

Excipient Harms and Tampering of Opioid Analgesics

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Disclosure

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- Dr. Dasgupta is a part-time employee of the RADARS System. The RADARS System was not involved in this presentation or research.

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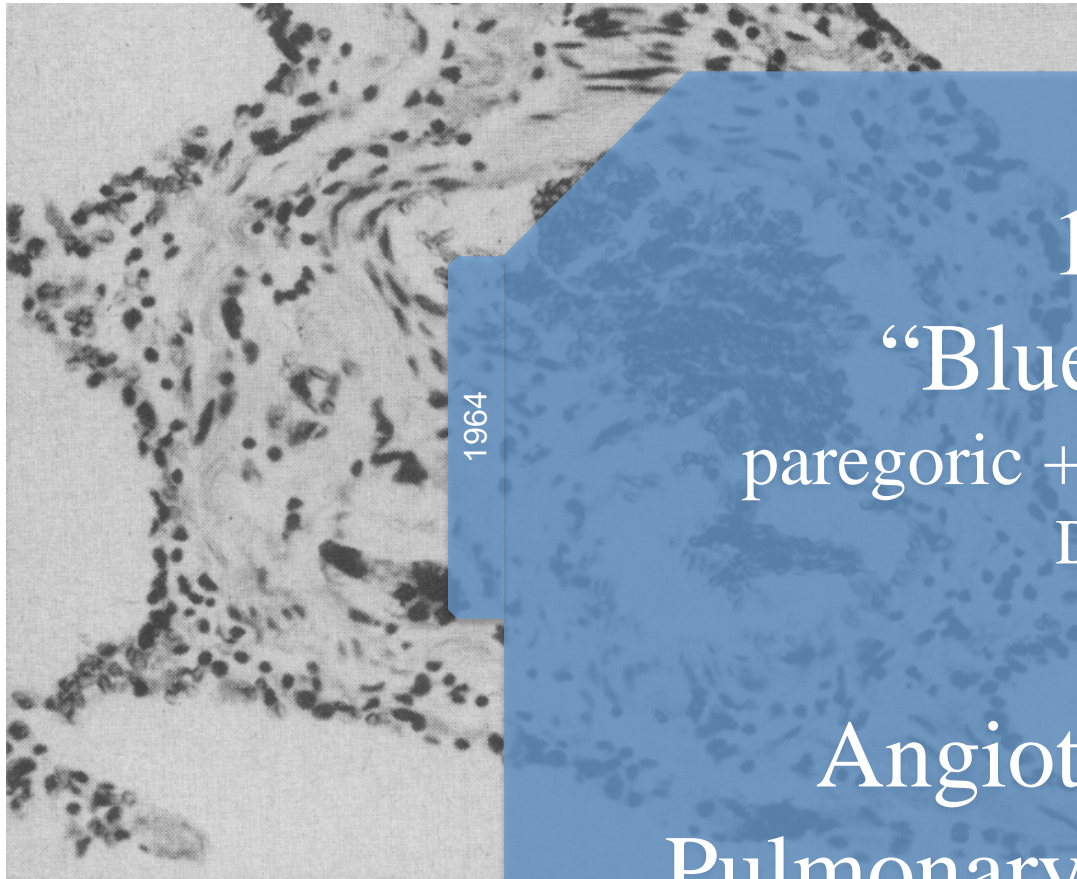
Outline

- Excipient harms by decade
- Example: temazepam ADF in the UK
- Framework for excipient harm and tampering



Excipient Harms by Decade

Excipient Harms



1964

1964

“Blue Velvet”

paregoric + tripelennamine

Detroit

Angiothrombotic
Pulmonary Hypertension

Crystalline structures in small pulmonary artery.



