On Parents, Children And the Drugs Between Them

"Memories from Toronto"

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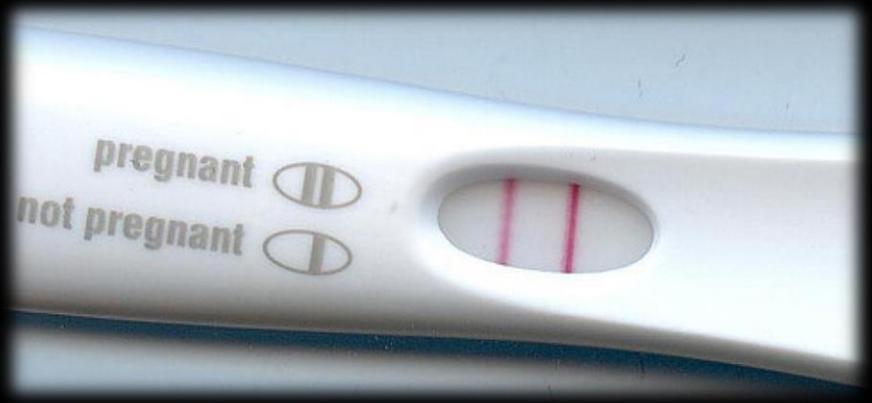
The Hospital for Sick Children
THE SLAIGHT FAMILY ATRIUM
SickKids
THE GARRON FAMILY CANCER CENTRE
PARKING
170 ELIZABETH STREET
EMERGENCY

Case #1

Case #1

- 32 y/o woman
- PMH: depression & anxiety, treated with escitalopram 20mg OD
- She has been taking escitalopram until yesterday
- Discovers she is pregnant, 6 weeks



Case #1

Google

GlaxoSmithKline

GlaxoSmithKline
Three Franklin Plaza
3F0615
PO Box 7404
Philadelphia PA 19101

Tel. 214 751 4000
www.gsk.com

December, 2005

IMPORTANT PRESCRIBING INFORMATION

Dear Healthcare Professional:

In September, 2005, GlaxoSmithKline (GSK) wrote to you regarding changes to the Pregnancy subsection of the PRECAUTIONS section in the labels for PAXIL® (paroxetine HCl) and PAXIL CR® (paroxetine HCl) Controlled-Release Tablets. These revisions were in response to preliminary data from a GSK-sponsored epidemiologic study of major congenital malformations in infants born to women taking antidepressants during the first trimester of pregnancy, which suggested an increased risk of congenital malformations with maternal exposure to paroxetine.

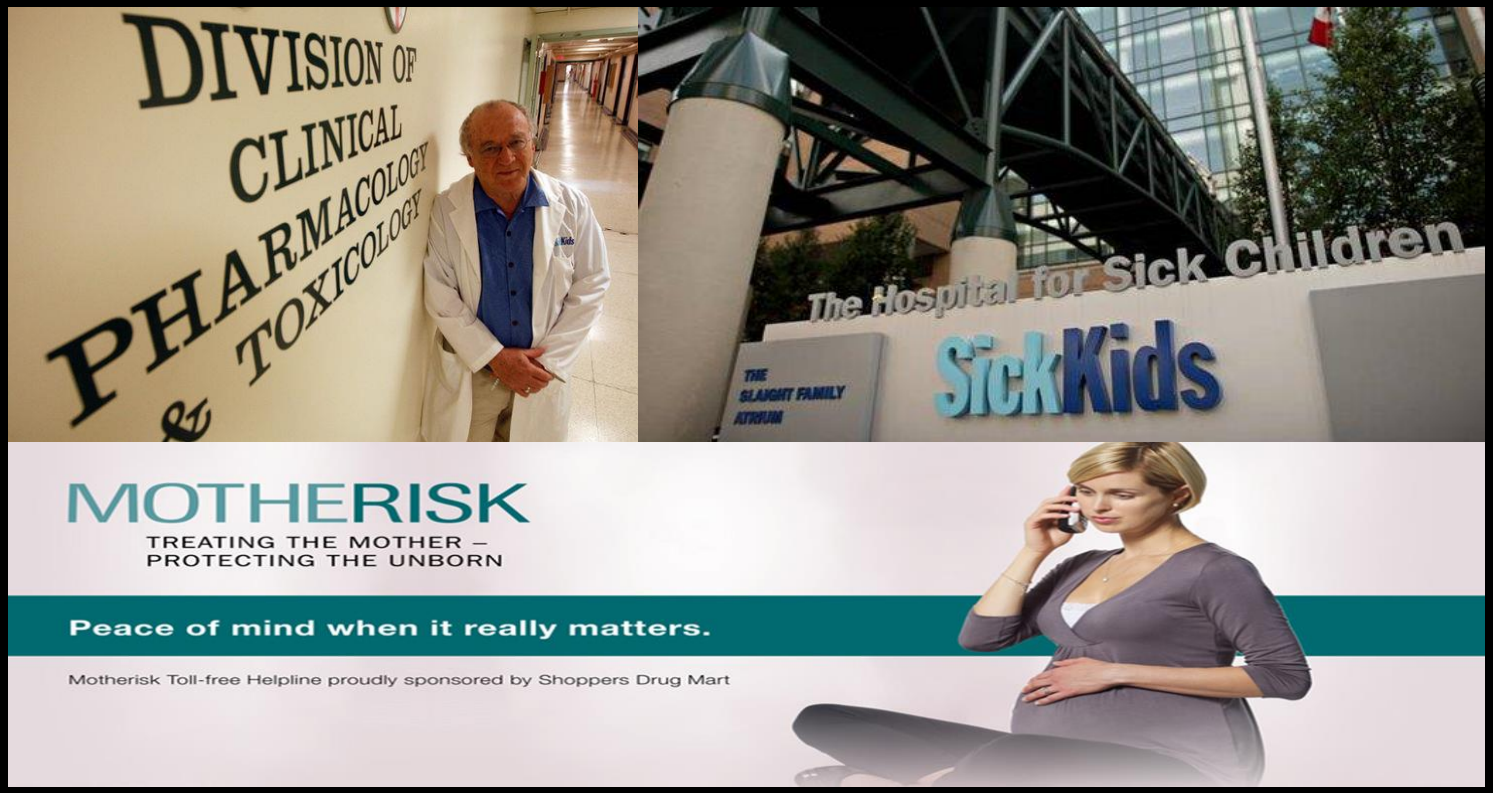
2-fold increased risk for cardiovascular defects, in particular VSD

