Polypharmacy:
A Rational Evidence-informed Approach with a Touch of Common Sense

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therapeuticseducation.org
mystudies.org
@medmyths

Get handout here - https://therapeuticseducation.org/handouts
WHY!!
We all need to do a better job when it comes to medications
POLYPHARMACY
does NOT= >5 meds

It means taking medications/supplements which are not providing a complete or clinically important effect or are given at doses larger than is required to achieve that effect

For symptoms

For prevention

if one was fully informed by the best available evidence about benefits and harms one would not take them
BOTH COULD BE POLYPHARMACY
MY BELIEF

All Health Care Providers should have their practice underpinned by the best available evidence

Evidence-Based Practice (EBP)
WHAT IT IS
IT'S A WAY OF THINKING

EVIDENCE-BASED PRACTICE
BEST AVAILABLE EVIDENCE
USED IN A HIERARCHICAL WAY TO
ANSWER CLINICAL QUESTIONS

Patient
Intervention
Comparator
Outcome

BEST AVAILABLE EVIDENCE PYRAMID

Systematic review/meta-analysis
RCT
Cohort
Case Control
Case Report
“Expert” Opinion

USING CLINICAL EXPERTISE

Diagnostician
Knowledge Broker
Communicator
Being Kind & Careful

INFORMING PATIENTS & ELICITING & INTEGRATING PREFERENCES
Combine Evidence with Common Sense

SHHH. MY COMMON SENSE IS TINGLING.

Common Sense
“So rare that it’s a superpower”
Three Approaches

Dose issues
Symptom issues
Prevention issues
This simple concept can eliminate most medication problems

USE VERY LOW DOSES
The doses in these books are all “WRONG” for individual patients.
Everyone is a genetic mongrel
It’s a dose thing

“more than 80% of ADRs causing admission or occurring in hospital ... are dose related, an ‘accentuation’ of the known pharmacological effect of the drug, and thus predictable and potentially avoidable”

"Unless the condition is severe or life-threatening, drug treatment can be started at a very low dose (half or one-quarter the recommended starting dose)"


Most of the effect of a medication comes from the "low" starting doses AND doubling a dose never doubles the effect - in fact it sometimes has no additional effect
# A sample of Low-Dose RCT Evidence

<table>
<thead>
<tr>
<th>Medication</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.25 mg hydrochlorothiazide</td>
<td>first marketed at 50 to 200 mg daily</td>
</tr>
<tr>
<td>6.25 mg captopril</td>
<td>25 mg PO TID is still a commonly recommended initial starting dose for hypertension</td>
</tr>
<tr>
<td>25 mg sildenafil (Viagra)</td>
<td>effective dose for erectile dysfunction</td>
</tr>
<tr>
<td>25 mg sumatriptan (Imitrex)</td>
<td>works as well as 100 mg</td>
</tr>
<tr>
<td>5 mg daily fluoxetine (Prozac)</td>
<td>similar effects to those seen at 20 mg and 40 mg daily</td>
</tr>
<tr>
<td>0.25 mg ezetimibe (Ezetrol)</td>
<td>1/40th of the recommended initial starting dose provides 50% of the LDL lowering effect</td>
</tr>
<tr>
<td>15 mg elemental iron daily</td>
<td>as effective for anemia in elderly as 50 mg and 150 mg with a lower incidence of side effects</td>
</tr>
<tr>
<td>150 mg daily bupropion (Zyban)</td>
<td>produces the same rate of smoking cessation at one year as 300 mg daily (1.0 mg BID)</td>
</tr>
<tr>
<td>0.5 mg BID varenicline (Champix)</td>
<td></td>
</tr>
<tr>
<td>10 mg atorvastatin</td>
<td>produces 2/3 of the effect on cholesterol as that seen with an 80 mg (8-fold increase) dose</td>
</tr>
<tr>
<td>200 mg ibuprofen (Motrin)</td>
<td>as effective as 400 mg for migraine headache</td>
</tr>
<tr>
<td>25 mg ranitidine (Zantac)</td>
<td>as effective as 125 mg for heartburn relief</td>
</tr>
<tr>
<td>1.8 mg colchicine</td>
<td>as effective as 4.8 mg for acute gout with less adverse events</td>
</tr>
</tbody>
</table>
Doxepin (Sinequan)

