Hot topics in clinical pharmacology 2016

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Welcome to ASCEPT The Australasian Society of Clinical and Experimental Pharmacologists and Toxicologists
Issues for ASCEPT

• Increasing workload
• Deprescribing, repurposing of ‘old’ drugs, pharmacokinetics of medicinal cannabis and therapeutic drug monitoring (cancer drugs)
• Relationship of non physicians to allied health and scientists in ASCEPT
• Training the workforce
• Hospital/Uni/Government/Regulatory positions
Deprescribing

- Programs around Australia
  - ADeN
  - Geriatric deprescribing
  - Deprescribing in general medical patients
  - Deprescribing in palliative care
  - Inter alia
What is it?

Describes the **rationalisation** of medicines that provide a limited benefit in patients, due to **changing medical and patient factors over time**.

‘Potentially’ inappropriate is an **inappropriate term** – all medications are potentially inappropriate when prescribed poorly.

Medications should be ceased based on a number of factors including efficacy, toxicity and the changing ratio.
Relevance to ASCEPT

Multiple physician groups examining deprescribing. This is a good thing!

Several themes are common and relate to knowledge, skills and know-how in clinical pharmacology. E.g. translation of clinical trial data to ‘real world.’

Problems when patients have (multiple) comorbidity.
Problems with drug interactions.
Problems knowing if new symptoms/signs are due to prescribing or a new disease.
Palliative care

Support Care Cancer (2014) 22:1113–1119

REVIEW ARTICLE

Reducing potentially inappropriate medications in palliative cancer patients: evidence to support deprescribing approaches

Julian Lindsay · Michael Dooley · Jennifer Martin ·
Michael Fay · Alison Kearney · Michael Barras

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Key factors of the identified trials</th>
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<tbody>
<tr>
<td></td>
<td>Number</td>
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<tr>
<td>Riechelmann et al. 2009 [13]</td>
<td>372</td>
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<tr>
<td>Fede et al. 2011 [1]</td>
<td>87</td>
</tr>
<tr>
<td>Todd et al. 2013 [14]</td>
<td>20</td>
</tr>
<tr>
<td>Nyborg et al. 2012 [19]</td>
<td>445,900</td>
</tr>
<tr>
<td>Bongue et al. 2011 [17]</td>
<td>35,259</td>
</tr>
<tr>
<td>Gallagher et al. 2011 (May) [20]</td>
<td>900</td>
</tr>
<tr>
<td>Garfinkel et al. 2010 [21]</td>
<td>70</td>
</tr>
<tr>
<td>Gallagher et al. 2011 (June) [10]</td>
<td>382</td>
</tr>
</tbody>
</table>
Palliative Care

- evidence that inappropriate medicines (IM) are commonly prescribed in palliative care
- no studies that have identified the ACTUAL impact of ceasing IM in this setting
- published tools and implemented strategies have focused on the elderly populations
- Further research to establish clear guidelines for the identification of IMs in palliative care practice as well as interventional studies assessing the outcomes of ceasing IMs in these patients is needed
The Scott algorithm - A QUM framework
AMJ 2011

1) What current medications
3) Life expectancy
4) Overall care goals for patient
5) Confirm current indications for ongoing treatment
7) Estimate the magnitude of benefit versus harm
9) Identify drugs that may be discontinued

Reduction in inappropriate polypharmacy: the process of deprescribing.
Scott IA\textsuperscript{1}, Hilmer SN\textsuperscript{2}, Reeve E\textsuperscript{3}, Potter K\textsuperscript{4}, Le Couteur D\textsuperscript{5}, Rigby D\textsuperscript{6}, Gnjidic D\textsuperscript{7}, Del Mar CB\textsuperscript{8}, Roughead EE\textsuperscript{9}, Page A\textsuperscript{10}, Jansen J\textsuperscript{11}, Martin JH\textsuperscript{12}. 
Why too much medicine is a problem for many older people

A/Prof Sarah Hilmer, BScMed(Hons) MBBS(Hons) FRACP PhD
Departments of Aged Care and Clinical Pharmacology, RNSH
Northern Clinical School, Sydney Medical School
Kolling Institute of Medical Research
Cannabis

- Too fast too soon or not soon enough
- Why can’t patients self titrate
- Why does it have to be regulated/registered/GMP.
- Which drug/chemical/combination
- Plant vs. synthetic
- Where grown – consistency, stability
- Where regulated
- Route of administration, dose, frequency
- Script vs. patient titrate
Varieties of Cannabinoids

- **Endocannabinoids**: In your brain and body
  - Anandamide, 2-AG, Noladin ether, etc.

