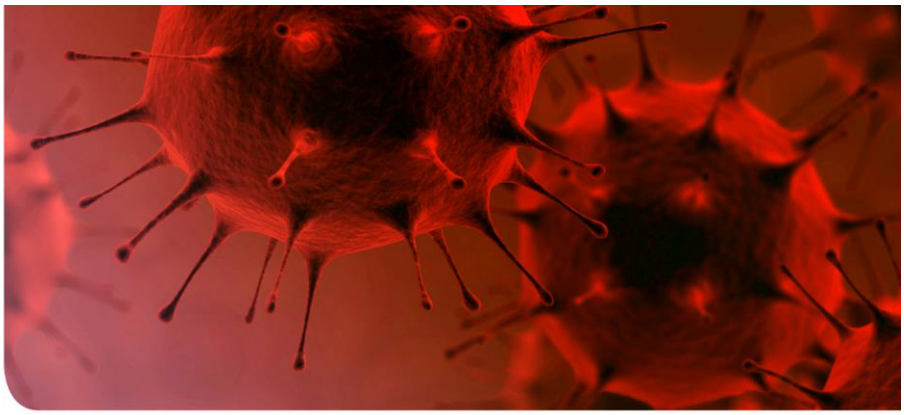

Medicinal Cannabis

Case studies

Disclosures

- Cases prepared by Dr David Baker and Dr Robert Page
- Reviewed by A/Professor Vicki Kotsirilos AM, Dr. Danial Schecter
- Dr David Baker has received trial funding, travel support to attend conferences and participated in advisory boards for ViiV, Gilead,
- Dr. Danial Schecter is Chief Medical Advisor, Auscann

Purpose of workshop

- Case based
- Practical approach to prescribing
- Patient selection
- Medication selection
- Application process
- Prescribing and dispensing
- Monitoring
- Side effects

Case study 1

- 74 year old
- Refractory chronic pain
- Cervical and lumbar spine spondylosis with radiculopathy
- Peripheral neuropathy
- Multiple co-morbidities including:
  - HIV 1988 – well controlled
  - Depression – in remission – no current treatment
  - Insomnia
  - Dyslipidaemia

Case study 1: chronic pain

- Regular reviews with neurologist
- Previous cervical decompression
- Multiple lumbar corticosteroid injections with minimal benefit
- Pain is refractory despite
  - pregabalin 300mg bd
  - oxycodone sustained release 10 mg nocte
  - meloxicam 7.5mg 1 daily with meals
  - diazepam 5mg nocte prn
- Previously tried (and failed):
  - Duloxetine
- Non-pharmacological management includes physiotherapist review and regular swimming

Case study 1: HIV

- HIV +ve, 1988
- CD4 nadir = 380
- CD4 current = 536
- No AIDS complications
- VL < 20
- Triumeq - Abacavir/dolutegravir/lamivudine 1 daily

Case study 1: Medicinal cannabis?

- TGA: 'Guidance for the use of medicinal cannabis in Australia: Overview'
- Acknowledges that in many cases there are very limited data from which to draw specific recommendations for treatment.
- Medicinal cannabis is not considered a first-line therapy for any indication.
- A medical practitioner should complete a comprehensive clinical assessment of the patient before applying for access to medicinal cannabis.
- It is suggested that an initial treatment plan indicate that the medicinal cannabis product be used for a one-month trial to determine the effectiveness of the medication for the patient's condition/symptoms.

Department of Health Therapeutic Drug Administration. Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia, December 2017.
https://www.tga.gov.au/publication/guidance-use-medicinal-cannabis-australia-overview

Case study 1: Medicinal cannabis?

- The TGA document 'Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia' provides a review of the literature pertaining to the use of cannabis in Chronic Non-Cancer Pain (CNCP).
- This states: '*Overall, we can be moderately confident that CNCP patients receiving medicinal cannabis are more likely to achieve between 30% and 50% reductions in pain and to report a reduction in pain ratings than patients given a placebo. The evidence was strongest for nabiximols, which was the most likely cannabinoid to be associated with reduction in overall pain scores*.'

