



Drug-Induced Diseases: Prevention, Detection and Management

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Disclosure

- The program chair and presenters for this continuing education activity have reported no relevant financial relationships.

Learning Objectives

- Describe the epidemiology of drug-induced diseases and their impact on morbidity, mortality, and health-care resource utilization
- Explain methods of prevention for drug-induced diseases
- Develop a patient-specific treatment regimen for a patient with one or more drug-induced cardiovascular diseases
- Develop a patient-specific treatment regimen for a patient with one or more drug-induced kidney diseases
- Develop a patient-specific treatment regimen for a patient with drug-induced liver disease

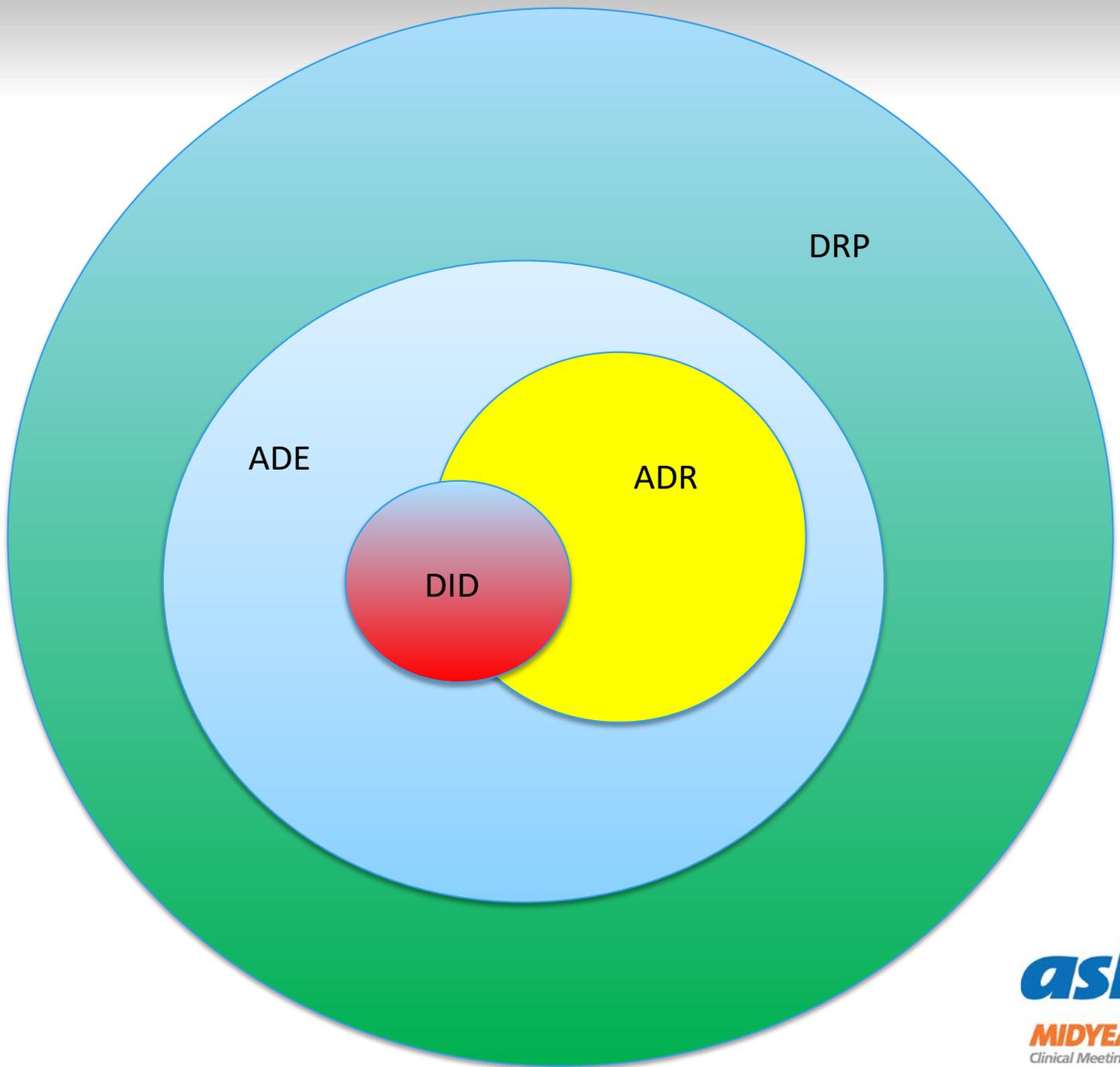


Epidemiology and Public Health Implications of Drug-Induced Diseases

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Vocabulary

- **Drug Related Problem:** An event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes.
- **Adverse Drug Event:** Any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment.
- **Adverse Drug Reaction:** A response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis, or therapy of disease or for the modification of physiologic function.
- **Drug-Induced Disease:** An unintended effect of a drug that results in mortality or morbidity with symptoms sufficient to prompt a patient to seek medical attention and/or require hospitalization.



“Magic Bullets”

- When used properly, drugs improve life.
- Few concerns about the quality of drugs available to us.
- Drug therapy represents the most cost-effective form of medical treatment available.

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Death Toll Challenges Rezulin Safety Claim

Medicine: Liver-related fatalities climb despite drug maker's assurances. FDA to reassess approval.

March 18, 1999 | DAVID WILLMAN | TIMES STAFF WRITER

WASHINGTON — It was a bold claim. On Dec. 31, the Warner-Lambert Co. assured the federal government that liver-related deaths linked to Rezulin, its controversial drug for adult-onset diabetes, had declined dramatically from the previous year.

The company, with sales of Rezulin topping \$1 billion, also distributed the claim to doctors and on the Internet.

But medical reports collected by Warner-Lambert and the Food and Drug Administration tell a different story.

Reports of liver-related fatalities in which Rezulin was cited as a contributing factor have more than quadrupled, from 14 in 1997 to 65 in 1998, according to newly obtained federal records. An additional 12 liver-related deaths were reported in the first six weeks of this year.

Drugs Removed from US Market

Drug	Generic Name	Use	Yrs	Reason for Withdrawal
Zelmid	Zimelidine	Anti-depressant	0	Guillain-Barre' Syndrome
Omniflox	Temafloxacin	Antibiotic	0	Hypoglycemia, Hemolytic anemia, Kidney dysfunction
Palladone	Hydromorphone - ER	Pain	0	Release issues - fatalaties with alcohol use
Redux	Dexfenfluramine	Diet	1	Valvular disease
Duract	Bromfenac	Pain	1	Hepatotoxic
Posicor	Mibefradil	Hypertension	1	Fatal drug interactions
Micturin	Terodiline	Incontinence	2	QT Prolongation
Raxar	Grepafloxacin	Antibiotic	2	Torsade de pointes
Raplon	Rapacuronium	Neuromuscular Blocker	2	Bronchospasm, Unexplained death

Drugs Removed from US Market

Selacryn	Tienilic acid	Hypertension	3	Hepatotoxic
Rezulin	Troglitazone	DM	3	Hepatotoxic
Baycol	Cerivastatin	Cholesterol	3	Rhabdomyolysis, Kidney failure
Bextra	Valdecoxib	NSAID	4	CV Risk, TEN, GI Bleed
Vioxx	Rofecoxib	NSAID	5	MI, Stroke
Zelnorm	Tegaserod	IBS	5	MI, Stroke, Angina
Raptiva	Efalizumab	Psoriasis	6	Progressive multifocal leukoencephalopathy
Propulsid	Cisapride	GERD	7	Arrhythmias
Tequin	Gatifloxacin	Antibiotic	7	Hypo/hyperglycemia

