New Ways to Identify and Mitigate Adverse Drug Events and Get Paid for It

NCPA 2019 Annual Convention

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Founder, CEO, Chair, Tabula Rasa Healthcare, Inc

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Disclosure

Calvin H. Knowlton is the founder, CEO, and chair of Tabula Rasa Healthcare, Inc. The conflict of interest was resolved by peer review of the slide content.

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Pharmacist and Pharmacy Technician Learning Objectives

• Review basic metabolic pathways and pharmacokinetic principles for drug activation and elimination.

• Identify common drug combinations that increase a patient’s risk of adverse drug events.

• Discuss strategies to mitigating adverse drug events in a community pharmacy setting.

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Please go to **MEET.PS/ADES** to answer poll questions!
When one uses multi-drug simultaneous analysis to identify and mitigate preventable ADEs, this is what you can expect.

<table>
<thead>
<tr>
<th>Community Pharmacy</th>
<th>Models</th>
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</thead>
<tbody>
<tr>
<td>Metrics</td>
<td>Closed System Monthly Touches (Prospective)</td>
<td>EMTM 1-2 Touches/yr (Retrospective)</td>
<td>SaaS Closed System PharmD/MD Groups</td>
<td></td>
</tr>
<tr>
<td>PMPY ($) Documented Saving</td>
<td>$3,996 PMPY*</td>
<td>$2,530 PMPY**</td>
<td>$3,596 PMPY***</td>
<td></td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>42.9%</td>
<td>---</td>
<td>22.5%</td>
<td></td>
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<tr>
<td>ER Visits</td>
<td>20.4%</td>
<td>---</td>
<td>28.2%</td>
<td></td>
</tr>
<tr>
<td>ROI ($)</td>
<td>13:1</td>
<td>4:1</td>
<td>10:1</td>
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A Minute on Aggregated Sedative Burden

- Dizziness
  - Gait disturbances / Falls
- Dependence
  - Physical
  - Psychological
- Tolerance

- Daytime Sleepiness
  - Sedentary
  - Social Isolation
- Memory Impairment
  - Anterograde Amnesia
  - Depression


A Minute on Anticholinergic Burden

Anticholinergic Side Effects

- Red as a beet
- Crazy as a loon
- Dry as a bone

What is the 10/6 on his hat?

*In Alice’s Adventures, it is the hat’s price tag - 10 shillings, 6 pence*. 

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A Minute on Anticholinergic Burden

• Agitation / delirium
  – Onset or worsening BPSD

• Cardiac dysrhythmias
  – Arrhythmias

• Constipation
  – Fecal impaction
  – Paralytic ileus

• Urinary retention
  – Increased UTI

• Dry mouth
  – Dysphagia
  – Dental caries

• Blurred vision
  – Gait disturbances / falls


BPSD = behavioral and psychological symptoms of dementia
UTI = urinary tract infection

Anticholinergic Cognitive Function Decline

Anticholinergic drugs and risk of dementia: case-control study
Kathryn Richardson,1 Chris Fox,1 Ian Macleod,2 Nicholas Sand,1 Yoon K. Loo,3 Antony Arthur,3 Phear M. Mans3,4, Cyndia M. Greaves,1 Katrina Matthews,1 Katherine Bennett,1 Rod J. Camplejohn,1,1 Malar Brunt1,1 Louise Robinson,2 Carol Struyf,3 Fiona L. Matthews,2,2 George M. Savva1

Original Investigation
Association Between Anticholinergic Medication Use and Cognition, Brain Metabolism, and Brain Atrophy in Cognitively Normal Older Adults

RESEARCH
Cumulative Use of Strong Anticholinergics and Incident Dementia: A Prospective Cohort Study

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Aggregated ACh Burden + Aggregated Sedative Burden = Cognitive Burden

A Minute on Aggregated Long QTc Syndrome

Basic Electrophysiological Concepts

Triggers
- Bradycardia, pause
- Gender and Age
- Hypokalemia
- Hypomagnesemia
- Diuretics
- Antiarrhythmics
- QT prolonging drugs
  - Multi-drug, simultaneous Interactions
- Comorbidities
- QTc interval

http://curriculum.toxicology.wikispaces.net/Cardiotoxic+drugs
A Minute on Competitive Inhibition & Bioavailability & Chronopharmacology

