

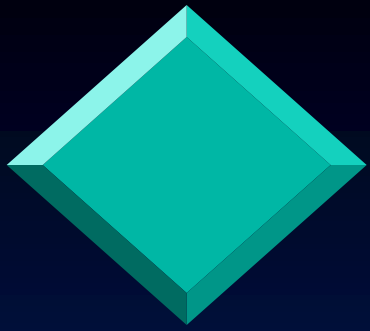
Psychotropic Drug-Related Problems in the Elderly

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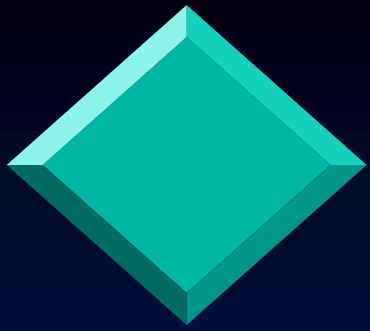
Repatriation General Hospital

Daw Park



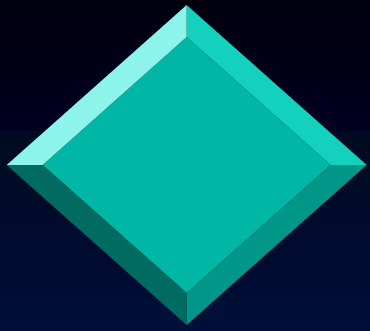
Drug related problems

- **Much confusion exists about terminology to describe drug-related harm**
- **Previous focus has been directed at ADRs and drug interactions**
- **Confusion regarding medical error, adverse drug events, preventability factors etc**



Medical Error

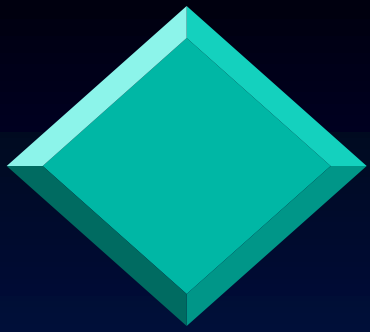
- **Even when there has been great attention to achieve outcomes without prescribing problems, medical errors are common**
- **Approaches targeting systems rather than individuals work best for prevention**
- **Institutional care settings such as hospitals, RACFs can be a dangerous place where medications are concerned**



Sobering statistics

- ❖ **SA research study analysed data on medication-related hospitalisations**
 - ◆ Nearly 23,000 hospital separations associated with ADRs per annum
 - ◆ 80,000 medication-related hospital admissions in Australia each year
 - ◆ Direct costs associated with hospitalisation of approximately \$350 million annually.





Sobering statistics

- ❖ Data from ABS, Institute of Health and Welfare, ACHS & Patient Safety Foundation
- ❖ 2-4% of all hospital admissions (& up to 30% for patients > 75 years of age) related to medications; up to 75% potentially preventable.
- ❖ Of coded adverse events that contributed to death, 27% involved an ADE, as did 20% of adverse events identified at discharge and 43% at general practice encounters

Sobering statistics



Sweden

Denmark

Scotland

Singapore

France

Canada

Germany

Italy

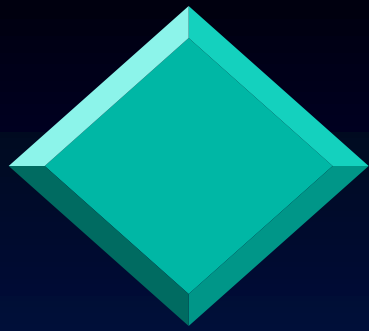
Taiwan

Switzerland

Netherlands

Spain



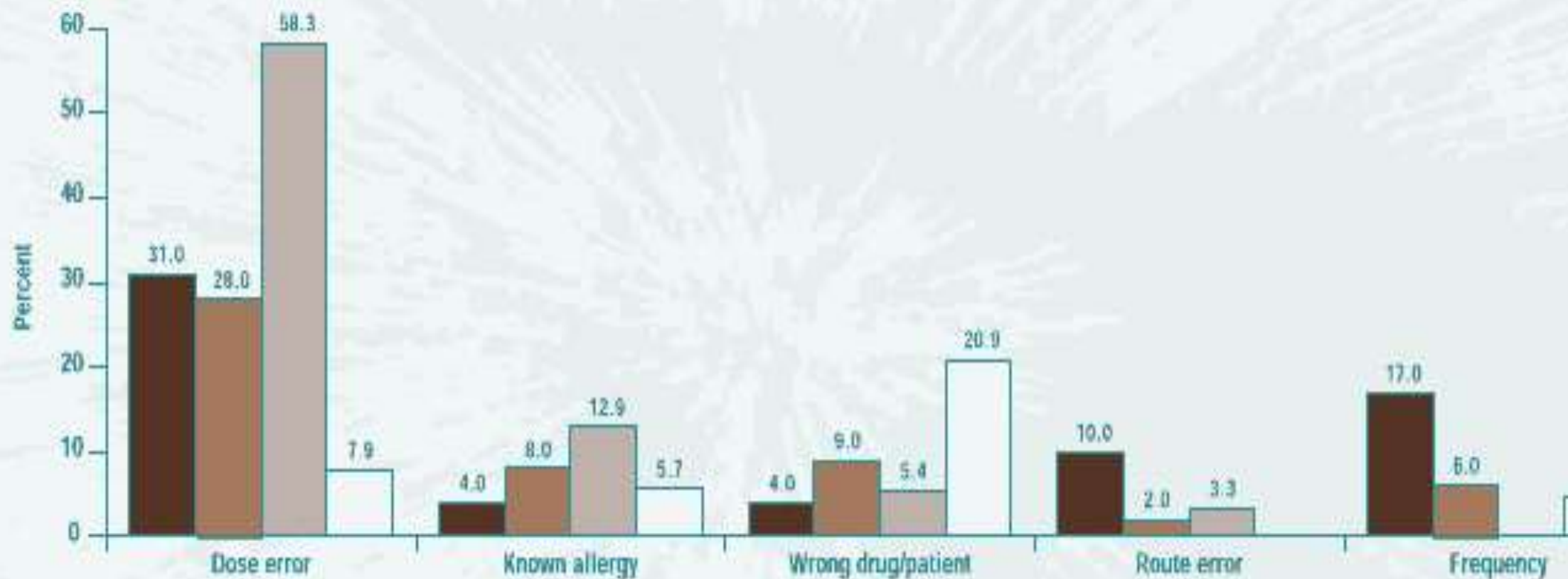


Sobering statistics



- ❖ **Approx. 700,000 physicians in US**
 - ◆ Estimate of accidental deaths caused by physicians per year is 120,000, accidental deaths per physician approximately 0.171 (US Dept Health & Human Services)
- ❖ **80,000,000 gun owners in US**
 - ◆ The number of accidental gun deaths per year, all age groups, estimated at 1,500
 - ◆ Accidental deaths per gun owner is 0.000188 (FBI)
- ❖ **Statistically, doctors approximately 900 times more dangerous than gun owners**

Figure 2. Commonly studied medication errors as causes of adverse drug events (ADEs): percent of ADEs for each cause

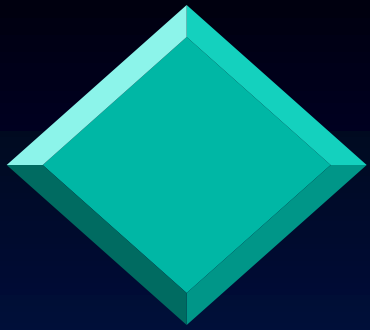


■ Bates DW, Boyle DL, Vander Vliet MB, et al. Relationship between medication errors and adverse drug events. *J Gen Intern Med* 1995;10(4):199-205.

■ Leape LL, Bates DW, Cullen DJ, et al. Systems analysis of adverse drug events. *JAMA* 1995;274(1):35-43.

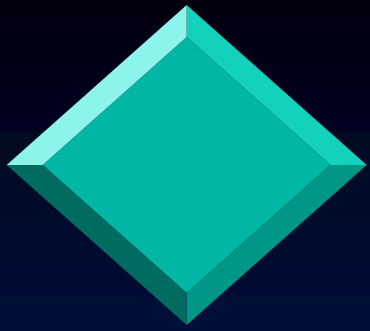
■ Lesar TS, Briceland L, Stein DS. Factors related to errors in medication prescribing. *JAMA* 1997;277(4):312-7.

□ Thomas EJ, Studdert DM, Newhouse JP, et al. Costs of medical injuries in Utah and Colorado. *Inquiry* 1999;36(3):255-64.



We are 99.9% confident!

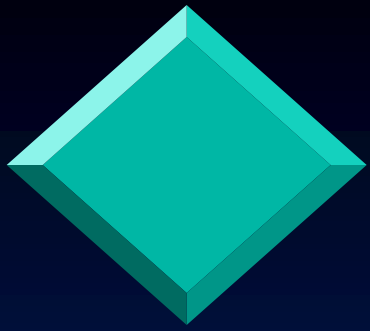
**“ We are 99.9% confident that we
can get you into hospital and out of
hospital without causing you a serious
drug-related problem.”**



We are 99.9% confident!