Department of Health Therapeutic Drug Administration. Guidance for the use of medicinal cannabis in the treatment of chronic non-cancer pain in Australia, December 2017.
https://www.tga.gov.au/.../guidance-use-medicinal-cannabis-treatment-chronic-non-cancer-pain.pdf

Case study 1: Evidence for medicinal cannabis

- Multiple sclerosis
→ Spasticity
→ Pain (esp neuropathic)
- Palliative care
→ Chemotherapy-induced nausea and vomiting
→ Neuropathic pain
- Nausea and vomiting
- Epilepsy
→ CBD: used as an adjuvant to other antiepileptic drugs
- Chronic non-cancer pain (esp neuropathic)

Case study 1: Contraindications / Cautions

Contraindicated

- Pregnancy and lactation
- Psychosis
- Allergy (hypersensitivity) to cannabinoids

Caution

- Unstable coronary or cerebral artery disease, due to tachycardia and possible hypotension due to THC. Produces no QTc changes.
- Children and teens remains the subject of debate
- Smoked products should be avoided in COPD and asthma
- Problematic substance use

Caroline A. MacCalluma, Ethan B. Russ. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine, March 2018 Volume 49, Pages 12–19

Case study 1: Product selection

Administration factors in cannabis delivery methods.

Issue	Smoking/vaporisation	Oral	Oromucosal	Topical
Onset (min)	5–10	60–180	15–45	Variable
Duration (h)	2–4	6–8	6–8	Variable
Pro	Rapid action, advantage for acute or episodic symptoms (nausea/pain)	Less odor, convenient and discrete, advantage for chronic disease/symptoms	Pharmaceutical form (nabiximols) available, with documented efficacy and safety.	Less systemic effect, good for localised symptoms
Con	Dexterity required, vaporisers may be expensive, and not all are portable	Titration challenges due to delayed onset	Expensive, spotty availability	Only local effects

Caroline A. MacCalluma, Ethan B. Russ. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine, March 2018 Volume 49, Pages 12–19

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Case study 1: Product selection

- Patient interested in trial of medicinal cannabis
- THC/CBD 1:1 formulations have best evidence
- Examples: Sativex, Tilray 10:10, Canntrust 1:1

→ *Sativex* (nabiximol*)* oral spray, 10 mL (90 actuations of 100 microlitres) - Each 100 microlitre spray contains 2.7 mg THC and 2.5 mg CBD.

SATIVEX Product information https://www.tga.gov.au/sites/default/files/auspar-nabiximols-130927-pi.pdf

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Case study 1: Potential for drug interactions

- CYP inducers may cause reductions in Cmax and AUC of THC
  → Rifampicin (CYP3A4 inducer) caused 40% reduction in THC Cmax, 20% reduction in AUC. Decreases also observed for CBD (50% and 60% reduction, respectively). Likely that other inducers will reduce levels.
- THC is CYP1A2 inducer
- CBD is CYP3A4 and CYP2D6 inhibitor
  → Theoretical effects on certain drug levels – but no evidence of clinically relevant effects on drug levels/effects.
- Care should be taken with hypnotics, sedatives and drugs with potential sedating effects as there may be an additive effect on sedation and muscle relaxing effects.
- Cannabinoids may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly.

SATIVEX Product information https://www.tga.gov.au/sites/default/files/auspar-nabiximols-130927-pi.pdf

Case study 1: Access

- "Sativex is indicated as treatment, for symptom improvement in patients with moderate to severe spasticity due to multiple sclerosis (MS)…."
- TGA approved for this indication but can be prescribed 'off label' without an SAS application and dispensed from community pharmacy
- Need to complete S8 application (state based)

SATIVEX Product information https://www.tga.gov.au/sites/default/files/auspar-nabiximols-130927-pi.pdf

Case study 1: Access

- Major barrier is cost at about $750 for 3 vials
- Alternative products are cheaper but require TGA SAS application

Case study 1: Product selection

Tilray FS THC10:CBD10

Supplier: Tilray
Trade name / device name: Tilray FS THC10:CBD10
Dose Form: Oil Solution
Recommended price per unit: $45 (excludes shipping)
Strength: 10mg/mL + 10mg/mL
Package: 25mL Vial
Lead Time: 1 - 3 days

Cannimed 10:10

Supplier: Health House International
Trade name / device name: Cannimed 10:10
Dose Form: Oil
Recommended price per unit: 350 (includes shipping fee)
Strength: 10mg CBD 10mg THC per mL
Package: 60 mL Vial
Lead Time: 24 hours

Cannimed 1:20

Supplier: Health House International
Trade name / device name: Cannimed 1:20
Dose Form: Oil
Recommended price per unit: 350 (includes shipping fee)
Strength: 1 mg THC 20 mg CBD / mL
Package: 60 mL Vial
Lead Time: 24 hours

