DRUG & THERAPEUTICS INFORMATION SERVICE
DATIS

Older people and harms from medicines: A pharmacy perspective

Debra Rowett
Director
Drug and Therapeutics Information Service
Repatriation General Hospital, South Australia

How do we see harms from medicines?

- From a society’s perspective
- From a clinician’s perspective
- From patient’s perspective

How do we see harms from medicines?

- Adverse or negative consequences associated with medicines have been documented since the earliest of medical writings but a broader societal concern with medicine related problems is more a modern phenomena.

Older Australians at higher risk of Medication Related problems

- Over 1 in 4 adverse drug events in older people is considered preventable.
- One in three unplanned hospital admissions for Australians aged over 75 years is related to medicines use; half of these are considered preventable.
  - 230,000 hospital admissions each year
  - 500,000 visits to the general practitioner each year
  - Cost over $1.2 billion
- More hospitalisations than are due to diabetes, asthma or heart failure

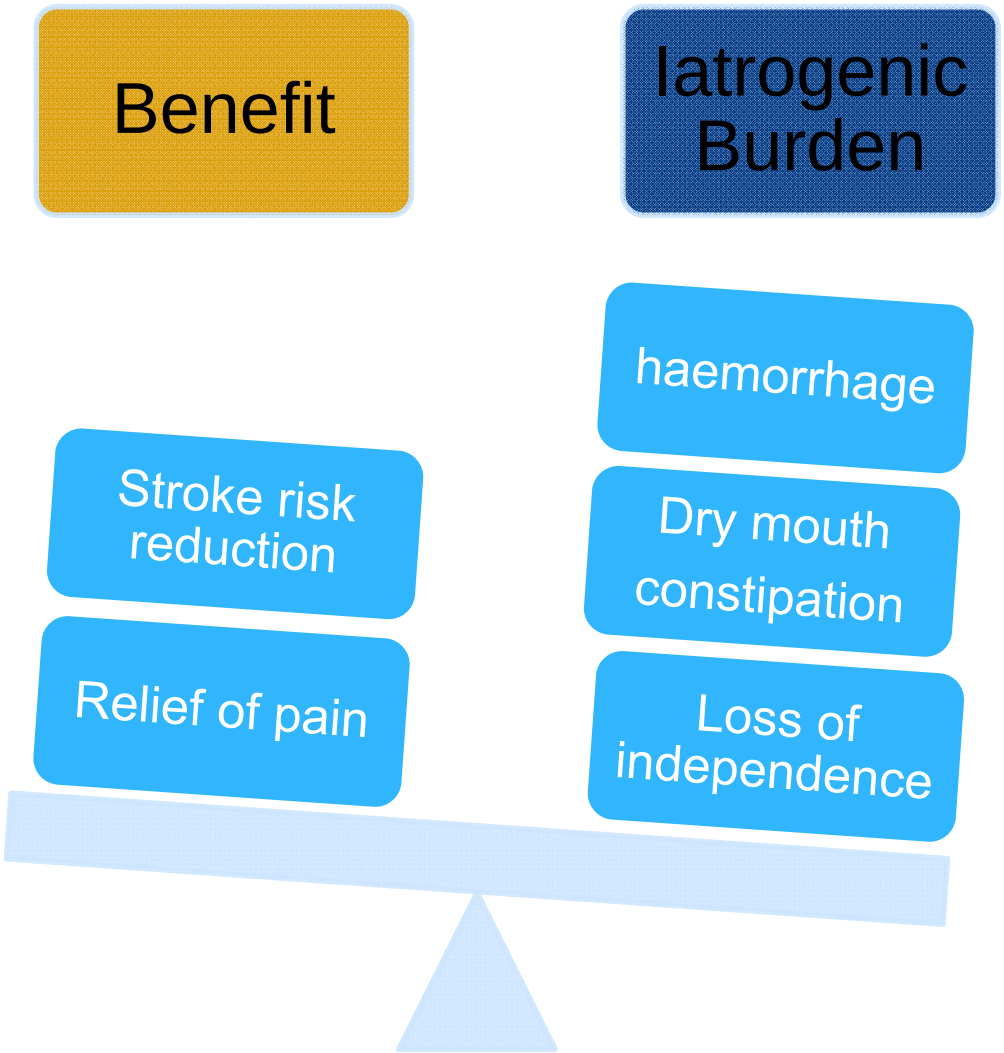
Literature Review: Medication Safety in Australia 2013 Roughead and Semple

Maximising Outcomes Minimising Harms

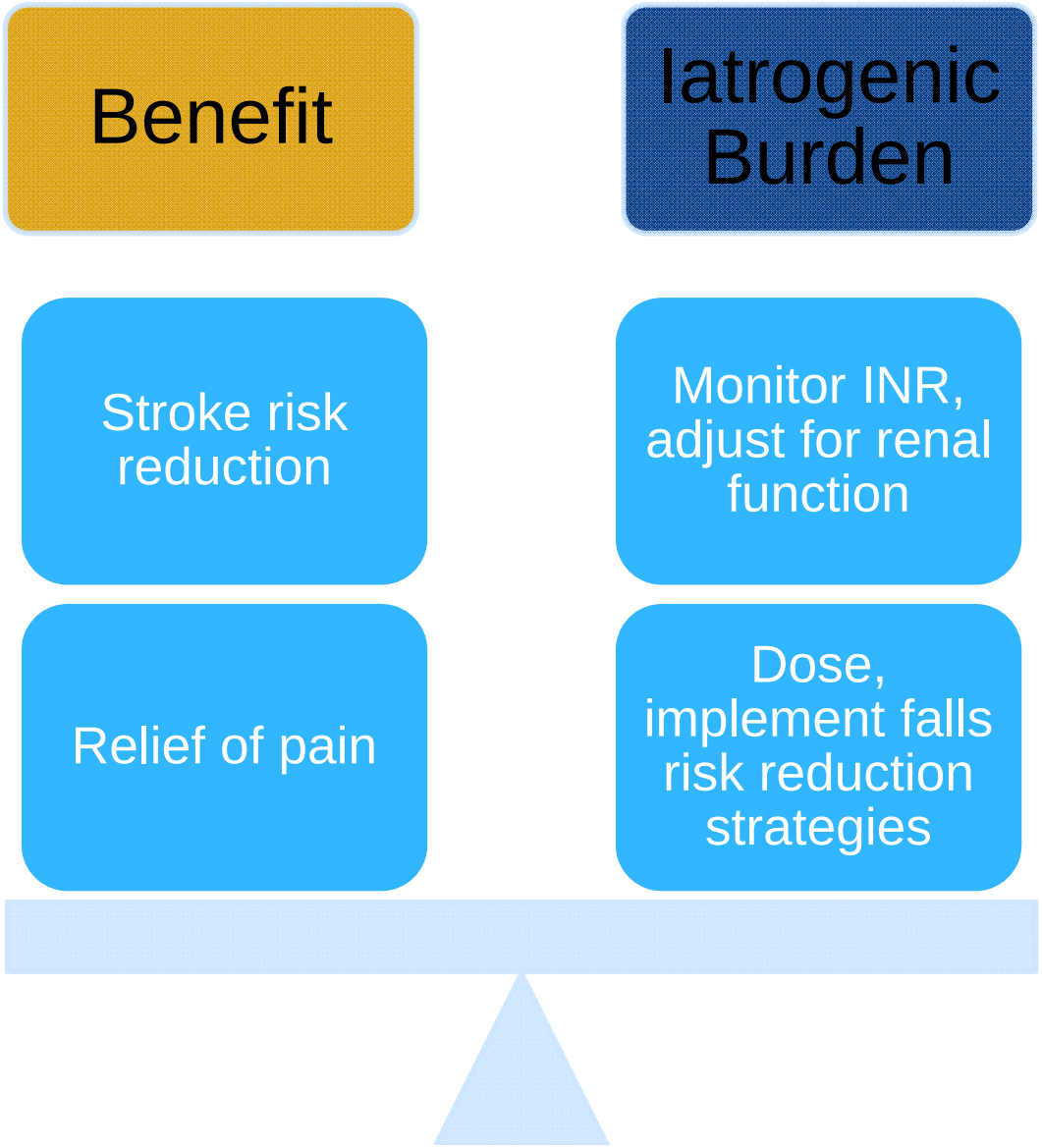
- There is compelling evidence that medicines have contributed to decreasing symptom burden, health service utilisation and had mortality benefits.

- However, medicines also cause adverse or negative consequences.

