Drug Interaction Recommendations in the US MEC: Incorporating science into clinical recommendations

Erin Berry-Bibee, MD MPH
Guest researcher
Division of Reproductive Health/CDC
Assistant Professor
Department of OB/GYN UNC Chapel Hill

Process

1. Identify area of scientific or clinical concern
2. Conduct systematic review
3. Present evidence to panel of family planning experts and stakeholders
4. Discuss data and generate clinical recommendations

1. Identify area of scientific or clinical concern

- **CIRE system**
  - *Continuous Identification of Research Evidence*
  - Helps identify new data as it is published
- **Public and Provider inquiry**
  - Helps us meet clinical needs of providers
  - Identifies new areas of clinical concern that might not be identified through CIRE system

2. Conduct systematic review

- PRIMSA guidelines for systematic reviews
- Inclusion criteria for most drug interaction reviews
  - Published peer-reviewed articles in any language from any year
  - Any methodology
  - Outcomes
    - Clinical- Effectiveness and adverse events related to both test drug and contraceptive (e.g. pregnancies, ovulation data, breakthrough bleeding)
    - Pharmacokinetic (PK)- include any
- Quality
  - Clinical- USPSTF system
  - PK- either did not grade or generated our own grading system

Quality rating system for PK studies developed for the systemic review of psychotropic drugs and St. John's wort *

- **Three Overall Quality Categories:**
  - *Good*- No important limitations, meets all criteria.
  - *Fair*- Clear limitations to study design but no fatal flaws.
  - *Poor*- One or more fatal flaws that likely invalidate results.
- **9-items**
  - Design
  - Sample size
  - Population
  - Exposure
  - Outcome(s)
  - Timing
  - Intersubject variability
  - Steady state
  - Assay and Analysis Validation

*Developed in collaboration with MJ Kim (FDA)

