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Pharmacy

Updates in Pharmacy:
Labeling Changes in Pregnancy/Lactation &
New Agents in the Treatment of Major Depressive Disorder

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Organization	None
Government	None

Objectives

- Describe the FDA updates to the pregnancy and lactation prescription drug labeling
- Identify newly approved agents for the treatment of major depressive disorder

Audience Poll #1

"I routinely look at the FDA pregnancy categories to guide medication selection in pregnant patients"

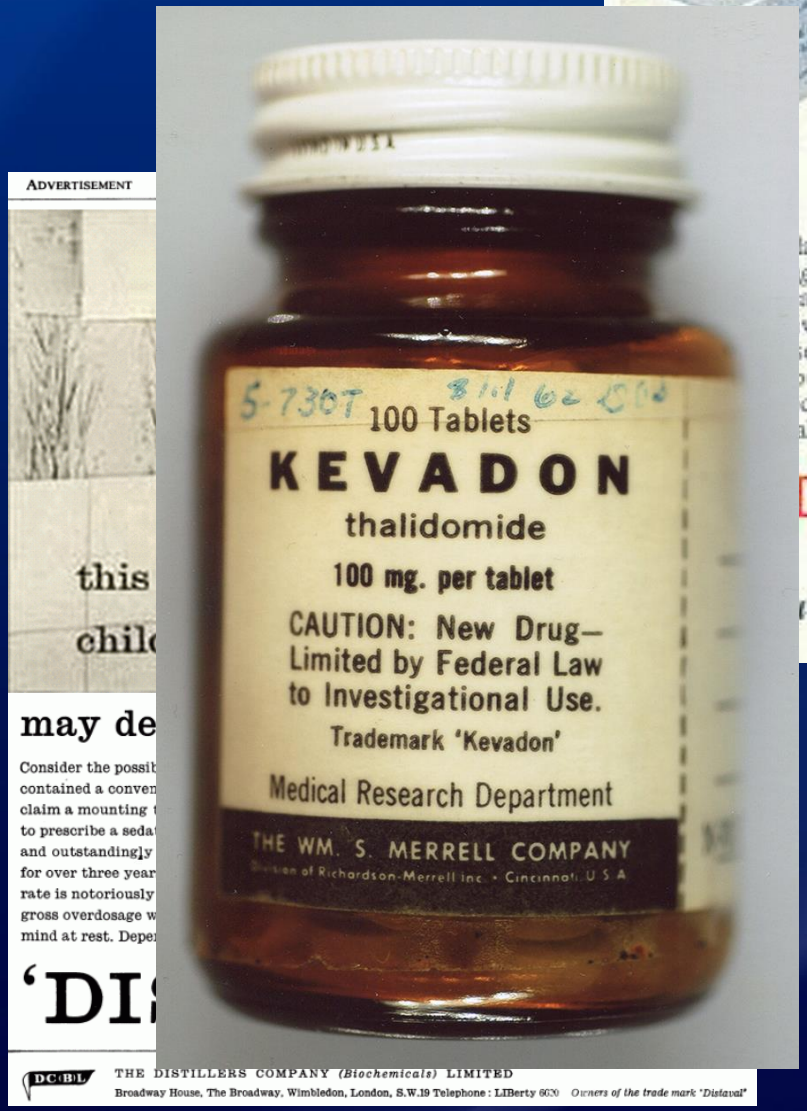
A) True

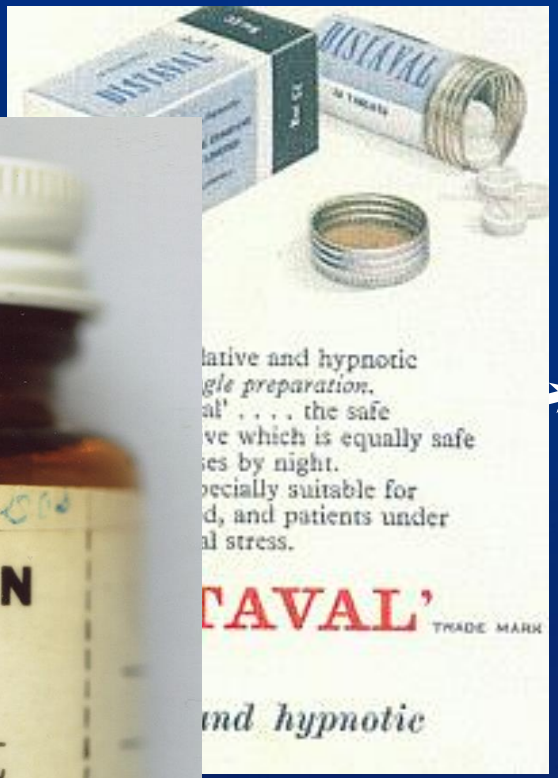
B) False

FDA Pregnancy Categories

Kefauver-Harris Amendments: required manufacturers to prove medications are *BOTH* safe and efficacious

1962





