Drug-Related Hospital Visits
How Big Is The Problem?

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Objectives

- To discuss the overall health care impact of drug-related hospitalization.
- To discuss factors associated with identifying patients at risk and drugs commonly associated with drug-related hospitalization.
- To discuss strategies pharmacists can utilize in your practice to minimize drug-related hospitalizations.

Definitions

- **Adverse Drug Reaction (ADR)**
  - "Any noxious, unintended, and undesired effect of a drug, which occurs at doses used in humans for prophylaxis, diagnosis or therapy”  
  - WHO Definition
  - Excludes: therapeutic failures, intentional/accidental poisonings, drug abuse, medication errors in administration (too much/little drug), drug interaction, noncompliance

- **Adverse Drug Event (ADE)**
  - ADR in addition to medication errors (errors in prescribing, dispensing, patient adherence and monitoring)

Drug-Related Problems

Hepler & Strand Am J Hosp Pharm 1990;47:533-43

- Untreated Indication
- Improper Drug Selection
- Subtherapeutic Dosage
- Failure to Receive Drug
- Overdose
- Adverse Drug Reaction
- Drug Interaction
- Drug without Indication

Drug-Related Morbidity


- Annually in the USA drug-related morbidity account for:
  - 17 million emergency department (ED) visits
  - 8.7 million hospital admissions
- Majority of literature focus on drug-related hospitalizations specifically related to adverse drug reactions (ADRs)
- Many patients present only to the ED/AC without requiring admission and for drug-related reasons other than ADRs

Conflict of Interest Declaration

- No financial interest (stocks/shares) in the sale of any drugs
- Not supported by any research funding from industry
- Not on any industry advisory boards
- Not a paid industry consultant
- Not supported by industry for any educational activities
- Not paid speaker honorarium by any company for any product pertaining to this presentation
Incidence of Adverse Drug Reactions in Hospitalized Patients

A Meta-analysis of Prospective Studies

Jason Lazarou, MSc, Bruce H. Pomeranz, MD, PhD, Paul N. Corey, PhD

OBJECTIVE—To estimate the incidence of serious and fatal adverse drug reactions (ADR) in hospitalized patients.

METHODS—Our electronic database was searched from 1966 to 1998. From 153 articles, we selected 39 prospective studies from 19 studies in which the incidence of ADRs was estimated.

RESULTS—The estimated overall incidence of ADRs causing admission to hospital was 10.9%. The estimated overall incidence of ADRs was 2.1%. The estimated overall incidence of ADRs causing admission to hospital was 10.9%. The estimated overall incidence of ADRs was 2.1%. The estimated overall incidence of ADRs causing admission to hospital was 10.9%.

CONCLUSIONS—The incidence of ADRs causing admission to hospital was 10.9%. The incidence of ADRs was 2.1%. The incidence of ADRs causing admission to hospital was 10.9%. The incidence of ADRs was 2.1%. The incidence of ADRs causing admission to hospital was 10.9%.
Drug-Related Emergency Department Visits

Prospective Studies

- 5 studies (1998-2003) evaluating ~12,000 patients
- DRV: 4.3-28.1% of all ED visits
- 2 US studies estimated DRV at 22% and 28.1%
- Hospitalization Rate: 8.6-27.3%
- Preventability: 38-70%
- Cost: $576/EDV & $4834/adm ($US)

Incidence and Preventability of Adverse Drug Events Among Older Persons in the Ambulatory Setting

Gurwitz et al. JAMA 2003;289:1107-116

<table>
<thead>
<tr>
<th>Category of Severity (%)</th>
<th>Overall N=1523</th>
<th>Preventable N=421</th>
<th>Nonpreventable N=1102</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate/1000 person-yrs (95% CI)</td>
<td>50.1 (47.6-52.6)</td>
<td>13.8 (12.5-16.2)</td>
<td>36.3 (34.1-38.4)</td>
</tr>
</tbody>
</table>

- Fatal: 11 (0.7) 5 (1.2) 6 (0.5)
- Life Threatening: 136 (8.9) 72 (37.1) 64 (5.8)
- Serious: 431 (28.3) 167 (39.7) 264 (24.0)
- Significant: 945 (62.0) 177 (42.0) 768 (69.7%)

