualifying as oral cleft cases. The pooled birth prevalence of oral clefts was 3.6 (95% CI 0.9 to 6.3) per 1000 infants in the topiramate cohort, 1.4 (95% CI 0.8 to 2.1) per 1000 infants in the FE cohort and 0.7 (95% CI 0.2 to 1.1) per 1000 infants in the SMP cohort (Table 11). Standardised by site, the prevalence ratio (PR) for topiramate vs. FE was 2.5 (95%CI 1.0 to 6.0) and for topiramate vs. SMP was 5.4 (95% CI 2.0 to 14.6). Adjusted for propensity score, the PR was 2.8 (95% CI 1.1 to 7.1) for topiramate vs. FE and 6.5 (95% CI 2.1 to 20.2) for topiramate vs. SMP. In additional analyses evaluating the topiramate monotherapy subcohort, there was no evidence of a dose-response relationship, but there was a suggestion of a duration-response relationship compared with the other cohorts.

Presuming that this relationship is causal, the authors estimate that for every 1000 infants exposed to topiramate during the first trimester, one could expect an additional one or two cases of oral cleft. The authors conclude consistent with other recent epidemiologic research, first trimester topiramate exposure was associated with an elevated birth prevalence of oral clefts.

Table 11: Case counts and birth prevalence of oral clefts by research centre and overall, standardised by centre

	Topiramate cohort		Formerly exposed cohort		Similar medical profile cohort	
Center	Cases* (*N*)	Birth prevalence† (95% CI)	Cases* (*N*)	Birth prevalence† (95% CI)	Cases* (N)	Birth prevalence† (95% CI)
Total	7 (1,945)	3.6 (0.9–6.3)	20 (13,512)	1.4 (0.8–2.1)	9 (13,614)	0.7 (0.2–1.1)
HealthCore	3 (495)	6.1 (1.3–17.6)	3 (2,935)	1.0 (0.2–3.0)	1 (3,465)	0.3 (0.0–1.6)
KPNC	0 (119)	0.0 (0.0–30.5)	4 (2,044)	2.0 (0.5–5.0)	0 (833)	0.0 (0.0–4.4)
OptumInsight	3 (748)	4.0 (0.8–11.7)	7 (4,196)	1.7 (0.7–3.4)	4 (5,235)	0.8 (0.2–2.0)
Truven Health	1 (583)	1.7 (0.04–9.5)	6 (4,337)	1.4 (0.5–3.0)	4 (4,081)	1.0 (0.3–2.5)

CI, confidence interval; KPNC, Kaiser Permanente Northern California.
*Number of clinically confirmed cases (total cohort size).
†Birth prevalence expressed in cases per 1000 infants.

Comments:

The FDA asked the sponsor of Qsymia (phentermine + topiramate) to conduct this epidemiological study looking at the risk for oral clefts and major congenital malformations in offspring of women exposed to topiramate during early pregnancy. This followed the FDA's classification of topiramate as a category D medicine and the expectation that more widespread use among women of childbearing potential would occur with this new product.

Recent population-based estimates of oral cleft prevalence in the US ranged from 0.76 to 1.70 per 1000 live births. This study found a moderate increase in birth prevalence of oral clefts in infants exposed to topiramate *in utero* during the first trimester.

3.1.8 Alsaad et al 2015 – First trimester exposure to topiramate and the risk of oral clefts in the offspring: A systematic review and meta-analysis [21]

The authors conducted a systematic review and meta-analysis of all eligible studies that investigated oral clefts in infants whose mothers took topiramate during the first trimester of pregnancy. The literature search covered 1 January 1996 to 30 September 2014.

Of the 2327 publications reviewed, 7 articles were identified (Table 12). However, one study (Hunt et al 2008) did not include a control group and therefore was included only in the single group analysis of the overall incidence rate for oral cleft.

