Safety Review – Antipsychotic in-utero exposure and neonatal extrapyramidal and withdrawal adverse events. V 2.0 May 2011

Background

On the 22nd February 2011 the U.S. Food and Drug Administration (FDA) made an online notification to consumers and healthcare professionals informing them that it had updated the *Pregnancy* section of drug labels for the entire class of antipsychotic drugs (typical and atypical). The new drug labels now contain more and consistent information about the potential risk for abnormal muscle movements (extrapyramidal signs or EPS) and withdrawal symptoms in newborns whose mothers were treated with these drugs during the third trimester of pregnancy.

The symptoms of EPS and withdrawal in newborns may include agitation, abnormally increased or decreased muscle tone, tremor, sleepiness, severe difficulty breathing, and difficulty in feeding. In some newborns, the symptoms subside within hours or days and do not require specific treatment; other newborns may require longer hospital stays.

The FDA reported that a search of their Adverse Event Reporting System (AERS) database through to 29 October 2008 identified 69 cases of neonatal EPS or withdrawal with all antipsychotic drugs.

Since December 2010 the following additional information appears on the US label for all antipsychotics:

> **Pregnancy**
>
> *Non-Teratogenic Effects*
>
> Neonates exposed to antipsychotic drugs (including **XXXX**) during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms following delivery. There have been reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required intensive care unit support and prolonged hospitalization.
>
> **XXXX** should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Janssen-Cilag, the Sponsor for Haldol, Risperdal and Invega notified the TGA by e-mail on the 23 February 2011 that they would be "working on updating the Australian PI soon to include this information for all our antipsychotic products".

On 25 February 2011 Pfizer Australia notified the TGA of the FDA antipsychotic label change but did not identify if they would be taking any action in Australia.

Antispychotic medication registered in Australia as of 24 February 2011 and the ADEC Pregnancy Category

1. Amisulpride B3
2. Aripiprazole B3
3. Ziprsidone B3
4. Clozapine C
5. Paliperidone B3
6. Risperidone B3
7. Quetiapine B3
8. Olanzapine B3
9. Sertindole B3
10. Haloperidol C
11. Chlorpromazine C
12. Trifluperazine C
13. Fluphenazine C
14. Flupenthixol C
15. Pericyazine C
16. Droperidol C
17. Zuclopenthixol C

TGA ADR Database

The TGA ADR database was searched using the following medDRA terms to capture neonatal extrapyramidal and/or withdrawal syndrome: Convulsion neonatal, Drug withdrawal syndrome neonatal, Dyskinesia neonatal, Encephalopathy neonatal, Feeding disorder neonatal, Fever neonatal, Hyperkinesia neonatal, Hypertonia neonatal, Hypokinesia neonatal, Hypothermia neonatal, Hypotonia neonatal, Hypoventilation neonatal, Neonatal anoxia, Neonatal asphyxia, Neonatal aspiration, Neonatal complications of substance abuse, Neonatal hypoxia, Neonatal oversedation, Neonatal respiratory depression, Neonatal respiratory distress syndrome, Neonatal respiratory failure, Neonatal tachypnoea, Neonatal tetany, Respiratory disorder neonatal. All antipsychotics currently registered in Australia were selected for the search. Separate searches were conducted for each of: age=0; drug withdrawal; and the pregnancy, puerperium and perinatal conditions SOC.

There were 19 case reports (excluding duplicates) identified (see Appendix 1) 18 of which involved an atypical antipsychotic medication. ADR 261303 and 259307 were duplicates as were 222910 and 226793. There were 2 cases with a concomitant typical antipsychotic suspected. There were 6 cases where an antipsychotic was sole suspected. Of the 19 case reports, the most common adverse events were neonatal drug withdrawal (14), jitteriness (8), agitation/nervousness (7), feeding problems (6), tremor (5), respiratory problems (5), hypertonia (4), irritability (4), somnolence (3), pronounced startle reflex (3), hypotonia (2), myoclonus/muscle twitching (2) and neonatal convulsion (2). Quetiapine was suspected in 10 reports, olanzapine in 4, risperidone in 3, haloperidol in 2, clozapinee in 1 and chlorpromazine in 1. There were 6 reports where an atypical antipsychotic was the sole suspected medication. Outcome was not recorded in many reports but in those where it was, all recovered although some required prolonged hospitalisation. Onset was poorly recorded for many of the reports but in those where it was, the onset occurred from 0 to 7 days following birth..

International data
A VigiBase search was conducted for atypical and typical antipsychotics using the same search criteria described above. Up to 15 February 2011, there were 130 reports for atypical antipsychotics and 33 reports for typical antipsychotics.

