

# The fundamentals of good prescribing

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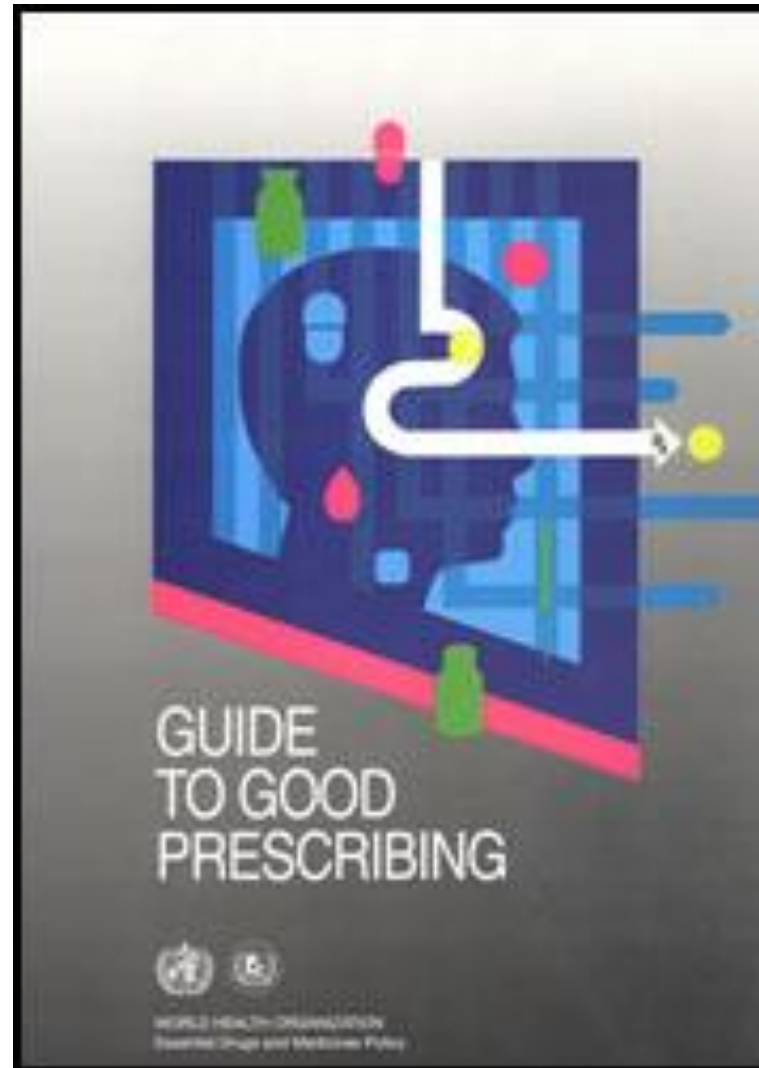
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# What I will cover today

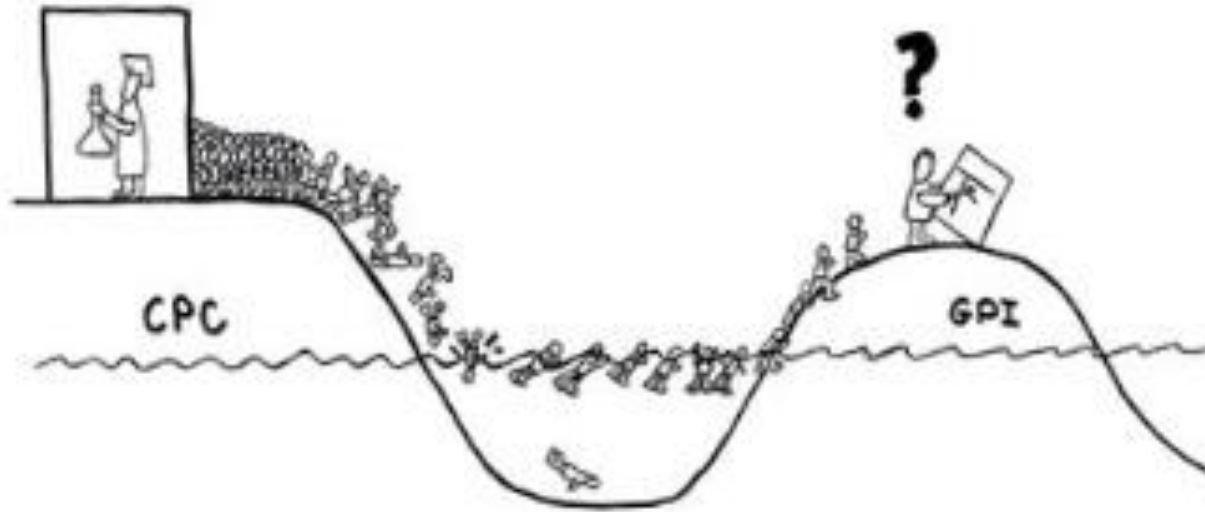
- Good prescribing for the medical & non-medical prescriber
- Prescribing in special groups
- How to avoid some common pitfalls of prescribing

# The bible for prescribers

Published by the WHO, 1996



The reason the guide was written:  
The disconnect between medical school learnings  
and the real world



# The concept of the WHO Guide to Good Prescribing

- The manual presents medical students with a 6-step model of rational prescribing.
- Step 1: Define the patient's problem
- Step 2: Specify the therapeutic objective
- Step 3: Choose your standard treatment and verify its suitability
- Step 4: Start treatment
- Step 5: Give information, instructions, and warnings
- Step 6: Monitor (and stop?) treatment

# Step 1: define the patient's problem

- Make the diagnosis or...
- Assess the risk factors

# Step 1: Some diagnoses are straightforward

- Those that have an easily defined syndrome
  - Eg. Hypertension
    - Diabetes
    - Hypercholesterolaemia
    - Strep throat
    - Vaginal thrush
    - Pregnancy

# Some diagnoses are not

- Patients with multimorbidity, polypharmacy and a new symptom
- Eg. A 81yo woman with L heart failure (previous MI), a new fracture in her spine, chronic renal impairment, AF, poor vision, mild cognitive impairment
- Meds: frusemide 40mg daily, cilazapril 1mg daily, metoprolol CR 47.5mg daily, paracetamol 1g qid, alendronate plus 1 weekly, dabigatran 110mg bid. Recently had a course of antibiotics (3<sup>rd</sup> this year) for bacteriuria, presents with diarrhoea and a fall.



# Diagnosing hypertension

- **Stage one (mild) hypertension** is defined as a clinic BP  $\geq 140/90$  mmHg, or an average daytime ambulatory BP of  $\geq 135/85$
- **Stage two (moderate) hypertension** is defined as a clinic BP  $\geq 160/100$  mmHg, or an average daytime ambulatory BP of  $\geq 150/95$
- 
- **Severe hypertension** is defined as a systolic pressure of  $\geq 180$  mmHg, or a diastolic pressure of  $\geq 110$  mmHg.

# However... actually...

- What if the patient has “white coat hypertension”?
- What if she is pregnant?
- Is there a secondary cause for the hypertension?
- How accurate are automated BP recorders (the ones sold in pharmacies)?
- What if the measurement is different in each arm?
- How many times should I check it to be sure?
- What position should I check it in?

# Making an ACCURATE diagnosis

- Take reading twice
- Two minutes apart
- Measure both arms
- If concern about white coat hypertension – request 24h recording
- Patient must be at rest
- About 10% of home monitors don't read accurately

If the clinic blood pressure is  $\geq 140/90$  mmHg a clinical evaluation should be conducted to:

- Confirm a diagnosis of hypertension
- Assess the patient's cardiovascular risk
  - Lipids, smoking, DBM
- Determine if any end organ damage has occurred
  - ECG, urinalysis, fundoscopy, CXR
- Detect any causes of secondary hypertension
  - Cushings, phaeo, hypothyroidism, acromegaly, hypercalcaemia, alcohol, drugs, obesity ....

# OK then.....what about hyperlipidaemia?

- Easy!
- Do a blood test
- Treat if high
- Which blood test?
- Does the patient have to fast?
- Are there other causes of abnormal lipids?
- Does it matter?

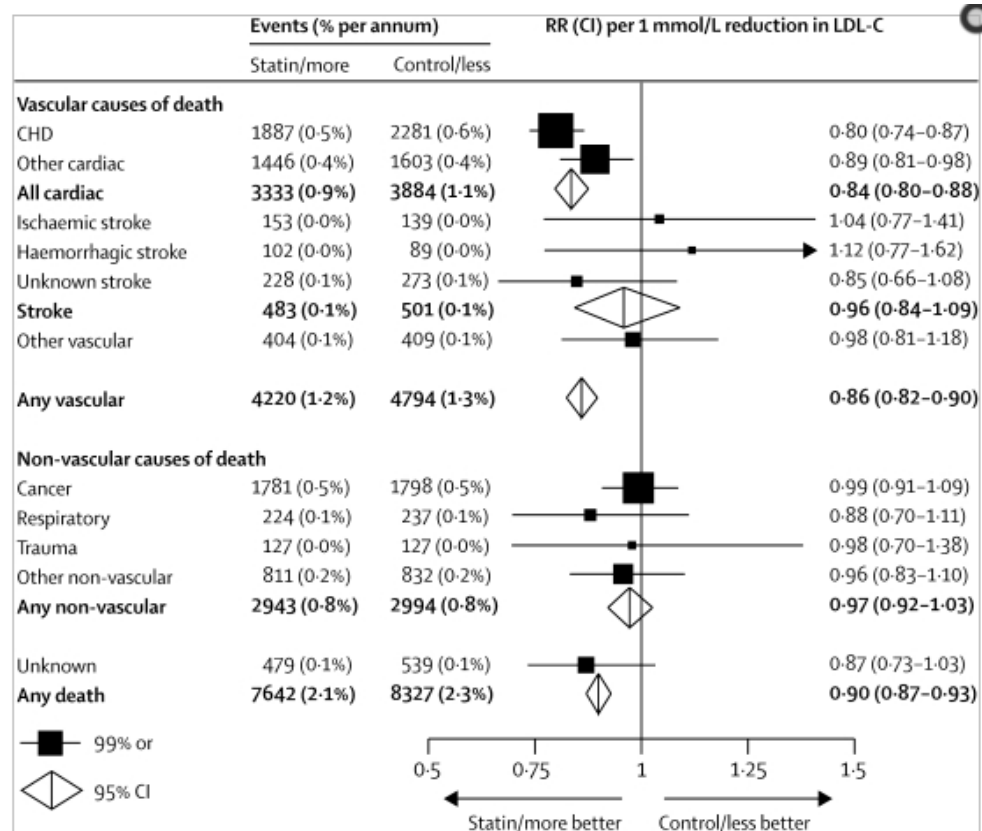
# Testing for hyperlipidaemia

- Is undertaken as part of a CV risk assessment
- Is important if lipids need to be tightly controlled
  - Post CABG

# **Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials.**

- All patients had existing CAD
  - Across all 26 trials, all-cause mortality was reduced by 10% per 1.0 mmol/L LDL reduction (RR 0.90, 95% CI 0.87-0.93;  $p < 0.0001$ )
  - Significant reductions in deaths due to coronary heart disease (RR 0.80, 99% CI 0.74-0.87;  $p < 0.0001$ )
  - Other cardiac causes (RR 0.89, 99% CI 0.81-0.98;  $p = 0.002$ )
  - Sounds good!
- 
- Cholesterol Treatment Trialists Collaboration, Lancet 2010

# Actual numbers



Effects on cause-specific mortality per 1.0 mmol/L reduction in LDL cholesterol

- Mortality was reduced from 2.3% to 2.1%

- ARR 0.2%

RRR 10% ( $2.3/0.2=10$ )

NNT =  $1/0.2\%=500$



# In essence

- Intensification of the lipid-lowering regime will benefit one person in 500

## 2. Specify the therapeutic objective:

- Is the drug to prevent something?
- If so, is it primary or secondary prevention?
- Is it to relieve symptoms?
- Is it to prolong life?
- Is it curative?