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Wendt VE 1964, JAMA, PMID: 14122687

Excipient Harms



1976

Methamphetamine inhaler
Intravenous injection of liquid
squeezed from cotton pledglet
Dallas

Granulomas
Pulmonary Hypertension

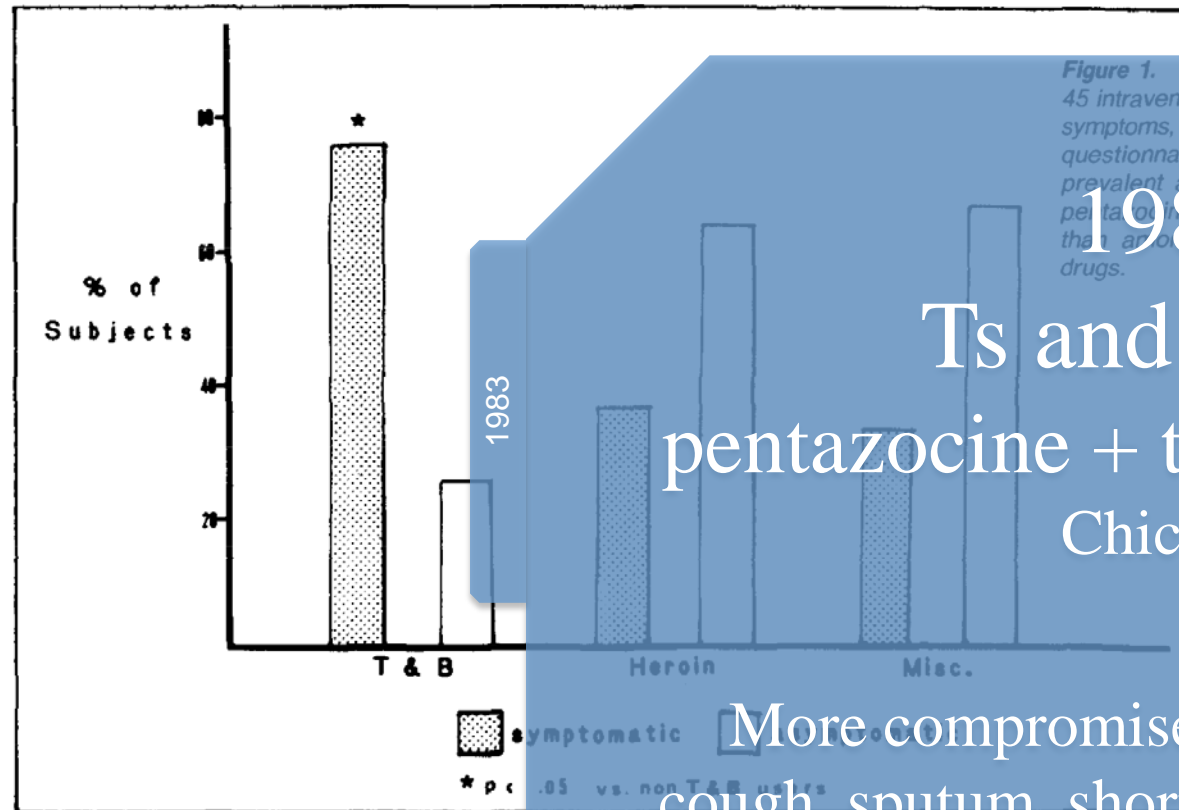
Absence of fine vessels in all but upper right quadrant.



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Robertson CH 1976, *Am J Med*, PMID: 984069

Excipient Harms



1983
Ts and Blues
pentazocine + tripeleonnamine
Chicago

More compromised lung function,
cough, sputum, shortness of breath than
heroin injectors