Canntrust 1:1 Drops

Supplier: Canntrust Incorporated Canada
Trade name / device name: 1:1 Drops
Dose Form: Oil
Recommended price per unit: $280
Strength: 12.5 mg/ml and 12.5 mg/ml
Package: 40 ml vial
Lead Time: Orders received by 12 pm will be dispatched the next day

Tilray FS THC 2.5/CBD 2.5 capsules

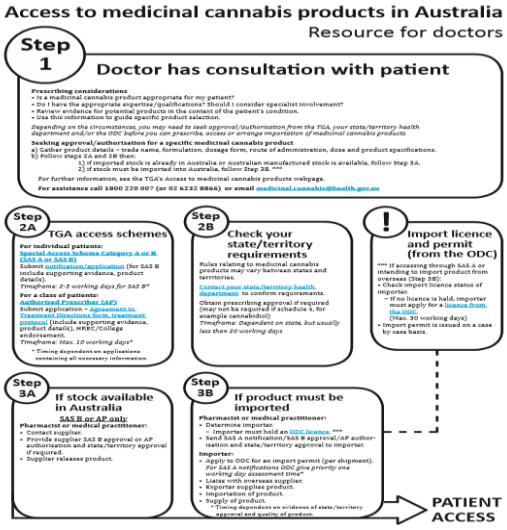
Supplier: Tilray
Trade name / device name: Tilray FS THC 2.5/CBD 2.5 capsules
Dose Form: Capsules
Recommended price per unit: $100
Strength: 2.5 mg THC and 2.5 mg CBD per capsule
Package: 30 capsules
Lead Time: 1 - 3 days

Tilray THC25:CBD25

Supplier: Tilray
Trade name / device name: Tilray FS THC25:CBD25
Dose Form: Oil Solution
Recommended price per unit: $338 (excludes shipping)
Strength: 25mg/mL + 25mg/mL
Package: 25mL Vial
Lead Time: 1-3 days

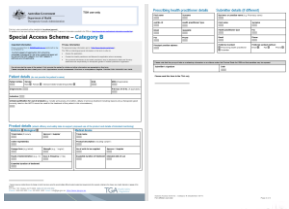
https://cannabisaccess.com.au/

Case study 1: Application process



Case study 1: Application process

- SAS form required for all products (except Sativex – S8 application)
- Complete SAS category B form and submit with cover letter
- Complete application to state authority (NSW has combined application form)
- See Access to medicinal cannabis products: steps to using access schemes https://www.tga.gov.au/access-medicinal-cannabis-products-steps-using-access-scheme



https://www.tga.gov.au/form/special-access-scheme

Case study 1: Application process

- Need to complete patient details on the application, may need to include cover letter.
- NSW Cannabis Medicines Advisory Service can assist with this form and a cover letter (exceptionally helpful 1800 217 257)

Patient details (do not provide the patient's name)

Patient initials	**Gender** Male ☐ Female ☐ Intersex/Indeterminate/Unspecified ☐	**DOB**	**MRN** (if applicable)
Diagnosis(es)			**Previous SAS No.** (if applicable)
Indication			
Clinical justification for use of product(e.g. Include seriousness of condition, details of previous treatment including reasons why a therapeutic good currently listed on the ARTG cannot be used for the treatment of this patient in this circumstance)			

https://www.tga.gov.au/form/special-access-scheme

Case study 1: Application process

Need to complete product details on the application

Product details (attach efficacy and safety data to support proposed use of the product and details of intended monitoring)

Medicine ☐ **Biological** ☐

Trade Name (if known)	**Sponsor / Supplier**
Active ingredient(s)	
Dosage form (e.g. tablet)	**Strength** (e.g., 1 mg/ml)
Route of administration (e.g., IV)	**Dose & frequency** (1 tds)
Expected duration of treatment	

Medical device

Trade name	
Product description (including variant[1])	
No of units to be supplied	**Sponsor / Supplier**
Expected duration of treatment	**Intended date of use**

https://www.tga.gov.au/form/special-access-scheme

Case study 1: Application process: Cover letter

- Cover letter should include:
  - Patient health conditions for which cannabinoids may be beneficial
  - Previous treatments
  - Other relevant issues: substance use; psychological ill-health; concurrent medications
  - Relevant evidence indicating beneficial therapeutic effect

- "The use of cannabis products in patients with HIV has been studied for sleep, calorific intake and neuropathy (Woolridge et al., 2005, Haney et al., 2007 and Bedi et al., 2010). The prevalence of self-medication with cannabis for pain in this population is high (Woolridge et al., 2005)."