- **Phytocannabinoids**: In plants
  - THC, CBD, CBG, CBDV, THCV, CBC, CBN, THCV, etc.

- **Synthetic cannabinoids**: From the lab
  - Nabilone, HU-210, AB-PINACA, JWH-018, etc.
Brain regions that express the CB₁ cannabinoid receptor

Red = abundant CB₁ receptor expression  Black = moderately abundant CB₁ receptor expression

Cerebral Cortex
higher cognitive functions

Hypothalamus
temperature regulation, salt/water balance, reproductive function, energy balance

Prefrontal Cortex
executive function

Basal ganglia
cognition, learning, emotional response, motor control

Amygdala
emotional response, fear

Hippocampus
learning, memory, stress

Periaqueductal Gray
analgesia

Nucleus of the Solitary Tract
visceral sensation, nausea/vomiting

Cerebellum
posture

Brain Stem
sleep arousal, temperature regulation, motor control

Spinal cord
peripheral sensation including pain

>100 cannabinoids in the plant. Most are non-psychoactive.

Each has its own pharmacological actions and therapeutic potential.

“Entourage” effects
Cannabinoids in chronic pain
Systematic review: Whiting et al JAMA June 2015

### Figure 2. Improvement in Pain

<table>
<thead>
<tr>
<th>Improvement in Pain With Cannabinoid vs Placebo by Study</th>
<th>Cannabinoid Events</th>
<th>Placebo Events</th>
<th>Odds Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuberculosis lymphangiectasia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tetrahydrocannabinol (smoked)</td>
<td>13</td>
<td>6</td>
<td>3.43 (1.03-11.48)</td>
</tr>
<tr>
<td>Abrams et al, 77, 2007</td>
<td></td>
<td></td>
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<tr>
<td>Nabiximols</td>
<td></td>
<td></td>
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<tr>
<td>GW Pharmaceuticals, 22, 2005</td>
<td>54</td>
<td>59</td>
<td>0.86 (0.54-1.37)</td>
</tr>
<tr>
<td>Johnson et al, 69, 2005</td>
<td>23</td>
<td>12</td>
<td>2.81 (1.22-6.50)</td>
</tr>
<tr>
<td>Langford et al, 65, 2013</td>
<td>84</td>
<td>77</td>
<td>1.25 (0.81-1.91)</td>
</tr>
<tr>
<td>Nurmikko et al, 76, 2007</td>
<td>16</td>
<td>9</td>
<td>2.00 (0.81-4.96)</td>
</tr>
<tr>
<td>Portenoy et al, 67, 2012</td>
<td>22</td>
<td>24</td>
<td>0.90 (0.46-1.76)</td>
</tr>
<tr>
<td>Selvarajah et al, 70, 2010</td>
<td>8</td>
<td>9</td>
<td>0.63 (0.14-2.82)</td>
</tr>
<tr>
<td>Serpell et al, 88, 2014</td>
<td>34</td>
<td>19</td>
<td>1.97 (1.05-3.70)</td>
</tr>
<tr>
<td>Subtotal $I^2 = 44.5%, (P = .94)$</td>
<td>241</td>
<td>209</td>
<td>1.32 (0.94-1.86)</td>
</tr>
<tr>
<td>Overall $I^2 = 47.6%, (P = .64)$</td>
<td>254</td>
<td>215</td>
<td>1.41 (0.99-2.00)</td>
</tr>
</tbody>
</table>

Odds indicate 30% or greater improvement in pain with cannabinoid compared with placebo, stratified according to cannabinoid. The square data markers indicate odds ratios (ORs) from primary studies, with sizes reflecting the statistical weight of the study using random-effects meta-analysis. The horizontal lines indicate 95% CIs. The blue diamond data markers represent the subtotal and overall OR and 95% CI. The vertical dashed line shows the summary effect estimate, the dotted shows the line of no effect (OR = 1).
Role of clinical pharmacology

- 3 NSW Health funded studies
- 2 have requested early phase pharmacology studies to assess:
  - GMP/regulatory issues
  - Timing of administration (relevant PK parameter)
  - Route of administration – ADME
  - Linking PK with PD
  - Generates knowledge on
    - starting dose
    - dose range for different patient
    - different modes of admin

The NSW Government has committed $3.5 million to explore the use of cannabis products in providing relief for children with severe drug-resistant epilepsy.

These trials are part of the NSW Government’s commitment to develop a better understanding of how cannabis products can provide relief to children with severe drug-resistant epilepsy.

