Clinically Relevant Drug Interactions

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Objectives

- Evaluate the impact of alerting on a large number of potential interactions.
- Formulate a list of medications that have a high potential to interact.
- Evaluate the consequences of drug interactions.
- Provide suggestions for improving the alerting system.

Overview

- 5-26% of adverse drug reactions (ADR) are attributed to drug interactions.
- 60-90% of alerts are overridden
- ~330 drug alerts have to be reviewed to prevent a single ADR of any severity.
- 2700 to prevent a serious ADR
- 44,000 to prevent death or disability
There is a fairly high degree of agreement among computerized systems on the significance of drug-drug interactions

- True
- False

Drug Interactions

- Level 1
  - Severe drug interactions
  - Drug combinations that should never be used together
- Level 2
  - Less severe but requires clinicians to justify coadministration
- Level 3
  - Requires no action by clinician

Problems in determining significance of interactions

- Definition of clinical significance
- Screening programs used
- Background information provided or not provided (clinical decision support)
- Potential vs. actual interactions
- Different patient populations
Who’s at highest risk for a drug interaction?

- Elderly
- Polypharmacy
  - 40% for patients taking 5 medications
  - 80% for patients taking 7 or more
- 60% of statin rhabdomyolysis cases are caused by a drug interaction
- Coadministration of drugs that prolong QT interval + additional risk factors
- Multiple providers & pharmacies

When Should We Worry?

- If you worry about the dosing of a drug when given alone, you should worry when given with a reported precipitant drug
- Narrow therapeutic range
- When patient has multiple factors that may impair or enhance elimination of object drug

Factors influencing interaction outcomes

- Patient factors
  - Age
  - Genetics
  - Diseases
  - Diet/nutrition
  - Environment
  - Smoking
  - Alcohol
- Drug Factors
  - Dose
  - Duration
  - Dosing times
  - Sequence
  - Route
  - Dosage form
Drug interaction alerts

- ~67,000 community pharmacies in the US
- Filled over 4 billion prescriptions in 2013
- Of all claims submitted in a state Medicaid pharmacy program, 0.81% generated an alert
- Extrapolated from the previous studies,
  - 32.4 million alerts would have occurred in pharmacies, of which 1.6-10.8 million would be clinically relevant

Why don’t many reported drug interactions cause harm?

- Wide therapeutic range
- Patients on low dose (or low concentrations) of object drug
- Many patients have good clearance
- Class interactions don’t apply to all in class
- Case reports can be flawed
- Interactions are not constant and can vary with each occurrence

A 55 y/o female is on lithium & you want to prescribe furosemide for excess edema. The system flags an interaction. What should be done next?

- Override the interaction
- Decrease the lithium dose
- Continue the medication but monitor a level
### Important Drug Interactions in the Elderly

<table>
<thead>
<tr>
<th>Drug-Drug Interaction</th>
<th>Observed Adverse Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE inhibitors + K-sparing diuretics</td>
<td>Hospitalization for hyperkalemia</td>
</tr>
<tr>
<td>ACE inhibitors + co-trimoxazole</td>
<td>Hospitalization for hyperkalemia</td>
</tr>
<tr>
<td>Benzodiazepines + CYP3A4 inhibitors</td>
<td>Hospitalization for hip fracture</td>
</tr>
<tr>
<td>Calcium channel blockers + macrolides</td>
<td>Hospitalization for hypotension or shock</td>
</tr>
<tr>
<td>Digenic + macrolides</td>
<td>Hospitalization for digenic toxicity</td>
</tr>
<tr>
<td>Lithium + ACE inhibitors, loop diuretics</td>
<td>Hospitalization for lithium toxicity</td>
</tr>
<tr>
<td>Phenytion + co-trimoxazole</td>
<td>Hospitalization for phenytion toxicity</td>
</tr>
<tr>
<td>Glipizide or glyburide + CYP2C9 inhibitors</td>
<td>Hospitalization for hypoglycemia</td>
</tr>
<tr>
<td>Tamoxifen + paroxetine</td>
<td>Death from breast cancer</td>
</tr>
<tr>
<td>Theophylline + ciprofloxacin</td>
<td>Hospitalization for theophylline toxicity</td>
</tr>
<tr>
<td>Warfarin + co-trimoxazole or NSAIDs</td>
<td>Hospitalizations for GI bleeding</td>
</tr>
</tbody>
</table>