Case #1

- Anxious, she books an appointment for elective termination, for next week.

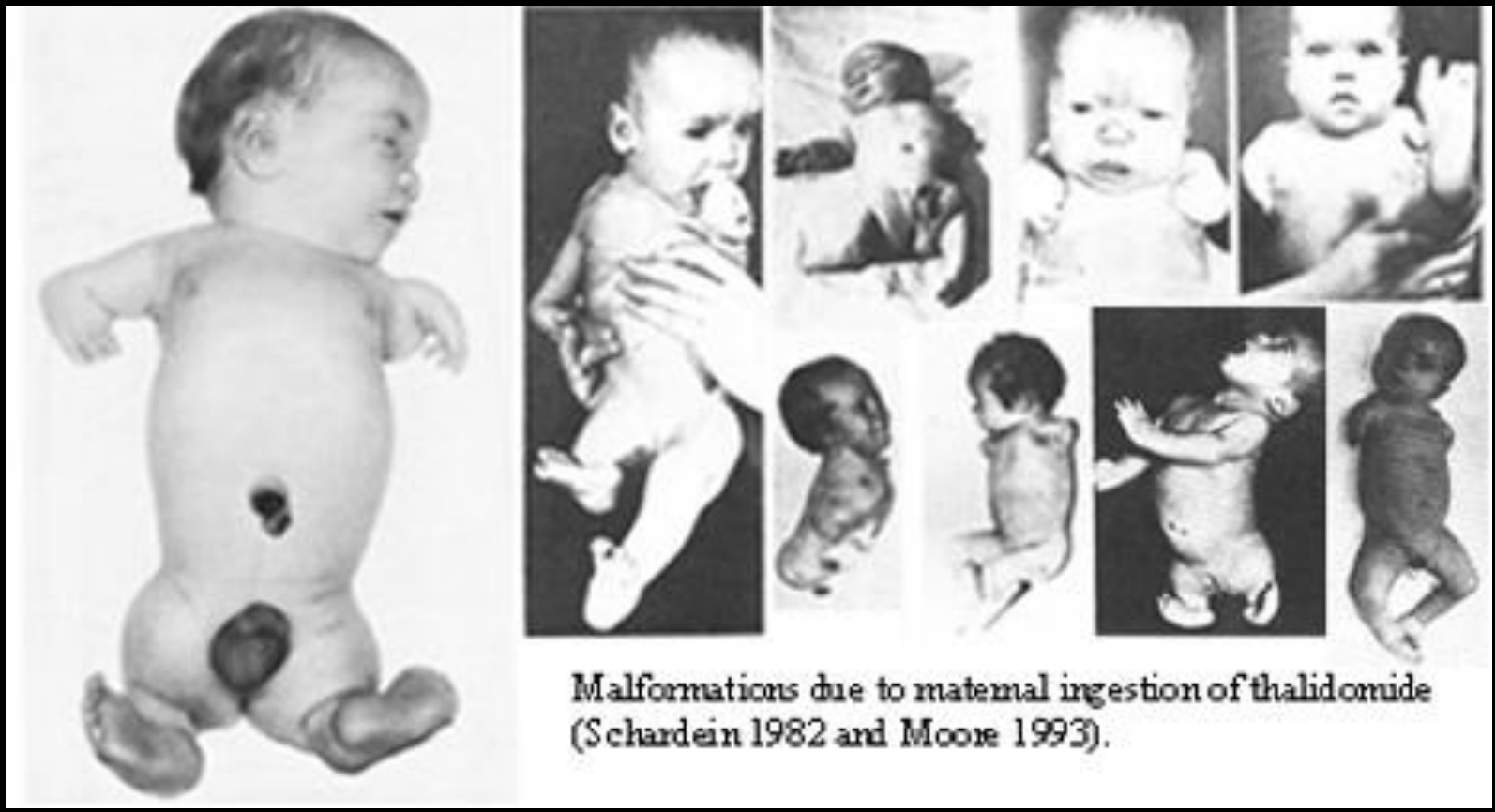
- She books an appointment to the MotheRisk clinic, SickKids, following an advice of a friend

Case #1



reproductive toxicology

Reproductive toxicology



Malformations due to maternal ingestion of thalidomide (Schardein 1982 and Moore 1993).

Complexity of studying drug safety in pregnancy

- Due to obvious ethical issues, very few randomized controlled trials exist.

- Observational studies are used, with limitations:
  - Small sample size
  - Bias (missing data on important confounders)
  - Questionable adherence
  - Questionable timing of exposure
  - Other medications used

- Incidence of major anomalies in the general population: 2-5%

Creators of information

- Teratogen information services (TIS) provide evidence-based information regarding the benefit/risk of different exposures during pregnancy and lactation.

