Hot topics in clinical pharmacology 2016

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ASCEPT

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

ASCEPT

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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
DOI 10.1007/s00520-013-2098-7

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 1 Key factors of the identified trials

	Number	Population type	Study type	% $n>1$ PIM	Criteria for discontinuation	Was an outcome measured?
Riechelmann et al. 2009 [13]	372	Cancer patients	Retrospective audit	22 %	Medical officer assessment	No
Fede et al. 2011 [1]	87	Cancer patients	Cross-sectional survey	24 %	5-point table	No
Todd et al. 2013 [14]	20	Lung cancer patients	Retrospective audit	95 %	Medical team assessment	No
Nyborg et al. 2012 [19]	445,900	>70 years	Retrospective audit	34.8 %	NORGEP criteria	No
Buck et al. 2009 [15]	61,251	>65 years	Cross-sectional audit	23 %	Beers Criteria/Zhan Criteria	No
Bongue et al. 2011 [17]	35,259	>75 years	Cross-sectional audit	35.6 %	French PIM list	No
Gallagher et al. 2011 (May) [20]	900	>65 years	Prospective audit	51.3 %	STOPP/START algorithm	No
Garfinkel et al. 2010 [21]	70	"Elderly" referred patients	Cohort study	58 %	The good palliative–geriatric practice algorithm	Yes
Gallagher et al. 2011 (June) [10]	382	>65 years	RCT	58.4 %	STOPP/START algorithm	Yes

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

JAMA Intern Med. 2015 May;175(5):827-34. doi: 10.1001/jamainternmed.2015.0324.

Reducing inappropriate polypharmacy: the process of deprescribing.

Scott IA[1], Hilmer SN[2], Reeve E[3], Potter K[4], Le Couteur D[5], Rigby D[6], Gnjidic D[7], Del Mar CB[8], Roughead EE[9], Page A[10], Jansen J[11], Martin JH[12].