### Medications with potentially serious drug-drug interactions

- Cyclosporine
- Digoxin
- Lithium
- Monoamine oxidase inhibitors
- Protease inhibitors
- Selective serotonin reuptake inhibitors
- Warfarin

### Which of these medications should be avoided during warfarin therapy?

- Metronidazole
- Rifampin
- TMP/SMX
- Cephalexin
A 68 y/o female taking warfarin, who was previously well-controlled on a stable dose, has recently been difficult to anticoagulate. Review of her medications reveals the addition of fluconazole. Some consider empirically lowering warfarin by?

- 20%
- 25%
- 30%
- 40%

**Patient on warfarin? Steer clear of these drugs**

<table>
<thead>
<tr>
<th>Category</th>
<th>Medications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiarrhythmics</td>
<td>amiodarone</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>ciprofloxacin, metronidazole, rifampin, trimethoprim/sulfamethoxazole</td>
</tr>
<tr>
<td>Anticonvulsants</td>
<td>carbamazepine, valproate</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>fluoxetine, paroxetine, sertraline, trimadone</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>fluoroquinolone</td>
</tr>
<tr>
<td>Diuretics</td>
<td>spironolactone</td>
</tr>
<tr>
<td>GI drugs</td>
<td>cimetidine, esomeprazole, lansoprazole, omeprazole, pantoprazole, ranitidine</td>
</tr>
<tr>
<td>NSAIDs</td>
<td>aspirin, celecoxib, diclofenac, ibuprofen, indomethacin, ketorolac, naproxen, piroxicam</td>
</tr>
</tbody>
</table>

**Medications with potentially serious drug-drug interactions continued**

- Fluoroquinolone → Ca, Al, Mg, Fe
  - ↓ absorption of fluoroquinolone by 75%
  - Take 2 hours apart
- Phosphodiesterase inhibitors → nitrates
  - 123 deaths
- OCs → rifampin
- Clonidine → propranolol
- Glyburide → sulfamethoxazole/trimethoprim

The Journal of Family Practice 2010; 59(6):322-29
Medications that can increase potassium levels

- Angiotensin-converting enzyme inhibitors
- Angiotensin-receptor blockers
- Drospirenone
- Heparin
- Immunosuppressants (cyclosporines & tacrolimus)
- Nonsteroidal anti-inflammatory drugs
- Potassium-containing salt substitutes
- Potassium-sparing diuretics
- Potassium-supplements
- Succinylcholine
- Sulfamethoxazole/trimethoprim

If using spironolactone with an ACE inhibitor, when should a potassium level be checked?

- 24 hours
- 48 hours
- 72 hours
- 1 week

Is there evidence of harm?
Absence of Drug-Disease Interaction Alert Leads to a Child's Death

- 12 y/o girl given azithromycin for otitis media & sinusitis
- 4 days into treatment experienced palpitations, nausea, dizziness & fainting
- In ER showed complete AV block associated with QT prolongation then quickly developed torsades & ventricular fibrillation


Which of the following is true about QT prolongation & the risk of torsades de pointes?

- QTc prolongation is defined as greater than 440ms for all patients.
- Most patient with QT prolongation will eventually develop torsades de pointes.
- An increase of 60ms from the baseline QTc is a risk factor for drug-induced torsades de pointes.
- A QTc interval of 440 ms or greater will increase the risk for torsades de pointes 2-3 fold.

QT prolongation

- Rare but life-threatening
- Inhibit the movement of K into cardiac cells following depolarization
  - Delays repolarization
  - Torsade de pointes
- QT interval > 500 ms
- Risk factors: women, age >68, baseline QTc >450 ms, EF <40%, K <3.5 mEq/L, MI, sepsis, loop diuretic or QT prolonging medications
- Examples: sotalol, fluoroquinolone, macrolides, haloperidol, citalopram, methadone

Pharmacy Times, August 15, 2009 Pharmacist's Letter 2015 #150226
If a computer system alerts an interaction between sertraline & rasagiline, what is your next step?