# If it is to prevent something

- How good is the evidence that it works?
- EG. Mrs J had a fall and fractured her hip. She was subsequently diagnosed with osteoporosis (T score -2.5). She was started on Fosamax Plus. She has been taking the drug for 3 weeks and feels nauseous. She asks you how effective it is anyway in preventing another fractured hip.
- What do you say?

# How effective is oral Alendronate Plus at preventing another fractured hip?

- Absolute risk reduction
- Relative risk reduction
  
- What is the difference?
  
- How best to explain this to Mrs J

# Risk reduction- Alendronate in secondary prevention of # hip

- Mrs J's risk of having another fracture without Rx = 14%
- Mrs J's risk of having another fracture with Rx = 13%
- Absolute risk reduction= 1% ( $14-13=1$ )
- Relative risk reduction= 7% ( $14-13=1$ ,  $1/14 \times 100\%= 7\%$ )
- NNT=  $1/1\% = 100$

Mrs J's sister, Mrs K decides that she should protect herself from a hip # as well.

- Mrs K has osteoporosis, but has never had a fracture
- What is her risk of having a hip fracture?
- What is her risk reduction with Fosamax?

- Mrs K's risk of suffering a hip fracture = 3.2% over 5 years
- Mrs K's risk if she takes Fosamax = 3.2%
- Mrs K's risk if she doesn't take Fosamax = 3.2%
- Don't recommend this to her!

# The problem with primary prevention using drugs

- Doesn't work very well
  - Statins for primary prevention of CV disease
  - Aspirin for prevention of CV disease
  - Anti-hypertensives to prevent CVA
  - Warfarin to prevent cardio-embolic CVA in AF
  - Dabigatran to prevent cardio-embolic CVA in AF
- But the drugs can cause ADEs



# The problem with primary prevention using drugs

Statins	All cause mortality	ARR 0.6% (if risk 10-20%/year). RRR 12% over 4 years
Aspirin	CV disease	ARR 0.07%/year
Anti-hypertensives	CVA	ARR 1%, RRR 30%
Warfarin	CVA in AF	ARR 4.1%, RRR 66%
Dabigatran	CVA in AF	ARR 3.8%, RRR 79%

*BMJ 2009;338:b2376*

# *The benefits of statins in people without established cardiovascular disease but with cardiovascular risk factors: meta-analysis of randomised controlled trials*

**Results** 10 trials enrolled a total of 70 388 people, of whom 23 681 (34%) were women and 16 078 (23%) had diabetes mellitus. Mean follow-up was 4.1 years. Treatment with statins significantly reduced the risk of all cause mortality (odds ratio 0.88, 95% confidence interval 0.81 to 0.96), major coronary events (0.70, 0.61 to 0.81), and major cerebrovascular events (0.81, 0.71 to 0.93). No evidence of an increased risk of cancer was observed. There was no significant heterogeneity of the treatment effect in clinical subgroups.

***BMJ 2009;338:b2376***

During a mean follow-up of 4.1 years 5.7% (1925/33 793) of participants died in the control group compared with 5.1% (1725/33 683) in the statin group. Statin therapy was therefore associated with a 12% risk reduction in all cause mortality compared with the control (odds ratio 0.88, 95% confidence interval 0.81 to 0.96; fig 2↓ and table 2↓). The annual rate for all cause mortality with placebo in our study was 1.4% (fig 2). Overall, 5.4% (1266/23 946) of participants in the control group had a major coronary event compared with 4.1% (966/23 823) in the statin group, a 30% risk reduction (odds ratio 0.70, 95% confidence interval 0.61 to 0.81). The annual rate for major coronary events with placebo in our study was 1.1% (fig 2). Overall, 2.3% (767/33 793) of participants in the control group had a major cerebrovascular event compared with 1.9% (627/33 683) in the statin group, a 19% risk reduction (0.81,

Absolute reduction in all-cause mortality 5.7%-5.1% = 0.6%  
NNT= 1/0.6% or  
1/0.006=167 for 4y

# Treatment of hypertension

Approximately 54% of strokes can be attributed worldwide to high BP values in both gender and in all ages.<sup>4</sup> As a consequence, hypertensive subjects are 3 to 4 times more likely to have a stroke than the normotensives.<sup>8</sup> In particular, it was established that a 2 mmHg rise in systolic BP in middle life is associated with 10% increase in risk of stroke.<sup>9</sup> In addition the relationship between BP and risk of first stroke is direct, continuous and independent, with the risk increasing continuously above a BP of 115/75 mmHg.<sup>5</sup>

Ravenni et al. Primary Stroke Prevention and hypertension treatment. Which is the first line strategy? Neurology Int 2011;

Despite the overwhelming evidence that HT represents the first risk factor for stroke and that the cerebrovascular benefits the most from BP lowering, no randomized clinical trials provided a BP target for effective primary prevention of stroke.<sup>30</sup> Current international guidelines recommend a systolic/diastolic goal of <140/<90 mmHg in the general population and <130/<80 mmHg in diabetic subjects and in those with renal disease.<sup>31,32</sup> Whether a lower target has further benefits in primary stroke prevention is uncertain. Although in a meta-

None of these trials included patients >80yo who were living in rest homes, or the frail elderly.

This is an evidence free zone

## Step 3. Verify suitability of drug

- Even if the drug seems to be appropriate for the condition...
- Is it appropriate for the patient?
- Does the patient have contraindications to it?
- Does the drug interact with their other medications
- What if the patient has poor renal function?
- What if they are pregnant or hoping to become so?

# Mr GJ

- 80yo
- T2DBM, diabetic nephropathy, HT, previous MI
- Rx: cilazapril 1mg daily, Lantus 16u daily, Humalog 5u tds, frusemide 40mg daily, metoprolol CR 47.5mg daily, simvastatin 20mg od
- Develops a flu-like illness and pneumonia
- Is admitted to hospital

- Mr GJ is treated with cefuroxime and erythromycin
- His stay is complicated by AKI due to rhabdomyolysis
- Unfortunately, he dies
- Why?



# Rhabdomyolysis

- Muscle breakdown
  - Products in the urine and blood
  - Hyperkalaemia, DIC
- 
- Mr GJ's rhabdo was caused by a drug interaction
  - Which one?



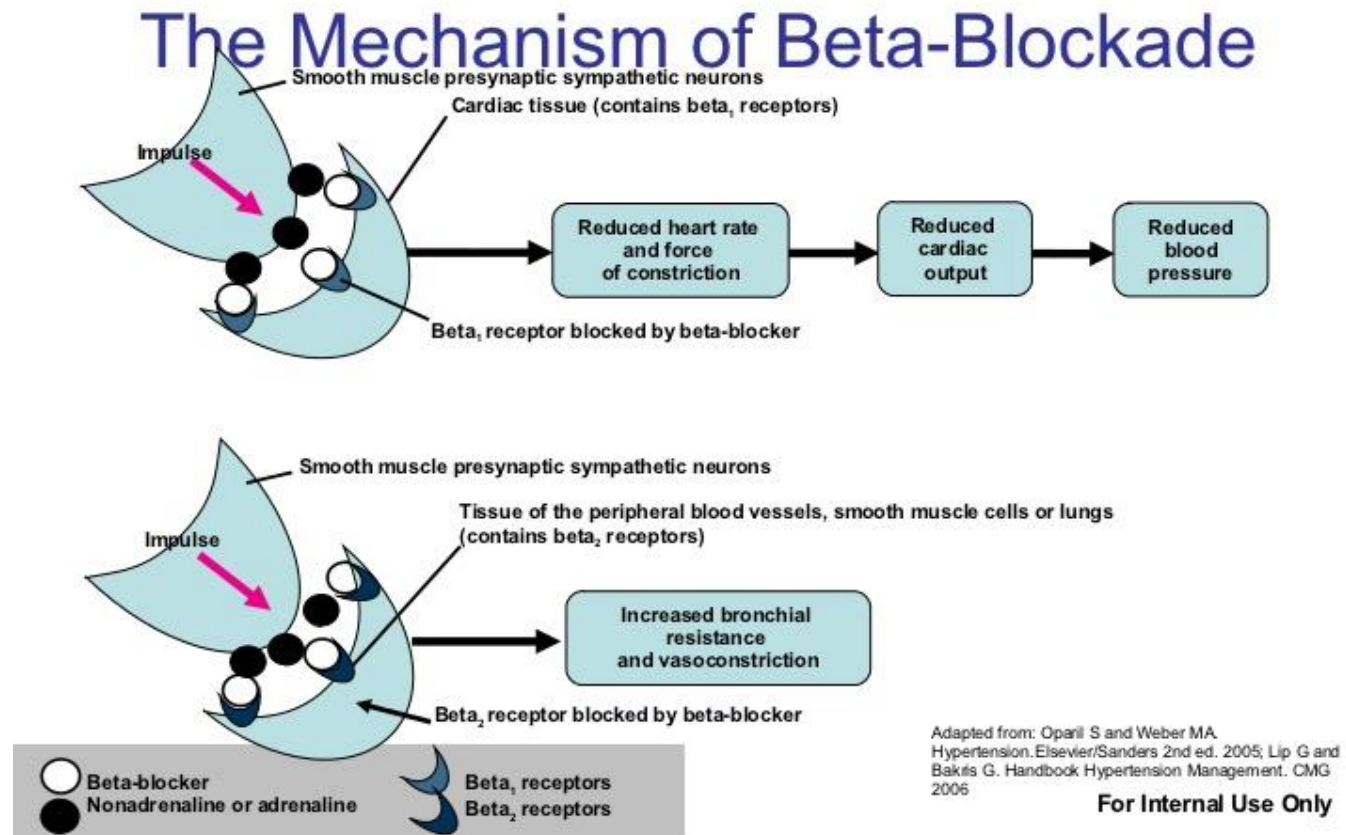
# Mrs CX

- 44yo
- Asthmatic
- On salbutamol and fluticasone
  
- Visits GP with migraine (worst ever) requesting analgesia
- Locum GP – does not read her notes
- Prescribes daily propranolol for migraine prophylaxis