Depression - start 25-50 mg - optimal 75mg - 150mg up to 300mg

“The results support the effectiveness of low doses (25-50 mg) of doxepin to improve sleep”


Sleep 2007; 30: 1555–61

All three doses worked better than placebo
AND
NO side effects over placebo

A recommended low dose was still 25-50 times TOO HIGH
Approaches differ depending on outcome

Every patient is an experiment - dose and effect

SYMPTOMS - we can usually figure out if it is working - but it is tricky

PREVENTION - one will never know if it worked

Expectations
Symptoms
You primarily need to know IF it works and DID it work

Safety, cost and convenience

Older medications first - safety

Head-to-head studies are uncommon

Doses in the CPS are “wrong”

N-of-1 studies

Let the patient tell you
Symptom NNTs

PPIs, sildenafil - NNT ~2
NSAIDs, opioids - pain NNT ~3-5
Antidepressants - severe depression - NNT ~10
Ipratropium - asthma attack - NNT ~11
Cholinesterase inhibitors - ADAS-Cog >4 - NNT ~10
Sleeping pills - improvement in sleep quality - NNT ~13
Steroids - sore throat - NNT ~3, Bell’s palsy - NNT ~10
Antibiotics - acute COPD exacerbation - NNT ~5
Topical antibiotics - bacterial conjunctivitis - NNT ~7
But you need to know what goes on in the placebo group

<table>
<thead>
<tr>
<th>Response in the placebo group</th>
<th>If a person has responded, what is the % chance it was the medication</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RCT Benefit 10% - NNT 10</td>
</tr>
<tr>
<td></td>
<td>RCT Benefit 20% - NNT 5</td>
</tr>
<tr>
<td>0%</td>
<td>~100%</td>
</tr>
<tr>
<td>10%</td>
<td>~50%</td>
</tr>
<tr>
<td>20%</td>
<td>~33%</td>
</tr>
<tr>
<td>30%</td>
<td>~25%</td>
</tr>
<tr>
<td>40%</td>
<td>~20%</td>
</tr>
</tbody>
</table>

~100%  | ~66%  | ~50%  | ~40%  | ~33%  |
The Placebo Group Effect

not the placebo effect and these are ballpark numbers

~0% - general anesthesia
~5% - psychosis
~10% - sildenafil, OCD
~20% - Alzheimer’s meds, acetaminophen for headaches, side effects
~25% - menopausal symptoms, migraine (frequency/severity)
~30% - blood pressure goal, depression, anxiety, PTSD, PPIs/H2RA, sore throat, NSAIDs of OA, inhalers for COPD
~40% - panic disorders
When a medication has “worked”, if you were a betting person you would bet that it probably wasn't because the medication worked.
Cut tablets/the dose in half

It's not as scary as you think

...or is it?
Tapering Antidepressants

Taper - approximately 25% will have a recurrence of depression over 18 months

Leave them on - approximately 10% will have a recurrence of depression

15% will be “harmed” and 85% will “benefit” because they are on medications apparently unnecessarily
“Rebound” after PPI withdrawal in healthy people

120 healthy volunteers
12 weeks of placebo or
8 weeks of esomeprazole 40 mg daily and then 4 weeks of placebo

Reporting dyspepsia, heartburn or acid regurg during weeks 9-12
Placebo ~ 5%
PPI ~ 20%

Gastroenterology 2009;137:80-7
PPI withdrawal in asymptomatic GERD patients

71 patients - tried to titrate dose down over 3-6 months
42% still on PPI - median reinstitution time 14 days
34% ended up on H2RA
7% on prokinetic agent
1% on both
16% no-drugs

223 patients on lansoprazole 30mg BID
50% ended up on rabeprazole 20mg daily
10% off all drugs

56% with erosive esophagitis failed
31% of those with endoscopic-negative failed

Gastroenterology 2001;121:1095–1100
Aliment Pharmacol Ther 2007;25:709–711
Clinical Question: In elderly patients, what are the risks and benefits of stopping long-term antipsychotics (initiated for behavioral concerns)?

Bottom-line: In elderly patients on long-term antipsychotics, withdrawal of antipsychotics in four patients may prevent one death at two years. After discontinuation, neuropsychiatric symptoms appear to vary little, although one study suggests stopping after four months can cause one in four more patients to have a relapse of neuropsychiatric symptoms.

