CHALLENGES OF CANNABIS IN PAEDIATRIC PALLIATIVE CARE

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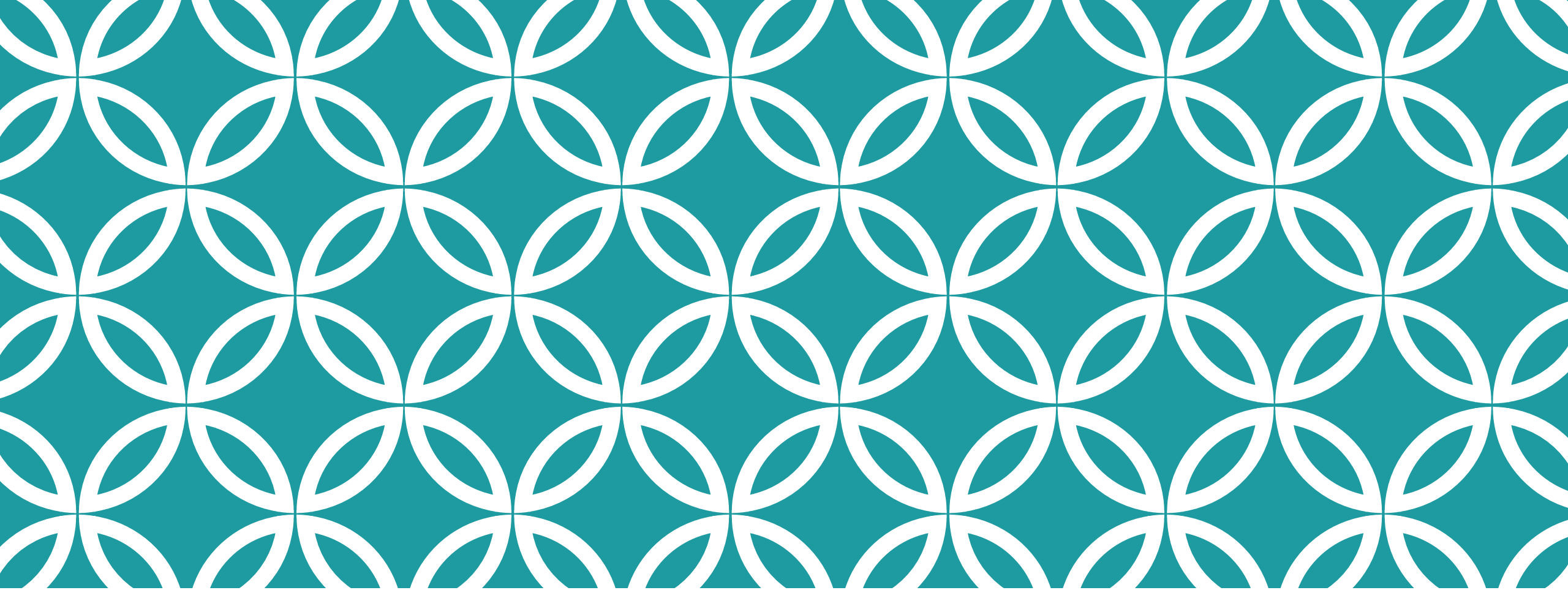
WHAT IS CANNABIS?

When talking about Cannabis, there are only 3 species of interest:

- Cannabis Sativa
- Cannabis Indica
- Cannabis Ruderalis – of minor significance

Cannabis is defined as the flowering or fruiting tops of the plant

- Excludes the leave and the seeds when don't accompanied by the tops



CANNABIS CONFUSION

Is it really as simple as THC and CBD

WHAT'S IN CANNABIS

Cannabis Contains:

- 750 chemical compounds
- 104 different Cannabinoid

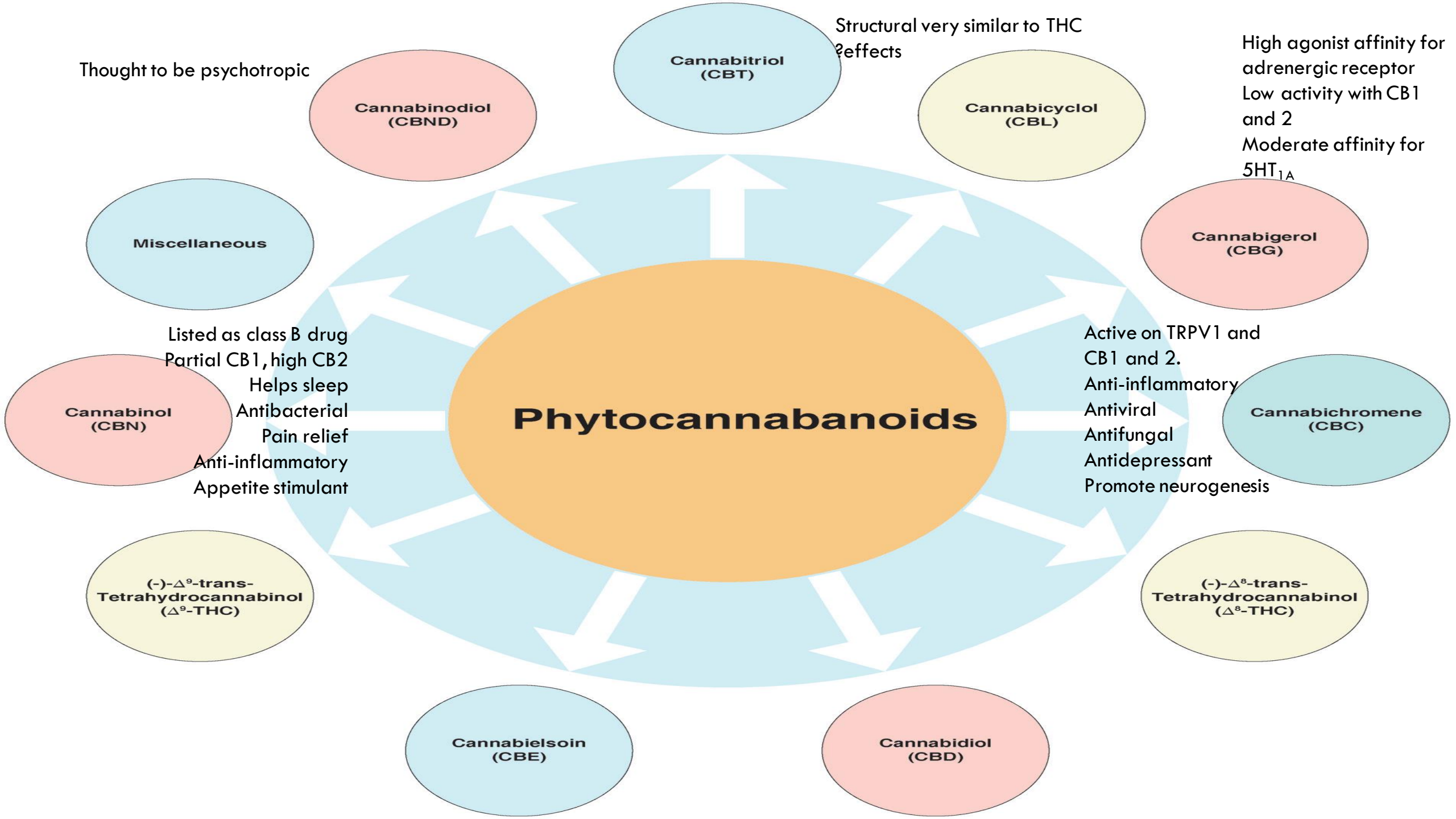
Principle Cannabinoids of Therapeutic Interest (at present)