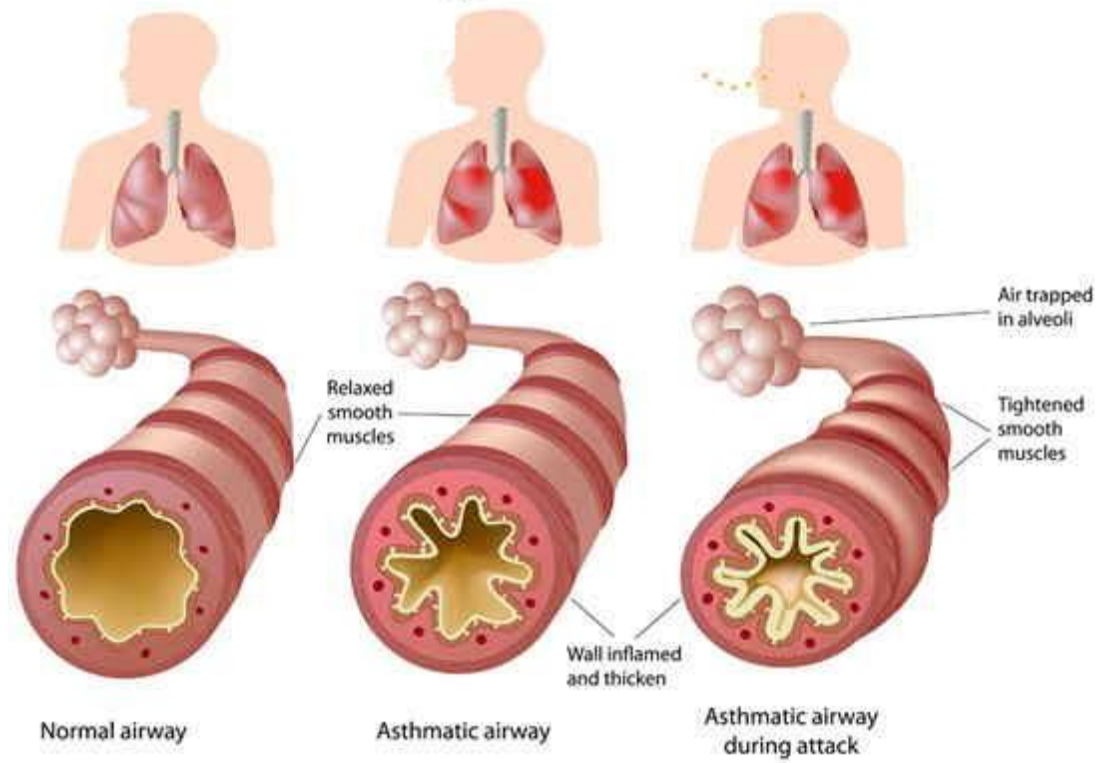
- Mrs CX gets the script filled at her usual pharmacy
  - Takes 1 tablet in the pharmacy
  - About 15 minutes later she has severe respiratory distress, wheezy
  - Ambulance called
- 
- Mrs CX unable to be resuscitated

- Why?

# Beta blockers vasoconstrict and bronchoconstrict



## Pathology of Asthma



## 4. Treat (prescribe drug)

- Is a loading dose required?
- Or start low and go slow?
- Is TDM needed?

# When to use a loading dose

- When action is needed pronto (seizures, arrhythmia)
- For drugs with a large volume of distribution

# When to start low and go slow

- The frail elderly
- Poor physiological reserve



## 5. Give information, instructions and warnings

- What is the treatment?  
What is it for?
- How often to take it
- How much to take
- How to know if it is working
- What side effects to expect and what to do about them

## 6. Monitor (and stop?) Rx

- How do we monitor effect?
- Can we see it?
- Is it simple like checking heart rate/BP?
- Is it more abstract like “no seizures”
- Is TDM required?
- Is the patient cured?
- If the Rx is preventative, how do we know if its working?

# Some drugs requiring TDM

Drug	Therapeutic range	Toxicity symptoms
Digoxin	1-2.5nmol/L	Bradycardia, green-yellow vision
Phenytoin	10-20mg/L	Nystagmus, ataxia
Carbamazepine	17-51mcmol/L	Sedation, ataxia
Lithium	0.8-1.2mg/L	Tremor, renal impairment
Flecainide	0.2-1mcg/L	Serious arrhythmia

# Mrs F

- 78yo
- Multiple medical problems
- Seizure 6 years earlier, probably post-CVA
- Started on phenytoin at that time
- Had been discharged to primary care
- Admitted with sepsis
- Pus oozing from teeth
- [Phenytoin] = 107mg/L (40-80)

# Phenytoin-induced gingavitis



- Mrs F's phenytoin level had not been checked for about 4 years
- She had continued to take 300mg daily
- Now much smaller and frailer

# What is polypharmacy?

- My definition is:
- Use of potentially inappropriate drugs
- Other people say:
- >5
- >10
- Hyperpharmacotherapy
- Multiple medication use



Remember:  
Polypharmacy  
is NOT always  
inappropriate  
or  
problematic

# Why does it matter?

- Increases morbidity – drug interactions, ADEs, falls, impaired cognition, impaired confidence, AKI, delirium, hypoglycaemia
- Increases mortality – falls (# hip, ICH especially), hypoglycaemia, delirium, drug interactions ....
- Increases cost



# How common is polypharmacy?

- Very
- In NZ in 2013/14 2.6% of population prescribed >10 drugs and 8.5% prescribed 5-9 drugs
- In the frail elderly use of potentially inappropriate drugs is the norm

## Frailty Criteria

Unintentional weight loss, as evidenced by a loss of at least 4 Kg or greater than 5% of body weight in the prior year  
“How’s your appetite been in the last year or so?” “Have you lost or gained weight?”

Reduced grip strength

Physical slowness, based on measured time to walk a distance of 5 metres  
“Because of a health problem, do you have difficulty walking 100 metres?’ or ‘... climbing one flight of stairs without resting?”

Poor endurance, as indicated by self-reported exhaustion  
“In the last month, have you had too little energy to do the things you wanted to do?”

Low physical activity  
“How often do you engage in activities that require a low or moderate level of energy such as gardening, cleaning the car, or doing a walk?”

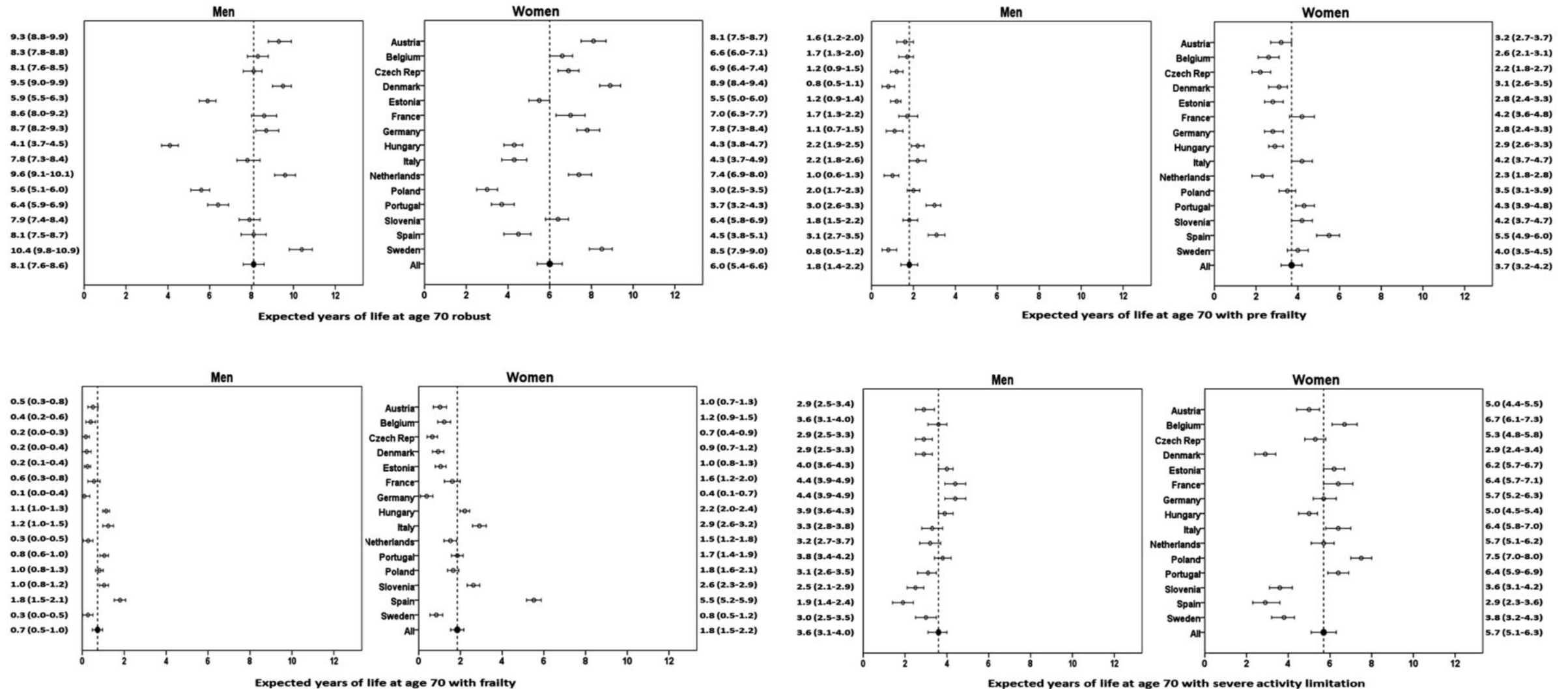
Diagnoses of cardiovascular disease, pulmonary disease, diabetes, arthritis, impaired cognition and depression were found to be more prevalent in frail elderly.

Studies also have identified obesity as a significant risk factor for frailty in women.

7% of the population aged 65 and older and 25% of the population aged 80 and over meet the criteria for frailty.

Detection of walking speed  $<0.8$  m/s is a simple approach to the diagnosis of frailty in the primary care setting.