Multi-drug Simultaneous Interactions via Pathway Metabolism

Obsolete 1x1 Comparison
- Most DDI software programs provide info on only 2-drug combinations AND
- Do not take into account pharmacokinetic concepts

Poor Application with Polypharmacy
- Unable to assess multidrug combinations simultaneously
- Application of results to patients with chronic conditions with polypharmacy is difficult

“Alert fatigue” or “Pop-up fatigue”
- The result is “alert fatigue,” as reported by 20%-40% of clinicians
- This further limits the assessment of multidrug potential DIs

Example: Competitive Inhibition

Pharmacokinetics:
- Rosuvastatin
- Diphenhydramine
- Oxycodone
- Omeprazole
Or, maybe like this?

• If two meds (or three) are vying for the same gene/enzyme and their affinity coefficient is similar, the one with the higher mg dosage will occupy the space first.

• For Instance:
  • CYP2D6
  • Both metoprolol and diphenhydramine have a high affinity for 2D6. If 25mg of metoprolol & 50mg of diphenhydramine are taking simultaneously, the 25mg of metoprolol loses the battle, and continues around the body at full strength.

• So, you should advise that they are taken at a different time of day.

A New Way To Think About Applying the Science

From Traditional One-to-One Drug Analysis

This One-to-One Drug Interaction software is four decades old, and is embedded in EHRs, Pharmacies, PBMs, etc.

To Simultaneous Multi-Drug Analysis

Proprietary and Patented Concurrent analysis from perspectives of Pharmacokinetics (including Pharmacogenomics), Pharmacodynamics and Chronopharmacology
Summary

- Pharmacodynamics
  - Aggregated Sedative Burden
  - Aggregated Anticholinergic Burden
  - Prolonged QTc Burden

- Pharmacokinetics/Pharmacogenomics
  - Drug/Gene Pairs
  - Competitive Inhibition / Chronopharmacology
  - Bioavailability
  - Creatinine Clearance
  - Relative Odds Ratio for ADEs

This is fully aggregated and logarithmically calculated into a Medication Risk Score, from 0 to 50.

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Please go to MEET.PS/ADES to answer poll questions!
Some Questions

• Applying these sciences that only pharmacists own, can you envision doing this, by appointment, in your practice and collecting a monthly fee for the service – not associated with any PBM?

• Can you envision a “concierge pharmacist” appointment-based model?
Some Questions

- Why would patients be willing to pay you for this service?
  - Because Adverse Drug Events are a preventable pandemic, and they lead to higher medical costs and lower quality of life

- How is this happening?
  - Because our 50-year old one-drug to one-drug interaction system embedded within our pharmacy management systems, and EHRs, and PBMs, etc. is not able to apply the science to personalized the medication regimen ... but you are able to do so.
Typology: Adverse Drug Events are NOT Medication Errors

A medication error is defined as “inappropriate use of a drug that may or may not result in harm;” such errors may occur during prescribing, transcribing, dispensing, administering, adherence, or monitoring of a drug.

In contrast, ADEs are “harms directly caused by a medication at normal doses.”

Leading Causes of Death

#1 – Heart Disease: 635,260

Patients taking two concurrent medications have a 13% risk of an adverse drug event, rising to 38% for four medications, and 82% for seven or more medications taken simultaneously.

#2 – Cancer: 598,038

#3 – Adverse Drug Events: 173,000 (If ADEs were a disease)

- 100,000 reported, actually underreported
- 73,000 from opioids - overwhelms the metabolic pathway due to sheer dose, or, due to competitive inhibition

#4 – Chronic Lower Respiratory Diseases: 154,596
Not just deaths, but preventable morbidity