ENTIS
EUROPEAN NETWORK OF TERATOLOGY INFORMATION SERVICES

MOTHERISK
TREATING THE MOTHER – PROTECTING THE UNBORN

Raising Mom's Awareness. Reducing Baby's Risk.
OTIS
Organization of Teratology Information Specialists

Antidepressants in pregnancy

Antidepressants in pregnancy

- Up to 25% of women of childbearing age suffer from depression.
- Up to 50% of all pregnancies are unplanned; by the time of discovery the fetus may have already been exposed.
- Women are increasingly using SSRIs in pregnancy

Br J Clin Pharmacol. 2008

2005

SSRIs AND BIRTH DEFECTS

WHAT ARE SSRIs?

Selective serotonin reuptake inhibitors (SSRIs) are the most popular antidepressant drugs used to treat depression and other mental illnesses worldwide. Scientists believe that depression can be triggered by a lack of the chemical serotonin, and these drugs maintain higher levels of serotonin in the brain to correct the issue.

USE

Antidepressants are popular in the United States. In 2010, more than 24.4 million prescriptions were filled for generic Prozac.

RISK

Research has linked SSRI use during pregnancy with serious birth defects, including persistent pulmonary hypertension of the newborn (PPHN), heart defects, respiratory distress, anencephaly and cleft lip/palate. The FDA has stated: "There are no adequate and well-controlled studies of SSRIs in pregnant women."

33%

Risk of respiratory distress for newborns of mothers taking an SSRI antidepressant during the third trimester; the normal risk is about 7 percent.

60%

Increased risk of heart defects for infants born to mothers who take SSRIs during their first trimester

IN 2005, DANISH RESEARCHERS FOUND THAT IF A MOTHER TAKES AN SSRI DURING THE FIRST TRIMESTER, HER CHILD HAS A 60 PERCENT GREATER CHANCE OF DEVELOPING A HEART PROBLEM THAN THE GENERAL POPULATION.

4X

Women who take more than one SSRI during their first trimester have a fourfold greater chance of having babies with right ventricular defects

drugwatch.com 800-452-0949 facebook.com/drugsideeffects/

Consequences of early reports

Women abruptly discontinued their SSRIs

- Fatal cases were reported in Canada
- 3-fold increase in the risk for a major depressive relapse

J Psychiatry Neurosci 2001, JAMA 2006, Can Fam Physician 2011

Women chose to avoid SSRIs during pregnancy – untreated depression

- Adverse maternal and neonatal outcomes

Obstet Gynecol 2004, N Engl J Med 2011, Am J Obstet Gynecol 2014

Early reports - potential flaws

- Women who receive antidepressants usually have more severe depression than women who do not receive medications - confounding by indication

- Newborns exposed to antidepressants may be more carefully assessed than other newborns, leading to ascertainment bias

Clin Ther 2007

N Engl J Med 2011

ARE SSRIs teratogens?

- Biological plausibility:
  - Potential target sites have been identified where serotonin could regulate key cellular processes in cardiac development

    Reprod Toxicol. 2011

- Experimental animal studies do not suggest an increased risk of congenital anomalies with SSRIs.

- Dose-response relationship was never observed

- Paroxetine is the most commonly reported SSRI associated with congenital anomalies, but no “class effect” was clearly demonstrated

