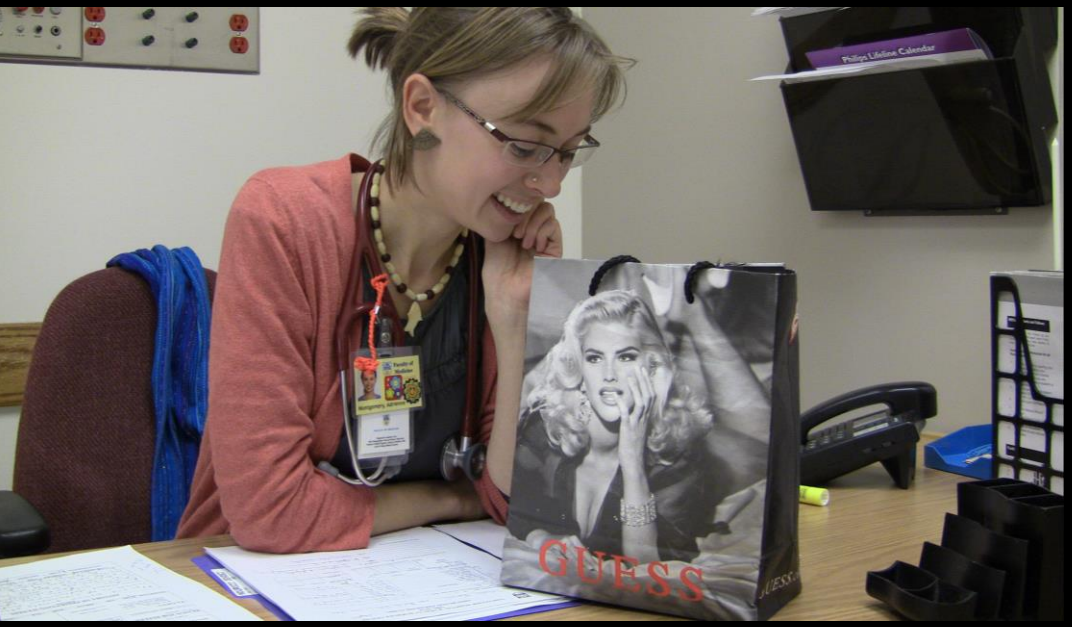
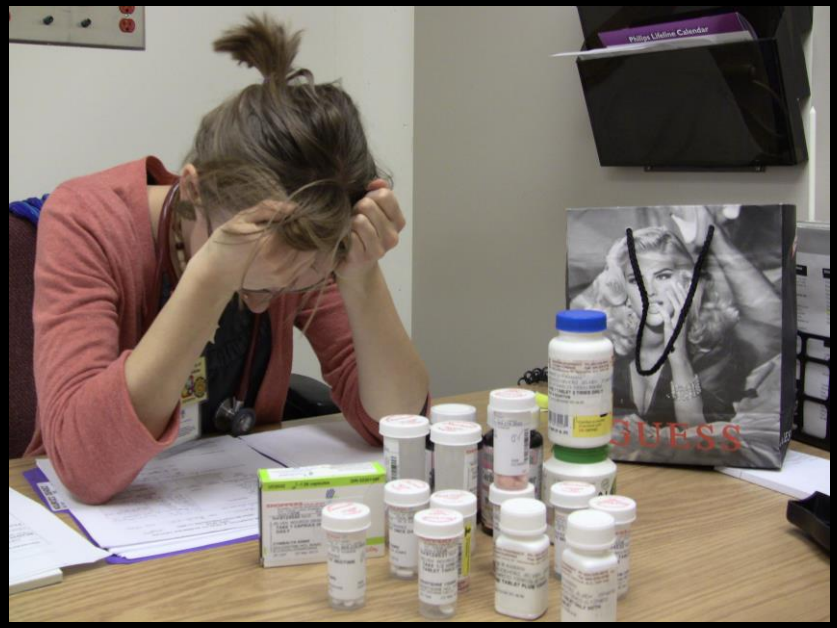
Deprescribing: the solution to irrational polypharmacy





Emily G. McDonald MD, CM, M.Sc. and Thomas L. Perry MD,CM

Preventing Overdiagnosis 2017

Quebec – August 17, 2017

Deprescribing: the solution to irrational polypharmacy

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Videos of patients suffering from polypharmacy have been removed

Consent extended only to live presentation for health education

COI declaration

Thomas L. Perry, M.D., FRCPC

- part-time salary from UBC Therapeutics Initiative
- medical practice income
- medical-legal consultation
- **consultant to litigation in USA and Canada against pharmaceutical manufacturers for fraudulent or inappropriate marketing**
- **no relationship with pharmaceutical companies**

Mitigation: I try to seek truth and be sure what I say could withstand cross-examination

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

How would YOU respond to this situation?