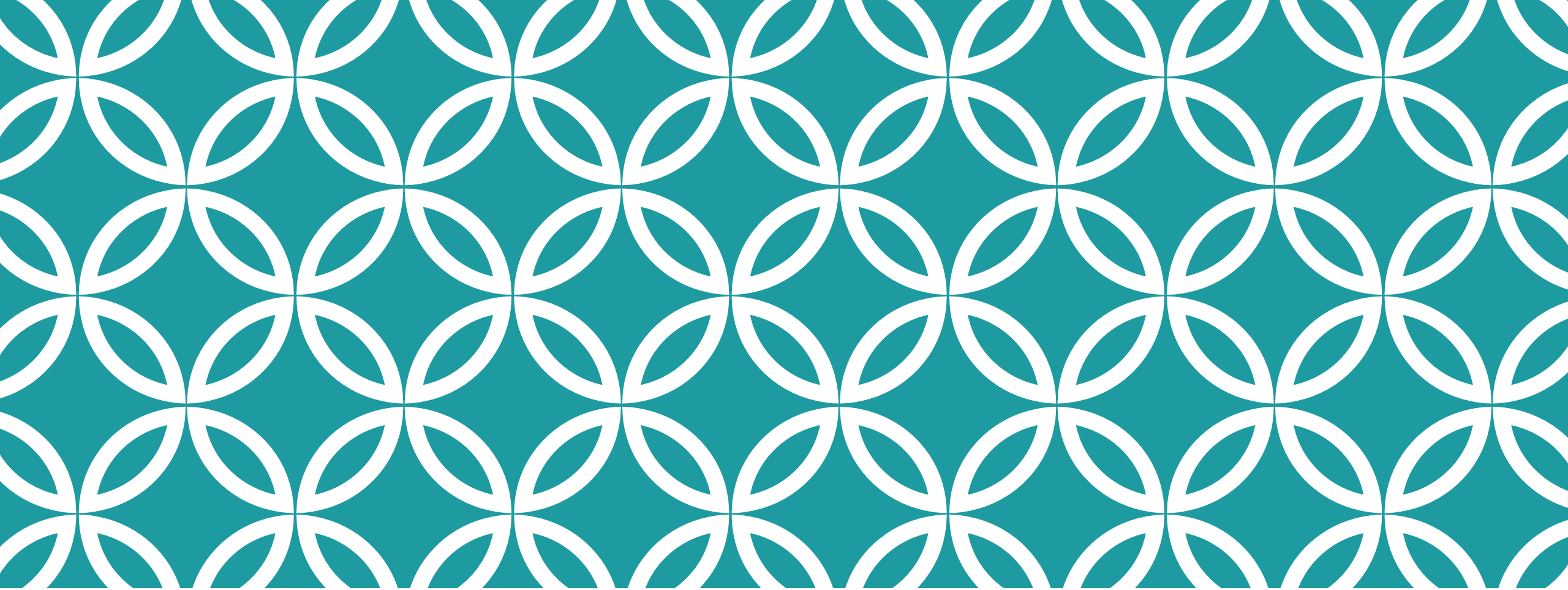
- Delta-9-Tetrahydrocannabinoid (THC) – principle psychoactive component
- Cannabidiol (CBD) – no psychoactivity
- Cannabinol (CBN) - no psychoactivity

BUT

Generally Plants contain more THC than CBD

- Content of THC vs CBD varies due to deliberate manipulation or breeding
- THC content has increased over last 10 years from 5% to 12-16% or higher.


Phytocannabanoids
Cannabinodiol (CBND)
Thought to be psychotropic
Cannabitriol (CBT)
Structural very similar to THC
?effects
Cannabicyclol (CBL)
High agonist affinity for adrenergic receptor
Low activity with CB1 and 2
Moderate affinity for 5HT1A
Miscellaneous
Cannabigerol (CBG)
Listed as class B drug
Partial CB1, high CB2
Helps sleep
Antibacterial
Pain relief
Anti-inflammatory
Appetite stimulant
Cannabinol (CBN)
Active on TRPV1 and CB1 and 2.
Anti-inflammatory
Antiviral
Antifungal
Antidepressant
Promote neurogenesis
Cannabichromene (CBC)
(-)-Δ9-trans-Tetrahydrocannabinol (Δ9-THC)
(-)-Δ8-trans-Tetrahydrocannabinol (Δ8-THC)
Cannabielsoin (CBE)
Cannabidiol (CBD)



DIFFERENTIATION AND DISTINCTION

WHEN **PEOPLE** TALK ABOUT **CANNABIS** WHAT DO THEY MEAN?

Clarification is extremely important

Currently available are:

- Hemp oils
- CBD oils
- THC oils
- Combination THC and CBD oils

Pharmaceutically produced medication

- Drugs licensed for use in specific indications with evidence to back use from RCTs
  - Nabiximol (Sativex) in MS – (S)
  - Nabilone in CINV – (S)
  - Epidiolex – (NS) – (with regulators for evaluation prior to potential licensing in Dravets and Lennox-Gastaut syndrome)

Term Cannabis oil or hemp oil is often used as an umbrella term

- Patients
- Carers
- Healthcare professional

Isn't omeprazole the same as itraconazole?