Newer data

Danish Medical Birth Registry

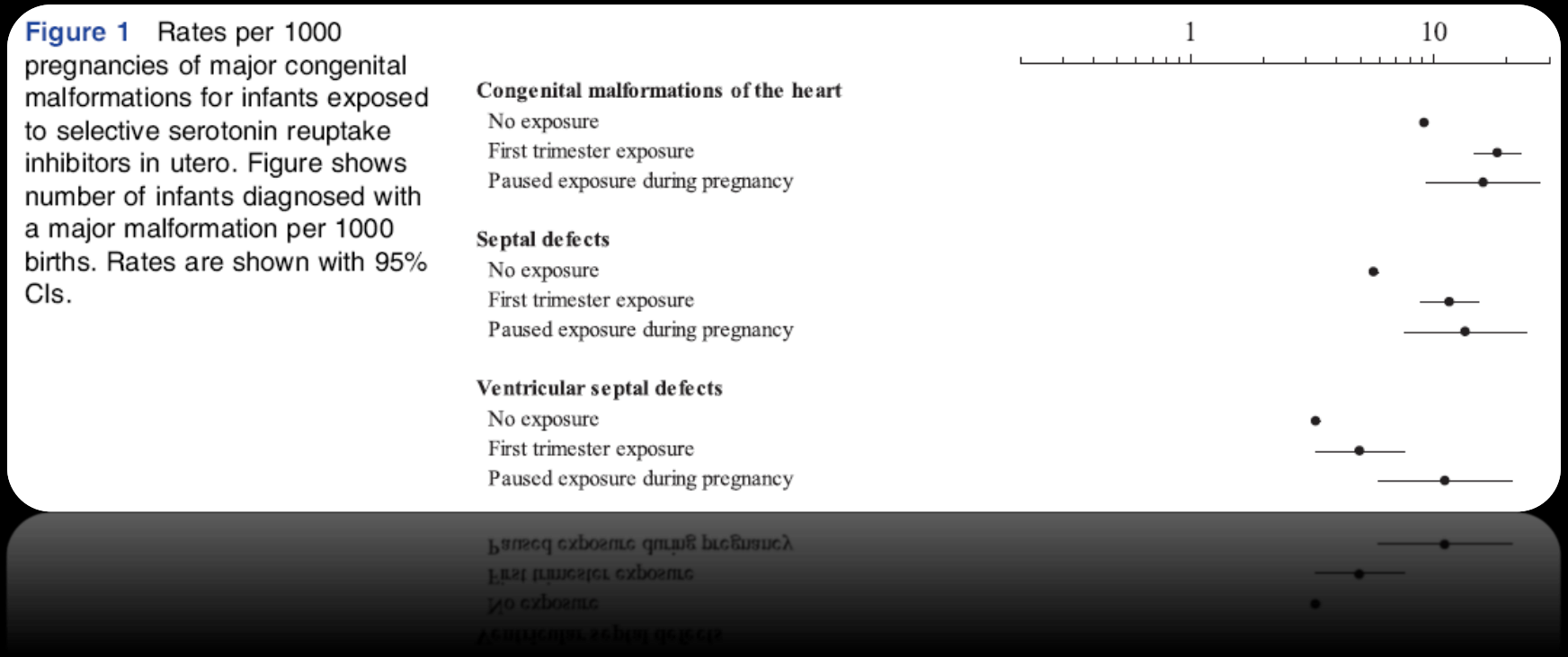


Figure 1 Rates per 1000 pregnancies of major congenital malformations for infants exposed to selective serotonin reuptake inhibitors in utero. Figure shows number of infants diagnosed with a major malformation per 1000 births. Rates are shown with 95% CIs.

BMJ Open 2012

Newer data – meta-analysis

ORIGINAL RESEARCH

American Heart Association | American Stroke Association

Selective Serotonin Reuptake Inhibitors (SSRIs) and the Risk of Congenital Heart Defects: A Meta-Analysis of Prospective Cohort Studies

Shang Wang, MD, PhD; Lijuan Yang, MD; Lian Wang, MD; Ling Gao, MD; Biao Xu, MD; Yunyun Xiong, MD, PhD

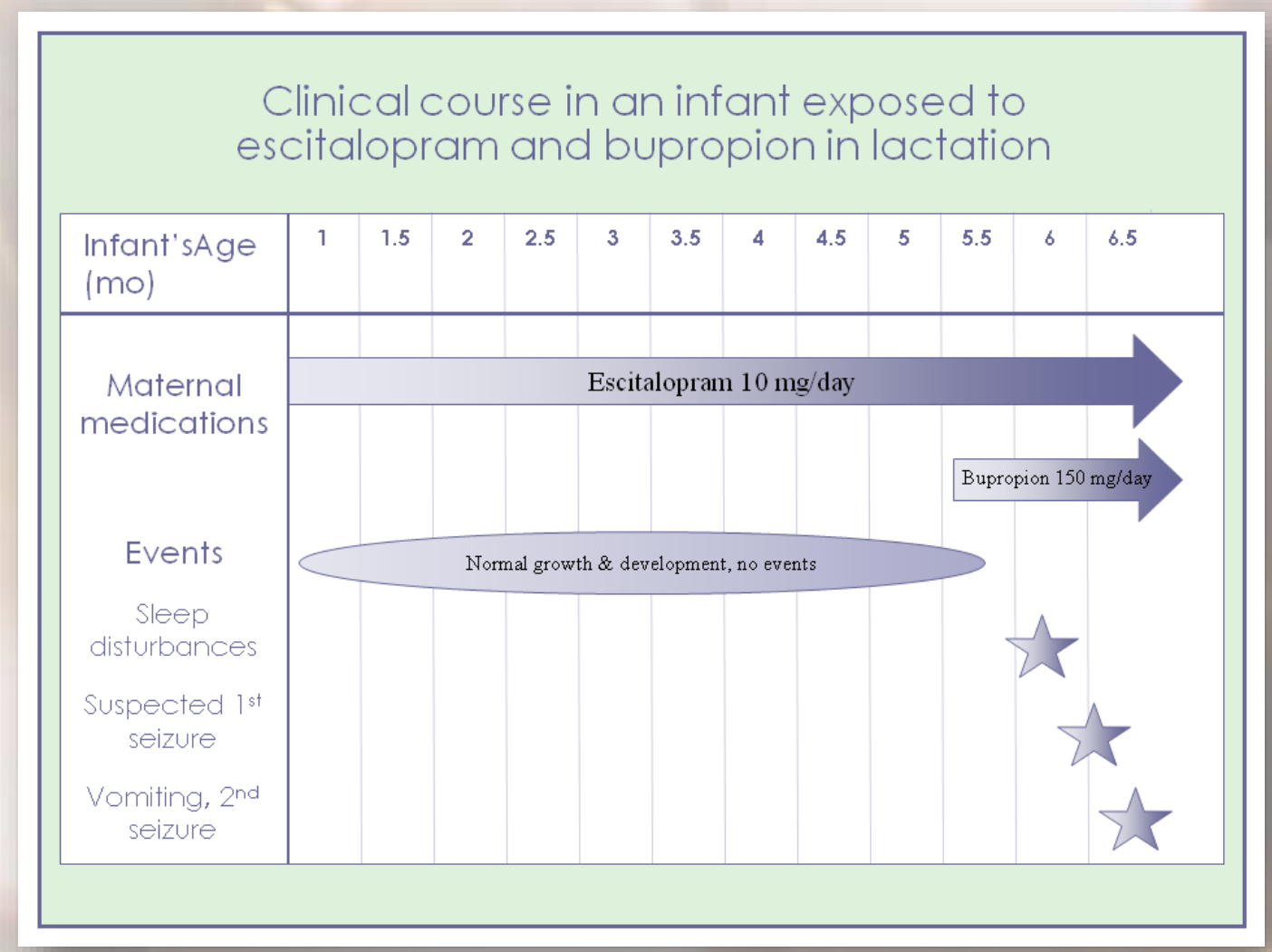
Methods and Results—PubMed and EMBASE up to July 2014 were searched for population-based cohort studies that reported SSRIs in pregnant women during the first trimester and live infants' heart defects at follow-up. A meta-analysis of published data was undertaken primarily by means of fixed-effects models. Four cohort studies including 1 996 519 participants were included with a mean follow-up period ranging from discharge to 72 months. SSRIs were not associated with increased risks of heart defects 1.06 (95% confidence interval: 0.94 to 1.18).