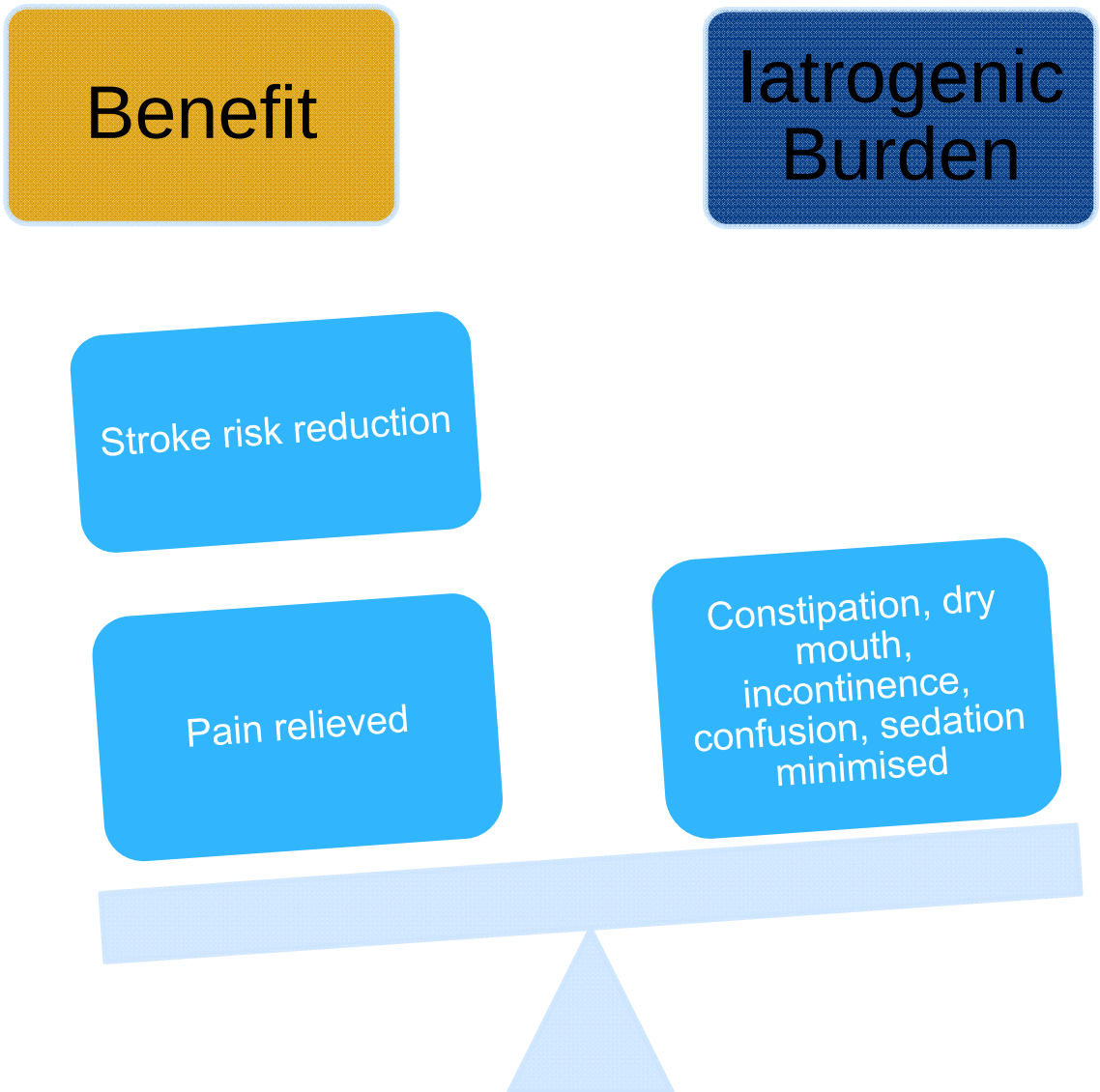
Balance benefit with iatrogenic burden



Balance benefit with iatrogenic burden



Balance benefit with iatrogenic burden



Therapeutics

Efficacy **Safety**

Trial design principally to examine efficacy in single conditions – often exclude those with multimorbidity

Efficacy Safety

Maximising outcomes Minimising harm

- Full safety profile of the drug is not known when a drug enters the market and can change over the lifecycle of the drugs use

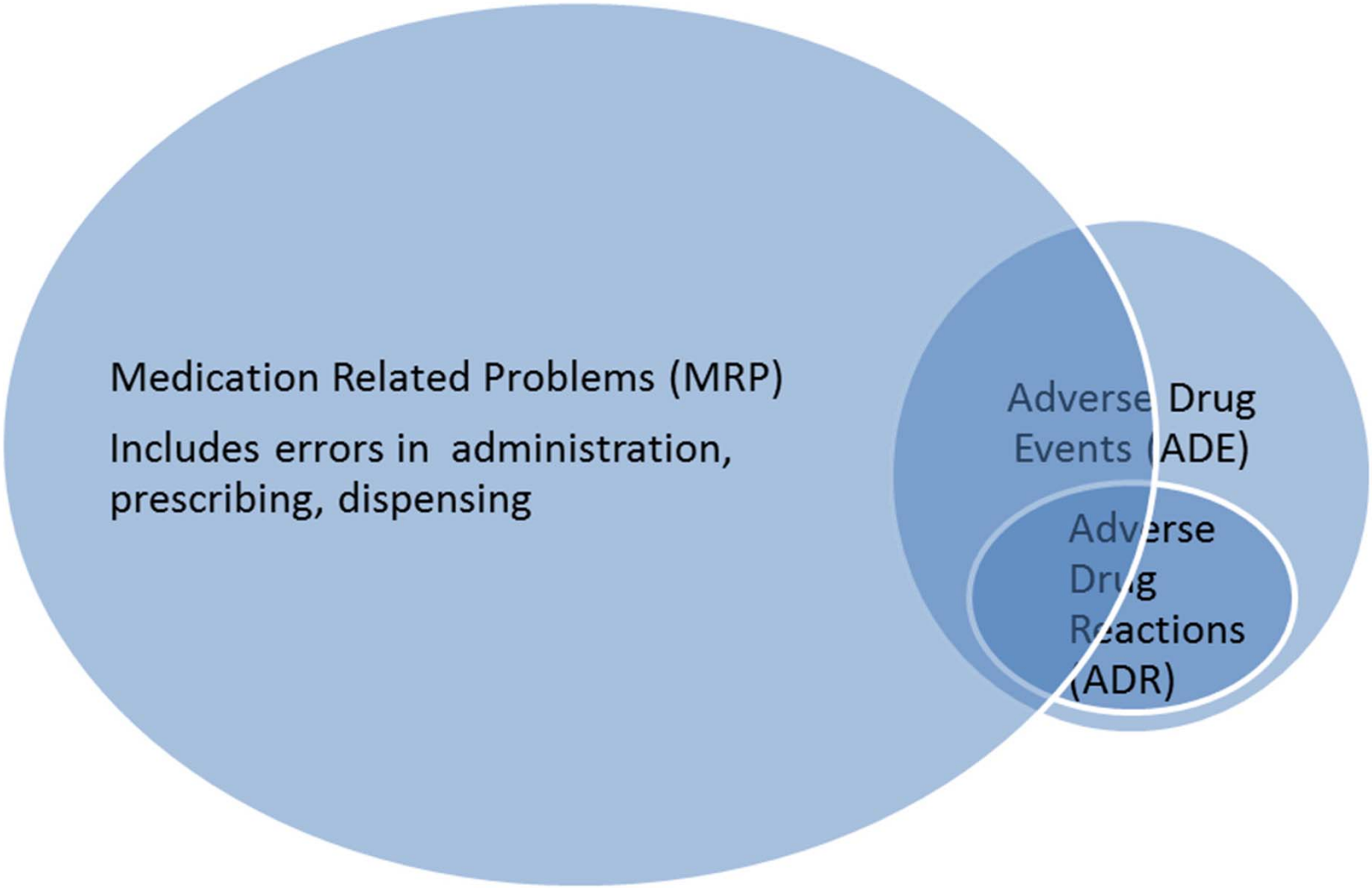
- Measures used to identify adverse effects often limited to what is known, potential versus actual harm

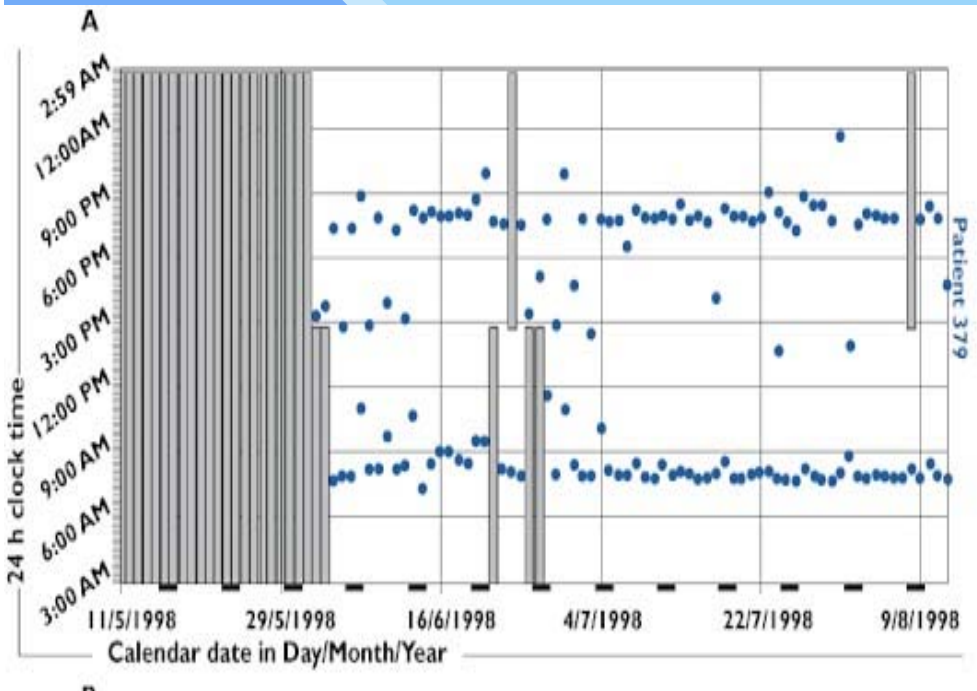
Older people and harms from medicines: A pharmacy perspective

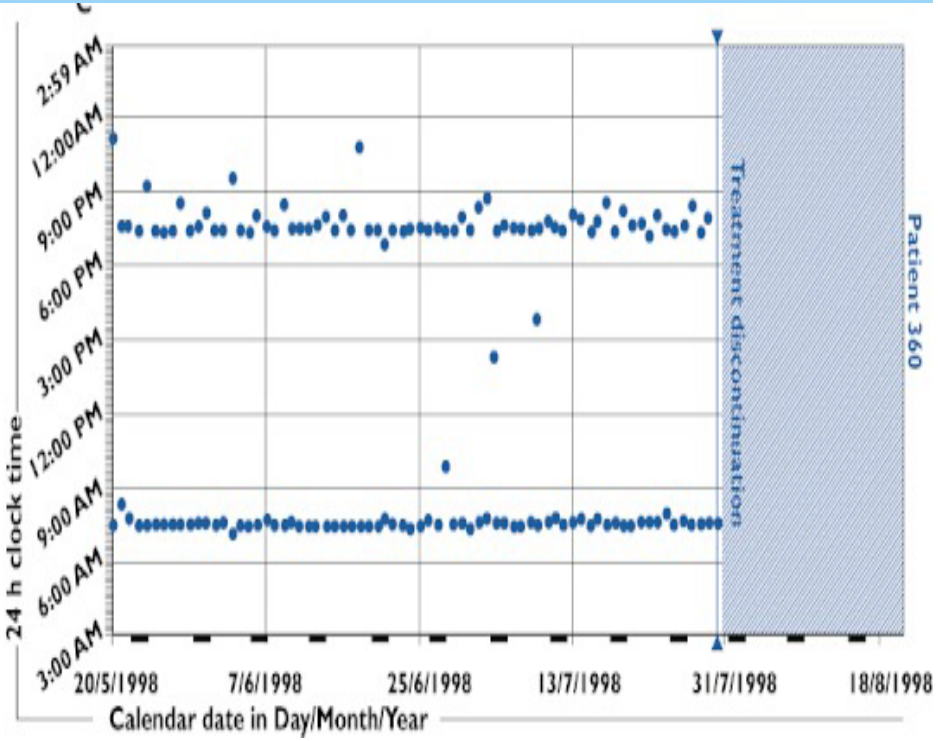
- Need to take account of patient preferences and choices – what they consider are important adverse effects or outcomes from their medicines