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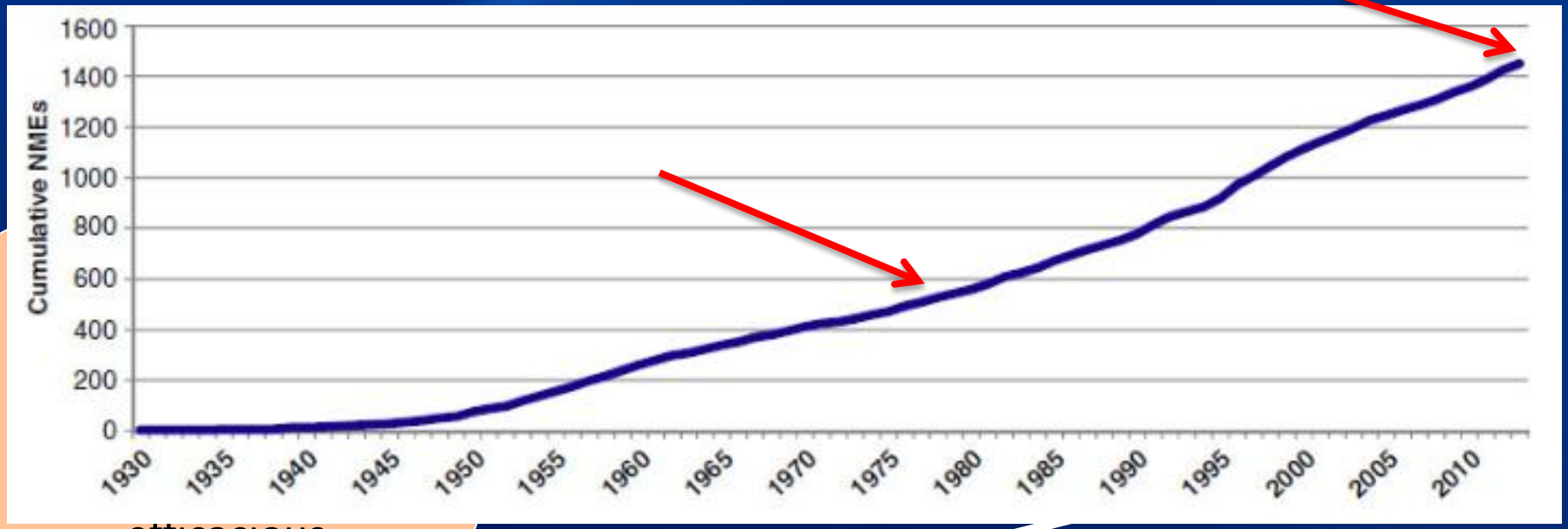
http://www.accessdata.fda.gov/



efficacious

1962

1979

FDA developed the *Labeling for Prescription Drugs Used in Man*: introduced pregnancy labeling regulations and the "letter categories" of risk

Categories A, B, C, D, X

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http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

Audience Poll #2

A 34 year female is prescribed sertraline for the management of major depressive disorder. She has been taking the medication for 6 years. Unexpectedly she discovered she is 10 weeks pregnant…

Which of the following statements best describes sertraline (category C) in this situation

A) Human studies involving sertraline have demonstrated adverse events to the fetus