Why too much medicine is a problem for many older people

SYDNEY MEDICAL SCHOOL

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

Geoff and Elaine Penney
Ageing Research Unit

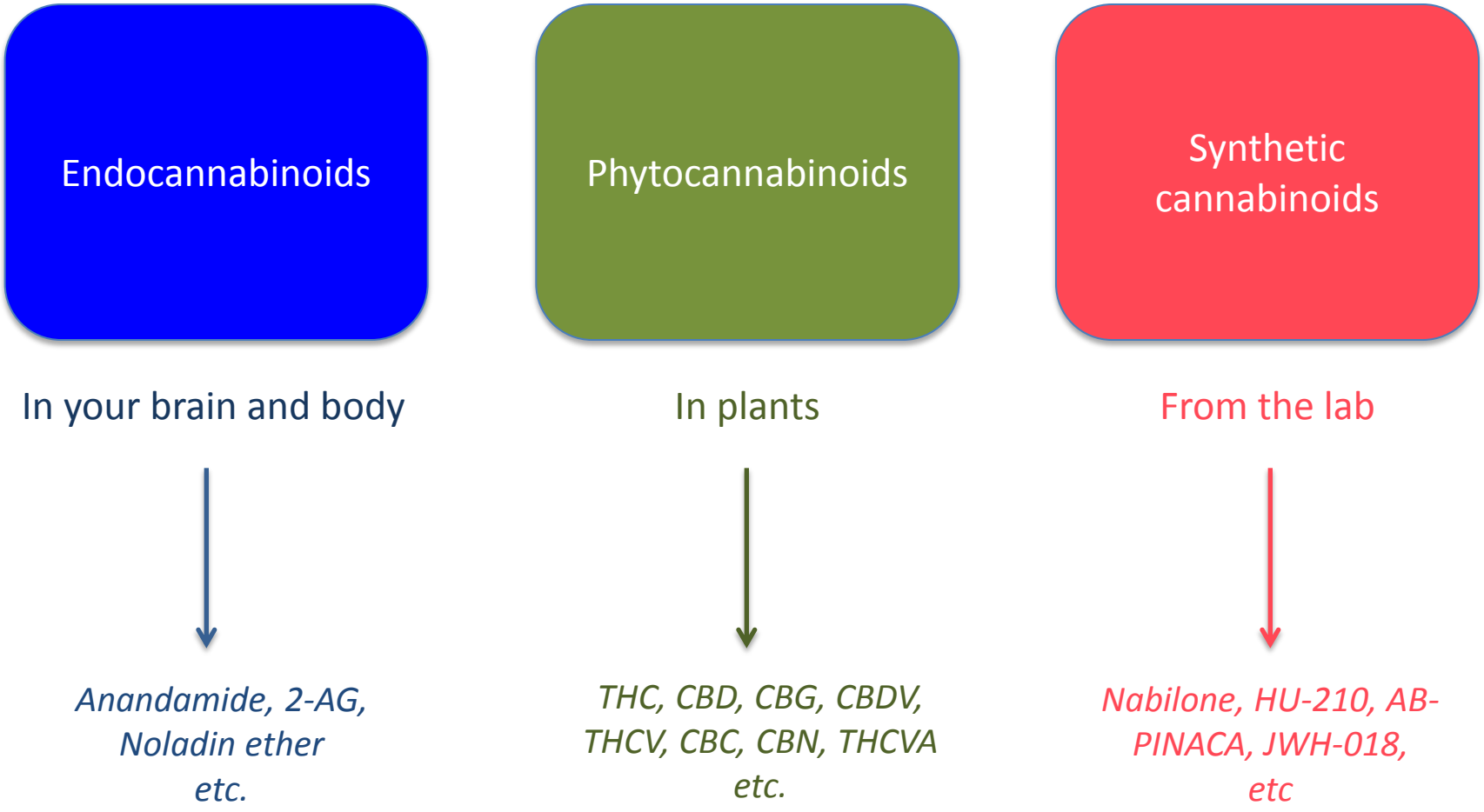
KOLLING
Institute of
Medical Research

Health
Northern Sydney
Local Health District
Department of Aged Care
Department of Clinical Pharmacology
Northern Therapeutics Unit