Medication list: alphabetical order

1. Canagliflozin 300 mg/d
2. Celecoxib 200 mg/d
3. Compounded cream (amitriptyline, ketamine, etc.)
4. Cyclobenzaprine 10 mg/d
5. Gliclazide MR 30 mg/d
6. Insulin glargine 30 units bid
7. Metformin 500 mg bid
8. Mirtazapine 30 mg/d
9. Morphine SR 10 mg a.m., 20 mg p.m. (was 70 mg/d)
10. Nabilone 2 mg/d (as 1 mg)
11. Quinine sulfate 300 mg hs
12. Venlafaxine ER 150 mg/d

Age 67 (seen 2016):

- Chronic shoulder injury R > L
- Started morphine SR and IR 2002 at rehab program
- Referred re “appropriateness” of morphine 70 mg/d (stable dose)
- Also treated for “depression” and “insomnia”

Workshop objectives

1. Helping us all move from talk to action in:

- Clinical deprescribing
- Teaching others how to do it
- Identifying barriers to inertia

2. Sharing ideas on what works or doesn't work, and how we can enlist more younger prescribers and patients to resist irrational polypharmacy and encourage sensible deprescribing.

Satisfied patient and professional?

“They didn’t know what was keeping me alive then.”

“But I feel much more alive now!”

Courtesy Maud van Breemen, UBC TI

Canadian medical student - February 2017

(see "Choosing wisely: one person at a time" workshop Aug. 18, 2017)

"I'm on psychiatry and someone presented a case of a depressed patient. The number of drugs was astounding":

Duloxetine, pregabalin, quetiapine, olanzapine, methadone 160 mg/day (not unusual in Canada)

"She was super sedated and the team's response was to start modafinil! … I could not believe it. They were also discussing starting lithium (!) …
I asked a few questions but everyone was shocked when I brought up the possibility that the polypharmacy was a factor in her ongoing symptoms & 'treatment resistance'.

"Anyway, just wanted to let you know your teaching has had a lasting effect!" **(8 day elective was effective!)**

Old doctor's approach: Pontification 2014:

probably ineffective – can't compete with guidelines

1. Re-evaluate goals of therapy
2. Apply absolute risk differences
3. Consider simple pharmacology & physiology
4. Avoid unnecessary costs
5. Reassess ongoing value
6. Common sense & Golden Rule
7. Always stop at least 1 drug

therapeutics letter ©

THERAPEUTICS INITIATIVE Evidence Based Drug Therapy

therapeutics letter
June - July 2014

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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Is a much simpler message better?

“They didn’t know what was keeping me alive then.”

“But I feel much more alive now!”

Deconstructing language helps!

(another shameless plug for Aug 18th 14:30 h workshop)

"She **will definitely benefit** from an antidepressant"

- **??? (probability from RCT ≈ 10%)**

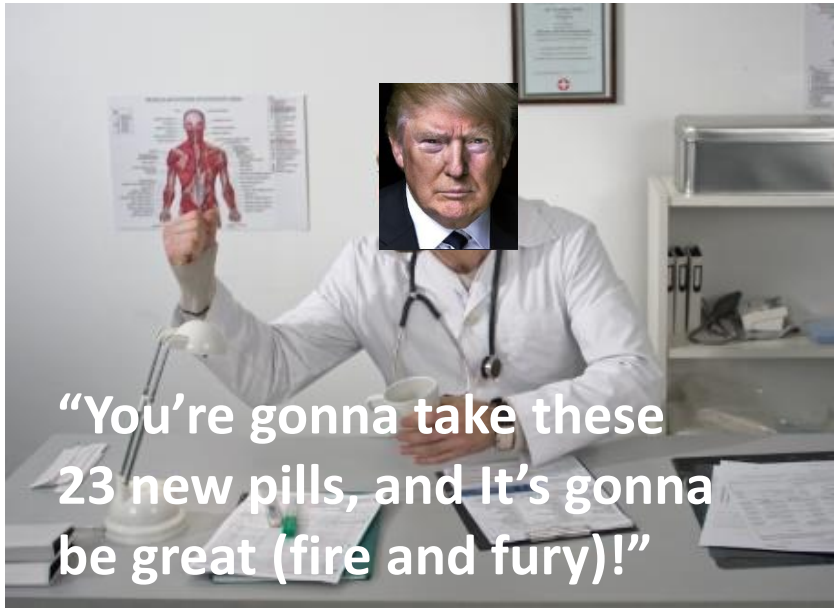
"His diabetes **should be treated aggressively**."

- **Should we be "aggressive" in health care?**

"Her gabapentin dose **needs to be increased** to ≥ 2400 mg/d!"

