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Foetal Anti-Convulsant Syndrome New Zealand

Addressing the past, present, and future for people of childbearing potential on anti-seizure medicines

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Addressing past harm

People harmed by anti-seizure medicines during pregnancy deserve support, recognition, and closure.

How to achieve this

Restorative process

- Implement a nationwide restorative process for anyone affected by anti-seizure medicines in pregnancy e.g. people with FACS, families, whanau, communities, healthcare professionals, governmental bodies/organisations.

Apology

- A formal apology should be given by the Government of New Zealand, to the people and families affected by anti-seizure medicines in pregnancy.

Education

- When ACC has a claim through Treatment Injury for FACS related cases then education is provided to the particular DHB.

Diagnosis and support

- Establishment of a FACS expert diagnostic pathway team for babies/children/adults exposed to anti-seizure medicine(s) during pregnancy.
    - A retrospective national lookback of people exposed to anti-seizure medicines during pregnancy
    - If a person is deemed to have been affected by anti-seizure medicine(s) during pregnancy then they either receive ACC (if eligible) or Disability Support Services (MOH)
    - The "Diagnosis and management of individuals with Fetal Valproate Spectrum Disorder; a consensus statement from the European Reference Network for Congenital Malformations and Intellectual Disability" guidelines should be followed. https://ojrd.biomedcentral.com/track/pdf/10.1186/s13023-019-1064-y.pdf
    - FACS and the respective individual syndromes should be recognised as a disability.

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Addressing present needs

People currently on anti-seizure medicines deserve informed consent, informed choice, and a whole of system approach.

How to achieve this

Risk mitigation

- Require healthcare professionals to adhere to The Code of Health and Disability Services Consumers' Rights and fully inform consumers regarding the risks of anti-seizure medicines in pregnancy.
- Design a colour coded system which clearly indicates which category the medicine falls into.
    - Under each colour there would be a set of either mandatory requirements (e.g. for red zone medicines) or recommendation/guidelines (e.g. for light blue zone medicines) to be followed.
      Please see tables on pgs. 16-17 which come from https://ansm.sante.fr/actualites/antiepileptiques-au-cours-de-la-grossesse-etat-actuel-des-connaissances-sur-les-risques-de-malformations-et-de-troubles-neuro-developpementaux to give an indication of how colour coding could be done, but recommendations for each medicine has not be given.
- Have alerts, flow charts and/or other systems in place to ensure warnings and information regarding anti-seizure medicine use in pregnancy is occurring, and healthcare professionals not just Xing out of it.
- When a review is conducted on an anti-seizure medicine then consumer groups and/or individuals should be part of the consultation process of the review.
- Legislative/regulatory changes
    - Make it compulsory for medicines to remain in original packaging, with pregnancy warnings, including pictogram, on them if they are known, or suspected, to be harmful during pregnancy.
    - Make it compulsory for medicines to have a pregnancy pictogram on the blister foil if the medicine is known, or suspected, to be harmful to an unborn baby.
    - Make consumer medicine information (CMI) sheets legislative. The CMI needs to have compulsory information around pregnancy, risk to a foetus and breastfeeding that is an easy read of the information in the datasheet.
    - Legislation to make patient information leaflets in boxes compulsory, and messaging that is consistent with the CMI sheet.
    - Make it compulsory to provide information, including resources to the consumer and healthcare professionals around anti-seizure medicines in pregnancy.
- Special Authority (under PHARMAC/MOH), or something similar, for sodium valproate (Epilim) for people of childbearing potential.
- Have a collaborative meeting with regulators, councils etc for anyone who prescribes, dispensers or provides support to people of childbearing potential that are on anti-seizure medicines.
- Medicines regulatory authority to talk about off label prescribing, and when talking to media mention other therapeutic uses of the medicine e.g. bipolar, pain relief.

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Surveillance

- A post marketing surveillance needs to be established in regards to exposure to anti-seizure medicines and pregnancy.
- Pregnancy register/registry needs to be established.
- All FACS diagnosis to be coded against ICD and SNOMED.

