Strategies for Improving Drug Interaction Alerts for Clinical Decision Support (CDS)

Karl Matuszewski, MS, PharmD, VP Clinical Editorial, First Databank

FDA Advisory Committee Meeting, September 25, 2013
FDB (First Databank)

• FDB is a subsidiary of Hearst Corporation and the leading provider of drug knowledge that helps healthcare professionals make precise medication-related decisions.

• FDB creates and maintains widely used drug knowledge, software for drug knowledge integration, and drug reference products. The firm has partnered with other information system developers to make drug information useful within the workflow for a wide range of healthcare professionals.

• FDB’s drug knowledge supports pharmacy dispensing, formulary management, drug pricing analysis, medical insurance claims processing, computerized prescriber order entry (CPOE), electronic health/medical records (EHR/EMR), electronic prescribing, and electronic medication administration records (EMAR) systems.

• FDB influences the incidence of medication errors and adverse events associated with prescription drugs that have an impact on healthcare costs and the overall quality of patient care.
Medication CDS lives in a complicated realm, but editorial policies supporting evidence-based content is a focus for FDB.

Three pronged approach to alert fatigue has FDB moving the mark clinically.

Content with additional drug or patient parameters and filters including med cycle focus.
FDB FOUNDATIONAL APPROACH

Surveillance for Evidence
CDS Lives in this Realm
A Multitude of Changing Factors in Clinical Decision Making

- EVIDENCE
  - Biomed Literature
  - Clinical Reviews
  - Guidelines
  - Manufacturer Labeling

- CONSTRAINTS
  - Time
  - Workflow
  - Local Practice
  - Reimbursement

- PATIENT INFORMATION
  - Problem/Med
  - Tests & Procedures
  - Coded Data

- PRESCRIBER
  - Education/Training
  - Experience
  - Goals or Values
EVIDENCE is in the Eye of the Beholder!
Drug Knowledgebase Maintenance/Data Curation

- **Content creation responsibilities**
  - Experienced Clinical Pharmacists with honed judgment, expert review prn
  - Understanding of health system applications and workflow

- **Capture drug information**
  - “trigger events” – tracking systems
  - Accountable assessment plan

- **Comprehensive evidence review**
  - timely review enforced
  - compliance with Editorial Policies
  - consistent with quality controls
  - new knowledge sources acquired (drug metabolism literature database)
Evaluations of Drug Interactions (EDI)

- Loose-leaf reference started in 1984, bimonthly updates
- 18 chapters, 2000 pages, based on major therapeutic classes
- 14 member external advisory board
- Sections: Title of DDI, summary, related drugs, mechanism, recommendations, references, tables
FDB DDI Severity Level Breakdown, N ~ 1600

- SL 1: 41%
- SL 2: 31%
- SL 3: 24%
- SL 9: 4%
New antiepileptic drug safety information is not transmitted systematically and accepted by U.S. neurologists ☆

Sarah G. Bella, Martha Matsumotoa, Susan J. Shawb, Jason Brandtc, Gregory L. Kraussa,
a Johns Hopkins University, Department of Neurology, 600 N. Wolfe St., Meyer 2-147, Baltimore, MD 21287, USA
b University of Southern California, Keck School of Medicine, Department of Neurology, Rancho Los Amigo National Rehabilitation Center, 7601 E. Imperial Highway, HB 145, Downey, CA 90242, USA
c Johns Hopkins University, Division of Medical Psychology, 600 N. Wolfe St., Meyer 218, Baltimore, MD 21287, USA

Highlights

- Survey US neurologists' knowledge of FDA safety warnings for AEDs.
- Respondents received safety information non-systematically from multiple sources.
- One-fifth (20%) did not recognize recently identified, serious AED safety risks (e.g., suicidality, birth defects, side effects).
- FDA-recommended pharmacogenomic screening for carbamazepine was not carried out.
- Neurologists would prefer receiving FDA safety updates via specialty organizations.
## Pace of “official” Change Notice

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<th>Year</th>
<th>FDA MedWatch Alerts</th>
<th>Drug Safety Withdrawals</th>
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<td>2010</td>
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Making Headway with Alert Management

- Fine-tune Existing Content
- Create Additional Parameters and Filters
- Local Customization

New, Highly-Specific Decision Support
Drug-Drug Interactions: FDB Making Hard Choices

- Over 75 drug interaction pairs are strength-breakouts
- Drug interaction applications can take advantage of route breakouts (e.g., topicals)
- Limiting class effects - clopidogrel/proton pump inhibitors
  - esomeprazole (Nexium) & omeprazole (Prilosec), Severity Level=2
  - lansoprazole (Prevacid), pantoprazole (Protonix) changed to Severity Level=3
Fine-Tuned Content: Drug-Drug Interactions
Breakout Ingredients & Adjusting Severity Level based on agent-level evidence

Selected Macrolides
clarithromycin, erythromycin

**Drug-Drug Interaction**

Selected HMG CoA Reductase Inhibitors ("statins")

- simvastatin
- cerivastatin
- lovastatin
- atorvastatin >20mg
- atorvastatin <= 20mg

Bottom Line: Fewer Inappropriate Alerts
FDB’s AlertSpace™
Allowing for Local Customization
Implementation of Authoritative DDI Subsets
CUSTOM SEVERITY LEVEL- Targeted Alerts

Severity Level: 2-Severe Interaction
Action is required to reduce the risk of severe adverse interaction.

