**Principles of Conservative Prescribing**

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**CURRENT CONFLICTS/ DISCLOSURES**

- Commercial -NONE
- Grant Funding:  
  - AHRQ - PROMISES Ambulatory Safety & Malpractice  
  - AHRQ CERT HIT–CEDAR (Adverse Drug Reaction detection); UIC Patient Safety CERT  
  - FDA - CPOE Evaluation CPOEMS  
  - Harvard Risk Management Fndn – Diagnosis Errors  
  - Commonwealth Fund –Medical Home Evaluation  
  - ONC –RAND- Clinical Decision Support  
  - NSPF- USP MedMarx CPOE Errors

**Outline**

- What is conservative prescribing
  - 24 Principles for more judicious, careful rational drug use

**DISCLOSURES**

Original FLIP Project Work Funded by  
Attorney Generals’ Consumer & Prescriber Education Program (Neurontin Settlement)  
Cook County Hospital- UIC College of Pharmacy Formulary Leveraged Improved Prescribing Project

Speaker conflicts resolved through peer review.
Outline

• What is conservative prescribing
  ....and dispensing, ...and counseling
  – 24 Principles for more judicious, careful rational drug use

Role for pharmacist, pharmacy in this new paradigm
  – Benefits for patients and pharmacist
  – New thinking and roles
U.S. Deaths from Vioxx
More than Vietnam War

- 1/1999–9/2004: 106.7 million rofecoxib prescriptions in US
  - 17.6% were high-dose, mostly to older patients
- In 2 Merck-sponsored randomized trials: 2.25 relative risks for AMI
  - 5x for high-dose rofecoxib and 2x for the standard dose
- Background rate AMI control NSAID users varied from 7.9 per
  1000 person-years in CLASS1 to 12.4 per 1000 person-years
  in TennCare.
- Using Merck studies relative risks w/ these background rates
  88,000–140,000 excess cases serious coronary disease in US
- Using US national case-fatality rate 44%, suggests thousands of
  deaths attributable to rofecoxib use (~38,000–61,000)

Graham Lancet 2005

Womens Health Initiative (WHI) Estrogen Rx

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Relative risk (95% CI)</th>
<th>Change in number of women per 10,000 women in one year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>1.26 (1.02–1.55)</td>
<td>8 more</td>
</tr>
<tr>
<td>Heart disease</td>
<td>1.29 (1.00–1.63)</td>
<td>7 more</td>
</tr>
<tr>
<td>Strokes</td>
<td>1.10 (1.02–1.18)</td>
<td>8 more</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>2.12 (1.35–3.28)</td>
<td>0 more</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>1.64 (1.15–2.32)</td>
<td>1 case</td>
</tr>
<tr>
<td>Hip fracture</td>
<td>1.34 (1.22–1.47)</td>
<td>3 more</td>
</tr>
</tbody>
</table>

NEJM 2007

The Decrease in Breast-Cancer Incidence in 2003 in the United States

Peter M. Pardini, Ph.D., M.D.; Kathleen A. Grimes, Ph.D.; Maria Holmberg, M.D.; Christine D. Stuk, M.D.; Susan T. Oshinock, M.D.; Ph.D.; Fratila, Ph.D.; Brenda K. Johnson, Ph.D.; and Donald L. Berry, Ph.D.

SPECIAL REPORT

Summary

An initial analysis of data from the National Cancer Institute’s Surveillance, Epidemiology, and End Results (SEER) registries shows that the incidence of breast cancer in women in the United States fell sharply by 4.7% in 2003, an unprecedented decrease in breast cancer by an average of about 0.8% per year, a decline that was similar across most age groups. The decrease, which was expected to continue, was observed in all major racial and ethnic groups and in all geographic regions. This unprecedented decline occurred in the absence of major policy changes or major advances in breast cancer screening or treatment. This finding has generated significant interest among researchers, clinicians, and policymakers, and has led to efforts to understand the underlying causes of this decline.
A. Think beyond drugs

- Consider, learn prescribe nondrug rx such as diet, exercise or physical therapy
- Look for and treat underlying causes rather than just masking symptoms with drugs
- Prevention rather than just treatment of advanced disease.