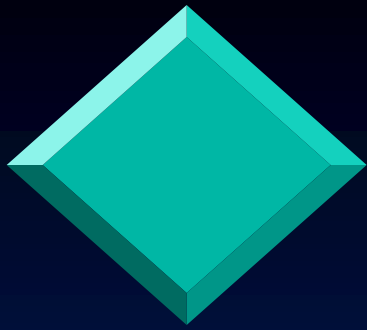
- **Two unsafe landings at major airports per day**
- **16,000 pieces of mail lost in the USA per hour**
- **32,000 bank cheques deducted from the wrong account per hour**





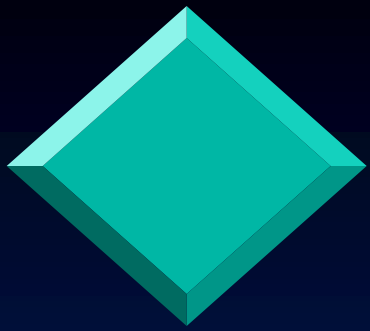
Drug administration Error

- **300 bed hospital, each patient taking three drugs, average of 1.5 occasions of administration per day for each drug**
- **1350 occasions of administration per day, 9,450 per week, 37,800 per month, 454,000 per annum**
- **99.9% accuracy = approx. 500 administration errors per annum**



Drug administration Error

- **What goes wrong?**
 - **Wrong drugs**
 - **Wrong dose**
 - **Dose given when order held, or held in error**
 - **Wrong patient**
 - **Wrong route of administration**
 - **Misinterpretation of orders**
 - **Dispensing error**
 - **Others**



Public perceptions

Environment

Airline travel

Health care

Nuclear power

7 = safe 1 = unsafe

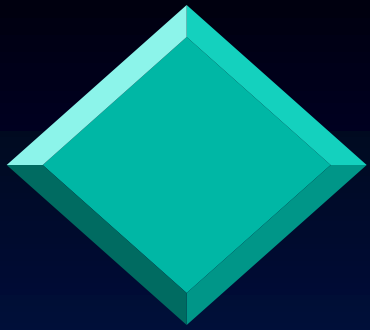
Risk score

5.2

4.9

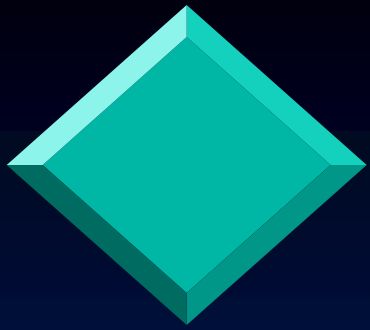
4.2





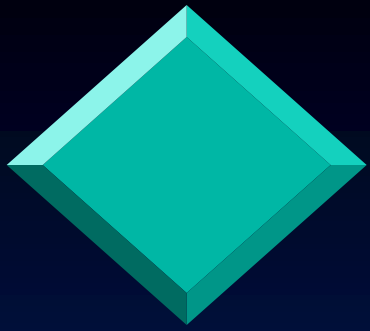
Drug related problems

- **Work of Charles Hepler and Linda Strand in Minnesota in 1980s and 1990s**
- **Developed the concept of drug-related problems to describe the full range of issues causing harm associated with medications**
- **Broader considerations than ADRs and drug interactions**



Drug related problems

- **Broad framework to facilitate service delivery (e.g. medication review)**
- **Collection and reporting of more meaningful information about challenges for patients**
- **Underpins research methodology to characterize issues in specific groups and inform better services**