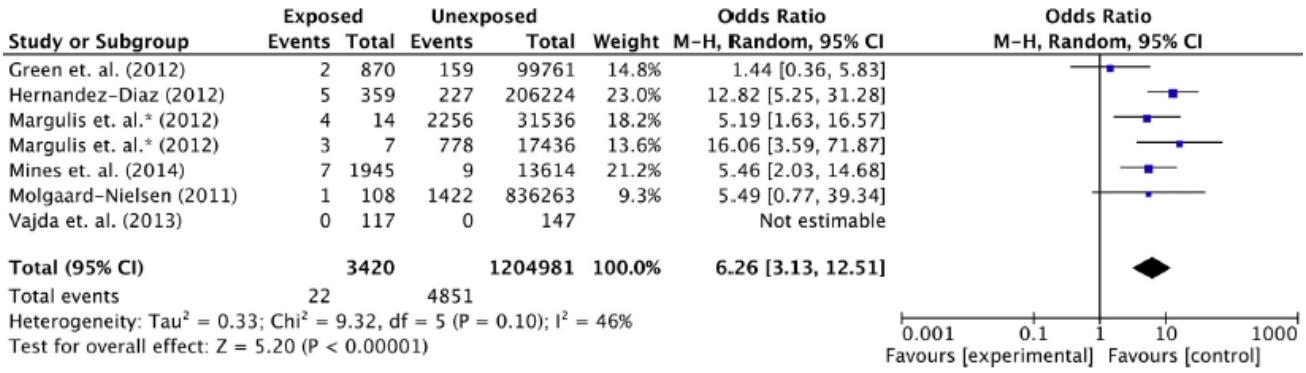
6 studies met the inclusion criteria for the meta-analysis, including 3420 patients and 1,204,981 controls. As shown in Figure 4, the odds ratio (OR) of oral cleft after first trimester exposure to topiramate was 6.26 (95% CI 3.13 to 12.51). The chi-square test for heterogeneity was negative suggesting that included studies were combinable. The quality score for the included studies ranged from 56 to 78%. When considering only the exposed groups, including the additional publication by Hunt et al that did not have a control group, the summary incidence rate for oral clefts following maternal exposure to topiramate in the first trimester was 0.36% (95% CI 0.25 to 0.48), which is higher than the reported rates expected in women taking no antiepileptic (ie, 0.07%). The studies by Mines et al and Hernandez-Diaz et al accounted for most of the relative weight (21.2% and 23%, respectively). When these two studies were excluded, the OR for oral clefts remained significant.

Table 12: Characteristics of controlled studies evaluating women exposed to topiramate during the first trimester and reporting data on oral clefts

Study (year)	Study design	Study period	Country	Journal	OC in TPM-exposed group	OC in TPM-unexposed group	Number of exposed/non-exposed
Mines D. (2014)	Retrospective-cohort	1997–2011	United States	Pharmacoepidemiology and Drug Safety	7	9	1945/13,614
Hunt S. (2008)	Prospective-observational-follow-up	Through 31 August 2007	United Kingdom	Neurology	2	None	70/none
Hernandez-Diaz S. (2012)	Prospective-observational-follow-up	1997–2011	North America	Neurology	5	227	359/206,224
Molgaard-Nielsen D. (2011)	Population-based cohort	1996–2008	Denmark	Journal of American Medical Association	1	1422	108/836,263
Margulis A. (2012)	Case–control	BDS 1997–2009	United States	American Journal of	3	778	7/17,436
		NBDPS 1997–2007	United States	Obstetrics and Gynecology	4	2256	14/31,536
Green M. (2012)	Retrospective-cohort	2002–2010	United States	Headache	2	159	870/99,761
Vadja F. (2013)	Prospective-observational-follow-up	1999–2013	Australia	Acta Neurologica Scandinavica	0	0	117/147

Abbreviations: BDS, Boston University Slone Epidemiology Centre Birth Defects Study; NBDPS, National Birth Defects Prevention Study; OC, oral clefts; TPM, topiramate.

Figure 4: Summation of studies reporting the rate of oral clefts



Note: The Margulis et al study consists of two large case-control studies. The first one is from the Boston Slone Epidemiology Center Birth Defects Study (BDS). The second one is from the National Birth Defects Prevention Study (NBDPS).

The authors conclude this study provides strong evidence that topiramate is associated with an increased risk of oral cleft in infants exposed to topiramate during embryogenesis and should lead to a careful review of topiramate use in women of reproductive ages.

Comments:

This meta-analysis included the 7 studies described above (sections 3.1.1 to 3.1.7). There was a 6-fold increased risk of oral cleft but the 95% confidence interval is wide (3.13 to 12.51).

3.1.9 Castilla-Puentes et al 2014 – Topiramate monotherapy use in women with and without epilepsy: Pregnancy and neonatal outcomes [22]

Janssen Research & Development (sponsor of Topamax) conducted this retrospective study in their global safety database. Spontaneous postmarketing reports involving women who used topiramate monotherapy during pregnancy were retrieved. Fetal or neonatal outcomes were examined to see if there were differences in the reporting and patterns of these outcomes for pregnant women with and without epilepsy.

Reports from 18 July 1995 (international birth date) to 30 April 2011 were retrieved. The global safety database includes reports from various sources including pregnancy registries, healthcare professionals, health authorities, clinical studies, consumers and the medical literature. All formulations for topiramate used as monotherapy were selected for analysis. Monotherapy was defined as any report where no other antiepileptic was listed either as a suspect or concomitant medicine regardless of indication.