Thinking beyond drugs

1. Seek non-drug alternatives as a first rather than as a last resort.
Drugs: What else can you do

- Hypertension
- Pain
- Insomnia
- Anxiety
- Worry
- Arthritis
- Overweight
- Lipids
- CHF
- Asthma
- Headaches
- Fatigue
- Neuropathy
- Infections

Drugs: What else can you do?

- Diet modification
- Exercise
- Lifestyle changes
- Supportive counseling
- Smoking cessation
- Meditation
- Orthotics
- Physical therapy
- Accupuncture
- Relationships
- Allergen removal
- Surgery
- Topical Rx

Thinking beyond drugs

2. Consider potentially treatable underlying causes of problems rather than just treating the symptoms with a drug.

Diagnose rather than mask sx

- “Arthritis” pain --? statin related
  --? celiac sprue
  --? work-related trauma
- Impotence --? pituitary tumor
  --? drug related
  --? marital discord
- Allergies --? environmental causes
  (plant, pet, shampoo)

Thinking beyond drugs

3. Look for opportunities for prevention rather than focusing on treating symptoms or advanced disease.
B. More strategic prescribing

- Learn just a few drugs, learn well
- Defer drug treatment if drugs can be safely started after a trial of non-drug therapy
- Avoid frequent/unwarranted drug switching
- Be circumspect about unproven drug uses
- Whenever possible, start only 1 new drug

Practicing more strategic prescribing

- 4. Use the “test of time” as a diagnostic and therapeutic trial whenever possible
Deferring to later time

- Reassurance and open door w/ option to start rx later
- When is this just as efficacious?
  - Otitis media w/ effusion
  - Sinusitis—even bacterial
  - Back-pain
  - Selected cancers
  - Need for research

IDSA Clinical Practice Guideline for Acute Bacterial Rhinosinusitis in Children and Adults

Evidence-based guidelines for the diagnosis and initial management of suspected acute bacterial rhinosinusitis in adults and children were prepared by a multidisciplinary expert panel of the Infectious Diseases Society of America supported by clinicians and investigators representing internal medicine, pediatrics, emergency medicine, otolaryngology, public health, community medicine, and adult and pediatric otolaryngology. These guidelines were developed by the American Society for Microbiology, the Infectious Disease Society of America, and the American Academy of Otolaryngology. 

EXECUTIVE SUMMARY

- Management based on risk assessment for antibiotic

Practicing more strategic prescribing

5. Use only a few drugs and learn to use them well.

Learn a few drugs well

- Master dosing, adverse effects, interactions, even pill appearance prevents errors

Practicing more strategic prescribing

6. Avoid frequent or “impulse” switching of drugs without clear, compelling evidence-based reasons.
Practicing more strategic prescribing

7. Be skeptical about "individualizing" therapy

Claim that results only apply to "average" patient, not yours
Industry way to dismiss disappointing trials
Ad hoc empiric unscientific trials fraught with error and hazards
Yes, when drives precaution—Geriatric, liver disease, low literacy

Practicing more strategic prescribing

8. Whenever possible, start only one drug at a time.

Treat Everything at Once?

HBP
Headaches
UTI
Trichomonas
Dyspepsia
Onychomycosis

...all on 1st visit

C. Heightened vigilance for adverse effects:

How can you interpret adverse event?
Even if improves: which drug to attribute
Ignorance of drug-drug interactions (DDI)
Fixed drug combinations a problem here?

Suspect drug reactions when patients report problems
Educate patients about side effects so they can anticipate and report reactions
Be aware of drug withdrawal syndromes
**Vigilance w/ adverse effects**

- Have high index of suspicion for adverse drug effects

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**Suspect new & old drug reactions**

- No matter how weird or unlikely
- Consider possibility that unreported – Heroes – discovery of ADRs not just of new drugs

