


Identifying and Preventing Clinically Important Drug-Drug Interactions: Concordance Among Compendia & Selection Process



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Outline

- Discuss the drug-drug interaction (DDI) severity rating system used by compendia
- Discuss agreement between compendia on DDI severity ratings
- Describe the process for identifying clinically important DDI
 - Selection of specific DDIs
 - Modified Delphi Process using Expert Panel



Concordance Among Compendia

Research Question:

What is the level of agreement among commonly used drug-drug interaction (DDI) compendia with regard to the severity ratings of 'major' drug-drug interactions?

Problems with Identifying Drug-Drug Interactions

“Major” Drug Interactions (at *Medication Class Level*) by Compendium

Compendium	No.
MicroMedex <i>DRUG-REAX</i> ®	275
<i>Evaluation of Drug Interactions</i>	64
<i>Drug Interactions: Analysis and Management</i>	94
<i>Drug Interaction Facts</i>	141
Total	406*

* Sum of column exceeds total due to duplicate interactions.

Which Drug-Drug Interaction Reference?

- DDIs in 4 of 4: 2.2% (9/406)
 - DDIs in 3 of 4: 8.6% (35/406)
 - DDIs in 2 of 4: 17.4% (71/406)
 - DDIs in 1 of 4: 71.7% (291/406)
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- Agreement on Severity Ratings for Major Drug-Drug Interactions Among Compendia
 - Intraclass Correlation Coefficient: -0.092



Identifying Clinically Important Drug-Drug Interactions

Objective:

Develop a list of the clinically important DDIs that are likely to be encountered in outpatient settings and detected by drug utilization review systems.



Methods

- Review compendia for “major” interactions
 - DDI listed in at least 3 compendia
 - Additional criteria:
 - Available in US for human use
 - Medications likely to be dispensed in community pharmacy
 - Medications likely captured in electronic database
 - Interacting medications not used for therapeutic benefit
- Identify evidence for selected DDIs
 - Compendia citations
 - Medline and International Pharmaceutical Abstracts (1995 to 2002)
 - Developed executive summary of supporting literature



Methods

- Expert Panel
 - Members: 2 Physicians, 3 Pharmacists
 - Modified Delphi Technique (3 Rounds)
 - Independent rating of drug-drug interactions
 - Survey instrument (16 items)
 - Quality and quantity of evidence
 - Severity of interaction
 - Probability of interaction
 - Probability of coadministration



Results

- 62 DDIs identified
- 18 DDIs excluded
- 10 DDIs were added by expert panel

Results – 25 Clinically important drug-drug interactions

Benzodiazepines	↔	Azole anti-fungals
Carbamazepine	↔	Propoxyphene
Cyclosporine	↔	Rifamycins
Digoxin	↔	Clarithromycin
Ergot alkaloids	↔	Macrolide antibiotics
Oral contraceptives	↔	Rifampin
Ganciclovir	↔	Zidovudine

Results – 25 Clinically important drug-drug interactions – con't

Methotrexate	↔	Trimethoprim
Nitrates	↔	Sildenafil
Pimozide	↔	Macrolide antibiotics
Pimozide	↔	Azole anti-fungals
Theophylline	↔	Quinolones
Theophylline	↔	Fluvoxamine
Thiopurines	↔	Allopurinol

Results – 25 Clinically important drug-drug interactions – con't

MAO inhibitors ↔ Dextromethorphan

MAO inhibitors ↔ Anorexiant

MAO inhibitors ↔ Sympathomimetics

MAO inhibitors ↔ Meperidine

MAO inhibitors ↔ SSRIs

Results – 25 Clinically important drug-drug interactions – con't

Anticoagulants	↔	Thyroid hormones
Warfarin	↔	Barbiturates
Warfarin	↔	Cimetidine
Warfarin	↔	Fibric acid derivatives
Warfarin	↔	NSAIDs
Warfarin	↔	Sulfinpyrazone



Identifying Clinically Important Drug-Drug Interactions

- Underlying Assumptions/goals
 - Interactions likely to cause harm if undetected
 - Focus on ambulatory prescribing
 - Prescription products (not over-the-counter)
 - Excluded
 - Medications likely to be used together for therapeutic effect
 - Interactions occurring on discontinuation of one of the medications
 - Medications available for use in 2002



Limitations

- Use of an expert panel
- Reliance on drug interaction compendia
- Different rating systems used among compendia