Excipient Harms

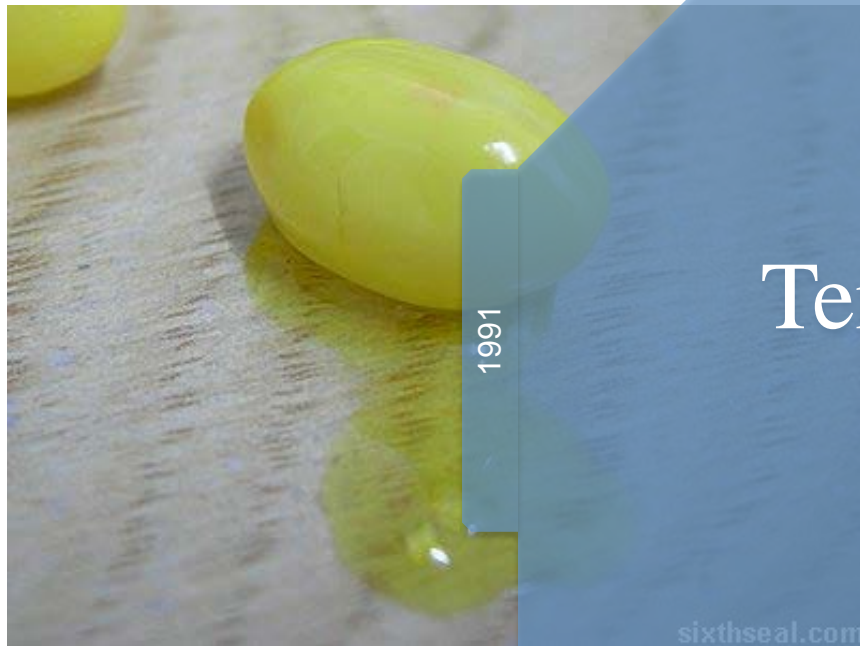


Figure 1 Toxicity of intra-arterial Temazepam (case 9). These gangrenous fingers were subsequently amputated.

1991-94
Temazepam gel caps
ADF Reformulation
United Kingdom

Gangrene
Limb loss



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Image: Dodd TJ 1994, *J Clin Path*, PMID: 8063932
Review: Strang J 1992, *Br J Addict*, PMID: 1358296

ADF Harms

2007

2007
Suboxone
buprenorphine + naloxone
Malaysia

Increased injection
frequency

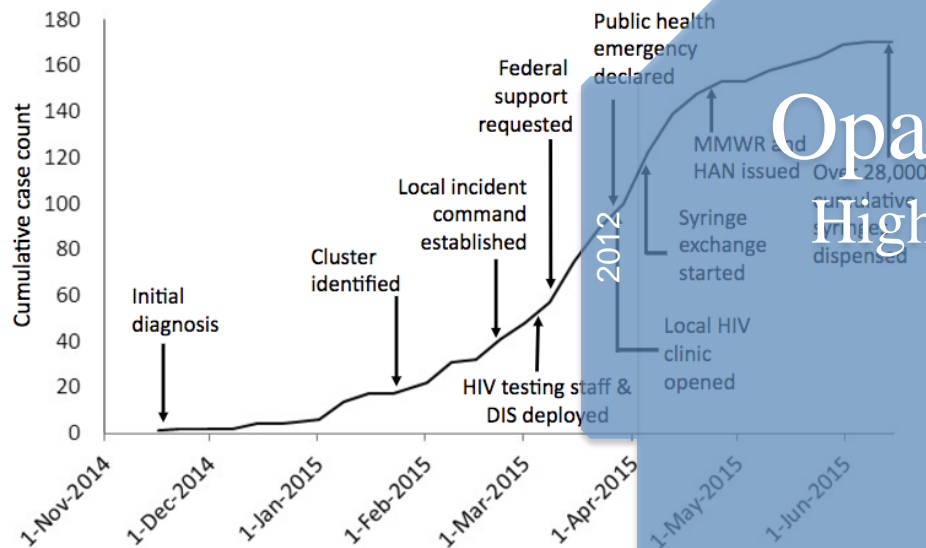


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Vicknasingam B 2010, *Drug Alc Dep*, PMID: 20478668

Excipient Harms

Cumulative HIV infections diagnosed,
Scott County, Indiana through June 14, 2015 (n=170)



2012-15

Opana ER (oxymorphone)

High molecular weight polyethylene

oxide excipient for “ADF”

Indiana, Tennessee

Centers for Disease Control and Prevention
MMWR
Morbidity and Mortality Weekly Report
Weekly, Vol. 62, No. 1
January 11, 2013