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**Table 1. Rates of Adverse Drug Events:**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Adverse Events</th>
<th>Event Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total adverse drug events</td>
<td>181</td>
<td>27.4</td>
</tr>
<tr>
<td>Severity</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatal or life-threatening</td>
<td>0</td>
<td>—</td>
</tr>
<tr>
<td>Serious</td>
<td>24 (13)</td>
<td>3.6</td>
</tr>
<tr>
<td>Significant</td>
<td>157 (87)</td>
<td>23.8</td>
</tr>
<tr>
<td>Preventability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ameliorable</td>
<td>54 (28)</td>
<td>7.7</td>
</tr>
<tr>
<td>Preventable</td>
<td>10 (3)</td>
<td>3.0</td>
</tr>
<tr>
<td>Not preventable</td>
<td>110 (61)</td>
<td>16.6</td>
</tr>
<tr>
<td>Serious and preventable or ameliorable</td>
<td>11 (6)</td>
<td>1.7</td>
</tr>
</tbody>
</table>

**Generic Questions – All Medications**

**SINCE STARTING THE MEDICATION HAVE YOU HAD ANY NEW OR WORSENING PROBLEMS WITH:**

- Stomach or intestinal problems?
- Nausea/vomiting
- Diarrhea
- Constipation
- Stomach pain
- Nausea
- Problems with memory or confusion?
- Memory problems
- Confusion
- Muscle aches?
- Skin rash?
- Dizziness or problems with balance?
- Frequent headaches?
- Problems with sexual function?
- Have you gained or lost more than 10 pounds?
Vigilance with adverse effects

- 10. Educate patients about possible adverse drug reactions to ensure they are recognized as early as possible.

Worry about drugs, not about warning patients

- MDs fail to discuss risks 65-91% of time
- Fears that would “scare off compliance” misguided and unfounded.
- Early recognition far outweighs risk of suggestion

Can MDS Warn of Potential Side Effects w/out Fear of Causing them?

- RCT discharge education for pts receiving scripts for ACE-I, NSAID, TMP/SMX
  - 2 intervention, 2 control firms U Wisc
- Interviewed by phone 14 days later
- No difference incidence targeted side effects between 2 groups (38% vs. 37%)

Lamb Arch Intern Med 1994

Vigilance with adverse effects

- 11. Be alert to clues that you may be treating withdrawal symptoms.
Rebound effect of withdrawing PPI from healthy volunteers

D. Caution/skepticism new drugs:

- Seek out, use unbiased info sources
- Wait until drugs have sufficient time on market to be proven to be safe
- Be skeptical about surrogate markers of benefit (such as improving a lab test)
- Avoid stretching indications to pt or diseases different than those in trials
- Avoid seduction by elegant molecular pharmacology w/out proven benefits
- Beware of trial selective reporting.

Skepticism towards new drugs

- 12. Learn about new drugs and new indications from trustworthy, unbiased sources, independent drug bulletins, and colleagues with reputations for integrity and conservative prescribing.
Prescrire’s ratings of new products and indications over the last 10 years

<table>
<thead>
<tr>
<th>Rating</th>
<th>#</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bravo</td>
<td>7</td>
<td>0.2%</td>
</tr>
<tr>
<td>A real advance</td>
<td>77</td>
<td>2.7%</td>
</tr>
<tr>
<td>Offers an advantage</td>
<td>217</td>
<td>7.6%</td>
</tr>
<tr>
<td>Possibly helpful</td>
<td>455</td>
<td>15.8%</td>
</tr>
<tr>
<td>Nothing new</td>
<td>1,913</td>
<td>66.6%</td>
</tr>
<tr>
<td>Not acceptable</td>
<td>80</td>
<td>2.8%</td>
</tr>
<tr>
<td>Judgment reserved</td>
<td>122</td>
<td>4.2%</td>
</tr>
<tr>
<td>Total</td>
<td>2,871</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Timming of New Black Box Warnings and Withdrawals for Prescription Medications**

**Skepticism towards new drugs**

13. Even if seemingly safer or more effective for a particular indication, don’t be in a rush to use new drugs.

14. Be certain the drug actually improves patient-centered clinical outcomes, rather than just treating or masking a “surrogate marker.”
**Surrogate Endpoints**

- Blood pressure
- HbA1C
- Serum Glucose
- Serum cholesterol
- HDL
- Hemoglobin
- PVC’s
- Cardiac output
- Serum Sodium
- CD4 count
- HIV Viral Load
- FEV1
- Albuminuria
- Tumor markers
- Tumor size
- Composites