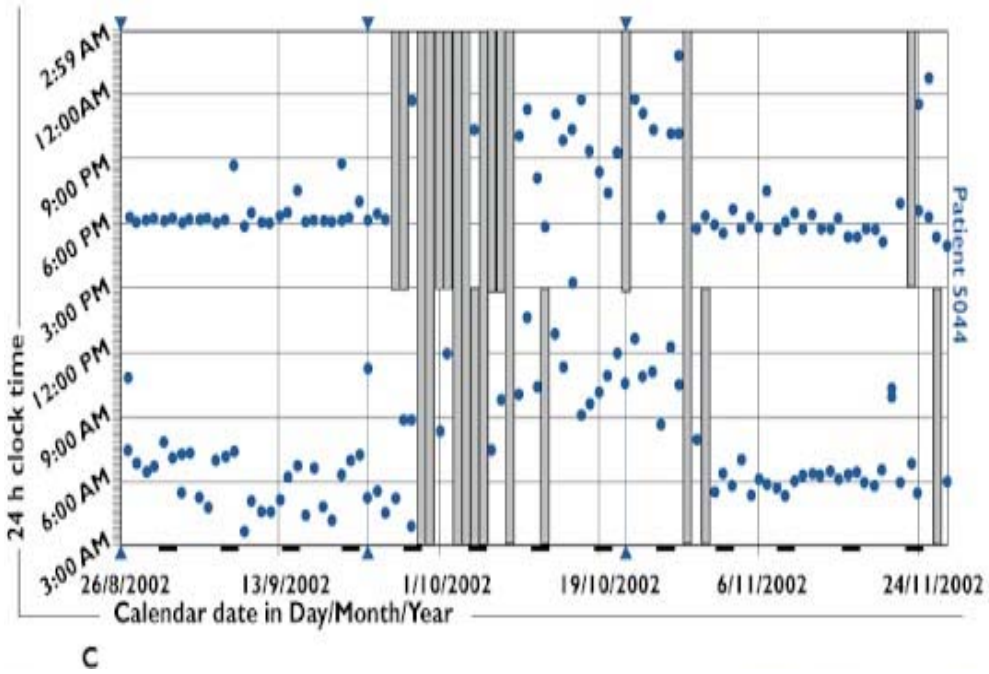
Older people and harms from medicines: A pharmacy perspective

- Increasing use of medicines
- Increasing duration of therapy
- Increasing potential for drug - drug interactions
- Increasing potential for drug - disease interactions


Medication Related Problems (MRP)
Includes errors in administration, prescribing, dispensing
Adverse Drug Events (ADE)
Adverse Drug Reactions (ADR)







Patient medication adherence not always what you think

And there may be good reasons

A new taxonomy for describing and defining adherence to medications. Vrijens B, De Geest S, Hughes DA, et al. Br J Clin Pharmacol. 2012 May;73(5):691-705.

ORIGINAL INVESTIGATION

LESS IS MORE

Development and Validation of a Score to Assess Risk of Adverse Drug Reactions Among In-Hospital Patients 65 Years or Older

The GerontoNet ADR Risk Score

Graziano Onder, MD, PhD; Mirko Petrovic, MD, PhD; Balamurugan Tangiisuran, MPharm, PhD; Marieke C. Meinardi, MD; Winih P. Markito-Notenboom, MD; Annemie Somers, MPharm; Chakravarthi Rajkumar, MD, PhD; Roberto Bernabei, MD; Tischa J. M. van der Cammen, MD, PhD

Arch Intern Med. 2010;170(13):1142-1148

Article

Cognitive Effects of Atypical Antipsychotic Medications in Patients With Alzheimer's Disease: Outcomes From CATIE

Cheryl L.P. Vigen, Ph.D.
Wendy J. Mack, Ph.D.
Richard S.E. Keefe, Ph.D.
Mary Sano, Ph.D.
David L. Sultzer, M.D.
T. Scott Stroup, M.D.
Karen S. Dagerman, M.S.
John K. Hsiao, M.D.
Barry D. Lebowitz, Ph.D.
Constantine G. Lyketsos, M.D., M.H.S.
Pierre N. Tariot, M.D.
Ling Zheng, Ph.D.
Lon S. Schneider, M.D.

Objective: The impact of the atypical antipsychotics olanzapine, quetiapine, and risperidone on cognition in patients with Alzheimer's disease is unclear. The authors assessed the effects of time and treatment on neuropsychological functioning during the Clinical Antipsychotic Trials of Intervention Effectiveness–Alzheimer's Disease study (CATIE-AD).

Method: CATIE-AD included 421 outpatients with Alzheimer's disease and psychosis or agitated/aggressive behavior who were randomly assigned to receive masked, flexible-dose olanzapine, quetiapine, risperidone, or placebo. Based on their clinicians' judgment, patients could discontinue the originally assigned medication and receive another randomly assigned medication. Patients were followed for 36 weeks, and cognitive assessments were obtained at baseline and at 12, 24, and 36 weeks. Outcomes were compared for 357 patients for whom data were available for at least one cognitive measure at baseline and one follow-up assessment that took place after they had been

Antipsychotics are of limited benefit in the treatment of people with behavioural and psychological symptoms of dementia

Antipsychotics in dementia

What concerns are associated with prescribing antipsychotics for people with dementia?

The Banerjee report (November 2009) was an independent report commissioned by the Department of Health[1]. It supports the need to follow NICE/SCIE guidelines[2] with regard to behavioural and psychological symptoms of dementia. It recognised the **limited benefits** that have been demonstrated in clinical trials for antipsychotics when used to treat behavioural and psychological symptoms of dementia (BPSD). The report concluded that:

- Antipsychotics are in general over-prescribed for the treatment of behavioural and psychological symptoms of dementia.
- About 180,000 people with dementia are treated with antipsychotic medication in England per year.
- Of these, up to 36,000 may derive some benefit from treatment, but an additional 1,800 may die and an additional 1,620 suffer a cerebrovascular adverse event (around half of which may be severe) per year.
- If support was available to provide alternative methods of managing behavioural problems, prescribing of antipsychotics could be reduced by up to two-thirds in people with dementia.

Raising the quality of care for people with dementia and their carers is a major Government priority[3,4].

Is there a place for the prescribing of antipsychotics for people with BPSD?

Pharmacological interventions, including antipsychotics, have only a limited role in the management of non-cognitive symptoms of dementia[4]. The NICE dementia quality standard[6] states 'the goal for the proportion of people with dementia and mild-to-moderate non-cognitive symptoms who are prescribed antipsychotic medication should be 0%'.

- NICE/Social Care Institute for Excellence (SCIE) clinical guideline[2] states that people with dementia who develop non-cognitive symptoms or behaviour that challenges should be offered a pharmacological intervention in the first instance **only if they are severely distressed or there is an immediate risk of harm to the person or others.**
- Choose an antipsychotic after an individual risk–benefit analysis.
  - Start on a low dose and then titrate upwards.
  - Limit treatment time and review regularly (at least every 3 months or according to clinical need).
- For less severe distress and/or agitation, initially use a non-drug option.
- **Do not use** antipsychotic drugs for mild to moderate non-cognitive symptoms in:

ARCH

Care homes' use of medicines study: prevalence, causes and potential harm of medication errors in care homes for older people

N D Barber,[1] D P Alldred,[2] D K Raynor,[2] R Dickinson,[2] S Garfield,[1] B Jesson,[1] R Lim,[3] I Savage,[1] C Standage,[2] P Buckle,[3] J Carpenter,[4] B Franklin,[1,5] M Woloshynowych,[5] A G Zermansky[2]

Differential risk of death in older residents in nursing homes prescribed specific antipsychotic drugs: population based cohort study

K F Huybrechts *instructor in medicine*[1], T Gerhard *assistant professor*[2], S Crystal *board of governors professor*[2], M Olfson *professor of clinical psychiatry*[3], J Avorn *professor of medicine*[1], R Levin *programmer*[1], J A Lucas *assistant research professor*[4], S Schneeweiss *associate professor of medicine*[1]

Adverse drug events masquerading as Geriatric syndromes

TABLE 1 Signs and symptoms of medicines-related problems and potential contributing medicines*[9,10]

COMMON PRESENTING SIGNS AND SYMPTOMS	POTENTIAL CONTRIBUTING MEDICINES AND MEDICINE CLASSES
Dizziness/fainting	Anticholinergic medicines,† antidepressants, antihypertensives, antipsychotics, benzodiazepines
Falls	Antidepressants, antipsychotics, benzodiazepines, opioids
Agitation/tremors	Antipsychotics, metoclopramide, prochlorperazine
Confusion	Anticholinergic medicines, antipsychotics, benzodiazepines
Shortness of breath	Heart failure medicine under/not prescribed
Rash/itch	Antibiotics, anti-epileptics, opioids
Bleeding/bruising	Aspirin, clopidogrel, NSAIDs, oral anticoagulants
Nausea/anorexia	Digoxin overdose, metformin (especially when starting metformin in patients with kidney impairment, or in patients who are not adhering to therapy), opioids
Constipation	Calcium supplements, diltiazem, iron supplements, opioids, verapamil
Urinary incontinence	Antipsychotics, benzodiazepines, cholinesterase inhibitors, diuretics
Impaired physical function‡	Cumulative exposure to anticholinergic and sedative medicines

http://www.nps.org.au/publications/health-professional/medicinewise-news/2013/older-wiser-safer