Withdrawal of antipsychotics - for every 4 people, you prevent 1 death and 1 study suggests that 1 in 4 will have a relapse of neuropsychiatric symptoms

Antipsychotics also worsen cognition
Donepezil withdrawal

- 295 Community dwelling patients on donepezil (most >2 yrs)
  - mean age 77, mean MMSE 9, followed 1 yr.
  - Stopping of med worsened MSE by 1.9 pts
    - Less effect (1.3) if severe dementia (<9 MSE)
    - Don’t give number attaining MCID (1.4)
  - Withdrawal from study more if stopped!
  - Death: no difference

MedStopper is a deprescribing resource for healthcare professionals and their patients.

1. Frail elderly? ☐

2. Generic or Brand Name: hydro

3. Select Condition Treated: hydrochlorothiazide

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Brand Name</th>
<th>Condition Treated</th>
<th>Add to MedStopper</th>
</tr>
</thead>
<tbody>
<tr>
<td>hydrochlorothiazide</td>
<td>Microzide</td>
<td>Blood pressure</td>
<td>☑</td>
</tr>
<tr>
<td>hydrocortisone</td>
<td>Solu-Cortef</td>
<td>Select Condition</td>
<td>☐</td>
</tr>
<tr>
<td>hydrocortisone</td>
<td>Prelone</td>
<td>Select Condition</td>
<td>☑</td>
</tr>
</tbody>
</table>

MedStopper Plan

- Arrange medications by: Stopping Priority
--clear all medications
- print plan

- Suggested taper approach
- Possible symptoms when stopping or tapering
- Beers/Stopp Criteria

- Details

- return of gastrointestinal symptoms (nausea, diarrhea, abdominal pain)
- return of hypothyroid symptoms (weakness, weight gain, hair loss)
- return of gastrointestinal symptoms (nausea, diarrhea, abdominal pain)
- abdominal pain, heart rate, blood pressure (re-measure for up to 6 months)
Symptom meds
PPIs, NSAIDs etc

Typically one should reduce the dose “slowly” - cut the dose in half or do something similar - change interval.

The dose likely wasn’t right in the first place.

Put the onus on, and give the power to, the patient to find the right dose.
Prevention
“Unfortunately, depending on how their reliability is measured, up to 50% of guidelines can be considered untrustworthy. This carries serious consequences for patients’ safety, resource use and health economics burden.”
Factors involved in deciding to start preventive treatment: qualitative study of clinicians’ and lay people’s attitudes

David K Lewis, Jude Robinson, Ewan Wilkinson

Qualitative study using semi-structured interviews

“Many of the preferences expressed by the clinicians and lay people in this study are at odds with recommendations in guidelines”
Calculate ballpark 10-yr risk of CVD - BP, chol, diabetes
Make estimate of benefit based on the best available evidence
Gives a list of adverse effects to discuss
Calculate ballpark annual risk of stroke - based on risk factors - BP, chol, diabetes
Make estimate of benefit based on the best available evidence - all agents
Make estimate of a GI bleed
Optimal management of elderly pts with vascular disease (DEBATE)

RCT, f/u 3.4 years 400 patients - avg age 80, all CVD
Usual care (primary care) or specialized care
“Evidence-Based” European CPG for chronic CVD

“it was possible and safe to institute evidence-based cardiovascular treatments and improve risk factors in patients 75 years or older in a pragmatic setting.”

Am Heart J 2006;152:585-92
Outcome

Systolic BP: 7.8 mmHg lower
Diastolic BP: 3.9 mmHg lower
Glucose: 0.55 mmol/L lower
Cholesterol: 0.78 mmol/L lower
LDL: 0.73 mmol/L lower (45% to target)
MEDS: ACE (+30%) & statin (+50%)

PREDICTED BENEFIT
UKPDS risk engine
18% CVD risk reduced to 14%
NNT = 25

ACTUAL BENEFIT - NONE
IN BOTH GROUPS
Mortality 18%
Stroke 6%
MI/coronary death 16%

NNT = infinite
Treatment of Hypertension in Patients 80 Years of Age or Older

Patients

3,845 patients with a SBP > 160 mm Hg, TC 5.3 mmol/L, 12% history of CVD, 60% were female, average age was 83, BMI 25

Treatment

Indapamide (1.25 mg) - then indapamide plus perindopril (2 or 4mg) or placebo daily