Literature Review
A brief keyword literature search (neonatal/extrapyramidal syndrome/withdrawal syndrome/ antipsychotic) revealed a number of case reports for neonatal extrapyramidal symptoms and/or withdrawal reactions including a review of global post-market reports for risperidone.[1] The National (Australian) Register of Antipsychotic Medication in Pregnancy was accessed on-line and to December 2010 the registry had 149 patients enrolled.[2] The most frequently prescribed antipsychotics in this group were quetiapine (42%; n=62), olanzapine (14%; n=21) and aripiprazole (8%; n=12). No results of any observational neonatal outcomes from the registry have been published to date.

Approved Australian Product Information (PI) Documents
All antipsychotic innovator PI's were reviewed. Only the phenothiazine antipsychotics and sertindole contain warnings about the potential for dose related neonatal neurological /extrapyramidal disturbances in neonates exposed in-utero during the third trimester. Appendix 2 outlines the PI review including the relevant Sponsor's and generic products.

Summary of Product Characteristics (SmPC) for UK licensed antipsychotics
Amisulpride
"If amisulpride is used during pregnancy, neonates may show adverse effects of amisulpride and thus appropriate monitoring should be considered".

Aripiprazole
Nil

Clozapine
Nil

Ziprasidone
Not marketed in the UK.

Paliperidone
"The use of antipsychotics during the last trimester of pregnancy has resulted in long term but reversible neurological disturbances of extrapyramidal nature in the infant. INVEGA should not be used during pregnancy unless clearly necessary".

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[1] Coppola D, Russo LJ, Kwarta RF Jr, Varughese R, Schmider J. Evaluating the postmarketing experience of risperidone use during pregnancy: pregnancy and neonatal outcomes. Drug Saf. 2007;30:247-64.
[2] Monash Alfred Psychiatry Research Centre. The National Register of Antipsychotic Medication in Pregnancy 2010 Newsletter [internet] [cited 25 February 2011]. Available from: http://www.maprc.org.au/sites/www.maprc.org.au/files/NRAMP%20Newsletter%20Issue%204%20December%202010.pdf

Risperidone:
"According to postmarketing data reversible extrapyramidal symptoms in the neonate were observed following the use of risperidone during the last trimester of pregnancy. Consequently newborns should be monitored carefully".

Quetiapine
"Following pregnancies in which SEROQUEL was used, neonatal withdrawal symptoms were observed".

Olanzapine
"Spontaneous reports have been very rarely received on tremor, hypertonia, lethargy and sleepiness, in infants born to mothers who had used olanzapine during the 3rd trimester".

Haloperidol
"Reversible extrapyrimidal symptoms have been observed in neonates exposed to haloperidol in utero during the last trimester of pregnancy. Haldol should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible".

Zuclopenthixol
"The newborn of mothers treated with neuroleptics in late pregnancy, or labour, may show signs of intoxication such as lethargy, tremor and hyper excitability, and have a low Apgar score".

Phenothiazines (e.g. chlorpromazine)
"Possible effects on the neonate include lethargy, paradoxical hyperexcitability, tremor and low Apgar score".

Conclusion
In clinical settings patients with severe psychotic or affective disorders may be maintained on antipsychotic medication during pregnancy in situations where the risk of untreated illness out way the potential risks to the pregnancy. Acute perinatal psychotic illness often requires treatment with antipsychotic medication in situations where there are high risks to the health and well-being of the mother, the unborn child and/or other individuals. A number of post-market reports of extrapyramidal symptoms and/or withdrawal symptoms in the neonate have been reported in Australia and internationally. The level of severity of such events appears quite variable. There is non-clinical and/or clinical evidence for antipsychotics crossing the placental barrier. While many reports contain confounding factors (e.g. maternal illness related factors, concomitant suspected medications, obstetric and peri-natal complications), there is biological plausibility for the reactions given that certain central nervous system drug-receptor interactions occur across all classes of antipsychotics, for example dopamine receptor blockade. The product information documents for all antipsychotics in the US now have warnings regarding these potential adverse reactions. With the exception of aripiprazole and clozapine, the antipsychotic SmPC's include similar warnings.

Recommendations
The product information for all antipsychotic medications registered in Australia should be updated with a class effect warning regarding the risk of neonatal extrapyramidal and/or withdrawal symptoms and signs occurring in neonates exposed to antipsychotics in the third trimester of pregnancy. This would align the Australian approved PI's with international labelling for antipsychotics and reflect the post-market experience. The following is proposed as a standard statement in the pregnancy section:

> *Non-teratogenic class effect*: Neonates exposed to antipsychotic drugs (including **DRUG NAME**) during the third trimester of pregnancy are at risk of experiencing extrapyramidal neurological disturbances and/or withdrawal symptoms following delivery. There have been post-market reports of agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress, and feeding disorder in these neonates. These complications have varied in severity; while in some cases symptoms have been self-limited, in other cases neonates have required additional medical treatment or monitoring.
>
> **DRUG NAME** should be used during pregnancy only if the anticipated benefit outweighs the risk and the administered dose and duration of treatment should be as low and as short as possible.