Recognise when a medicine is prescribed to treat ADRs caused by a current medicine

- Your examples

Other examples

Medicine		Adverse drug reaction (ADR)		Second medicine prescribed to treat ADR of first medicine
Cholinesterase inhibitor	→	Incontinence	→	Anticholinergics (e.g. oxybutynin)
NSAIDs	→	Hypertension	→	Antihypertensives
Thiazide diuretics	→	Hyperuricaemia, gout	→	Allopurinol or colchicine
Metoclopramide	→	Symptoms of parkinsonism	→	Levodopa
ACE inhibitor	→	Cough	→	Cough suppressant and/or antibiotic
Antipsychotics	→	Extrapyramidal adverse effects	→	Levodopa, anticholinergics

NSAIDs non-steroidal anti-inflammatory drugs, **ACE** angiotensin converting enzyme

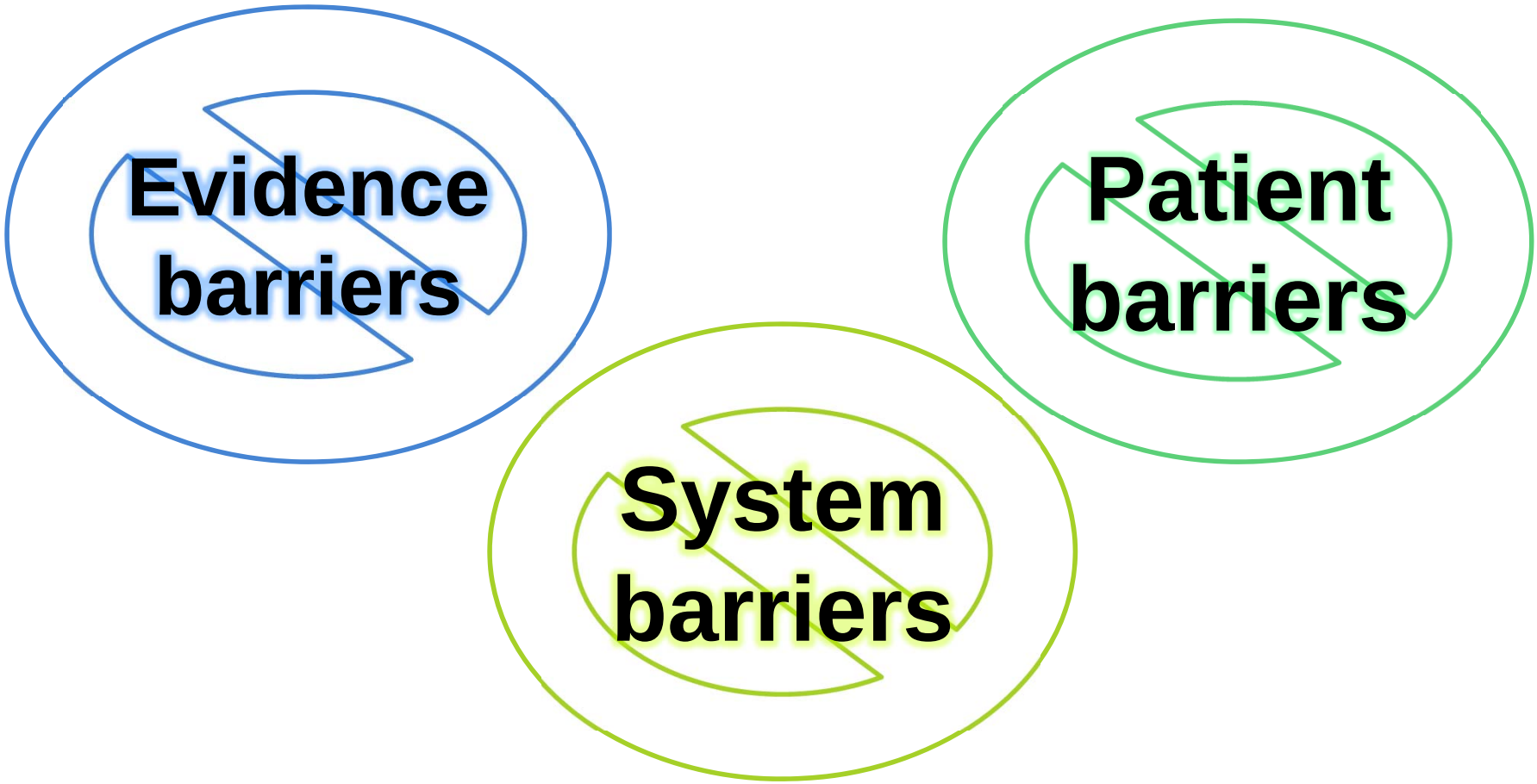
Kalisch LM, Caughey GE, Roughead EE, Gilbert AL. The prescribing cascade. Aust Prescr 2011;34:162-6

.

"ANY NEW SYMPTOM IN AN OLDER PERSON SHOULD BE CONSIDERED A DRUG SIDE EFFECT UNTIL PROVEN OTHERWISE."

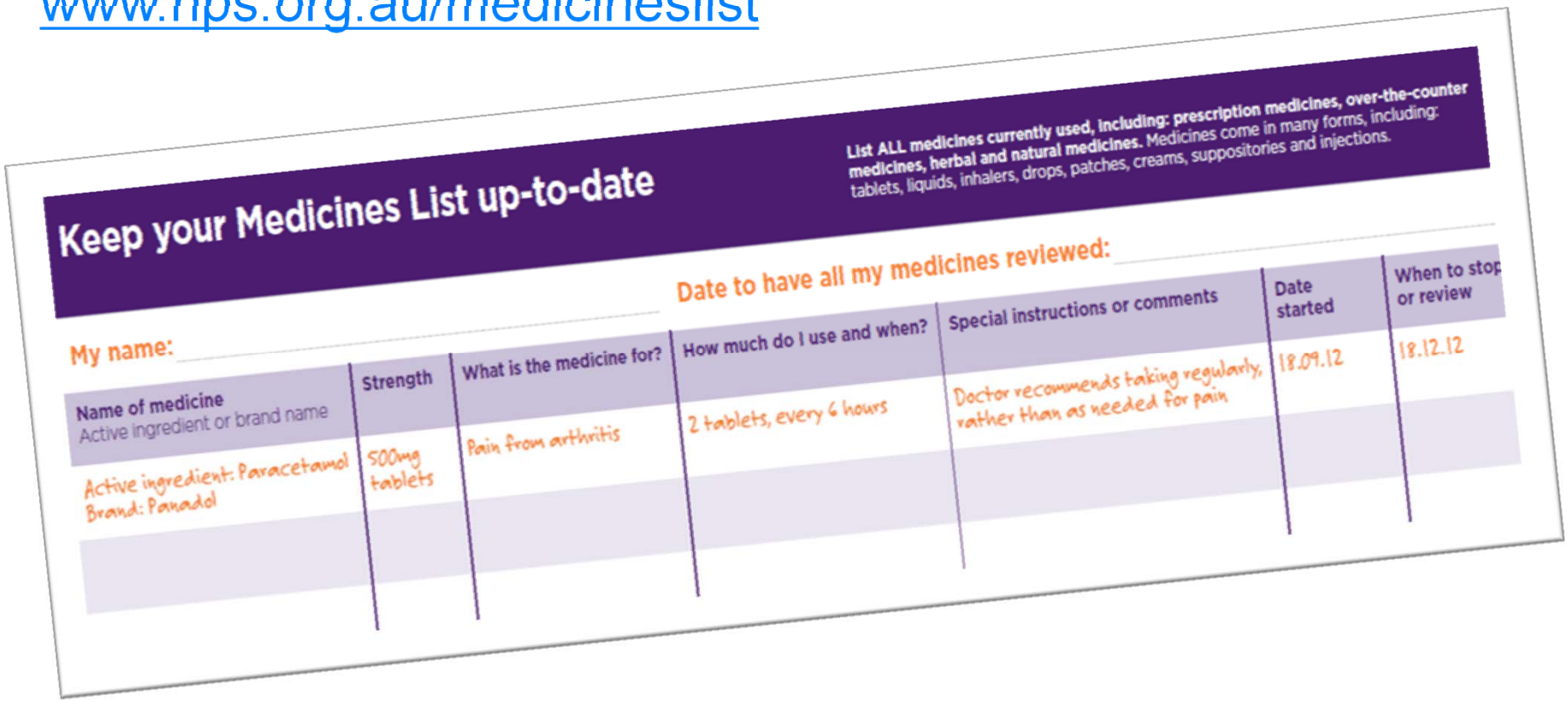
Avorn J, Shrank WH. Adverse Drug Reactions in Elderly People: A substantial cause of preventable illness. BMJ 2008;336:956-7.

Barriers to stopping medicines in older people



Encourage your patients to have an accurate and up to date medicines list

- Includes prescription, over the counter and complementary medicines.
- With documented doses, strengths and directions for use.
- Download a Medicines List from www.nps.org.au/medicineslist



Keep your Medicines List up-to-date

List ALL medicines currently used, including: prescription medicines, over-the-counter medicines, herbal and natural medicines. Medicines come in many forms, including: tablets, liquids, inhalers, drops, patches, creams, suppositories and injections.