Prevention

- Funding for the Conporto, Event Detection and Mitigation (EDM) software throughout all GP practices, pharmacies, and hospital settings. This should be done for a minimum of 5 years to see if this can make a difference. Currently sodium valproate is the only anti-seizure medicine listed on the EDM. All anti-seizure medicines should be on the EDM.
- Recall people of childbearing potential that are currently on sodium valproate, to ensure they are fully informed.
- Continue to have an ACC FACS Prevention team.
- When ACC has a claim through Treatment Injury for FACS related cases then education is provided to the particular DHB.
- Hold education sessions by an expert medical professional and member of FACSNZ, for healthcare professionals to engage with them about providing information and resources to their consumers.
- Launch an awareness campaign into the prevention of FACS, by informed decision making.

Maternity

- The baby's NHI number should be flagged immediately after birth and noted on their record what medicines the baby had been exposed to, the dose, and gestation.
- Maternity documentation to include exposure to medicines during pregnancy, particularly those that are suspected or known to cause harm to an unborn baby.

Diagnosis and support

- Establishment of a FACS expert diagnostic pathway team for babies/children/adults exposed to anti-seizure medicine(s) during pregnancy.
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    - If a person is deemed to have been affected by anti-seizure medicine(s) during pregnancy then they either receive ACC (if eligible) or Disability Support Services (MOH)
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Addressing future peoples' needs

People who will take anti-seizure medicines deserve a system that is working with them and their baby's interests.

How to achieve this

Risk mitigation

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- Design a colour coded system which clearly indicates which category the medicine falls into.
    - Under each colour there would be a set of either mandatory requirements (e.g. for red zone medicines) or recommendation/guidelines (e.g. for light blue zone medicines) to be followed.
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- Special Authority (under PHARMAC/MOH), or something similar, for sodium valproate (Epilim) for people of childbearing potential.
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- Have a collaborative meeting with regulators, councils etc for anyone who prescribes, dispensers or provides support to people of childbearing potential that are on anti-seizure medicines.
- Medicines regulatory authority to talk about off label prescribing, and when talking to media mention other therapeutic uses of the medicine e.g. bipolar, pain relief.

Overall responsibility

- The agency (or something new created) that has the appetite to change, with legislative authority.

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TABLE 2 : COMPARISON TABLE OF MALFORMATION AND NEURODEVELOPMENTAL RISKS FOLLOWING *IN UTERO* EXPOSURE TO ANTIEPILEPTICS

