

Best Practices in DDI-Related Content and Management

FDA, 2013

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Overview

- Clinical decision support in general
- Current state with DDIs
- DDIs in particular
 - Evidence
- How DDI alerts actually implemented
- Recommendations regarding DDIs
 - Content—which DDIs
 - Management—how to deliver
- Conclusions

Ten Commandments for Effective Clinical Decision Support

1. Speed is everything
2. Anticipate needs and deliver in real time
3. Fit into the user's workflow
4. Little things can make a big difference
5. Physicians resist stopping
6. Changing direction is fine
7. Simple interventions work best
8. Asking for information is OK—but be sure you really need it
9. Monitor impact, get feedback, and respond
10. Knowledge-based systems must be managed and maintained

Current Approach Regarding DDIs Broadly

- Most institutions obtain their knowledge databases from one of several vendors
 - Not practical for most organizations to maintain these databases which are complex
- However for DDIs in particular too many warnings sometimes given
 - Too many warnings included
 - Way alerts delivered often suboptimal
- Over-alerting can have perverse effects
 - Make systems very hard for providers to use
 - Organizations may turn off decision support
- Both content and management have room for improvement

Drug-Drug Interactions and Harm

- Clear that certain DDIs can be associated with injuries
 - Glyburide and clo-trimoxazole resulting in hypoglycemia (OR 6.6)
 - If admitted with digoxin toxicity 12 times more likely to have received clarithromycin

Juurlink et al, JAMA 2003
- However, DDIs are responsible for a low proportion of adverse drug events overall
 - <5% in most studies
- Yet in many systems are responsible for a high proportion of alerts

Medication Safety: Refining the Rules

- In most systems most alerts get overridden
- We identified a highly selected set of drug alerts for the outpatient setting
- Over 6 months, 18,115 alerts
 - 12,933 (71%) non-interruptive
 - 5,182 (29%) interruptive
 - Of interruptive, 67% were accepted

Impact of Tiering on Inpatient DDI Alerts

- Two academic medical centers
- Same knowledge base
 - Site A used 3 tiers
 - Site B had all of the alerts as interruptive (Level 2)
- Results
 - 100% of most severe vs. 34% at non-tiered
 - Overall alert acceptance higher at tiered site (29% vs 10%, $p < .001$)

Paterno, et al, JAMIA 2009

Human Factors and Alarms (I)

- Need uniform alerting mechanisms and standardized alarm responses
- Alarm philosophies should minimize false alerts
- Placement of alerts impacts the likelihood that users will see these alerts
 - Visibility is critical, and font size should be large enough to be readily legible
 - All visual alerts should be prioritized

Human Factors and Alarms (II)

- Color should help cue the user about the level of a specific alert, and the number of colors used should be minimized
- To make visual alerts more distinct, it is important to minimize the number of visual features that are shared between alerts
- Text-based information should be succinct

Human Factors Principles and Alert Acceptance

- 50,788 DDI alerts analyzed, both inpatient and outpatient
- Providers accepted only 1.4% of the non-interruptive alerts
- For interruptive alerts, user acceptance positively correlated with:
 - Alert frequency 1.30, (1.23-1.38)
 - Quality of display 4.75, (3.87-5.84)
 - Alert level 1.74, (1.63-1.86)

Human Factors Principles and Alert Acceptance (II)

- Alert acceptance was higher:
 - In inpatients 2.63, (2.32-2.97)
 - For drugs with dose-dependent toxicity 1.13, (1.07-1.21)
- Textual information influenced reaction
 - Providers were more likely to modify the prescription if the message contained detailed advice on how to manage the DDI

Drug-Drug Interaction Level 2

LMR OMA28 - Microsoft Internet Explorer provided by Compaq

File Edit View Favorites Tools Help

Address <http://ppd.partners.org/scripts/phsweb.mwl?APP=LMR&OPT=LMR&SESSION=7851809> Go Links