# Why does frailty matter?



# Life Expectancy in frailty

- European women 70yo LE <2y
- European men 70yo LE <1y

# LE for non-frail adults

Male		Female	
Age years	Expected number of years of life remaining	Age years	Expected number of years of life remaining
65	18.8	65	21.2
70	15.0	70	17.1
75	11.5	75	13.3
80	8.6	80	9.8
85	6.2	85	6.9
90	4.5	90	4.8

**Table 1:** Life expectancy by age for older New Zealand male and female populations, 2009 - 20120

# Frail elderly are not like 'normal' elderly

- Shorter LE
- Less physiological reserve
- More likely to suffer ADE (especially Type A)
- Less likely to live independantly

# Changes in prescribing for frail elderly

- Focus is on quality of life, not prevention of future illness
- Many frail elderly have a LE < 1 year
- Many medications that are good practice for a fit elderly person are likely to cause harm>good in a frail elderly
- Remember frailty is a medical diagnosis with a worse outcome than most cancers

# Geriatric syndromes

- Old people complain of symptoms
- Pain, incontinence, anxiety, urinary difficulties, insomnia – these are not diseases, but cause ↓ QOL



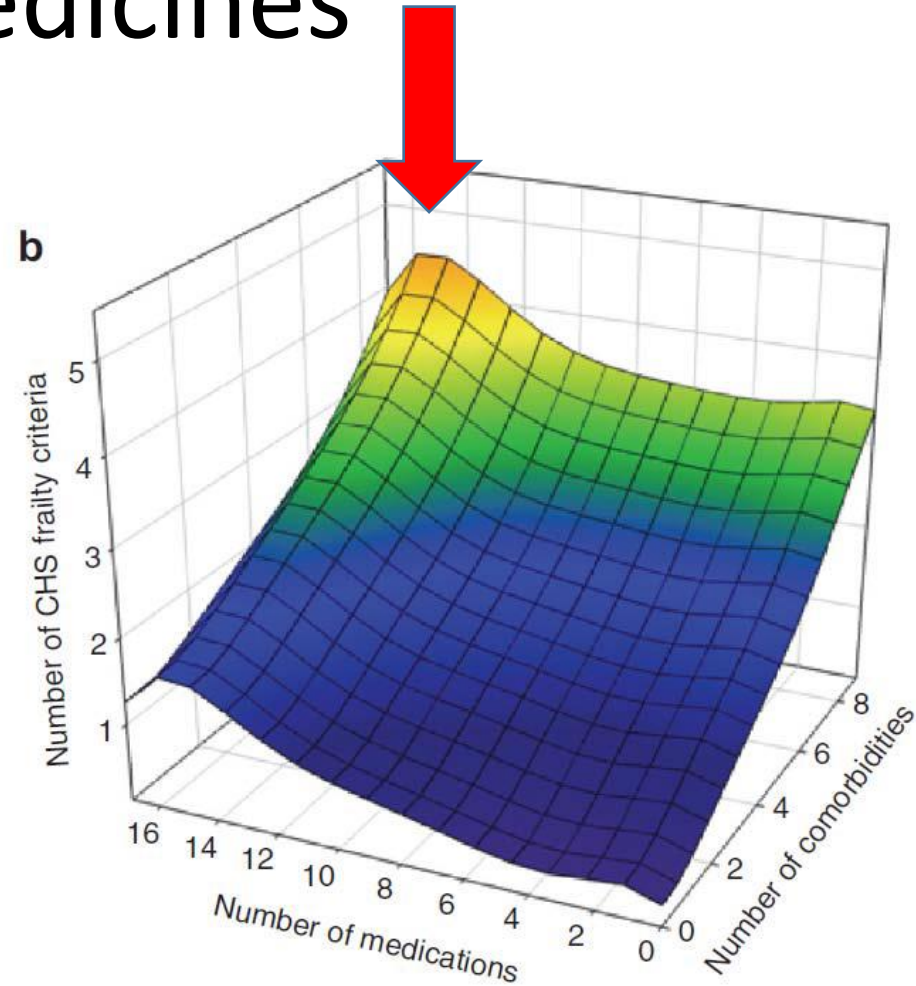
- They are often prescribed drugs for these complaints



# What is prescribed for pain, incontinence, insomnia, anxiety, dementia

- Analgesia – paracetamol then opioids
- Transient gastric upset - PPIs
- Incontinence & urinary difficulties – oxybutynin, tamsulosin, doxazosin, antibiotics
- Insomnia – zopiclone, temazepam, quetiapine (!!!!!)
- Anxiety – quetiapine (!!!!!), benzodiazepines
- Dementia – donepezil, quetiapine, risperidone, rivastigmine

The frailest people have BOTH most illnesses and most medicines



# Polypharmacy and CHAMP: risk per additional medication

Outcomes	Unadjusted OR (95% CI)	P-value
Frailty	1.27 (1.20, 1.34)	<0.0001
Disability	1.17 (1.10, 1.23)	<0.0001
Mortality	1.15 (1.11, 1.20)	<0.0001
Falls	1.13 (1.09, 1.17)	<0.0001
Cognitive impairment	0.98 (0.93, 1.03)	0.49
<i>Abbreviations:</i> CI, confidence interval; OR, odds ratio. ORs are for risk with increasing number of medications by one.		

and remained highly significant with multivariate analysis

# The harms of inappropriate medication use



# DBI- Drug Burden Index

- An increased drug burden for anticholinergic and sedative medications was associated with impaired performance on mobility and cognitive testing in high-functioning community-based older adults.
- Total number of medications was not associated with impaired performance when **sedatives and anticholinergics** were excluded.
- A high DBI has been correlated with increased risk for functional decline in community dwellers and with increased risk of falls in residents in long-term care facilities.

# DBI - anticholinergics

- ADEs include memory impairment, confusion, hallucinations, dry mouth, blurred vision, constipation, nausea, urinary retention, impaired sweating, and tachycardia
- Anticholinergics can precipitate an acute glaucoma episode in patients with narrow angle glaucoma
- Anticholinergics can precipitate acute urinary retention in patients with BPH

# Anticholinergics cause cognitive decline and worsen/hasten dementia

- In a study of 6912 adults aged  $\geq 65$ , those taking anticholinergic drugs were at  $\uparrow$  risk for **cognitive decline and dementia** and risk  $\downarrow$  with medication discontinuation
- In a population of 3434 adults aged  $\geq 65$  in one healthcare setting, who had no baseline dementia and who were followed for 10 years, the risk of **dementia and Alzheimer's disease**  $\uparrow$  in a dose-response relationship with use of anticholinergic drug classes (primarily first generation antihistamines, TCAs, and bladder anticholinergics)



High anticholinergic activity	Low anticholinergic activity
	All antibiotics
Amitriptyline, Amoxapine, Clomipramine, Doxepin, Imipramine, Paroxetine, Trimipramine	Bupropion, Fluoxetine, Mirtazapine, Sertraline, Venlafaxine  Desipramine and Nortriptyline best TCAs
Chlorpheniramine, Cyproheptadine, Dimenhydrinate, Diphenhydramine,	No antihistamines
Oxybutynin, Tolterodine	No anti-spasmodics for the bladder
Chlorpromazine, Clozapine, Fluphenazine, Loxapine Olanzapine, Perphenazine, Pimozide, Quetiapine, Thiothixene, Trifluoperazine	Haloperidol, Risperidone, Ziprasidone
Atropine, Cimetidine, Dicyclomine, Loperamide, Prochlorperazine, Promethazine, Propantheline, Ranitidine	Metoclopramide
Pethidine	Codeine, Fentanyl, Morphine, Oxycodone, Tramadol



# Side effects of anti-psychotics

BPJ 40;2011

	Extrapyramidal	Sedation	Weight gain	Hyperglycaemia	Anticholinergic	Orthostatic hypotension
<b>Atypical antipsychotics</b>						
Risperidone	●●	●● initially	●●	●●	●	●● initially
Quetiapine	●*	●●●	●●	●●●	●●	●●
Olanzapine	●	●●●	●●●	●●●	●●●	●
Clozapine	●	●●●	●●●	●●●	●●●	●●
Amisulpride	●●*	●	●	●	●	●
Aripiprazole	●	●	●	●	●	●
Ziprasidone	●	●●	●	●	●	●●
<b>Typical antipsychotics</b>						
Haloperidol	●●●	●	●●	●●	●	●
Chlorpromazine	●●	●●●	●●●	●●●	●●●	●●●

Approximate frequency of adverse effects: ● (<2%) = negligible or absent; ● (>2%) = infrequent; ●● (>10%) = moderately frequent; ●●● (>30%) = frequent. \* rarely a problem at usual therapeutic doses

# Drugs used to treat “risk factors”

- Anti-hypertensives
- Statins
- Bisphosphonates
- Aspirin/warfarin/dabigatrin/rivaroxaban

# A few examples of problematic ADRs

## Benzodiazepines and Risk of Hip Fractures in Older People

### A Review of the Evidence

10% of hip fractures in Australia are attributable to benzodiazepines

**Table I.** Epidemiological studies of the relationship between benzodiazepine use and risk of hip fracture

Reference	Year	Country and time period	Sample size	Results <sup>a</sup>
<b>Cohort studies</b>				
Cummings et al. <sup>[16]</sup>	1995	USA 1986–1988	9516 subjects, 192 cases	<b>1.6 (1.1–2.4)</b>
<b>Population-based case-control studies</b>				
Ray et al. <sup>[17]</sup>	1989	Canada 1977–1985 <sup>b</sup>	4501 cases, 24 041 controls	$t_{1/2} < 24\text{h}$ : 1.1 (0.9–1.3); $t_{1/2} > 24\text{h}$ : <b>1.7 (1.5–2.0)</b>
Cumming and Klineberg <sup>[18]</sup>	1993	Australia 1990–1991	209 cases, 207 controls	<b>1.6 (1.0–2.5)</b>
Herings et al. <sup>[19]</sup>	1995	Netherlands 1986–1992 <sup>b</sup>	493 cases, 1311 controls	<b>1.6 (1.2–2.1)</b> ; $t_{1/2} < 24\text{h}$ : <b>1.5 (1.1–2.0)</b> ; $t_{1/2} > 24\text{h}$ : 1.3 (0.7–2.4)
Wang et al. <sup>[20]</sup>	2001	USA 1993–1995 <sup>b</sup>	1222 cases, 4888 controls	<b>1.5 (1.2–1.8)</b> ; short-acting: <b>1.5 (p &lt; 0.05)</b> ; long-acting: 1.3 (p > 0.05)
<i>Case-control studies of hip fractures only in nursing homes</i>				
Sgadari et al. <sup>[21]</sup>	2000	USA 1992–1996 <sup>b</sup>	9752 cases, 38 564 controls	1.1 (1.0–1.2); $t_{1/2} < 24\text{h}$ : 1.1 (1.0–1.2); $t_{1/2} > 24\text{h}$ : 1.2 (1.0–1.5)
<i>Case-control studies of hip fractures only in hospitals</i>				
Lichtenstein et al. <sup>[22]</sup>	1994	Canada 1983–1985	129 cases, 234 controls	<b>2.1 (1.1–3.8)</b>