	Malformation risks				Decreased hormonal contraceptive efficacy	Neurodevelopmental risks		Other risk factors identified
	Teratogenicity in animals	↗ in the **overall** frequency of **major** malformations [1]	Type of malformations the most overrepresented	Dose-effect relationship		Data available (order of magnitude)	Results / Conclusions	
Valproate	Yes	x4-5	Neural tube defects, oral clefts, hypospadias, cardiac defects, facial dysmorphia, craniostenosis, renal and uro-genital defects, limb defects, multiple malformation syndromes	Yes	No	Few data (~100 pregnancies)	**Confirmed risk:** ♦ **reduced DQ/ID** ♦ **developmental delay** ♦ **autism spectrum disorder** Data suggest an increase in attention deficit/ hyperactivity disorder	Severe exposure
Topiramate	Yes	**x3**	Oral clefts, hypospadias (+ low birth weight, growth retardation and small-for-gestational age, microcephalia)	The data tend towards a dose-effect relationship but it remains to be confirmed	Yes	Very few data	Potential risk (signal): Neurodevelopmental disorder cases reported. The risk cannot be ruled out and is to be considered.	♦ Severe exposure and ↗ ♦ Over-representation of the women ♦ Off-label
Phenobarbital / Primidone	Yes	**x3**	Cardiac, oral clefts, hypospadias, facial dysmorphia, hand and foot deformities (including hypoplasia of the fingers), microcephalia	Dose-effect relationship suggested but it remains to be confirmed	Yes	(Very) few data	Contradictory studies, neurodevelopmental disorder cases reported. The risk cannot be ruled out and is to be considered.	
Phenytoin / fosphenytoin	Yes	**x2-3**	Cardiac, oral clefts, hypospadias, facial dysmorphia, hand and foot deformities (including hypoplasia of the fingers), microcephalia	Lack of data	Yes	(Very) few data	Contradictory studies, neurodevelopmental disorder cases reported. The risk cannot be ruled out and is to be considered.	
Carbamazepine	Yes	**Up to x3**	Neural tube defect, cardiac, oral clefts, hypospadias, facial dysmorphia, microcephalia, hand and foot deformities (including hypoplasia of the fingers)	The data tend towards a dose-effect relationship	Yes	Few data (~100 pregnancies)	Contradictory studies, neurodevelopmental disorder cases reported. The risk cannot be ruled out and is to be considered.	Severe exposure
Pregabalin	Yes	**Potential risk (signal) -** Few data (<200 pregnancies[2]) (Central nervous system?)		Lack of data	No	Additional data requested	Data insufficient to be able to conclude	♦ Very severe exposure and ↗ ♦ Off-label
Gabapentine	Yes	Few data (~250 pregnancies[2]): insufficient to be able to conclude (Renal?)		Lack of data	No			♦ Very severe exposure and ↗ ♦ Off-label
Zonisamide	Yes	Data insufficient to conclude but specific risk profile to be considered: **growth retardation and small for gestational age**		Lack of data	No	Non-existent or almost non-existent	Non-existent or almost non-existent data: no conclusion possible	Off-label
Vigabatrin	Yes	Data insufficient to conclude but specific risk profile to be considered: **Visual field abnormality**		Lack of data	No study			
Felbamate	No	Data insufficient to conclude but specific risk profile to be considered: **Haematological toxicity / hepatotoxicity**		Lack of data	Yes			

[1] Increase compared to the frequency observed in the general population (which is 2-3)
[2] Number of pregnancies exposed in the 1st trimester, collected prospectively.

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	Malformation risks				Decreased hormonal contraceptive efficacy	Neurodevelopmental risks		Other risk factors identified
	Teratogenicity in animals	↗ in the **overall** frequency of **major** malformations[1]	Type of malformations the most overrepresented	Dose-effect relationship		Data available (order of magnitude)	Results/ Conclusions	
Perampanel	To be reviewed	Data almost non-existent (< 10 pregnancies[2]) or very few (<50 pregnancies[2]): no conclusion possible		Lack of data	Yes	Non-existent or almost non-existent	Non-existent or almost non-existent data: no conclusion possible	
Lacosamide	Insufficient				No			
Retigabine	Insufficient				No			
Eslicarbazepine	Yes				Yes			
Ethosuximide	Yes				No study			
Rufinamide	Yes				Yes			
Tiagabine	Yes				No			
Retigabine	To be reviewed				Yes			
Oxcarbazepine	Yes	The data available (**300 – 1,000 pregnancies**[2]) do not agree with a substantial increase in the overall risk of major malformations. Further studies are required to confirm or disprove it.	Little or not studied	Lack of data	Yes	Data almost non-existent	Data insufficient to be able to conclude	Severe exposure
Levetiracetam	Yes	Data from main studies with appropriate methodology (~ **1,000 pregnancies**[2]) do not agree with a substantial increase in the overall risk of major malformations.	Little or not studied		No			
Lamotrigine	Yes	The data available (> **5000 pregnancies**[2]) do not agree with a substantial increase in the overall risk of major malformations.	Not applicable[1]	Dose-effect relationship reported in one study but not found in 3 other studies of the same size	Submission in DIWG meeting On 19 June 2017	Few data (~ 100)	Data too few to enable a final conclusion (no signal in terms of IQ, evaluated up to the age of 6)	Very severe exposure

[1] *To date, over-representation of a specific type of malformations has not been demonstrated, nevertheless potential signals were identified occasionally in one study but not reported in the other studies; this means additional research is required (see section on lamotrigine)*

Antiepileptics during pregnancy: Current state of knowledge on the risk of malformations and of neurodevelopmental disorders
Synthesis

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