Second Generation Antipsychotics

Sarah DeBrunner MD

Andi Favini MD

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Objectives

- Preconception considerations
- Morphologic teratogenicity
- Neurodevelopmental teratogenicity
- Other neonatal outcomes
- Placental Passage of SGAs
- Pharmacokinetic changes in pregnancy
- Lactation

NATIONAL CURRICULUM IN
REPRODUCTIVE
– PSYCHIATRY –

Preconception Considerations

Fertility

- Risperidone is known to cause hyperprolactinemia which reduces fertility. When this occurs, consider switching to an alternative SGA to facilitate conception.

Metabolic syndrome

- Several SGAs are associated with an increased risk of metabolic syndrome. Address modifiable risk factors (obesity) and optimize treatment of comorbid medical illnesses (dyslipidemia, diabetes).

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Morphologic Teratogenicity

Habermann et al:

- Increased risk of cardiovascular malformations (isolated ASDs and VSDs),

  (aOR 2.17; 95% CI 1.2-3.91)

  - Detection bias may account for the increase

Huybrechts et al:

- All SGAs, No increased risk, (aRR 1.05; 95% CI, 0.96 – 1.16)
- Small increased risk for one individual agent (Risperidone):

  Overall malformations (aRR 1.26; 95% CI, 1.02 – 1.56)

  Cardiac malformations (aRR 1.26; 95% CI, 0.88 – 1.81)

  "Finding should be viewed as initial safety signal that requires further study."

*Lurasidone, Iloperidone, Paliperidone – no human data yet

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

(Habermann et al Journal Clinical Psychopharmacology 2013, Huybrechts et al JAMA Psychiatry 2016,)

Neurodevelopment

Johnson et al:

- APs (FGA and SGA) exposure in utero lead to lower scores on a standard test of neuromotor performance(Infant Neurological International Battery) in infants at 6 months of age.

Peng et al:

- Infants exposed to SGAs had delayed development in cognitive, motor, social-emotional, and adaptive behavior as measured by the Bayley Scales of Infant and Toddler Development at 2 months of age but not at 12 months of age.

  - Limitations to studies include contribution of maternal illness
  - Neurodevelopmental effects may only cause short-term delay

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Johnson et al, Arch Gen Psychiatry 2012, Peng et al, Psychopharmacology 2013

Other Outcomes

- SGA use in utero is associated with inconsistent outcomes for the following:
  - Spontaneous abortion
  - Birth weight (low and high)
  - Preterm birth

- Neonatal complications: FDA issued warning (2011) for APs
  - EPS and Withdrawal/Toxicity signs (hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding problems)
  - Findings based on 69 case reports, majority of cases confounded by other factors (concomitant use of other drugs)
  - Habermann found an increased risk for neonatal adaption, but findings may also be a result of comedication and effects of maternal mental illness.

    SGA exposure 15.6% (n=37/237) compared to no exposure 4.2% (n=43/1014)

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Kulkarni et al Expert Op on Pharmacotherapy 2015, Habermann et al Journal of Clinical Psychopharmacology 2013, Sadowski et a

Placental Passage

- Placental Passage – defined as the ratio of umbilical cord to maternal plasma concentrations:
  - Olanzapine 72.1 % (highest transfer)
  - Haloperidol 65.5 %
  - Risperidone 49.2 %
  - Quetiapine 23.8 % (lowest transfer)

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Boden et al Arch General Psychiatry 2012

Antipsychotic Metabolism in Pregnancy

- Increase in pregnancy:
    - CYP2A6
    - CYP2D6 (decreased serum levels of risperidone, aripiprazole, iloperidone)
    - CYP2C9
    - uridine 5’-diphosphate glucuronosyltransferase
- Decrease in pregnancy:
    - CYP1A2 (increased serum levels of clozapine, olanzapine)
    - CYP2C19
- Dosing may need to be adjusted if symptoms emerge

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

Long Acting Injectable Antipsychotics

- LAIs
  - Data limited to case reports
  - Rely on oral AP risks to guide discussion on LAIs, more safety data needed
  - Weight should be given to continuing LAIs if patient stable prior to pregnancy, unknown risks associated with starting LAI during pregnancy
  - Bypass first pass hepatic metabolism – levels may stay more stable

NATIONAL CURRICULUM IN
REPRODUCTIVE
– PSYCHIATRY –

Lactation

- Drug excretion < 10% is generally considered negligible and compatible with breastfeeding, as it is unlikely to lead to dose related adverse events in the infant
- The 10% limit has been accepted by organizations such as the American Academy of Pediatrics

SGA	Relative Infant Dose (RID)	Special precautions
Clozapine	1.33 – 1.4%	Monitor for agranulocytosis
Olanzapine	0.3 – 2.2%	
Quetiapine	0.07 – 0.1%	
Risperidone	2.8 – 9.1%	
Ziprasidone	0.07 – 1.2%	
Aripirazole	1%	Can lower serum prolactin, which may affect milk supply

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –

In Summary

- Preconception:
  - Optimize management of metabolic syndrome to reduce pregnancy complications.
  - Risperidone may impact fertility if associated with hyperprolactinemia.

- Morphologic teratogenicity:
  - No increased risk for SGAs except risperidone which was associated with small increase in risk for congenital malformations, including cardiac malformations. More data is needed.

- Neurodevelopmental teratogenicity:
  - SGAs associated with initial neurodevelopmental delay that resolved by 12 months of age. Need to control for severity of maternal illness in future studies.

NATIONAL CURRICULUM IN
REPRODUCTIVE
– PSYCHIATRY –

In Summary

- EPS/neonatal adaptation:
  - Interpret FDA warning with caution. Studies have not adequately considered comedication and effects of maternal illness.
- Placental Passage of SGAs:
  - Highest rate of transfer for olanzapine, lowest for quetiapine.
- Pharmacokinetics:
  - Consider changes in hepatic metabolism in pregnancy and monitor symptoms closely.
- Lactation:
  - <10% relative infant dose for SGAs, which is considered acceptable or breast feeding.

NATIONAL CURRICULUM IN REPRODUCTIVE – PSYCHIATRY –