1163 reports were retrieved of women using topiramate monotherapy during pregnancy for any indication. Since some women used topiramate for more than one indication, there were a total of 1199 reported indications which were primarily for treatment of epilepsy (n=599) and migraine prophylaxis (n=240). Of the 1163 cases pregnancy outcome was reported in 50.6% (n=589). As shown in Table 13, live birth was the most frequently reported outcome regardless of indication (epilepsy 78.8%, migraine prophylaxis 59.3%, other indication 64.4%).

Table 13: Pregnancy outcomes by indication reported in women on topiramate monotherapy (n=609)

Pregnancy outcome	Indications					
	Epilepsy	Migraine (prophylaxis)	Other	Not reported	Miscellaneous	Total
Total	599	240	130	222	8	1199
Live birth	312	48	27	55	3	–
Spontaneous abortion	48	22	13	15	2	–
Fetal death	15	1	1	2	0	–
Elective or induced abortion	21	10	8	6	0	–
Subtotal	396	81	49	78	5	609
Continuing or ongoing	203	158	80	144	3	–
''Recovered''	0	1	1	0	0	–

Notes: Overall, 589 pregnancy outcomes (live birth, spontaneous abortion, fetal death, and elective or induced abortion) were reported. However, a mother may have been treated with topiramate monotherapy for more than 1 indication, hence, by indication a total of 609 pregnancy outcomes were reported.

Overall, 370 fetal or neonatal outcomes in 183 infants were reported. There were 72 major fetal or neonatal anomalies reported in 54 infants (Table 14). Cleft lip or palate anomalies; limb, hand or other skeletal anomalies; and respiratory or cardiovascular anomalies were the most often reported major fetal or neonatal anomalies. There were more major fetal or neonatal anomalies reported in patients being treated for epilepsy (53/79 anomaly-indication pairs) compared with patients being treated for migraine prophylaxis (10/79 anomaly-indication pairs).

The authors conclude although incidence rates cannot be calculated based on spontaneous adverse event reporting, this summary of reported pregnancy and neonatal outcomes with use of topiramate monotherapy suggests that the risk of major fetal or neonatal anomalies may differ based on the indication for topiramate. No new or previously unreported safety signals were identified with topiramate use during pregnancy.

Table 14: Major fetal or neonatal anomalies by indication for topiramate monotherapy (n=79)

Total no of anomalies (Body System Group Anomaly as MedDRA PT)	Indications			
	Epilepsy or seizure	Migraine (prophylaxis)	Other	Not reported
Total	53	10	11	5
Cleft lip or palate anomalies	15	2	4	2
Cleft palate	5[a,b,c,d]	2[e]	3[e,f]	0
Cleft lip	8[a,b,c,d]	0	1[g]	0
Cleft lip and palate	2	0	0	2
Respiratory or cardiovascular anomalies	12	1	1	2
Ventricular septal defect	8[h]	0	0	0
Transposition of the great vessels	1[i]	0	0	0
Cardiac disorder	1[i]	0	0	0
Aorta hypoplasia	1[i]	0	0	0
Coarctation of the aorta	1[h]	0	0	0
Heart disease congenital[j]	0	1	0	1
Atrial septal	0	0	0	1
Laryngeal cleft	0	0	1	0
Urogenital anomalies	7	0	1	0
Hypospadias	7[d]	0	0	0
Renal hypoplasia	0	0	1[g]	0
Limb or hand or other skeletal anomalies	13	2	0	1
Limb malformation	1[k]	0	0	0
Polydactyly	2[k]	1	0	0
Aplasia	2[l]	0	0	0
Syndactyly	1[m]	1[m]	0	0
Congenital hand malformation	1[n]	0	0	0
Limb reduction defect	1[n]	0	0	0
Craniosynostosis	1	0	0	0
Congenital cleft hand	1[n]	0	0	0
Phalangeal agenesis	1	0	0	0
Adactyly	1[k]	0	0	1[o]
Limb deformity[p]	1	0	0	0
CNS anomalies	4	3	5	0
Spina bifida	1[q]	1[r]	1[r]	0
Meningomyelocele	1	1[r]	1[r]	0
Hydrocephalus	2[l,q]	1[r]	2[r]	0
Anencephaly	0	0	1	0
Gastrointestinal anomalies	2	2	0	0
Gastrointestinal obstruction	1[s]	1[s]	0	0
Diaphragmatic hernia	1	0	0	0
Pyloric stenosis	0	1	0	0