Conclusions—SSRIs during the first trimester in pregnant women were not associated with increased risks for newborn heart defects. (*J Am Heart Assoc.* 2015;4:e001681 doi: 10.1161/JAHA.114.001681)

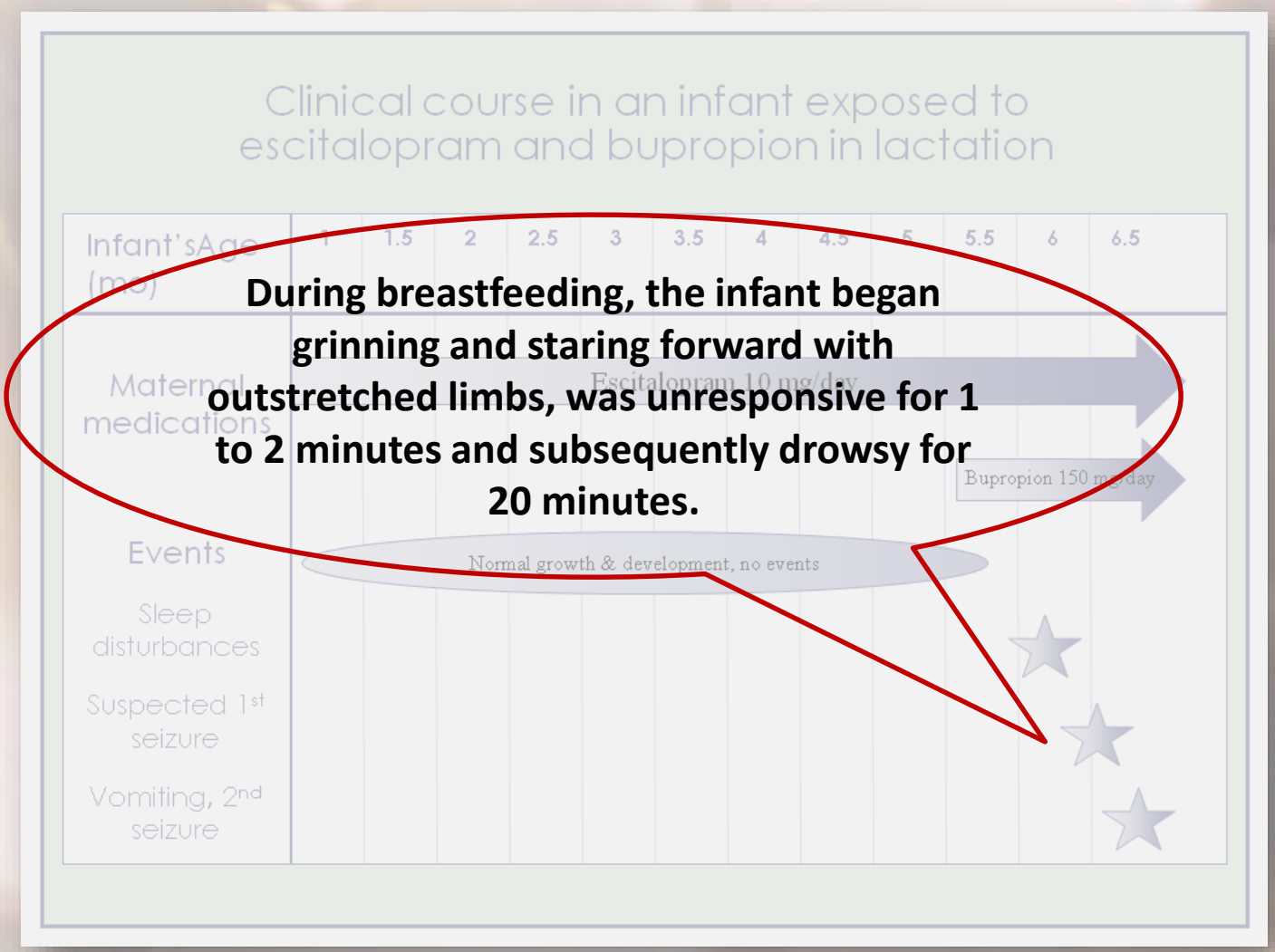
What's the verdict?

Case #2

Case #2


Clinical course in an infant exposed to escitalopram and bupropion in lactation
Infant'sAge (mo)
1
1.5
2
2.5
3
3.5
4
4.5
5
5.5
6
6.5
Maternal medications
Escitalopram 10 mg/day
Bupropion 150 mg/day
Events
Normal growth & development, no events
Sleep disturbances
Suspected 1st seizure
Vomiting, 2nd seizure