Drug related problems

Indicated drug not charted

Wrong drug

Too little drug

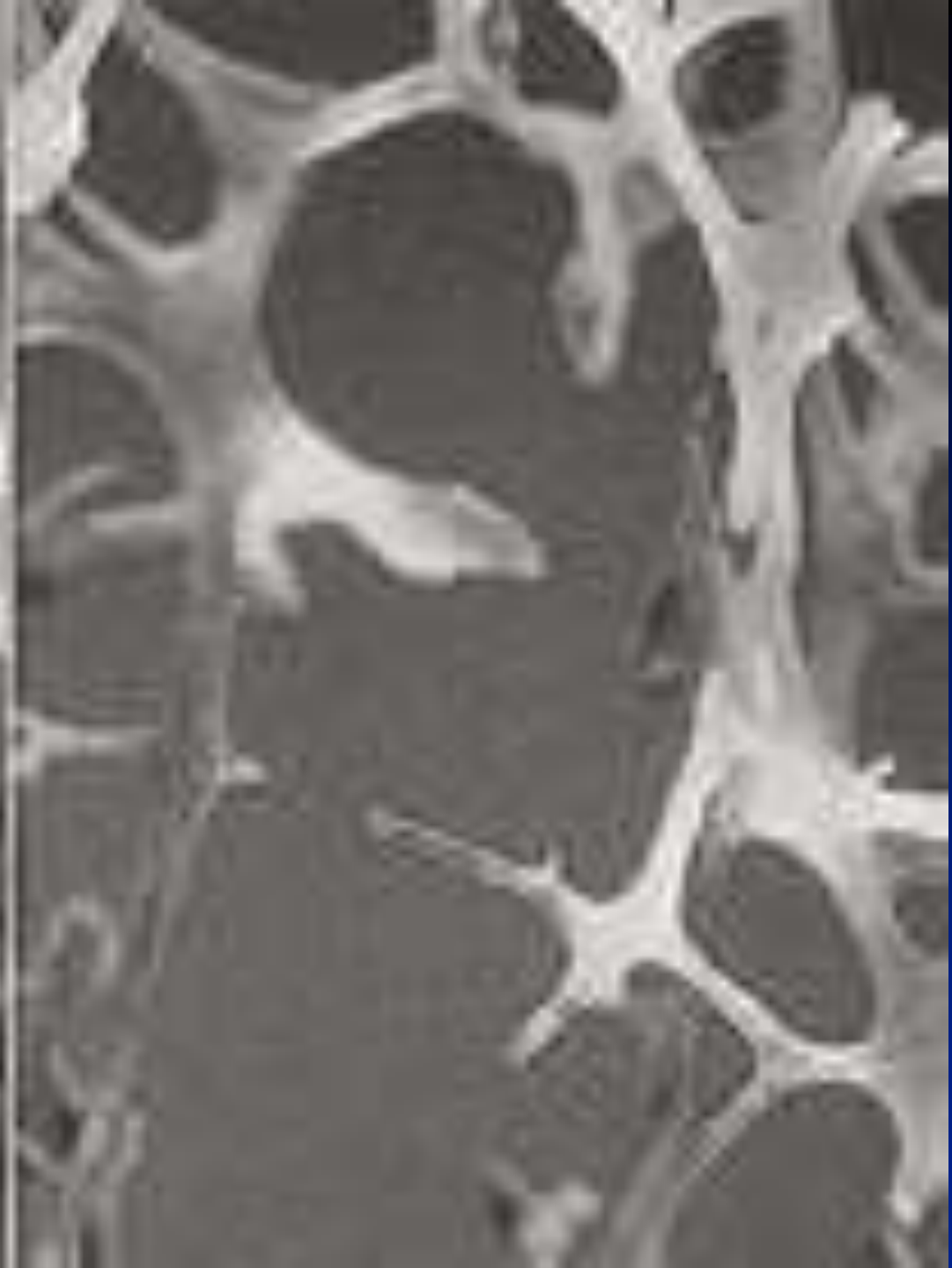
Too much of the drug

Adverse drug reaction

Drug interaction

Not receiving the prescribed drug

Receiving a drug not indicated



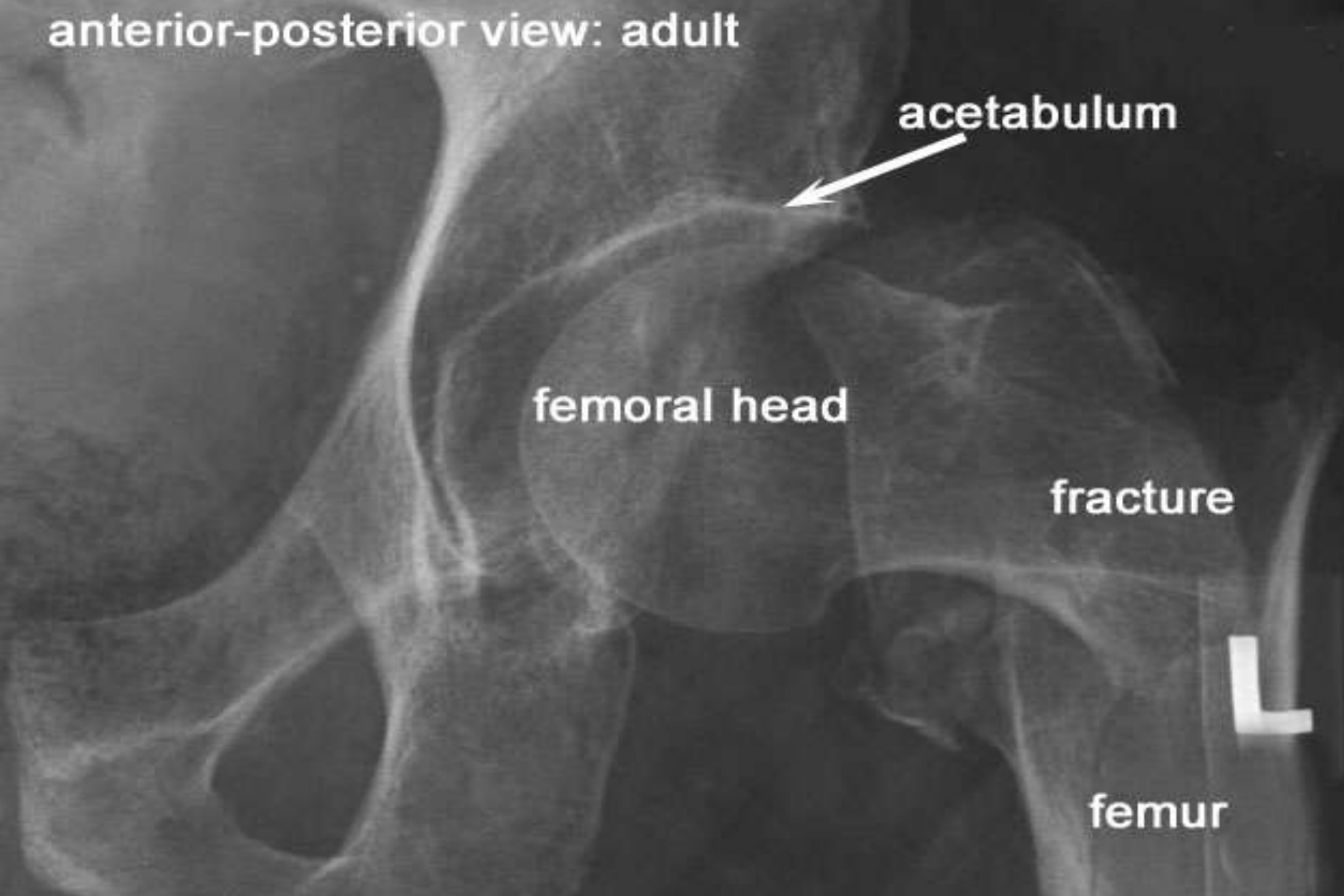
anterior-posterior view: adult

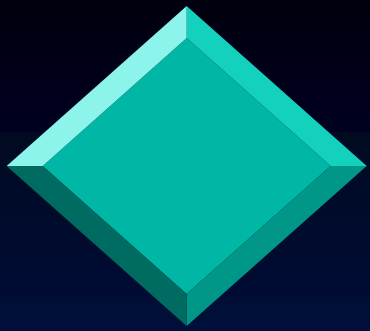
acetabulum

femoral head

fracture

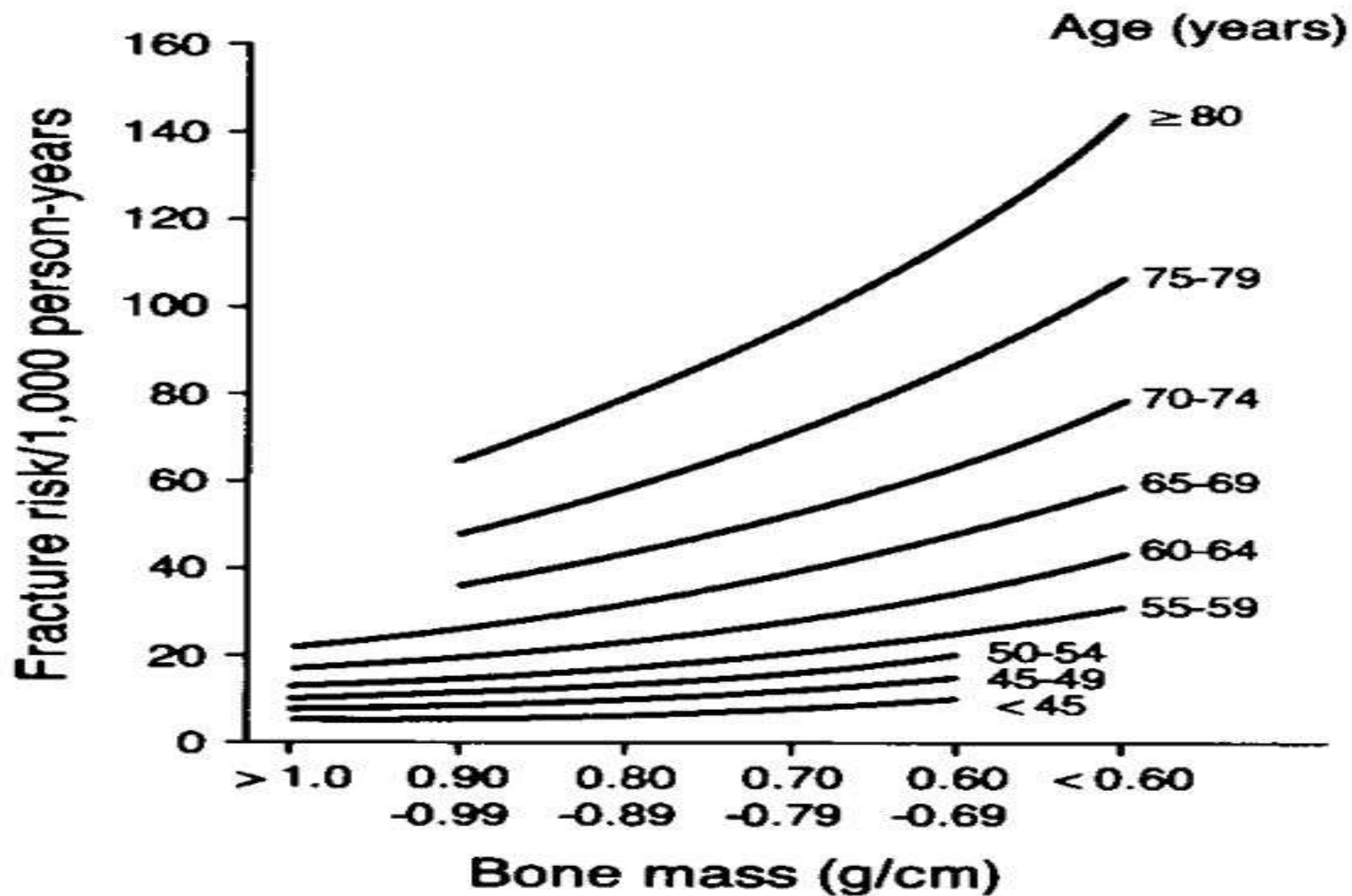
femur

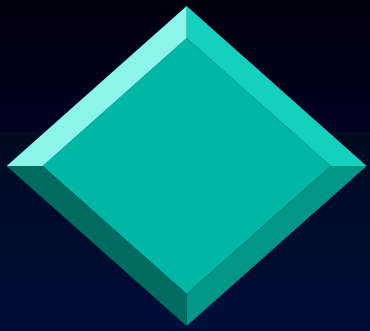




Risk Factors for Osteoporosis

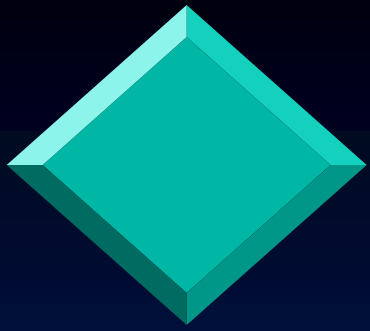
- Female
- Over 50 years old
- Low estrogen
- Body mass index $<19\text{kg}/\text{m}^2$
- Low bone mass
- History of fragility fractures (self/family)
- Poor nutrition (with deficient calcium and vitamin D intake)
- Smoking
- Excessive alcohol use
- Inactive lifestyle
- Steroid or anticonvulsant drug use





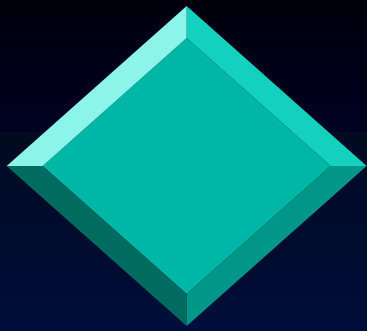
Psychotropics and BMD loss

- **Many psychotropics are associated with BMD loss**
- **Osteopaenia and osteoporosis**
- **Fracture risk, associated morbidity, disability and loss of functional capacity**
- **Elderly patients with psychiatric illness have multiple risk factors**

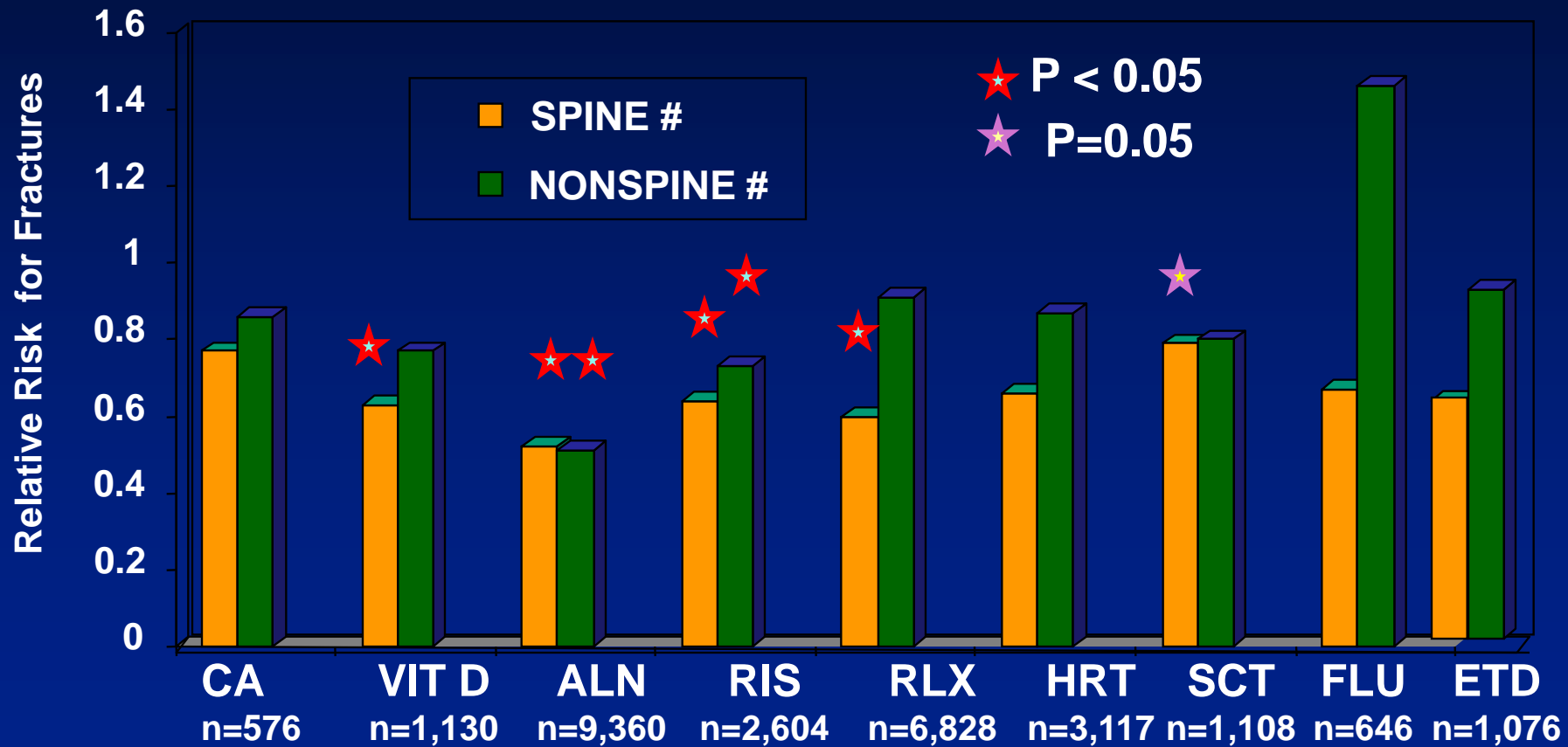


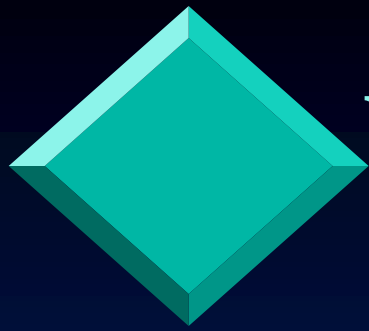
Valproate and BMD loss

- **L1-4 BMD score: -1.28 ± 0.8 with valproate compared to -0.23 ± 0.87 for controls** (Kumandas et al)
- **14% BMD reduction with valproate, considerable osteopaenia** (Sheth et al)
- **14% BMD reduction after correction for calcium intake** (Sato et al)



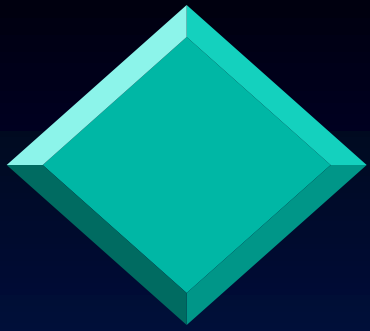
Indicated drug not charted





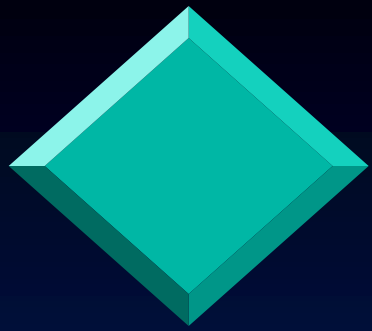
Wrong drug charted

- **Common use of antipsychotic agents for BPSD**
- **Some of the most hazardous drugs used most commonly**
- **Orthostasis, anticholinergic, sedative**
- **More appropriate choices available**



Antipsychotics for BPSD

- **BPSD can include agitation, aggression, psychosis, wandering**
- **DVA data reveals that 6000 community-dwelling Veterans prescribed APs over 12/12 period, average 9 prescriptions**
- **30% of Veterans with high care needs and 20% of those with low care needs in aged care prescribed antipsychotics**



ABC assessment for BPSD

A: Antecedents

What is causing the behaviour?