Notes: Overall, 72 major fetal or neonatal anomalies were reported in 54 infants A mother may have been treated with topiramate monotherapy for more than 1 indication; consequently, anomalies in such a case are associated with more than 1 indication. Hence, by indication a total of 79 fetal or neonatal anomalies were reported.
The footnotes identify anomalies that are associated with multiple maternal indications within the same neonate, in addition to identifying neonates with multiple malformations. Details regarding specific anomalies are also mentioned in the footnotes.
MedDRA, Medical Dictionary for Regulatory Activities; PT = (MedDRA) Preferred Term.
[a,b,c,d,g,h,q] Multiple malformations within the same neonate.
[e] Same neonate. The mother was treated with topiramate for migraine and increased intracranial pressure (i.e., ''Other'' indication).
[f] Includes 2 entries for the same neonate, reflecting the mother's treatment with topiramate for both binge eating and weight increase (i.e., ''Other'' indication).
[i] Multiple malformations within the same neonate. Cardiac disorder was coded for ''hole in heart.''
[j] Anomalies include 1 neonate with a single heart ventricle (maternal indication not reported) and another neonate with ''major cardiac anomalies'' (migraine [prophylaxis]).
[k] Multiple malformations within the same neonate. Polydactyly was coded for ''extra digit on one hand,'' adactyly was coded for ''missing toe,'' and limb malformation was coded for ''short leg''.
[l] Multiple malformations within the same neonate. In addition, aplasia was coded twice, once each for aplasia of the radius and the thumb.
[m,s] Same neonate. The mother was treated with topiramate for migraine and epilepsy.
[n] Multiple malformations within the same neonate. The limb reduction defect was coded for ''left ulnar longitude deficiency,'' and the congenital hand malformation was coded for ''three digits on each hand.'' The ''cleft hand'' occurred on the right side.
[o] Neonate had ''missing 4th and 5th fingers on both hands''.
[p] Neonate had a ''deformed right upper extremity''.
[r] Multiple malformations within the same neonate. The mother was treated with topiramate for headache and muscle contracture (i.e., ''Other'' indication).

Comments:

The limitations of this study are consistent with limitations of spontaneous reporting (eg, unknown numerator and denominator, comorbidities inconsistently reported).

Greater numbers of pregnancy cases with reported outcomes for patients with epilepsy compared with other indications could be the reason for higher numbers of reported major malformations (ie, reporting bias).

3.1.10 Silberstein 2016 – Topiramate in migraine prevention: A 2016 perspective [23]

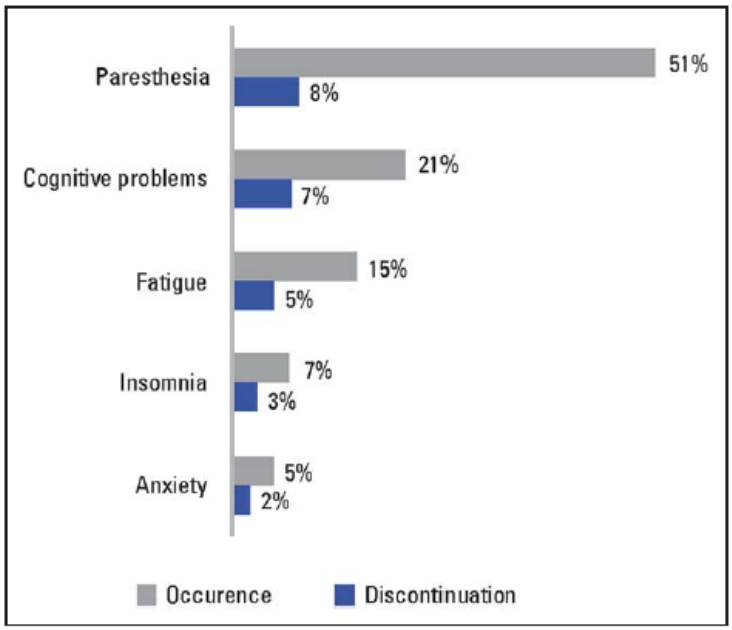
This article reviewed the profile of topiramate that has emerged out of the last 10 years of research and clinical use in migraine prophylaxis.

Topiramate has activity at multiple molecular targets which may account for its effectiveness in migraine whereas most other, more specific anticonvulsants are not. Based on RCTs, topiramate reduces migraine frequency and acute medicine use, improves quality of life and reduces disability in patients with episodic migraine and in those with chronic migraine with or without medication overuse headache. Its efficacy in chronic migraine is not improved by the addition of propranolol.

Consistent with clinicians' perceptions, migraine sufferers are more sensitive to topiramate-associated side effects than patients with epilepsy (eg, paraesthesias, cognitive symptoms). The greater susceptibility of migraine sufferers to adverse effects in general may reflect increased sensitivity of the migraine brain. Adverse effects leading to discontinuation in clinical trials of topiramate for migraine prevention are shown in Figure 5.

Postmarketing evidence has shown that first trimester exposure to topiramate monotherapy is associated with increased occurrence of cleft lip with or without cleft palate (pregnancy category D). In women who are planning to become pregnant, preventive therapy with topiramate should be discontinued recognising that the frequency and severity of migraine attacks tend to be substantially reduced during pregnancy.