Case #2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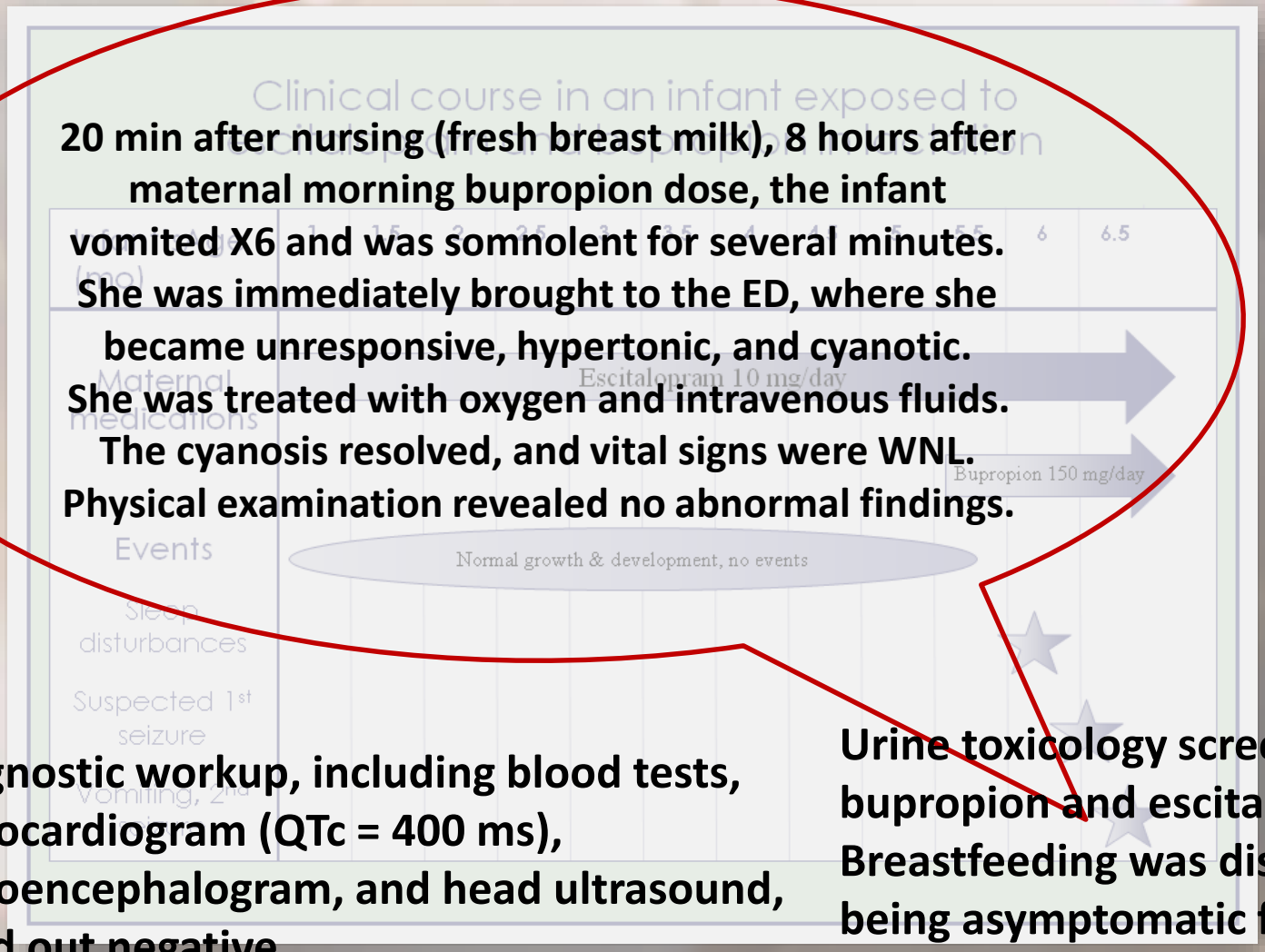
During breastfeeding, the infant began grinning and staring forward with outstretched limbs, was unresponsive for 1 to 2 minutes and subsequently drowsy for 20 minutes.

Case #2



20 min after nursing (fresh breast milk), 8 hours after maternal morning bupropion dose, the infant vomited X6 and was somnolent for several minutes. She was immediately brought to the ED, where she became unresponsive, hypertonic, and cyanotic. She was treated with oxygen and intravenous fluids. The cyanosis resolved, and vital signs were WNL. Physical examination revealed no abnormal findings.

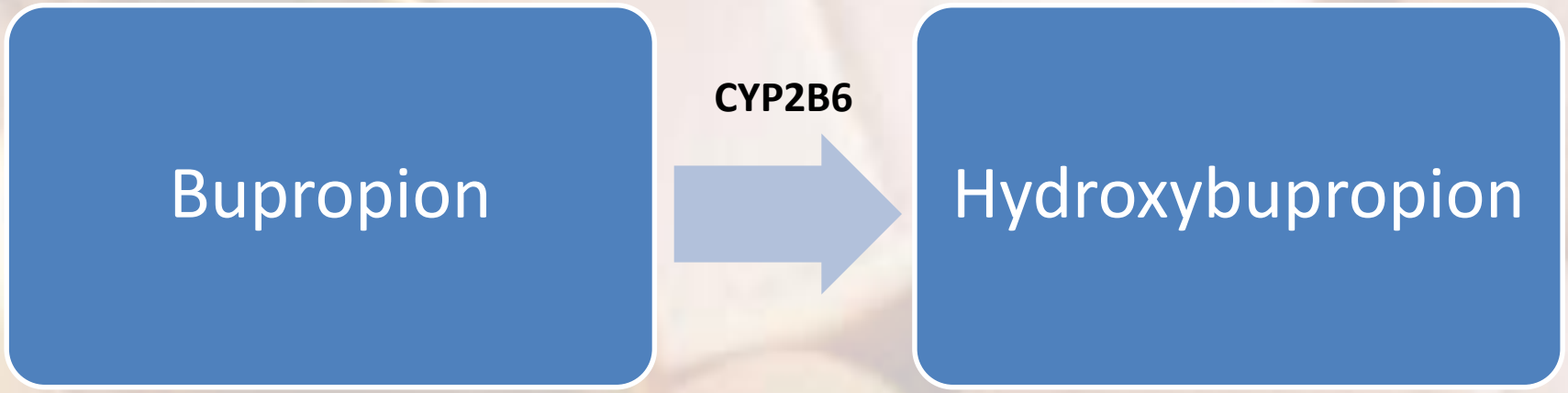
A diagnostic workup, including blood tests, electrocardiogram (QTc = 400 ms), electroencephalogram, and head ultrasound, turned out negative.

