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THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

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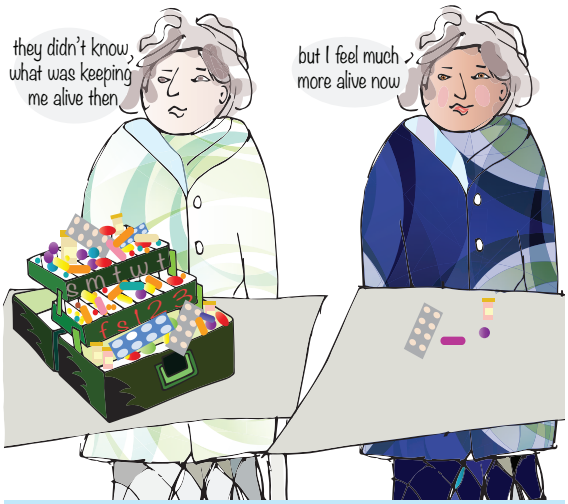
Reducing polypharmacy
A logical approach

Polypharmacy is the use of multiple medications by a patient. It is rapidly increasing in affluent populations worldwide, posing an increasing challenge for patients, their families and care providers.[1,2] From 1998-2008, Canadian seniors taking more than 5 prescription drugs doubled from 13% to 27-30%.[3-5] A patient taking more than 10 drugs was once an anomaly. Now this applies to 4% of British Columbians age 85 or older and 31% take at least 5 drugs. Percentages are much higher in long term care. See graphs at our website.

British Columbia has the lowest per capita drug costs in Canada, 27% below the national average, due in part to lower polypharmacy.[6] The difference was estimated to be about $341 million/year in 2013. However, current data suggest that there is ample room to improve.[7,8]

Exuberant prescribing is driven partly by population aging, but also by agressive marketing and application of chronic disease management guidelines that do not account for the complexities of multi-morbidity.[9] This affects costs, can worsen health status and often is not genuinely evidence-based.[10-14] Randomized controlled trials (RCT) mostly study idealized populations and can not reliably detect less common or long term harms, thus underestimating adverse effects of drugs.[15] Potential serious or even life-threatening adverse drug reactions (ADR) are not always considered in routine prescribing. ADR increase with age and the number of prescribed drugs. Even in the Emergency Department, many are not identified [16,17] and feedback to the prescriber(s) may be ineffectual. Complex medication regimes make it more difficult to prevent acute ADR, assess potential drug interactions, and to recognize chronic but subtle drug toxicity even during professional encounters, let alone for the patient at home.

Some advocate multidisciplinary team approaches or even hospitalization to address this challenge.[18,19] A Cochrane review of formal interventions in care homes did not find evidence for real world benefit [20], whereas another in people > 65 concluded that at least "inappropriate prescribing" and ADR can be reduced. [21] Using a simple approach based on a formal algorithm, an experienced Israeli geriatrician achieved a 58% reduction in polypharmacy in very elderly people, a mean reduction of 4.4 drugs per patient.[22] A similar approach has also been advocated in Australia.[23]



Rational prescribing requires restraint and wisdom in initiating chronic drug therapy, but also fundamental change in our philosophy of medicinal care. Complex medication regimes should be challenged routinely, and simplification welcomed when it can improve health. This Letter describes 7 steps that doctors, pharmacists, nurses, patients and their families can employ to become adept at "deprescribing".

1. Re-evaluate the goals of therapy

"Guideline-based medicine" drives much modern prescribing, but is often based on surrogate outcomes (e.g. A1C, bone density, blood pressure).[24] This may relate poorly or not at all to patient values and aspirations. For example, when quality of life clearly trumps longevity, using drugs intended to prevent death can be irrational. Conversely, when survival is paramount, drugs that increase mortality are inappropriate (e.g. antipsychotics in elderly people with dementia). A good starting point is to re-evaluate the goals of therapy.

Symptomatic treatments should meet a test of common sense: do this medicine's benefits meaningfully outweigh its harms? Drugs which slightly reduce symptom scores in a population are only worthwhile to the individual if their effect improves the quality of that person's life. If this cannot be demonstrated by a short therapeutic trial, there is no point in persisting.[25-27] Since all drugs cause significant problems for some people, especially frail elders, symptomatic benefits should clearly outweigh the associated harms.

Preventive treatments also warrant reappraisal. In the face of multiple or serious degenerative conditions expected to reduce longevity, are long term preventive strategies still relevant?[28]

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Diminished quality of life, serious adverse effects, or higher costs may outweigh the low probability of benefit. Preventive goals should always be explained and make sense to the individual patient or a substitute decision-maker.[29]

2. Apply absolute risk differences

Most drug treatments have modest benefits, estimated from RCT in populations that may not represent typical patients. Construing evidence realistically in terms of absolute risk reduction/increase (ARR/ARI) and numbers needed to treat for benefit/harm/net benefit (NNT/NNH/NNTB) can reduce clinician or patient anxiety about deprescribing. For prevention most NNT are large: > 10 to > several hundred over a period of years. With rare exceptions (e.g. initial combined antiplatelet therapy for drug-eluting stents), a decision to stop drug treatment is therefore unlikely to worsen outcome over the short term.