Figure 5: Adverse events with significantly greater discontinuation rates for topiramate vs. placebo



Source: Lainez et al [24] comparing occurrence and discontinuation rates in pooled data for topiramate 100 mg/day in double-blind, placebo controlled trials in episodic migraine.

Comments:

This article reviewed the efficacy and safety of topiramate, including information gathered during clinical trials and post-market. The author is based at the Jefferson Headache Center in Philadelphia.

3.1.11 Negro et al 2017 – Headache and pregnancy: a systematic review [25]

This systematic review summarised existing data on headache and pregnancy with a scope on clinical headache phenotypes, treatment of headaches in pregnancy and effects of headache medicines on the child during pregnancy and breastfeeding, headache-related complications, and diagnostics of headache in pregnancy.

Options in prescription preventive medicines are limited and it may be best to consider the safest interventions, which are lifestyle changes and behavioural treatment for stress management.

When pharmaceutical treatment is needed for migraine prevention beta-blockers (metoprolol and propranolol) are the first-line option in pregnant and breastfeeding women. Tricyclic antidepressants are considered the safest second-line option when beta-blockers are contraindicated or ineffective. Amitriptyline is the preferred tricyclic antidepressant.

The use of topiramate in pregnancy is associated with an increased risk of cleft lip/palate and low birth weight, especially when taken during the first trimester. The possible benefits as a migraine prevention do not seem to outweigh the risks. Therefore topiramate should be avoided in this context. Topiramate reaches infant plasma level up to 25% of maternal levels and newborns should be monitored for sedation, irritability, poor suckling, weight loss and diarrhoea. No other significant side effects have been reported.

Comments:

The use of tricyclic antidepressants for migraine prevention is off-label in New Zealand. This article explored the time course of migraines and other headaches during pregnancy, as well as treatment options for pregnant and breastfeeding women.

3.1.12 Hernandez-Diaz et al 2018 – Topiramate use early in pregnancy and the risk of oral clefts [26]

The objective was to assess the relative risk of oral clefts associated with maternal use of high and low doses of topiramate during the first trimester for epilepsy and non-epilepsy indications.

This was a population-based study nested in the US 2000–2010 Medicaid Analytic eXtract. The cohort included 1,360,101 pregnant women with a live-born infant enrolled in Medicaid from 3 months before conception through 1 month after delivery. There were 2425 in the topiramate group, 1,322,955 in the unexposed group and 2796 in the lamotrigine group. Oral clefts were defined as the presence of a recorded diagnosis in claims during the first 90 days after birth. Women with a topiramate dispensing during the first trimester were compared with those without any dispensing and with an active reference group of women with a lamotrigine dispensing during the first trimester. Risk ratios were estimated with generalised linear models with fine stratification on the propensity score of treatment to control for potential confounders. Stratified analyses by indication of use and dose were conducted.

Results are shown in Table 15. The risk of oral clefts at birth was 4.1 per 1000 in the 2425 infants born to women exposed to topiramate compared with 1.1 per 1000 in the unexposed group (RR 2.90, 95% CI 1.56 to 5.40) and 1.5 per 1000 in the lamotrigine group (RR 2.38, 95 % CI 0.71 to 7.96).

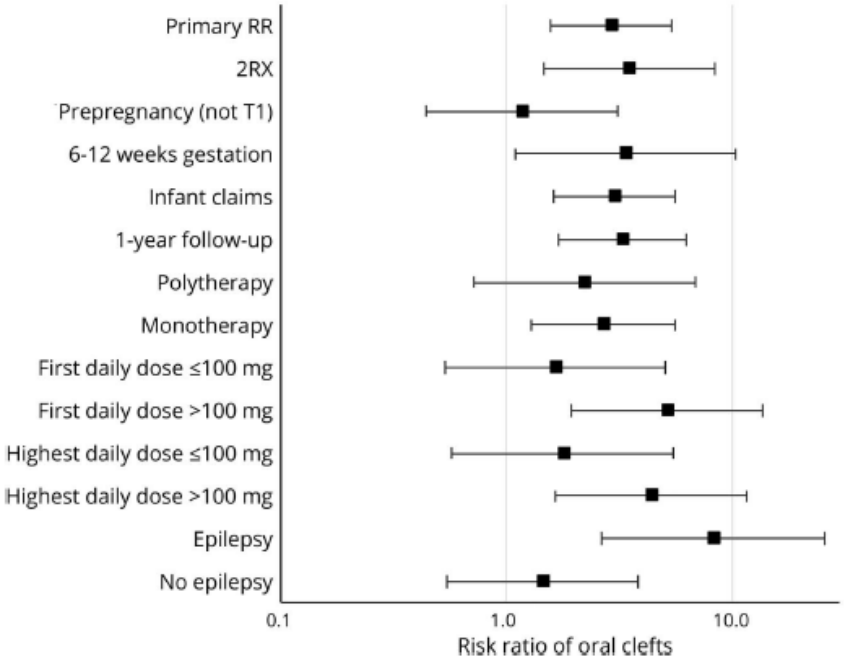
Results from secondary analyses are shown in Figure 6. The RR among women with epilepsy was 8.30 (95% CI 2.65 to 26.07); among women with other indications such as bipolar disorder, it was 1.45 (95% CI 0.54 to 3.86). The median daily dose for the first prescription filled during the first trimester was 200 mg for women with epilepsy and 100 mg for women without epilepsy. For topiramate monotherapy, the RR for oral clefts associated with doses ≤100 mg was 1.64 (95% CI 0.53 to 5.07) and for doses >100 mg it was 5.16 (95% CI 1.94 to 13.73). Results were similar when lamotrigine was used as a reference group.