**Clinically Relevant Endpoints**

- Mortality or survival benefit
- Clinically important change experienced directly by the patient
  - Reduced pain
  - Improved functional status
  - Improved quality of life

**CAST**
Suppression PVCs increased risk of sudden death

**CONCORDE**
Improving CD4 w/ AZT did not improve HIV pts’ survival

**CHOIR and CREATE**
Higher Hb levels w/ erythropoietin worsened dialysis pts outcomes

**ENHANCE**
Vytorin combination more effective in lowering lipids but no clinical benefit

**ACCORD**
More intensive A1C lowering worsened outcomes in type 2 DM; Increased risk death overall and CV

**ADVANCE**
Tighter control did not reduce cardiovascular events

**VADT**
No significant decrease CV events with tighter glucose control over 7.5 yrs

**NICE-SUGAR**
Intense glucose control increased mortality in adult ICU patients.
Current FDA issues with Regulation of Surrogate Endpoints

- **Cancer Drugs: Objective Response Rate (ORR)**

- **Accelerated approval** (1992)
  - Formal acceptance of surrogates
  - Endpoints "reasonably likely to predict clinical benefit"
  - Early marketing approval contingent upon post-marketing studies confirming clinical benefit

Table 1. Hypoglycemic Episodes and Intensive Therapy

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<th>Variable</th>
<th>Standard Therapy (N=895)</th>
<th>Intensive Therapy (N=897)</th>
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<tbody>
<tr>
<td>Epileptic visits with impaired consciousness</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>Epileptic visits with complete loss of consciousness</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Nuchal rigidity</td>
<td>44</td>
<td>152</td>
</tr>
<tr>
<td>Total episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>With symptoms</td>
<td>383</td>
<td>1338</td>
</tr>
<tr>
<td>Without symptoms</td>
<td>49</td>
<td>233</td>
</tr>
<tr>
<td>Relieved by food or sugar intake</td>
<td>421</td>
<td>1536</td>
</tr>
<tr>
<td>Measurement of blood glucose during episode</td>
<td>368</td>
<td>1382</td>
</tr>
<tr>
<td>With documented blood glucose &lt;50 mg/dl (2.8 mmol/L)</td>
<td>52</td>
<td>203</td>
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P<0.001 for all differences between the two groups.

Table 2. ACRIN Study

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**Surrogate Endpoints And FDA's Accelerated Approval Process**

The challenges are greater than they seem.

By Thomas R. Flemint

ABSTRACT: There is interest in approaches allowing more rapid availability of new interventions, particularly for diseases presenting risks of death or serious illness. The accelerated approval regulatory process is intended to address this need by allowing marketing of interventions shown in Phase III trials to predict overall survival or other important clinical benefit. The surrogates endpoints and the accelerated approval process. Challenges issues must be addressed to avoid compromising what is truly in the best interest of public health, the reliability as well as timely evaluation of new intervention's safety and efficacy.
Skepticism towards new drugs

15. Be vigilant about “indications creep.”

• Creeping Indications
  Creeping Populations
  
  • What is precise population studied and therapeutic niche
  • Not just triptans for headaches, neurontin for pain
  • When should these drugs be used

• Skepticism towards new drugs

16. Do not be seduced by elegant molecular pharmacology or drug physiology.

• Designer drugs
  
  • Allopurinol – 1st designer drug. No side effects since natural purine analogue
Skepticism towards new drugs

17. Beware of selective reporting of studies.

E. Work w/pts for shared agenda

- Do not automatically accede to requests for drugs pt heard advertised
- Consider non adherence before adding rx
- Avoid restarting previously unsuccessful drugs
- Discontinue meds not needed; not working
- Respect pt' own reservations about drugs
Work w/patient for a shared agenda

• 18. Do not hastily or uncritically succumb to patient requests for drugs, especially drugs they have heard advertised.

\[\text{Drugs don't work in patients who don't take them. — C. Everett Koop, M.D.}\]

Work w/patient for a shared agenda

• 19. Avoid mistakenly prescribing additional drugs for “refractory” problems, failing to appreciate the potential for patient nonadherence.