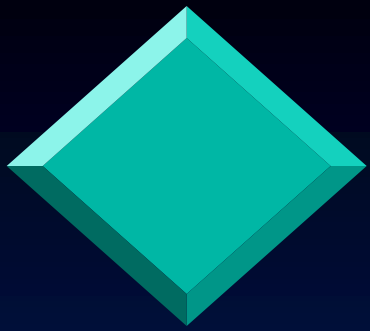
What are the circumstances leading up to the events?

B: Behaviour

What is the nature of the behaviour?

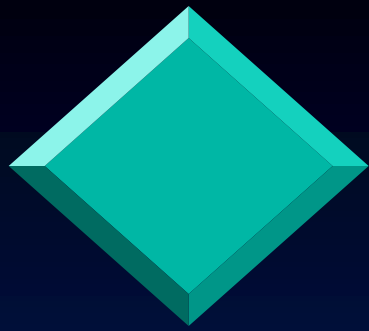
C: Consequences

For the patient, other patients, staff



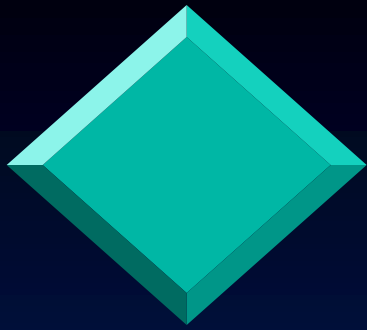
Alternatives to antipsychotics

- **Short-acting BZD for acute anxiety of agitation, limit to 2/52 where possible, be aware that these drugs may also exacerbate cognitive dysfunction**
- **Anticholinesterase and other cognitive enhancement drugs – may improve QOL and have a good safety profile**
- **Antidepressants for depression-specific symptoms, not for BPSD**



Issues with antipsychotics

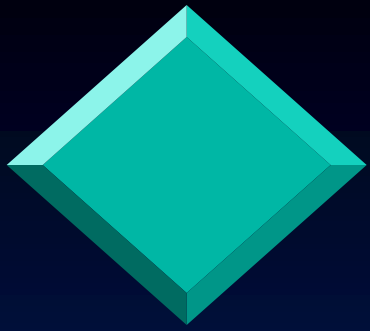
- **Confusion**
- **Parkinsonian side effects**
- **Falls and fractures**
- **Akathisa, tardive dyskinesia**
- **Diabetes**
- **Cerebrovascular events**



Cerebrovascular events and antipsychotics

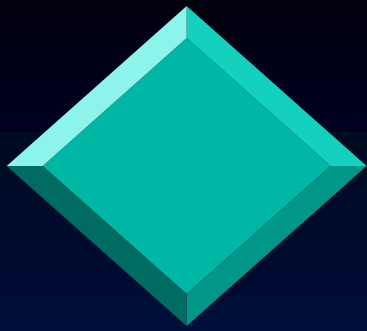
- **US FDA warning for greater mortality risk, evidence is inconsistent**
- **Cerebrovascular events vs strokes**
- **Atypical agents may not be less safe**
- **Balance against overall mortality risk with under-managed BPSD**





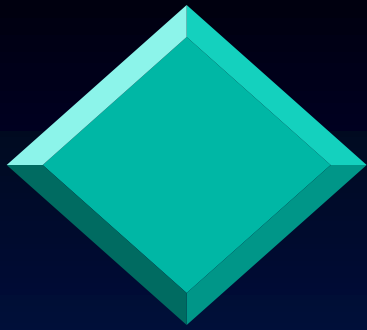
Dosage too low

- **Commence at lower end of the dosage range but be prepared to titrate dosages**
- **Consider temporarily suspending treatment or backing off if adverse effects occur**



Anticholinesterases

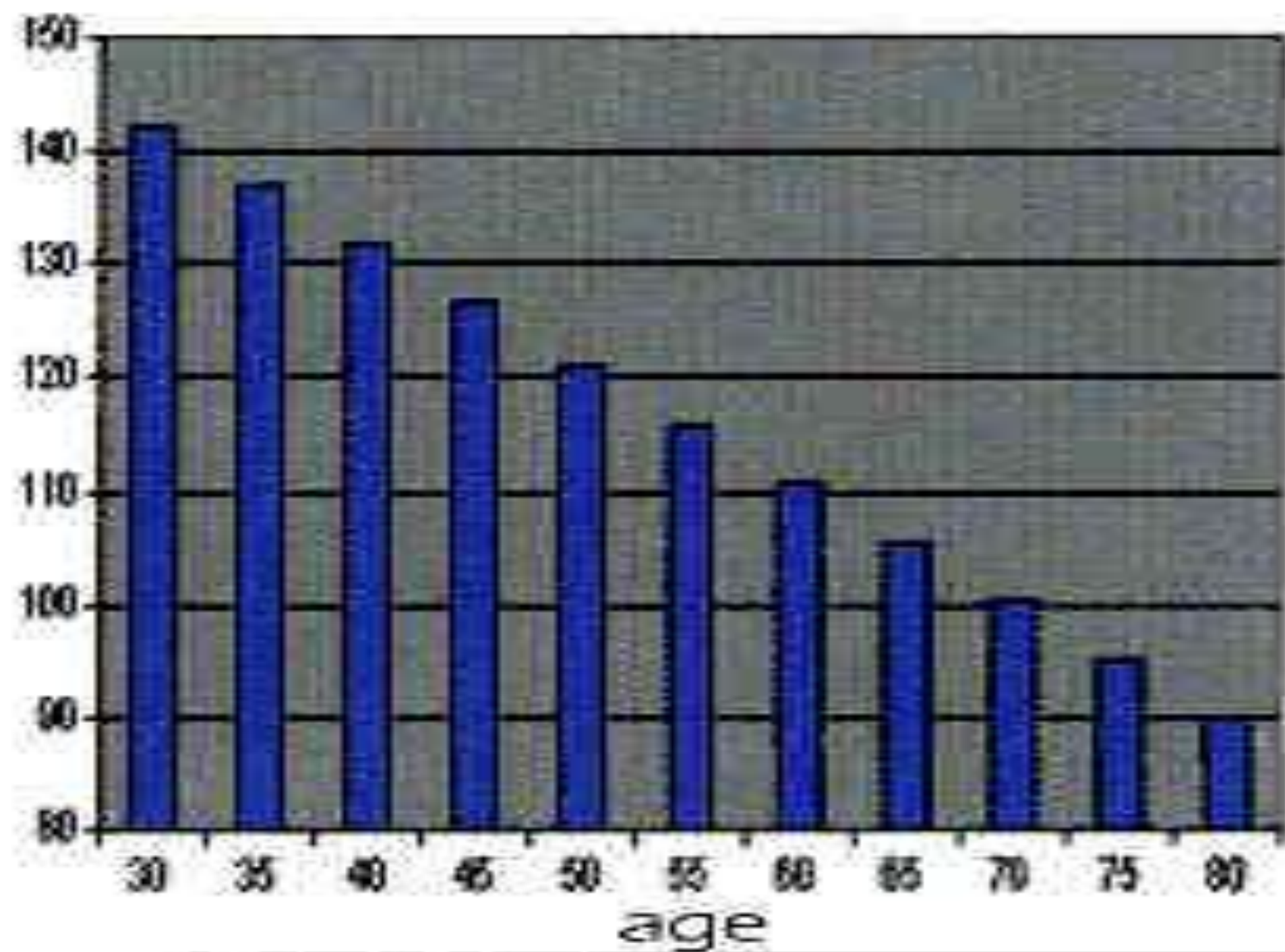
| | Galantamine | Donepezil | Rivastigmine |
|---|--|-----------------------|--|
| Class | <i>Tertiary alkaloid (daffodil derivative)</i> | <i>Piperidine</i> | <i>Carbamate</i> |
| Inhibition of Anticholinesterase | <i>Reversible</i> | <i>Reversible</i> | <i>Pseudo-irreversible (produces carbamylated complex)</i> |
| Half life | <i>5 to 6 hours</i> | <i>70 to 80 hours</i> | <i>Short but inactivates enzyme for ~10 hours</i> |
| Frequency of dosage | <i>Twice daily</i> | <i>Daily</i> | <i>Twice daily</i> |
| Dose Range | <i>4mg bd to 12mg bd</i> | <i>5 to 10mg</i> | <i>1.5mg bd to 6mg bd</i> |

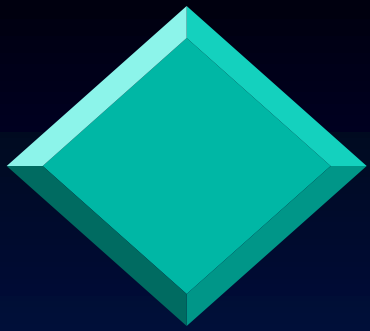


Dosage too high

- **Older people with psychiatric illness often require modifications to dosage for multiple reasons:**
 - **Pharmacodynamic sensitivity**
 - **Alterations in body composition**
 - **Changed pharmacokinetic profile**