Oetest, Clovis AS824

11489945 (BWH) 08/09/1972 (31 yrs.) F NH

Select Desktop Pt Chart: Medications Oncology Custom Reports Admin Sign Results Resource Popup

Warning

You are ordering: WARFARIN SODIUM

Drug - Drug Interaction

Alert Message	Keep New Order - select reason(s)
Patient is currently on: BACTRIM DS (TRIMETHOPRIM /SULFAMETHOXAZOL... 1 TAB PO BID	<input type="radio"/> Will D/C pre-existing drug
Pt. on Coumadin and Sulfamethoxazole: Possible elevated PT - Recommend to avoid concurrent use and/or to consider an alternative antibiotic but if co-therapy is warranted, Rec. to monitor PT.	Reasons for override:
	<input type="checkbox"/> Will adjust dose as recommended
	<input type="checkbox"/> Will monitor as recommended
	<input type="checkbox"/> Patient has already tolerated combination
	<input type="checkbox"/> No reasonable alternatives
	<input type="checkbox"/> Other <input type="text"/>

Continue New Order Cancel

Microsoft PowerPoint - [Presentation2] Internet

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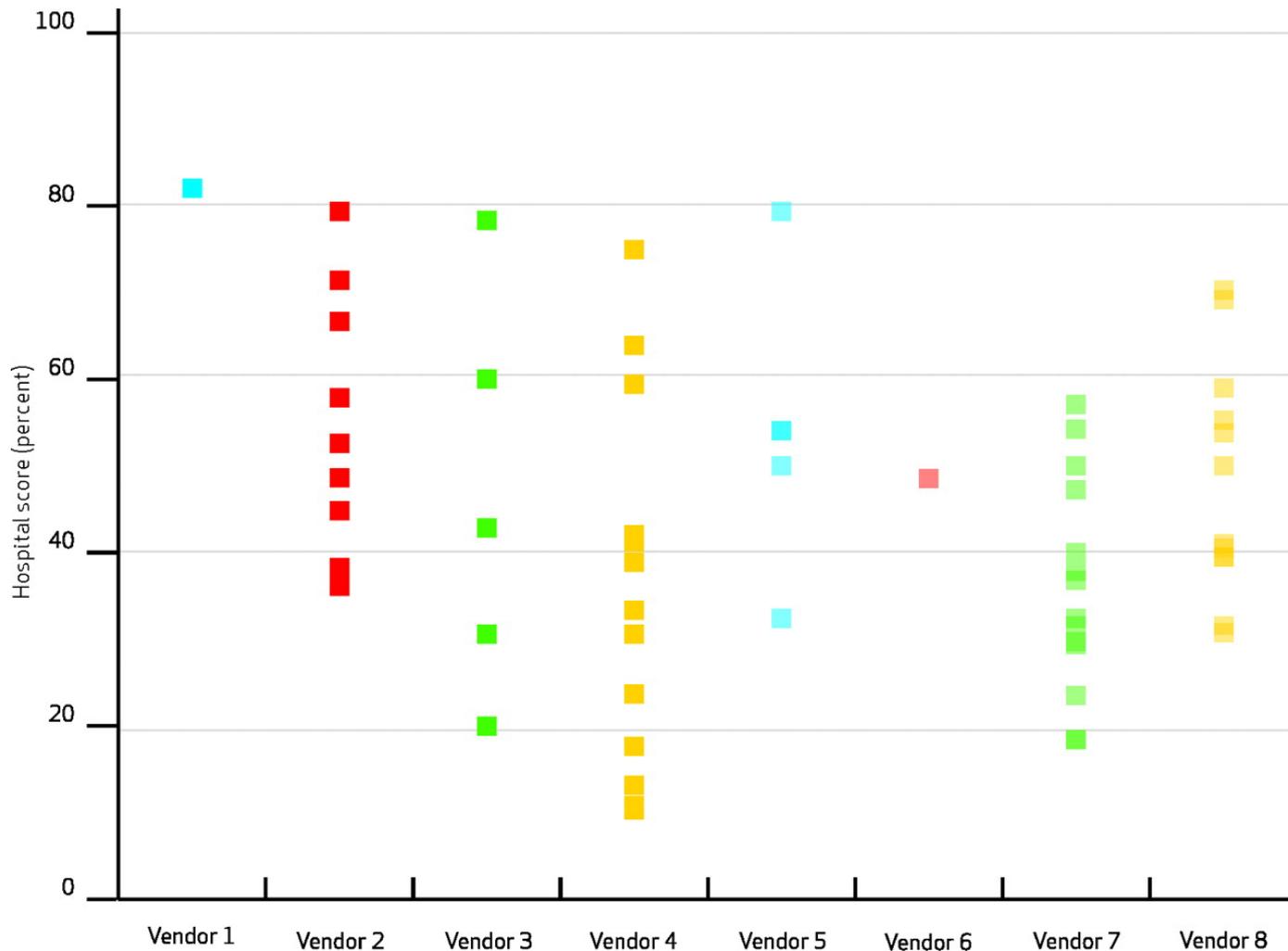
Leapfrog Testing Data

