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# Drug Safety and DILI

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# What is “Drug Safety”?

- All drugs have side effects
- A safe drug: its benefits outweigh its risks
- This is a population-based definition, not true for the person who gets the serious side effect
- Some people get great benefit, no side effects; others get severe side effect
- How to maximize benefit and minimize risk?



# Evaluating Drug Side Effects During Drug Development

- Safety testing performed in animals and then people
- Hard to uncover and assess every side effect:
  - Rare: might take 10,000 people to be sure of an effect occurring 1 in 1000
  - Common: where the side effect already occurs with some frequency without the drug
  - DILI: a combination of both problems
  - Doesn't occur in the tested population (pregnant women, drug interactions, real world patients)
  - Takes a long time to develop
    - Cancer—use in vitro and animal tests



# Evaluating Side Effects of Approved Drugs

- Always learn more after drug used widely
- New side effects may be recognized after 10 years or more of use
- Reports of cases by health professionals
- Data from clinical trials and registries
- Information from use in other countries
- Hope to use more active methods (Sentinel) with electronic health data in future



# Options Once Drug Safety Profile Understood

- Not approve/remove from market
- Risk Evaluation and Mitigation Strategy (REMS): restrict distribution, education, patient information
- Warnings on label
- List on label
- Develop better scientific understanding of side effect



# Scientific Understanding of Side Effects

- Why do a few people get a side effect while others don't?
- Some side effects seem like an overdose (excessive pharmacologic effect)
- Others are very rare and seemingly random (“idiosyncratic”)
- Some of this variability in human drug responses caused by people's genetic differences
- Other is caused by environment: drug interactions, misuse, overdose



# Genetic Differences in Drug Metabolizing Enzymes (DME's)

- DMEs process drugs inside the body
- There are a large number of DMEs and related proteins such as drug transporters that move drugs around in the body
- There are lots of different variants in DMEs and this is one reason people react differently to drugs
- For a single drug, there can be “ultra-rapid” metabolizers all the way to “non” metabolizers



# Effects of DME Variation

- Overdose: too much drug in the body
- No dose: no active drug (codeine)
- Secondhand dose: nursing mothers who are ultra-rapid metabolizers and codeine
- Variable dose: wide range of blood levels or effects at a given dose (warfarin)
- Different pathway: drug metabolites are different (could lead to different side effects)



# Genes and Immune Reactions to Drugs

- Genes generally influence the types of immune reactions that individuals have
- Some very serious drug side effects seem to be caused by a person's immune response to the drug (skin reactions, anaphylaxis)
- May be the cause of liver injury in some cases
- Tests are available to identify many immune system gene variants



# Genes and Drug Side Effects: Target Variation

- The drug “target” is the molecule that the drug acts on inside the body
- “Targets” can have genetic variation too
- People with target variants can have exaggerated pharmacologic response (like an overdose), or no response, or a bad response at an ordinary drug dose



# Evidence Needed to Add New Genetic Safety Information to Label

- Amount of evidence proportional to the importance of the information to decision-making (abacavir vs. carbamazepine example)
- Regulatory approach to safety matters is less restrictive than for efficacy claims
- Evidence required to change benefit/risk equation more substantial (e.g., to allow a drug back on market)
- This new science will require new regulatory approaches



# Summary

- Drug induced liver injury is a microcosm of many drug safety issues
- We can now test for some gene variants associated with serious drug-induced injury
- This type of testing can improve drug safety by not exposing people with high risk to the drug or by giving the correct dose



# Summary

- As we learn more, such genetic tests could be incorporated into drug development, to make drugs safer from the start
- FDA is developing the regulatory policies that will pertain to this new type of information