Drugs Removed from US Market

Orlaam	Levomethadyl	Opioid Dependence	10	Arrhythmias
Mylotarg	Gemtuzumab	AML	10	Veno-occlusive disease
Xigris	Drotrecogin alfa	Septic shock	10	No benefit
Hismanal	Astemizole	Antipsychotic	11	Torsade de pointes
Ergamisol	Levamisole	RA, Parasites	11	Neutropenia, Agranulocytosis
Merital Alival	Nomifensine	Antidepressant	13	Hemolytic anemia
Seldane	Terfenadine	Antihistamine	13	Arrhythmias
Meridia	Sibutramine	Diet	13	CV Risk, Stroke
Aprotinin	Trasylol	Hemostasis	14	MI, Stroke, Renal Damage
Trasylol	Aprotinin	Antifibrinolytic	14	Heart failure, Kidney damage, Stroke

Drugs Removed from US Market

DBI	Phenformin	DM	19	Lactic Acidosis
Permax	Pergolide	Parkinson's	19	Mitral, Tricuspid, Aortic Insufficiency
Quaalude	Methaqualone	Sedative/Hypnotic	23	Mania, Seizures, Convulsions, Death
Pondimin	Fenfluramine	Diet	24	Valvular disease
DES	Diethylstilbestrol	Miscarriage	31	Cancer, Birth defects
Cylert	Pemoline	ADHD/ADD	35	Hepatotoxic
Darvon	Propoxyphene	Pain	55	CV Risk

What the Record Shows

- 20% of drugs had serious adverse effects that were not identified before approval
- 20% of those drugs were ultimately withdrawn
- Serious adverse events occurred in 33% of drugs granted “Fast Track” approval
- Average response time is 10 years

Moore, TJ. New Drug: Caution Indicated. Arch Intern Med. 2012;172(21):1681-1682.

Magic Bullets?

When used properly, drugs improve life.

Few concerns about the quality of drugs available to us.

Drug therapy represents the most cost-effective form of medical treatment available.

When prescribed, dispensed or used improperly, drugs can kill.

Increasing concern about adverse effects discovered after a drug is marketed.

Is FDA failing us?

Mission of the FDA

- To promote the public health by promptly and efficiently reviewing clinical research and taking appropriate action on the marketing of regulated products in a timely manner;
- With respect to such products, protect the public health by ensuring that foods are safe, wholesome, sanitary, and properly labeled; human and veterinary drugs are safe and effective; there is reasonable assurance of the safety and effectiveness of devices intended for human use; cosmetics are safe and properly labeled, and; public health and safety are protected from electronic product radiation;

Source: The FDA Modernization Act of 1997 (PL 105-115)

“Safe and Effective”

- 2 well controlled, blinded, randomized clinical trials with clear separation of endpoints against placebo or an already approved standard intervention.
- Benefits of the new drug must outweigh untoward effects.

“Rule of Too”

Too Small

Too Brief

Too Healthy

Too Homogeneous

“Rule of Too”

Too Small

- 2,000 – 3,000 subjects
- Able to detect adverse reactions occurring with an incidence of $> 1/1000$

“Rule of Too”

Too Brief

- Only long enough to show efficacy
- 12 month study, regardless of size, will miss major adverse effects that occur only after 18 months of therapy

“Rule of Too”

Too Healthy

Too Homogeneous

- Exclude subjects who may confuse results
- Concurrent illness, concomitant medications, specific risk factors, patient subsets (young, old, pregnant)

“Too Healthy”

Subjects must be 25 – 55 years of age.

Exclusions:

- Women who are pregnant or who may become pregnant
- Women who are breast feeding
- Patients with a history of cigarette smoking within the last year
- Patients with renal disease (serum creatinine > 1.5)
- Patients with hepatic disease
- Patients with cardiac disease
- Patients with diabetes
- Patients with neuropathy

Pre-Marketing Trials

- Useful for demonstrating drug efficacy.
- Unable to predict the risk of drug-induced disease following release to the general population.

Post-Marketing Surveillance

- System is intended to identify drug-induced diseases unlikely to be detected during the pre-marketing process.
- Uses spontaneous, voluntary reporting of adverse events that occur following the use of a new drug.
 - MedWatch system
 - Vaccine Adverse Event Reporting System (VAERS)
- “Product Surveillance” is the responsibility of the manufacturer.
 - Submit 80% of ADR reports coming to the FDA

Post-Marketing Surveillance - Pitfalls

- Requires the observer to suspect that a condition is drug-induced and not simply the presentation of co-morbid condition.
- Requires the observer to prepare / submit reports (and follow-up information) without incentive.
- Requires the observer to admit to a decision that resulted in adverse consequences.

Post-Marketing Surveillance: Challenges

- Proving (Assessing) Causality
- Finding the numerator and denominator

Assessing Causality

Post Hoc Ergo Propter Hoc
(After this, therefore because of this)

Example:

The rooster crows immediately before sunrise; therefore the rooster causes the sun to rise.

Causal or Casual?

A patient begins therapy with a new oral hypoglycemic agent. One week later, he is admitted to a local hospital with an MI.

Is this a drug-induced disease or a co-morbidity?

“9 Points of Consideration”

Morges, Switzerland - 1981

1. Drug given prior to event?
2. Reaction at site of application?
3. Drug/Adverse reaction interval compatible with event?
4. ADR immediately following exposure and acute onset?
5. Rechallenge positive?
6. Dechallenge positive?
7. Were concomitant drugs stopped at the same time?
8. Same reaction to this drug before?
9. ADR known with the suspected drug?

Venulet J, Berneker GC, Ciucci AG (editors). Assessing causes of adverse drug reactions. London: Academic Press, 1982.

Assessing Causality

- WHO
- Naranjo
- RUCAM
- M&V
- DILN
- Karch
- Begaud
- Liverpool
- Etc.

WHO ¹	Naranjo ²	RUCAM ³	M&V ⁴	DILN ⁵
Certain		Highly Probable	Definite	Definite
Probable / Likely	Definite	Probable	Probable	Highly Likely
Possible	Probable	Possible	Possible	Probable
Unlikely	Possible	Not Likely	Not Likely	Possible
More data needed (2)	Doubtful	Excluded	Excluded	Unlikely

¹ World Health Organization: The Use of the WHO:UMC System for Standardised Case Causality Assessment. Geneva:WHO, 2014.

² Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther. 1981;30:239-245.

³ Roussel Uclaf Causality Assessment Method: Benichou C. Criteria of drug-induced liver disorders. Report of an international consensus meeting. J Hepatol. 1990;11:272-276.

⁴ Maria & Victorino: Maria VA, Victorino RM. Development and validation of a clinical scale for the diagnosis of drug-induced hepatitis. Hepatology. 1997;26:664-669.

⁵ Drug-Induced Liver Injury Network: Fontana RJ, Watkins PB, Bonkovsky HL, Chalasani N, Davern T, Serano J, et al. Rationale, design and conduct of the Drug-Induced Liver Injury Network (DILIN) prospective study. Drug Saf. 2009;32:55-68.

WHO Causation Categories

C1 - Certain

Plausible time, not related to underlying condition, concurrent disease, other drugs or chemicals, related pharmacologically, positive dechallenge, positive rechallenge

C2 - Probable

Reasonable time, unlikely to be related to concurrent disease, other drugs, positive dechallenge, no rechallenge

C3 - Possible

Reasonable time, may be due to concurrent disease, other drugs, no information on dechallenge

C4 - Unlikely

Improbable temporal relationship, other confounding factors such as drugs, chemicals, underlying disease

C5 – Conditional / Unclassified

Reported as an adverse reaction but more data is needed for proper assessment

C6 – Unassessable / Unclassifiable

Report suggesting an adverse reaction but cannot be judged because of insufficient or contradictory information

Naranjo ADR Probability Scale

Question	Points
Are there previous conclusive reports on this reaction?	Yes (+1) No (0) Don't know (0)
Did the adverse event appear after the suspected drug was administered?	Yes (+2) No (-1) Don't know (0)
Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was administered?	Yes (+1) No (0) Don't know (0)
Did the adverse reaction reappear when the drug was readministered?	Yes (+2) No (-1) Don't know (0)
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	Yes (-1) No (+2) Don't know (0)
Did the reaction reappear when a placebo was given?	Yes (-1) No (+1) Don't know (0)
Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	Yes (+1) No (0) Don't know (0)
Was the reaction more severe when the dose increased, or less severe when dose was decreased?	Yes (+1) No (0) Don't know (0)
Did the patient have a similar reaction to the same or similar drug in any previous exposure?	Yes (+1) No (0) Don't know (0)
Was the adverse event confirmed by any objective evidence?	Yes (+1) No (0) Don't know (0)