ADE Category	Percent Detected (95 percent confidence interval)		
<i>Addressed by Basic Clinical Decision Support</i>			
Drug-allergy contraindication	83.3	(77.7	87.8)
Inappropriate single dose	46.4	(34.5	56.6)
Therapeutic duplication	54.5	(43.7	64.9)
Drug-drug interaction	52.4	(43.4	61.3)
Inappropriate route	65.3	(55.7	72.5)
<i>Addressed by Advanced Clinical Decision Support</i>			
Inappropriate cumulative (daily) dose	39.1	(28.9	50.4)
Inappropriate dosing (patient weight)	36.7	(27.9	46.4)
Age contraindication	14.1	(7.9	24.0)
Labs--creatinine	20.2	(12.9	30.1)
Labs-other	26.1	(18.7	35.1)
Drug-diagnosis contraindication	15.0	(9.9	22.1)
Corollary orders (monitoring)	27.0	(19.7	35.7)

Safety Results of CPOE Decision Support Among Hospitals

- 62 hospitals voluntarily participated
- Simulation detection only 53% of orders which would have been fatal
- Detected only 10-82% of orders which would have caused serious ADEs
- Almost no relationship with vendor

Metzger et al, Health Affairs 2010



Jane Metzger, Emily Welebob, David W. Bates, Stuart Lipsitz, and David C. Classen,
 Mixed Results In The Safety Performance Of Computerized Physician Order Entry,
 Health Affairs, Vol 29, Issue 4, 655-663

HealthAffairs

Content—Which Alerts

- Interrupt with only most important warnings and tier
 - Jury still out regarding non-interruptive warnings
- Have regular review
- Track how providers are responding as practices change
- Sharing regarding this would help
 - Would be a common good
 - RAND work a start
 - Could be international

Management—How to Deliver

- Follow human factors principles
 - Tier
 - Uniform
 - Placement
 - Different levels of warning should appear different
 - Use color wisely
 - Succinct textual information

DDI list with details on the interaction and supporting evidence obtained from FDB, Micromedex, Cerner Multum, Hansten & Horn's book, Royal Dutch Association for the Advancement of Pharmacy

Stage 1:

List of 31 DDI class pairs



- 5 Drug Duplication pairs removed (ID # 1, 2 10, 17, 19)
- 2 DDI pairs demoted to lower level (ID # 9, 18)
- 2 DDI pairs deleted as drugs no longer prescribed/available
- 1 DDI deleted as no proper supporting evidence (ID#7)

Stage 2:

List of 21 DDI class pairs



- 3 DDI pairs demoted to lower level (ID#13, 14, 15)
- 1 DDI pair deleted as drugs no longer available
- 1 pair combined with another DDI pair