Importance of Therapy Intensification and Medication Nonadherence for Blood Pressure Control in Patients With Coronary Disease

\[\text{Background: Despite the importance of blood pressure control (BP) in coronary patients, persistent poor adherence is a major challenge. Several studies have found that medication adherence is an important predictor of BP control, independent of medication used. The objective of this study was to assess the association between medication adherence and BP control in patients with coronary disease.}\]

\[\text{Methods: We retrospectively analyzed data from a national database of patients with coronary disease, including 3,000 patients with BP control. The main outcome was BP control, defined as a systolic BP of <140 mm Hg and diastolic BP of <90 mm Hg. The main predictor was medication adherence, measured by the Proportion of Days Covered (PDC).}\]

\[\text{Results: Patients with PDC > 0.80 had significantly lower BP compared with those with PDC < 0.80 (p < 0.001). In adjusted analyses, the association between adherence and BP control remained significant (odds ratio, 1.5; confidence interval, 1.2-1.8). The results were consistent across subgroups defined by age, sex, and coronary disease type.}\]

\[\text{Conclusion: Medication adherence is an important determinant of BP control in patients with coronary disease.}\]

Work w/patient for a shared agenda

• 20. Avoid (either knowingly, or unknowingly because of lack of complete drug history) repeating prescriptions for drugs a patient has previously tried unsuccessfully or had an adverse reaction.

[Graph: Medication adherence and therapy intensification across the 3 BP control groups (PDC indicates proportion of days covered). Ho Arch Int Med 2008]
Work w/patient for a shared agenda

- 21. Discontinue drugs that are not working or no longer needed.

Geriatrics - the art of taking older adults off drugs they no longer need

Shaughnessy - Am Fam Physician 2007

Work w/patient for a shared agenda

- 22. Work with patients’ desires to be conservative with medications

F. Consider long-term, broader impacts

- Weigh not just short term benefits but also long-term pt outcomes & ecologic impacts
- Recognize improved prescribing systems and better monitoring may outweigh marginal benefits of new drugs.

Consider longer-term, broader impacts

- 23. Think beyond short term drug effects, which may be beneficial, but also consider longer term benefits and risks.
Long Term Efficacy?

• Anti-fungals
• Obesity drugs
• 1st generation anti-psychotics
• DES
• Ecology of drugs in water supply

Consider longer-term, broader impacts

• 24. Look for opportunities to improve local prescribing systems, changes that can make prescribing and medication use safer.

Hey, we’re just in the middle here
Don’t blame or preach to pharmacists

What can we do anyway?
1. Help patient articulate their (often legitimate) concerns and to be a sounding board – Hear out patient
2. Help delineate options/alternatives to better understand their diseases, choices, options - Not practicing medicine, but legitimate pharmacy patient education role
3. Help pts define questions they want to ask MD. – empowering patients who have questions
4. More serious cases, obligation to posing questions to doctor directly - known allergy, overdose, but also selected cases of drug selection.
  ❖ Takes courage, diplomacy: how to define, achieve this ideal

“The pharmacist is the single most underused resource in the modern hospital

Lucian L. Leape, MD Harvard School of Public Health. ACP Observer 3/2000
More (business) is Better? …or Less is More (business)

- Realign pharmacists incentives, thinking
- More drugs – more wasted inventory
  - Recalls, shelf space, expired drugs
- Knowledge, familiarity w/ essential drugs
  - ↓ errors, anticipate problems, less to learn/recall
- Patient trust - not just pushing or filling drugs
  - Long term relationships better model
- New drugs, less faith, more evidence

What’s in it for us?

Conservative Prescribing = Liberation for Pharmacists

- Lack of Conservative Prescribing has led to various dyfunctionalities undermining quality of work of life of pharmacists.
- Hassles and calls to Doctors
  - Symptoms/consequences of Cons Rx Failure
    - “Prior auth”
    - “Not covered”
    - “Tier 3”
    - “Non preferred brand”
    - “Switches”

Conclusions

- From “newer is better” to “fewer and more time-tested is best” to achieve better balance
- Need for new paradigm and role for pharmacy: overcoming complacency and understanding and advocating best rx for patients, and questioning where not
- We need to figure out how to operationalize this together……starting now!