Naranjo ADR Probability Scale

Probability that adverse drug event has occurred:

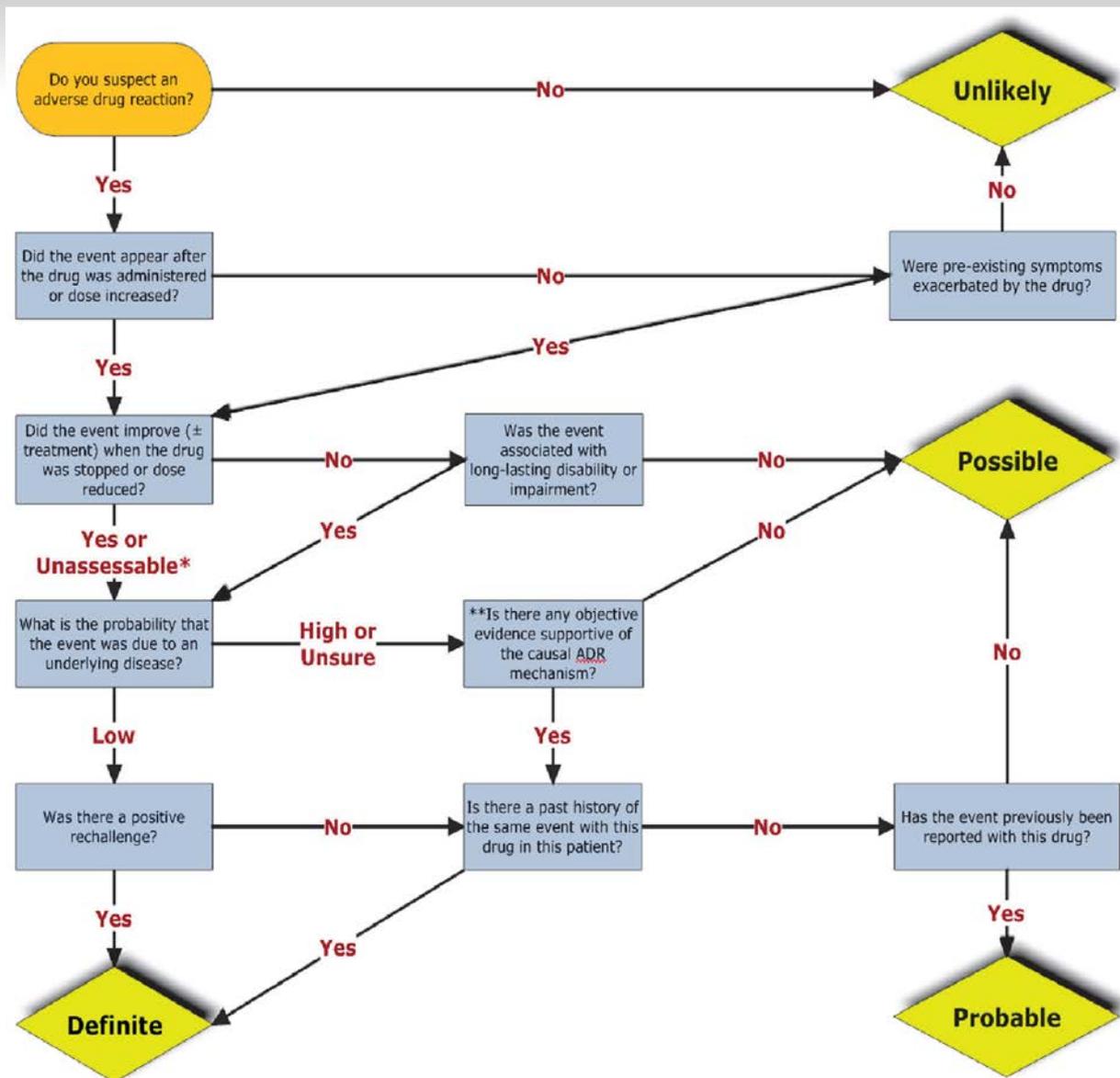
≥ 9 highly probable

≥ 5 probable

≥ 1 possible

0 doubtful

Naranjo CA, Busto U, Sellers EM, et al. A method for estimating the probability of adverse drug reactions. Clin Pharmacol Ther 1981;30:239-45



Gallagher RM, Kirkham JJ, Mason JR, et al. Development and inter-rater reliability of the Liverpool adverse drug reaction causality assessment tool. PLoS One 2011;6:e28096

Post-Marketing Surveillance: Challenges

- Proving (Assessing) Causality
- Finding the numerator and denominator

Finding Numerator/Denominator

“Manufacturer’s post-marketing data indicates that hearing loss with a drug occurs with a frequency of 1 in 10,000.”

Post-Marketing Surveillance - Pitfalls

“One Case in Ten Thousand”

- Numerator
 - How many events occurred but weren't recognized or reported?
 - How many reports were received that didn't actually reflect an adverse event?
- Denominator:
 - How much drug was manufactured but is still somewhere in the supply chain?
 - How many patients actually took the drugs that were prescribed?

Developing a Better System

- Better reporters
- Better systems to retrieve and manage the data
- Better ways to disseminate new knowledge to those who need to know

FDA's Sentinel Initiative

- In 2007, the FDA Amendments Act (FDAAA) required development of an Active Post-marketing Risk Identification and Analysis program.
- FDA in collaboration with public, academic, and private entities has been developing methods to obtain access to disparate data sources and validated methods to create a system to link and analyze safety data from multiple sources.
- The first phase (2008) of this initiative was a “mini-Sentinel pilot” to help guide the development of the Sentinel System.

FDA's Sentinel Initiative

- The “full” Sentinel System, was launched in February, 2016.
- The system currently allows the FDA to access electronic healthcare data from over 193 million patients from multiple data partners.
- The Sentinel System is intended to complement, but not replace, other surveillance tools.

LAMPS

(Large Automated Multi-Purpose Population-Based Systems)

- Created by large health care networks, hospital systems, government agencies.
- Collect and analyze data regarding every drug prescribed, test done, disease diagnosed, etc. etc.
- Can identify an association between seemingly unrelated events (“signals”)

Limitations of LAMPS

- Power is tied to size of the database:
 - Limited data regarding any single drug
 - Limited data regarding new drugs
 - Limited data regarding population subsets



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Drug-Induced Cardiovascular Diseases

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Drug-Induced Cardiovascular Diseases

- Hypertension
- Acute coronary syndromes
- Heart failure
- Valvular and pericardial diseases

Drug-Induced Cardiovascular Diseases

- **Hypertension**
- Acute coronary syndromes
- Heart failure
- Valvular and pericardial diseases

Drug-Induced Hypertension

Drug	Incidence	Mechanism
Amphetamines	?	SNS stimulation
Antihypertensive agents*	?	Abrupt discontinuation → overstimulation of α or β -receptors
Bevacizumab	8-18%	Stimulation of RAA?
Bupropion	2-6%	?
Caffeine	?	SNS stimulation
Celecoxib	2.4-12.5%	Na & H ₂ O retention
Cocaine	?	SNS stimulation
Corticosteroids	?	Na & H ₂ O retention
Cyclosporine	11-50%	Increased prostaglandin production leading to increased fluid volume
Darbepoetin/Erythropoetin	23-24%	Increased blood volume

*Abrupt discontinuation

Renin-angiotensin-aldosterone; SNS = Sympathetic nervous system

Wilson L, Saseen JJ. Hypertension. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Drug-Induced Hypertension