Bedi, G., Foltin, R., Gunderson, E., Rabkin, J., Hart, C., & Comer, S. et al. (2010). Efficacy and tolerability of high-dose dronabinol maintenance in HIV-positive marijuana smokers: a controlled laboratory study. Psychopharmacology, 212(4), 675-686. http://dx.doi.org/10.1007/s00213-010-1995-4

Woolridge, E., Barton, S., Samuel, J., Osorio, J., Dougherty, A., & Holdcroft, A. (2005). Cannabis Use in HIV for Pain and Other Medical Symptoms. Journal Of Pain And Symptom Management, 29(4), 358-367. http://dx.doi.org/10.1016/j.jpainsymman.2004.07.011

Haney, M., Gunderson, E., Rabkin, J., Hart, C., Vosburg, S., Comer, S., & Foltin, R. (2007). Dronabinol and Marijuana in HIV-Positive Marijuana Smokers. JAIDS Journal Of Acquired Immune Deficiency Syndromes, 45(5), 545-554. http://dx.doi.org/10.1097/qai.0b013e31811ed205

Case study 1: Application process cover letter

Other relevant inclusions in cover letter:

- Careful monitoring will be implemented for adverse effects. If adverse effects occur the cannabis medicine will be ceased.
- Substance abuse issues addressed (if relevant)
- Have advised him that patients taking THC should not drive (check local state laws).
- No interactions between medicinal cannabis and the patient's antiretrovirals are currently known.
- Given his age I am cognisant of the additive risk of CNS depression with his current benzazepine and opioid medications and associated increased falls risk.
- If successful in this application I intend to start treatment at 1 spray nocte and increase by one to two sprays per week ('start low and go slow').
- Regular review of response to cannabis will be undertaken using relevant monitoring tools. If treatment is unsuccessful it will be ceased.

Case study 1: Side-effects and cautions

- Potential side-effects: depression, worsening of immune functioning, abdominal pain, dizziness, euphoria, nausea, paranoid reaction, somnolence, abnormal thinking, vomiting, asthenia, balance problems, confusion, disorientation, diarrhoea, drowsiness, dry mouth, fatigue and hallucinations.
- Alterations in pulse rate and blood pressure have been observed following initial dose introduction so caution during initial dose titration is essential.
- Use of medicinal cannabis is not recommended in patients with unstable coronary and cerebrovascular disease.
- Caution should be taken when treating patients with a history of epilepsy, or recurrent seizures.

Case study 1: Product selection

- Psychiatric adverse events including disorientation (4.1% vs 0.8%), depression (2.9% vs 2.0%), euphoric mood (2.2% vs 0.9%), and dissociation (1.7% vs 0.1%) occurred more frequently in patients given Sativex than in those given placebo in clinical trials.
- Approximately 10% more patients given Sativex experienced a psychiatric adverse event than those given placebo (17.6% vs 7.8%).
- Side-effects are generally mild and do not cause significant negative clinical effects – if concerning people just stop taking it
- Patients with a personal or family history of psychotic illness should not receive Sativex. Patients with a history of depression should be closely monitored and Sativex discontinued if clinically significant worsening of symptoms occurs on therapy.

SATIVEX Product information https://www.tga.gov.au/sites/default/files/auspar-nabiximols-130927-pi.pdf

Case study 1: Side effects

Table 4
Adverse events associated with cannabis-based medicines.

Side effect	Most common	Common	Rare
Drowsiness/fatigue	✓		
Dizziness	✓		
Dry mouth	✓		
Cough, phlegm, bronchitis (Smoking only)	✓		
Anxiety	✓		
Nausea	✓		
Cognitive effects	✓		
Euphoria		✓	
Blurred vision		✓	
Headache		✓	
Orthostatic hypotension			✓
Toxic psychosis/paranoia			✓
Depression			✓
Ataxia/dyscoordination			✓
Tachycardia (after titration)			✓
Cannabis hyperemesis			✓
Diarrhea			✓

Caroline A. MacCalluma, Ethan B. Russ. Practical considerations in medical cannabis administration and dosing. European Journal of Internal Medicine, March 2018 Volume 49, Pages 12–19

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Patient informed consent

I confirm that my doctor has provided me with:

- ☐ information concerning the treatment/ procedure;
- ☐ information about the medicinal cannabis product, its concentration, its dosage, how to use it, when to take it, how to store the medicinal cannabis product and the proposed duration of treatment. Note, the medicinal cannabis is stored at room temperature away from sunlight;
- ☐ information about the risks and complications, including those specific to my individual circumstances;
- ☐ advice that I cannot drive or operate machinery while undergoing treatment with medicinal cannabis containing tetra-hydrocannabinol
- ☐ advice that research has shown a patient may test positive (for marijuana / cannabis) to a random drug test while being treated with medicinal cannabis and will be subject to current laws which prohibit driving under the influence of cannabis
- ☐ information about available alternative treatment options; and
- ☐ as answered my specific questions and concerns about the chosen treatment / procedure.

