Pharmacodynamic principles for safe practice
“Poisons in small doses are the best medicines; and useful medicines in too large doses are poisonous.”

William Withering

1741 - 1799
Diagram A: Effect vs Drug Dose

Diagram B: Effect vs Serum Drug Concentration with Optimal Zone
Drug response intensity is not proportional to the drug concentration ($C_D$)

<table>
<thead>
<tr>
<th>ED50</th>
<th>Effect</th>
<th>Gain</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 x</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>2 x</td>
<td>67%</td>
<td>17%</td>
</tr>
<tr>
<td>4 x</td>
<td>80%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Daily dose ED50 for statins
Simvastatin 12mg
Atorvastatin 3mg
### Statin Dose - Response (% reduction Total Chol)

(comparative data, Atorvastatin data sheet from multiple phase 3 and 4 clinical trials)

<table>
<thead>
<tr>
<th>Drug</th>
<th>5</th>
<th>10</th>
<th>20</th>
<th>40</th>
<th>80</th>
</tr>
</thead>
<tbody>
<tr>
<td>Daily dose (mg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Simvastatin</td>
<td>23%</td>
<td>27%</td>
<td>32%</td>
<td>37%</td>
<td>42%*</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>38%</td>
<td>43%</td>
<td>48%</td>
<td>53%</td>
<td>-</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>-</td>
<td>37%</td>
<td>43%</td>
<td>49%</td>
<td>55%</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>-</td>
<td>20%</td>
<td>24%</td>
<td>29%</td>
<td>33%</td>
</tr>
</tbody>
</table>
Statin dosing (Dimmit et al RACP 2015)

- Starting dose 10mg simvastatin and atorvastatin.
- 6% gain with each dose doubling.
- Risk > benefit for high dose 80 mg Simva./Atorva: 6 fold increase in abn. LFTs.
- CV risk reduction with statins does not appear until after several years, and does not require high doses.
- There is no evidence to support titration of statin dose against T Chol or LDL levels.
"Usual dose" concept

Toxic

"Average dose given according to experience"

ignores individual variability

Ineffective
Variation in drug dose required to produce a target response in a group of patients

The concept of a "usual dose" is illogical and pharmacologically naive.
## Lowering of recommended daily doses

<table>
<thead>
<tr>
<th>drug</th>
<th>historic (mg/day)</th>
<th>New Ethicals rec.</th>
<th>Average daily dose (case response)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BFZ</td>
<td>5 - 10</td>
<td>2.5 - 10</td>
<td>2.5</td>
</tr>
<tr>
<td>Captopril</td>
<td>300 - 400</td>
<td>50 - 100</td>
<td>37.5</td>
</tr>
<tr>
<td>Atenolol</td>
<td>200 - 400</td>
<td>50 - 100</td>
<td>50</td>
</tr>
</tbody>
</table>
minimum effective dose

ED 50

minimum toxic dose

minimum effective dose
“Therapeutic index”

Ratio between the dose required to cause adverse effects and that required for efficacy.

Note: Phenytoin
Perhexiline
Digoxin
Gentamycin

The higher the TI the safer the drug
Phenytoin dose/conc.  
NB: individual variability
Drug formulation

Critical factors: Dissolution, Disintegration, Gastric emptying (Digoxin + Metoclopramide)

• Conventional: stnd. tablet/capsule:
  – NB: drug absorption and systemic availability are dependent on the drug properties, but not the formulation.

• Non Standard: modified formulation (eg. CD, SR or patch).
  – Drug absorption is slowed, drug action may change, but metabolism & elimination are unaffected:

• Pro-drug: metabolic step frees drug for systemic availability (ACE-Is, Clopidogrel).
Slow release (‘retard’, SR, CD etc)

• Advantages
  – Reduced type 1 dose dependent side effects
  – Improved adherence to ‘once a day’ dosing regimen ??
  – Maintain ‘market share’.

• Disadvantages
  – Formulation technology is complex.
  – Tends to increase individual variability in dose response eg. Metoprolol SR
  – May not provide effect for stated duration – eg ‘once a day’.
Sustained release formulations
Fixed dose combinations

“Accuretic” = Quinapril + Hydrochlorothiazide
“Hyzaar” = Losartan + Hydrochlorothiazide
– Etc.

• Individual components cannot be titrated.
• Combination cannot be titrated, unless multiple dose formulations are available.
• ACE-I dose does not reflect synergistic effect of Thiazide when used in combination.
• Produced to extend market position?