Leads to misunderstanding and representation of available literature

- To generate a perceived strong pro cannabis argument
- For nefarious means by some with a vested interest in cannabis production

WHY IS CANNABIS FRONT PAGE NEWS?

MEDIA SAYS CANNABIS WILL ……..

or has cure(d) (my) cancer

- Brain (a + c)
- Prostate
- Leukaemia (c)
- Neuroblastoma (c)
- Rhabdomyosarcoma (c)
- Breast
- Lung

take away the pain

stop seizure

stimulate appetite

Treat anxiety

Help sleep

Reduce spasticity

Modify behaviour

Stop nausea

MY FAVOURITE ARGUMENTS …….

Its natural

Its NOT toxic

It's a conspiracy with collusion of the healthcare industry and the pharmaceutical industry

I have a friend who said they knew someone whose brother's son's son had condition X who said after 1 dose of cannabis they were cured

EVERYTHING ELSE HAS FAILED SO WHAT HARM IS THERE IN TRYING THIS

TRUE OR FALSE – CANNABIS IS NOW LEGAL!!!

TRUE……AS LONG AS

Cannabis derived medicines licensed for use by an appropriate regulatory body is legal and can be prescribed by:

- A doctor who is a specialist in that field

Use of cannabis derived medicines in used outside of these approved (licensed) indications, is allowed, if:

- There is evidence to support use – NOT anecdotal evidence – facebook / twitter are not references
  - Including safety as well as efficacy
  - Gold standard evidence = RCT vs placebo or ideally current therapeutic gold standard.
- Use must only by specialist in the field
- Use in this manner is deemed unlicensed prescribing – prescriber takes full (PERSONAL) responsibility for what happens to the patient – including if harm was to come to the patient as a result of prescribing

Prescribing is only allowed for approved medicinal substances, regulated by MHRA or EMEA.


"YOU ARE FAKE NEWS"

FALSE

Medical professionals can NOT prescribe CBD oils not produced by a regulated pharmaceutical company who has been granted marketing license and authorisation by MHRA or EMEA.

CBD oils produced by non-MHRA regulated companies are legal (but NON-PRESCRIBABLE) if:

- Contains less than 0.2% THC
- Sold for use as a 'health food supplement' or a 'beauty product'
- Most CBD products will contain some THC!
  - The UK and europe has set the maximum THC content of hemp products at 0.2%.

They remain illegal if:

- CBD oil is illegal, IF……
  - Contains >0.2% THC
  - Advertised and sold for use with purported medicinal benefit – and not granted approval by MHRA / EMEA.

THC alone remains illegal!!!


@IamHaPPyToast

ROSES ARE RED, VIOLETS ARE BLUE, IF CBD IS LEGAL WHY IS IT A PROBLEM FOR YOU?

HOW ARE OILS REGULATED?

In short – they are not!

Oils sold as health food supplements require only to be fit for human consumption.

Some oils will provide HPLC information as proof of quality but…..

WELCOME TO THE 21ST CENTURY

Pace of modern life means time is a precious commodity.

- Anecdotal evidence and pro argument for efficacy based on anecdotal evidence has overtaken true evidence based research

Social Media – Sorry Dr Seus has retired but Dr Google will see you now!

- Able to present instant results
- Easy to digest
- Important information in 140 characters or less

Led us to an unprecedented situation where ***'drug'*** public knowledge exceeds (medical) professional knowledge

CANNABINOID PHARMACOLOGY

The science bit!

CANNABINOID RECEPTORS PHARMACOLOGY

Cannabis has been used medicinally since 3000BC, use continued until 1930's

THC was isolated and structure elucidate in 1960's

CB1 and CB2 receptors found in late 1990's

Receptors are located pre-synaptically and responsible for neurotransmitter release at both excitatory and inhibitory synapses

Regulate variety of physiological functions, such as:

- Neuronal Development
- Energy Metabolism etc

Distribution of receptors is thought to account for observed effects

- CB1 – highest concentration in CNS and on peripheral nervous system.

  FX on pleasure, memory, thought, concentration, sensory and time perceptions and co-ordinated movement

- CB2 – highest concentration in peripheral tissue and immune cells

  May have fx on immuno-suppression and anti-inflammatory effects.