B) A category C medication is safer than a category D medication

C) Potential benefits may warrant use of the drug despite potential risks

D) The patient should be switched to an alternative agent that is category B

FDA Pregnancy Categories

Category	Definition
A	Adequate, well-controlled studies **failed to demonstrate fetal risks**
B	**Animal studies failed to demonstrate a risk** to the fetus, but **no** adequate, well-controlled **studies of humans** exist ***-OR-*** **Animal studies demonstrate a risk**, **and no** adequate, well-controlled **studies in humans have been done**
C	**Animal studies have show adverse effect on the fetus, but there are no adequate studies of humans**. The benefits from the medication might be acceptable despite its potential risks -OR- **Animal data and data from human studies are not available**
D	**Evidence exists of human fetal risk** based on adverse reaction data from investigational or marketing experience or studies of humans, **but the potential benefits** from the use of the drug in pregnant women **might be acceptable** despite its potential risks
X	Studies in animals or humans have demonstrated fetal abnormalities or there is positive evidence of fetal risk based on adverse reaction reports from investigational or marketing experience, or both. The **risk involved in the use of the drug in pregnant women clearly outweighs any possible benefits**.

Pharmacotherapy. 2014; 34: 389-95

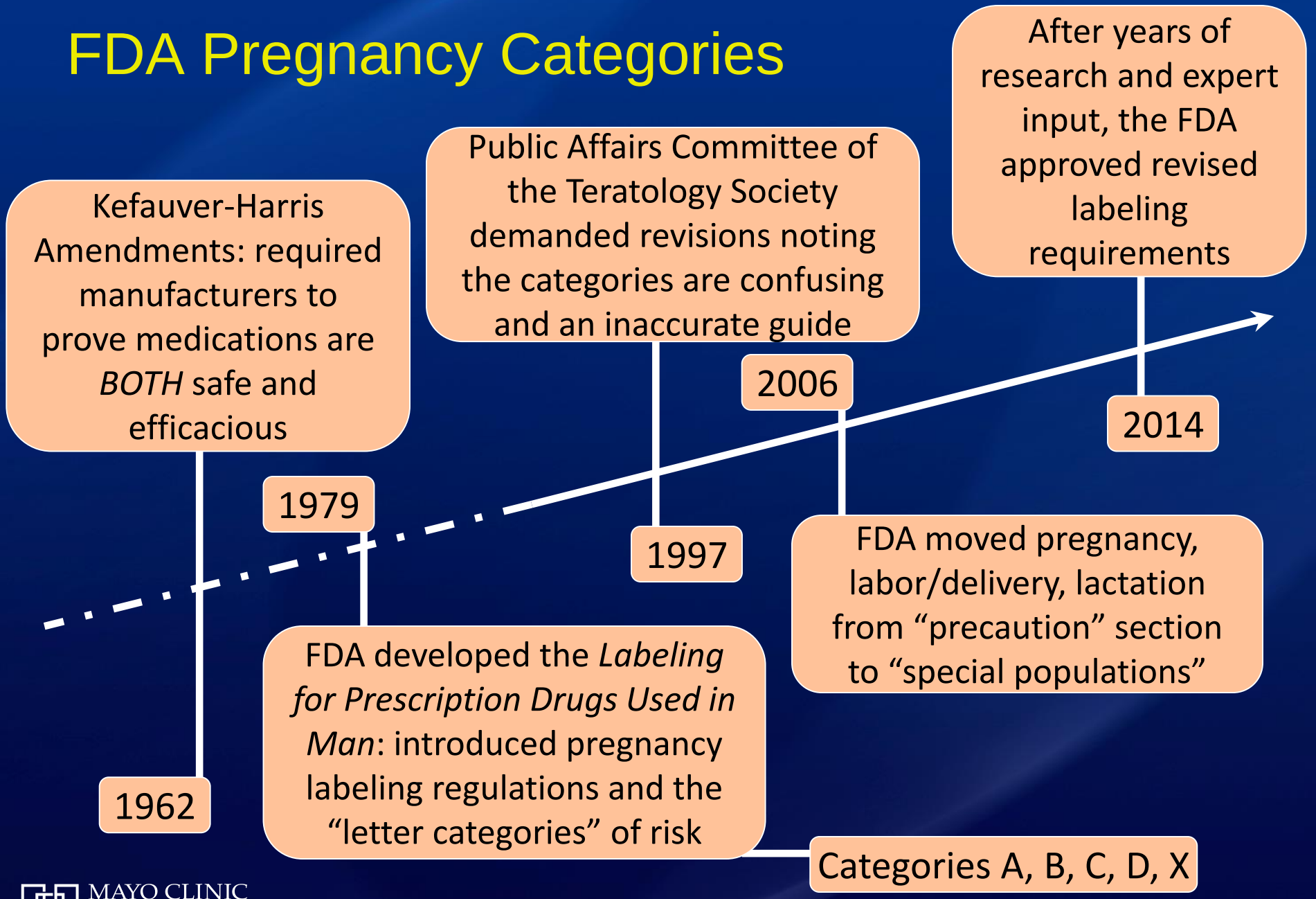
FDA Pregnancy Categories

- **Pros:**
  - Easy…A, B, C, D, or X
- **Cons:**
  - Simplistic relative to the complexity
  - Confusing and often misused
    - Categories to do not represent a graded risk system
    - Two drugs within the same category may not carry the same risk
  - Deficient of important information
    - Timing of exposure
    - Focuses on only structural abnormalities and not developmental outcomes

FDA Pregnancy Categories: Other Concerns

- Agents can change category over time
  - Paroxetine: category C → D
  - Bupropion: category B →C
- New drugs may simply lack data
  - Lurasidone: category B
- Theoretical risks may still be greater than the unknown
  - Clozapine: category B
- A large percentage of medications are category C
  - Category X = 4.6% vs. category C = 66%

FDA Pregnancy Categories



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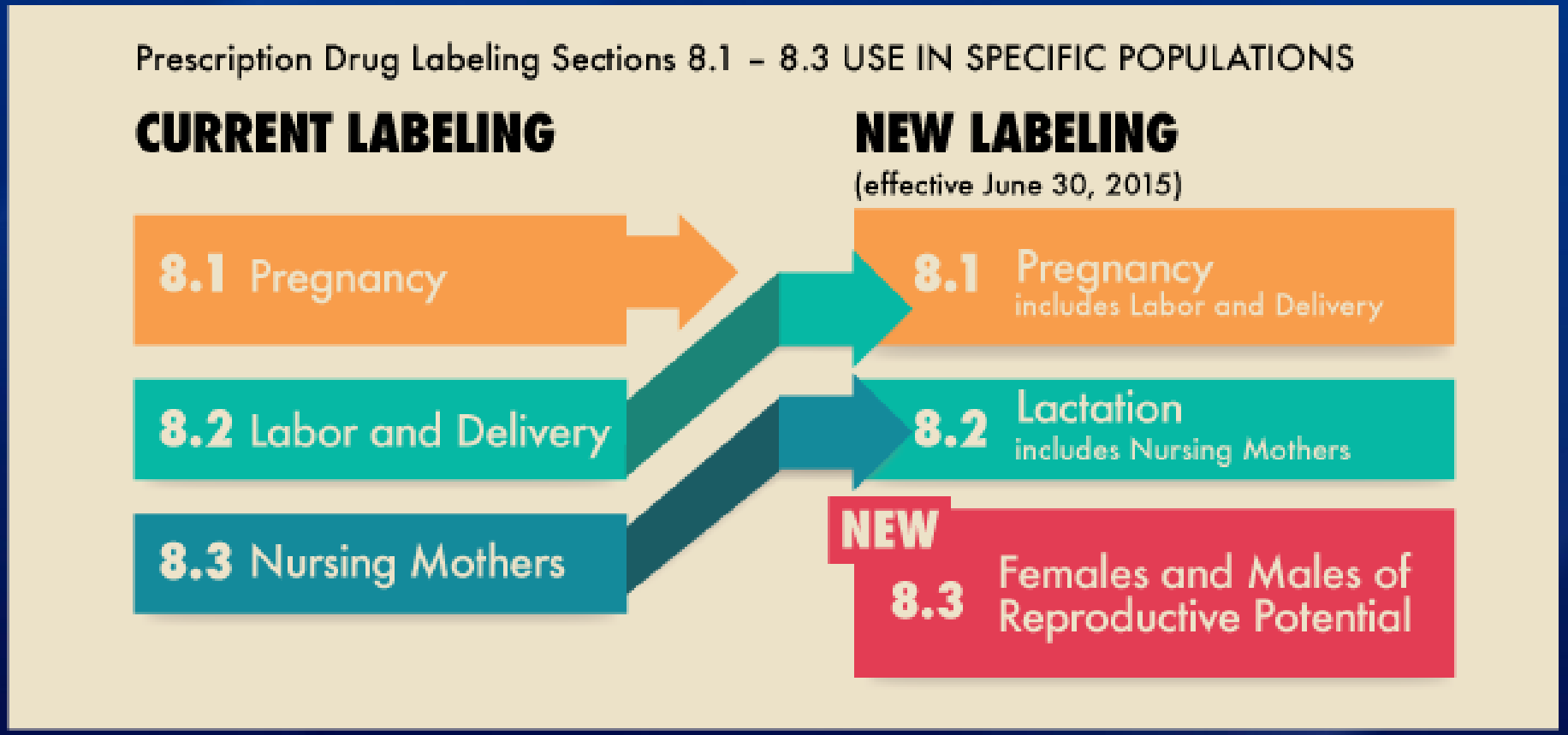
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