Drug	Incidence	Mechanism
Desvenlafaxine/venlafaxine	1.3-13%	?
Ephedra alkaloids	?	SNS stimulation
Ergot alkaloids	?	SNS stimulation
Estrogen-containing oral contraceptives	5%	Increases hepatic production of angiotensinogen, stimulation of RAA
MAO inhibitors	?	SNS stimulation
NSAIDs	2.4-12.5%	Na & H ₂ O retention
Phenylephrine/pseudoephedrine	?	SNS stimulation
Sibutramine	?	SNS stimulation
Tacrolimus	47-50%	Increased prostaglandin production leading to increased fluid volume
Testosterone	3%	SNS stimulation, fluid retention

MAO = Monoamine oxidase; NSAIDs = Nonsteroidal anti-inflammatory drugs; RAA = Renin-angiotensin-aldosterone; SNS = Sympathetic nervous system

Wilson L, Saseen JJ. Hypertension. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Drug-Induced Hypertension

■ Risk Factors:

- History of hypertension
- History of drug-induced hypertension
- Decreased glomerular filtration rate (especially < 60 mL/min/1.73m²)
- Metabolic syndrome
- Older age

Management of Drug-Induced Hypertension

Drug	Management
Most drugs	Discontinue offending agent
Cyclosporine	Stage 1 hypertension – reduce dose by 25% Stage 2 hypertension – reduce dose by 50%, and consider antihypertensive therapy (dihydropyridine CCBs preferred)
Oral contraceptives	Monitor blood pressure for up to 3 months after d/c If no other form of contraception feasible – use lowest estrogen/progestin product and treat with antihypertensive therapy
Darbepoetin/erythropoetin	Use lowest effective dose Reduce dose if Hg approaches 12 g/dL or if Hg increase is greater than 1 g/dL in 2-week period Subcutaneous administration preferred
Rebound hypertension from d/c of beta-blockers of central alpha-agonists	Re-initiate therapy with antihypertensive drug at previous long-term dose Gradually taper if therapy to be continued

Patient Case

■ Chief Complaint:

- 59 year-old woman was evaluated in a hypertension clinic for persistent hypertension

■ History of Present Illness:

- 12-year history of hypertension controlled on hydrochlorothiazide
- During the past 6 months, her blood pressure progressively increased and is now refractory to additional therapy with felodipine and clonidine

Patient Case

■ Past Medical History:

- Hypertension x 12 years
- Osteoarthritis diagnosed 6 months ago

■ Medications:

- Hydrochlorothiazide 25 mg orally once daily
- Felodipine 10 mg orally once daily
- Clonidine 0.2 mg orally twice daily
- Celecoxib 200 mg orally once daily

Patient Case

- **Vital signs:**
 - Blood pressure 182/94 mm Hg
 - Heart rate 101 bpm
 - Respiratory rate 16/min
 - Temperature 98.6°F
- **Pertinent physical exam/Laboratory data:**
 - Heart and lung exam normal
 - 1-2+ ankle edema
 - Serum creatinine 1.2 mg/dL

Patient Case

- **Management:**
 - Celecoxib discontinued
 - Followup blood pressure 3 weeks later:
 - 136/86 mm Hg

Drug-Induced Cardiovascular Diseases

- Hypertension
- **Acute coronary syndromes**
- Heart failure
- Valvular and pericardial diseases

Drug-Induced Acute Coronary Syndromes

Drug	Incidence	Mechanism
Selective COX-2 inhibitors	RR 1.86 (1.33-2.54)	?
Non-selective COX-2 inhibitors (diclofenac)	RR 1.63 (1.12-2.37)	?
Cocaine	0.7-6.0%	Coronary artery vasoconstriction Coronary thrombosis Accelerated atherosclerosis
Abacavir Didanosine	RR 1.5 (1.47-2.45) RR 1.49 (1.14-1.95)	Adverse metabolic effects
Protease inhibitors	RR 1.16 (1.10-1.23)	Adverse metabolic effects
Estrogen/oral contraceptives	?	Prothrombotic effects
Rosiglitazone	OR 1.43 (1.03-1.98)	?

COX = Cyclo-oxygenase; OR = Odds ratio; RR = Relative risk

Sowinski KM. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Drug-Induced Acute Coronary Syndromes

Risk Factors

- **All:**
 - Pre-existing coronary disease
- **Cocaine:**
 - Cigarette smoking
 - Alcohol
- **Estrogen/oral contraceptives:**
 - Age > 35 years
 - High doses
 - Cigarette smoking
 - Hypertension

Management of Drug-Induced Acute Coronary Syndromes

Drug	Management
Most drugs	<ul style="list-style-type: none">• Discontinue offending agent• Manage as for non-drug-induced acute coronary syndromes
Cocaine	<ul style="list-style-type: none">• O₂• Oral antiplatelet agents, aspirin, P2Y₁₂ inhibitor• IV nitroglycerin• Avoid beta-blocker use in acute phase.<ul style="list-style-type: none">○ Labetalol does not offer any advantage○ Carvedilol has not been studied• Benzodiazepines for anxiety (hypertension, tachycardia)• STEMI – PCI preferred over thrombolytics• Unfractionated heparin, enoxaparin, direct thrombin inhibitors• IV glycoprotein IIB/IIIA inhibitors• CCBs in patients who do not respond to benzodiazepines or nitroglycerin

Sowinski KM. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Circulation 2008;117:1897-1907.

Drug-Induced Cardiovascular Diseases

- Hypertension
- Acute coronary syndromes
- **Heart failure**
- Valvular and pericardial diseases

Drug-Induced Heart Failure

Drug	Incidence	Mechanism
Alpha-1 blockers	RR 2.04 (1.79-2.32)	?
Antiarrhythmic agents (disopyramide, flecainide, dronedarone)	5-10%	Negative inotropic activity
Anthracyclines	0-20%	Myocardial toxicity
Beta-blockers	2%	Inhibition of beta-receptors
Biologics (bevacizumab, infliximab, trastuzumab)	RR 2.84-4.74	VGEF inhibition, myocardial toxicity
CCBs (diltiazem, verapamil, nifedipine)	Up to 25%	Negative inotropic activity
Corticosteroids	OR 2.7 (2.5-2.9)	Na, H ₂ O retention
COX-2 inhibitors	Up to 2%	Na, H ₂ O retention
DPP-4 inhibitors	HR 1.27 (1.07-5.51)	?
Glitazones	Up to 14%	Fluid retention
NSAIDs	RR 1.8-9.9	Na, H ₂ O retention

CCBs = Calcium channel blockers; COX = Cyclooxygenase; DPP = Dipeptidyl peptidase;

NSAIDs = Nonsteroidal anti-inflammatory drugs; OR = Odds ratio; RR = Relative risk

Al Hamarneh YN, Tsuyuki RT, et al. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017; In press.

Anthracycline-Induced Heart Failure

Risk Factors (Adults)

- Cumulative doxorubicin dose > 550 mg/min²
- Older age
- 3-week schedule of administration
- Concomitant cardiac irradiation
- Concomitant use of cyclophosphamide, amsacrine, 5-FU, dactinomycin, mithramycin, mitomycin, or vincristine

Page RL II, et al. Circulation 2016;134:e32-e69.

Al Hamarneh YN, Tsuyuki RT. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Drug-Induced Heart Failure

Prevention

- Avoid negative inotropic agents in patients with pre-existing heart failure
- Prevent beta-blocker-induced heart failure exacerbations by initiating low doses and titrating to target dose slowly over 6-8 weeks
- Anthracycline-induced heart failure:
 - Dexrazoxane (when cumulative doxorubicin dose reaches 300 mg/m²)

Page RL II, et al. Circulation 2016;134:e32-e69.

Al Hamarneh YN, Tsuyuki RT. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Drug-Induced Heart Failure Management

- Discontinue offending drug
- Aggressive diuresis
- Treatment same as for non-drug-induced heart failure

Page RL II, et al. Circulation 2016;134:e32-e69.