- **Why? Probability of benefit**

Is near zero, toxicity ≈ certain



Experienced doctor's simple approach:

Dr. Tom Finucane could not be here, but sent this advice

Billion-dollar drugs that cause more harm than good: STOP

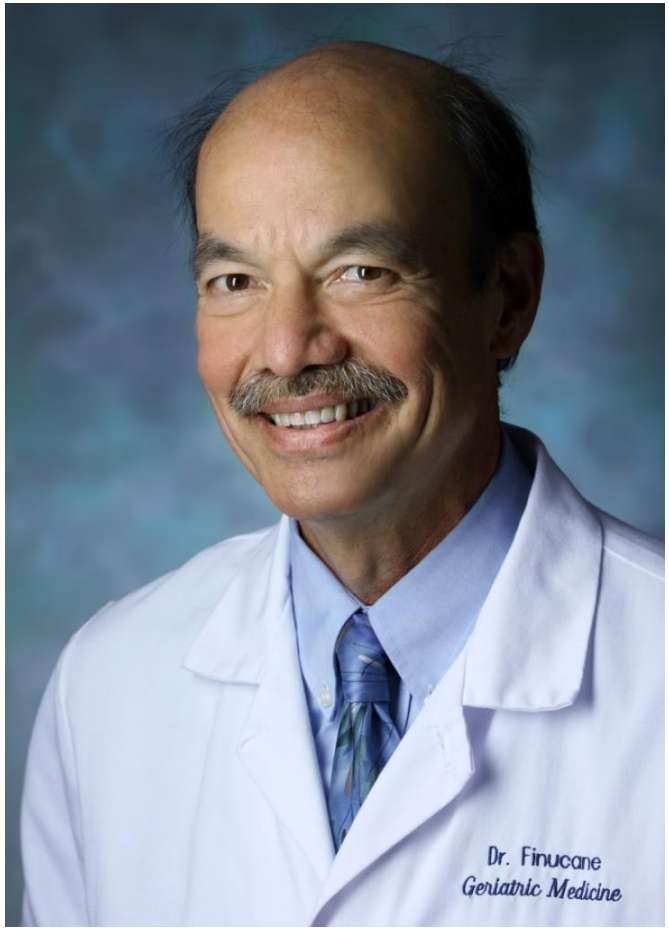
1. PPI for heartburn (same as GERD):

- chordates from sharks to humans have proton pumps – OK to disrupt them???

2. Insulin for DM2:

- lots of known harm;
- no RCT evidence of meaningful benefit;
- ? carcinogenic;
- harmfully expensive

See also Dr. Finucane forthcoming video lecture at:
http://gwcehp.learnercommunity.com/dcrx
Washington, DC - Centre for Rational Prescribing



Tom Finucane (Johns Hopkins)

Simple advice from Dr. Tom Finucane, Geriatrics, JHMI

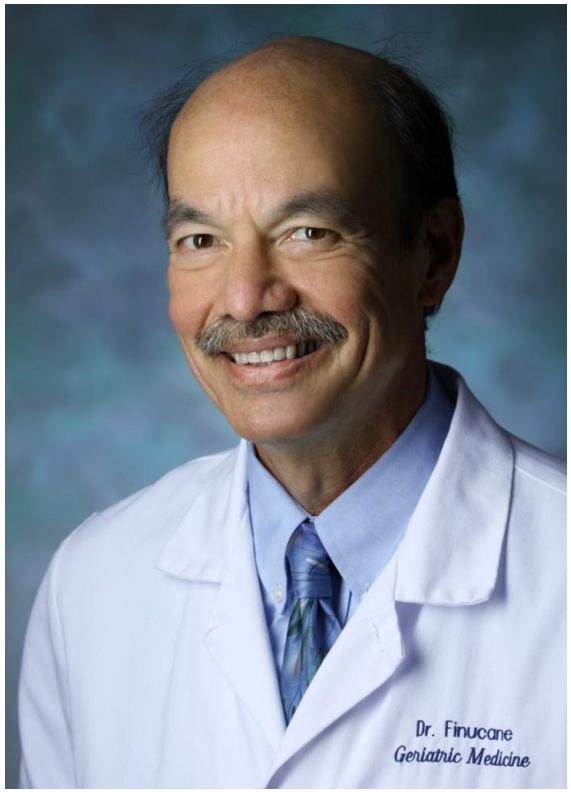
Billion-dollar drugs that cause more harm than good (2): STOP

3. Antipsychotics in patients with psychotic symptoms, or delirium:

- black box warning for death based on consistent, strong evidence;
- SR shows no benefit in delirium;
- worse suffering in palliative care delirium

4. Benzodiazepines:

- cohort study suggests ↑ all cause mortality;
- central benzo deficiency syndrome is rare



Dr. No (disguised as Dr. Yes)

Case 2: **how would YOU handle this or teach others?**

- This woman had profound tremor, asterixis, myoclonic jerks, some mild encephalopathy
- She recovered but developed withdrawal after pregabalin, tramadol, bupropion, nortriptyline, topiramate all stopped at once …
- Required brief hospitalization for fluids, and resentful of withdrawal, but recovered fast
- Would it have been better to "go slowly" and prolong intoxication?