Relatively large NNT also apply to many symptomatic therapies (e.g. for pain or depression), such that only a small minority of patients can be expected to benefit.[30-32] Understanding this can encourage reassessment of long term therapy that may be futile, if not harmful.

3. Consider simple pharmacology and physiology

For **symptomatic** therapy (e.g. analgesics, bronchodilators, psychotropic drugs) dose-response relationships are often weak.[33] Understanding this can make it as reasonable to reduce a drug dose as it was to increase it. If symptoms do not worsen, common sense suggests further reduction or discontinuation. For **prevention** too, evidence of a dose-response is often lacking.[34] A lower-dose strategy can reduce harms from treatment along with costs.

Complexity inevitably increases the chance of harmful drug interactions. Most drugs undergo hepatic metabolism, raising the potential for pharmacokinetic as well as physiological interactions.[35] Blood concentration of molecules excreted unchanged by the kidney (e.g. lithium, gabapentin, pregabalin, digoxin) can rise dramatically as the glomerular filtration rate (GFR) drops, producing toxicity in a previously tolerant patient. Appreciating this makes "pruning" a medication list inherently sensible.

Product monographs are rich and easily searchable sources of information for adverse effects and elimination half-lives.[36] Knowing T½ can make it less intimidating to taper drugs rapidly, or stop them, with follow-up. For drugs taken once daily such as amlodipine (mean T½ 35-50 h), lithium, tricyclic antidepressants and cyclobenzaprine (T½ about 24 h), or fluoxetine (T½ 4-16 days for drug/active metabolite) symptomatic withdrawal is unlikely within the first 24-48 hours. Ultra-long acting drugs like thyroxine (T½ about 1 week), amiodarone (T½ about 8 weeks), or digoxin with reduced GFR (T½ > 2 days) do not typically require tapering. In type 2 diabetes, suspending hypoglycemic drugs will rarely lead to a crisis in an informed, alert patient. In contrast, drugs that induce tolerance or dependence (e.g. psychoactive drugs, corticosteroids, beta blockers) may require tapering for safety.

4. Avoid unnecessary drug costs

It can be professionally satisfying to relieve people of cost burdens that are pointless, wasteful, or even directly harmful to their health. Even when drugs are "free" to the patient, their cost is born by society and resources consumed for medicines are not available for other useful purposes. Some patients assume that all prescriptions are warranted, and will not spontaneously question their necessity. When evaluating complex polypharmacy, a focus on the most expensive drugs can lend clarity and purpose to a time-limited clinical encounter when it is not obvious where to begin.

5. Reassess the ongoing value of individual and combination drugs

Some drugs never approved for chronic use nevertheless "stick" to patients like an unwanted acquaintance, even in the absence of pharmacological dependence. The vast majority have never been studied long term. For example phenytoin started after an isolated seizure, or anticoagulants after a single episode of paroxysmal atrial fibrillation can acquire a life of their own because the associated diagnoses command fear. Proton pump inhibitors initiated for control of acid reflux or after a GI bleed should not be continued indefinitely without purpose. Some combinations may add harm without benefit.[37] From antihypertensives to psychotropics, drugs previously considered necessary can be discontinued safely.[18,38]

6. Use common sense and the Golden Rule

Considering whether one or more drugs make common sense can be integrated with the question: **"Would I take this drug under these circumstances?"** For example, does the small potential benefit of a bisphosphonate or statin in a frail elderly person with dementia warrant any likely harms? When savings on drug costs also allow a higher quality of life, the answer may become obvious.

7. Aim to stop at least 1 drug and monitor

This is a reasonable goal for each clinical encounter with polypharmacy. Avoiding new and stopping old prescriptions are the only means to reduce polypharmacy, so a commitment to change is a precondition to success. Experienced clinicians know this is often a happy way to end a consultation both for the patient and the professional.

References and graphs at: **www.ti.ubc.ca/letter90**

The draft of this Therapeutics Letter was submitted for review to 90 experts and primary care physicians in order to correct any inaccuracies and to ensure that the information is concise and relevant to clinicians.