My name:

Date to have all my medicines reviewed:

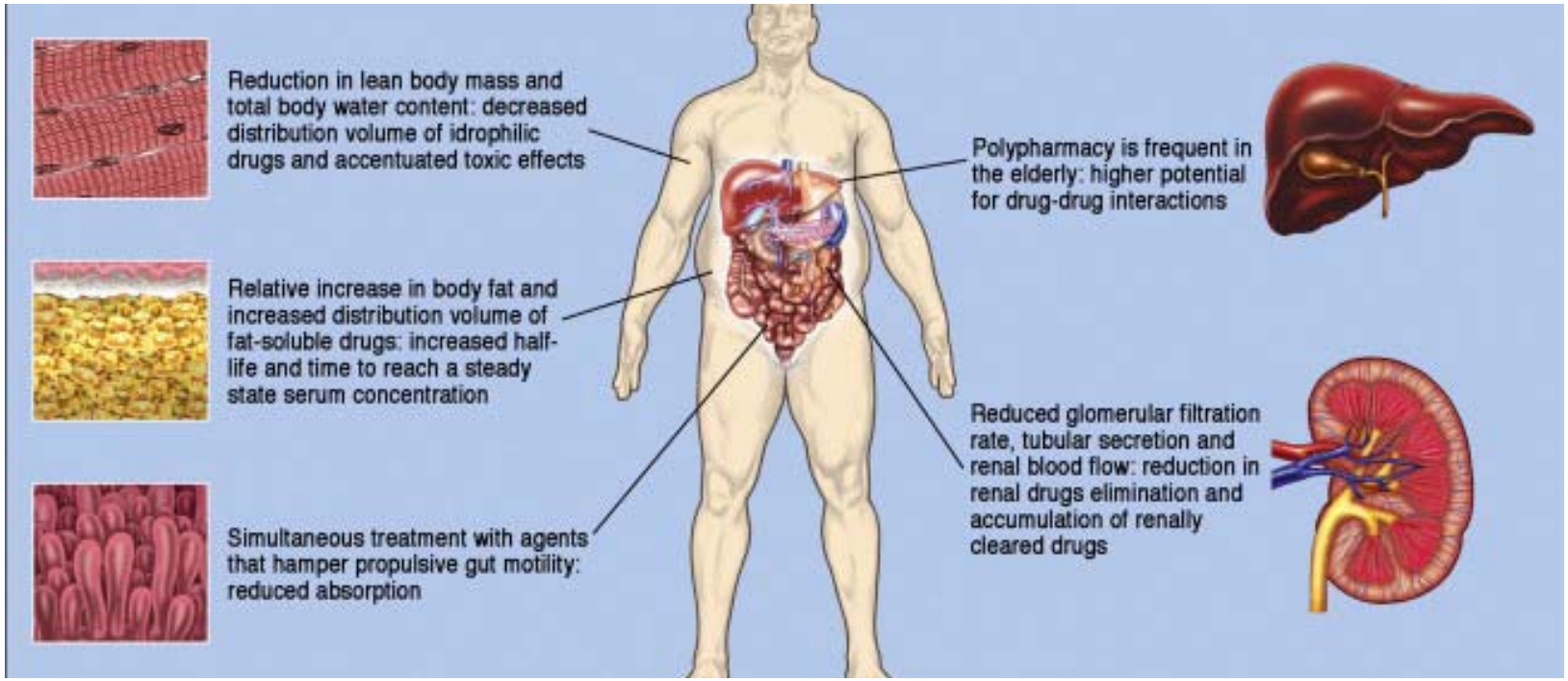
Name of medicine Active ingredient or brand name	Strength	What is the medicine for?	How much do I use and when?	Special instructions or comments	Date started	When to stop or review
Active ingredient: Paracetamol Brand: Panadol	500mg tablets	Pain from arthritis	2 tablets, every 6 hours	Doctor recommends taking regularly, rather than as needed for pain	18.09.12	18.12.12

Encourage your patients to have an accurate and up to date medicines list

- An up to date medicines list can help:
  - identify potential drug-related causes of new symptoms (prevent prescribing cascade),
  - define and eliminate duplication of therapies,
  - highlight drug interactions,
  - identify medicines prescribed by other doctors,
  - save time when managing medicines.

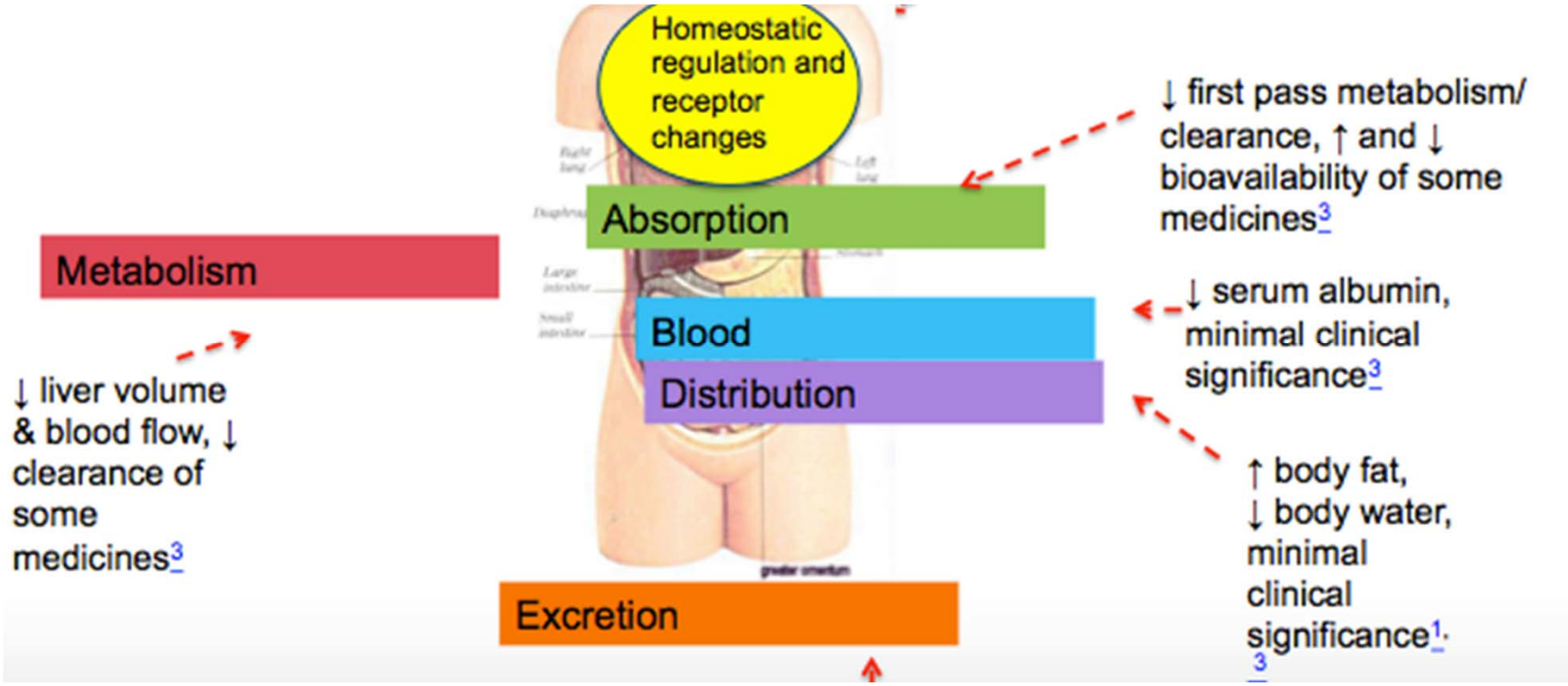
- Studies have shown **frail older people** may display profound changes in the pharmacokinetics and pharmacodynamics of some medicines compared to **robust older people,** putting them at risk of medicines-related problems.
- McLachlan AJ, et al. Br J Clin Pharmacol 2011;71:351-64.

Physiological changes in the elderly



PK changes: Absorption, distribution, metabolism, excretion
PD changes: Drug receptors, target organ response

Physiological changes impact on PK & PD



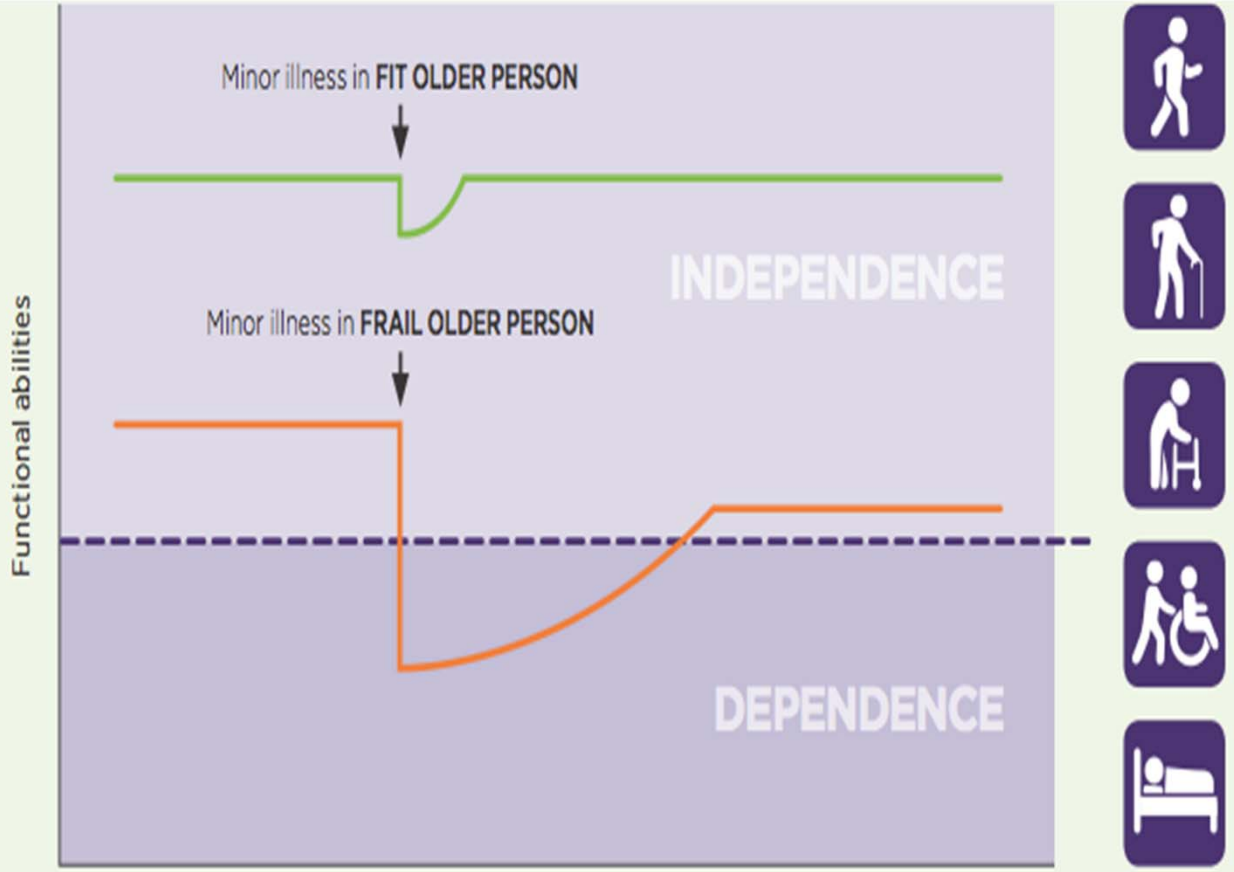
Recognise changing health and vulnerability

AGEING-RELATED CHANGES THAT AFFECT MEDICINES USE

Frail older people are more affected by pharmacokinetic and pharmacodynamic changes.[20]

Pharmacokinetic[20]
impaired kidney function*

Pharmacodynamic[22]
changes in receptors and target organ responses



* Refer to the Insert for a list of renally excreted medicines.