- Override the alert
- Continue the medication
- Discontinue one medication

Drug-Induced Serotonin Syndrome

- 18 y/o college female with a history of depression who was being treated with phenelzine.
- Admitted to hospital with agitation, disorientation, fever & jerky body movements
- She was given meperidine & haloperidol
- She fell asleep & temperature raised to 107
- Cardiac arrest and death
- 7,349 cases of serotonin syndrome reported causing 118 deaths

Serotonin Syndrome

- Life-threatening condition associated with increased serotonergic activity in the CNS
- When does it occur?
  - Within 6-24 hours
  - MAOI before starting SSRIs. MAOIs binds to monoamine oxidase for the life of the enzyme
- Symptoms: clonus, muscle rigidity, tremor, hyperreflexia, agitation, diaphoresis, tachycardia, hypertension, hyperthermia, & slow continuous, horizontal eye movement
- Very few medications (mainly MAOIs) are capable of producing severe symptoms
- 14-day washout period between discontinuing MAO inhibitor and starting another serotonergic medication.
“Asthma sufferer wins $28.6 million award”

- 24 y/o man on theophylline went to ER for an infection; prescribed ciprofloxacin by ER physician
- Theophylline concentrations doubled; patients had permanent brain damage
- Patient awarded $22.5 million in pain & suffering

Alert response options

- Immediately override without consideration
- Determine that there is no interaction because the drug combination is not relevant

Relevant alert response options

- Adjust monitoring of safety & effectiveness
- Provide additional information to patient
- Set up therapeutic drug monitoring
- Adjust dose
- Use different medication
What do pharmacists do?
- 74% override with no further action
- 19% override & discuss with the patient
- 4% prescriber contacted & no change in therapy
- 3% prescriber contacted & medication changed

Why pharmacists react that way?
- 54.5% believed that >70% of DDI alerts in the previous week were clinically insignificant.

How do physicians respond?
- 24,034 prescriptions over 3 month period
- 3129 (13%) DDI alerts (moderate severity/strong evidence & high severity with moderate or strong evidence)
- 89.4% of high-severity DDI alerts were overridden
  - Resulting in 3 ADEs
  - Physician reviews judged 36.5% of alerts as inappropriate
Justification for Overrides

- Interactions not clinically significant: 21.6%
- Patient’s medication list inaccurate: 8%
- Course of therapy of one of the agents was limited: 6.2%
- Patient currently tolerates (21.6%) or had tolerated combination in the past (12.3%)

How do physicians respond?

- 22% of 220 prescribers with alert systems in office admitted to frequent overrides without proper check
- Perception that alerts are often irrelevant
- 90% thought it should be more difficult to override potentially lethal interactions

The Delicate Balance

- Evaluating potential is time consuming
- Notification is time consuming
- Workload is very high
- If harm occurs = low esteem & litigation
Attitudes when interaction alert customization possible

- Increased confidence in computer system.
- Decreased belief that alerts were meaningless.
- Increased agreement that the DDI alerts were easily differentiated from other alerts.
- Decreased belief that alerts were a waste of time.
- Increased confidence in ability to determine clinical significance of DDI.

J Am Pharm Assoc; 2003 46(2):148-153

Customizing Software Systems

- Reduce burden of severe interactions by 65%
- One hospital decreased from 25,000 alerts per day to 500 major alerts per day.
- Maintain a regularly updated list of significant alerts that require direct prescriber notification.
- Identify low-value interactions that should be considered for elimination.
- Review bypassed alerts on a daily basis to make sure clinically significant alerts haven’t been bypassed.

Which of the following is a clinically important interaction you can use to test the quality of your drug interaction software system?

- Ophthalmic erythromycin ointment and carbamezepine
- Warfarin and digoxin
- Warfarin and TMP/SMX
- Metformin and warfarin
Tools for testing drug interaction software

Pharmacy Quality Alliance drug interactions to evaluate Medicare D plans

Improving the System

- Create smarter systems
- No longer on a medication
- Topicals
- Been on medication for a while
- Dose-dependent interactions
- Alert only clinically significant interactions
- "Hard Stop" alerts
Conclusions

- Most interactions are not clinically significant.
- Many, if not most, drug interactions can be avoided.
- We are responsible for making drug therapy safe for our patients.
- We need to work together to change the system so it works better
  - Reduce alert fatigue
  - Make important interactions difficult to override