<table>
<thead>
<tr>
<th>3.5 million</th>
<th>1.3 million</th>
<th>350,000</th>
<th>39%</th>
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<tbody>
<tr>
<td>Physician Office Visits</td>
<td>Emergency Department Visits</td>
<td>Hospitalizations</td>
<td>Of Seniors in U.S. on 5+ meds (Approx. 20 million people)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>2 million</th>
<th>1.7 to 4.6</th>
<th>20.4%</th>
<th>50%</th>
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<tbody>
<tr>
<td>Affected Hospital Stays</td>
<td>Increased Days Per Affected Hospital Stay</td>
<td>Readmissions</td>
<td>Of Seniors in U.K. on 5+ meds (increase of 12% from 20 years ago)</td>
</tr>
</tbody>
</table>

Adverse Drug Events is estimated to be the 3rd leading cause of death—ahead of pulmonary disease, diabetes, AIDS, pneumonia, accidents, and automobile deaths.

Source: [https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm110632.htm](https://www.fda.gov/drugs/developmentapprovalprocess/developmentresources/druginteractionslabeling/ucm110632.htm)

ADEs are collinear with # of meds

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ADEs Impact - Cost Of Drug-Related Morbidity and Mortality Studies

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<tr>
<td>$67</td>
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<tr>
<td>$101</td>
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It still rings true: For every dollar we spend on prescription medication, we spend more than another dollar trying to address problems caused by the medications.

One In Five Seniors Experienced Adverse Drug Reactions In 2018

Polypharmacy – a 300% Increase in 20 years... from 14% to 42%

Three Drivers of Medication Overload

- Cultural Shift
  - 30 yrs of DTC
  - Pill for every ill
  - Medications are “care”
- System Fragmentation
  - Polypharmacy
  - No Quarterback
- Information Dearth*
  - Anachronistic Tools
  - Lack of Optimal Prescribing CE

* = Pharmacists’ Thrust
Prescribing Cascade

Prescribing a medication for a symptom that is actually a side effect from one or a combination of other medications.

Why Are ADEs Such A Problem?

- Polypharmacy & Prescribing Cascade
- PBMs – 2 meds/class based upon what?
- PK/PGx/PD/CP disuse atrophy
- Anachronistic Pharmacy Incentives
- Existing tools analyze 1:1 drug interactions
**Stuck in the Past: Precision Pharmacotherapy Is Not Widely Adopted**

- **Formularies** are developed by PBMs based on economic principles vs. drug metabolism

- **Pharmacogenomic (PGx)** testing in clinical practice has been slow due to key barriers:
  - Lack of Guidelines
  - Variability in Available Tests per Lab
  - *It’s much more than Drug-Gene Pairs*
  - Prescribers not schooled on PK/PGx/PD

*Widespread adoption of PGx depends on its successful integration into routine pharmacotherapy, through medication decision support tools*

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**Clinical Pharmacology & Therapeutics, June 2019 Vol 105 No 6**

To assist doctors and pharmacists, clinical decision support systems have been developed and incorporated into EHRs or computerized provider order entry. The help provided by these tools comes in the form of alerts that interrupt the workflow. These alert systems are sold by a variety of vendors and exhibit some inconsistencies or disagreements. In addition, doctors and pharmacists do not find the alerts useful for specific patients. Studies showed that healthcare providers exhibit “alert fatigue” and tend to dismiss and override the warnings, and no approaches have been found to decrease low-relevant alerts in a predictable and safe way. To address these problems,

*Past, Present, and Future of Drug-Drug Interactions*

Kerri M. Leo, *PharmD, BCPS, BCACP*”

Despite these significant advances, there is an urgent need to develop meaningful databases for doctors and pharmacists and to improve their education as well as that of patients and their families to decrease the prevalence and severity of DDIs in general clinical practice.
Clinical Pharmacology & Therapeutics, June 2019 Vol 105 No 6

Come Dance With Me: Transformative Changes in the Science and Practice of Drug-Drug Interactions
Karthik Verkasikerstam and Arni Rostami-Hodjeian

Medication Risk Score Distribution (N=24,251 Medicare Members)

From One Patient ... to Retrospective Risk Stratification Sample Analysis for Many Patients

Medication Risk Score Distribution (N=24,251 Medicare Members)

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Correlation Of Risk Score To Medical Costs 13.5 mln patients, Part D, 2016

Note: *Data represent a Medicare PDP population, raw data collected over ten months and annualized.