AED in Older Patients in Ambulatory Care

Gurwitz et al. JAMA 2003;289:1107-116

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>26.0</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>14.7</td>
</tr>
<tr>
<td>Diuretics</td>
<td>13.3</td>
</tr>
<tr>
<td>Nonopioid Analgesics</td>
<td>11.8</td>
</tr>
<tr>
<td>Anticoagulants</td>
<td>7.9</td>
</tr>
<tr>
<td>Hypoglycemics</td>
<td>6.8</td>
</tr>
<tr>
<td>Steroids</td>
<td>5.3</td>
</tr>
<tr>
<td>Opioids</td>
<td>4.9</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>3.2</td>
</tr>
<tr>
<td>Antihypertensives</td>
<td>2.0</td>
</tr>
</tbody>
</table>

Drug Related Emergency Department Visits


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- Prospective Studies
- 5 studies (1998-2003) evaluating ~12,000 patients
- DRV: 4.3-28.1% of all ED visits
- Hospitalization Rate: 8.6-27.3%
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ADE in Older Patients in Ambulatory Care
Gurwitz et al. JAMA 2003;289:1107-16

- 27.6% ADE Preventable
- Monitoring 60.8%
- Prescribing 58.4%
- Adherence 21.1%
- Dispensing <2.0%

Patient Impact

<table>
<thead>
<tr>
<th>Impact</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>70.3%</td>
</tr>
<tr>
<td>Mild</td>
<td>14.6%</td>
</tr>
<tr>
<td>Moderate</td>
<td>9.0%</td>
</tr>
<tr>
<td>Severe</td>
<td>0.3%</td>
</tr>
<tr>
<td>Death</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

Adverse Drug Events in Ambulatory Care
Gandhi et al. NEJM 2003;348:1556-64

Rate and Severity of Adverse Drug Events
N=661

<table>
<thead>
<tr>
<th>Event</th>
<th>No.</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADR</td>
<td>162</td>
<td>25.0%</td>
</tr>
<tr>
<td>(181 events)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Severity

- Fatal/Life Threatening: 0, 0%
- Serious: 24, 13%
- Significant: 157, 87%

Preventability

- Ameliorable/Preventable: 71, 39%

Adverse Drug Events After Hospital DC

76/400 = 19% experienced ADE within 3-weeks of hospital DC
47/76 = 62% preventable/ameliorable

Severity of Injuries

<table>
<thead>
<tr>
<th>Injuries</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lab Abnormality</td>
<td>3%</td>
</tr>
<tr>
<td>1 day Symptoms</td>
<td>1%</td>
</tr>
<tr>
<td>&gt;1 day Symptoms</td>
<td>64%</td>
</tr>
<tr>
<td>Nonperm Disability</td>
<td>30%</td>
</tr>
<tr>
<td>Perm Disability</td>
<td>3%</td>
</tr>
</tbody>
</table>

Health Services Utilization

<table>
<thead>
<tr>
<th>Service</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>50%</td>
</tr>
<tr>
<td>MD Office Visit</td>
<td>9%</td>
</tr>
<tr>
<td>Laboratory</td>
<td>5%</td>
</tr>
<tr>
<td>EDV</td>
<td>11%</td>
</tr>
<tr>
<td>Admission</td>
<td>24%</td>
</tr>
</tbody>
</table>
Drug Interactions at Hospital Discharge
- Retrospective review of patients discharged from hospital
- N=500
- 60% had at least one potential drug interaction
- 747 potential drug interactions
- 54% were new at the time of discharge
- Severity:
  - 12% major
  - 70% moderate
  - 18% minor

Drug Interactions in the Hospitalized Elderly
- Design:
  - 3 population-based, nested case-control studies
- Time Period:
  - January 1, 1994 - December 31, 2000, Ontario
- Data Source:
  - Ontario Drug Benefit Program
  - Canadian Institute for Health Information Discharge Abstract DB
- Patients:
  - >65 years of age, glyburide, digoxin, ACEI
- Exposure:
  - glyburide- cotrimoxazole, digoxin-clarithromycin, ACEI-K-sparing
  - glyburide-amoxicillin, digoxin-cefuroxime, ACEI-indapamide