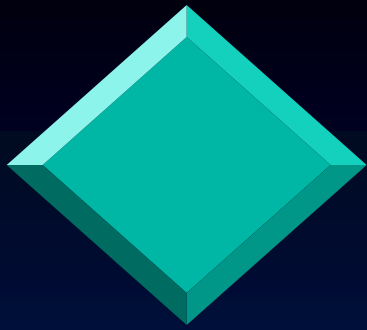
ml/min





Dosage too high

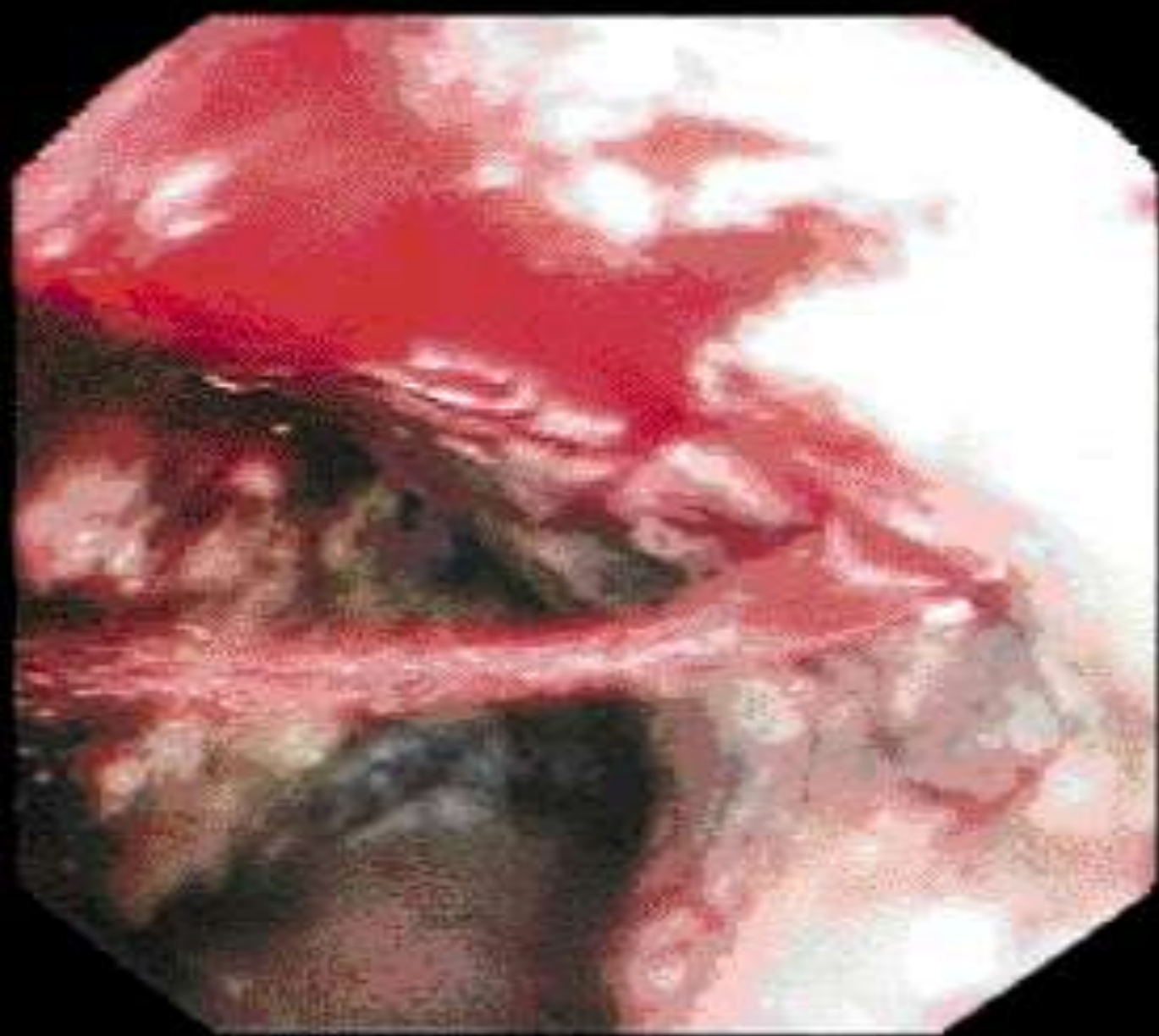
- **Many drugs require dosage adjustment for elderly patients**
- **CNS active agents commonly overdosed in the elderly, particularly those with renal impairment**
- **Reduce dosage for venlafaxine, reboxetine, gabapentin, lithium & others**

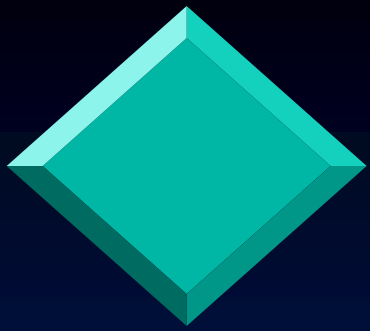


Commonly overdosed psychotropic drugs

- **SSRI have a flat dose-response relationship, but this is not so for dosage vs ADRs**
- **Atypical antipsychotic drugs often dosed above proven and safe range**
- **Doses of many drugs may not accommodate *evolving* changes in renal function**

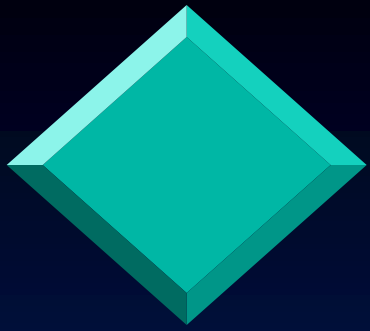






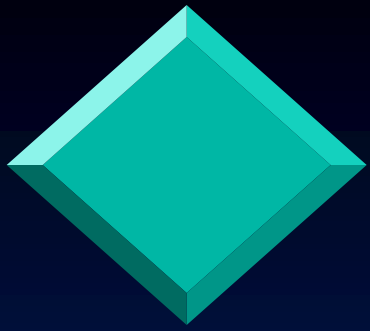
Adverse Drug Reactions

- **Older people clearly at risk**
- **Polypharmacy an important contributor**
- **Major organ dysfunction predisposes**
- **Many high-risk drug categories are well known to clinicians, others are more subtle**



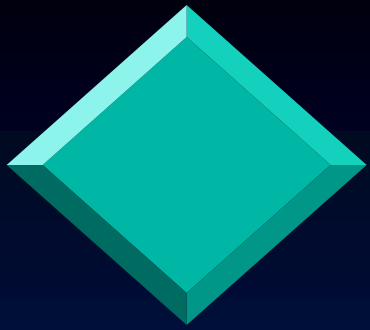
SIADH

- **Syndrome of Inappropriate Antidiuretic Hormone secretion**
- **Hyponatraemia with euvolaemia and inability to dilute urine output**
- **Prominent association with psychotropics, particularly SSRIs, venlafaxine, CBZ, TCAs and antipsychotics**



SIADH and SSRIs

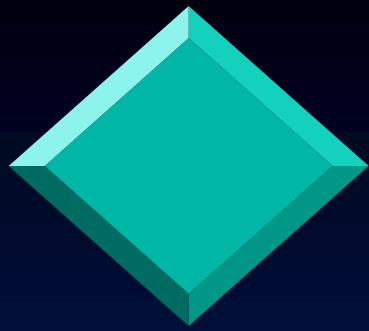
- **Incidence thought to be approximately 1 in 200 elderly patients treated, RR \cong 5.6**
- **Risk factors:**
 - **Older age, female gender**
 - **Low body weight**
 - **Previous history of hyponatraemia**
 - **Concurrent use of other implicated agents**



SIADH and SSRIs

- **Check serum sodium before and after initiation of therapy**
- **Investigate with urinary electrolytes if necessary**
- **Discontinue implicated agent, fluid restriction, demeclocycline**
- **? lithium**

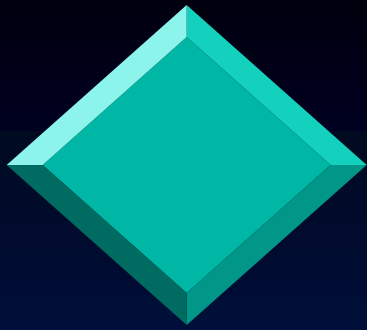




Pharmacoepidemiology & SSRIs

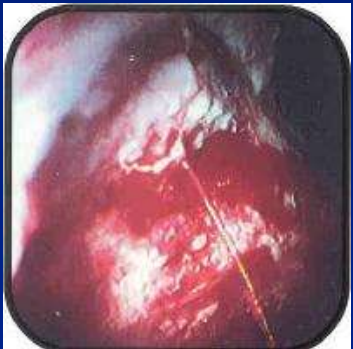
- ❖ Signal regarding abnormal haemostasis not recognised prior to widespread use
- ❖ First report of prolonged bleeding time in NEJM in 1990, many followed
- ❖ Prescribing information for SSRIs reveals many clues –purpura, petechial rash, ecchymosis, epistaxis, menorrhagia and rectal bleeding - some are listed as “common”.





Bleeding and SSRIs

- ❖ More information has evolved from large-scale pharmacoepidemiological studies and post-marketing surveillance
 - ◆ Dutch researchers used data collected over an eight year period from more than 64 000 new SSRI users and found risk of hospitalization for abnormal bleeding markedly increased
 - ◆ SSRIs significantly increase likelihood of major haemorrhagic events, especially upper GI bleeding, particularly increased by concurrent treatment with NSAIDs, aspirin or oral anticoagulants, but may be mitigated by PPIs