# Falls: Polypharmacy and psychotropic medicines

JAGS AUGUST 2005–VOL. 53, NO. 8

ATYPICAL ANTIPSYCHOTICS AND FALLS

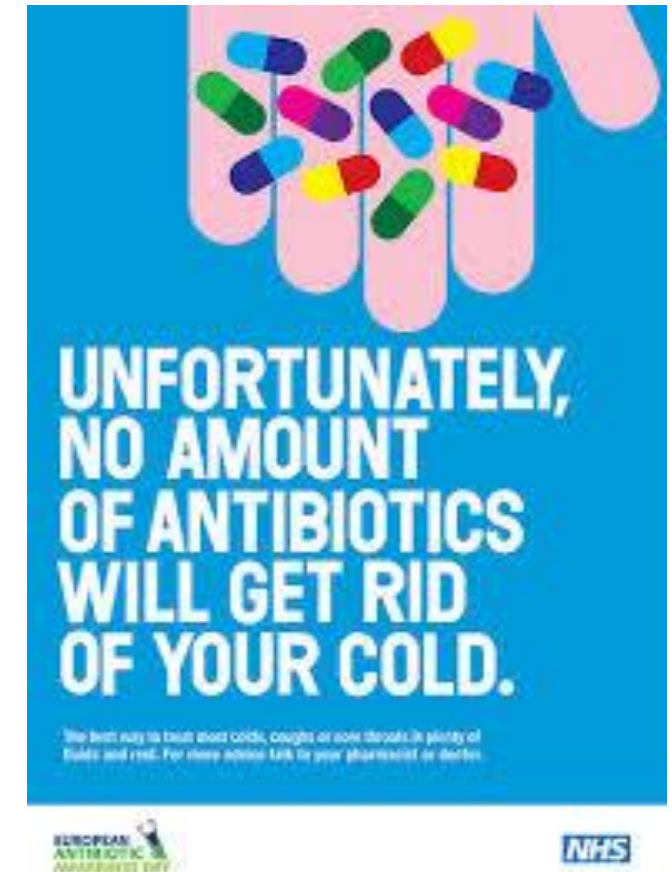
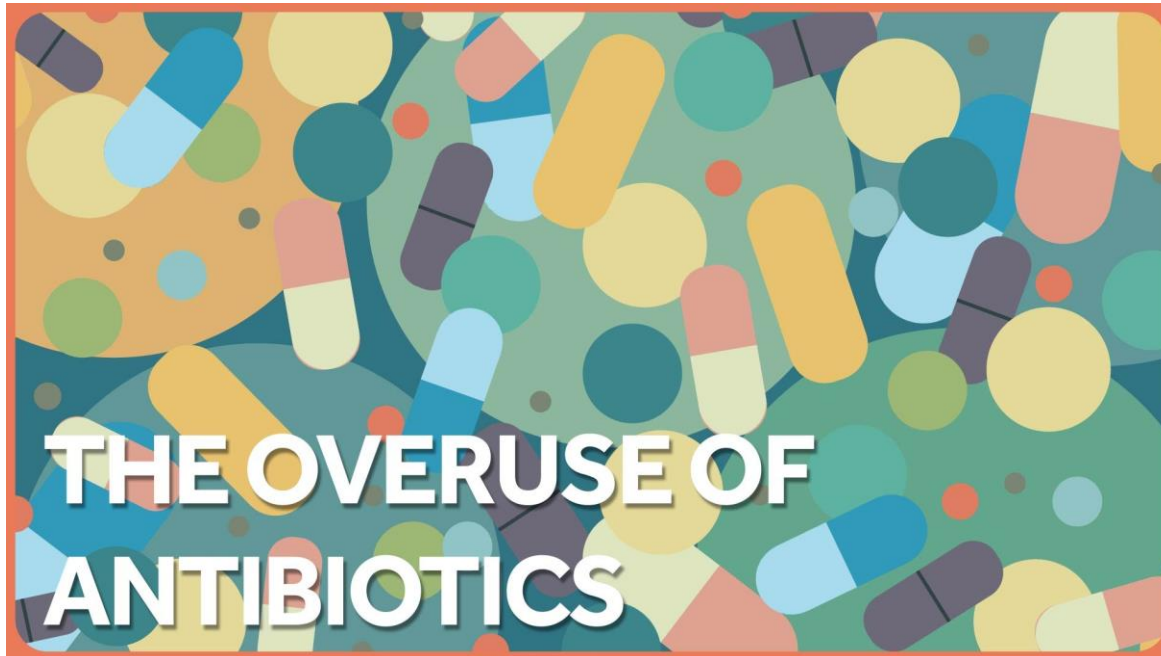
Table 2. Unadjusted Relative Risks for Use of Psychotropic Medications and Falls

Medication	Total n	Fallers n (%)	Relative Risks	95% Confidence Interval
No psychotropic use	898	69 (7.7)	1.00	Referent
Antidepressants	565	85 (15.0)	1.96	1.45–2.64
Sedatives/anxiolytics	663	97 (14.6)	1.90	1.42–2.55
Olanzapine alone	26	5 (19.2)	2.50	1.10–5.68
Olanzapine and other psychotropics	56	14 (25.0)	3.25	1.96–5.40
Risperidone alone	13	1 (7.7)	1.00	0.15–6.67
Risperidone and other psychotropics	25	6 (24.0)	3.12	1.50–6.50
Typical antipsychotic only	73	9 (12.3)	1.60	0.84–3.08
Typical antipsychotic and other psychotropics*	96	19 (19.8)	2.57	1.62–4.08

\* Excludes twelve users of typical antipsychotics who also used olanzapine or risperidone.

# Harms of inappropriate antibiotics

- Clostridium difficile
- Resistance (ESBL, VRE, etc)
- Diarrhoea



# ESBL - Extended-spectrum beta-lactamases

- ESBL are enzymes produced by GNB (mainly *E. coli*) responsible for resistance against penicillins & cephalosporins
- The spread of ESBL-producing bacteria worldwide has become a serious public health concern
- Around 50% of cases are in the community
- Risk factors for such infection include comorbidity, frequent use of health resources, prior use of antibiotics, recurrent UTI, older age and male sex.
- These patients are at risk of receiving inappropriate empirical therapy, resulting in increased morbidity and mortality.

# What about NZ?

- At Canterbury Health Laboratories (CHL) in 2004 there were 5 patients with ESBL-producing E. Coli
  - By 2012 the number of patients with ESBL-producing Enterobacteriaceae was nearly 200 patients, with 11 different species identified.
  - This number had already been eclipsed in the first 8 months of 2013.
- 
- Creighton, J. Sceptibility testing of extended-spectrum- $\beta$ -lactamase (ESBL)- producing Enterobacteriaceae against oral antimicrobials, including fosfomycin and mecillinam NZ J Med Lab Science 2014

- Enterobacteriaceae are spread by hand carriage, contaminated food and water.
- Risk factors for acquisition of ESBL-producing Enterobacteriaceae include previous exposure to antibiotics, previous health care intervention or resident of a long term care facility, or indwelling urinary catheter use



# From BPAC

- Antibiotic treatment is indicated for all people who have symptoms of a urinary tract infection (UTI). A urine culture is not required in the case of uncomplicated infection, however, it is recommended that urine culture (and antibiotic susceptibility) is obtained for males, women who are pregnant, children and people who do not respond to empiric antibiotic treatment within two days, as well as those with “complicated” infection (i.e. other than cystitis).
- BPJ 2013;54

# Uncomplicated cystitis

- In community settings, most uncomplicated cystitis is in women between 20-60
- Acute symptoms are dysuria, urgency, urge- in this setting 95% will have cystitis
- In other patient groups (children, elderly, men) these symptoms are much less likely to represent acute uncomplicated cystitis

# Treatment options for uncomplicated cystitis

- None
  - Alkalinising sachets and increased hydration
  - NSAIDs (1 trial)
  - 3 days trimethoprim
  - 5 days nitrofurantoin
- 
- 3 days AB less likely to lead to resistance or gut flora problems

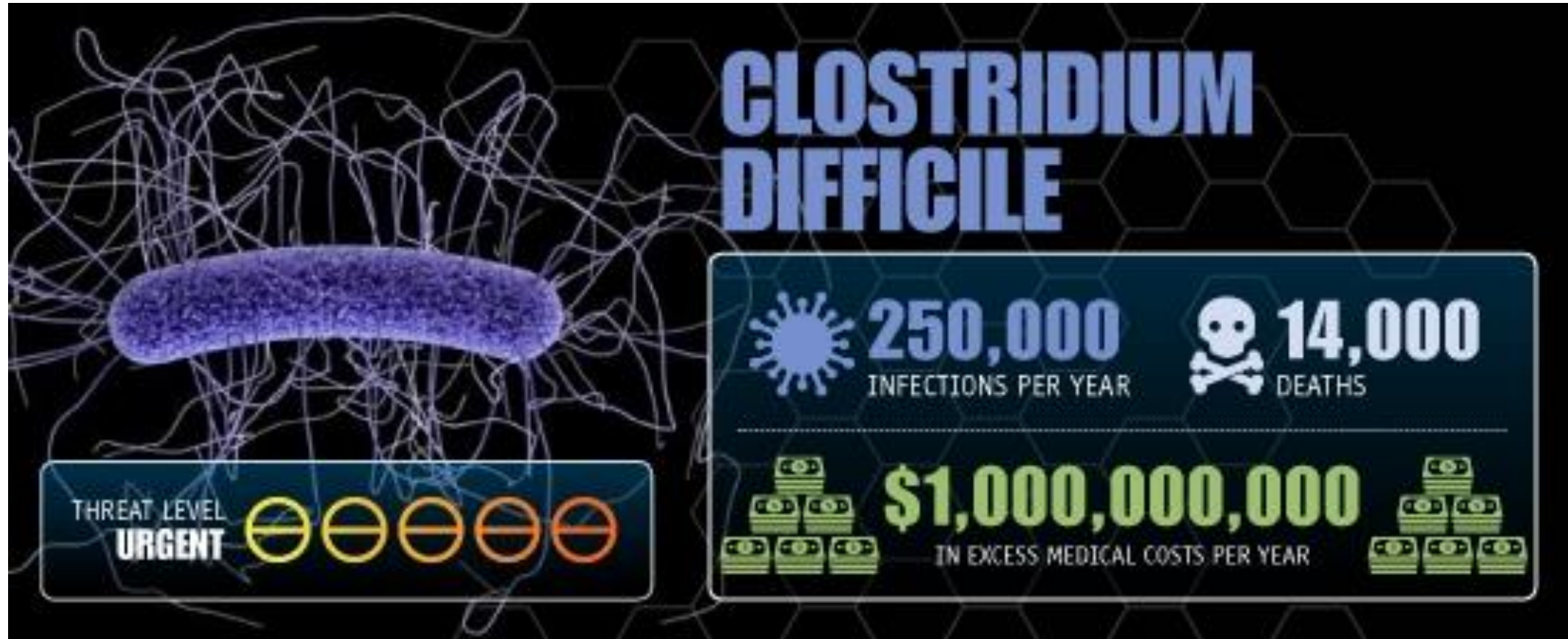
# The problem with empiric Rx of UTI in other groups

- Urinary symptoms are very common in older women
  - About 5% have interstitial cystitis
- Genuine UTI may have no symptoms in this group
- Asymptomatic bacteriuria is common
  - Preschool girls, < 2%
  - Pregnant women about 6% **TREAT**
  - Women aged 65-80y about 25%
  - Men aged 65-80y about 10%
  - Women > 80y about about 30%
  - Men > 80y about 15%