Frail older people display low resilience to minor stressors (e.g. urinary tract infection).[19]

Symptom cascades

Some of these cascades are well recognised such as constipation and opioids, delirium and confusion following opioids, benzodiazepines and antipsychotics and the list goes on…..

Common symptoms

Dry mouth

It is a common symptom that may be caused by underlying disease, or as a consequence of surgery, radiotherapy for some head and neck cancers, fluid restriction in people with end stage heart failure and many many medicines.

Commonly used medicines for symptoms such as pain, nausea, agitation, delirium, confusion may all contribute to dry mouth. Careful assessment is required to identify reversible causes.

Medication Issues

Xerostomia (Dry Mouth)

A variety of drugs, especially those with anticholinergic effects, can cause xerostomia (dry mouth), particularly with issues of polypharmacy and the elderly. When the quality and quantity of saliva is reduced oral diseases can develop very quickly.

The following drug classes can contribute to xerostomia (dry mouth), some generic examples are listed but this is not comprehensive:

- Tricyclic antidepressants (amitriptyline, doxepin, dothiepin)
- Selective serotonin reuptake inhibitors (citalopram, paroxetine)
- Monoamine oxidase inhibitors (moclobemide, phenelzine)
- Anticholinergic agents (oxybutynin, tolterodine, hyoscine, inhaled tiotropium)
- Opioids (codeine, morphine, oxycodone, methadone)
- Diuretics (frusemide, hydrochlorothiazide)
- Antipsychotic drugs (chlorpromazine, haloperidol, olanzapine)
- Antihistamines (promethazine, dexchlorpheniramine)
- Lithium
- Proton pump inhibitors (omeprazole, lansoprazole)
- ACE inhibitors (captopril, enalapril, lisinopril)
- Oral retinoids (isotretinoin, tretinoin)
- Benzodiazepines (diazepam, temazepam)
- Chemotherapy (capecitabine; many drugs cause mucositis)
- Other miscellaneous agents (carbamazepine, sibutramine, tramadol)

Urge Incontinence

- The prevalence of urinary incontinence in men is about a third that in women until age 80 when rates converge.

- One survey of frail older community dwelling people found prevalence rates of 52% of women and 49% of men.

Urge Incontinence

- A recent meta-analysis found that patients with urge incontinence were almost twice as likely to fall as patients without

Anticholinergic action

- Drugs with similar physiologic actions interfere with the action of acetylcholine at muscarinic receptor sites

- Atropine-like effects referred to as parasympatholytic, anticholinergic, antimuscarinic

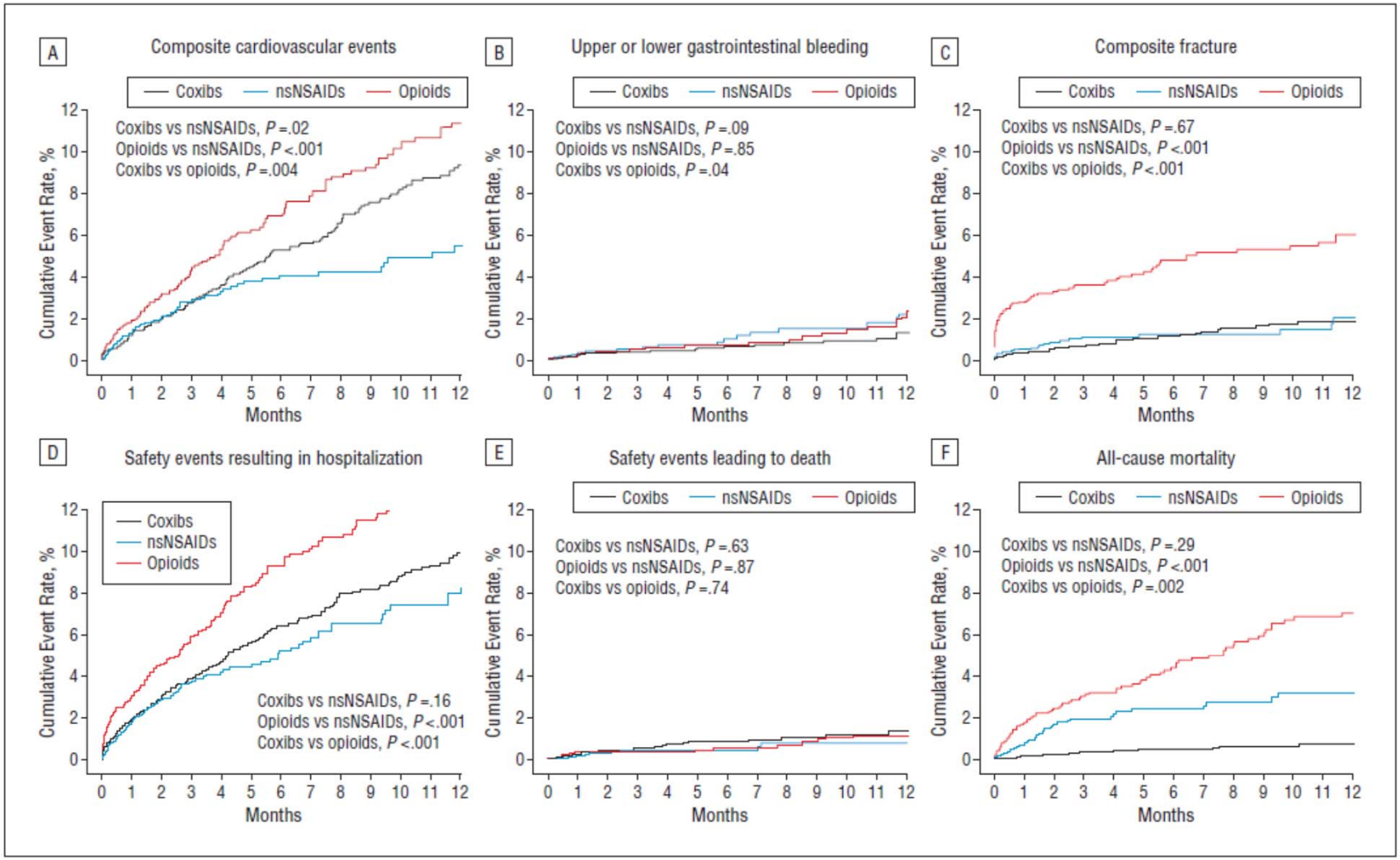
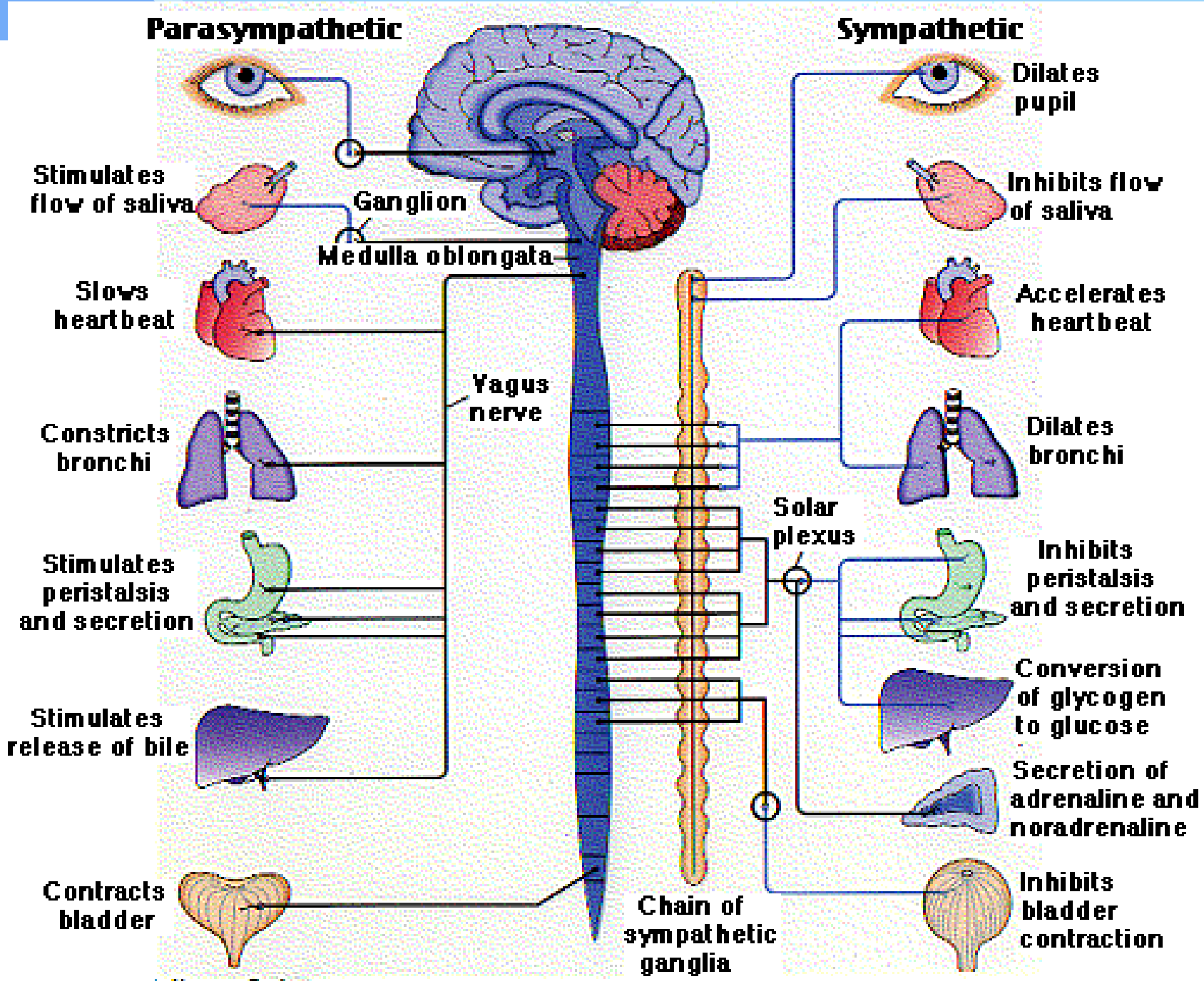