Thrombotic Thrombocytopenic Purpura (TTP)-Like Illness Associated with
Intravenous Opana ER Abuse — Tennessee, 2012

On August 13, 2012, a nephrologist reported to the Tennessee Department of Health (TDH) three cases of unexplained thrombotic thrombocytopenic purpura (TTP), a rare but serious blood disorder characterized by microangiopathic hemolytic anemia and thrombocytopenia. The annual incidence is approximately 1 per 100,000 population (1,2,3). In the United States, TTP is most commonly associated with Shiga toxin-producing *Escherichia coli* (STEC) and the use of drugs, including platelet aggregation inhibitors, quinine, and cocaine (1,4). The three patients were intravenous (IV) drug users who reported injecting Opana ER (oxycodone) and identified other cases of TTP-like illness that might be associated with injection-drug use. TDH conducted a statewide investigation. By the end of October, a total of 15 such cases had been reported; none were fatal. A case-control study was conducted, and investigators determined that the cases of TTP-like illness were associated with dissolving and injecting tablets of Opana ER (Purdue Pharma, LLC, Kalamazoo, MI) rather than the extended-release form of oxycodone (an opioid pain reliever) (Purdue Pharma, LLC, Kalamazoo, MI). Of the 15 patients, 12 reported injecting reformulated Opana ER. Seven of the 12 patients reported injecting Opana ER with the addition of a liquid. Twelve patients reported chronic hepatitis C or had positive

dehydrogenase and the presence of schistocytes) and thrombocytopenia in a person with a hospital admission platelet count $\leq 50,000/\mu\text{L}$, in the absence of certain known causes of TTP. By the end of October 2012, a total of 15 cases had been reported in Tennessee. TDH interviewed patients in person and reviewed medical charts. Among the 15 patients, 12 reported injecting Opana ER (oxycodone) and 3 reported injecting other drugs. The 15 patients ranged in age from 22 to 49 years (median: 34 years). The earliest diagnosis of TTP-like illness was April 16, 2012 (Figure). Seven of the 15 patients were from the same rural community, and five were from nearby counties, and three were from counties in middle Tennessee.

The 15 patients were further categorized by presence or absence of a concurrent infection (as evidenced by sepsis) as a possible etiology. Clinical characteristics were similar among patients with and without infection (Table). Patients reported symptoms typical of TTP-like illness, including nausea, vomiting, and abdominal pain. Seven patients were treated for sepsis. Twelve were treated with plasma exchange. Median admission platelet counts for patients without and with infection were $20,000/\mu\text{L}$ (range: 9,000–49,000/ μL), and $16,000/\mu\text{L}$ (range: 9,000–49,000/ μL), respectively.

Brooks JT & Adams J. March 13-14, 2017 FDA Advisory Committee
Peters PJ 2016, NEJM, PMID: 27468059
Hunt R 2017, Blood, PMID: 27864296



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Temazepam in the United Kingdom 1989-1996

Temazepam in the United Kingdom

- Temazepam used for sleep, anxiety
- 1980s: Liquid-filled gel capsules
- Late 1980s: Reports of widespread intravenous injection
- Home Office requests withdrawal of liquid-filled gel capsules
- 1989: Manufacturers reformulate with Gelthix[®]
 - Solid gel capsules (high MW crystalline waxes)
 - Called “abuse-resistant” by industry, gov’t, physicians
- Reduction in intravenous injection