The next TI Best Evidence course is at Surrey Memorial Hospital on Nov. 1, 2014. See: **ti.ubc.ca/BestEvidence**

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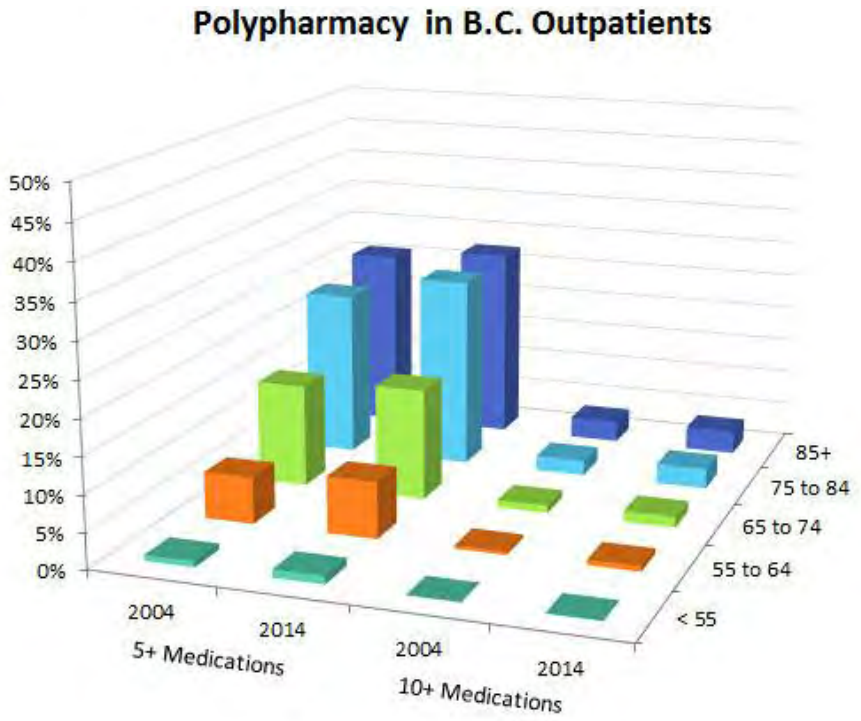
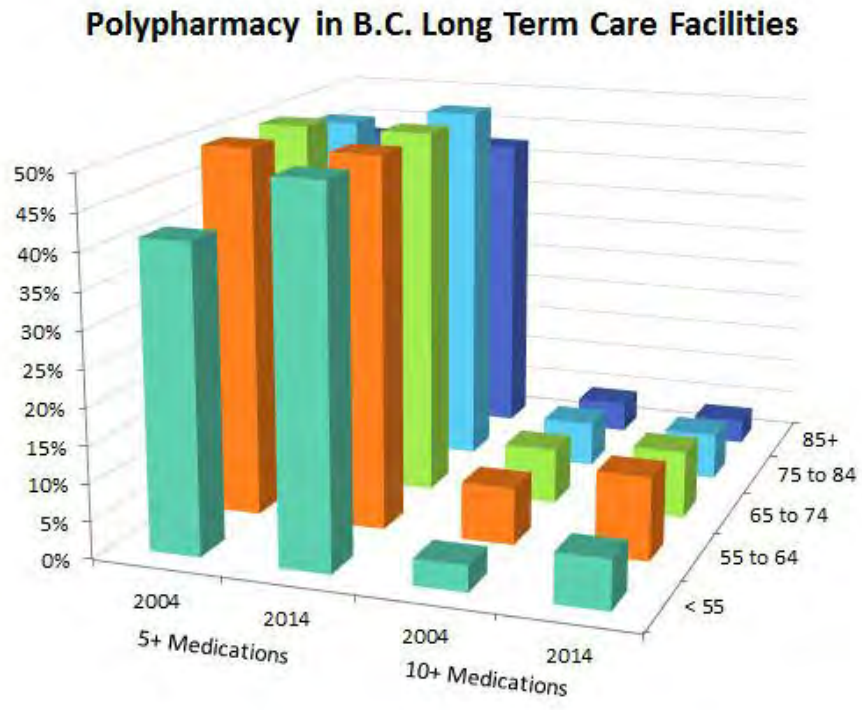
Graphs





ASSUMPTIONS USED TO GENERATE GRAPHS FROM PHARMACARE DATA

1) Polypharmacy is calculated at July 1st of each year and uses the service date and number of days supply dispensed to determine concurrent therapies. It is assumed that the prevalence of polypharmacy on July 1st is representative of any day of the year.

2) Age was determined as of July 1st of each year.

3) Concurrent therapies refer to different active ingredients. Multiple prescriptions for the same chemical or active ingredient are counted only once.

4) Provincial population data from BC Stats http://www.bcstats.gov.bc.ca/StatisticsBySubject/Demography/PopulationEstimates.aspx Accessed August 2014.

5) The figures do not include drugs which typicallly are not intended to exert systemic actions or are rarely used, from the following list of drug exclusion categories provided by the Pharmaceutical Services Division of the B.C. Ministry of Health:

- antihistamines
- anti-infectives
- dental agents
- diagnostic agents
- antitussives, expectorants, mucolytic agents
- heavy metal antagonists
- local anesthetics
- oxytocics
- serums, toxoids, vaccines
- skin and mucous membrane preparations (e.g. creams and ointments, eye drops)
- vitamins
- disinfectants
- non-drug items

6) Long Term Care residents' use of prescription drugs was determined using claims adjudicated under PharmaCare Plan B - Long Term Care.

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