Figure. Kaplan-Meier curves for the cumulative incidence of the 6 composite safety measures. A, Composite cardiovascular events. B, Upper or lower gastrointestinal tract bleeding. C, Composite fracture. D, Any of the individual safety events resulting in hospitalization. E, Any of the individual safety events leading to immediate death or a hospitalization with death. F, All-cause mortality. *P* values were determined with the log-rank test. Coxibs indicates selective cyclooxygenase-2 inhibitors; nsNSAIDs, nonselective nonsteroidal anti-inflammatory drugs.

Solomon D et al Arch Intern Med. 2010;170(22):1968-1978


Parasympathetic
Sympathetic
Dilates pupil
Stimulates flow of saliva
Ganglion
Medulla oblongata
Inhibits flow of saliva
Slows heartbeat
Accelerates heartbeat
Yagus nerve
Constricts bronchi
Dilates bronchi
Solar plexus
Stimulates peristalsis and secretion
Inhibits peristalsis and secretion
Conversion of glycogen to glucose
Stimulates release of bile
Secretion of adrenaline and noradrenaline
Contracts bladder
Chain of sympathetic ganglia
Inhibits bladder contraction

The Australian Pain Society's Pain in Residential Aged Care Facilities: Management Strategies. This publication was funded by the Australian Government Department of Health and Ageing, under the National Palliative Care Program.
Copies of the kit may download in PDF format: http://www.health.gov.au/internet/main/publishing.nsf/Content/ageingpublicat-pain-management.htm

ORIGINAL INVESTIGATION

The Comparative Safety of Analgesics in Older Adults With Arthritis

Daniel H. Solomon, MD, MPH; Jeremy A. Rassen, ScD; Robert J. Glynn, PhD; Joy Lee, BA; Raisa Levin, MS; Sebastian Schneeweiss, MD, ScD

Arch Intern Med. 2010;170(22):1968-1978

Background: The safety of alternative analgesics is unclear. We examined the comparative safety of nonselective NSAIDs (nsNSAIDs), selective cyclooxygenase 2 inhibitors (coxibs), and opioids.

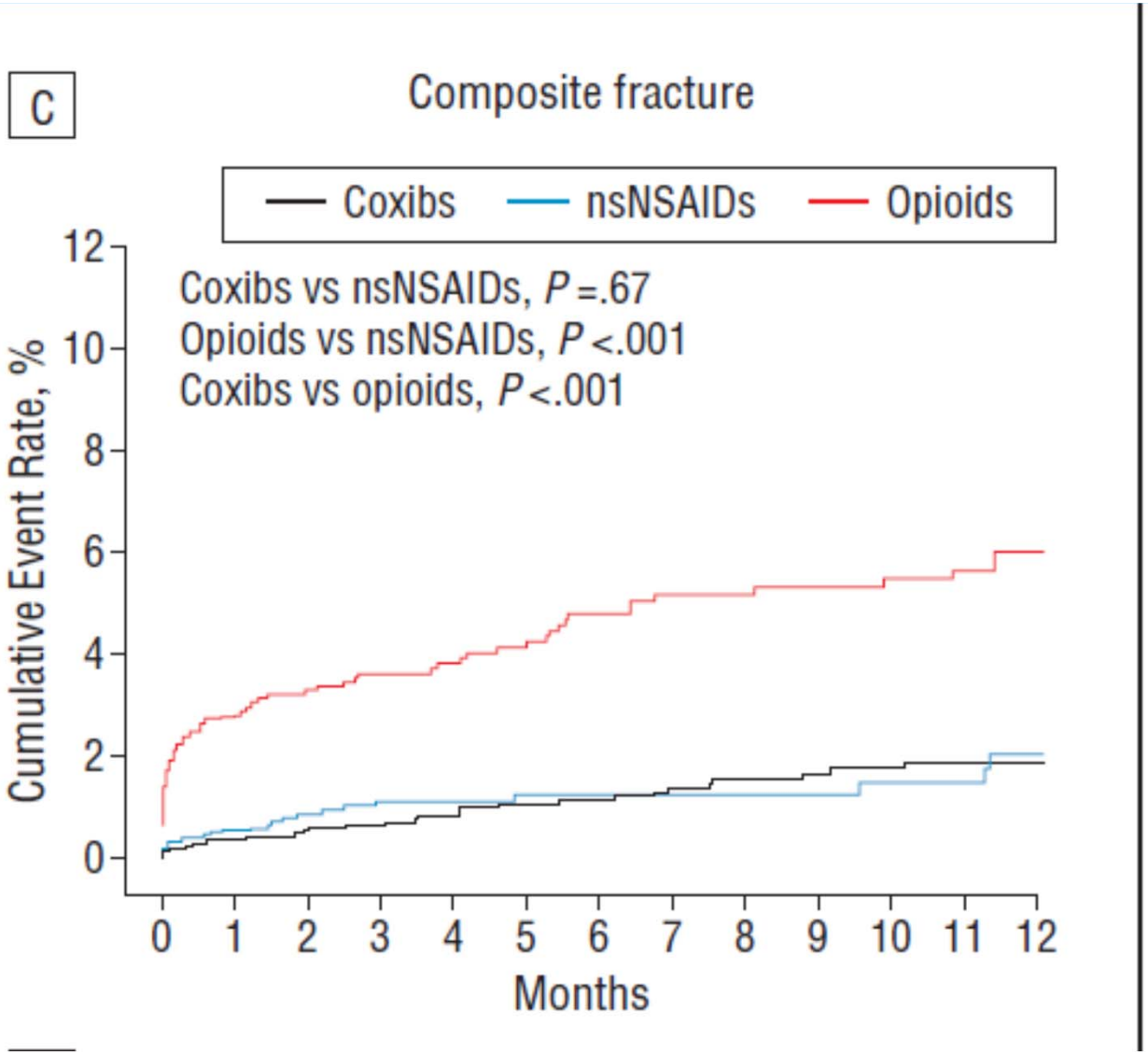
Methods: Medicare beneficiaries from Pennsylvania and New Jersey who initiated therapy with an nsNSAID, a coxib, or an opioid from January 1, 1999, through December 31, 2005, were matched on propensity scores. We studied the risk of adverse events related to analgesics using incidence rates and adjusted hazard ratios (HRs) from Cox proportional hazards regression.

Results: The mean age of participants was 80.0 years, and almost 85% were female. After propensity score matching, the 3 analgesic cohorts were well balanced on baseline covariates. Compared with nsNSAIDs, coxibs (HR, 1.28; 95% confidence interval [CI], 1.01-1.62) and opioids (1.77; 1.39-2.24) exhibited elevated relative risk for cardiovascular events. Gastrointestinal tract bleeding risk was reduced for coxib users (HR, 0.60; 95% CI, 0.35-1.00) but was similar for opioid users. Use of coxibs and nsNSAIDs resulted in a similar risk for fracture; however, fracture risk was elevated with opioid use (HR, 4.47; 95% CI, 3.12-6.41). Use of opioids (HR, 1.68; 95% CI, 1.37-2.07) but not coxibs was associated with an increased risk for safety events requiring hospitalization compared with use of nsNSAIDs. In addition, use of opioids (HR, 1.87; 95 CI, 1.39-2.53) but not coxibs raised the risk of all-cause mortality compared with use of nsNSAIDs.

Conclusions: The comparative safety of analgesics varies depending on the safety event studied. Opioid use exhibits an increased relative risk of many safety events compared with nsNSAIDs.

Arch Intern Med. 2010;170(22):1968-1978

Solomon D et al Arch Intern Med. 2010;170(22):1968-1978



Solomon D et al Arch Intern Med. 2010;170(22):1968-1978

Prescription of opioid analgesics and related harms in Australia

Amanda Roxburgh
MCrim, MPsych(Clin), MAPS, Senior Researcher[1]

Raimondo Bruno
BSc(Hons), PhD, MAPS, Senior Lecturer[2]

Briony Larance
BSc(Psych)(Hons), Senior Researcher[1]

Lucy Burns
MPH, GradDipHealthPolicy, PhD, Senior Lecturer[1]

1 National Drug and Alcohol Research Centre, University of New South Wales, Sydney, NSW.
2 School of Psychology, University of Tasmania, Hobart, TAS.

a.roxburgh@unsw.edu.au

MJA 2011; 195: 280–284
doi: 10.5694/mja10.11450

There has been growing concern among Australian medical professionals about the increase in prescribing of opioid analgesic preparations (particularly morphine and oxycodone) over the past decade. Australia's consumption of opioid analgesics is ranked 10th internationally; North America ranks first. Per capita consumption of oxycodone and morphine preparations in Australia is relatively high (ranked third and fifth respectively, internationally); Canada ranks first for oxycodone and Austria first for morphine.[1] Consumption levels in Australia are still well below the top-ranking countries. Previous research in Australia has documented increases in the number of prescriptions for morphine in the late 1990s[2,3] and, more recently, increases in consumption of oxycodone.[4]

Morphine and oxycodone have legitimate and important treatment indications in the management of pain. Access to effective pain management is an important human right, and pain, both acute and chronic, imposes a major public

Abstract

Objective: To document trends in: (i) prescribing of morphine and oxycodone; (ii) hospital separations for overdose; (iii) presentations for treatment of problems associated with these drugs; and (iv) oxycodone-related mortality data in Australia.