CB1 / 2

Activation of CB1 – prevents influx of Ca^{2+} Preventing neurotransmitter release

- Particularly:
  - GABA
  - Noradrenaline
  - L-Glutamate
  - Dopamine
  - Serotonin
  - Acetylcholine

CB2 activation has traditionally related to modulation of immunologic effect

BUT – thought to contribute to anti-nociceptive effect by reducing release of pro-inflammatory mediators

IS IT REALLY ONLY ABOUT CB1 / 2

Non cannabinoid receptor signalling is just as significant as CB1 / 2 interaction

Long thought to be an association with cannabinoids and opioid receptors

- THC has been thought to be act synergistically with morphine – potentiating nociception
  - Some references suggesting reliance on interaction with Mu, others suggesting interaction with kappa and / or delta

Emerging evidence of interaction with:

- Adenosine receptors – anti-inflammatory effects – through inhibition of TNF alpha release
- NMDA
- AMPA
- TRPV1 (Vanilloid)
- PPAR – role in cancer – metastasis, angiogenesis
- Serotonin – 5HT1 or 3
- Cholinergic – evidence of nicotine modulating the effects of THC

Rehousing the orphans –GPR55, 118 etc.

THC / CBD CLINICAL PHARMACOLOGY

THC – partial agonist at both CB1 and CB2.

- Achieves psychoactive effect through likely modulation of gamma-aminobutyric acid (GABA) and glutamate following binding to CB1 in brain.
- Theory – can abolish psychoactive side effects of THC by selective antagonism of CB1.

CBD – does not appear to bind to either CB1 or CB2, but interacts with other non-endocannabinoid signalling pathways

- CBD – 'multi-target drugs'

CBD is polyphenolic in nature conferring anti-oxidant properties.

CBD can enhance THC's tolerability by reducing its psychoactivity

PHARMACOKINETICS

THC

Bio-availability: 5 – 20%

Time to onset of action post oral ingestion is also delayed.

- Peak plasma levels of THC occurs after 1 – 6 hours

Highly lipophilic

T½ THC – 20 to 30hours

Highly protein bound 95-99%

Hepatic metabolism

- Results in generation of 11-OH-THC a potent psychoactive metabolite

CBD

- Bio-availability: 6 – 19%
- Time to onset of action post oral ingestion is also delayed.
- Highly lipophilic
- T½ CBD – 9 to 32 hours
- CBD – highly protein bound

- CBD & THC hepatically metabolized by cytochrome P450 2C19 & 3A4
- Known to inhibit 2C19 and 3A4
  - CBD – Potent inhibitor

	Metabolizing enzyme	Enzyme inhibition	Enzyme induction
Smoked cannabis	2C9, 2C19, 3A4	3A4, 2B6, 2C9, 2D6	1A2
Tetrahydrocannabinol	2C9, 3A4	3A4	—
Cannabidiol	2C19, 3A4	2B6, 2C9, 2D6, 3A4	—
Nabilone	2C9	—	—
Dronabinol	2C9, 3A4	3A4	—

EVIDENCE IN CLINICAL PRACTISE

Mostly petri dish and adult, Paediatric Data is Sparse or remains poorly studied.

CANNABIS AND PAIN

Cannabis and Pain

CANNABIS – ANALGESIC EFFECTS (ADULTS)

CB1 receptors in CNS and peripheral nerve terminals, CB2 receptors on peripheral tissues

- CB1 agonist = analgesic effects in CNS
- Dual CB1 & CB2 agonists = analgesic effects in peripheral tissue.

2 studies have examined effect of oral THC on cancer pain

- 1st – Double blind, PCT – 10pts
  - Doses of 15mg-20mg THC ass. With substantial analgesic effects, with anti-emetic and appetite stimulation
  - Follow up with 36 pt showed 10mg produced analgesic effect over a 7 hour observational window comparable to 60mg of codeine and 20mg comparable to 120mg codeine.
    - Higher THC doses more sedating than codeine
- 2nd - plant extract with controlled cannabinoid content in oramucosal spray form, Multicentre, DB, PCT
  - THC:CBD nabiximol c/f THC extract alone c/f placebo
  - THC:CBD spray efficacious with better pain control and less sleep disruption c/f placebo.
  - High dose arm 11-16 spray/day compared unfavourably with placebo in terms of S/E, low dose arm compared favourably
  - Open label extension with 46 pt showed continuing benefit with LT use without requiring increase dose of sprays or other analgesics