Scoring Process

16 DDI class pairs
for scoring

Rating of clinical significance --
9 point scale

- 1 DDI scored <6 points: recommended demotion to lower level

Final List

15 DDI class pairs

Examples from Panel Evaluation of List

Suggested DDI Pair	Suggestions from the Panel	Modifications	Status	Final DDI Pair
Atazanavir - Gastric pH Alkalinizing Agents (Proton Pump Inhibitors, H2 blockers)	Only include PPIs and remove H2 Blockers from gastric precipitant Class based on the supporting literature evidence		Accepted	Atazanavir - Proton Pump Inhibitors (PPIs)
Statins – Protease Inhibitors	Expand Precipitant class to include CYP 3A4 Inhibitors. Removed Cerivastatin due to off market status.	Expanded the precipitant class to include other 3A4 inhibitors like Protease Inhibitors, Macrolides, Rifampin, Amiodarone, Azoles.	Accepted	Statins – CYP3A4 Inhibitors
Abatacept - Tumor Necrosis Factor (TNF) Inhibitors	Therapeutic duplication		Deleted	
Febuxostat - Theophylline	Only a theoretical interaction with no corroborating evidence		Deleted	

High-Priority DDIs

- 15 drug-class pairs endorsed as highly clinically significant DDIs
 - Should never be co-prescribed
 - Candidates for “hard-stop” alerts
 - Checking completeness would require further research, but represents best available consensus
- Less-significant DDIs are still significant
 - *Much more prevalent* and probably cause much more harm
 - Tend to depend on patient characteristics, drug dosages and timing, concomitant conditions such as hypokalemia, etc.
- To improve sensitivity and specificity of DDI warnings:
 - Need much more investment in evidence review and generation
 - Methods to make DDI alerts conditional on other patient data

Low-Priority DDIs

- Alert fatigue is a serious problem
- Used consensus approach to identify low-yield DDIs
 - Used data from several sources to identify potential candidates
- Created a list of 33 DDIs that do not warrant interruptive status
 - Account for many of the DDIs displayed in some systems
- A consortium to maintain this list would be helpful

Adherence to Black-Box Warnings

- Identified all patients with 2002 black-box warning
 - 55 of 95 warnings required clarification to be computable
- 324,578 patients prescribed a medication
 - 33,779 (10.4%) got a drug with a black-box warning
- Of 1107 getting a drug with a DDI warning, 401 (36%) also got a contraindicated drug
- Black-box warnings were often imprecise
- Violations appeared frequently
 - Need better assessment of actual level of risk in individual situation

Lasser et al, Arch Int Med, 2006

Marginal Benefit of Adding Black-Box Warnings Not Already Included

- Assessed impacted of adding BB warnings
 - Actually slightly higher non-adherence after intervention (5.1% after, 4.8% before)
- Violations did decrease though for important categories
 - For DDIs 6.1% vs. 1.8%, $p < 0.0001$
 - For drug-pregnancy, 5.1% vs. 3.6%, $p = 0.01$
- Overall adding more did not improve adherence, though did for important subcategories

Conclusions (I)

- Checking for DDIs can be highly beneficial
- But substantial work to do
 - Which alerts to display
 - Consensus will help greatly—RAND work good start
 - How to display them
- Best practices re which alerts
 - Sort out how sharing could be enabled
- Best practices regarding how to display
- DDI warnings today are a big problem in clinical systems which don't follow best practices
- Also need to leverage systems to build underlying evidence base which needs to be much more robust
 - Broad EHR adoption should help a lot

FDA and Drug-drug Interactions

- If possible, would help to include in label both simple messages and more detail
- Regarding format, few data available but using IT approaches can use multiple
 - Forest plots/tables/narrative
- Data suggest users only consult referential material about 2% of the time
- Many complex situations like multiple drugs, interaction changing over time—labeling will need to evolve