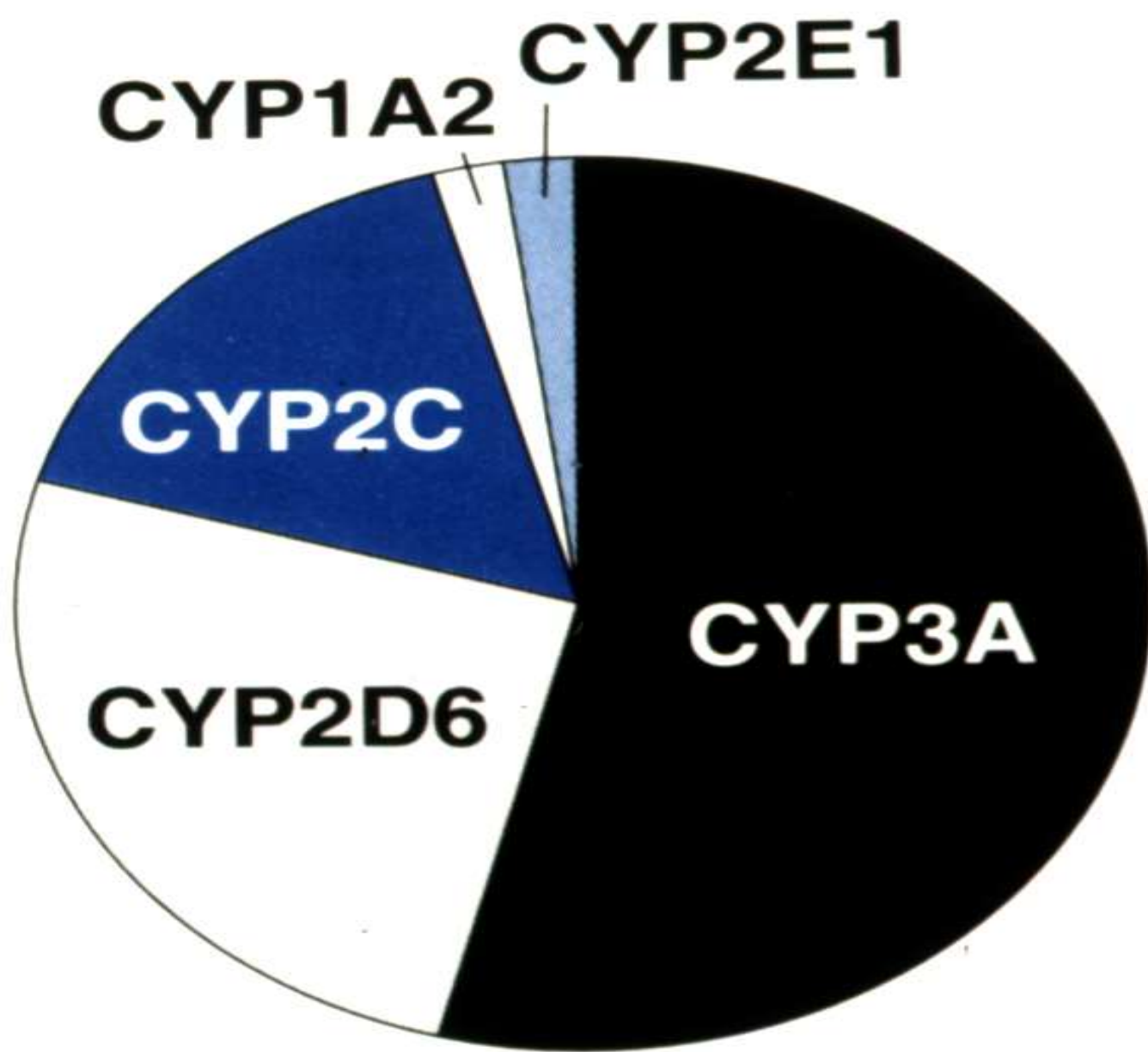
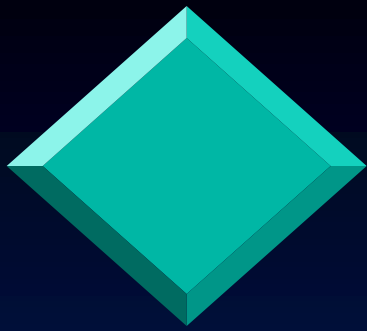
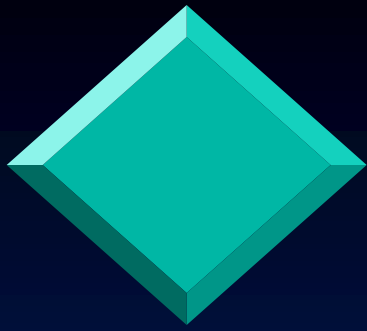


Figure 1-4. The proportion of drugs metabolized by the major cytochrome P450 enzymes.



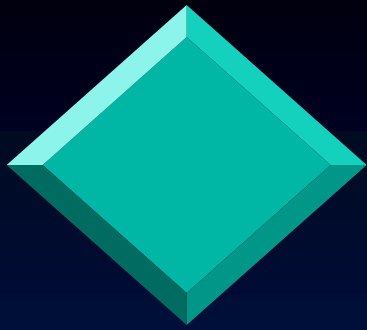
Antidepressant Interactions

- **CYP1A2**
 - **Fluvoxamine**
- **CYP2D6**
 - **Paroxetine, fluoxetine**
 - **Other SSRIs**
- **CYP3A4**
 - **Nefazodone, fluvoxamine**
 - **Norfluoxetine**



Antidepressant Interactions

- **CYP1A2**
 - Theophylline, Olanzapine, Donepezil
- **CYP2D6**
 - Flecainide, haloperidol, beta blockers
 - Opioids, perhexiline
- **CYP3A4**
 - Alprazolam, amiodarone, CBZ
 - CyA, cisapride, zopiclone



Not receiving prescribed drug

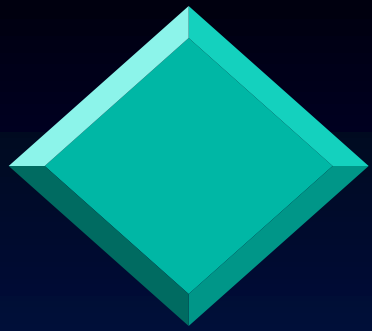
- ❖ **Patients may be prescribed the correct drug at the correct dose by the correct route and yet still not receive the drug**
- ❖ **Many factors can contribute**





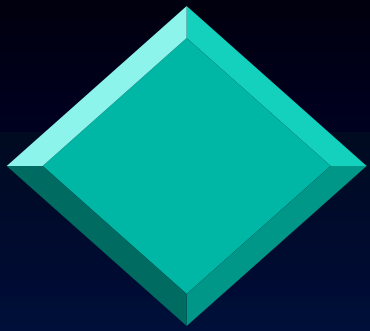
Historically, certain computer programs were written using two digits rather than four to define the applicable year. Accordingly, the company's software may recognize a date using "00" as 1900 rather than the year 2000.





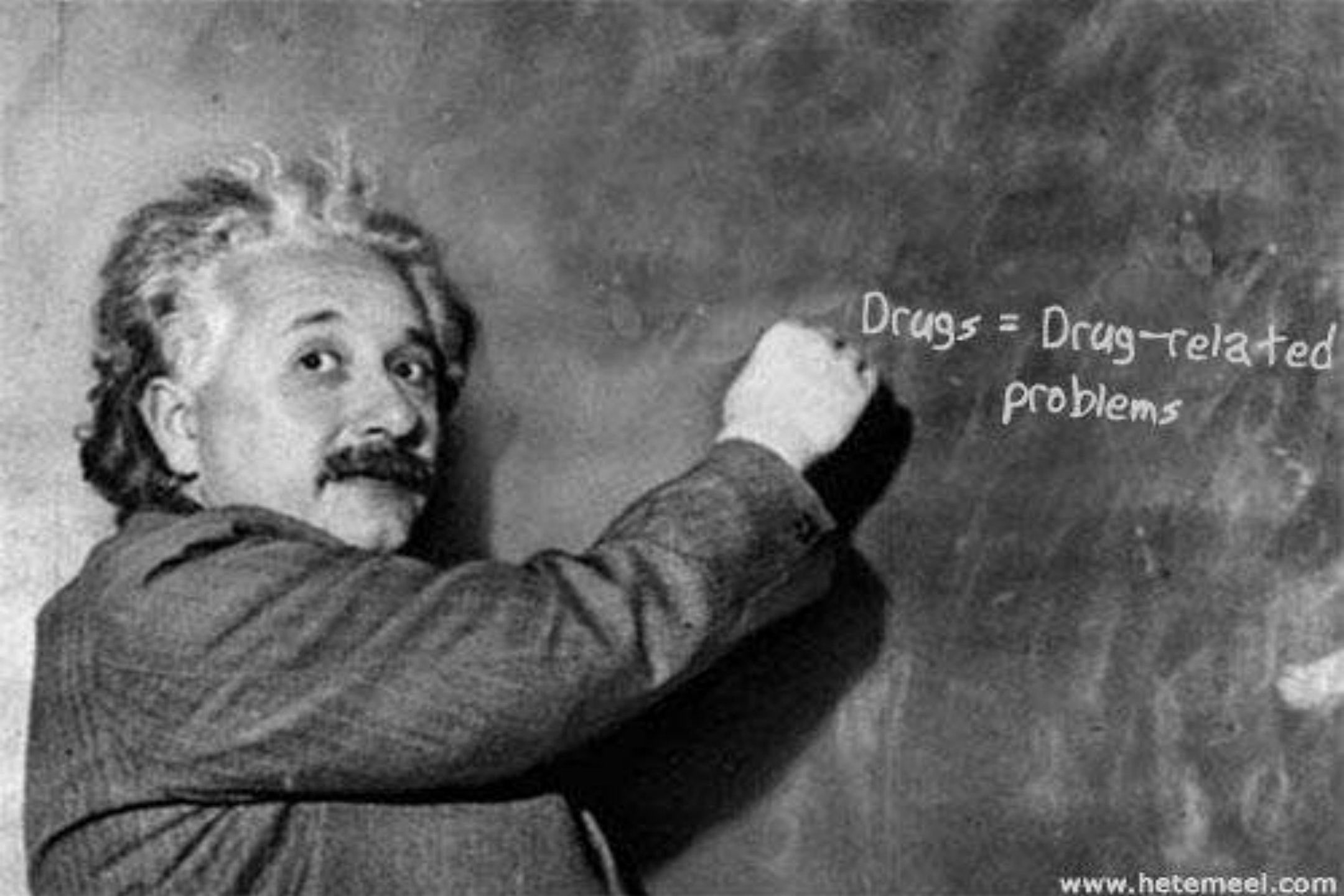
Adherence problems

- **Attitudinal or cultural issues**
- **Poor understanding**
- **Eyesight**
- **Physical limitations**
- **Confusion, delirium, dementia**
- **Chain of supply**
- **Financial issues**

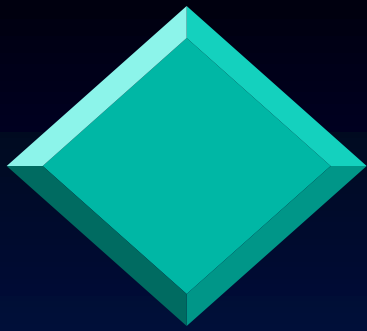


Drugs not indicated

- **Psychotropic medications are widely used, but may not always be required:**
- **Recent research in South Australia**
 - **924 residents in hostels and nursing homes**
 - **BZD: n = 408 (44%)**
 - **Antipsychotics: n = 222 (23.9%)**
 - **TCAs: n = 76, 50% < 50 mg**
 - **> 85% with at least one psychotropic**

A black and white photograph of Albert Einstein, with his characteristic wild hair and mustache, looking back over his shoulder while writing on a chalkboard. He is wearing a dark, long-sleeved jacket. The chalkboard is dark and has some faint, illegible markings. The text he is writing is in white chalk.