# In all other patients a MSU should be sent to the lab

- Empiric treatment should not be given
- Treat as UTI only if symptomatic

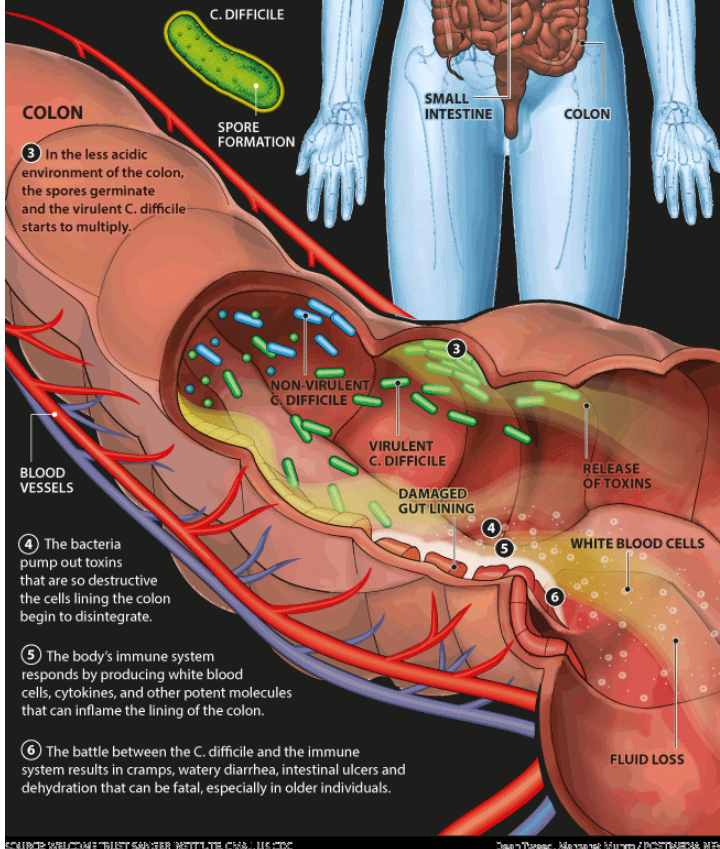
# C Diff toxin in the USA



# ANATOMY OF A C. DIFFICILE INFECTION

*Clostridium difficile* is a common microbe found in washrooms, on pets and even food. It is kept in check in the human intestine by normal gut microbes. Life threatening infections can occur when intestinal microbes are disrupted by antibiotics, giving virulent strains of *C. difficile* a chance to multiply.

- ① Spores of virulent *C. difficile*, which tend to be found in health care settings, are ingested.
- ② The nearly indestructible spores survive the harsh conditions in the stomach and pass through to the intestines.



- Wellington Hospital has between 10 and 12 cases of C Diff each month, Capital & Coast District Health Board infectious diseases specialist Tim Blackmore said.

- Stuff 30/10/12

- Antibiotics knock out many common bowel microorganisms, and allow overgrowth of the hardy ones
- When the *C. difficile* bacteria take over they release a toxin into the bowel
- The toxin causes diarrhoea, fevers, pain, fluid losses and can cause toxic megacolon & death
- Risk of infection increases with age, with 90% of fatal *C. difficile* infections occurring in patients over 65 years old.



# Other risk factors for C. Difficile

- Achlorhydria or hypochlorhydria
- Gastric juices kill C. Difficile and neutralise its toxin
- In a retrospective analysis of > 100,000 discharged patients from a Boston hospital.
- Researchers examined co-prescribed acid suppression therapy (no suppression, H2RA Rx, daily PPI Rx or > daily PPI)
- As the level of suppression increased, the risk of nosocomial C Diff increased from 0.3% in patients not receiving acid suppression, to 0.6% in those receiving H2RA therapy, to 0.9% in those receiving daily PPI treatment, and to 1.4% in those receiving more frequent PPI therapy.
- Howell JAMA, 2010

# Two recent meta-analyses looked at the link between PPIs and CDI.

- 23 studies (300,000 patients) found a 65% increase (relative risk 1.69,  $p < 0.001$ ) in the incidence of CDI among patients on PPIs.
- 42 studies totalling 313,000 patients showed a 1.74 odds ratio ( $p < 0.001$ ) for patients receiving PPI therapy to develop CDI as compared with patients not taking PPIs.
- Janarthanan Am J Gastroenterology, Kwok Am J Gastroenterology (both 2012)

# PPIs can be life-savers

- Healing peptic ulcers (short term use)
- Stress gastritis in ICU (short term use)
- Gastroprotection for patients on aspirin or NSAIDs (long term use)
- Barrett's oesophagus (long term use)
- Zollinger-Ellison syndrome (rare)

# However, many patients use PPIs long term for...

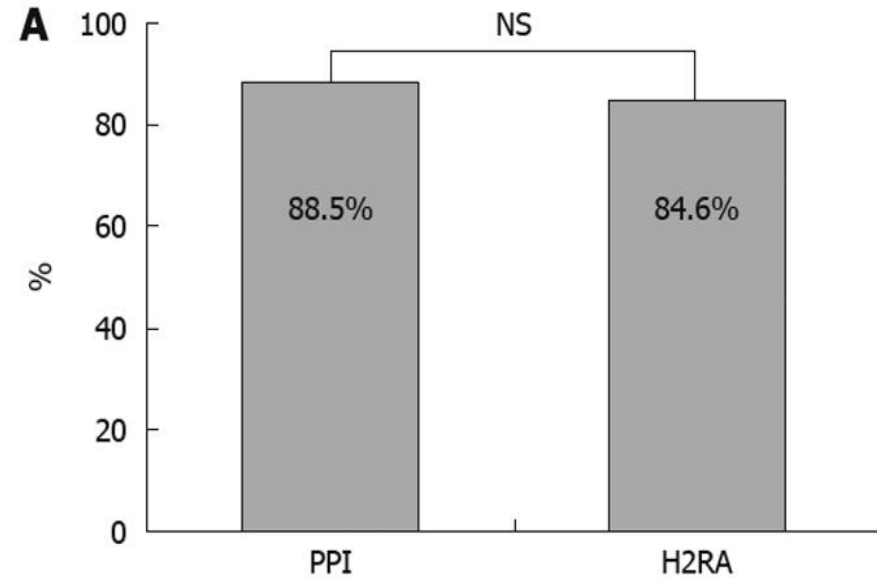
- GORD
- Dyspepsia
- Long-term gastroprotection after the aspirin has been stopped!
- The effects of long-term hypochlorhydria are only starting to be recognised

# Some ADEs of long term PPI

- Reduced absorption of Fe, Ca and Mg
- Impaired breakdown and absorption of micronutrients such as Vitamin B12
- Permissive of bacterial overgrowth in the stomach and lower GIT
- Development of benign polyps in the fundus glands which resolve on discontinuation

# Gastroprotection

- Peptic ulcer healing was endoscopically achieved in 88.5% of PPI group and in 84.6% of H2RA group
- There was no significant difference between the two groups
- Is it time to return to ranitidine?



Japanese study of patients who had had a GI bleed on aspirin. They were all H Pylori negative. Patients were randomised to either a PPI or H2RA, and healing checked at 8 weeks.

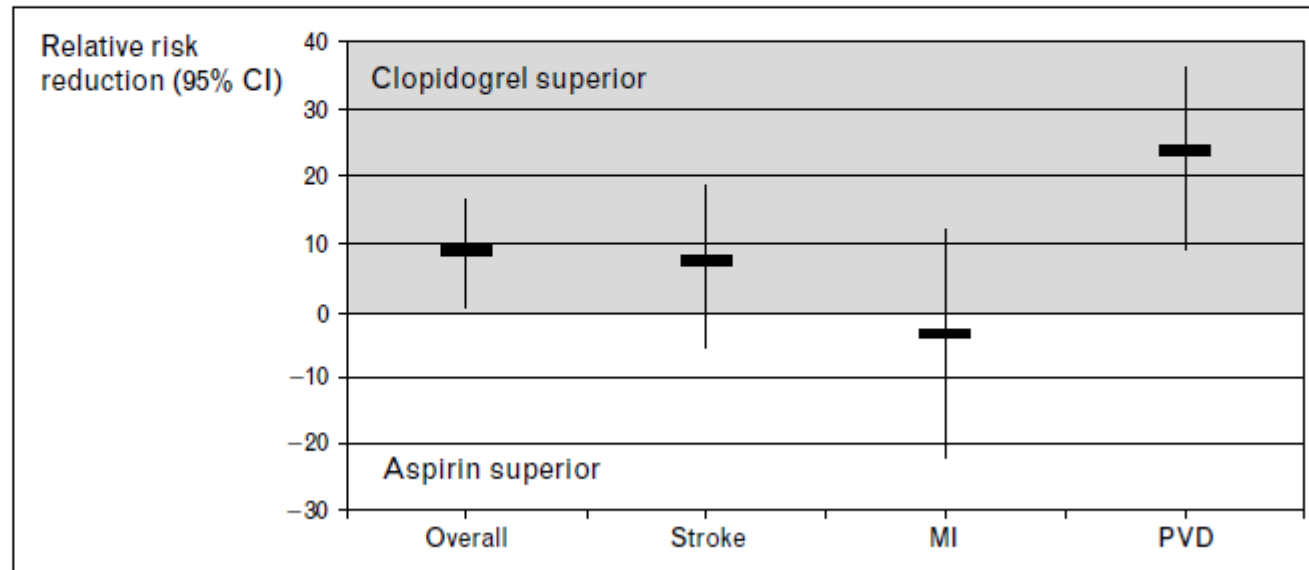
# Alternatives to PPI gastroprotection

- H2RA – fallen out of favour, but probably equally effective for aspirin-induced but not for NSAID
- Low dose PPI
- Clopidogrel instead of aspirin (doesn't need gastroprotection) for anti-platelet effect
- Warfarin/dabigatrin/rivaroxaban if used for AF

# Clopidogrel for secondary prevention

**Figure 2** Estimated composite treatment effect in Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE)

Estimated composite treatment effect (estimate and 95% CI) in Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE), with treatment effects above zero showing benefit for clopidogrel and effects below zero benefit for aspirin. Effects are shown for the overall study findings and by study subpopulations. MI, myocardial infarction; PVD, peripheral vascular disease.

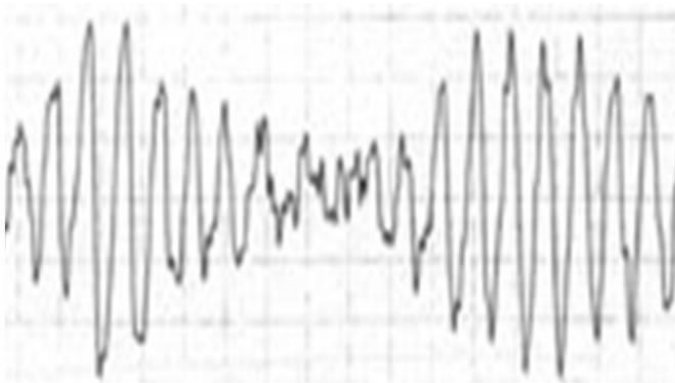


Clopidogrel as effective as aspirin in secondary prevention



# PPIs cause hypomagnesaemia

- Now not uncommon to see patients admitted with VERY low Mg
- Magnesium is required for calcium and phosphate homeostasis



Polymorphic VT (Torsade de Pointes) -  
Wide QRS complexes, regular ventricular  
rhythm with characteristic symmetrical  
variation in wave formation

fastbleep))



# PPI induced hypoMg

- Class effect
- Occurs after a median of 5 years, but range 14 days to 13 years
- Recovery averages 4 days after stopping PPI
- Rechallenge led to hypoMg again in 4 days
- H2RAs not associated with hypoMg

# PPI induced fractures

- 2 studies reported long-term PPI, esp at high doses, increased risk of hip fractures.
- A nested case control study using the GP Research database from the UK
- The study cohort consisted of PPI users and non-users of acid suppression drugs who were >50y & years old and included all patients with an incident hip fractures between 1987–2000
- Both PPIs(OR 1.44, 95% CI-1.3–1.59) and H2Rs(OR 1.23, 95% CI-1.09–1.40) taken for  $\geq 1$ y were associated with an increased risk of hip fractures
- The results of this study were consistent with another 2006 study, a Danish study by Vestergaard which showed that PPI use was associated with an increased risk of hip fractures (OR, 1.45, 95% CI-1.28–1.165)
- Risk is associated with increasing dose and length of Rx
- JAMA 2006:Dec 27

# Hypertension – coming to a place near you

- Patients aged 55-65 years who do not have HT have a **90%** lifetime risk of developing stage 1 hypertension (blood pressure 140 to 159/90 to 99 mmHg) and a **40 percent** lifetime risk of developing stage 2 hypertension (blood pressure  $\geq 160/\geq 100$  mmHg)
- This is mainly due to age-related hardening of the arteries
- Lesson: Almost everyone develops HT in later life. In many patients this will never cause problems.