Cannabis

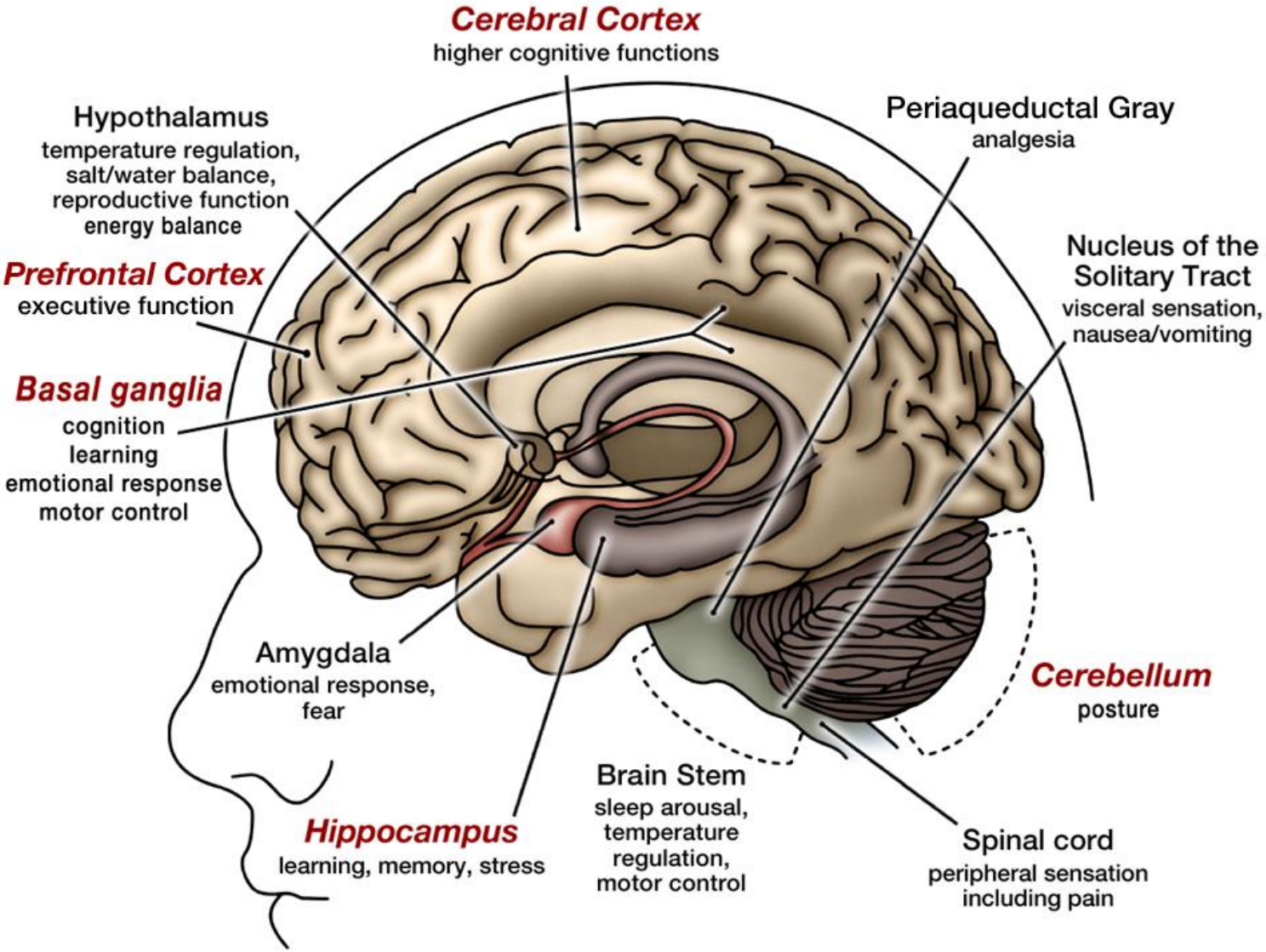
- Too fast too soon or not soon
- Why can’t patients self titrate
- Why does it have to be regulated/registered/GMP.
- Which drug/chemical/combination
- Plant vs. synthetic
- Where grown – consistency, stability
- Where regulated
- Route of administration, dose, frequency
- Script vs. patient titrate

