Unintended Consequences of Drug-Drug Interaction Alerts
The Partners Experience

October 13-14, 2009
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Agenda

• Partners HealthCare
  – Background
  – Clinical Information Systems
  – Clinical Decision Support

• DDI Alerts
  – Background

• Unintended Consequences
  – 3 Case Studies

• Conclusions
Partners HealthCare is a non-profit integrated delivery system

- Eleven hospitals
  - Two academic medical centers
    - Brigham and Women’s Hospital and Massachusetts General Hospital
  - 7,000 physicians
  - Four million outpatient visits and 160,000 admissions/year
  - Teaching affiliates of the Harvard Medical School
  - $6.4 B in revenues
Our hospitals have implemented a variety of clinical information systems to support their closed loop medication management systems.

<table>
<thead>
<tr>
<th></th>
<th>Order Entry</th>
<th>Pharmacy</th>
<th>eMAR</th>
<th>Clinical Documentation</th>
</tr>
</thead>
<tbody>
<tr>
<td>BWH</td>
<td>BWH</td>
<td>BWH</td>
<td>PHS</td>
<td>Vendor</td>
</tr>
<tr>
<td>MGH</td>
<td>MGH</td>
<td>Vendor</td>
<td>PHS</td>
<td>Vendor</td>
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<td>Community Hospitals</td>
<td>Vendor</td>
<td>Vendor</td>
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- Three outpatient electronic health records (2 proprietary, 1 vendor)
Clinical decision support is developed both locally and at the enterprise level

- **Local decision support:**
  - Site-specific
  - Formulary management, order sets, templates, protocols, reminders

- **Enterprise-level decision support:**
  - Drug dosing in renal failure, drug dosing in geriatric patients, **drug-drug interactions**, therapeutic duplication
Our DDI alert knowledge base is proprietary

• First implemented locally at BWH in 1996
• Implemented across the Partners enterprise in 2003
• Customized for physician order entry applications, but also fires in inpatient pharmacy systems
• One knowledge base across the enterprise
• Standard implementation
  – Some UI decisions are left at discretion of the consuming application
The DDI knowledge base is overseen by Medication Knowledge Management Committee (MKC)

- Purpose/composition of Committee
- Pharmacists (frontline clinical and Medication Knowledge Management group) directly manage DDI knowledge base
4 steps in the DDI alert review process

1. Identification of alerts to be reviewed:
   - New alerts
   - Revisions to existing alerts

2. Systematic review

3. Recommendation by MKM pharmacist
   - Should alert should be included in knowledge base
   - Categorization / tiering of alerts
   - Warning message

4. Final deliberation by Committee → decision
8 criteria are considered when evaluating a DDI alert

1. Clinical effect of interaction
2. Severity and rapidity of onset
3. Mechanism of interaction
4. Recommended management
5. Nature of supporting documentation
6. Common clinical practice
7. Workflow issues
8. Specialists’ expert opinion
Level 1 alerts are hard stops

Clinician must cancel current order or discontinue pre-existing order
Level 2 alerts are interruptive

Prescriber must:
- cancel current order
- cancel existing order
- select an override reason
Level 3 alerts are informational.

Order entry process is not interrupted.

Patient is on Amiodarone and Atorvastatin - May increase Atorvastatin levels resulting in increased risk of myopathy or rhabdomyolysis - Use with caution.
Approx. 450-500 potential DDI alerts are reviewed annually

- Level 1: 140
- Level 2: 1233
- Level 3: 1252

Data collected July 2009
DDI alerts triggered in 4.6% of orders

Level 1: <1%
Level 2: 26%
Level 3: 74%

Over-ridden without modification: 59%
Cancelled order: 23%
Modified order: 18%

Based on analysis conducted in 2007
Tiered alerting of DDIs associated with higher compliance rates

• Retrospective analysis of DDI alerts in inpatient order entry setting
• Compared compliance rates of DDI alerts (tiered vs non-tiered presentation)
• Conclusions:
  – Tiered alerting associated with higher compliance rates (29% vs 10%, p<0.001)
  – Lack of tiering associated with high override rate of more severe alerts (100% vs 34% for Level 1 hard stops)

Unintended Consequences
Case Study 1: Clopidogrel and PPIs

- Jan 2009: FDA releases early communication about ongoing safety review
- March 2009: Retrospective cohort study suggests concomitant use of clopidogrel and PPI is associated with increased risk of adverse outcomes
- MKC implements a Level 2 interruptive alert with following warning message:

  “Patient is on PPI and clopidogrel. May result in decreased clopidogrel efficacy due to metabolism of PPI. Concurrent use is not recommended.”