# Hypertension in the >80s

- Hyvet trial assigned 3845 patients  $\geq 80$  years of age with a sustained SBP  $\geq 160$  mm Hg to either indapamide or placebo.
- Perindopril (2 or 4 mg), or matching placebo, was added if necessary to achieve the target blood pressure of 150/80 mm Hg.
- The primary end point was fatal or nonfatal stroke.
- At 2 years, the mean blood pressure while sitting was 15.0/6.1 mm Hg lower in the active-treatment group
- Patients with dementia or in a RH were excuded

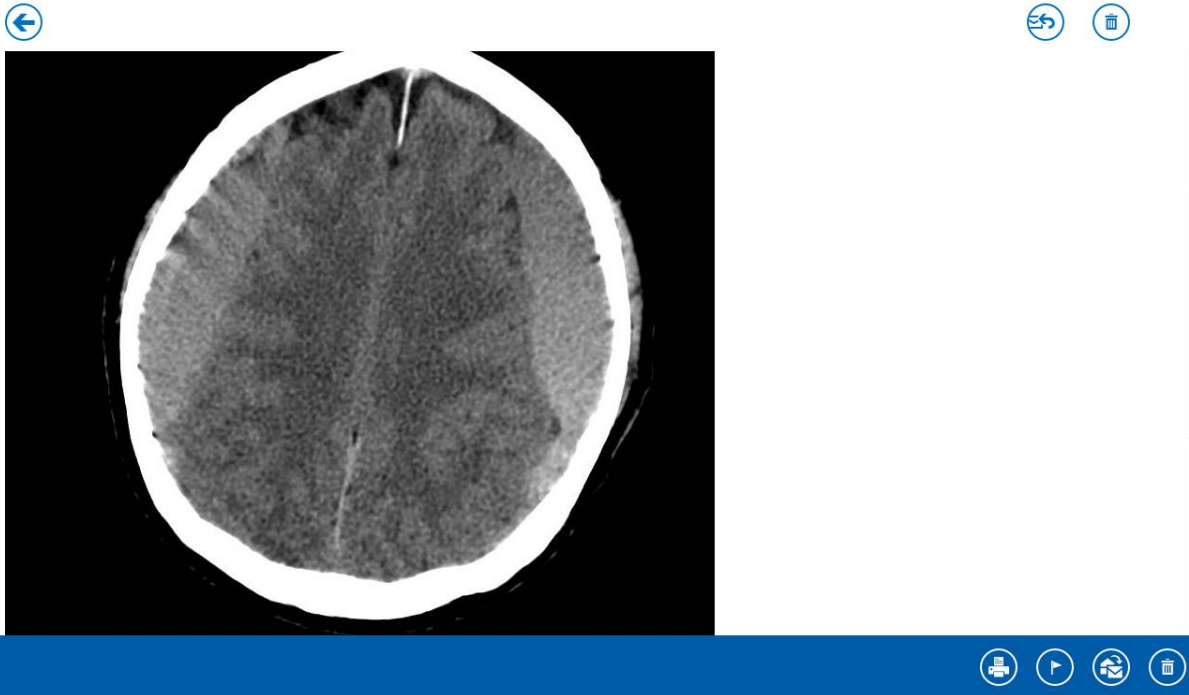
# HYVET trial

- In an ITT analysis, active treatment was associated with
  - 30% reduction in the rate of fatal or nonfatal stroke (95% confidence interval [CI], -1 to 51; P=0.06)
  - 39% reduction in the rate of death from stroke (95% CI, 1 to 62; P=0.05)
  - 21% reduction in the rate of death from any cause (95% CI, 4 to 35; P=0.02)
  - 23% reduction in the rate of death from cardiovascular causes (95% CI, -1 to 40; P=0.06)
  - 64% reduction in the rate of heart failure (95% CI, 42 to 78; P<0.001)
- So Rx reduced death from any cause, except CV causes!
- Didn't change the risk of stroke (which was the primary endpoint)
- Did reduce rate of HF

# Treating hypertension in the frail elderly

- Stop or decrease treatment
- Taper and discontinue antihypertensive drugs if seated resting SBP <140mmHg
- It is not certain whether to discontinue treatment if the patient has a history of stroke
- The target seated SBP can be adjusted upward if there is symptomatic orthostatic hypotension or if standing SBP <140mmHg
- Before stopping, consider whether the medication is treating additional conditions such as AF or symptomatic heart failure

# If the patient is on aspirin etc, they should not run high BPs

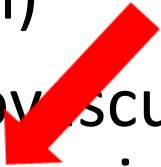


- 83yo Samoan man
- On aspirin for primary prevention
- T2DBM, HT
- Presented “off legs”, confused
- BP 178/88
- Anyone know the diagnosis?



# Risk factors for chronic subdural hematoma include the following:

- Chronic alcoholism
- Epilepsy
- Coagulopathy
- Anticoagulant therapy (including aspirin)
- Cardiovascular disease (eg, hypertension, arteriosclerosis)
- Thrombocytopenia
- Diabetes mellitus



# Orthostatic hypotension

- Fall in BP within 3 minutes of standing of 20mmHg systolic or 10mmHg diastolic
- Symptoms: Lightheadedness, weakness, cognitive impairment, blurred vision, angina, coat hanger pain, falls
- OH is associated with an increased risk of hospitalisation and death
- It is uncommon in the healthy elderly (6%)
- However, occurs in 30–70% of frail elderly

# Orthostatic hypotension- may be asymptomatic

- In 205 patients whose SBP dropped by  $\geq 60$  mmHg on standing, 43% had typical symptoms, 24% had atypical symptoms (e.g., backache or headache) and 33% denied any symptoms at all
  - So a negative response to a question like 'do you get dizzy or light-headed when you stand up' is not adequate screening for OH
  - Many Rx cause OH by multiple mechanisms, including diuretics, vasodilators, alteration of autonomic reflexes (TCAs) CNS depression.
  - This include alcohol; antihypertensives; diuretics; other cardiovascular agents such as nitrates; and CNS agents, such as antiparkinsonian drugs, antidepressants, neuroleptics and sedative agents
- 
- Mader SL. Orthostatic hypotension in older patients. *Aging Health* 2, 54–61 (2006).

# Bradycardia (officially $HR < 50 \text{ bpm}$ )

- Bradycardia can cause lots of problems & is very common
- Many elderly take multiple AV nodal blockers
- Eg. diltiazem/verapamil, beta blockers, digoxin, amiodarone
- Other drugs causing bradycardia include cholinesterase inhibitors eg donepezil
- Many elderly have co-existent sinus node dysfunction, meaning they are more prone to drug induced bradycardia

# Drug induced bradycardia

- Bradycardia may be asymptomatic but can present with syncope, fatigue, dizziness, cognitive impairment, angina, heart failure, and just “off legs”.
- When using drugs that can cause bradycardia, checking the HR is always worthwhile
- Some valvular disorders are better managed with a higher HR.
- If  $HR < 60$ , decrease dose of nodal blocker

# Lessons for today

- The WHO guide to good prescribing is simple and effective
- Know your stats (ARR, RRR, NNT and NNH)
- Know your patient
- Know your drugs- all will be fine!!







# Polypharmacy – identify the issues

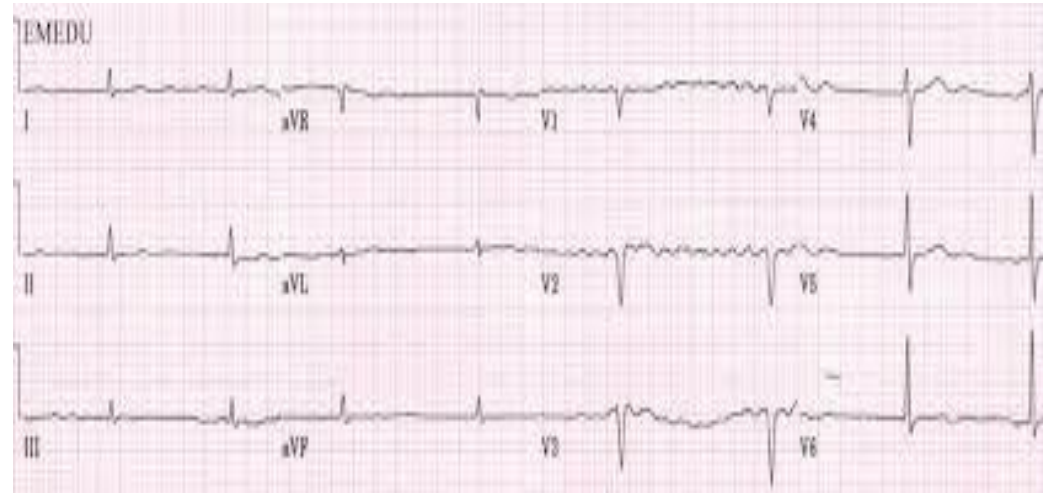
- Pat is an 84yo woman, widowed 10y ago
- She lives alone with home help 3x week for shopping, showering, cleaning. She doesn't drive after a scare 3y ago (hit a parked car, which she didn't recollect)
- Pat has 2 children (daughter in Auckland and son in Brisbane)
- Pat's medical history includes a previous hip fracture (2014) after which she was in hospital for > a month, hypertension, OA of her spine, depression and anxiety, AF with mild rate-related heart failure
- Pat's eGFR is 36ml/min, her albumin is 22g/L (>35) and her INR is 1.0

# Pat's medications

- NKDA
  - Alendronate plus 1 weekly
  - BFZ 2.5mg mane
  - Diltiazem CD 240mg mane
  - Amlodipine 5mg daily
  - Aspirin EC 100mg daily
  - Omeprazole 40mg daily
  - Dothiepin 75mg nocte
  - Fentanyl patch 50mcg/hr (back & hip pain)
  - Metamucil 1 tsp mane
- Pat's complaints include:
  - Lightheadedness on standing and worry about a further fall
  - Sedation
  - Constipation (BO every 2-3 days)
  - ?worsening of her heart failure (ankle oedema)
  - Anxiety that she may have to go into residential care and leave her cat behind