I acknowledge that I will need to attend my regular reviews as discussed with my doctor and report any benefits and/or side effects that I may encounter.

I acknowledge that there is no guarantee that this treatment will improve my condition.

I understand that this medical cannabis product is not registered for use in Australia but an application will be made for access approval under the provisions of the Special Access Scheme and Authorised Prescribers Scheme.

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Case study 1: Sample dosing guide

Day	Number of sprays in the morning	Number of sprays in the evening	(Total number of sprays per day)
1	0	1	1
2	0	1	1
3	0	2	2
4	0	2	2
5	1	2	3
6	1	3	4
7	1	4	5
8	2	4	6
9	2	5	7
10	3	5	8
11	3	6	9
12	4	6	10
13	4	7	11
14	5	7	12

SATIVEX Product information https://www.tga.gov.au/sites/default/files/auspar-nabiximols-130927-pi.pdf

Case study 1: Monitoring

- Pre-defined measure/s of efficacy will be negotiated with the patient prior to commencement of therapy (for example, the validated The Pain Self-Efficacy Rating Scale (PSEQ)), and reviewed at regular intervals.

Pain Self Efficacy Rating Scale (PSEQ) obtained online from Australian Agency for Clinical Innovation Pain Management Network: Resources for Chronic Pain available at: https://www.aci.health.nsw.gov.au/chronic-pain/health-professionals/assessment [accessed online on 17/4/18]

Case study 1: Monitoring

- **Monitoring and reporting that will be undertaken (include details of interval and duration of monitoring)**
- Each patient will be monitored under a specific plan. The plan will monitor clinical response (i.e. reduced pain and improved symptoms) and record and adverse reaction – psychological or physical. Each plan will follow this following schedule at a minimum with more frequent monitoring for specific patients if required.
- Reviews will be conducted by me on a fortnightly basis for the first two months to ensure compliance of the MC; thereafter on a monthly basis for the first six months. The frequency of visits after the 6 month period, will vary case by case. If treatment with MC provides clinical benefit and has no adverse effects, periods of review can extend up to 3 months.
- **b. Process of investigating and reporting adverse events**
- Adverse events will be reported to Adverse Drug Reaction Advisory Committee (ADRAC). See: https://www.tga.gov.au/form/blue-card-adverse-reaction-reporting-form

Case study 1: Practical issues

- Have to organise dispensing point (eg local pharmacy)
- The pharmacy needs to have an account with the supplier
- You may need to add the product to your clinic software
- You need to write an S8 prescription
- You will need to renew your application every year

Case 2: History

- 62 year old patient with neuropathic, chronic non-cancer pain (CNCP)
- Severe left-sided brachial plexus injury in 1990. Experiences episodes of intense, sharp left arm pain daily.

- Previously trialled the following medications:
  - Carbamazepine (no analgesic effect)
  - Duloxetine (no analgesic effect)

- His current medications include:
  - Amitriptyline 10mg before bed
  - Valproate 500mg twice a day
  - Pregabalin 300mg twice a day
  - Oxycodone 5 mg mane

- Attended a pain clinic on a number of occasions and completed the 'Reboot' program at St Vincent's hospital in 2016.

Case study 2: HIV

- HIV +ve, 1983
- CD4 nadir = 380
- CD4 current = 842
- No AIDS complications
- VL < 20
- Darunavir/r, lamivudine, efavirenz
- Abacavir HLAB5701+ve

Case 2: problem list

- 1970 Smoking >30 pack year smoking history
- 1970 Syphilis - treated
- 1983 HIV infection
- 1990 Brachial plexus injury
- 1990 Hepatitis C (cleared post treatment)
- 1993 Alcohol abuse
- 1998 Bronchitis chronic
- 1998 Sleep apnoea
- 1999 Lumbar disc prolapse, decompression 2005
- 2009 Hyperlipidaemia
- 2013 Pericarditis
- 2013 Diverticulitis
- 2014 Chronic Obstructive Pulmonary Disease
- 2014 Osteoporosis