NSW researchers at the Sydney Children’s Hospitals Network, Dr John Lawson and Dr Deepak Gill, will lead the development and conduct of these trials using cannabis-derived products that are manufactured and supplied by GW Pharmaceuticals.

The new partnership facilitates four key outcomes for NSW:
- a world first phase 2 clinical trial for a novel product, cannabidiol (CBDV)
- a compassionate access scheme for Epidiolex®
- provision for NSW to host future clinical trials of GW products.
- a phase 4 clinical trial of Epidiolex® (based on success of phase 3 studies)
Vaporising cannabis

• Similar to ‘e-cigarettes’
• Vaporising heats cannabis at lower temperature than ‘smoking’. Higher bioavailability.
• No side stream smoke (fewer concerns re: passive smoking)
• Peak THC effects: typically 15-90 min after dose, psychoactive effects for 2-3 hours
Factors that affect drug-benefit/toxicity

What do we adjust for and how do we dose adjust?

- Symptom
- Route of administration
- $t_{1/2}$, clearance
- Age, gender, presence of other diseases
- Obesity
- Known/unknown drug AND FOOD interactions
- Patient side effects - tolerability
- Surrogates of efficacy or toxicity
- Drug supply/chemistry
Colorado dispensary
Implications for clinicians

• Use of illicit cannabis for ‘medical’ purposes is common in some areas of medicine.
  • Most patients will not disclose & most doctors won’t ask
• Medical cannabis will become more common in Australia
  – Increasing advocacy despite unclear evidence of efficacy for most conditions
  – What role for health providers?
• Need for better understanding and education of health providers of the potential harms and therapeutic roles of cannabinoids.

Medical Journal of Australia June 6, 2016 Martin J and Bonomo Y.
Regulatory and pricing areas

• Review/Reform of Therapeutic Goods Administration

• BIOSIMILARS
  – Difference between biosimilars and generics
  – Industry issues (e.g. Guild) vs. patient issues vs. doctor/patients relationship
  – Comparative pharmacokinetics and pharmacodynamics
Repurposing of old drugs

• Valproate
• Hydralazine
• Prochlorperazine
• Docetaxal

Repurposing some older drugs that cross the blood–brain barrier and have potential anticancer activity to provide new treatment options for glioblastoma

Dayle Rundle-Thiele,1 Richard Head,2 Leah Cosgrove3 & Jennifer H. Martin4
## Table 1

Existing drugs with potential antineoplastic effects as demonstrated through *in vitro* studies.