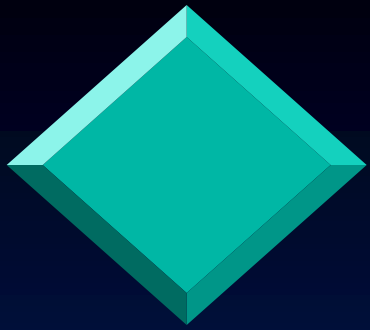
Drugs = Drug-related
problems



Jim's journey ...



- ❖ **72 year-old Korean War Veteran**
 - ❖ **Little or no contact with medical services**
 - ❖ **Little regular medication:**
 - ❖ **Metoprolol 50 mg bd (HT)**
 - ❖ **Smokes 30 cigarettes per day, drinks 8-10 standard drinks daily, weighs 105 kg**
 - ❖ **Convinced by his family to seek help, diagnosed with PTSD & depression**

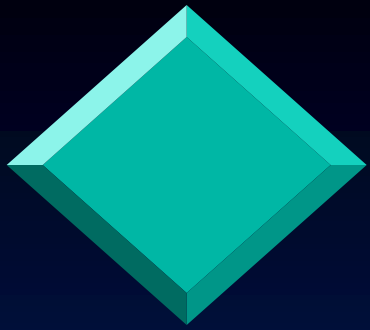


Jim's journey ...

- ❖ **Day 1 – one medication (metoprolol)**
- ❖ **Begins paroxetine 20 mg daily**
- ❖ **2/52 later presents to his GP:**
 - “I’m crook doc...
that medication is no good”**
- ❖ **BP 90/45**
- ❖ **HR 35 BPM**

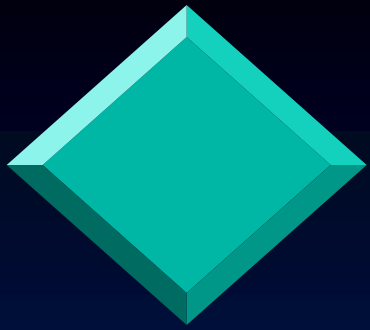
A 3D ribbon diagram of the Cytochrome P450 protein structure. The protein backbone is shown in a light grey color, forming a complex fold with multiple alpha-helices and beta-sheets. In the center of the protein, a heme prosthetic group is highlighted in red, showing its characteristic porphyrin ring structure. The entire structure is set against a black background.

CYTOCHROME P450



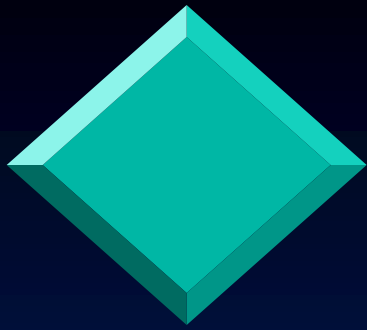
Jim's journey ...

- ❖ **Day 14 – two medications**
 - ❖ metoprolol, mirtazapine 30 mg daily
- ❖ **Attends on day 30 for routine follow-up, reports agitation & insomnia, weight gain**
- ❖ **Day 40 – three medications**
 - ❖ metoprolol, mirtazapine, olanzapine (5mg bd)
 - ❖ Body weight now 115 kg



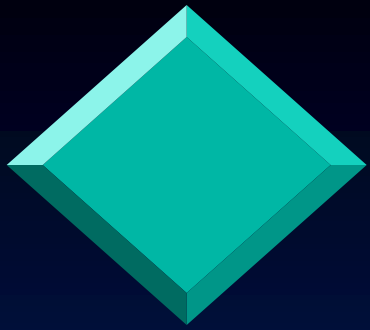
Jim's journey ...

- ❖ **Day 45 – results of investigations to hand**
 - ❖ Fasting BGL 12.5 mmol/L
 - ❖ Total cholesterol 6.6 mmol/L
- ❖ **Day 60 – now taking seven regular meds:**
 - ❖ Metoprolol
 - ❖ Mirtazapine
 - ❖ Olanzapine
 - ❖ Aspirin 100 mg daily
 - ❖ Metformin 500 mg bd
 - ❖ Ramipril 5 mg daily
 - ❖ Simvastatin 20 mg daily



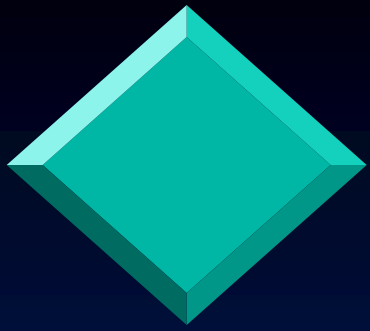
Jim's journey ...

- ❖ **Day 80 –taking seven regular medications**
 - ❖ Metoprolol
 - ❖ Mirtazapine
 - ❖ Olanzapine
 - ❖ Aspirin 100 mg daily
 - ❖ Metformin 500 mg bd
 - ❖ Ramipril 5 mg daily
 - ❖ Simvastatin 20 mg daily
- ❖ **Complains of severe back, & knee pain**
- ❖ **Apprehension about NSAIDs from GI viewpoint, → trial of tramadol 50 mg tds**



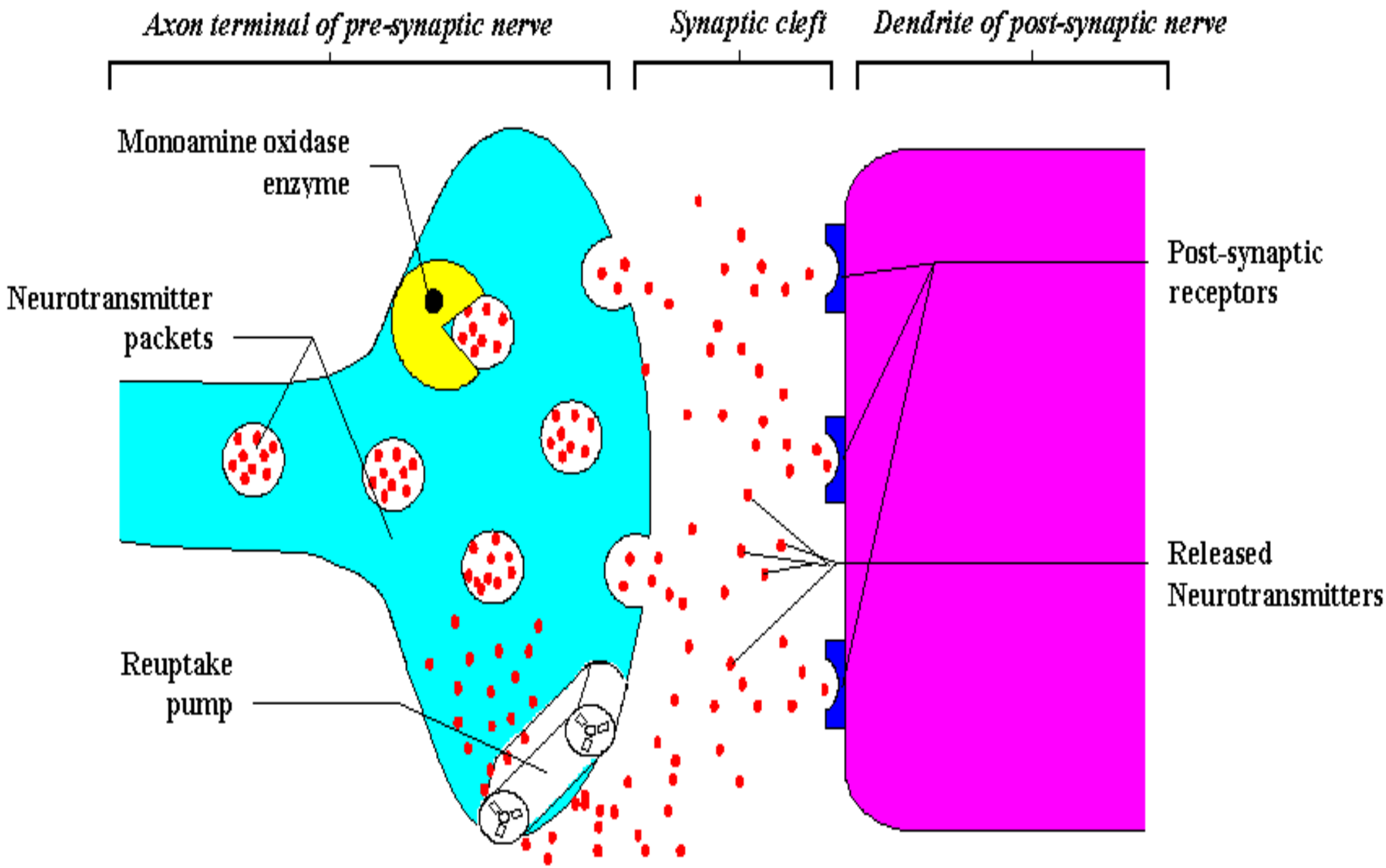
Jim's journey ...