Implementation of the *Final Rule*

- The *Rule* went into effect on June 30, 2015 and will affect all drugs differently

Drug Approval Date	Required Action
Before 6/30/2001	Does NOT need to conform
After 6/30/2001 through 6/30/15	3 – 5 years 6/30/2018 – 6/30/20
After 6/30/15	Time of submission
ALL prescription drugs for human use Must have Pregnancy Category REMOVED by 6/30/2018	

New Labeling



- Creates a standardized approach to providing information for all medications

http://www.fda.gov

Pregnancy (including labor and delivery) 8.1

- General information
  - Including registry information (if available)
- Risk Summary
  - Fetal risk summary and information on background risk in the general population
- Clinical considerations
  - Maternal and fetal risks
  - Dose adjustments
  - Risk of untreated disease and therapeutic alternatives
  - Labor or delivery considerations
- Data
  - Human data presented first when available

Lactation 8.2

- When available to include:
  - Detection of drug in human milk
  - Effects seen on the child
  - Information on minimizing exposure
  - List monitoring parameters

Females & Males of Reproductive Potential 8.3

- Not required if none of the subheadings are applicable
- Subheadings describe:
  - If pregnancy testing or contraceptions is required before, during, or after drug therapy
  - If there are any known drug-associated fertility effects on those with reproductive potential

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to REXULTI during pregnancy. For more information contact the National Pregnancy Registry for Atypical Antipsychotics at 1-866-961-2388 or visit http://womensmentalhealth.org/clinical-and-research-programs/pregnancyregistry/.

Risk Summary

Adequate and well-controlled studies have not been conducted with REXULTI in pregnant women to inform drug-associated risks. However, neonates whose mothers are exposed to antipsychotic drugs, like REXULTI, during the third trimester of pregnancy are at risk for extrapyramidal and/or withdrawal symptoms. In animal reproduction studies, no teratogenicity was observed with oral administration of brexpiprazole to pregnant rats and rabbits during organogenesis at doses up to 73 and 146 times, respectively, of maximum recommended human dose (MRHD) of 4 mg/day on a mg/m^2 basis. However, when pregnant rats were administered brexpiprazole during the period of organogenesis through lactation, the number of perinatal deaths of pups was increased at 73 times the MRHD *[see Data]*. The background risk of major birth defects and miscarriage for the indicated population(s) is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Clinical Considerations

Fetal/Neonatal Adverse Reactions

Extrapyramidal and/or withdrawal symptoms, including agitation, hypertonia, hypotonia, tremor, somnolence, respiratory distress and feeding disorder have been reported in neonates whose mothers were exposed to antipsychotic drugs during the third trimester of pregnancy. These symptoms have varied in severity. Some neonates recovered within hours or days without specific treatment; others required prolonged hospitalization. Monitor neonates for extrapyramidal and/or withdrawal symptoms and manage symptoms appropriately.