Table 15: Risk of oral clefts among infants exposed to topiramate during the first trimester compared to infants exposed to lamotrigine and to unexposed infants

Oral clefts	Unexposed (n = 1,322,955)	Lamotrigine (n = 2,796)	Topiramate (n = 2,425)
Events, n	1,501	<11[b]	<11[b]
Risk (per 1,000)	1.1	1.5	4.1
Unadjusted RR (95% CI)	Reference	1.89 (0.85–4.21)	3.63 (1.95–6.76)
PS-adjusted RR (95% CI)		1.89 (0.85–4.21)	2.90 (1.56–5.40)
Unadjusted RR (95% CI)	NA	Reference	2.30 (0.69–7.64)[a]
PS-adjusted RR (95% CI)			2.38 (0.71–7.96)[a]

Abbreviations: CI = confidence interval; NA = not applicable; PS = propensity score; RR = risk ratio.
Medicaid Analytic eXtract, 2000 to 2010.
[a] Analyses comparing topiramate and lamotrigine were restricted to patients who did not concomitantly use topiramate and lamotrigine during the 90 days before the last menstrual period through the end of the first trimester.
[b] In accordance with the data-use agreement, we do not report information for frequency cells with less than 11 cases.

Figure 6: Secondary and sensitivity analyses with the unexposed group as reference

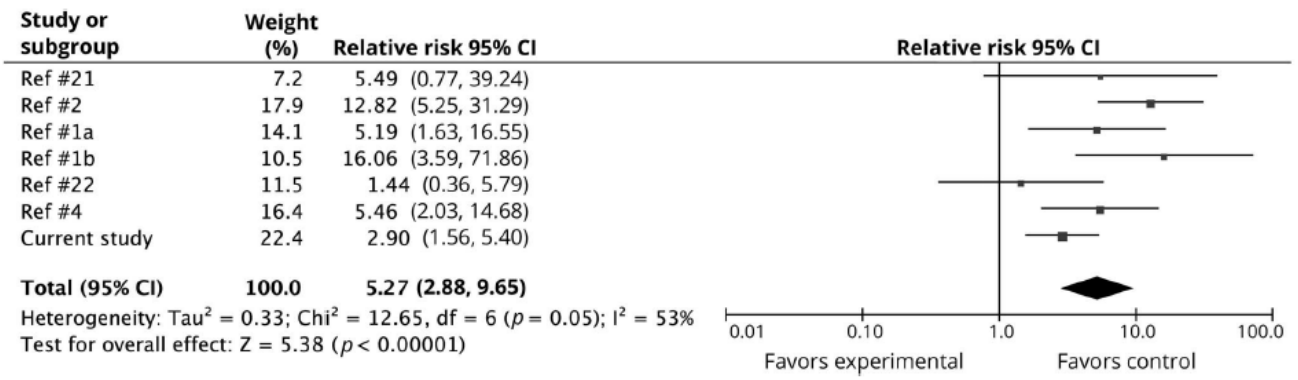


Adjusted risk ratio (RR) of oral clefts (dots) and 95% confident intervals (CIs, lines). Medicaid Analytic eXtract, 2000 to 2010. Relative risk estimate for the primary analysis is referred to as primary RR (2.90, 95% CI 1.56–5.40). Rx = prescription; T1 = first trimester.

Overall at least 6 studies have reported a risk for oral clefts among prenatally exposed live births >5 times larger than reference populations (Figure 7). The Green et al (2012) study did not find an association. However, this was based on 2 topiramate-exposed cases and the 95% CI for the RR included a 5-fold increased risk, therefore it was not inconsistent with the other findings.

The authors conclude the risk of oral clefts associated with use of topiramate early in pregnancy was more pronounced in women with epilepsy who used higher doses. Approximately 1 in 1000 infants is born with an oral cleft. Assuming that the association is causal, the observed RR would translate to a risk on the order of 5 cases of oral clefts per 1000 pregnancies exposed to topiramate at daily doses >100 mg in the first trimester.