Drug Interactions in the Hospitalized Elderly

Hospitalization Within 1 Week of Drug Initiation

<table>
<thead>
<tr>
<th>Drug Interaction</th>
<th>Case</th>
<th>Control</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glyburide-Co-trimoxazole</td>
<td>3.9%</td>
<td>0.4%</td>
<td>6.6 (4.5-9.7)</td>
</tr>
<tr>
<td>Glyburide-Amoxicillin</td>
<td>1.1%</td>
<td>0.6%</td>
<td></td>
</tr>
<tr>
<td>Digoxin-Clarithromycin</td>
<td>2.6%</td>
<td>0.2%</td>
<td>11.7 (7.5-18.2)</td>
</tr>
<tr>
<td>Digoxin-Cefuroxime</td>
<td>0.3%</td>
<td>0.1%</td>
<td></td>
</tr>
<tr>
<td>ACEI-K-sparing Diuretic</td>
<td>8.2%</td>
<td>0.3%</td>
<td>20.3 (13.4-30.7)</td>
</tr>
<tr>
<td>ACEI-Indapamide</td>
<td>0.6%</td>
<td>0.4%</td>
<td></td>
</tr>
</tbody>
</table>

Who is at Risk?
- Elderly tend to receive more medications
- Illnesses tend to be treated with "high-risk" medications
- Drug interactions occur due to polypharmacy
- Poor compliance
- Altered pharmacokinetics/pharmacodynamics

- Multiple Medications
  - 5% (1-2 meds) → 10-20% (>5 meds) → 50% (>10 meds)

- Particular Drug Classes

Which Drug Classes?
- Antibiotics
- Anticoagulants
- Digoxin
- Diuretics
- Hypoglycemic Agents
- NSAIDS

60-70% of all ADE!!

Drug Classes Associated Hospital Visits
- Antibiotics
  - Most likely to be non-preventable
  - ADR: GI, allergic reactions
  - Compliance, wrong antibiotic, drug interactions
  - Antimicrobial resistance
Community-Acquired Infections
- Meningitis
- Otitis Media
- Sinusitis
- Pharyngitis
- Bronchitis
- Pneumonia
- Endocarditis
- Intra-abdominal
- Genitourinary
- Skin and Soft Tissue

"Spiraling Empiricism"

"The imprecision of clinical practice establishes context; the litigious nature of our society unnerves; the absence of toxicity permits; and the sum of these encourages the incontinent, extemporaneous use of antimicrobial agents"

Jerome Kim 1989

Penicillin-Resistant S. pneumoniae
Canadian Isolates 1988, 1993-2002

Ciprofloxacin-Resistant S. pneumoniae
Canadian Isolates 1988, 1993-2002

Levofloxacin-Resistant S. pneumoniae
Canadian Isolates 1995-2002

Brief Report

RESISTANCE TO LEVOFLOXACIN AND FAILURE OF TREATMENT OF PNEUMOCOCCAL PNEUMONIA

Ross Davidson, Ph.D., Rodrigo Cavalcanti, M.D., James L. Brunton, M.D., Darrin J. Bast, Ph.D., Joyce C.S. de Azevedo, Ph.D., Pamela Kirsey, M.D., Christine Fleming, M.L.T., and Donald E. Low, M.D.
Appropriate Use of Antibiotics

Appropriate use of antibiotics can be defined as "the cost-effective use of antimicrobials which maximizes clinical therapeutic effect, while minimizing both drug-related toxicity and development of antimicrobial resistance."

WHO 2000

Drug Classes Associated Hospital Visits

- **Anticoagulants**
  - very common
  - one of the most dangerous
  - INR too high or too low
  - anticipate drug interactions!
  - **MONITOR, MONITOR, MONITOR!**

- **Diuretics**
  - furosemide, thiazides, spironolactone
  - ADR: fluid & electrolyte disturbances

- **Beta-Blockers/Calcium Channel Blockers**
  - Digoxin
    - usually mild toxicity (CNS, GI) but potentially dangerous (CV)
    - elderly and/or renal dysfunction are at greatest risk factors
    - no need to push dose in CHF...<1.0 nmol/L
      - JACC 2002:39:946-53

- **Hypoglycemics**
  - insulin/oral hypoglycemics
  - non-BG ADR:
    - glitazones (CV)
    - metformin (lactic acidosis)

As outlined in the original AVANDIA® Product Monograph under the "Warnings" section, physicians should be aware that hyperidrosis (oils) can cause fluid retention, which can exacerbate or lead to congestive heart failure. Patients at risk for heart failure (particularly those on insulin) should be monitored for signs and symptoms of heart failure. AVANDIA® should be discontinued if any deterioration in cardiac status occurs. In addition, AVANDIA® is not indicated in patients with New York Heart Association (NYHA) Class III and IV cardiac status. For further emphasis, this important information regarding NTHA Class III & IV patients has been moved from the "Precautions" section to the "Warnings" section of the Product Monograph.