Urine toxicology screening revealed bupropion and escitalopram. Breastfeeding was discontinued. After being asymptomatic for 48 hours, she was discharged.

Drug induced seizures in a breast-fed infant

Neuman et. al, Ann Pharmacother. 2014

Phamacokinetics of bupropion



At steady state, HB levels are 4-10 fold higher than BUP levels.

Jefferson JW et al, Clin Ther. 2005

Data in our patient

- $[BUP]_{ss}$ = 0.12 ng/mL (based on milk levels and calculated dose)
- $[HB]_{ss}$ should have ranged 0.48-1.2 ng/mL.
- However, the observed concentration was 11.2 ng/mL.
- Possible explanations:
  - Most of the HB originated in the breast milk, rather than metabolism by the infant.
  - Immature elimination pathways in the infant (BUP accumulation)

Bupropion, escitalopram and seizures

- The epileptogenic nature of bupropion therapy is well described in adults.
- The adverse events in our case were associated with levels that are lower than the reported “therapeutic range”.
- Possible explanations:
  - Higher susceptibility in infants.
  - Concomitant use of bupropion and SSRI was shown to increase the risk of seizures.
    - Possible CYP2D6 inhibition, additive effects

Pisani F, Drug Saf. 2002

Spigset O, Acta Psychiatr Scand. 1997

Mothers are urged to breast-feed

Case #2 - Conclusion

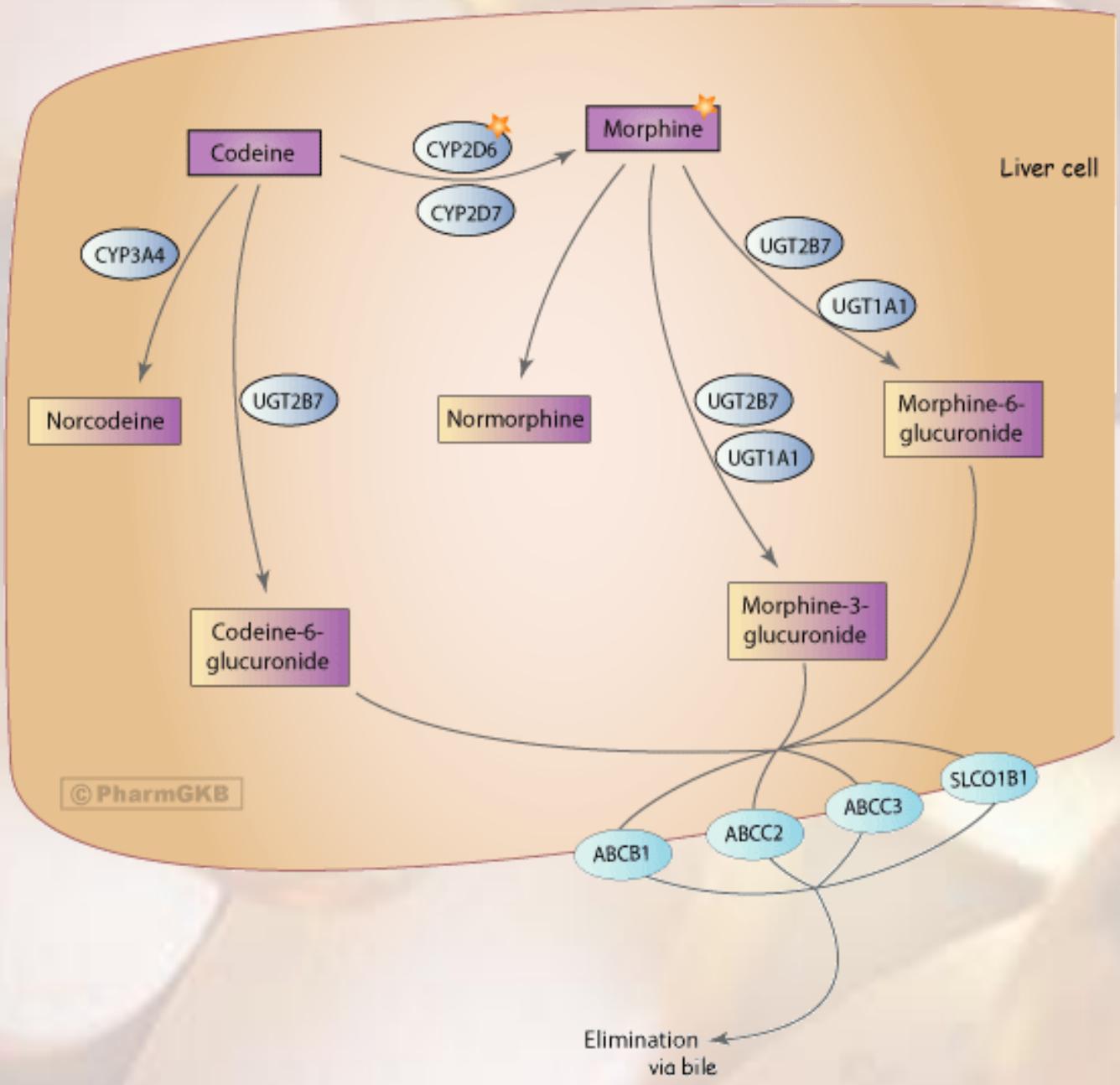
- Breastfeeding infants are increasingly exposed to maternal medications
- Psychotropic drugs, especially in combinations, require clinical monitoring of the infant and awareness of potential harm

Can exposures to drugs via breastmilk be fatal ?

