Management of Teratogenic Medications

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This presentation may use the terms ‘woman/women’ and ‘female(s)’ to refer to people capable of becoming pregnant. These terms refer to people who were assigned a biologic sex of female; information in this presentation applies to all people of childbearing potential regardless of gender identity.

Objectives

- The pharmacist participant will be able to:
  - Discuss the history of FDA pregnancy category letters
  - Describe the FDA Pregnancy and Lactation Labeling Rule
  - Identify common teratogenic medications taken by women of childbearing age
  - Given a patient on a teratogenic medication, discuss best practices for managing their medication therapy, including contraceptive options and possible drug interactions

- The pharmacy technician participant will be able to:
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How comfortable are you discussing teratogenic medications with patients?

A. Extremely comfortable
B. Somewhat comfortable
C. Neutral
D. Somewhat uncomfortable
E. Extremely uncomfortable

Why does it matter?

- Pregnancy & medication use
  - In the United States, 9 out of 10 pregnant people take at least one medication during pregnancy
  - Pregnant people take an average of 2.6 medications at any time during pregnancy

Placental Drug Transfer

- Almost all drugs will cross the placenta to reach the fetus
- The greatest risk of adverse drug effects on the fetus is probably during organogenesis during the first trimester
  - Some exceptions, though
- Transplacental can be beneficial to treat specific fetal conditions
  - Steroids administered to mom to promote fetal lung maturation
Teratogen

- Any agent that can disturb the development of an embryo or fetus
- May cause a birth defect in the child
- May cause termination of pregnancy
- Classes of teratogens include radiation, maternal infections, chemicals, and drugs

Why does it matter?

- "6% of females become pregnant while taking a potentially teratogenic medication"
- Retrospective database review (2004)
  - 4.6% (n=6976) received a category X drug within 270 days of delivery

Why does it matter?

- Prescription claims data (2010)
  - 18% of females receiving category X medications also received oral contraceptives
  - Refill patterns suggested non-adherence to oral contraceptives (similar to general pop. 18-44 years old)
- Retrospective chart review (2019)
  - 10% of females prescribed a teratogenic medication
  - 62% of these were not using birth control

Why does it matter?

- Retrospective review for reproductive life plans (2016)
  - Medication list included in only 75% of plans
  - 8% of females reported use of at least one potentially teratogenic medication
  - 29% of these reported using contraception
- Retrospective chart review (2017)
  - Females taking warfarin (category X)
  - Contraceptive method documented in only 19% of PCP visits after initiation of warfarin
  - Gynecologic consultation associated with greater use of more effective contraception

Why does it matter?

- Retrospective observational study (2015)
  - 26% of females prescribed potentially teratogenic antiepileptic drugs (AEDs) reported using contraception
  - 89% of females using AEDs and oral contraceptives had potential drug-drug interactions
  - Less than 7% had received contraceptive counseling

Why does it matter?

- Physician survey (2010)
  - 62.3% had cared for people of childbearing potential taking cat D or X medications in the past year
  - 58.1% felt residency did not adequately prepare them to counsel about contraceptives
- Focus group (2009)
  - Most common source of “counseling” was a pamphlet
Patient perspectives

• “They never asked me if I planned on becoming pregnant soon, unless it was for, like, a research study. No, they never really have, and I just wonder how much it has to do with me being single.”

• “I could see him [my doctor] asking the question, “Are you planning a family?” or something like that. But everybody… don’t want children! Everybody’s not in the planning your family stage.”

Source: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2806515/

Patient perspectives

• The two things they pushed were the pill and abstinence… they briefly discussed the other options, but it was not really a choice, it was like, this is what you should do.”

• “No one ever explained anything to me, ever. They just said you are going to have to be on hormonal birth control.”

• “Looking back, I wish it [contraceptive counseling] had been longer because now that I know more about various types of birth control and the various side effects… I wish they would have told me some of those things.”

Source: https://jamanetwork.com/journals/jamadermatology/fullarticle/1783063

Patient perspectives

• In these qualitative studies, participants expressed a preference for their provider to not make assumptions about their reproductive life plans, and to provide comprehensive contraceptive counseling.