Data

Animal Data

Pregnant rats were treated with oral doses of 3, 10, and 30 mg/kg/day (7.3, 24, and 73 times the MRHD on a mg/m^2 basis) of brexpiprazole during the period of organogenesis. Brexpiprazole was not teratogenic and did not cause adverse developmental effects at doses up to 73 times the MRHD.

Pregnant rabbits were treated with oral doses of 10, 30, and 150 mg/kg/day (49, 146, and 730 times the MRHD) of brexpiprazole during the period of organogenesis. Brexpiprazole was not teratogenic and did not cause adverse developmental effects at doses up to 146 times the MRHD. Findings of decreased body weight, retarded ossification, and increased incidences of visceral and skeletal variations were observed in fetuses at 730 times the MRHD, a dose that induced maternal toxicity.

In a study in which pregnant rats were administered oral doses of 3, 10, and 30 mg/kg/day (7.3, 24, and 73 times the MRHD) during the period of organogenesis and through lactation, the number of live-born pups was decreased and early postnatal deaths increased at a dose 73 times the MRHD. Impaired nursing by dams, and low birth weight and decreased body weight gain in pups were observed at 73 times, but not at 24 times, the MRHD.

8.2 Lactation

Risk Summary

Lactation studies have not been conducted to assess the presence of brexpiprazole in human milk, the effects of brexpiprazole on the breastfed infant, or the effects of brexpiprazole on milk production. Brexpiprazole is present in rat milk. The development and health benefits of breastfeeding should be considered along with the mother's clinical need for REXULTI and any potential adverse effects on the breastfed infant from REXULTI or from the underlying maternal condition.

Resources

- DailyMed
  - The official provider of FDA label information
  - PDFs or Web based viewing
  - Free
  - https://dailymed.nlm.nih.gov/

- MICROMEDEX
  - Subscription service
  - Direct information from:
    - Shepard's: A Catalog of Teratogenic Agents
    - Teratogen Information System (TERIS)
    - REPROTOX

Resources

- Shepard's: A Catalog of Teratogenic Agents
  - 13th, ed. ~$285
- Teratogen Information System (TERIS)
  - Assesses quality of data and overall teratogenic risk of >4100 agents and exposures
  - Paid version provides access to Shepard's Catalog
  - $250/year
- REPROTOX (reprotox.org)
  - 5000+ agents and exposures
  - Paid version: can request research on unlisted meds
  - $200/year; mobile app available

Resources

- MotherToBaby.org (formerly OTIS.org)
  - Organization of Teratology Information Services (OTIS)
  - Phone-based counseling resource for pregnant women
  - Online (free) drug fact sheets of numerous medications, herbal products, vaccines, maternal medical conditions, substances of abuse, household and occupation exposures
- LactMED (through http://toxnet.nlm.nih.gov)
  - Information on drugs to which breastfeeding mothers may be exposed
  - Information on drug levels that may be found in breast milk and possible clinical effects on the infant
  - FREE (mobile app available)

Other Resources

- Briggs GG, et al. Drugs in pregnancy and lactation. 8th ed.
- Schaefer C, et al. Drugs during pregnancy and lactation. 3rd ed.

New Medications Approved for MDD

Antidepressant Timeline

1950s	Monoamine oxidase inhibitors
1960s	Tricyclic Antidepressants
1980s	Bupropion (1985)
	Fluoxetine (1987)
1990s	Venlafaxine (1993)
	Remeron (1996)
2000s	Atypicals antipsychotics (aripiprazole, quetiapine, olanzapine/fluoxetine, brexpiprazole)
	The “Me-too” era (escitalopram, desvenlafaxine, levomilnacipran)
	Vilazodone
	Vortioxetine

http://www.fda.gov

Vilazodone (Viibryd)