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Drug-Induced Cardiovascular Diseases

- Hypertension
- Acute coronary syndromes
- Heart failure
- **Valvular and pericardial diseases**

Drug-Induced Heart Valve Disease

Drug	Incidence	Mechanism
Bromocriptine	?	?
Cabergoline	Up to 69%	Activation of 5-hydroxytryptamine 2B subtype of serotonin receptor, promoting serotonin release
Dexfenfluramine	Up to 38%	“
Dexfenfluramine/phentermine	Up to 38%	“
Ergotamine	?	“
Fenfluramine	Up to 38%	“
Fenfluramine/phentermine	Up to 38%	“
MDMA	Up to 14%	“
Pergolide	Up to 78%	“
Methysergide	< 1%	?

Spinler SA, Silvestry FE. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Drug-Induced Pericarditis

Drug	Incidence	Mechanism
Cancer chemotherapy	?	Direct cytotoxicity
Clozapine	?	?
Cromolyn sodium	?	?
Hydralazine	2%	SLE-like syndrome
Isoniazid	30%	SLE-like syndrome
Methyldopa	?	SLE-like syndrome
Methysergide	0.02%	?
Minoxidil	4-20%	?
Procainamide	18-57%	SLE-like syndrome

Spinler SA, Silvestry FE. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Drug-Induced Heart Valve Disease

Risk Factors

Drug	Risk Factors
Fenfluramine Dexfenfluramine	Duration of use > 3 months Older age Female sex Dose > 60 mg daily
Ergotamine Methysergide	Ergotamine dose > 6 mg daily Methysergide dose > 8 mg daily Continuous (vs episodic) use Duration of use > 9 months
Cabergoline Pergolide	Cumulative dose > 1000 mg Longer duration of use Hypertension Male sex

Spinler SA, Silvestry FE. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Drug-Induced Pericarditis

Risk Factors

Drug	Risk Factors
Cancer chemotherapy	High doses (eg total cyclophosphamide dose > 174 mg/kg)
Minoxidil	Kidney disease

Spinler SA, Silvestry FE. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In press).

Drug-Induced Heart Valve Disease or Pericarditis

Management

- **Valve Disease:**
 - Discontinue offending agent
 - Valve replacement or repair
 - Treat heart failure symptoms with diuretics and vasodilators
- **Pericarditis:**
 - Discontinue offending agent
 - NSAIDs
 - Corticosteroids for drug-induced SLE
 - Surgical pericardectomy
 - Pericardiocentesis

Key Takeaways

- Drugs may cause or exacerbate cardiovascular diseases
 - Hypertension, ACS, heart failure, valve disease, pericarditis, arrhythmias
- Pharmacists should be aware of drugs that may cause or exacerbate specific cardiovascular diseases
- Pharmacists should be aware of risk factors for and methods of prevention and management of drug-induced cardiovascular diseases



Drug-Induced Kidney Diseases

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Drug-induced Kidney Diseases

- Acute kidney injury
 - Community-acquired
 - Hospital-acquired
- Chronic kidney disease

Acute Kidney Injury (AKI)

Defined as:

- Increase in SCr by ≥ 0.3 mg/dl (≥ 26.5 mmol/l) within 48 hours; or
- Increase in SCr to ≥ 1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume < 0.5 ml/kg/h for 6 hours.

Barton Pai A, Wegrzyn NM. Acute Kidney Injury. In: Tisdale JE, Miller DA, eds. Drug-Induced Diseases. Prevention, Detection and Management, 3rd ed, ASHP, 2017 (In Press).

Case Study

- The patient is a 65-year-old woman who presents to the clinic for follow-up evaluation of her type 2 diabetes and dyslipidemia. She also has a past medical history of stage 2 chronic kidney disease with proteinuria, hypothyroidism, hypertension, and allergic rhinitis.
- She reports having nausea, vomiting, and a low-grade fever last week. She reports her fever resolved with Motrin, but she still feels ill.
- Her weight is usually about 145 pounds (66 kg), and she now weighs 150 lbs (68 kg).
- Upon preliminary examination, she was found to have 2+ pitting edema, elevated blood pressure, and crackles on auscultation.

Signs and Symptoms

- Early onset signs and symptoms
 - Fatigue
 - Reduced urine output
 - Edema
- Other signs and symptoms
- AKI versus CKD
- Case study

Case Study

- **Medications:**
- Lisinopril 20 mg/hydrochlorothiazide 12.5 mg PO QD
- Fexofenadine 180 mg PO QD
- Atorvastatin 10 mg PO QD
- Glipizide 5 mg PO QD
- Metoprolol 50 mg PO BID
- Levothyroxine 25 mcg PO QD
- Ibuprofen 400 to 800 mg as needed for arthritis pain and fever

Mechanisms of Drug-Induced AKI

Drug	Mechanism
ACE inhibitors and ARBs	Efferent arteriole vasodilation especially when renin–angiotensin–aldosterone system–dependent vasoconstriction is present
NSAIDs and COX-2 inhibitors	Hemodynamic: Inhibition of prostaglandin-dependent afferent arteriole vasoconstriction Acute interstitial nephritis: T cells infiltrate the kidney interstitium, imitating an immunologic response
Aminoglycosides	Saturable accumulation of aminoglycosides in the S1 and S2 segments of the proximal tubule, leading to inhibition of phospholipases and cell death
Amphotericin B	Afferent arteriole vasoconstriction; altered tubule cell permeability leading to cell lysis

Mechanisms of Drug-induced AKI

Radiocontrast media	Afferent arteriole vasoconstriction and reactive oxygen species– mediated tubular toxicity
Cisplatin	Tubular cell toxicity secondary to binding to mitochondrial DNA, impairing cellular function and inducing apoptosis
Acyclovir, sulfadiazine, indinavir	Supersaturation of the urine with solute, resulting in crystal formation
Lithium	Development of minimal-change disease and focal segmental glomerulosclerosis

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Case Study

- ***Baseline creatinine 0.9 mg/dL (3 months ago)***
- **Physical exam findings**
- VS: BP 165/95, pulse 85 bpm, RR 22/min, 37.6°C
- Chest: Basilar crackles, inspiratory wheezes
- CV: RRR, S1, S2 normal
- MS/Ext: 2 + pitting edema
- Urinalysis: Color, yellow; character, hazy; glucose (-); ketones (-); specific gravity 1.010; pH 5; (+) protein; no bacteria; nitrite (-); blood (-); osmolality 325 mOsm/; urinary sodium 77 mEq/L; creatinine 25 mg/dL

Case Study

- **Laboratory values:**
- Sodium 137 mEq/L, potassium 4.1 mEq/L, chloride 106 mEq/L, bicarbonate 22 mEq/L, BUN 32 mg/dL, SCr 1.8 mg/dL, glucose 120 mg/dL, WBC 6,900, hemoglobin 14.4, and hematocrit 42%.
- **Interview information:**
- Takes medications as prescribed.
- She has been taking all of her medications for years, with the exception of ibuprofen which she started 3-4 weeks ago.
- Fasting glucose ranges from 110 to 125 mg/dL.

