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1-800-Bad-Drug Advertisements: *The Good, The Bad, and The Ugly*

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Disclosures

- No personal or financial relationships relevant to this presentation existed during the past 12 months.

Advertising for DOAC Injury Lawsuit

Product Liability Lawsuits in Context

- Chance for people harmed by drug to seek damages from manufacturer

- Tort
  - Civil wrong for which a remedy may be obtained (usually damages)
  - Goals
    - Loss allocation: efficiency (pragmatism) and fairness (justice)
    - Compensation: restoration of injured party
    - Deterrence

- Types of torts
  - Intentional
  - Strict liability
  - Negligence: duty, breach, causation, and injury
    - Pharmaceuticals: failure to warn

Failure to Warn

- Claim components
  - Manufacturer knowledge of the drug's risk: actual or constructive
  - Improper warning of the drug's risk
    - Not commensurate with scope and extent of danger
    - Delayed
    - Inappropriate tone
  - Causation
    - More likely than not: varying interpretations

- Case: dabigatran (Pradaxa)
  - Failure to warn: risk of serious, excessive, uncontrollable bleeding
  - Settlement: $650 million in May 2014 to 4,000 families

DTC vs. 1-800-bad drug advertisements

DTC advertisements	1-800-bad-drug advertisements
❑ Primary regulator	
❑ FDA	❑ State bar associations
❑ Audience	
❑ With indicated condition	❑ Intended: injured on drug
	❑ Unintended: uninjured on drug
❑ Impact	
❑ Initiation	❑ Discontinuation
❑ Physician-mediated	❑ Physician- or un-mediated

1-800-Bad-Drug Considerations

Possible strengths	Possible weaknesses
❑ Awareness	
❑ Legal remedy	
❑ Risk(s)	❑ Risk-benefit distortion
❑ Empowerment: attorney access	
❑ Informed decision-making	❑ Fear-based decision-making

Physician-Mediated Impact Study

- Survey methods
  - Email invitation: CardioSurve and PCP Research Now panelists
  - Time period: June 12, 2013 – July 12, 2013
- Results
  - Response rates: 144 cardiologists (33%), 253 PCPs (13%)

Asked about treatment seen in…	DTC Advertisements	1-800-Bad-Drug Advertisements
Cardiologists	15%	11%
PCPs	22%	13%

Would consider honoring request for change in treatment program if…	CHADS2 Score=1	Patient mentions legal liability or is litigious
Cardiologists	63%	25%
PCPs	57%	30%

-ACC. Unpublished (2016).

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Utilization Impact Study

- Design
  - Markets: Boston and Atlanta
  - Medicare utilization data
  - Time period: December 2008 – December 2009
  - Segmented regression analysis
  - Dependent variable: prescription fills
    - Drugs: metclopramide (Reglan), fentanyl transdermal patch (Duragesic), exenatide (Byetta), varenicline (Chantix), pregabalin (Lyrica), quetiapine (Seroquel), paroxetine (Paxil)
  - Independent variable of interest: advertising volume

- Results
  - "Attorney advertising was positively associated with prescription rate ($p > 0.01$) for five of the seven drugs."

-Tippett & Chen. Drug Saf (2015).

FAERS Study

- Design: case report review
- Database: FDA Adverse Event Reporting System
- Time period: September 2014 – December 2015
- Results
  - 31 patients experiencing serious AE after stopping rivaroxaban after watching 1-800-bad-drug advertisements
    - Mean age: 72 (range: 45-90)
    - Male-to-female ratio: 1:1.4
    - 75% stroke or transient ischemic attack
    - 6% death
- Limitation: unknown denominator

-Burton & Peacock. Heart Rhythm Soc (2016).

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Content Analysis Study

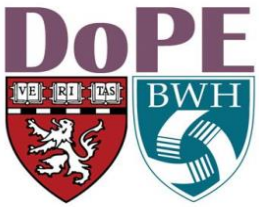
- Design
  - Markets: Boston and Atlanta
  - Type of advertisement: locally-targeted legal services
  - Time period: June 15, 2009 – January 4, 2010
  - Coding: double independent, consensus resolution
- Selected results: 56 unique advertisements
    - Adverse event frequency: 0%
    - Benefits of use: 59% via audio or text
    - Recommendation to consult a physician: 39% via text
    - Attorney/firm disclosure: 11% not within first 20 seconds

-Tippett. Am J Law Med (2014).

Conclusions, Next Steps, and Solutions

- Conclusion: limited evidence of negative impact but reasonable concerns
- Further empirical research
- Potential solutions
  - Physician inoculation
  - Legal intervention
  - Prohibition: Unlikely given commercial free speech jurisprudence
  - Disclosure requirements
    - Benefits of use
    - Frequency of harm
    - Sponsor

Supplemental Slides



First consideration: Is the product unreasonably dangerous?