Duration

Followed for 1.8 years

Results

BP differences at the end (15/6 mm Hg lower) - 74% on both drugs

## BP elderly results

<table>
<thead>
<tr>
<th></th>
<th>Fatal or non-fatal stroke (%)</th>
<th>Serious adverse event (%)</th>
<th>Overall mortality (%)</th>
<th>MI (%)</th>
<th>Any cardiovascular event (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>3.6</td>
<td>23.4</td>
<td>12.3</td>
<td>0.5</td>
<td>10</td>
</tr>
<tr>
<td>Inda/perin</td>
<td>2.9</td>
<td>18.5</td>
<td>10.1</td>
<td>0.6</td>
<td>7.1</td>
</tr>
</tbody>
</table>

### Relative risk reduction

<table>
<thead>
<tr>
<th></th>
<th>21</th>
<th>18</th>
<th>29</th>
</tr>
</thead>
</table>

### Absolute risk reduction

<table>
<thead>
<tr>
<th></th>
<th>P=0.06</th>
<th>4.9</th>
<th>2.2</th>
<th>NSS</th>
<th>2.9</th>
</tr>
</thead>
</table>

### Number needed to treat

<table>
<thead>
<tr>
<th></th>
<th>20</th>
<th>45</th>
<th>35</th>
</tr>
</thead>
</table>

No mention of adverse effects
# All the TARGET dose evidence

<table>
<thead>
<tr>
<th>Drug</th>
<th>High/low dose</th>
<th>Duration (years)</th>
<th>Absolute Benefits</th>
<th>Absolute Harms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enalapril</td>
<td>4x</td>
<td>0.5</td>
<td>None</td>
<td>8%</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>7-15x</td>
<td>4</td>
<td>4/6%</td>
<td>3/7%</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>4x</td>
<td>0.5</td>
<td>None</td>
<td>10%</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>8x</td>
<td>4</td>
<td>None</td>
<td>20%</td>
</tr>
<tr>
<td>Losartan</td>
<td>3x</td>
<td>5</td>
<td>3%</td>
<td>3/7%</td>
</tr>
</tbody>
</table>

Benefits - primarily hospitalizations
Harms - hypotension, withdrawal, dose reduction
Titration to target dose of bisoprolol vs. carvedilol in elderly patients with heart failure: the CIBIS-ELD trial

883 heart failure patients - age - 73

66% class II, 29% class III

Randomised to bisoprolol (10 mg daily) or carvedilol (25 mg BID) and slowly up-titrated patients to the “RECOMMENDED” doses

<table>
<thead>
<tr>
<th>Fraction of dose</th>
<th>0</th>
<th>1/8</th>
<th>1/4</th>
<th>1/2</th>
<th>FULL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients on dose at end/12 weeks</td>
<td>10%</td>
<td>10%</td>
<td>25%</td>
<td>25%</td>
<td>30%</td>
</tr>
</tbody>
</table>

Eur J Heart Fail 2011;13:670-80
Prevention medications do NOT make you feel better

primary prevention
  1-2% benefit over 5 years - 98-99% do not

secondary prevention
  5-10% benefit over 5 years - 90-95% do not

lab tests
false positives
witch hunt
evidence plus patient values - 1/3 not adherent
Risk reduction meds

ASA, statins - you can just stop them
Fibrates - please just stop them
Blood pressure and diabetes drugs?

dosage should be reduced by 50%, with reassessment of blood pressure at 2 weeks

if the patient is still normotensive, reduce the dosage by another 50% (i.e., to 25% of the initial dose) and recheck the blood pressure in another 2 weeks
Use ‘tricks’ to get patient interest

THEIR ARGUMENTS

I’ve taken these for years and now you are telling me I don’t need them

But these are for my heart!!

It’s OK, I don’t pay for my medications

But my “specialist” says I need these

“If it isn’t broken then don’t fix it”
YOUR ARGUMENTS

Well your renal function/hepatic function are decreased

Look what you’ve been able to do for yourself

You take control and figure out the dose - you teach me what works

Your specialist doesn’t know you like I do

We can always restart if we need to
KEEP CALM BECAUSE LESS IS MORE

KEEP CALM AND USE VERY LOW DOSES

KEEP CALM AND TAPER ON
KEEP CALM AND DO THE RIGHT THING