Risk Factors for Drug-Induced AKI

- Concomitant administration of nephrotoxins
- Elderly
- Hemodynamic dose-dependent effects
- Known allergic response to agent (acute interstitial nephritis)
- Preexisting chronic kidney disease
- Prolonged therapy with nephrotoxins
- Renin-dependent disease states

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Approaches to help prevent drug-induced AKI

- Avoid use of drugs associated with AKI in patients at risk
- Avoid concurrent use of other agents that affect renal hemodynamics
- Avoid over-diuresis
- Avoid concomitant exposure to nephrotoxins
- Consider once-daily dosing with aminoglycosides (amikacin, gentamicin, tobramycin)
- Counsel patients regarding increased risk if volume depletion occurs and need to maintain adequate fluid intake
- Consider preferential use of lipid-based products (amphotericin B)

Approaches to help prevent drug-induced AKI

- Consider preferential use of non-ionic, iso-osmolar radio contrast media
- Dose reduction (drugs with hemodynamic effects)
- Limit duration of therapy for drugs associated with AKI, when possible
- Maintain adequate hydration
- Prophylaxis with *N*-acetylcysteine or isotonic sodium bicarbonate infusion in patients at high risk for radiocontrast media-induced AKI
- Start at lowest dose (drugs with hemodynamic effects)

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Drug-Induced Kidney Diseases

- Acute kidney injury
 - Community-acquired
 - Hospital-acquired
- **Chronic kidney disease**

Stages of Chronic Kidney Disease (CKD)

Stage	Description	GFR (mL/min/1.73 m ²)
1	Kidney damage with no or increased GFR	> 90
2	Kidney damage with mildly decreased GFR	60-89
3	Moderate decrease in GFR	30-59
4	Severe decrease in GFR	15-29
5	Kidney failure	< 15 (or dialysis)

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Mechanisms of Drug-Induced CKD

Drug	Mechanism
Cyclosporine, tacrolimus	Interstitial fibrosis, tubular atrophy, afferent arteriopathy
Lithium	Polyuria, interstitial fibrosis, tubular atrophy, tubular cysts
Antipyretic analgesics	Combination of at least 2 agents, plus caffeine or codeine. Papillary necrosis, interstitial fibrosis
Aristolochic acid (Chinese herbs)	Interstitial fibrosis, tubular atrophy

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Mechanisms of Drug-Induced CKD

Drug	Mechanism
Carmustine/ lomustine	Interstitial fibrosis, tubular necrosis, glomerulosclerosis
Cidofovir/indinavir/ ifosfamide	Tubular atrophy
Cisplatin	Interstitial fibrosis, tubular atrophy
Gold salts	Proteinuria, membranous GN, immune complex mesangial GN
Mitomycin C	Vascular disease, interstitial fibrosis, tubular atrophy
Propylthiouracil	Tubulointerstitial nephritis
Streptozocin	Interstitial fibrosis, tubular atrophy, glomerulosclerosis

Risk factors

- Vary depending on causative agent
- Cyclosporine/tacrolimus
 - Age > 50
 - Pre-existing CKD
 - Higher cumulative dose & increased duration of exposure
 - Number of episodes of AKI & number of rejection episodes
 - Poor kidney function in the first 3-12 months post-op
 - Postoperative AKI
- Other examples

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Approaches to Prevent Drug-Induced CKD

- Cyclosporine/tacrolimus
- Lithium
- Antipyretic analgesics
- Chinese herbs (aristolochic acid)

Proton Pump Inhibitors

- Should PPIs be added to the list?

Key Takeaways

- Key Takeaway #1

Identifying patients at risk for development of AKI and CKD and implementing preventative measures to decrease its occurrence or severity is critical

- Key Takeaway #2

There is no effective drug therapy for treatment of AKI or CKD.

- Key Takeaway #3

Patients with a history of CKD are at risk of drug-induced AKI



Drug-Induced Liver Disease

Scott S. Malinowski, PharmD

Clinical Assistant Professor

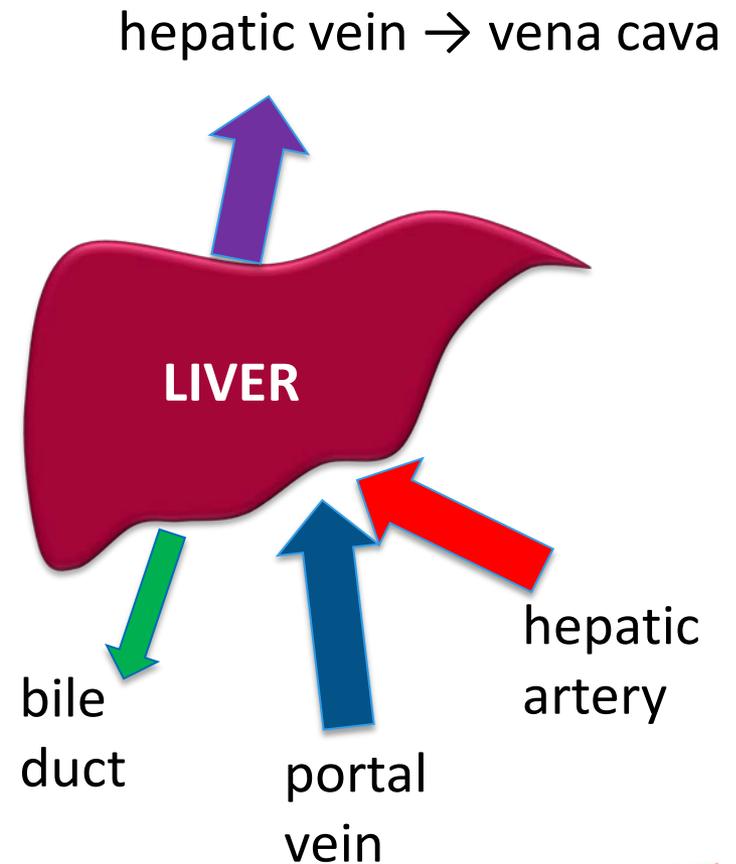
University of Mississippi School of Pharmacy

Introduction

- Definition of drug-induced liver injury (DILI)
- Terminology
- Impact of DILI
 - Market withdrawal
 - Acute liver failure (ALF)
- Importance of the hepatobiliary system

Liver Anatomy and Physiology

- Functions of the liver
 - Removal of toxins/waste
 - Nutrient metabolism
 - Nutrient storage
 - Protein/clotting factor synthesis
 - Bile production
 - Immune system
 - Drug metabolism



Liver Anatomy and Physiology

- Lobes
- Lobules
- Sinusoids
 - Kupffer cells
 - Hepatocytes
- Canaliculi – bile collection vessels
- Bile ducts → gallbladder

Hepatic Enzymes

- Aminotransferases: ALT, AST
 - Functions
 - Response to injury ← **hepatocytes**
 - Elevations do not always correlate with severity of injury
- Alkaline phosphatase, GGT, 5NT
 - Functions
 - Response to injury ← **bile ducts**
- Cytochrome P450 system