In postmarketing experience with AVANDIA®, adverse events potentially related to volume expansion (e.g., congestive heart failure, pulmonary edema and pleural effusions) have been reported. It is important to also note that these adverse events, including AVANDIA®, are contraindicated in patients with acute heart failure. This contraindication is new to the Product Monograph.
Drug Classes Associated Hospital Visits

- **NSAIDS**
  - seen daily in ED,...many studies identified as most common ADR
  - ADR: GI, renal dysfunction, worsening CHF, allergic reaction
  - avoid if possible, be aware of high-risk patients, minimize risk
  - COX-2 inhibitors?

NSAID Related GI Adverse Effects

- 1-4%/year
- ~50% have detected lesion
- 20% have warning symptoms
- Endoscopic Lesions 80%
- Symptoms 10-50%

Consumption of NSAIDs and the Development of Congestive Heart Failure in Elderly Patients

<table>
<thead>
<tr>
<th>History of Heart Disease</th>
<th>Use of NSAID</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No Heart Disease</td>
<td>No NSAID</td>
<td>1.0 (Reference)</td>
</tr>
<tr>
<td></td>
<td>Use of NSAID</td>
<td>1.6 (0.7-3.7)</td>
</tr>
<tr>
<td></td>
<td>Use of NSAID</td>
<td>2.5 (1.4-4.3)</td>
</tr>
</tbody>
</table>

Honourable Mention!

- CNS Depressants
- Opioids
- Antiepileptic Drugs
- Complementary and Alternative Medicines
How Can Drug-Related Visits be Prevented?

- Minimize the Risk!
- Be aware of high-risk patients/drugs
- Individualize the dose
- Avoid duplication of therapy
- If you don’t need it, don’t start it…if it is not working stop it!
- MONITOR, MONITOR, MONITOR!
- Anticipate drug interactions
- Patient counseling
- Compliance tools
- New ≠ Better….and ALWAYS means……
  …..we don’t know yet about ADRs & drug interactions!

Patient Compliance

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Post-Marketing Surveillance
Friedman et al. JAMA 1999;281:1728-34

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. Exposed During Testing</th>
<th>No. Exposed Prior to Withdrawal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terfenadine</td>
<td>5000</td>
<td>7,500,000</td>
</tr>
<tr>
<td>Fenfluramine</td>
<td>340</td>
<td>6,900,000</td>
</tr>
<tr>
<td>Dexfenfluramine</td>
<td>1200</td>
<td>2,300,000</td>
</tr>
</tbody>
</table>

Medication Errors.....The Preventable Errors!

Factors Associated with Errors in Prescribing
Lesar et al. JAMA 1997;277:312-17

- 2103 medication errors (3.99/1000 orders)
- 696 errors created potential for adverse outcome

<table>
<thead>
<tr>
<th>Error</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overdosing</td>
<td>291</td>
<td>41.8</td>
</tr>
<tr>
<td>Underdosing</td>
<td>115</td>
<td>16.5</td>
</tr>
<tr>
<td>Prescribing Allergic Medication</td>
<td>90</td>
<td>12.9</td>
</tr>
<tr>
<td>Inappropriate Dosage form</td>
<td>81</td>
<td>11.6</td>
</tr>
<tr>
<td>Wrong Drug</td>
<td>35</td>
<td>5.0</td>
</tr>
<tr>
<td>Duplicate Therapy</td>
<td>35</td>
<td>5.0</td>
</tr>
<tr>
<td>Wrong Route</td>
<td>23</td>
<td>3.3</td>
</tr>
<tr>
<td>Other</td>
<td>26</td>
<td>3.7</td>
</tr>
</tbody>
</table>