  Ho PM et al. JAMA 2009;301:937-44
In June 2009, feedback received from cardiologist

- Differing opinions re: interpretation/clinical significance of study
- Presentation of alert
Level 2 interruptive alert

Which drug will be discontinued?

<table>
<thead>
<tr>
<th>Alert Message</th>
<th>Reasons for override</th>
</tr>
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<tbody>
<tr>
<td>Patient is currently on: Clopidogrel 75 MG PO QD</td>
<td></td>
</tr>
<tr>
<td>Patient is on PPI and clopidogrel. May result in decreased clopidogrel efficacy due to metabolism of PPI. Concurrent use is not recommended.</td>
<td></td>
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<tr>
<td>[ ] Will adjust dose as recommended</td>
<td></td>
</tr>
<tr>
<td>[ ] Will monitor as recommended</td>
<td></td>
</tr>
<tr>
<td>[ ] Patient has already tolerated combination</td>
<td></td>
</tr>
<tr>
<td>[ ] No reasonable alternatives</td>
<td></td>
</tr>
<tr>
<td>[ ] Other</td>
<td></td>
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</table>
MKC reconvenes and takes following actions

- Alert changed to Level 3 informational alert
- Reports run to identify prescribers who saw the alert and discontinued clopidogrel
- Recommendation made to EHR Product Management group that presentation of alerts be examined to see if user interface (UI) improvements could be made

“Thanks for the notice .... this is a worrisome case where the interaction between the two drugs is suspect at best and should never have reached this level of warning in the first place. Moreover, if any drug were to be stopped it should have been the PPI.”
Case Study 2: Erythromycin and Calcium Channel Blockers

- Sept 2004: retrospective cohort study suggests that concurrent use of erythromycin and strong inhibitors of CYP3A be avoided due to risk of sudden death
  - Adjusted rate of sudden death from cardiac causes was five times higher

- MKC implements Level 1 (hard stop) alert between:
  - diltiazem and erythromycin
  - verapamil and erythromycin

Within a month, feedback received from Cardiologists

- IV diltiazem/verapamil for rapid AFib in patients on erythromycin
- MKC amends decision so that alert is changed from Level 1 (hard stop) to Level 2 (interruptive) alert for IV diltiazem/verapamil and erythromycin
  - Different alerts for same 2 drugs to account for different patient scenarios
Case Study 3: Nitroglycerin and sildenafil

- Viagra and Revatio prescribing information state that concurrent use of sildenafil and nitrates is contraindicated
- MKC implements Level 1 (hard stop) alert
MKC receives feedback

• Valid contexts of use for concurrent administration of nitroglycerin and sildenafil
  – Inpatient setting: patients with diagnosis of pulmonary hypertension with angina
  – Outpatient setting: “A patient who has prn nitroglycerin for emergency use in case angina should ever occur (and has in fact never used it) also occasionally used Viagra. The DDI program does not permit any over-ride on this combination. Let’s fix it!”

• Prescriber workarounds
  – Incomplete medication lists
  – Prevent other clinical decision support from firing
MKC implements different alerts for same 2 drugs

<table>
<thead>
<tr>
<th>Nitroglycerin</th>
<th>Sildenafil</th>
<th>Alert Level</th>
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<tbody>
<tr>
<td>IV</td>
<td>regularly scheduled sildenafil (PPH)</td>
<td>2</td>
</tr>
<tr>
<td>IV</td>
<td>prn sildenafil (ED)</td>
<td>2</td>
</tr>
<tr>
<td>po</td>
<td>regularly scheduled sildenafil (PPH)</td>
<td>1</td>
</tr>
<tr>
<td>po</td>
<td>prn sildenafil (ED)</td>
<td>1</td>
</tr>
<tr>
<td>top/transdermal</td>
<td>regularly scheduled sildenafil (PPH)</td>
<td>2</td>
</tr>
<tr>
<td>top/transdermal</td>
<td>prn sildenafil (ED)</td>
<td>2</td>
</tr>
<tr>
<td>SL prn</td>
<td>regularly scheduled sildenafil (PPH)</td>
<td>1</td>
</tr>
<tr>
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<td>prn sildenafil (ED)</td>
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</table>
Conclusions (1)

- At Partners Healthcare, we spend significant time/resources maintaining our proprietary DDI alert knowledge base
  - Flexibility to customize rules
- Make every effort to make good decisions based on clinical evidence, clinical practice and workflow issues
Conclusions (2)

• Sometimes our decisions have unintended consequences that cause us to re-examine our original recommendations
  – Constant re-evaluation is good
  – Optimizes DDI alerting by presenting clinicians with meaningful alerts
Thank you!

Thanks to Saverio Maviglia, MD, MSc – Chair of MKC and John Doole, PharmD – Secretary of MKC