Drugs for pain: pregabalin (Lyrica), tramadol SR, bupropion (Wellbutrin) for "HRT", nortriptyline, topiramate (Topamax), esomeprazole (Nexium)

Practical tricks of the trade

1. Rank medication list **quickly** by priority:

- **probably useful**
- Irrelevant or uncertain
- **probably/potentially harmful**

2. **Recognize likely drug interactions** (kinetic or dynamic); avoid potentially dangerous ones – e.g. multiple drugs that slow heart rate or impair K+ excretion or GFR

3. **Use T ½ elim** to plan safe deprescribing – see example

4. **Challenge rather than worship** unsupported, impractical, or potentially dangerous prescriptions originated by specialists.

You think YOUR life is complicated?

Polypharmacy after MVA (frighteningly common)

Young woman after car crash (pain):

1. Lansoprazole 20mg/d
2. Atorvastatin 40mg/d
3. Pregabalin 225mg at bedtime
4. Solifenacin 5mg/d
5. Topiramate 100mg at bedtime
6. Aripiprazole 5mg/d
7. Sertraline 250mg/d
8. Nortriptyline 40mg at bedtime
9. Vortioxetine 20mg at bedtime
10. Trazodone (100mg at bedtime)
11. Zopiclone (7.5mg at bedtime)
12. “prn” Cyclobenzaprine at bedtime
13. “prn: Ketorolac Injectable IM
14. “prn” hydromorphone 1-2 mg
15. “prn” Acetaminophen (paracetamol)
16. “”prn” methocarbamol, THC pills, marijuana

If this list doesn’t frighten you, it should!

But what to do about it?

Practical tricks of the trade

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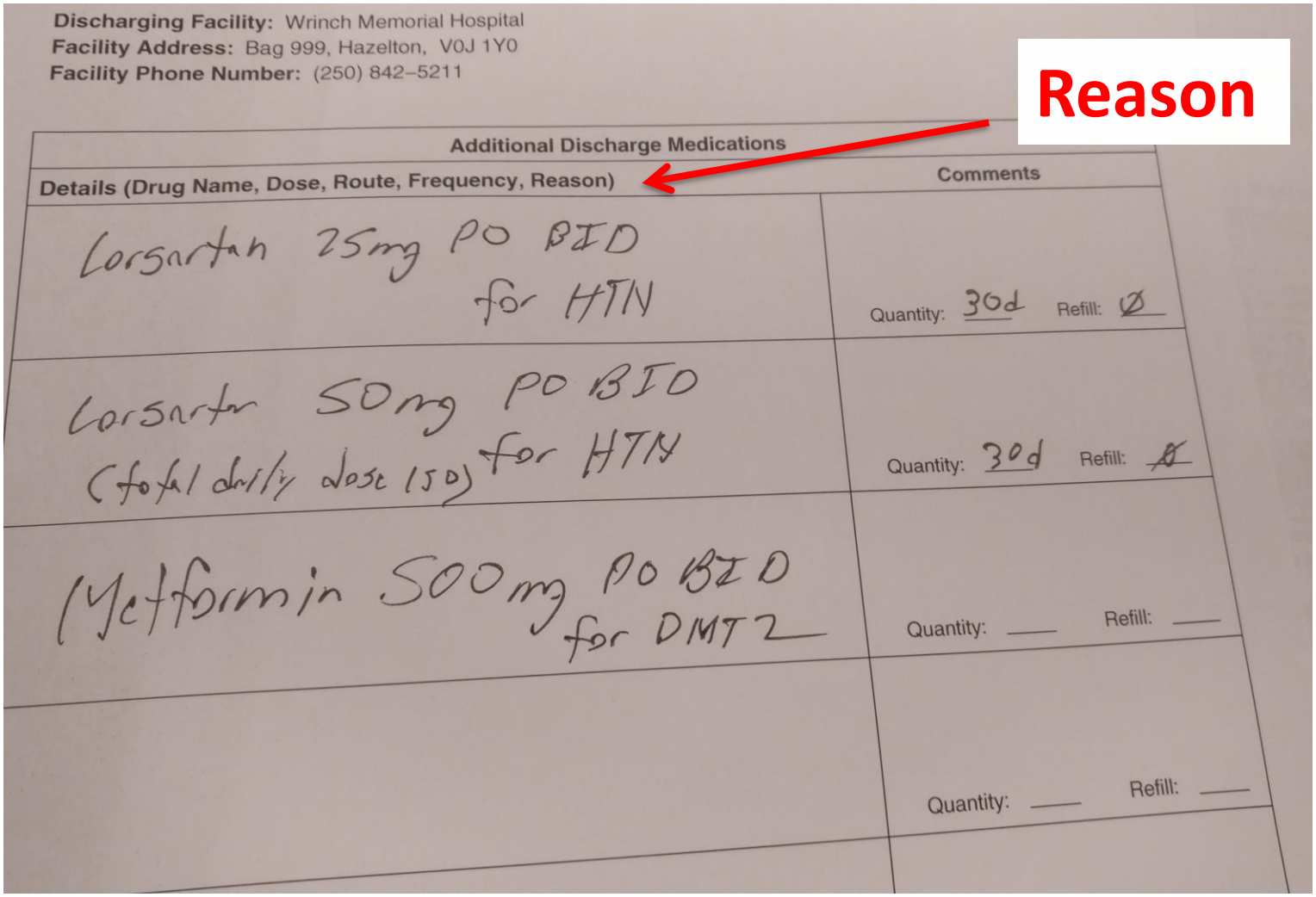
Knowing the reason for a drug helps!