RCT, PC crossover study of Nabiximol in 16 pt with chemo induced neuropathic pain showed no difference, though responder study show 5 pt had reduction in pain

Observational study of nabilone, showed pts had less pain, nausea, anxiety & distress with decrease use of opiates, NSAIDs, TCA, gabapentin, dex, metoclopramide, ondansetron

CANNABIS AND NAUSEA

Cannabis and Anti-emetic

CLINICAL EVIDENCE

Initial studies conducted using pure THC analogue – no CBD – (1975-1979)

- 2 x RCT DB inc. paed onc patients in US determined THC superior to placebo
- 3rd study – THC superior to prochlorperazine, contrasted with adult study of no proven benefit
- 4th Placebo controlled study – cast doubt on THC efficacy and suggested usefulness based on chemo agent used.

No studies since comparing to newer anti-emetic of $5HT_3$ or now NK1.

Of note since studies modern cannabis and cannabis products vary in terms of potency and dosing – do studies still have merit

CBD containing products have yet to be tested

Of interest the expected S/E profile of nabilone a synthetic THC analogue appears far similar to that of CBD than THC

- Do previously unknown cannabinoid receptor interactions occur?

HEARTS OVER MINDS

Cannabis and Cancer

THE CONTROVERSY

In Cancer:

- Most of the argument for use stems from in vitro studies conducted against standard cancer cell lines
  - Cancer – is an evolutionary, polyclonal disease
  - Efficacy may be expected where CB receptors are up-regulated

Generally:

- Clinical data is limited or in the case of paediatrics non-existent and anecdotal
  - Patients / Carers expectations when using Cannabis / cannabinoids

- Where studies are present, data is:
  - Of small sample size
  - Poor experimental design
  - Limited / minimal outcome data beyond the immediate time point.

ADULTS – CLINICAL EVIDENCE

No. of studies – limited

Pre-clinical data has formed the basis of limited studies in man

To date 1 CT examining effects of THC on cancer

- Phase 1 study – Guzman et al – intracranial admin. Of THC in recurrent GBM
  - 9 patients
  - In 2 of 9 (22%) THC reduced tumour growth and progression – determined by MRI and biomarker expression.
  - Safe and tolerable - no psychoactive effect from intracranial admin.
  - No control group, study did not comment on survival time

2 current on going studies:

- 1. Nabiximol vs placebo (with TMZ) in recurrent GBM
- 2. Pure CBD as monotherapy for solid tumours