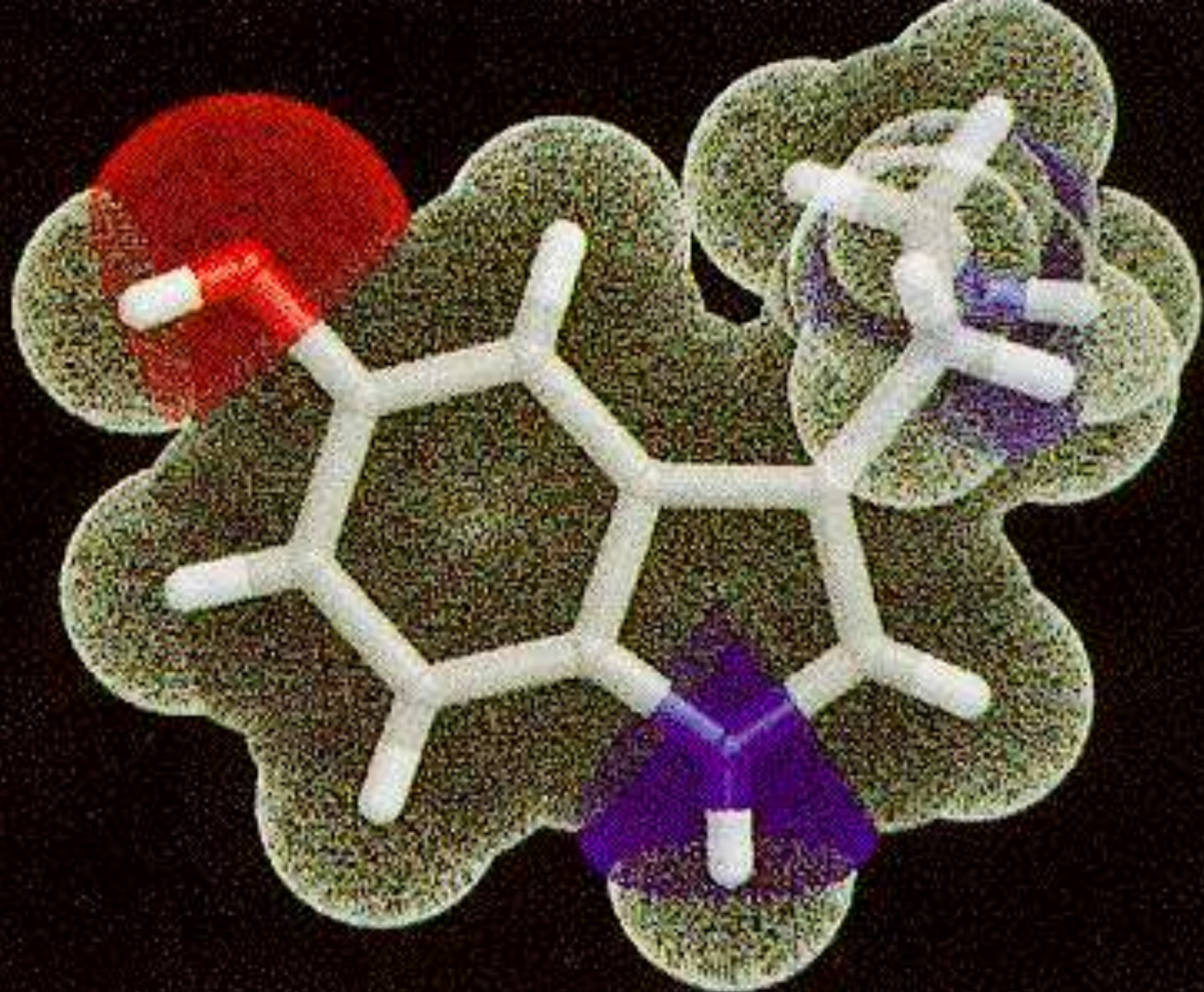
- ❖ **Two days later Jim presents to hospital:**
 - **Fever**
 - **Hypotension**
 - **Diaphoresis**
 - **hyperreflexia and myoclonic jerks**
- ❖ **Tramadol ceased, discharged 3/7 later**

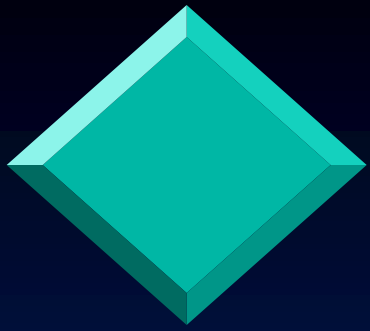


Serotonin Syndrome

- ❖ **First described in 1960 as a tryptophan/MAOI interaction**
- ❖ **More than 200 cases since that time in pharmacology, psychiatry, pharmacy, neurology and anaesthetics journals around the world**







Diagnostic Criteria

Altered MS

Hyperreflexia

Agitation

Shivering

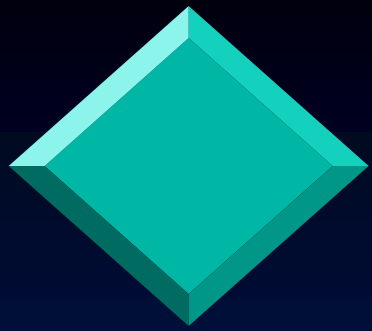
Tremor

Fever

Diarrhoea

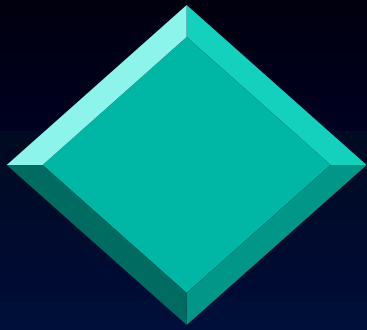
Myoclonus

Ataxia

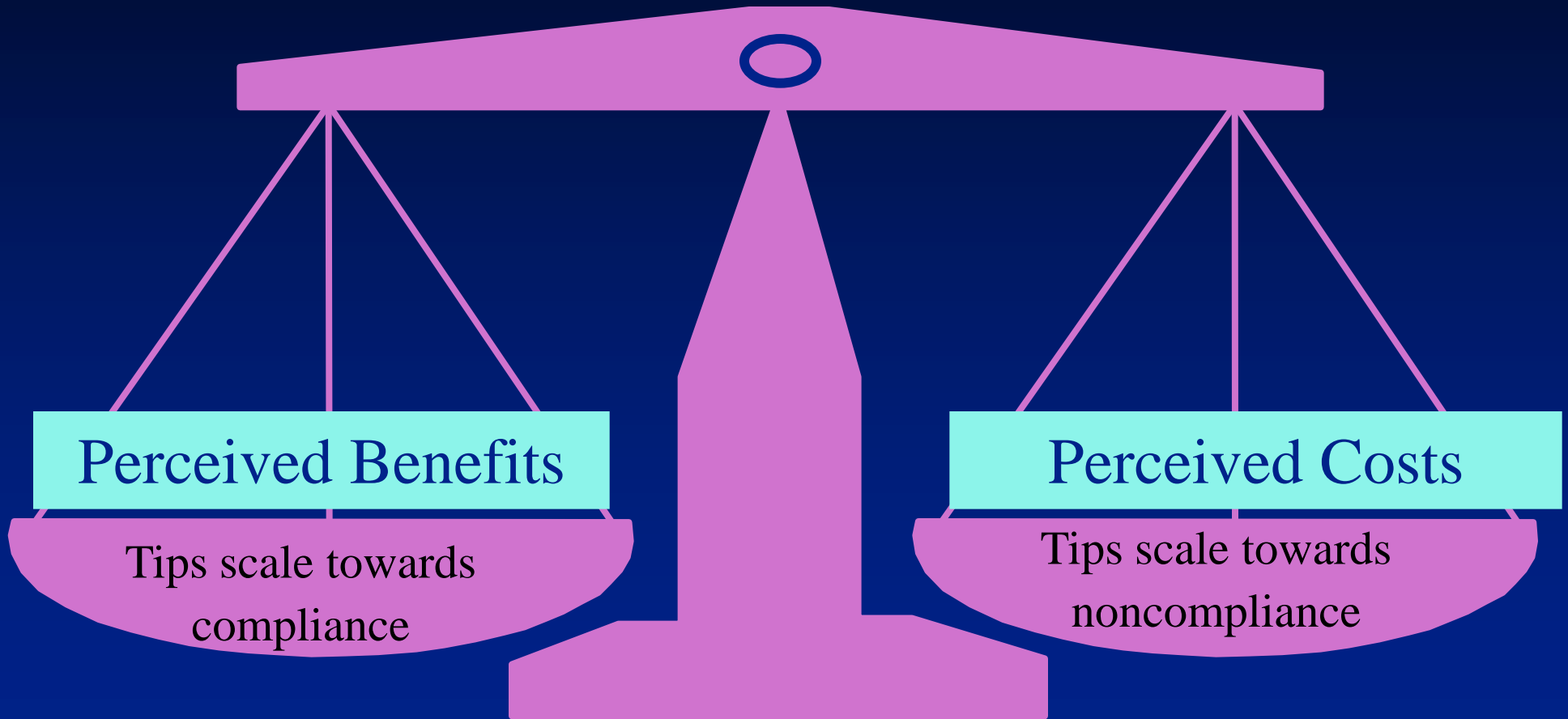


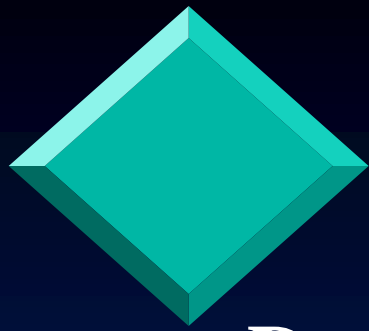
Jim's journey ...

- ❖ **Day 100 – Jim is taking no medications!**
- ❖ **Phone call to his psychiatrist – has stopped all of his prescribed drugs**
- ❖ **Drinking > bottle of rum per day**
- ❖ **In crisis, eventually convinced to present for admission**



Health Belief Model of Compliance



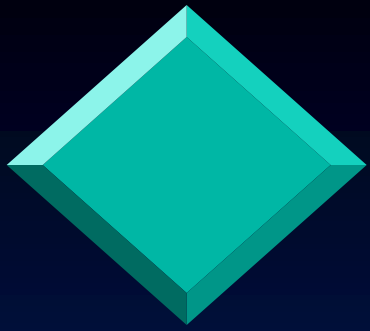


Jim's journey ...

❖ Day 120 – Jim taking 11 regular meds:

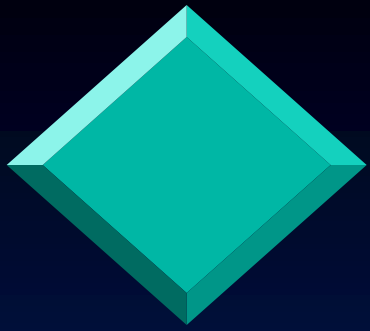
- ❖ Metoprolol 50 mg bd
- ❖ Venlafaxine 225 mg daily
- ❖ Quetiapine 100 mg
- ❖ Zopiclone 7.5 mg at night
- ❖ Thiamine 100 mg daily
- ❖ Aspirin 100 mg daily
- ❖ Metformin 1000 mg bd
- ❖ Ramipril 5 mg daily
- ❖ Simvastatin 20 mg daily
- ❖ Paracetamol 665 x 2 tds
- ❖ Transdermal nicotine patches





What has Jim taught us?

- ❖ **Complex interplay between psychotropic drugs, comorbidities, psychosocial factors**
- ❖ **Considerable potential for hazards**
- ❖ **Jim's journey is one taken by thousands every year**
- ❖ **Jim's destination is at least in part determined by us ...**



In conclusion ...

- **Drug-related problems are common, particularly amongst elderly, those with cognitive disorders and those treated with psychotropic drugs**
- **Consider potential impact of all eight classes**
- **Employ strategies to address potential for drug-related harm**