Indication-based discharge prescription by FAX – northern BC, 2017

If a tiny hospital can do this – why can't we?

1. Let's try ranking by priority – quickly!
(or is it hopeless?)

Psychotropic drugs:

For pain?

- Pregabalin 225mg (? pain)
- Topiramate 100mg (? pain)
- Nortriptyline 40mg bedtime
- Cyclobenzaprine bedtime
- Ketorolac Injectable
- Hydromorphone 1-2mg
- Acetaminophen
- methocarbamol, THC, MJ

For depression?

- Aripiprazole 5mg/d
- Sertraline 250mg/d
- Vortioxetine 20mg/d

… psychotropic drugs:

For insomnia?

- Trazodone 100mg at bedtime
- Zopiclone 7.5mg at bedtime
- ? Nortriptyline 40mg bedtime

Drugs ? to counter AE:

- Lansoprazole 20 mg/d
- Solifenacin 5mg/d

Preventive drugs:

- Atorvastatin

It may not be hopeless if we challenge EVERYTHING!

But if we're not the prescriber, it will require some kind of logic and plan …

How much time is one human life worth?

Ranking drugs for symptoms by benefit

It should be easy for symptoms if we probe for straightforward answers and **listen**, e.g.:

- **"That one really helps me"** (me gusta mucho, c'est très bon, mycket bra, 很好, etc.)
- **"They started them all at once, so I can't tell!"**
- "**I never liked that one**, but I really like my …"

WHY DON'T WE ASK MORE OFTEN?

How would YOU respond to this situation?

85 y/o hospitalized for "alcohol w/d" has "high BP", osteoporosis, "colitis", insomnia, chronic pain, etc.

Regular psychotropics:

1. **mirtazapine 45 mg/d (h.s.)**
2. **quetiapine 300 mg/d (h.s.)**
3. **zopiclone 15 mg/d (h.s.)**
4. **pregabalin 225 mg/d (divided doses)**

Other drugs:

1. felodipine 2.5 mg/d
2. telmisartan 80 mg/d
3. T4 25 mcg/d
4. rabeprazole 20 mg/d
5. CaC03 twice/d
6. Vit D 800 units/d
7. risedronate 35 mg/week
8. KCL 8 mEq twice/d
9. 5'-ASA 6 tablets/d

Practical tricks of the trade

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3. **Use T ½ elim** to plan safe deprescribing – see example

4. **Challenge rather than worship** unsupported, impractical, or potentially dangerous prescriptions originated by specialists.

How would YOU respond to this situation?

LOOK AGAIN on the right

Regular psychotropics:

1. mirtazapine 45 mg/d
2. quetiapine 300 mg/d
3. zopiclone 15 mg/d
4. pregabalin 225 mg/d

1. felodipine 2.5 mg/d
2. telmisartan 80 mg/d
3. T4 25 mcg/d
4. **rabeprazole 20 mg/d**
5. **CaC03 twice/d**
6. **Vit D 800 units/d**
7. **risedronate 35 mg/wk**
8. KCL 8 mEq twice/d
9. 5'-ASA 6 tablets/d

Ranking drugs for symptoms – by harm

- This woman is Parkinsonized and sedated and has trouble even saying where she has pain

Considering only her psychotropic drugs,

would YOU change anything?

DRUG	STOP	REDUCE	CONTINUE
Mirtazepine 45 mg/d			
Quetiapine 300 mg/d			
Zopiclone 15 mg/d			
Pregabalin 225 mg/d			

What about now? How should we teach this?