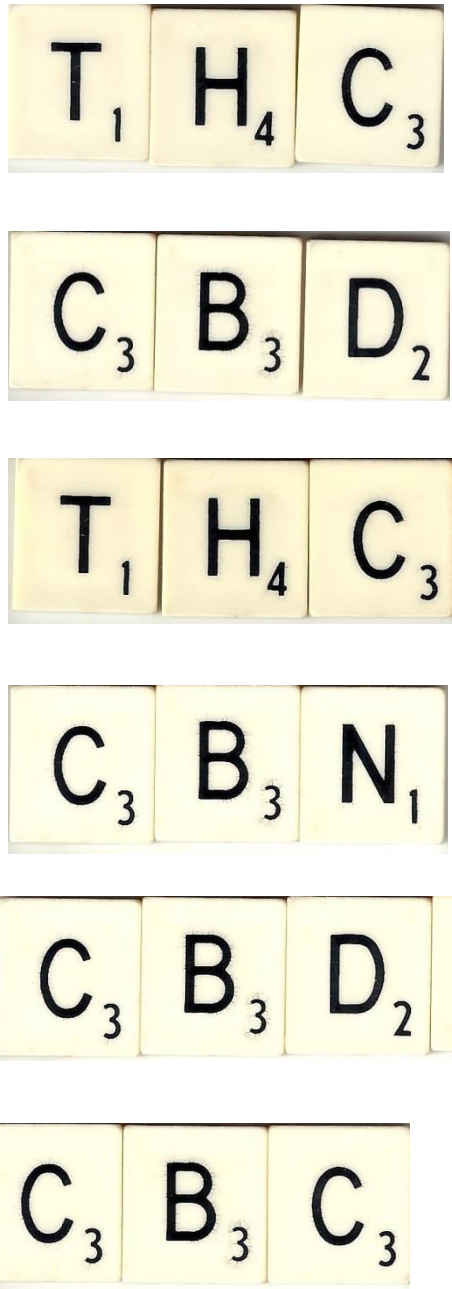
Varieties of Cannabinoids



Brain regions that express the CB_1 cannabinoid receptor

Red = abundant CB_1 receptor expression **Black = moderately abundant CB_1 receptor expression**





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

Each has its own pharmacological actions and therapeutic potential.

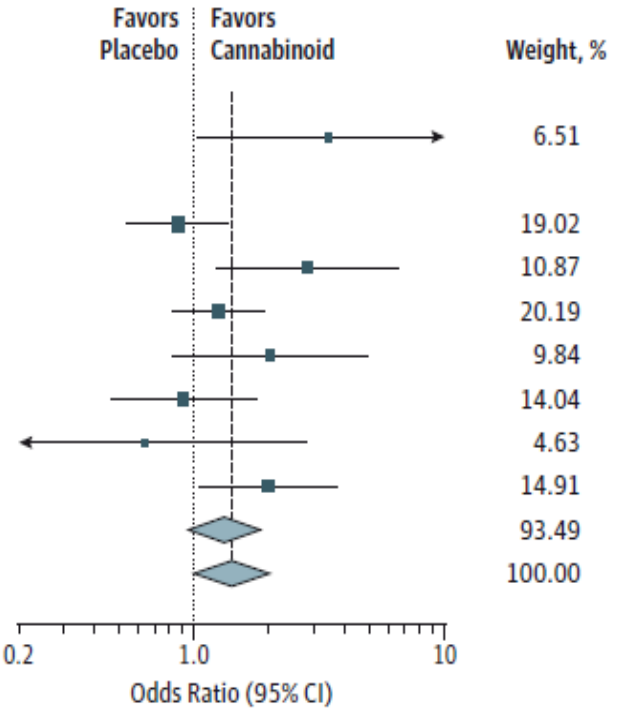
“Entourage” effects

Cannabinoids in chronic pain

Systematic review: Whiting et al JAMA June 2015

Figure 2. Improvement in Pain

Improvement in Pain With Cannabinoid vs Placebo by Study	Cannabinoid Events No.	Cannabinoid Events Total No.	Placebo Events No.	Placebo Events Total No.	Odds Ratio (95% CI)
Tetrahydrocannabinol (smoked)					
Abrams et al,[77] 2007	13	25	6	25	3.43 (1.03-11.48)
Nabiximols					
GW Pharmaceuticals,[22] 2005	54	149	59	148	0.86 (0.54-1.37)
Johnson et al,[69] 2010	23	53	12	56	2.81 (1.22-6.50)
Langford et al,[65] 2013	84	167	77	172	1.25 (0.81-1.91)
Nurmikko et al,[76] 2007	16	63	9	62	2.00 (0.81-4.96)
Portenoy et al,[67] 2012	22	90	24	91	0.90 (0.46-1.76)
Selvarajah et al,[70] 2010	8	15	9	14	0.63 (0.14-2.82)
Serpell et al,[88] 2014	34	123	19	117	1.97 (1.05-3.70)
Subtotal I^2 = 44.5%, (P = .0.94)	241	660	209	660	1.32 (0.94-1.86)
Overall I^2 = 47.6%, (P = .0.64)	254	685	215	685	1.41 (0.99-2.00)