NOTE: PT, albumin, bilirubin are better measures of liver function

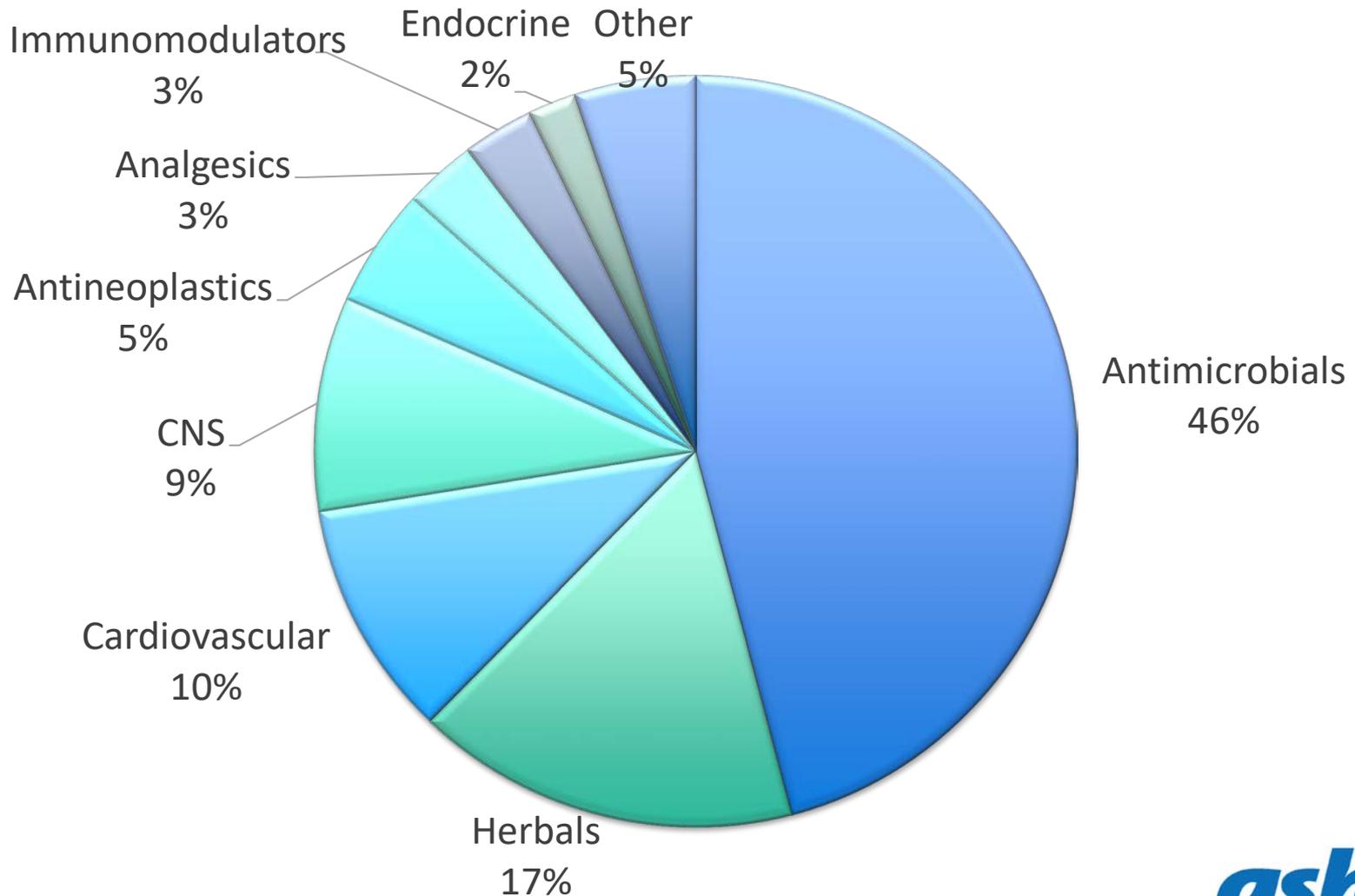
Epidemiology of DILI

- Increasingly problematic
- Challenges in determining incidence
- Post-marketing surveillance
- >50% of all cases of ALF are caused by drugs
(e.g. **acetaminophen**)

Causative Agents

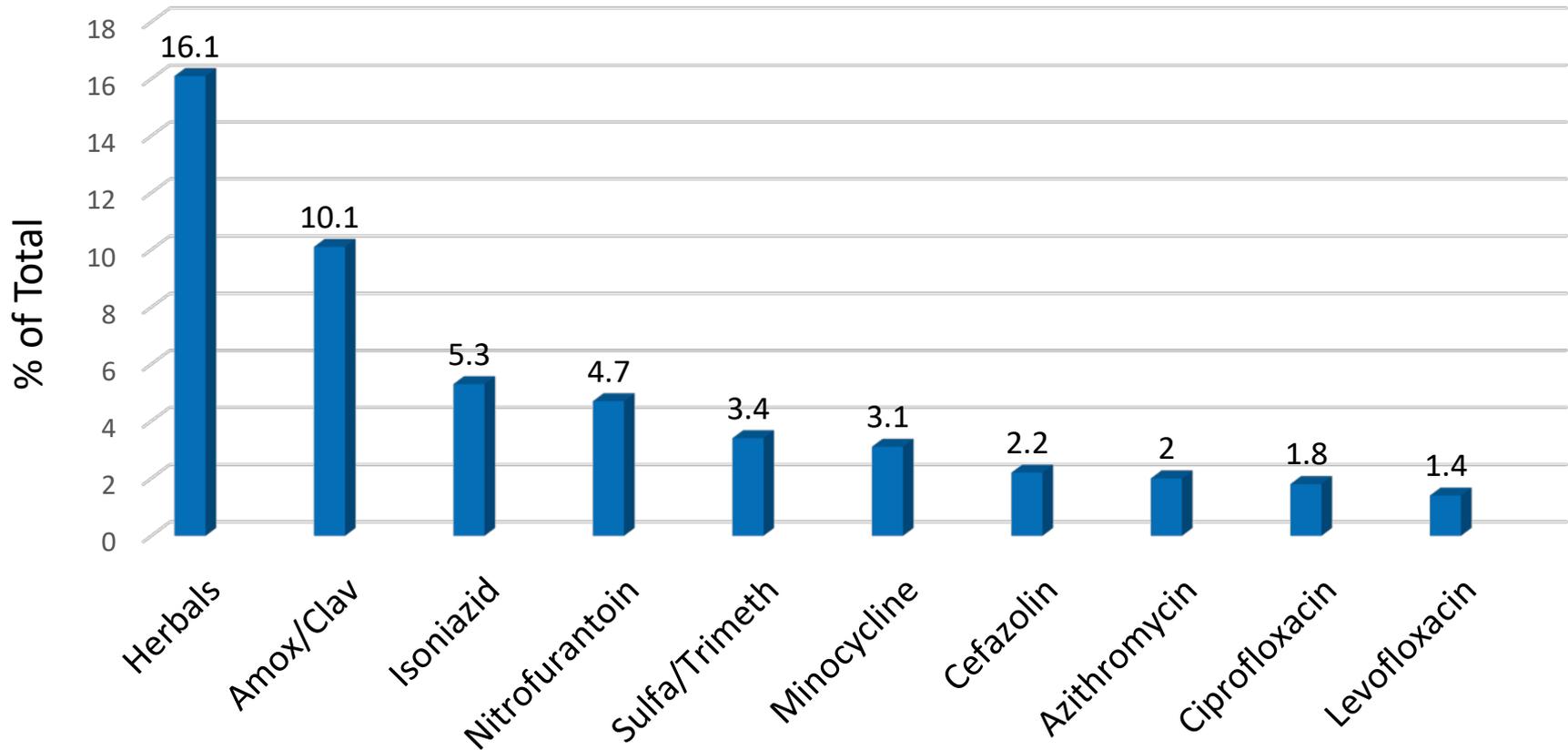
- LiverTox website
 - DILIN (established by NIDDK)
 - www.livertox.nih.gov
- >1000 agents associated with DILI
- Agents
 - Medications
 - Herbal and dietary supplements
 - Chemical toxins

Causative Agents* – by Medication Class



*non-acetaminophen

Causative Agents* – by Frequency



DILI Classification Schemes

- Mechanism of injury
 - Predictable
 - Idiosyncratic
- Clinical presentation
 - Hepatocellular injury
 - Cholestatic injury
 - Mixed
- Histologic features
 - Hepatitis
 - Cholestasis
 - Steatosis

Mechanism (Pathology) of DILI

- Predictable (e.g. **APAP, methotrexate**)
 - Dose-dependent
 - Fast onset
 - Reproducible
 - Intrinsic hepatotoxins
 - hepatocellular necrosis
- Idiosyncratic
 - Rare (0.01 – 1% of individuals taking the drug)
 - Unpredictable
 - Onset of DILI is variable
 - Tends to be immune-mediated

Classification by Presentation

- Hepatocellular injury (cytotoxic)
 - ↑↑↑ ALT/AST
 - ↑ Alk Phos
- Cholestatic injury
 - ↑↑ Alk Phos
 - ↑ ALT/AST
- Mixed
 - ↑↑ ALT/AST
 - ↑↑ Alk Phos

Distinguishing Between Types of DILI

$$R \text{ ratio} = \frac{\text{ALT/ULN}}{\text{Alk Phos/ULN}}$$

Type of Injury	Enzyme Abnormality	Ratio (R)
Hepatocellular	ALT ≥ 3 x ULN	≥ 5
Cholestasis	Alk Phos ≥ 2 x ULN	≤ 2
Mixed	ALT ≥ 3 x ULN Alk Phos ≥ 2 x ULN	2-5

Histologic Classification

- Hepatocyte damage
- Cholestasis
- Steatosis
- Hepatic venous outflow obstruction
- Sinusoidal obstruction syndrome (SOS)
 - a.k.a. veno-occlusive disease (VOD)
- Granulomas
- Phospholipidosis
- Peliosis hepatis
- Neoplasm