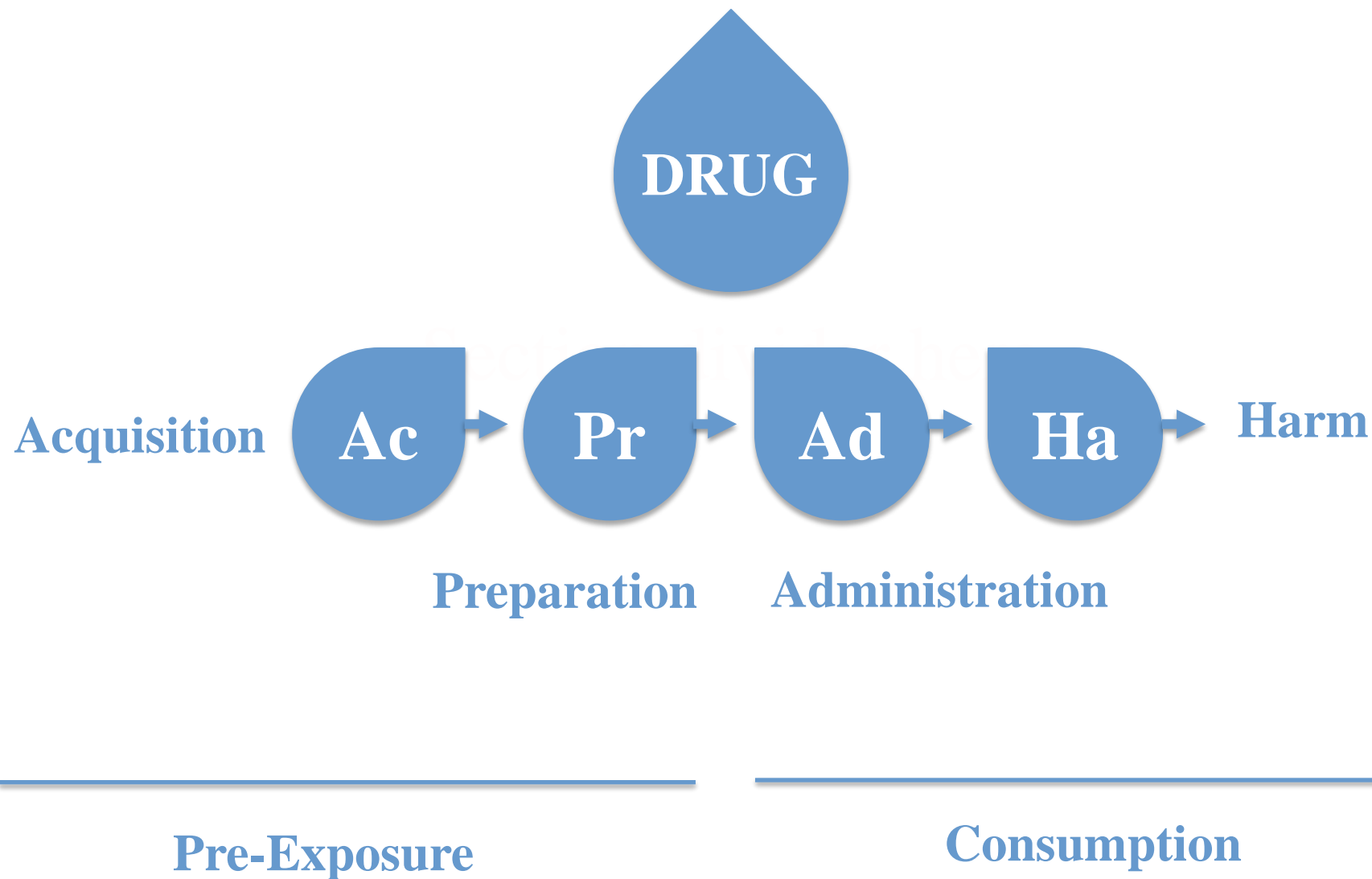
Temazepam in the United Kingdom

- 1991-1992: Reports emerge of *intra-arterial* injection
 - Hard gel can be boiled with water and injected
 - Need larger bore needle to inject into artery
 - Gel hardens in artery
 - Irritant effect of temazepam directly?
- 1992-4: Letters in *BMJ* of patients with severe ischaemic damage
 - Amputations, DVT, muscle necrosis, fasciotomies
- 1996: Temazepam capsules removed by NHS



Framework for Analyzing Harms

Considerations for analyzing events of harm arising from unintended routes of administration