Figure 7: Topiramate in early pregnancy and risk of oral clefts: Meta-analysis



Meta-analysis includes the relative risk estimate for the primary analysis from the current study (risk ratio = 2.90, 95% confidence interval [CI] 1.56–5.40). Size of the markers reflects the weight of the studies.

Notes: Ref #21 Molgaard-Nielsen et al 2011. Ref #2 Hernandez-Diaz et al 2012. Ref #1a & 1b Margulis et al 2012. Ref #22 Green et al 2012. Ref #4 Mines et al 2014.

Comments:

Lamotrigine was used as one of the comparison groups given the overlap of some indications in the US (epilepsy and bipolar). While lamotrigine is indicated for bipolar in New Zealand, topiramate isn't.

3.1.13 Blotiere et al 2019 – Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs [27]

This French nationwide cohort study assessed the association between exposure to monotherapy with 10 different antiepileptics during the first 2 months of pregnancy and the risk of 23 major congenital malformations.

Data was based on French healthcare databases including all pregnancies ≥20 weeks and ending between January 2011 and March 2015. Women were considered exposed when an antiepileptic was dispensed between 1 month before and 2 months after the start of pregnancy. The reference group included pregnant women with no reimbursement for an antiepileptic dispensing. Major congenital malformations were detected up to 12 months after birth (24 months for microcephaly, hypospadias and epispadias). Odds ratios (ORs) were adjusted for potential confounders for major congenital malformations with at least 5 cases. Otherwise, ORs with exact confidence intervals were calculated.

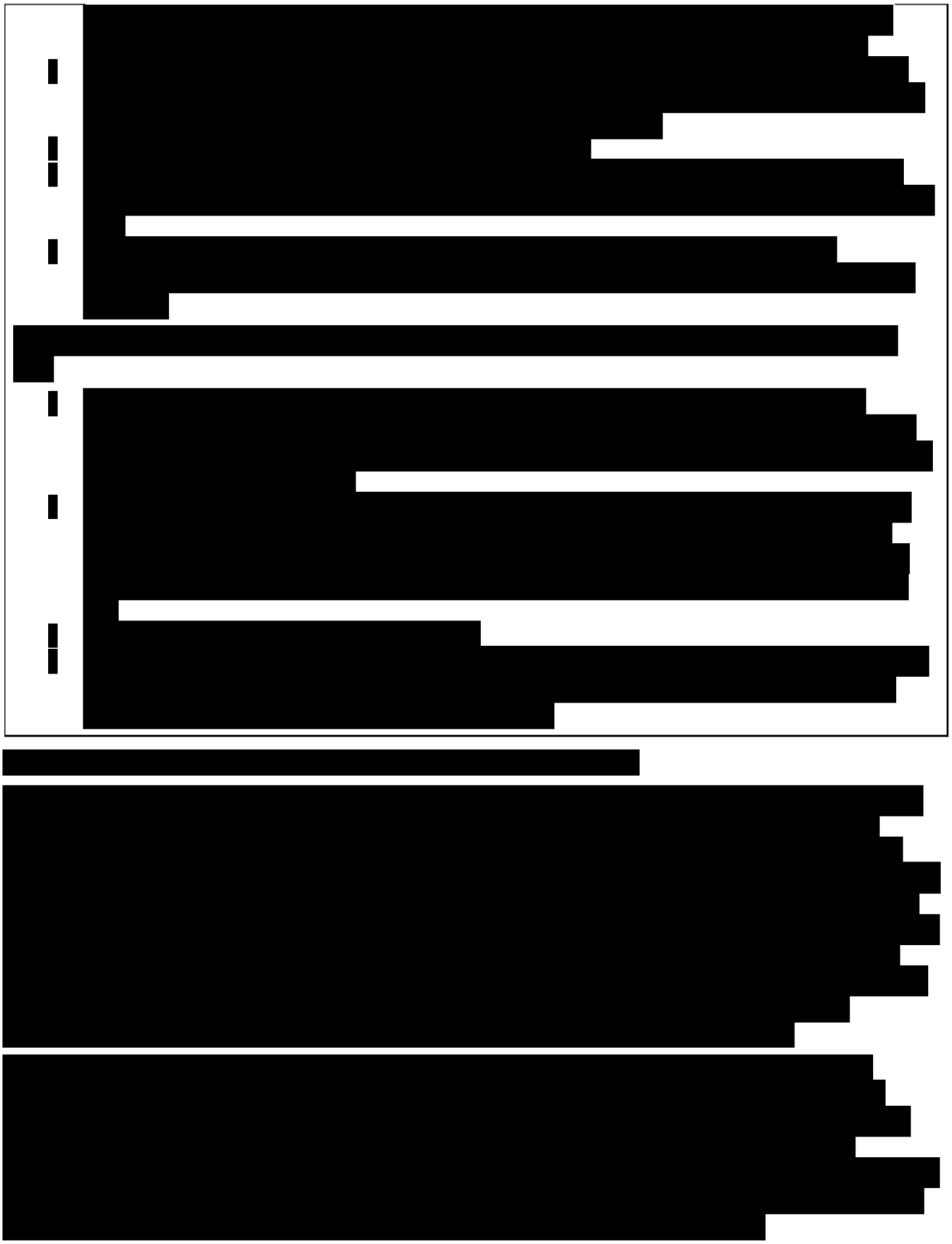
The cohort included 1,886,825 pregnancies of which 2997 were exposed to lamotrigine, 1671 to pregabalin, 980 to clonazepam, 913 to valproate, 579 to levetiracetam, 517 to topiramate, 512 to carbamazepine, 365 to gabapentin, 139 to oxcarbazepine, and 80 to phenobarbital. Exposure to valproate was associated with 8 specific types of major congenital malformations (eg, spina bifida OR 19.4, 95% CI 8.6 to 43.5). Exposure to topiramate was associated with an increased risk of cleft lip (OR 6.8 95% CI 1.4 to 20.0). There was no significant association for lamotrigine, levetiracetam, carbamazepine, oxcarbazepine, and gabapentin.