• Patients taking potentially teratogenic medications should be counseled on options, including safe & effective contraception to prevent pregnancy and switching medications if/when a pregnancy is desired.

FDA Pregnancy Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Adequate and well-controlled studies have failed to demonstrate risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).</td>
</tr>
<tr>
<td>B</td>
<td>Animal reproduction studies have failed to demonstrate risk to the fetus and there are no adequate and well-controlled studies in pregnant women.</td>
</tr>
<tr>
<td>C</td>
<td>Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.</td>
</tr>
<tr>
<td>X</td>
<td>Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.</td>
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1957: Thalidomide entered the market advertised as “completely safe” for everyone

1962: FDA inspector Frances Kelsey prevented thalidomide from approval in the US

1962: Kefauver-Harris Amendments to the Federal Food, Drug, and Cosmetic Act

1979: FDA introduces Pregnancy Category Letters

FDA Pregnancy Categories

<table>
<thead>
<tr>
<th>Category</th>
<th>Translation (from Drugs in Pregnancy &amp; Lactation)</th>
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<tbody>
<tr>
<td>A</td>
<td>The possibility of fetal harm appears remote.</td>
</tr>
<tr>
<td>B</td>
<td>If there is a clinical need for a drug in this category they are considered safe to use.</td>
</tr>
<tr>
<td>C</td>
<td>These drugs should be given only if the potential benefit justifies the potential risk to the fetus.</td>
</tr>
<tr>
<td>D</td>
<td>There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk.</td>
</tr>
<tr>
<td>X</td>
<td>The risk of use of the drug in pregnant women clearly outweigh any possible benefit. The drug is contraindicated in women who are, or may become pregnant.</td>
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FDA Pregnancy Categories

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<td>A</td>
<td>Multivitamins, levothyroxine</td>
</tr>
<tr>
<td>B</td>
<td>Diphenhydramine, penicillin, ondansetron</td>
</tr>
<tr>
<td>C</td>
<td>Aspirin (1st &amp; 2nd trimester), guaifenesin, fluconazole, clindamycin</td>
</tr>
<tr>
<td>D</td>
<td>ACE inhibitors (2nd &amp; 3rd trimester), gentamicin, valproate for seizures, ibuprofen (3rd trimester)</td>
</tr>
<tr>
<td>X</td>
<td>Isotretinoin, statins, valproate for migraine, oral contraceptives, warfarin</td>
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So what’s the problem?

- Pregnancy letter category system was criticized as overly simplistic, confusing, and inaccurate
- Little to no guidance about possible fetal injuries and their severity
- Misinterpreted as a grading system
- Outdated content
- A drug with adverse information in animals could be labeled as the same category as a drug with no animal information


Pregnancy & Lactation Labeling Rule (PLLR)

- 1997: Public Affairs Committee of the Teratology Society
- 2008: Proposal of PLLR
- 2015: Effective as of June 2015
- 2020: Pregnancy categories to be removed by June 2020

Intended to provide prescriber with the information needed to better evaluate risks vs. benefits


Pregnancy & Lactation Labeling Rule (PLLR)

- Eliminated the standard pregnancy category letters for prescription medications
- Provide the prescriber with relevant information needed to better evaluate the risks and benefits of pharmacologic treatment for patients that are pregnancy or lactating
- Explicitly states when no data are available


Pregnancy & Lactation Labeling Rule (PLLR)

- Effective date June 30, 2015
- All prescription drugs to remove pregnancy letter categories by June 2020 as a gradual process
- Reorganizes information in prescription drug labeling to more clearly describe available data to aid decisions and counseling of patients using prescription drugs

Changes in labeling

A patient comes to the pharmacy counter and asks you: “Is it safe to take voclosporin if I’m planning to get pregnant?”

A. Yes
B. No
C. Depends on risk/benefit for your personal medical conditions
D. I don’t know

Pregnancy & Lactation Labeling Rule (PLLR)

- Pregnancy (8.1)
  - Information from pregnancy exposure registry when available
  - Risk summary, clinical considerations, data
- Lactation (8.2)
  - Amount of drug in breast milk
  - Potential effects on infant
- Females & Males of Reproductive Potential (8.3)
  - Need for pregnancy testing
  - Contraception recommendations
  - Infertility

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Overview by Selected Disease States

- Each patient and their medication list should be evaluated individually
- The following are common disease states among reproductive-age females...
- that are also frequently treated with potentially teratogenic medications ("red flag" medications)...
- and/or have notable drug interactions with contraceptives...
- and/or have notable US CDC MEC considerations.
- Interprofessional management of the patient is likely needed.