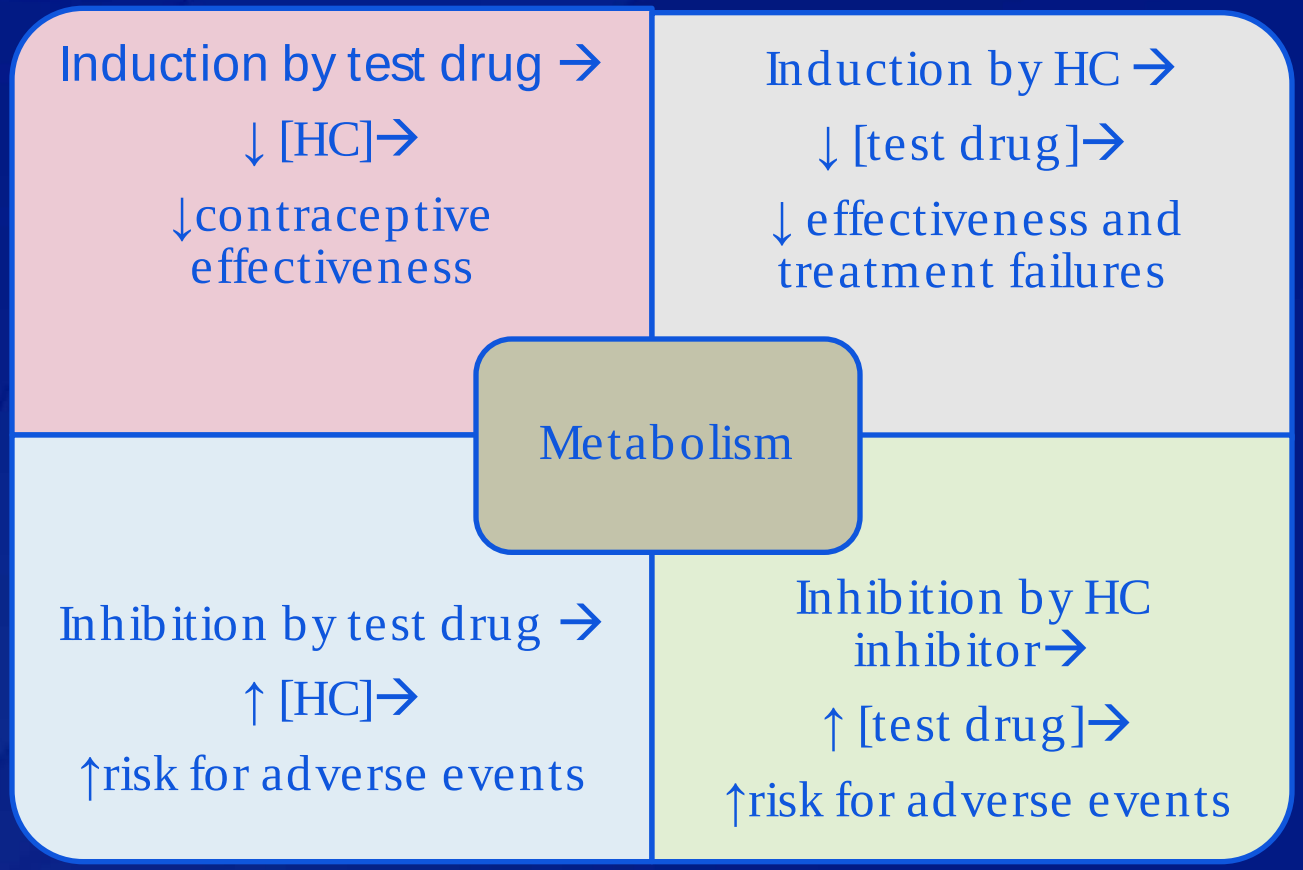
2. Conduct systematic review

- **What to do with other sources of information?**
  - FDA label
  - Non-peer-reviewed/unpublished results
- **Not a part of results of the systematic review**
  - No systematic way of searching for this kind of data
  - May be able to contribute to discussion points

3. Present evidence to panel of family planning experts and stakeholders

- Systematic review provided prior to panel meeting
- Data presented to panel
- Pertinent labeling information presented to panel

3. Present evidence to panel of family planning experts and stakeholders



Psychotropic drug	HC outcomes		Psychotropic outcomes	
	Clinical	PK	Clinical	PK
SSRIs	↔ fair	↔ good	↔ fair	↑/? poor
TCAs			↔ poor	↔/↑ fair/poor
Bupropion				↓/↔ good
Atypical Antipsychotics		↔ good		↔ fair
Oral Benzodiazapines			↔ fair	↔/↓ fair/poor
MAOIs				
Mirtazapine				
Trazadone				
Buspirone				
Hydroxyzine				

4. Discuss data and generate clinical recommendations

- **Guiding principles include**
  - When a "condition" may have impact on contraceptive effectiveness then efficacy is weighted along with safety in making the recommendations
    - Drug-drug interactions (DDIs)
    - Obesity
    - Medical condition which affects metabolism (e.g. liver disorders, CF)
  - Evidence driven decision making
  - For each condition/drug a recommendation is made for all contraceptive methods (even if data is only for COCs)

Challenges

- **Lack of clinical outcomes**
  - Contraceptive failure rates/pregnancy data
  - Adverse events associated with HC
  - Adverse events associated with the test drug
- **What pharmacodynamic outcomes are helpful to consider?**
- **How do we translate PK data into clinical recommendations that accurately reflect theoretical or proven concerns?**
  - Which PK parameters are "best" or "required" to look at?
  - Is there a threshold of change that should raise *clinical* concern
  - What to do with use of multiple drugs (ARVs in particular)

PK parameter rule(s)?

Contraceptive	Most important PK parameters	Acceptable/notable PK parameters
COC	AUC and C_{max}	?
Patch	?? AUC and C_{max}	?
Combined Vaginal Ring	?? AUC and C_{max}	?
DMPA	C_{min}, $C_{average}$=AUC	?
Implant	C_{min}, $C_{average}$=AUC	?
LNG-IUD	C_{min} , $C_{average}$=AUC	?

Challenges

- **Limited data on**
  - Drug interactions among obese women
  - Can we extrapolate across different progestin types
    - CHC studies with different progestins?
    - Across various POCs?
  - Non-oral formulations (e.g. vaginal ring, patch, injectable)
    - What is the role of the 1st pass effect?
    - What other difference in absorption/metabolism across the non-oral formulations might effect potential DDIs?
  - Efficacy → progestin; Adverse events→ estrogen ???

Challenges

- **Limited data on**
  - Progestin only contraceptives
    - Injectable→ high dose, different progestin.
    - Implant→ concern with ARVs, limited data on other potential DDIs
  - LNG-IUD→ are we ever concerned about DDIs?
    - Systemic LNG is present
      - What role does systemic LNG play in contraceptive efficacy?
      - Can systemic LNG act as s perpetrator drug? Victim drug?

Challenges

- Is there a way to access unpublished industry data for drug interaction studies in a systematic way?
- How do we asses the quality of PK studies?

For more information please contact Centers for Disease Control and Prevention

1600 Clifton Road NE, Atlanta, GA 30333
Telephone: 1-800-CDC-INFO (232-4636)/TTY: 1-888-232-6348
E-mail: cdcinfo@cdc.gov Web: http://www.cdc.gov