Excipient Harms and Tampering of Opioid Analgesics

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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

Crystalline structures in small pulmonary artery.

1964

“Blue Velvet”
paregoric + tripelennamine
Detroit

Angiothrombotic Pulmonary Hypertension

Wendt VE 1964, JAMA, PMID: 14122687
Excipient Harms

Absence of fine vessels in all but upper right quadrant.

1976 Methamphetamine inhaler
Intravenous injection of liquid squeezed from cotton pledglet
Dallas

Granulomas
Pulmonary Hypertension

Excipient Harms

1983

Ts and Blues
pentazocine + tripelennamine
Chicago

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

Excipient Harms

1991-94
Temazepam gel caps
ADF Reformulation
United Kingdom

Gangrene
Limb loss

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

Review: Strang J 1992, Br J Addict, PMID: 1358296
ADF Harms

2007 Suboxone
buprenorphine + naloxone
Malaysia

Increased injection frequency

Vicknasingam B 2010, Drug Alc Dep, PMID: 20478668
Excipient Harms

Opana ER (oxymorphone) high molecular weight polyethylene oxide excipient for “ADF”

Indiana, Tennessee

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

2012-15

2012

More frequent injection episodes with multiple injections

Brooks JT & Adams J, March 13-14, 2017 FDA Advisory Committee

Peters PJ 2016, *NEJM*, PMID: 27468059


On August 13, 2012, a nephrologist reported to the Tennessee Department of Health (TDH) that the patient had unexplained thrombotic thrombocytopenic purpura (TTP), a rare but serious blood disease characterized by microangiopathic hemolytic anemia and thrombocytopenia. The patient had been treated with oxymorphone (Opana® ER), a long-acting opioid analgesic, for chronic pain. TDH conducted two case-series analyses of select patients, including the initial patient, who were treated with oxymorphone and who were not treated with oxymorphone.

HIV, TTP

More frequent injection episodes with multiple injections
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

Review: Strang J 1992, Br J Addict, PMID: 1358296
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
Acquisition → Preparation → Administration → Harm

Pre-Exposure

Consumption
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

- Tourniquet
- Sharps disposal
- Alcohol pad
- Needle
- Filter
- Water
- Syringe
- Cooker

*Image courtesy of Nigel Brunsdon*
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 15µm.

Roux P 2011, Drug Alc Rev, PMID: 21545559
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
Ritual and Beliefs
## Administration

<table>
<thead>
<tr>
<th>Injection</th>
<th>Smoking</th>
</tr>
</thead>
<tbody>
<tr>
<td>Skin prep</td>
<td>Heat source</td>
</tr>
<tr>
<td>Vein</td>
<td>Device/Foil</td>
</tr>
<tr>
<td>Artery</td>
<td>“Choy”</td>
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<tr>
<td>Subcutaneous</td>
<td></td>
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<tr>
<td>Adipose</td>
<td></td>
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<tr>
<td>Muscle</td>
<td></td>
</tr>
<tr>
<td>Vessel location</td>
<td></td>
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<table>
<thead>
<tr>
<th>Snorting</th>
<th>Chewing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Straw</td>
<td>Mastication</td>
</tr>
<tr>
<td>Currency</td>
<td>Metabolism</td>
</tr>
<tr>
<td>Nasal spray rinse</td>
<td>Chaser</td>
</tr>
</tbody>
</table>
# 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?
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

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Citations


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