The authors conclude these results confirm the teratogenicity of valproate and topiramate.

3.2 Janssen-Cilag report

Janssen-Cilag is the sponsor for Topamax. Their response to Medsafe is summarised below (refer to Annex 1 for the full response).

[redacted]



[redacted]

Comments:
Data from this registry is included in the Topamax data sheet.

[redacted]

3.3 CARM data

The CARM database was searched for reports of congenital abnormalities with topiramate. One case (CARM ID 070638) was retrieved. This case was presented to the MARC at the June 2006 meeting and the information presented to the MARC at the time is attached as Annex 2 and is briefly described below.

This case was reported in February 2006 and concerned a male baby. He was exposed to fluoxetine, topiramate and carbamazepine [redacted]

At the time, the MARC considered topiramate and carbamazepine were more strongly implicated in this particular case. The causal association with fluoxetine, topiramate and carbamazepine was deemed to be possible for congenital anomaly. The MARC agreed no further regulatory action was required.

4 DISCUSSION AND CONCLUSIONS

Although migraine is not a fatal condition, it is a major cause of disability worldwide. It is more common in women than men and the prevalence peaks during childbearing years. Most pregnant women with a history of migraine report improvement in their migraines during pregnancy and this is possibly due to changes in estrogen levels.

According to the bpac^{nz} treatment guidelines, migraine prophylaxis can be considered for patients that find acute treatment to be inadequate, those that have more than 3 attacks per month and those that are at risk of medicine overuse headache. Beta-blockers are recommended first-line with amitriptyline (unapproved indication) as an alternative. Topiramate and sodium valproate (unapproved indication) are considered second-line medicines.

Topiramate (Topamax) was approved by Medsafe for migraine prevention in adults in 2004. As with the US and Australia, topiramate can be used during pregnancy if the potential benefit justifies the potential risk to the fetus. This is different to the UK where the use of topiramate for migraine prevention during pregnancy and in women of childbearing potential who are not using a highly effective method of contraception is contraindicated.

A meta-analysis of 7 studies by Alsaad et al 2015 concluded there is strong evidence that topiramate is associated with an increased risk of oral cleft in infants exposed to topiramate during embryogenesis and should lead to a careful review of topiramate use in women of reproductive ages. Studies since then have confirmed an increased risk of oral clefts, as well as an increased risk in low birth weight/small for gestational age.

There has been one New Zealand report of a major congenital malformation in a baby exposed to topiramate *in utero*. This was reported in February 2006. [redacted]

The 2 main risks with the use of topiramate during pregnancy appear to be up to a 10-fold increased risk for the development of oral clefts and an increased frequency of infants who are small for gestational age. Importantly, oral clefts occur in the first trimester of pregnancy before many women know they are pregnant. The current data sheet adequately describes these risks to enable a benefit risk discussion between the prescriber and patient. However, it is noted that many women experience a reduction in migraines during pregnancy so that treatment could be discontinued. In addition, the current indication allows the use of topiramate first-line for migraine prevention in adults.

5 ADVICE SOUGHT

The Committee is asked to advise if there is sufficient evidence and/or need to restrict the use of topiramate during pregnancy and/or women of childbearing potential for the prevention of migraines.

6 ANNEXES

1. Response from Janssen-Cilag [confidential]
2. CARM report 070638 [confidential]

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