- Since 1960s, courts hold sellers of "unreasonably dangerous" consumer goods strictly liable for the damages they cause, even if that damage was unforeseeable
  - Example: products with *manufacturing defects* or *design defects*
- Restatement (Second) of Torts, comment k [1965]: A pharmaceutical product "properly prepared, and accompanied by proper directions and warning, is not defective, nor is it unreasonably dangerous"

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Tort scholar William Prosser (1971)

- *"The argument that industries producing potentially dangerous products should make good the harm, distribute it by liability insurance, and add the cost to the price of the product, encounters reason for pause, when we consider two of the greatest medical boons to the human race, penicillin and cortisone, both have their dangerous side effects, and that drug companies might have been deterred from producing and selling them. Thus far courts have tended to hold the manufacturer to a high standard of care in preparing and testing drugs of unknown potentiality and in giving warning; but in the absence of evidence that this standard has not been met, they have refused to hold the maker liable for unforeseeable harm."*

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Failure to warn

- Bottom line: Hard to make claim that a properly manufactured, FDA-approved, adequately labeled drug is unreasonably dangerous

- Instead, product liability usually based on claim that there has been a failure to warn about side effects

- 3 main components to a claim:
  - Knowledge of the drug's risk by the manufacturer
  - Improper warning of the drug's risk
  - Causation of damages

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#1: Knowledge of risk

- Principle 1: Manufacturers are not liable for risks that they could not have known about
  - Chambers v Searle (1975): OCP argued as causing CVA
  - "Warnings contained in package insert…were a fair representation of the medical and scientific knowledge available at the time"
- Principle 2: Knowledge can be actual or constructive
  - *Actual knowledge*: Manufacturer knows of reasonable information suggesting a risk that it did not pass on to consumer (ex: paroxetine)
  - *Constructive knowledge*: Knowledge courts assume to be present even if it is not
    - Could have been acquired with reasonable care (ex: cerivastatin)
    - Mfr should have performed different or additional analyses to better understand important side effect

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#2: Has an adequate warning been provided?

- Principle 1: Warning must be commensurate with scope and extent of dangers associated with drug
  - Ex: troglitazone: Risks described as >3-fold elevations in LFTs when some were >20-fold
- Principle 2: Warning must not be subject to undue delay
  - Ex: cisapride: Manufacturer and FDA negotiated for 5 years over how to change drug's label to include safety data that had been submitted to agency but not made public
- Principle 3: Warning must be of appropriately urgent tone
  - Ex: rofecoxib: Cardiovascular adverse events initially described in vague terms, placed in less prominent "precautions" section of label

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#3: Did the product cause the injury?

- Different views of causation:
  - *Pharmacoepidemiologist*: Probabilistic causation
    - Drug linked to adverse event by statistical association at $p<0.05$
  - *Lawyer:* Legal causation, requiring clear causal chain from event to outcome

- 2 types of causation:
  - General causation: Is the product capable of causing the particular injury in a population of patients like the plaintiff?
  - Specific causation: Did the product in question cause the injury in this particular patient?

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General causation

- "More likely than not" standard
  - Compare with "clear and convincing evidence" and "beyond a reasonable doubt" standard from criminal law
- Varying interpretations
  - "Something more than association and a mere possibility of causation"
  - "Relative risk of >2.0"
    - Attributable risk in exposed group exceeds 50%
    - Ex: pyridoxime/doxylamine: "Plaintiffs must establish not just that their mother's ingestion of Bendectin somewhat increased the likelihood of birth defects, but that it more than doubled it" (9th Cir 1995)
    - Ex: Link between silicone breast implants and inflammatory disease: Court excluded study linking product and outcome with RR 1.24 because "so significantly close to 1.0" (11th Cir 1999)
  - Use of Bradford Hill criteria

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Bradford Hill criteria (1965)

1. Strength of association
2. Consistency and replication of findings
3. Specificity with respect to both the substance and injury at issue
4. Temporal relationship
5. Biological gradient and evidence of a dose-response relationship
6. Plausibility
7. Coherence
8. Experimental removal of exposure
9. Consideration of alternative explanation

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Adapted from Hill AB. The environment and disease: association or causation? Proc R Soc Med 1965;58:295-300

Specific causation

- Easy for instantaneous allergic reactions
- Harder for subacute or later-onset responses
- Ex: Shortly after starting rofecoxib, man has MI with very atypical presentation of 2 coronary artery clots close to each other
  - Texas Court of Appeals: No specific causation "Because … preexisting cardiovascular disease was another plausible cause of his death, the plaintiffs were required to offer evidence excluding that cause with reasonable certainty"
- Plaintiff must demonstrate that adequate warnings would have made a difference; if it would have made no difference in decision to prescribe or take drug, case can lack proximate cause

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The Learned Intermediary defense

- Manufacturer fills duty to warn by providing accurate and adequate warning to prescribing physician
  - Do not have to offer warnings about risks that are obvious or generally known to skilled medical practitioners
  - Physicians assumed to have constructive knowledge of information in label

- Learned intermediary defense can be forfeited if manufacturer markets drug aggressively via DTCA without adequate warnings to patients

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