Factors Associated with Errors in Prescribing
Lesar et al. JAMA 1997;277:312-17

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antibiotics</td>
<td>276</td>
<td>39.7</td>
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<tr>
<td>Cardiovascular</td>
<td>122</td>
<td>17.5</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>51</td>
<td>7.3</td>
</tr>
<tr>
<td>Narcotics</td>
<td>46</td>
<td>6.6</td>
</tr>
<tr>
<td>Nonsteroidal Antiinflammatories</td>
<td>25</td>
<td>3.6</td>
</tr>
<tr>
<td>Hormones</td>
<td>24</td>
<td>3.4</td>
</tr>
<tr>
<td>Minerals/Lytes</td>
<td>21</td>
<td>3.0</td>
</tr>
<tr>
<td>Xanthines</td>
<td>20</td>
<td>2.9</td>
</tr>
</tbody>
</table>

Case: Prescribing Error

ID: 74 yo M brought to ED by EHS at 2330h on Jan 13-04
CC: decreased LOC, drowsy, slurred speech
HPI: Patient had been in the ED 2 days prior secondary to a fall (rib #) and was DC on morphine. Developed slurred speech, hallucinations, disorientation this PM.

PMH:
- BPD
- Hypothyroidism
- Rib #
- MPTA: (as per patient/PNet)
  - Lithium 300 mg PO BID
  - Olanzapine 5 mg PO daily
  - Phenytoin 30 mg PO AM/15 mg PO PM
  - Levothyroxine 50 mcg PO daily
  - Zopiclone 15 mg PO HS PRN sleep
  - Morphine 10-20 mg PO Q4h PRN rib pain

In ED patient received:
- CT Head: Normal
- Meperedine 75 mg IM (0645h)
- At 0702h patient became agitated, diaphoretic, hyperthermic, hypotensive and increasingly rigid....seizure?
- VS: BP 63/30, HR 58, RR 18, T 37.7, O2 sat 96%
- Pt intubated using RSI
e Tambocaine 20 mg, succinylcholine 120 mg
- Lorazepam 2 mg IV, phenytoin 1000 mg
- consult ICU
- Paged while on route to the hospital....?
Case: Dispensing Error

**ID:** 44 yo F brought to ED by EHS at 1235h on May 21-03  
**CC:** Drowsy  
**HPI:** Patient reports becoming increasingly drowsy throughout the morning and following a late morning dental appointment had become drowsy and at times had difficulty staying awake.

**PMH:**  
- Asthma  
- NIDDM  
- Depression  
- Schizophrenia  

**MPTA:** (as per patient/PNet)  
- Glyburide 10 mg PO BID (LF: Apr 30)  
- Metformin 1000 mg PO BID (LF: Apr 30)  
- Paroxetine 30 mg PO daily (LF: May 20)  
- Lithium 1200 mg PO HS (LF May 20)  
- Clozapine 200 mg PO HS (LF: May 20)

**EHS also reports patient received:**  
- Last PM  
  - Clonazepam 4 mg  
  - Lorazepam 1 mg  
- This AM:  
  - Clonazepam 4 mg  
  - Gabapentin 600 mg  
  - Fluoxetine 40 mg  
  - Omeprazole 20 mg  
- **VS:** BP 138/85, HR 79, RR 12, T 36.6 C, O2 sat 99%  
- **PE:** Excessive drowsy but otherwise NC  
- **BG:** 9.3 mmol/L, all other bloodwork pending

**What may be happening with this patient?**

---

**Medication Errors: Nurses Survey**

*Cohen et al. Nursing 2003;33:36-46*

**Do I repeat a verbal order back to the prescriber?**

<table>
<thead>
<tr>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>66%</td>
<td>29%</td>
<td>6%</td>
</tr>
</tbody>
</table>

**When administering "high-risk" medications have I my calculations double-checked?**

<table>
<thead>
<tr>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>58%</td>
<td>37%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**I 'borrow' medications from other patients rather than wait for pharmacy?**

<table>
<thead>
<tr>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>43%</td>
<td>30%</td>
<td>28%</td>
</tr>
</tbody>
</table>

**Before administering medications I check patient's identity on ID bracelet?**

<table>
<thead>
<tr>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>57%</td>
<td>40%</td>
<td>3%</td>
</tr>
</tbody>
</table>

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**Medication Errors: Nurses Survey**

*Cohen et al. Nursing 2003;33:36-46*

**Before administering medications I check patient's allergy status?**

<table>
<thead>
<tr>
<th>Always</th>
<th>Sometimes</th>
<th>Never</th>
</tr>
</thead>
<tbody>
<tr>
<td>70%</td>
<td>28%</td>
<td>2%</td>
</tr>
</tbody>
</table>

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