Additional risk mitigation could be provided by informing prescribers through a Medicines Safety Update article.

Dr Kevin Dodd
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Office of Product Review
25 February 2011
V2 26 June 2011

Appendix 1 TGA ADR Database Review

ADR No	Relevant concomitant 3rd trimester drug exposure*	Time to onset from birth	Adverse events and comments	Outcome
26939	Haloperidol Lithium Orphenadrine	unknown	Hypotonia Jaundice Cyanosis	?
146025	Chlorpromazine Olanzapine Sertraline Methyldopa	unknown	Convulsion Muscle twitching Nervousness Drug withdrawal	NYR
154426	Clozapine	unknown	Hypokinesia Foetal distress	?
168800	Olanzapine	Unknown	Agitation neonatal Somnolence	?
182620	Seroquel ~~Amisulpride~~	1 day	Feeding problems Hypertonia. Drug withdrawal	R
192448	Olanzapine Paroxetine	At birth (meds ceased 48 hrs prior to delivery)	Foetal distress – emergency caesarean section. Drug withdrawal Hypertonia Tremor Agitation Respiratory distress Salivary hypersecretion. Confounders include possible paroxetine withdrawal and sepsis (blood cultures positive for strep)	N-ICU R
192793	Moclobemide Risperidone Sertraline	Day3.	All medications suspected as possible. Drug withdrawal neonatal	?
~~222910~~ Same as 226793 & 221907	~~Risperidone (oral and consta)~~	~~Day 6.~~	~~48 hours of jitteriness, myoclonus and increasing apnoeas.~~	
226793	Risperidone (long acting inj) Valproate	7 days.	Pre birth (29 weeks). Recurrent myoclonic jerks Jitteriness Drug withdrawal syndrome Apnoeas. Possible concomitant sepsis.	Transfer to another hospital. ?
234569	Venlafaxine Olanzapine	Birth (4 hrs)	Opisthotonus Jittery ? convulsion	Prolonged hospitalisation. R

			Confounded by possible venlafaxine withdrawal.	
242385	Risperidone	unknown	Drug withdrawal Jitteriness.	R
248842	Quetiapine	2 days.	Irritable Hypertonia Jittery Jaundiced Difficulty feeding.	N-ICU R
249117	Quetiapine Fluoxetine Lithium	unknown	Shallow breathing Tremor Excessive sneezing Irritable. Foetal distress. Drug withdrawal Confounded by possible SSRI withdrawal.	N-ICU x 5 days. R
~~250741~~	~~Olanzapine~~ ~~Antibiotic NOS~~ Not likely to be withdrawal	~~unknown~~	~~Obstructed labour requiring caesarean section. Difficulty feeding (gastritis) and poor sleeping for 6-12 weeks. Antibiotics for mastitis may have contributed to gastritis.~~	
~~252792~~	~~Quetiapine~~	~~At birth~~	~~Born by caesarean section due to maternal distress. Neonatal respiratory distress~~	
~~253286~~	~~Moclobemide~~ ~~Risperidone~~	~~unknown~~	~~Feeding difficulties Premature birth.~~	
254377	Quetiapine Fluoxetine	unknown	Floppy Drug withdrawal Jittery for 4 days.	R

ADR No	**Relevant concomitant 3rd trimester drug exposure***	**Time to onset from birth**	**Adverse events and comments**	**Outcome**
259307	Quetiapine Haloperidol Sertraline Venlafaxine	After birth	Premature birth. Respiratory distress Jaundiced Shaking and tremor Irritability Feeding difficulty Drug withdrawal Confounded by possible withdrawal from SSRI/SNRI.	N-ICU R after 5 days
261303	DUPLICATE OF 259307			
262320	Quetiapine Citalopram	After birth	Respiratory depression. Jittery Shaking Pronounced startle reflex	SCN R

			Agitation Drug withdrawal Confounded by possible withdrawal from SSRI.	
263544	Quetiapine Sertraline	?	Quetiapine withdrawn at 39/40 Drug withdrawal syndrome Agitation Irritability Somnolence Difficulty feeding Confounder: ? sertraline withdrawal	?
273261	Quetiapine	? soon after birth	Foetal tobacco smoke and alcohol e exposure Drug withdrawal. Jittery Agitation for 2 days. Jaundice and polycythemia.	R
276194	Quetiapine Lamotrigine ~~Escitalopram~~ ~~Sodium valproate~~ Ceased in T1	≤ 1 day	Quetiapine ceased at 39/40. Newborn delivered at 40/40 by caesarean section due to falure of progression of labour. Jittery Agitated Shaking Difficulty feeding Pronounced startle reflex Drug withdrawal Concomitant lamotrigine	6 months for symptoms to completely resolve
276604	Quetiapine Stemzine Aldomet Novorapid Protaphane	?	Withdrawal syndrome Pronounced startle reflex Difficulty feeding Drowsiness ? stemazine withdrawal	SCN R