Drug

Engineering

Active ingredient(s)

Excipients

ADF platform

Physical Identification

Counterfeit (misclassification bias)

Brand vs. generic (misclassification bias)

Street name

Adulterants (liquids)



Acquisition

Sourcing Social Dynamics

Intact vs. prepared

Price (bulk)

Online vs. hand-to-hand

Vendor reputation and trustworthiness

Logistics

Storage

Age of product, expiration

Fungal and bacterial contamination

Pocket lint



Basic Equipment for Injection



Image courtesy of Nigel Brunson



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Microfilters



Microfilters

Starch, microcrystalline cellulose, talc and other excipients have been shown to cause harm when injected.

In France, microfilters have been researched. Fitting on the tip of a syringe, these filters can remove 95%+ of particles between 5 μm and 15 μm .



Preparation

Materials

Work surface

Maceration implement

Substrate for dilution

Solubility additives (lemon, acid, vinegar, blood, saliva)

Filter

Cooker

Syringe

Methods

Heat

Freeze

Chemical extraction

Time

Aliquot and Power dynamics



Risks and Nuances of Preparation



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Ritual and Beliefs



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Administration

Injection

Skin prep

Vein

Artery

Subcutaneous

Adipose

Muscle

Vessel location

Smoking

Heat source

Device/Foil

“Choy”

Snorting

Straw

Currency

Nasal spray rinse

Chewing

Mastication

Metabolism

Chaser



Harms (a shortlist)

General Injection Harms

Cellulitis
Overdose
Polypharmacy
Addiction
Abscess
Viral hepatitis
HIV
Necrotizing fasciitis
Deep vein thrombosis
Edema
Endocarditis
Blood vessel collapse
Nerve damage
Frequent injection
Scarring

Heroin Injection Harms

Anthrax
Tetanus, wound botulism
(*Clostridium* spp.)
Harms from bulking agents and adulterants

Pharmaceutical Injection Harms

Pulmonary hypertension
Limb loss
Gangrene
Embolic events, granuloma, TTP

Chewing, Smoking and Snorting Harms

Dental damage
Hot smoke epithelial damage
Oral burns & lesions
Asthma
Nasal irritation
Sinus infection
Hearing loss?



Testing Excipients Pre-Marketing

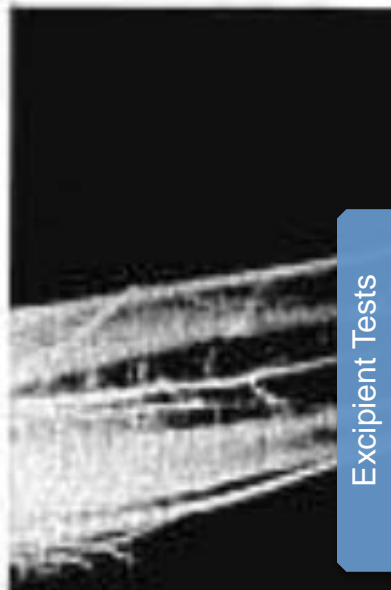


FIG. 2. Angiogram of the femoral artery demonstrating complete block in the femoral artery.

An older article offers a potential approach to pre-market testing.

Doctors in Israel encountered a patient with gangrene. Cause was suspected to be intra-arterial injection of codeine tablets containing microcrystalline cellulose (among other excipients). Injecting API vs. API + excipient into femoral arteries of dogs revealed detailed information on pathogenesis.



Conclusions

- Why do only certain people who inject experience the serious harms?
- We must assume that all opioid analgesics will be injected, even if infrequently
- Market withdrawals of ADFs have been precipitated by a few dozen localized cases of serious harms
- Can excipients approved for parenteral administration be a starting point for safer design of oral opioid analgesics?



Credits

- Nigel Brunsdon, InjectingAdvice.com
- Shilo Jama & Louise Vincent, Urban Survivors Union
- Eliza Wheeler, Harm Reduction Coalition

Questions? nab@unc.edu



Citations

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