<table>
<thead>
<tr>
<th>Class Drug</th>
<th>Primary Indications for use</th>
<th>Primary mechanism of action</th>
<th>Mechanism of antineoplastic effects</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Tricyclic antidepressants</strong></td>
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<tr>
<td>Amitriptyline</td>
<td>Major depression, Neuropathic pain</td>
<td>Inhibit reuptake of noradrenaline and serotonin at presynaptic nerve terminals</td>
<td>Reduce cellular proliferation and might induce apoptosis through aberrant MAPK pathway activity or inhibition of mitochondrial activity</td>
<td>Levkovitz et al. [22], Higgins and Pilkinson [25], Tzadok et al. [26]</td>
</tr>
<tr>
<td>Imipramine</td>
<td>Major depression, Neuropathic pain</td>
<td>Inhibit reuptake of noradrenaline and serotonin at presynaptic nerve terminals</td>
<td>Reduce cellular proliferation and might induce apoptosis through aberrant MAPK pathway activity or inhibition of mitochondrial activity</td>
<td>Levkovitz et al. [22], Higgins and Pilkinson [25], Tzadok et al. [26]</td>
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<tr>
<td>Cimipramine</td>
<td>Migraine prophylaxis</td>
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<td>Doxepin</td>
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<tr>
<td>Citalopram</td>
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<tr>
<td><strong>Selective serotonin reuptake inhibitors</strong></td>
<td>Major depression, Bipolar disorder, Anxiety disorders</td>
<td>Inhibit reuptake of serotonin at presynaptic nerve terminals</td>
<td>Reduce cellular proliferation and might induce apoptosis through aberrant MAPK pathway activity or inhibition of mitochondrial activity</td>
<td>Levkovitz et al. [22], Higgins and Pilkinson [25], Tzadok et al. [26]</td>
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<tr>
<td>Paroxetine</td>
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<td>Fluoxetine</td>
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<tr>
<td>Sertraline</td>
<td>Bulimia nervosa</td>
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<tr>
<td><strong>Phenothiazines</strong></td>
<td>Chemotherapy-induced emesis</td>
<td>Dopamine receptor antagonists</td>
<td>Might decrease cellular proliferation and increase cellular sensitivity to some chemotherapeutic agents</td>
<td>Sachios et al. [23], Tzadok et al. [26], Yde et al. [27]</td>
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<tr>
<td>Chlorpromazine</td>
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<td>Thioridazine</td>
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<tr>
<td>Perphenazine</td>
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<tr>
<td><strong>Valproic acid (valproate)</strong></td>
<td>Seizure disorders, Bipolar disorder, Migraine prophylaxis</td>
<td>Acts on GABA levels in the brain to reduce voltage-gated sodium, potassium and calcium channels</td>
<td>Acts as a histone deacetylase inhibitor and might contribute to chromatin condensation, growth arrest and apoptosis</td>
<td>Camphausen et al. [31], Chinnaiyan et al. [32], van Nifterik et al. [38]</td>
</tr>
<tr>
<td><strong>Levetiracetam</strong></td>
<td>Partial focal seizures, Adjunct in tonic-clonic and myoclonic seizures</td>
<td>Unknown</td>
<td>Might act as a histone deacetylase inhibitor, contributing to chromatin condensation, growth arrest and apoptosis</td>
<td>Bobustuc et al. [30]</td>
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<tr>
<td><strong>Statins</strong></td>
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<tr>
<td>Lovastatin</td>
<td>Hypercholesterolaemia</td>
<td>Inhibition of HMG-CoA reductase, the rate-limiting enzyme in the cholesterol synthesis pathway</td>
<td>Decreased activity in cell signalling pathways contributes to induction of apoptosis and decreased proliferation</td>
<td>Yanaee et al. [46], Yongjun et al. [47], Gabryś et al. [48], Wu et al. [49], Tapia-Perez et al. [50]</td>
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<tr>
<td>Pravastatin</td>
<td>Prevention of cardiovascular disease</td>
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<tr>
<td>Rosuvastatin</td>
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<tr>
<td>Simvastatin</td>
<td>Glaucoma</td>
<td></td>
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<tr>
<td><strong>Angiotensin-converting enzyme inhibitors</strong></td>
<td>Hypertension, Diabetic nephropathy</td>
<td>Decrease production of angiotensin II by inhibition of angiotensin converting-enzyme</td>
<td>Decreased proliferation and angiogenesis. Might also decrease invasion and migration via reduction of MMP-2 and MMP-9 expression</td>
<td>Rooprai et al. [56]</td>
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<tr>
<td>Captopril</td>
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<tr>
<td><strong>Angiotensin receptor blockers</strong></td>
<td>Hypertension, Diabetic nephropathy</td>
<td>Antagonists at angiotensin II type 1 receptors</td>
<td>Decreased angiogenesis as a result of decreased VEGF expression</td>
<td>Arrieta et al. [53], Rivera et al. [55]</td>
</tr>
<tr>
<td>Losartan</td>
<td></td>
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<tr>
<td><strong>Other antihypertensives</strong></td>
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<tr>
<td>Doxazosin</td>
<td>Hypertension, Benign prostatic hyperplasia</td>
<td>Antagonist at alpha-1 adrenoceptors</td>
<td>Reduction of cell migration, proliferation and apoptosis through activation of Ephrin A2 receptors</td>
<td>Petty et al. [61]</td>
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<tr>
<td><strong>Beta-blockers</strong></td>
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<tr>
<td>Propranolol*</td>
<td>Hypertension, Prevention of cardiovascular disease</td>
<td>Antagonists at beta-1 and/or beta-2 adrenoceptors</td>
<td>Reduction of angiogenesis through decreased expression of VEGF and MMP-9. Also decreases cell proliferation through unknown mechanisms</td>
<td>Kozanoglu et al. [67], Pasquier et al. [64]</td>
</tr>
<tr>
<td>Butoxamine</td>
<td></td>
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<tr>
<td>Metoprolol</td>
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<tr>
<td>Nebivolol</td>
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</table>
Dose Individualisation

• Previously known as ‘therapeutic drug monitoring’
• Easy to design, develop and apply data to dosing recommendations now available
• Dose documented, sample taken at correct time for PK result to be meaningful, high quality assay, for example

Assumes good PK data available
CONCLUSIONS

• Lot going on in Clinical Pharmacology
• Resources to maintain current teaching/training, research support, counter detailing and regulatory guidance are inadequate
• College is in a leadership position to effect change.
• However multiple funders and multiple vested interests.
• Keen to hear feedback from Fellows regarding potential solutions or collaborations.
“This new wonder drug is meant to keep the patient alive long enough to pay their bill.”