Results: CMS 5-yr Project: Enhanced Medication Therapy Management (EMTM) by Pharmacists

- 14.5 million people in these 7 states
- 4.8 million Blue Cross Plan patients
- 240,000 in Stand-alone Prescription Drug Plans
- 15% (~35,000) High Medication Risk Score
  - 15,000 Engaged in Year 1 (2017)
  - 28,000 Engaged in Year 2 (2018)
Results: CMS 5-yr Project: Enhanced Medication Therapy Management (EMTM) by Pharmacists

For the 15,000 High Medication Risk Score cohort which we engaged in 2017 we reduced their Medication Risk Score and...

- In August 2018 the CMS Actuaries -
- Reported that we saved $38 million ($2,500/pt) in our intervention group, which exceeded their expectation (i.e., >2%)
- In July 2019 CMS Actuaries announced that, again, we saved >2%
- This was due to reduction in physician visits and, mostly, reduction in hospitalizations.

Avg Total Yearly Cost Change Per Unit of MedWise Risk Score

Avg Cost by Part D risk score for MRS 0 to 30 for the entire eligible population - includes members w/ a medication safety review
- Total Part A and Part A&B cost (scale on right in $)
- Total Average A+B change is $683/unit of risk score

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MRS Delta Pre/Post Medication Safety Review for 1st MSR only...

If all recommendations were accepted the difference in avg risk score pre/post 1st Med Safety Review ranges from 1 point (@MRS<6) to 5 points (@MRS>25)

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Analytics re EMTM

- **Avg Cost**
  - There is a correlation between the *avg total cost* (sum of Part A and B claims) with *Part D Medication Risk Score*
  - The 12 month avg total Part A and B change is $683 / unit of risk score

- **Hospitalization rate (~200,000 pts, not touched by TRHC)**
  - There is a correlation between the *avg 12 month admission rate with Part D MedWise Risk Score*
    - @MRS=10 the admit rate is 26%
    - @MRS=20 the admit rate is 44%
    - @MRS=30 the admit rate is 64%

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Summary – the path toward pharmacists’ recognition as valuable contributors to patient care (and getting paid for it)

• Drugs with anti-cholinergic & sedative properties can affect cognitive & functional status considerably and lead to poor outcomes
• Co-administration of medications and, hence, competitive inhibition can significantly affect medication concentrations, have profound effects on medication response, and increase the risk of ADEs
• Long-QT Syndrome may lead to ventricular arrhythmias, such as Torsades de Pointes, which may be associated with sudden death
• Adverse events are common, and information can be learned from the FDA Adverse Events Reporting System
• Knowing a patient’s medication risk aids in personalizing a medication care plan

Opioid example as “prodrug” needs CYP2D6 for activation
Two Recent Studies - Inhibiting Opioid Conversion to Active Morphine Analog

**Study 1:** 74 year old median age:
1 of 2 patients have meds on board that inhibit opioid analgesic activation resulting in subsequent higher dosing of the opioid (study results depicted to the right)

**Study 2:** 46 year old median age:
1 of 4 patients in a separate study of a commercial population [50,000 patients] have meds on board that inhibit opioid analgesic activation, resulting in subsequent higher dosing of the opioid

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Think Concierge Pharmacist, with a fresh recurring revenue stream (not through PBMs)

- **Prospective/Concurrent**
  In your pharmacy, before filling a prescription.

- **Retrospective**
  With regional or national payers who are at-financial-risk for negative sequelae (like paying for hospitalizations) or in the nursing home construct

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Please go to MEET.PS/ADES to answer poll questions!
Waiting for the meeting to start
New Ways to Identify & Mitigate Adverse Drug Events and Get Paid for It - Handout

• List three new drugs or combinations that you were previously unaware increase a patient’s risk for adverse drug events, including the mechanism if you can.

• How can pharmacists mitigate adverse drug events in the community pharmacy setting?

• Community pharmacies can increase patient safety and revenue by _________________.

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Putting Science in Practice
A New Way for Pharmacists to Identify/Mitigate Adverse Drug Events and Get Paid for It

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