- Mechanism of action
  - Serotonin reuptake receptor inhibition
  - Partial agonist activity for 5HT1A (like buspirone)
- Dosing
  - Specific titration and administration recommendations
    - 10 mg X 7 days, 20 mg X 7 days, target dose → 40 mg once daily
    - Taken with food
- Side Effects
  - Diarrhea (28%), nausea (23%), vomiting, insomnia

https://dailymed.nlm.nih.gov/dailymed

Chonnam Med J. 2016 May;52(2):91-100

Vilazodone (Viibryd)

- Additional highlights
  - Minimal sexual side effects
    - 5HT1A postsynaptic activation facilitates dopamine release
  - Changes in weight similar to placebo
  - Faster onset?
    - Hypothesis related to quicker desensitization of 5HT1A auto-receptors
    - Not substantiated by any head-to-head trials
  - Numerous recent randomized, controlled trials indicating benefits also for generalized anxiety disorder
  - 40 mg (30): $249.96

https://dailymed.nlm.nih.gov/dailymed

Chonnam Med J. 2016 May;52(2):91-100

Vortioxetine (Brintellix…Trinellix)

- Mechanism of action
  - Serotonin reuptake receptor inhibition
  - 5HT1A agonist
  - 5HT1B partial agonist
  - 5HT1D, 5HT3 and *5HT7 antagonist*
- Dosing
  - Initial: 10 mg daily
  - Titrate to a maximum of 20 mg daily
- Side Effects
  - Nausea (20-30%), sexual dysfunction (20-30%)

https://dailymed.nlm.nih.gov/dailymed

Chonnam Med J. 2016 May;52(2):91-100

Vortioxetine (Trinellix)

- Additional highlights
  - 5HT1A, 5HT3, 5HT7 modulation is suggested to improve cognition
    - Katona, et al. demonstrated improved processing speed, verbal learning, and memory in elderly
  - FOCUS and CONNECT trials
    - Approved in Europe to improve cognitive function
    - February 2016 - FDA advisory panel backed the expanded indication
    - March 2016 - FDA declined to approve the new indication
  - 20 mg (30): $381.79

J Clin Psychiatry. 2014; 75: 1411-18
Neuropsychopharmacology. 2015; 40: 2025-37
Int J Neuropsychopharmacol. 2014; 17: 1557-67
Int J Neuropsychopharmacol. 2016 Jun 15. [Epub ahead of print]

Brexpiprazole (Rexulti)

- Mechanism of action
  - D2 and 5HT1A partial agonist
  - 5HT2A antagonist
  - Low H1 and M1 affinity
  - Compared to aripiprazole: lower D2 activity and higher affinity to 5HT2A receptors and the norepinephrine transporter
- MDD Dosing (adjunctive)
  - Initial: 0.5 - 1 mg daily; titrate to a maximum of 3 mg daily
- Side Effects
  - Akathisia vs. placebo; 9% vs. 2%
  - Mild effects on weight and lipids

Brexpiprazole (Rexulti)

- Additional highlights
  - Minimal weight gain
  - QTc changes similar to placebo
  - 91 hour half-life
- Cost barriers
  - 1 mg (30): $1121.69
  - 2 mg (30): $1121.69
  - 3 mg (30): $1121.69

Guidelines and New Agents

- Most guidelines are outdated
- American Psychiatric Association:
  - No robust data to suggest meaningful differences in response rates between classes
    - SSRIs, SNRIs, mirtazapine, bupropion
    - Select based on clinical features, comorbidities, side effects, interactions, cost, patient preference

Guidelines and New Agents

- Selection of new agents may be limited by cost barriers and limited long-term data
  - Vilazodone and vortioxetine may be reasonable second line monotherapy options
  - Brexpiprazole should be considered as a second or third line adjunctive agent
- Overlapping mechanisms make vilazodone and vortioxetine less ideal as an augmentation agent in some combinations
  - SSRI/SNRI properties of vilazodone and vortioxetine
  - 5HT1A, 5HT7 properties of vortioxetine and second generation antipsychotics
  - Potentially complementary with bupropion or mirtazapine

Questions/Discussion