Case 2: medication

- 3TC 300mg daily
- Darunavir 800mg daily
- Ritonavir 100mg daily
- Efavirenz 600mg daily
- Colchicine 500mcg daily
- Doxycycline 50mg daily
- Amitriptyline 10mg daily
- Valproate 500mg twice daily
- Atorvastatin 40mg daily
- Pregabalin 300mg twice daily
- Nicotine patch 21mg/24hrs
- Cholecalciferol 1000IU twice daily
- Rabeprazole 20mg daily
- Valaciclovir 500mg twice daily

- Allergies: Abacavir HLAB5701+ve, Severe

Case 2: Potential issues

- There is an additive risk of central nervous system depression with concurrent use of cannabis medicine and amitriptyline, pregabalin and oxycodone. In general, alcoholic beverages should be avoided. Colchicine may also increase sensitivity to CNS depressants. Cannabis medications may interact with alcohol, affecting co-ordination, concentration and ability to respond quickly.

- Risk of potential hepatotoxicity should also be considered with regard to the patient's history of intermittent excess alcohol consumption, HIV and colchicine therapy. Risk of cannabis-associated leukopenia may potentially be compounded by use in conjunction with colchicine.

Case 2: Potential issues

- CBD is metabolised by the CYP450 enzyme system.
- CBD has significant inhibitory effect on this system.
- Multiple other medications are metabolised via the CYP450 enzyme system, including amitriptyline (CYP1A2, CYP2C19, CYP2C9, CYP2D6, CYP3A4), atorvastatin (CYP3A4), colchicine (CYP3A4), darunavir (CYP3A4), efavirenz (CYP3A4) and oxycodone (CYP3A4).

  → While evidence of clinically-significant interactions is lacking, careful monitoring and potential dose titration should be considered.

Other potential interactions via CYP450 system:
-CBD may increase levels of macrolides, sildenafil, calcium channel blockers, antihistamines, benzodiazepines, haloperidol, cyclosporine, PPIs, atorvastatin, simvastatin, SSRIs, TCAs, antipsychotics, beta blockers, warfarin
-THC may decrease levels of clozapine, duloxetine, naproxen, olanzapine, haloperidol, chlorpromazine.

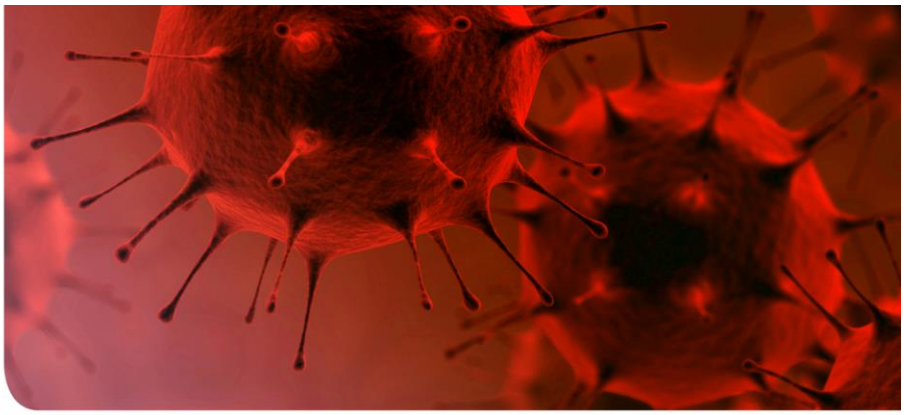
Case 2: should we trial medical cannabis?

- Patient very distressed by arm pain
- He reports some benefit with smoked cannabis
- He is wanting to stop smoking cigarettes
- But he continues to binge on alcohol

Any other concerns about medicinal cannabis?

- "While the RACP understands the community interest in cannabinoids as a therapeutic product, it emphasises that the usual regulatory processes designed to protect patients from serious harms are incomplete for medicinal cannabinoids, and that evidence for their effectiveness for many medical conditions at present limited."
- "Treatment of persistent non-cancer pain with opioid medicines similarly began with little supportive evidence and has been associated with an epidemic of overdose deaths and poor pain outcomes, resulting in ongoing suffering."

Martin J, Bonomo Y & Reynolds A. Compassion and evidence in prescribing cannabinoids: a perspective from the Royal Australian College of Physicians. Med J Aust. 2018 Feb 19;208(30):107-109.



Medical Cannabis

Case studies