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

MEDICINAL CANNABIS
CLINICAL TRIALS
FOR CHILDREN WITH
SEVERE EPILEPSY

NSW GOVERNMENT | Health

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, cannabidivarin (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)

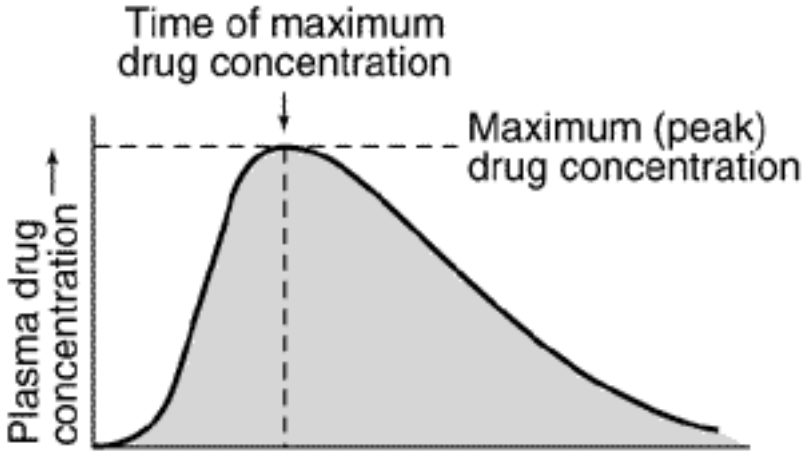
Vaporising cannabis

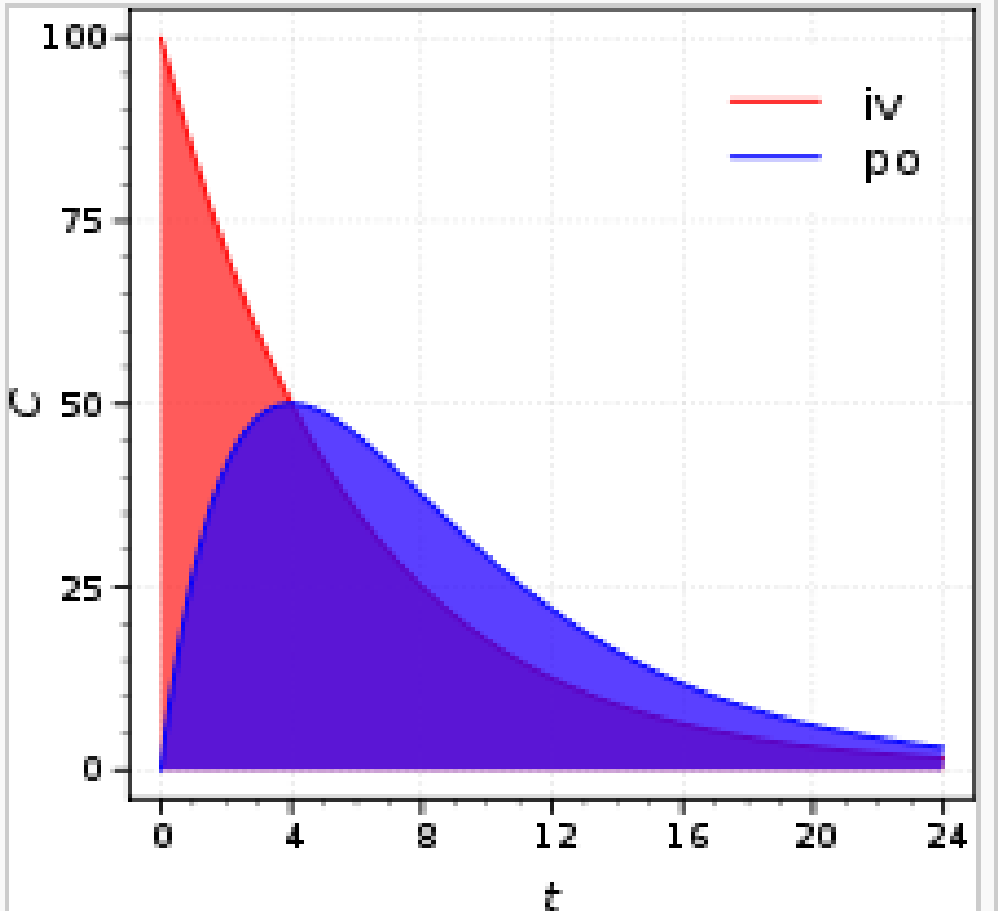
- Similar to ‘e-cigarettes’
- Vaporising heats cannabis at lower temperature than ‘smoking’. Higher bioavailability.
- No side stream smoke (fewer concerns re: passive smoking)
- Peak THC effects: typically 15-90 min after dose, psychoactive effects for 2-3 hours