Can exposures to drugs via breastmilk be fatal ?

- In 2005, a 13 days old baby was found dead.
- Postmortem analysis found extremely high levels of morphine
- Mother was treated with codeine since birth and was exclusively breastfeeding her baby

Lancet (2006)


Codeine
CYP2D6
CYP2D7
Morphine
Liver cell
CYP3A4
UGT2B7
UGT1A1
Norcodeine
UGT2B7
Normorphine
UGT2B7
UGT1A1
Morphine-6-glucuronide
Codeine-6-glucuronide
Morphine-3-glucuronide
SLCO1B1
ABCC3
ABCC2
ABCB1
© PharmGKB
Elimination via bile

Can exposures to drugs via breastmilk be fatal ?

- Genetic analysis revealed that the mother was a CYP2D6 ultrarapid-metabolizer (UM)

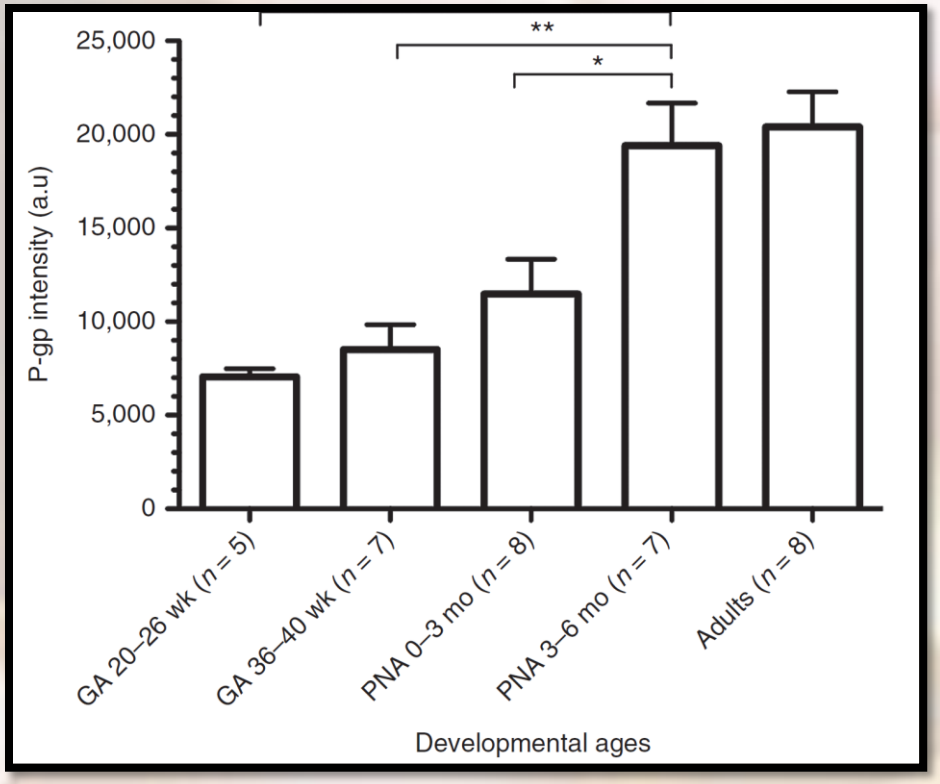
Lancet (2006)

CYP 2D6

- Increased enzyme activity – UM (ultrarapid metabolizers)
  - Multiple gene copies
    - 1% in Swedish Caucasians
    - 3.6% in Germany
    - 7-10% in Spain
    - 20% Saudi Arabians
    - 29% Black Ethiopians
    - 17% Jewish Ethiopeans
    - 12% Sepharadic Jews
    - 4-5% Yemenite Jews and Bedouines
- Clinical implications
    - Poor response to antidepressants requiring higher doses
    - Fatal codeine toxicity via breastfeeding

The plot thickens…

Drug transporters: P-gp, MRP1 – follow developmental pattern



Increased risk for opioid toxicity in neonates

Lam et al, Pediatric RESEARCH, 2015

What did we learn ?

What did we learn?

- Principles of teratology
- Antidepressants in pregnancy – ongoing debate
- Exposure to drugs via breastfeeding
- Drug induced seizures
- Drug-drug interactions
- Pediatric / developmental clinical pharmacology & toxicology


Sick Child
SickKi

שירותי רוקחות במכבי שירותי בריאות

- רוקח/ת קליני/ת (Pharm.D) בכל מרחב
- אגף רוקחות מחוזי
- פרמקולוגים קלינים במטה (ארצי)
- Therapeutic Drug Monitoring
- Pharmacogenetics
- Big Data Research (פרופ' ורדה שליו)
- חוברת מידע טרטולוגי שמתעדכנת תקופתית
- ייעוצים רוקחיים וירטואלים
- גישה ישירה למאגרי מידע – LexiComp, Micromedex ועוד

מכבי שירותי בריאות

יש קופות חולים ויש מכבי

Division of Clinical Pharmacology & Toxicology

- Israeli Poison Information Center
- Haifa Teratology Information Center
- Pediatric Clinical Pharmacology & Toxicology
- Pharmacogenetics
- Physiologically based pharmacokinetic models
- Occupational exposures

Thank you

Questions ?

galn2911@gmail.com