Mechanisms of DILI

- Hepatocellular injury - **pathologies**
 - Metabolic
 - Exposure to drug or toxic metabolite
 - Covalent binding
 - Oxidative stress
 - Metabolic disturbances
 - Immune-mediated
 - Sensitization of hepatocytes to cytokines (hapttenization)

Mechanisms of DILI

- Hepatocellular injury
 - Direct toxicity
 - Steatosis
 - Excessive deposition of triglycerides within the hepatocyte
 - Reduced utilization (β -oxidation interference)
 - Reduced elimination via VLDL export (**tetracycline**)
 - Increased uptake
 - Increased *de novo* lipogenesis
 - Mitochondrial accumulation (e.g. **tamoxifen**, **amiodarone**)
 - Can progress to steatohepatitis

Mechanisms of DILI

- Hepatocellular injury
 - Hepatic venous outflow obstruction (e.g. **oral contraceptives**)
 - Thrombosis → venous congestion → hepatomegaly → stretching of the hepatic capsule → abd pain
 - Sinusoidal obstruction syndrome (e.g. **busulfan, cyclophosphamide, melphalan**)
 - RUQ pain
 - Ascites
 - Jaundice

Mechanisms of DILI

- Cholestatic injury
 - Stagnant bile
 - Impaired secretion (from hepatocytes)
 - Outflow obstruction
 - Hepatocyte injury (e.g. **cyclosporine, anabolic steroids**)
 - Bile ductular cell injury (e.g. **amoxicillin-clavulanate**)
 - Direct injury
 - Adaptive immune response
 - Biliary tree
 - Obstructive jaundice

Risk Factors for DILI

- Older age (**amoxicillin-clavulanate, isoniazid, nitrofurantoin**)
- Younger age (**valproic acid, aspirin, erythromycin estolate**)
- Female gender
- Ethanol use/abuse (**APAP, isoniazid, methotrexate**)
- Malnutrition
- Concurrent drug therapy (CYP inhibition)
- Underlying disease states
- Genetic predisposition
- Obesity (**halothane**)

Clinical Presentation of DILI

- Nausea, vomiting
- Lethargy
- Abdominal discomfort
- Jaundice (+/- pruritus)
- Elevated liver enzymes

- ★ Many patients are asymptomatic
- ★ Some patients present in **acute liver failure**
 - Coagulopathy
 - Encephalopathy

Clinical Presentation of DILI

- Hepatocellular injury
 - Sn/sx occur within **days to weeks** after exposure
 - Lethargy, malaise
 - Abdominal discomfort
 - Jaundice
 - **Elevated ALT, AST (>3 x ULN)**
 - ★ If immune-mediated:
 - Fever
 - Rash
 - Arthralgia
 - Eosinophilia

Clinical Presentation of DILI

- Cholestatic injury
 - Sn/sx occur within **weeks to months** after exposure
 - Jaundice
 - **Pruritus**
 - Lethargy, malaise
 - Nausea, anorexia
 - Abdominal discomfort
 - **Elevated alkaline phosphatase (>2 x ULN)**
 - ★ If immune-mediated:
 - Fever
 - Rash
 - Arthralgia
 - Eosinophilia

Clinical Presentation of DILI

- Hepatic vein thrombosis
 - Presents as Budd-Chiari syndrome
 - Hepatomegaly, abd pain, ascites
- Sinusoidal obstruction syndrome
 - Sn/sx occur within **1 to 3 weeks** after exposure
 - Rapid weight gain
 - Ascites
 - Jaundice
 - RUQ pain
 - Portal hypertension

Morbidity and Mortality

- Most patients fully recover (quickly)
 - Cholestatic injury can weeks to months to fully resolve
- 5-10% of cases progress to “chronic DILI”
 - Chronic DILI can progress to cirrhosis
- Risk factors for mortality:
 - Pre-existing liver disease
 - Elevated serum creatinine (need for dialysis)
 - [Jaundice] + [total bilirubin >2 x ULN] + [ALT >3 x ULN]
 - Extended exposure to offending agent
- Spontaneous survival rates:
 - APAP associated DILI = 62%
 - Idiosyncratic reactions = 26%

Prevention of DILI

- Patient education (early recognition)
- Appropriate dosing
- Avoiding drug-drug and drug-food interactions
- Routine monitoring of liver enzymes(?)
- Routine liver biopsies(?)

Management of DILI

- Proper diagnosis
- **Discontinuation of offending agent**
- NEVER re-challenge!
- Supportive care
- Monitoring
 - Serial liver enzymes
 - Sn/sx of acute liver failure
- Antidotes:
 - *N*-acetylcysteine (NAC) for acetaminophen
 - L-carnitine for valproic acid

Management of DILI

- *N*-acetylcysteine (NAC) for **acetaminophen hepatotoxicity**
 - APAP responsible for 39-51% of all acute liver failure
 - APAP metabolism:
 - Glucuronidation
 - Sulfation
 - CYP2E1 (~10%)
 - Toxic metabolite: N-acetyl-p-benzoquinone imine (**NAPQI**)
 - Rapidly detoxified by **glutathione**
- NAC replenishes glutathione stores (via cysteine)

Management of DILI

- *N*-acetylcysteine (NAC) for **acetaminophen hepatotoxicity**
 - Rumack-Matthew nomogram
 - Oral formulation (Mucomyst®)
 - Loading dose: 140 mg/kg p.o.
→ 70 mg/kg p.o. q4h x 17 doses
 - Intravenous formulation (Acetadote®)
 - Loading dose: 150 mg/kg i.v. over 1 hr
 - Dose #2: 50 mg/kg i.v. over 4 hrs
 - Dose #3: 100 mg/kg i.v. over 16 hrs

Management of DILI

- 1-carnitine for **valproic acid hepatotoxicity**
 - Valproic acid predominantly metabolized via glucuronidation and β -oxidation, with small amount via **ω -oxidation** (\rightarrow **toxic metabolites**)
 - Carnitine is essential for β -oxidation
 - Valproic acid inhibits the synthesis of carnitine
 - Carnitine depletion \rightarrow shunting of valproic acid metabolism towards **ω -oxidation**
 - Carnitine supplementation increases the β -oxidation of valproic acid
 - \rightarrow limiting production of hepatotoxic metabolites

Management of DILI

- l-carnitine for **valproic acid hepatotoxicity**
 - No controlled studies in humans
 - Intravenous route preferred
 - Loading dose: 100 mg/kg i.v. over 30 mins,
→ 15 mg/kg i.v. q4h
 - Continued until clinical signs of poisoning resolve
 - Max dose of 6 grams

Key Takeaways - DILI

- Establishing diagnosis/causality is challenging
 - Diagnosis of exclusion
 - Idiosyncratic nature
 - Same drug can present in different ways
- Searchable database available
 - Excellent resource
 - www.livertox.nih.gov
- Primary treatment: withdrawal of offending agent
 - Most patients fully recover
 - Some will need a liver transplant

Active Learning #1

Match the following types of drug-induced liver injuries with their respective latency periods (time to onset of sn/sx):

- A. Hepatocellular injury
 - B. Cholestatic injury
-
- 1. Days to weeks
 - 2. Weeks to months

Active Learning #1

Match the following types of drug-induced liver injuries with their respective latency periods (time to onset of sn/sx):

- A. Hepatocellular injury → **Days to weeks**
 - B. Cholestatic injury → **Weeks to months**
-
- 1. Days to weeks
 - 2. Weeks to months

Active Learning #2

The medication (non-herbal, non-acetaminophen) most frequently associated with drug-induced liver disease is ____.

- A. Amoxicillin-clavulanate
- B. Atorvastatin
- C. Methotrexate
- D. Valproic acid

Active Learning #2

The medication (non-herbal, non-acetaminophen) most frequently associated with drug-induced liver disease is ____.

- A. Amoxicillin-clavulanate
- B. Atorvastatin
- C. Methotrexate
- D. Valproic acid



Drug-Induced Liver Disease

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