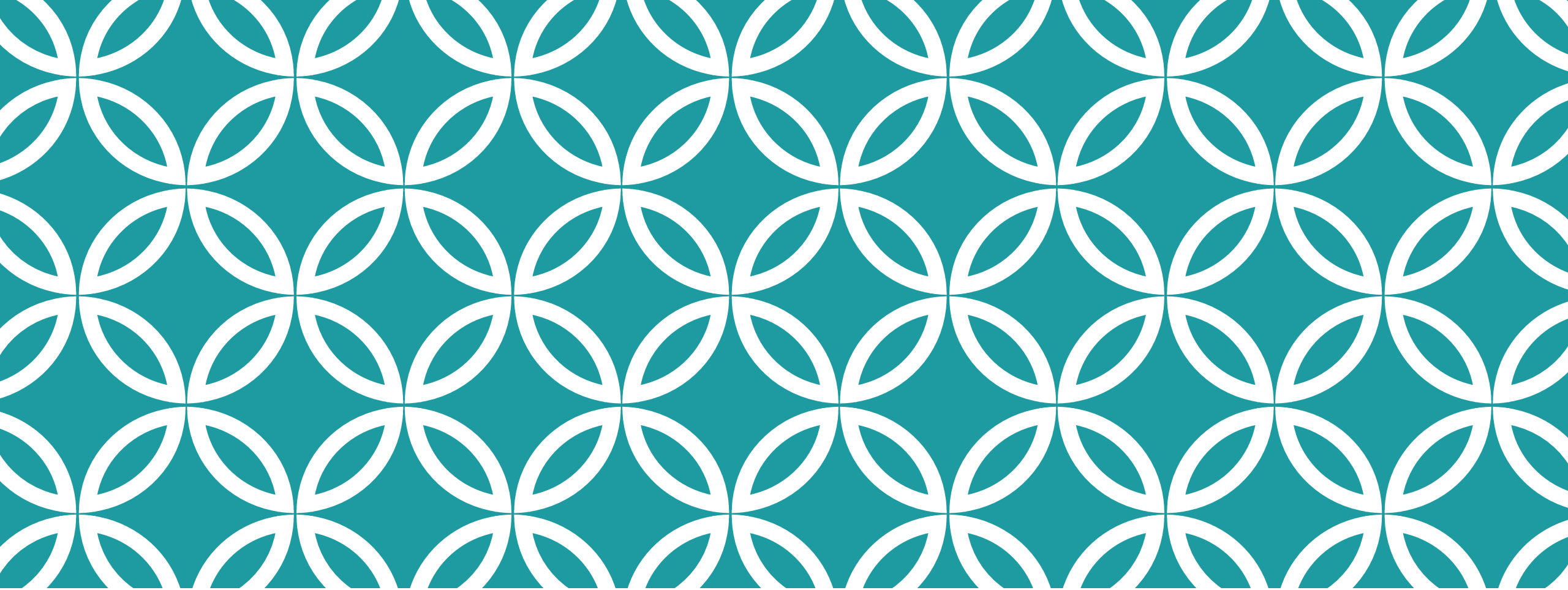
PAEDIATRICS

Most data for efficacy of cannabis in paediatric malignancy is anecdotal or extrapolated from pre-clinical evaluation of adult tumour types.

No clinical studies have been published to date.

Anti-tumour effect have only really been looked at in pre-clinical studies in 3 paediatric tumour types:

- Alveolar Rhabdomyosarcoma
- Osteosarcoma
- Neuroblastoma



TOXICITY

We don’t know

ACUTE AND CHRONIC TOXICITY

Acute Intoxication:

- Tacchycardia
- Xerostomia
- Conjunctival Irritation
- Somnolence
- Hypotension
- Psychological Effects:
  - Euphoria and Anxiolysis
  - Paranoia and short-term memory impairment

- Chronic Use has been associated with mental health issues, such as:
  - Psychosis
  - Schizophrenia
  - Depression
- Heavy use has also been linked to dependence

- Most acute side-effect will reverse though the intensity and exact profile will vary due to variety of strains , routes and dose
- Lipophilic nature allows cannabis to cross BBB = direct CNS effects
  - Therefore major concern in paediatrics about LT neuro-cognitive effects on developing brain.

CONCLUSION

The effects of chronic cannabis use and exposure to cannabinoids remains an unanswered question

Limited real life (practical) pharmacology

In the adult setting and in paediatrics cannabinoids are being used in some areas of practice – based on (good) quality evidence

- Nabilone – adult anti-emetic
- Nabiximol – adult neuropathic pain, spasticity appetite, MS

For new indications we are already behind public expectations

- Patience for outcomes of trials is non-existent – me too culture?

If the evidence is limited, why do parents elect to use it?

- The argument for cannabis IS compelling – on t'interweb at least!
  - Anecdotal
  - Insidious
- The argument against less so and tends to rely on the case that – ITS ILLEGAL!

With homeopathy and natural products our arguments were simpler

- With clinical based evidence of harm from drug interactions
- Homeopathy at its most potent is water

WHAT CAN WE DO?

-IGNORANCE IS BLISS

As with homeopathy we are in a difficult position

Inform and educate

- Benefit
- Risk
- Legalities – medico-legal and criminal legal

Data interpretation

Research

GOS PPC OVERVIEW IN ONCOLOGY

Crude Estimate:

89 PPC onc patients from 2015 – 2017

- 14 – Records mentioned use of Cannabis products
  - 16%
- 27Patients in total on database search with Cannabis products in same period
  - Oncology – 52% of all patients
- 9 (33%) with Brain tumours
- 2 (7%) Leukaemia
- 2 (7%) NBL
- 1 (3.5%) Osteosarcoma

That we know of!


THANK YOU FOR LISTENING
ANY QUESTIONS?


"YOU ARE FAKE NEWS"