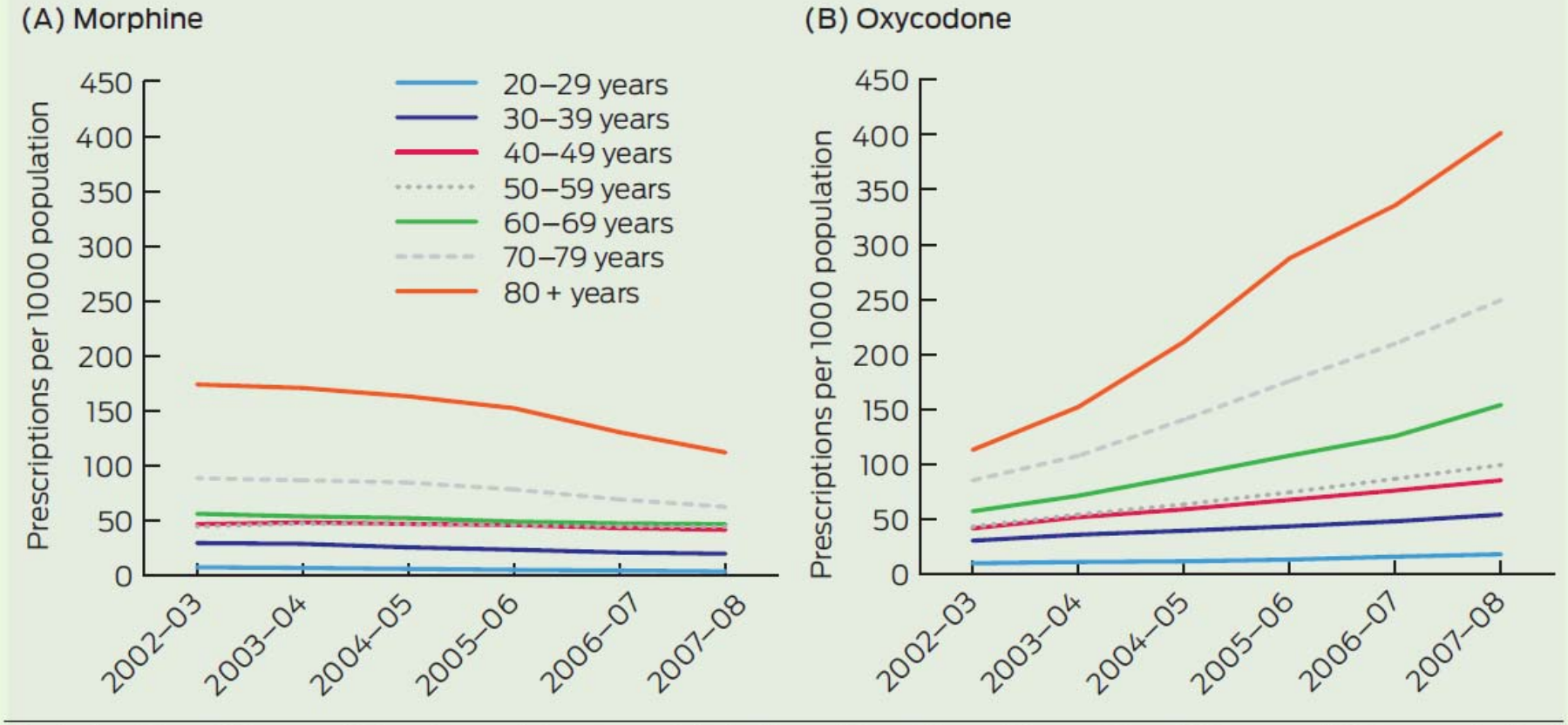
Design and setting: Cross-sectional study analysing prescriptions for morphine and oxycodone based on figures adjusted using Australian Bureau of Statistics estimated resident population and prospectively collected data from: (i) the National Hospital Morbidity Database on hospital separations primarily attributed to poisoning with opioids other than heroin ("other opioids"); (ii) the Alcohol and Other Drug Treatment National Minimum Data Set for treatment episodes where morphine or oxycodone were the primary or other drugs of concern; (iii) the National Coronial Information System on deaths where oxycodone was the underlying cause of death or a contributory factor.

Main outcome measures: Population-adjusted numbers of (i) prescriptions for morphine and oxycodone by 10-year age group, (ii) hospital separations for "other opioid" poisoning, and (iii) treatment episodes related to morphine or oxycodone; and (iv) number of oxycodone-related deaths.

Results: Prescriptions for morphine declined, while those for oxycodone increased. Prescriptions for both were highest among older Australians. Hospital separations for "other opioid" poisoning doubled between the financial years 2005–06 and 2006–07. Treatment episodes for morphine remained stable, while those for oxycodone increased. There were 465 oxycodone-related deaths recorded during 2001–2009.

Conclusions: Oxycodone prescriptions in Australia have increased, particularly among older Australians. The increase may, in part, reflect appropriate prescribing for pain among an ageing population. However we are unable to differentiate non-medical use from appropriate prescribing from this data. In comparison to heroin, the morbidity and mortality associated with oxycodone is relatively low in Australia. There is a continued need for comprehensive training of general practitioners in assessing patients with chronic non-malignant pain and prescribing of opioids for these patients, to minimise the potential for harms associated with use of these medications.

1 Prescriptions for morphine* and oxycodone† dispensed on the Pharmaceutical Benefits Scheme in Australia from 2002 to 2008, per thousand population, by 10-year age group‡

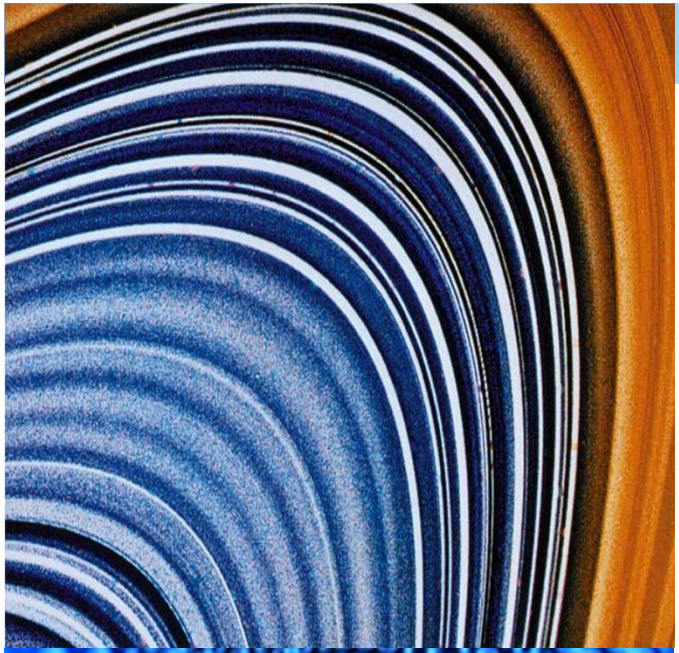


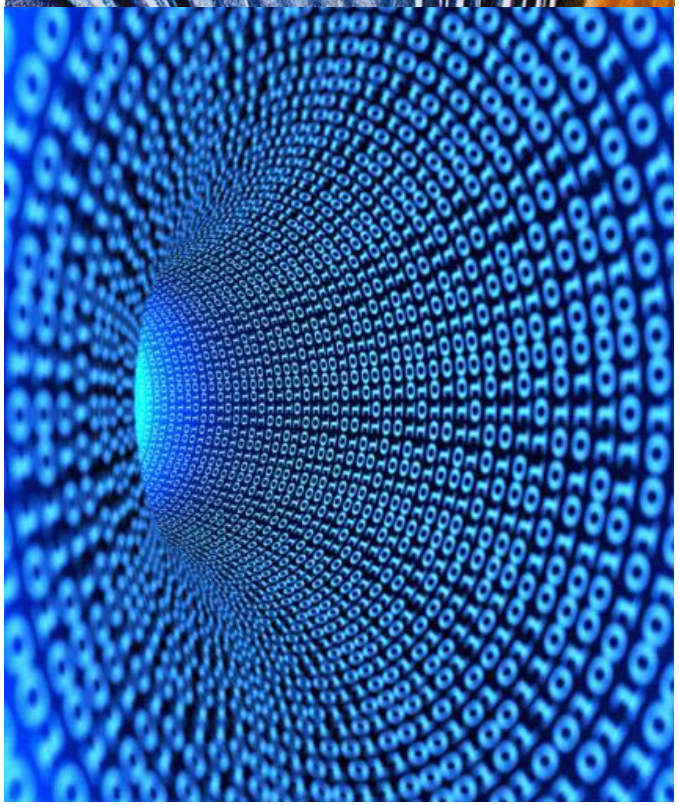
* Includes 10 mg, 20 mg and 30 mg immediate-release tablets; 5 mg, 10 mg, 15 mg, 30 mg, 60 mg, 100 mg and 200 mg controlled-release tablets; 30 mg, 60 mg, 90 mg and 120 mg controlled-release capsules; and 10 mg, 20 mg, 50 mg and 100 mg sustained-release capsules. † Includes 5 mg, 10 mg, 20 mg, 40 mg and 80 mg controlled release tablets and 5 mg, 10 mg, and 20 mg capsules. ‡ Data obtained from the Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee. ◆

Roxburgh A et al MJA 2011; 195: 280–284

- Need to be alert to adverse drug effects masquerading as geriatric syndromes

- Geriatric syndromes include delirium, falls, incontinence and frailty, are highly prevalent, multifactorial, and associated with substantial morbidity and poor outcomes.





“The real voyage of discovery consists not in seeking *new landscapes*, *but* in having *new eyes*." - Marcel *Proust*

Debra Rowett

Director

Drug and Therapeutics Information Service

Repatriation General Hospital, South Australia

debra.rowett@health.sa.gov.au