US CDC MEC
Summary Chart of U.S. Medical Eligibility Criteria for Contraceptive Use

Epilepsy
- carbamazepine; fosphenytoin; phenytoin phenobarbital; primidone; topiramate; valproate
- Possible drug interactions
  - Many antiepileptic drugs induce CYP450
  - phenytoin, carbamazepine, barbiturates, primidone, topiramate (especially at >200mg/d), oxcarbazepine
  - Non-enzyme inducing drugs: valproate, BZDs, gabapentin, levetiracetam

Anticoagulation
- warfarin (previously D/X)
- DOACs – very limited evidence in pregnancy
- Enoxaparin, heparin recommended in pregnancy
Anticoagulation

Migraine

- valproate; ergot derivatives; topiramate; NSAIDs in 3rd trimester
- Possible drug interactions
  - topiramate, nefazodone

Migraine

- methotrexate; leflunomide; mycophenolate mofetil
- Many biologics relatively safe; previously B/C

Autoimmune Disorders

Autoimmune Disorders
Autoimmune Disorders

Cardiovascular conditions
- ACE inhibitors; ARBs
- Statins

Other Considerations
- Diabetes
- HIV
- Depression
- Bipolar disorder
- Organ transplantation
- Other?

Patient Case

What recommendations are there for management of a pregnant patient who conceived while taking a potentially teratogenic anti-epileptic drug (AED)?
Patient Case

“You can’t get pregnant on this drug”

Patient Case

HPI: 24-year-old G0P0. Presents to clinic for confirmation of pregnancy after positive home pregnancy test (taken after two missed periods).

PMH: migraine with aura

Vital signs & labs WNL except:
positive urine HCG (115,000 mIU/ml)

Patient Case

Medication List:
Depakote 250mg, 1 tablet by mouth twice daily for migraine prophylaxis (taking for four months)

Nor-QD, 1 tablet by mouth daily
discontinued POPs after being told she “can’t” get pregnant when starting Depakote

Patient Case

Patient counseled on pregnancy options and would like to proceed with pregnancy, but wants to know “Will there be anything wrong with my baby?”

Valproate associated with increased risk of neural tube defects, craniofacial defects, limb malformations, hearing impairment, neurodevelopmental disorders, lower IQ

Neural tube defects: 1-2 per 100 births

Dose-dependent – but no safe threshold established

Risk highest in first trimester

Source: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=08a65cf4-7749-4ceb-6895-8f4805e2b01f

32 weeks
33 weeks
34 weeks
35 weeks
36 weeks
37 weeks
38 weeks
39 weeks
40 weeks
41 weeks
42 weeks
43 weeks
44 weeks
45 weeks
46 weeks
47 weeks
48 weeks
49 weeks
50 weeks
51 weeks
52 weeks
53 weeks
54 weeks

AED Pregnancy Registry:
https://www.aedpregnancyregistry.org/ or 888.233.2334

Recommend folic acid supplementation

D/C Depakote

Discussed beta blockers for prophylaxis; patient declined: “I’ll just deal with it.”

Encouraged follow-up for routine ultrasounds to detect neural tube defects and organ abnormalities

Source: https://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?setid=08a65cf4-7749-4ceb-6895-8f4805e2b01f
Patient Case

The patient asks what she should do about birth control in the future if she is to resume valproate. What recommendations do you have?

Conclusions

- Updated FDA labeling requirements (PLUR) provide additional information for evaluating risks & benefits of medication use in pregnancy
- Use of teratogenic medications by people of childbearing potential is common, but these patients often receive inadequate contraceptive counseling
- Many potentially teratogenic medications have drug interactions with hormonal contraceptives
- A team-based approach can help to optimize use of teratogenic medications and contraceptives

Questions?