R= recovered. NYR= not yet recovered. ?= unknown. N-ICU: required management in neonatal intensive care unit. SCN= special care nursery
*Unless stated medications continued up until delivery.
Version 2 (updated review of TGA database)

Appendix 2 Registered antipsychotics in Australia, Sponsor's, and PI review of neonatal complications

Antipsychotic	Sponsor and Trade Name (Innovator highlighted)	PI inclusion of neonatal extrapyramidal and/or withdrawal syndrome
Amisulpride	• Aspen Pharma (AMIPRIDE) • Sanofi-aventis (**SOLIAN,** AMISULPRIDE SANDOZ, AMISULPRIDE WINTHROP) • Alphapharm (SULPRIX)	NIL
Aripirazole	• Bristol-Myers Squibb (**ABILIFY**) • Alphapharm (ABYRAZ) • Sandoz (ARIPIRAZOLE SANDOZ) • Apotex (APO ARIPIPRAZOLE)	NIL
Clozapine	• Novartis (**CLOZARIL**) • Hospira (CLOPINE)	NIL
Ziprasidone	• Pfizer (**ZELDOX**)	NIL
Paliperidone	• Janssen-Cilag (**INVEGA**, INVEGA SUSTENNA)	NIL
Risperidone	• Janssen-Cilag (**RISPERDAL**, RISPERDAL CONSTA) • Apotex (APO-RISPERIDONE) • Ranbaxy (OZIDAL) • Lupin (PHARMACOR RISPERIDONE, RISPERIBELL) • Dr Reddy's Laboratories (REDILEP, RESPAZ, RISPERIDONE-DRLA, RISTAP) • Sigma (RISPA) • Genepharm (RISPERIDONE-GA) • Alphapharm (RIXADONE) • Accord Healthcare (RISPACCORD) • Generic Health (RISPERIDONE GENERICHEALTH) • Sandoz (RISPERIDONE SANDOZ) • Ascent (RISPERIDONE-GA) • Aspen Pharma (DOUGLAS RISPERIDONE) • Eris Pharmaceuticals (RISPERNIA) • Pharmacor (RISPERICOR)	NIL
Sertindole	• Lundbeck Australia (SERDOLECT)	There is evidence that certain neuroleptics given in high doses during the last trimester can cause neurological disturbances of the extrapyramidal type in children.

Quetiapine	• AstraZeneca (SEROQUEL, SEROQUEL XR)	NIL
Haloperidol	• Sigma Pharmaceuticals (**SERENACE**) • Janssen-Cilag (HALDOL)	NIL
Chlorpromazine	• Sanofi-aventis (**LARGACTIL**) • Orion Laboratories (ORION CHLORPROMAZINE MIXTURE)	When given in high doses during late pregnancy, phenothiazines have caused prolonged extrapyramidal disturbances in the child. **Liquid (Orion) PI also states: " with the first signs appearing within 24 hours and lasting as long as 9 months"
Trifluoperazine	• Goldshield Healthcare (STELAZINE)	When given in high doses during late pregnancy, phenothiazines have caused prolonged extrapyramidal disturbances in the child. There are also reports of prolonged jaundice and hyperreflexia or hyporeflexia in newborn infants whose mothers received phenothiazines.
Fluphenazine	• Bristol-Myers Squibb (MODECATE)	When given in high doses during late pregnancy, phenothiazines have caused prolonged neurological disturbances in the newborn infant. The safe use of Modecate during pregnancy has not been established. Usage of phenothiazines near term or during labour may result in significant maternal hypotension or other events (eg. neonatal jaundice, neonatal hypo or hyperreflexia or extrapyramidal symptoms) that may be detrimental to the health of the mother or the neonate.
Flupenthixol	• Lundbeck (FLUANAXOL)	NIL

Pericyazine	• Sanofi-aventis (NEULACTIL)	When given in high doses during late pregnancy, phenothiazines have caused prolonged extrapyramidal disturbances in the child.
Droperidol	• Phebra (DROLEPTAN)	When given in high doses during late pregnancy, butyrophenones may cause prolonged neurological disturbances in the neonate.
Zuclopenthixol	• Lundbeck (CLOPIXOL, CLOPIXOL ACUPHASE, CLOPIXOL DEPOT)	Zuclopenthixol crosses the placental barrier in small amounts. When given in high doses during late pregnancy, related compounds have caused prolonged extrapyramidal disturbances in the newborn infant.