# Pat's exam

- Looks tired, sleepy
- Weight 54kg
- MOCA 24/30 (cognition test)
- HR 50bpm irreg,irreg
- BP L 134/76
- BP S 112/60
- Ankle oedema, shoes have been modified (seam cut)



# ADEs in the elderly – why are they more common?

## PK changes

- Impaired renal function
  - ↓ renal Q
  - ↓ renal mass
- Impaired hepatic function
  - ↓ hepatic Q
- Increased adiposity:muscle
- *Mangoni Br J Clin Pharmacol* **57**:1 6–14 6

## PD changes

- Attenuated baroreceptor response
- Receptor downregulation

# ADEs in the elderly – why are they more common?

- PK changes
  - ↓ renal clearance of drugs
  - ↓ first pass elimination
  - ↑ VD of lipophilic drugs
  - ↓ VD hydrophilic drugs
- Accumulation of high  $F_u$  drugs and some drugs with active/toxic metabolites
- $F$  of drugs undergoing extensive first-pass metabolism eg. propranolol and labetalol ↑↑
- The main effect of the ↑ VD is ↑  $T_{1/2}$  of diazepam, thiopentone, lignocaine
- ↑↑ [gentamicin, digoxin, ethanol, theophylline]

# ADEs in the elderly – why are they more common?

- Attenuated baroreceptor response
- Receptor downregulation
- An inability to  $\uparrow$ HR and vasoconstrict in response to anti-hypertensives  $\rightarrow$  OH  $\rightarrow$  falls
- Some drugs are less effective eg. Beta-blockers, frusemide, beta agonists

# Formulation of Pat's problems

[illegible]

# My formulation of Pat's problems

Issue	Potential cause
Frailty	Polypharmacy, previous hip #
Risk of another fall and # hip	OH, bradycardia, CNS active drugs, osteoporosis, poorly fitting footwear
Osteoporosis	?PPI induced
Sedation, poor cognition	?opioid ?TCA ?frailty
Bradycardia	Diltiazem
OH	BFZ, diltiazem, opioid, dothiepin, amlodipine
Ankle oedema	Amlodipine, HF
Constipation	Opioid, TCA



# How would you change Pat's medication regimen?

From	To
Alendronate plus 1 weekly	
BFZ 2.5mg mane	
Diltiazem CD 120mg mane	
Amlodipine 5mg mane	
Aspirin EC 100mg mane	
Omeprazole 40mg daily	
Dothiepin 75mg nocte	
Fentanyl patch 50mcg/hr	
Metamucil 1 tsp mane	

# How would you change Pat's medication regimen?

From	To
Alendronate plus 1 weekly	? Zoledronic acid infusion (once yearly)
BFZ 2.5mg mane	Frusemide 20mg mane (if weight ↑ by 1kg)
Diltiazem CD 120mg mane	Metoprolol CR 23.75mg mane (titrate to HR 60)
Amlodipine 5mg mane	
Aspirin EC 100mg mane	Clopidogrel 75mg daily
Omeprazole 40mg daily	
Dothiepin 75mg nocte	Dothiepin 50mg nocte and reduce, or change to mirtazepine
Fentanyl patch 50mcg/hr	Fentanyl 25mcg/hr and reduce
Metamucil 1 tsp mane	Laxsol 2 bid

# Pat follow-up

- Reassess in a week or so (HR, BP L & S, MOCA, ECG, sedation)
- For chronic non-malignant pain, opioids are not very effective
- Other options are regular paracetamol, acupuncture, TENS
- Anxiety and depression are huge issues in chronic pain and loneliness
- Mirtazepine or low dose TCI is safest for falls in elderly

# Pat's follow up

- Looks less sedated and is clearer in thought
- HR 62, BP 176/86 (no OH)
- Bowels opening

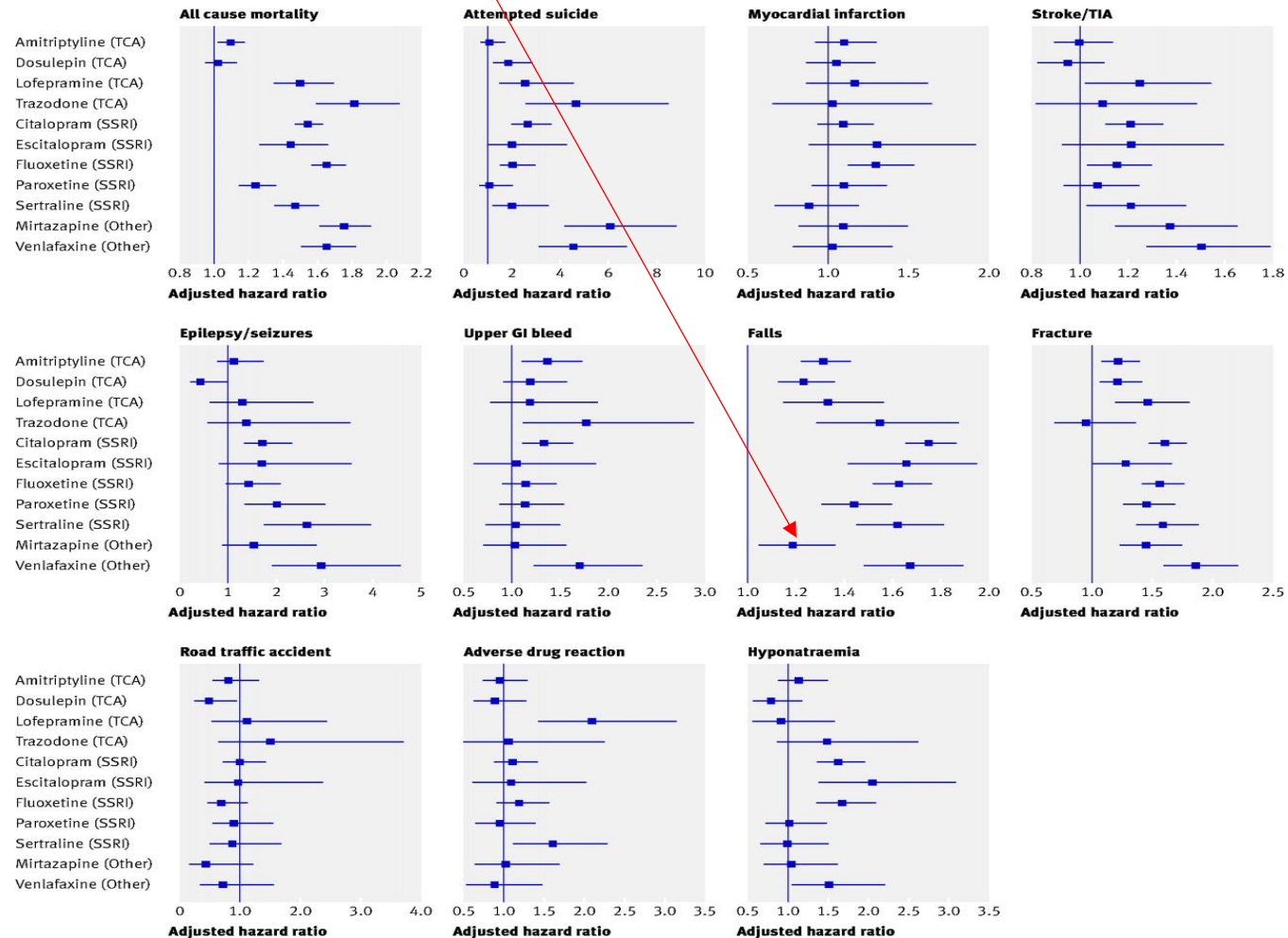
# Depression in the elderly

- Common
- Especially in RH residents and post major hospital admission
- Treatment works as well as it does in younger patients
- Drug choice depends on co-morbidities
- SSRIs and TCAs can both cause falls
- If choosing an SSRI citalopram has a shorter T<sub>1/2</sub> and doesn't inhibit CYP 2D6
- If choosing TCA nortriptyline is least anticholinergic

# Safest anti-depressants

- For falls, the best is mirtazapine, next is doxepin

*BMJ 2011;343:d4551*



# ADEs in the frail elderly

- Common
- Related to polypharmacy
- Related to anti-cholinergic and sedative burden
- Often are due to excessive dose in renal impairment
- Can result in geriatric syndromes which may be mistaken for normal ageing (falls, delirium/dementia)
- Can be minimised by oligopharmacy





# Inappropriate Polypharmacy- how to resolve it

Chris Cameron

# Inappropriate Polypharmacy is harmful

- Causes frailty
- Falls
- Hospitalisations
- Mortality
- Delirium
- Causes errors in prescribing, dispensing and administration

# How to treat polypharmacy

- Prevention is better than cure
- My strategies:
  - Know your patient
  - Know what you are treating
  - Know your drugs
  - Know your evidence
  - Talk to your patient
  - Prune, cut, trim
  - Review and revise

# 1) Know your patient



- Young man
- eGFR= 100ml/min
- Lean mass>>adipose
- Hepatic Q 1.5L/min
- Hepatic mass Normal
  
- Expected years to live - 50

# 1) Know your patient



- May be frail
- Adiposity >>lean muscle mass
- Liver Q 500ml/min
- GFR <60ml/min always
- Remember we lose 1% GFR per year after age 40
- Multimorbidity
- Expected years to live- 2

# Know what you are treating

- Patient 1
  - Treatment of risk factors will be appropriate
  - Long term view
- Patient 2
  - Treatment of risk factors inappropriate
  - Short term view
  - Avoid complications

# Know your patient

- Assessing frailty in the clinic/ pharmacy/ home
- Walking speed is easiest
  - Give patient 30sec and see how far they can walk (<24m –frailty likely)
  - Timed get up and go test
  - Do you need help to do your shopping (good screen)



# Know your drugs

- Medicines reconciliation
- Manage my Health
- See all drugs
- Include OTC
- Include injections
- Include steroid creams



# Know your evidence (or lack of)

- Very few clinical trials have elderly participants
- Hardly any have frail elderly participants
- Applying evidence from non-frail adults or non-old adults to elderly and frail elderly is not justifiable
- PK and PD differences

# Talk to your patient

- What is important to him/her?
- What is important to the family (may not be the same thing)?
- Is QOL more important than quantity of life?
- Are there troublesome symptoms that are poorly controlled?
- Have the family noted any changes in cognition, activity?
- Have there been falls?
- Do they take their medication? Do they need help to do so?
- If they don't take some/all of it, why not?

# Prune, cut trim if appropriate

- In frail all medication for primary prevention can be stopped (no evidence, life expectancy)
- In non-frail elderly this probably applies as well
- If there are falls, check for OH and bradycardia
- If there is OH, trim anti-hypertensives (some gradually)
- If there are symptoms and a drug is treating them may need to increase dose or change it
- Many drugs for secondary prevention can be stopped

# Review and revise

- See patient in a week
- Recheck how they are feeling
- Check what needs to be checked
- Refine

# Tools for reducing polypharmacy

- There are a few
- I don't use one
- Pill Pruner
- Stop/Start
- Beers criteria