The patient is much better, a “new woman”

Practical tricks of the trade

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Drug	Indication?	Toxicity?	Change	STOP?
Morphine SR 30 mg/d	Shoulder pain		**Added back to 60 mg/d**	
Nabilone 2 mg/d	pain	?		✓
Celecoxib 200 mg/d	temporary	?		✓
Cyclobenzaprine 10 mg/d	pain	?		✓
Venlafaxine XR 150 mg/d	“depression”	?		✓
Mirtazapine 30 mg/d	“depression”/sleep”	?		✓
Quinine 300 mg/d	Leg cramps	✕	?	
Canagliflozin 300 mg/d	DM2	? Low CBG	continued	later
Gliclazide MR 30 mg/d	DM2	Low CBG	continued	later
Insulin glargine 30 units bid	DM2	Low CBG		✓
Metformin 500 mg bid	DM2		continued	

Practical tricks of the trade

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Do you consider T ½ elimination or likely adverse effects to help you decide?

We may review **briefly** using a video:

- T ½ elim easy to find by internet or drug monograph
- Helps you know whether it's safe to stop something … long T ½ elim should not need taper!
- Kidneys more important than liver (except liver failure)

August 15, 2017

using clinical pharmacology rationally

PLOS | MEDICINE

RESEARCH ARTICLE

Benefits and safety of gabapentinoids in chronic low back pain: A systematic review and meta-analysis of randomized controlled trials

Harsha Shanthanna[1,2–], Ian Gilron[3], Manikandan Rajarathinam[1], Rizq AlAmri[1], Sriganesh Kamath[1,4], Lehana Thabane[1,2,5], Philip J. Devereaux[2,6], Mohit Bhandari[2,7]

Abstract

Background and objective

Chronic Low Back Pain (CLBP) is very common, with a lifetime prevalence between 51% and 80%. In majority, it is nonspecific in nature and multifactorial in etiology. Pregabalin (PG) and Gabapentin (GB) are gabapentinoids that have demonstrated benefit in neuropathic pain conditions. Despite no clear rationale, they are increasingly used for nonspecific CLBP. They necessitate prolonged use and are associated with adverse effects and increased cost. Recent guidelines from the National Health Service (NHS), England, expressed concerns on their off-label use, in addition to the risk of misuse. We aimed to assess the effectiveness and safety of gabapentinoids in adult CLBP patients.

toms. They are considered to be very effective for neuropathic pain (NP) conditions. Attempts at exploiting their therapeutic potential for other pain conditions have shown mixed results [10, 11]. Use of gabapentinoids for CLBP requires slow titration to therapeutic doses and establishing maintenance on a long-term basis. With prolonged treatment, the potential gain

Gabapentin and pregabalin are NOT very effective

But let's just think about their T ½ elimination:

Gabapentin mean = 6 h

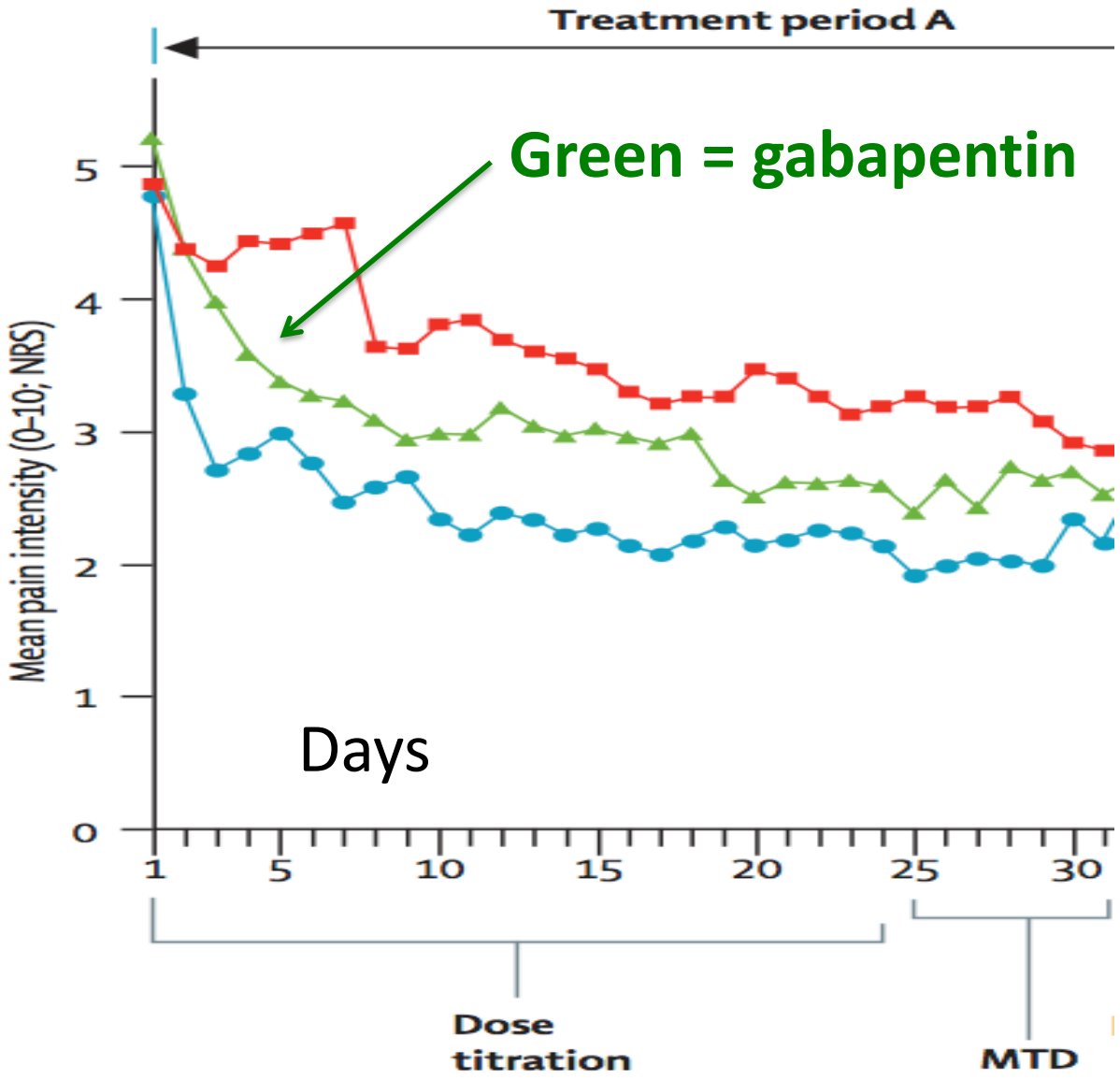
Pregabalin mean = 6 h

Both excreted unchanged by kidney

Predicted equilibrium at any dose about 1 day

Tools 2: using the real evidence – Gilron Lancet 2009

gabapentin: how long? how much? what cost?



Effect of gabapentin, if any, is immediate

Same phenomenon when you look for it

Oxycodone > gabapentin = placebo for shingles

(Dworkin RH et al., PAIN (2009), doi:10.1016/j.pain.2008.12.0222009)

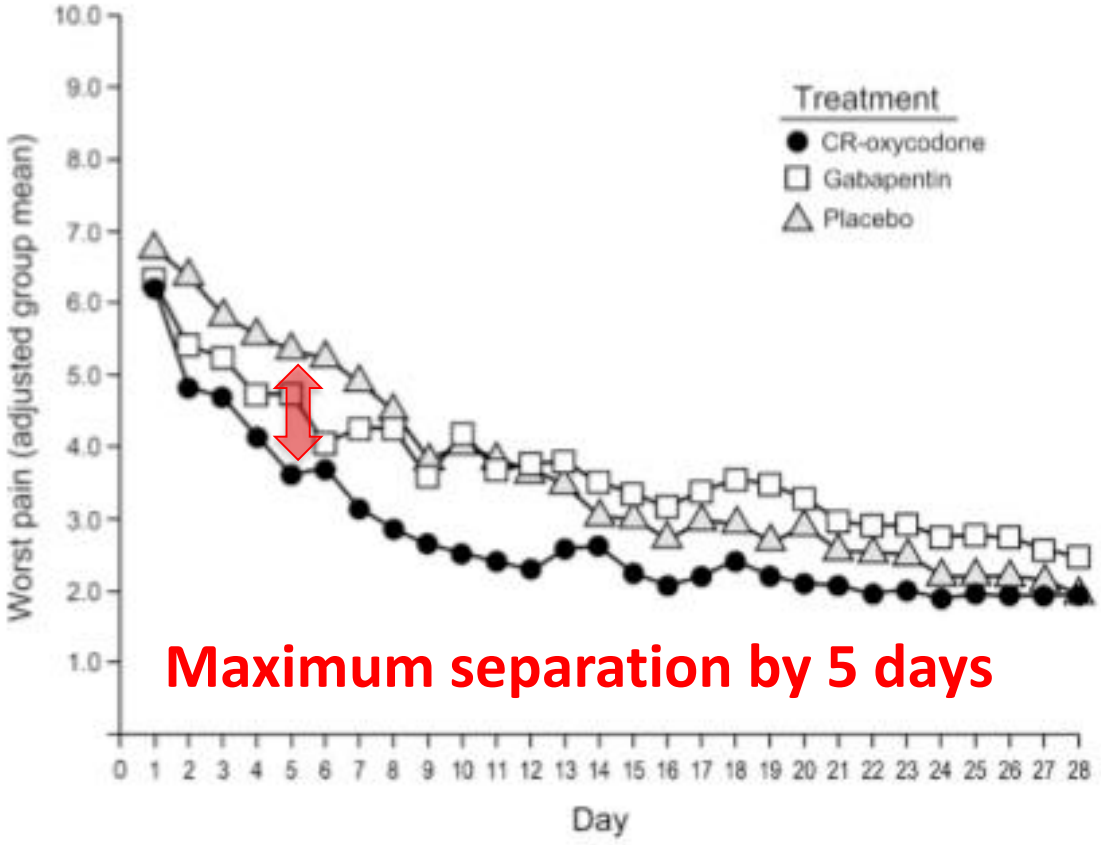


Fig. 2. Adjusted group mean daily diary ratings of worst pain in the past 24 h for the 28-day treatment period.