Clinical Effects: Contraindicated in some patients

Reference Categories: Manufacturer Information, Human Clinical Trial

Interaction Monograph

Monograph Title
Alteplase/Anticoagulants

Mechanism of Action
The concurrent use of alteplase and anticoagulants may increase the risk of bleeding.
### Crowd Source - Potential Top Customizations

Welcome to AlertSpace Top 10 Edits.

This view shows you how other AlertSpace customers are customizing their alerts. It shows the top ten customizations customers have made per module.

<table>
<thead>
<tr>
<th>Drug Drug Interactions</th>
<th>Duplicate Therapy</th>
<th>Allergy Picklist</th>
<th>Drug Allergy Allergen Group</th>
<th>Drug Allergy Excipient Ingredient</th>
<th>Drug Disease</th>
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</table>

| **2** | ACE INHIBITORS/HIGH-DOSE ASPIRIN |
| **1** | ABCIXIMAB/ANTICOAGULANTS |
| **1** | ACE INHIBITORS; ARBS/LITHIUM |
| **1** | 5HT-1D AGONISTS/ERGOTAMINES; METHYLSERGIDE |
| **1** | ANTICOAGULANTS/SELECTED CEPHALOSPORINS, INJECTABLE |
| **1** | 5HT-1D AGONISTS/SSRIS; SNRIS |
NEW FDB CAPABILITY
Customer Alert Reports Feedback Loop
Making Headway with Alert Management

- EVIDENCE - Allows fine-tuning of existing content
- Create additional parameters and filters
- Local customization
- Aggregated alert reports

New, Highly-Specific Decision Support
## Essential Alert Report Feedback Loop to Prioritize Evidence Review

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Creating Additional Parameters for DDI

• Patient
  – New exposure (vs. continued therapy)
  – Normal lab parameters (e.g., K+, INR)
  – # MDs ordering meds
  – Service location (e.g., clinic vs. ICU)
  – Co-morbidities (e.g., renal/hepatic deficits)
  – Pharmacogenomics (slow/fast metabolizers)

• Physician
  – Specialty (e.g., anesthesiology vs. family medicine)
  – Role (e.g., hospitalist vs. intern)

• Drug
  – Probability (rare vs. common) → % occurrence
  – Severity (mild thru severe) → o, /, x (use of standard symbols?)
Implementation for DDI screening Factors

• Who is looking and or acting on alerts?
  – Prescribing vs. dispensing vs. administering

• What other background CDS (implemented)
  – Duplicate therapy
  – Side effects
  – Drug-disease contraindications/precautions

• The user interface (design)
  – Recall and ignore (i.e., I already approved this combo)
  – Symbolic coding (e.g., green, yellow, red or icons)
  – Bundled or prioritized alerts (vs. long list strings)
  – Screen size viewing (32” vs mobile)
  – Audio alerts? Offering alternatives? Ordering labs/monitoring?
PI Issues for Drug Interactions

- Labeling mismatches between 2 drugs
- Label inconsistencies
- Imprecise label narrative
- Outdated labels
- Broad class effect statements
• The Highlights section states “QTc prolongation. Do not prescribe in combination with other drugs that prolong QTc. (5.11, 7.5, 7.6, 12.2).”

• Section 5.11 states “The use of XENAZINE should be avoided in combination with other drugs that are known to prolong QTc, including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval [see Drug Interactions (7.5, 7.6) and Use in Specific Populations (8.9)].”

• Section 7.5 states “Since XENAZINE causes a small increase in QTc prolongation (about 8 msec), the concomitant use with other drugs that are known to cause QTc prolongation should be avoided including antipsychotic medications (e.g., chlorpromazine, haloperidol, thioridazine, ziprasidone), antibiotics (e.g., moxifloxacin), Class 1A (e.g., quinidine, procainamide), and Class III (e.g., amiodarone, sotalol) antiarrhythmic medications or any other medications known to prolong the QTc interval.”

• Section 7.6 states “Adverse reactions associated with XENAZINE, such as QTc prolongation, NMS, and extrapyramidal disorders, may be exaggerated by concomitant use of dopamine antagonists, including antipsychotics (e.g., chlorpromazine, haloperidol, olanzapine, risperidone, thioridazine, ziprasidone) [see Warnings and Precautions (5.5, 5.9, 5.11, 5.12) and Drug Interactions (7.5)].”
Label and Approval History

Drug Name(s): XENAZINE
FDA Application No.: (NDA) 021894
Active Ingredients(s): TETRABENAZINE
Company: VALEANT BERMUDA

Label Information
What information does a label include?
Note: Not all labels are available in electronic format from FDA.

The latest approved label (approved 08/02/2013) is not available on this site for XENAZINE, NDA no. 021894
View the label approved on 07/06/2011 (PDF)
To see if other previously-approved labels are available on this site, go to the "Approval History" section of this page. Older labels are for historical information only and should not be used for clinical purposes.

Approval History
NDA 021894
Note: Not all reviews are available in electronic format from FDA. Older labels are for historical information only, and should not be used for clinical purposes. Approval dates can only be verified from 1984 to the present.

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<th>Letters, Reviews, Labels, Patient Package Insert</th>
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Medication Alerts live in a complicated realm, but evidence-based content is a focus for FDB.

FDB’s three pronged approach to alert fatigue has evolved, and continues to push the mark clinically.

Evolving evidence review sources and strategies needed, along with new module tools/tactics.

THANK YOU – Questions?