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


Time of maximum
drug concentration
Maximum (peak)
drug concentration
Plasma drug
concentration
Time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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

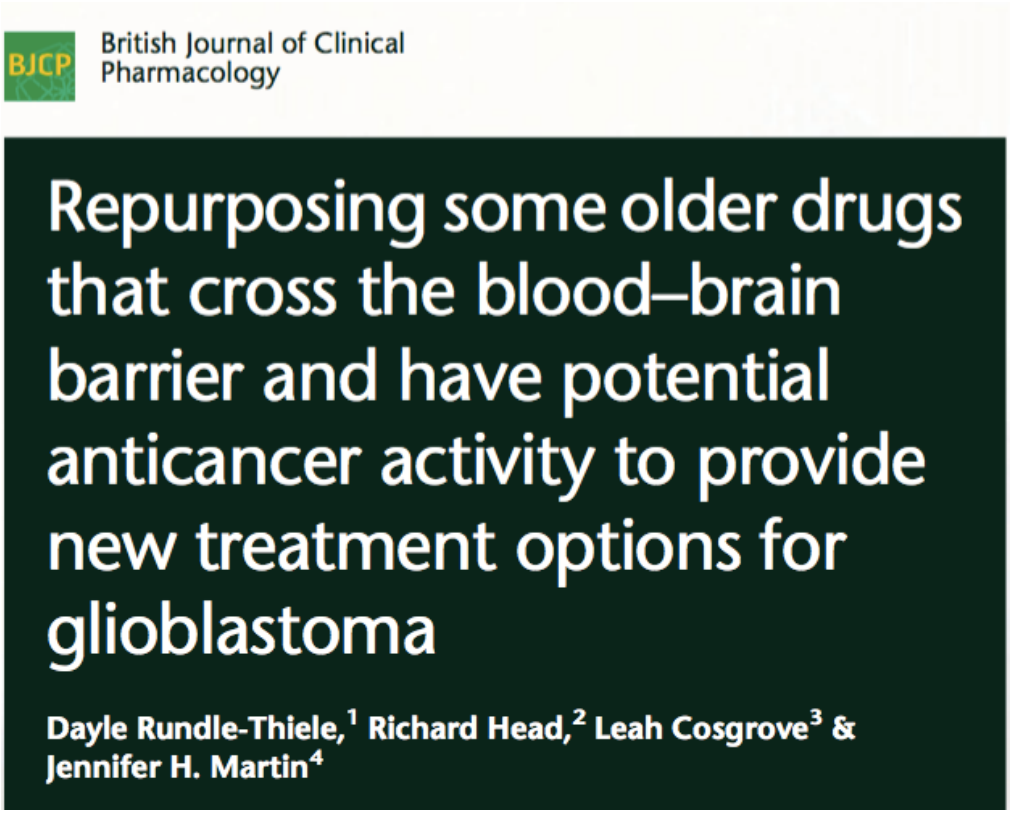

Table 1

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

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

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.

eFunnyCartoons.com

"This new wonder drug is meant to keep the patient alive long enough to pay their bill."