No evidence for improved clinical outcomes over separate prescription of components.
Once a day vs twice a day

Elliot. J Hypertension 1994
Drug interactions
Mrs NB aged 78

- Adm. dizziness & collapse, bp100/70, HR 34/min
- Symptomatic IHD - GTN spray
- Hypertension - Amlodipine (ankle swelling) - recently changed to Diltiazem.
- Tolerating treatment until she was prescribed erythromycin 5 days prior.
- S Cr 237 micmol/L
Mrs NB

• Medications:

  - Doxazocin 2mg bd
  - Sotalol 160mg SR daily
  - Aspirin 150mg daily
  - Diltiazem 240mg CD daily
  - Frusemide 40mg daily
  - Erythromycin 500mg tds
  - GTN spray

Discussion!
Drugs requiring dose adjustment in renal impairment

- morphine
- tramadol
- LMW Heparin
- allopurinol
- digoxin
- metformin
- gentamicin
- lithium
- cephalosporins (most)
- fluconazole
- sotalol & atenolol
- methotrexate
- bezafibrate
- simvastatin
- ciprofloxacin
- NSAIDs & COX2s
- ACE-inhibitors
Major enzyme inducers

Phenytoin; Phenobarbitone; Carbamazepine; Rifampicin; Corticosteroids

Others: chronic alcohol abuse; smoking; BBQ meats; Isoniazid; Omeprazole; cruciferous vegetables (brussell sprouts etc).

- CYP450 enzymes are inducible – except \textit{CYP2D6}.
  - increased first-pass metabolism,
  - increased clearance,
  - decreased t1/2,
  - lower steady state concentrations.
  - 2 weeks for full effect.
Major enzyme inhibitors

- Macrolides (erythromycin) & Amiodarone; (3A4).
- Azole anti-fungals; (many CYPs).
- Paroxetine/Fluoxetine; (2D6).
- Others: Metronidazole; Quinalones (ciprofloxacin); Trimethoprim; Protease inhibitors; Chloramphenicol; SSRI; Cimetidine; Grapefruit juice; Diltiazem and Verapamil.

- Less first-pass metabolism
- Less clearance
- Longer t1/2
- Higher steady state concentrations
- Immediate dose dependent effect.
P-glycoprotein interactions

- Quinidine + Loperamide, & Digoxin
- Verapamil + Digoxin
- Clarithromycin + Digoxin
- Ketoconazole + Dabigatran etixilate
- Verapamil + Dabigatran etixilate
- Diltiazem
- Amiodarone
- Grapefruit juice

NB: CYP 3A4 + Pgp “alliance” mechanism
High risk meds!

- Warfarin
- Itraconazole
- LMW Heparin
- Methotrexate
- Insulin
- Lithium
- Perhexiline
- Gentamicin
- Morphine
- NSAIDs

- Individually dangerous drugs
- Most commonly involved in drug interactions
Major drug/drug interactions

- Alpha blockers + Nitrates = syncope
- Ethanol + BDZ hypnotics = sedation and driving impairment.
- NSAIDs + Diuretics + ACE-I = renal failure
- Diltiazem + Statins = rhabdomyolysis
- Morphine + BDZs = respiratory failure
- SSRIs + Tramadol or Opiates = serotonergic syndrome.
- Antipsychotics + L-dopa = loss of dopa effect.
Major drug/drug interactions

- Aminoglycosides + Loop Diuretics or Cephalosporins = *renal failure*.
- Lithium + ACE-I's or Diuretics = *Li toxicity*.
- NSAIDs + ACE-I's = *loss of ACE-I effect*.
- Allopurinol + Azathioprine* = *aplastic anaemia*.
- Tamoxifen* + Paroxetine/Fluoxetine = *loss of endoxifen effect*.
- Codeine* + Paroxetine/Fluoxetine = *loss of analgesia*.
Drug/Disease interactions: “Contraindications”

- Renal impairment + any drug with renal $f_u > 75\%$ (Sotalol, Atenolol, Morphine, Aminoglycosides, Statins) = toxicity
- Hypertension + Ethanol, NSAIDs, Liquorice = accelerated hypertension.
- Elderly + CNS depressants – falls risk, warfarin, opiates, Alpha blockers = syncope
- Asthma + betablockers.
- eetct Beta blockers = respiratory failure
Know this!

- Six or more drugs means an 80% chance of a Drug Interaction.
  - More common in the elderly
  - Long term conditions
  - Multiple co-morbidities

Regular medicines review can reduce the risk
Individual variability means uncertainty!

- Pharmacotherapy is about managing uncertainty
  - Identify the clinical questions
  - Wisdom – use your practice experience
  - Evidence – critical awareness, healthy scepticism
  - Judgement

“Doubt is an unpleasant condition, but certainty is absurd” Voltaire
Aging effects

Figure 4. Influence of age on physiological function in man after maturity (from Kohn, 1978).