Reckless trial in PDPN (N = 325) – eventually published 2008 ?
final clinical study report dated February 7, 2000 (p. 53/3214)

Does this graph show a dose-response?

Does it show ⬆ effect vs. placebo over time???

Does it show an effect of gabapentin?

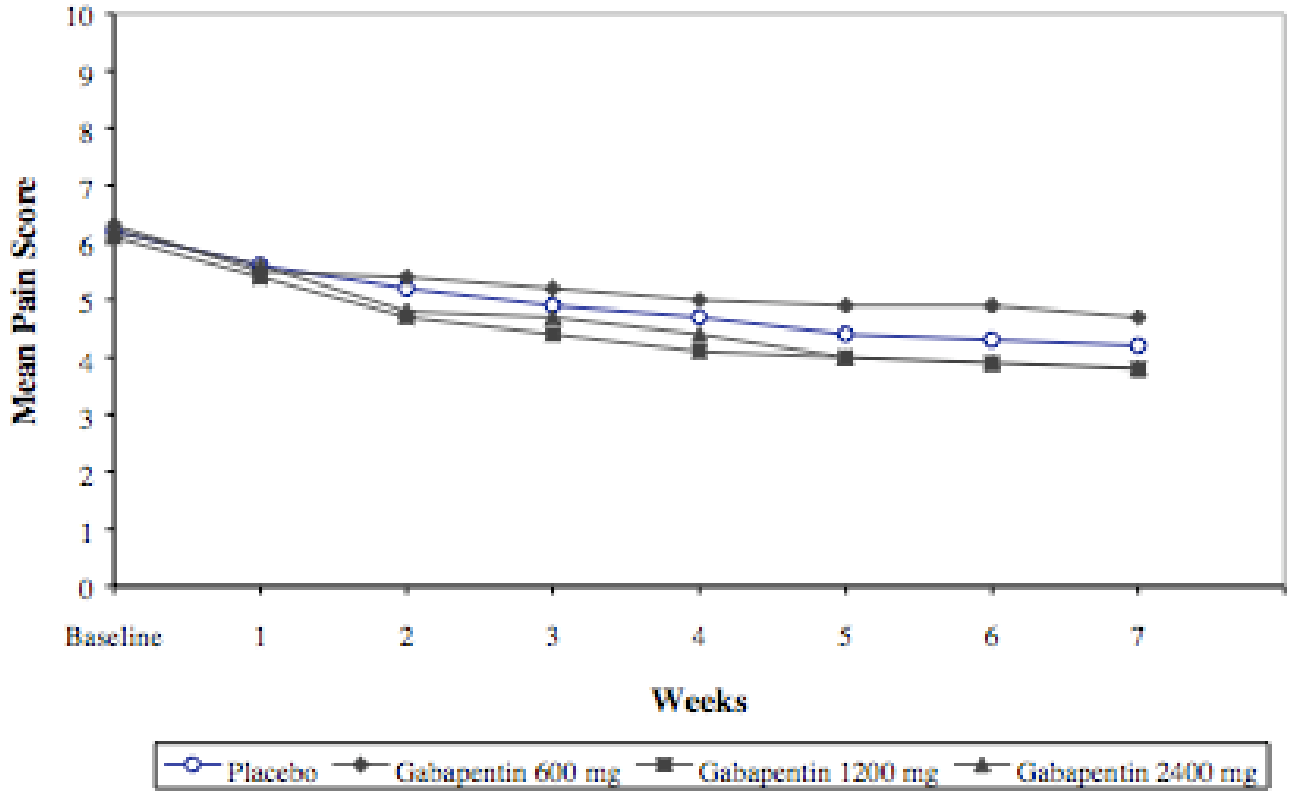


FIGURE 3: Weekly Mean Pain Score (Double-Blind Phase, ITT Population)

eGFR 12 mL/min; he took ASA, candesartan, felodipine, furosemide, metoprolol, allopurinol, gliclazide, pioglitazone

- This man developed encephalopathy from gabapentin at 900 mg/d. The measured T ½ elimination turned out to be 18 h … but he was probably also very sensitive to gabapentin toxicity
- Drug stopped and recovery over several days

#4 : celebrate reflex responses to “dogma alerts”

- “Adding a **third-generation** (…) will improve his (…)”
- “She **needs** to start … bid”
- “I **strongly recommend** … to prevent early death.”
- “Dual agent … is **indicated**.”
- “**Guidelines strongly recommend** … (Grade A recommendation, weak evidence)”