ANZCCP - Australian and New Zealand College of Cannabinoid Practitioners
Medicinal Cannabis Education and Authorized Prescriber Course

Anxiety

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Anxiety

- "A future-oriented affective state in which the individual prepares to cope with an uncertain but possible negative event in the absence of a triggering stimulus"
- Transient anxiety is a part of the human experience
- Pathological Anxiety is
  - Context independent
  - Prolonged
  - Excessive
  - Difficult to regulate

- The most common class of disorders listed in the DSM-5

Giacobbe P, Flint A. Diagnosis and Management of Anxiety Disorders. Continuum (Minneap Minn). 2018 Jun;24(3, BEHAVIORAL NEUROLOGY AND PSYCHIATRY):893-919. doi: 10.1212/CON.0000000000000607. PMID: 29851884

Anxiety- Prevalence

- 14.4% (2.3 million) of Australians aged 16-85 years had a 12-month history of Anxiety Disorder

  Australian Bureau of Statistics. (2009). National Survey of Mental Health and Wellbeing: Summary of Results, 4326.0, 2007. ABS: Canberra.
- Common presentation in general practice
- Commonly comorbid with other psychiatric and medical disorders
- Cause of significant morbidity

  Kyrios M, Mouding R, Nedeljkovic M. Anxiety disorders - assessment and management in general practice. Aust Fam Physician. 2011 Jun;40(6):370-4. PMID: 21655481.
- Significant comorbidity with depression (around 50%)
  - Can reach 90% in psychiatric patients

  (Aragones E., Pinol J.L., Labad A. Comorbidity of major depression with other common mental disorders in primary care patients. Aten Primaria. 2009;41:545–551. doi: 10.1016/j.aprim.2008.11.011.)

Common Symptoms- DSM V

- Feelings of uneasiness
- panic and fear
- sleep problems
- not being able to stay calm
- being cold and/or sweaty
- shortness of breath
- heart palpitations
- dry mouth
- nausea
- avoidance of situations

Generalized Anxiety Disorder- Diagnostic Criteria

- Excessive anxiety and worry (apprehensive expectation), occurring more days than not for at least
- 6 months, about a number of events or activities (such as work or school performance).
- The individual finds it difficult to control the worry.
- The anxiety and worry are associated with three (or more) of the following six symptoms (with at least some symptoms having been present for more days than not for the past 6 months):
  - Restlessness, feeling keyed up or on edge.
  - Being easily fatigued.
  - Difficulty concentrating or mind going blank.
  - Irritability.
  - Muscle tension.
  - Sleep disturbance (difficulty falling or staying asleep, or restless, unsatisfying sleep).
- Cause clinically significant distress or impairment in social, occupational, or other important areas of functioning.
- Not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication) or another medical condition (e.g., hyperthyroidism).
- The disturbance is not better explained by another medical disorder

Panic Disorders

- Characterized by brief (2-10 min) spells of overwhelming anxiety or fear, accompanied by somatic and cognitive symptoms
- An abrupt surge of intense fear or intense discomfort that reaches a peak within minutes and during which time four or more of the following symptoms occur:
- Palpitations, pounding heart, or accelerated heart rate
- Sweating
- Trembling or shaking
- Sensations of shortness of breath or smothering
- Feeling of choking
- Chest pain or discomfort
- Nausea or abdominal distress
- Feeling dizzy, unsteady, lightheaded, or faint
- Derealization (feelings of unreality) or depersonalization (being detached from oneself)
- Fear of losing control or "going crazy"
- Fear of dying
- Paresthesias (numbness or tingling sensation)
- Chills or heat sensation

Pathophysiology of Anxiety Disorders

- Anxious people seem to have dysfunctional processing in decision making situations
  - Spurious associations between unrelated events

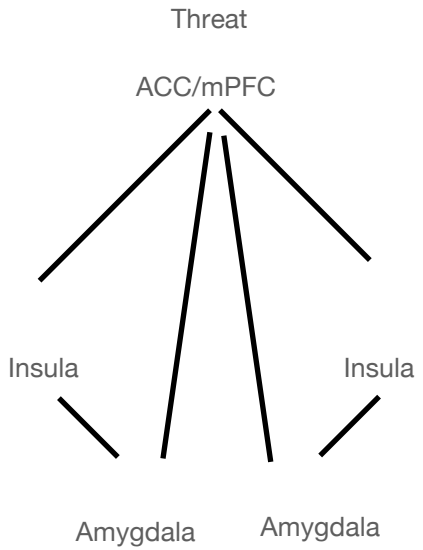
Huang H, Thompson W, Paulus MP. Computational dysfunctions in anxiety: failure to differentiate signal from noise. Biol Psychiatry 2017;82(6):440–446. doi:10.1016/j.biopsych. 2017.07.007

- Overestimation of risk
- Inappropriate associations between neutral stimuli and danger
  - Activation of fear-related circuits in the brain
  - Anxiety related behavioural responses

Craske MG, Stein MB. Anxiety. Lancet 2016; 388(10063):3048–3059. doi:10.1016/S0140–6736 (16)30381–6

Pathophysiology of Anxiety Disorders

- Perception of noxious stimuli activates the "threat circuit" in the brain
- Consisting of the reciprocal connections between the dorsomedial prefrontal cortex, insula, and amygdala. Williams LM. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress Anxiety 2017;34(1):9–24. doi:10.1002/ da.22556.
- Increased activation of the threat circuit is positively correlated to levels of anxiety in people with anxiety disorders. (Robinson OJ, Krimsky M, Lieberman L, et al. Towards a mechanistic understanding of pathological anxiety: the dorsal medial prefrontal-amygdala 'aversive amplification' circuit in unmedicated generalized and social anxiety disorders. Lancet Psychiatry 2014;1(4): 294–302. doi:10.1016/S2215–0366(14)70305–0.)



Adapted from: Williams LM. Defining biotypes for depression and anxiety based on large-scale circuit dysfunction: a theoretical review of the evidence and future directions for clinical translation. Depress Anxiety 2017;34(1):9–24. doi:10.1002/ da.22556.

Pathophysiology of Anxiety Disorders

- Bodily cues may be inappropriately interpreted as dangerous and processed as threats
  - Result in somatic preoccupation related anxiety

    Giacobbe P, Flint A. Diagnosis and Management of Anxiety Disorders. Continuum (Minneap Minn). 2018 Jun;24(3, BEHAVIORAL NEUROLOGY AND PSYCHIATRY):893-919. doi: 10.1212/CON.0000000000000607. PMID: 29851884.
- Greater amygdala activation has been observed in individuals with GAD, social anxiety disorder, and panic disorder when processing fearful facial expressions
- Individuals with panic disorder also had increased insula activation during this task Fonzo GA, Ramsawh HJ, Flagan TM, et al. Common and disorder-specific neural responses to emotional faces in generalised anxiety, social anxiety and panic disorders. Br J Psychiatry 2015; 206(3):206–215. doi:10.1192/bjp.bp.114.149880.

"Based on these data, anxiety disorders can then be characterized by increased vigilance to situations that are perceived as threatening, with concomitant maladaptive and prolonged activation of the threat circuit"

Giacobbe P, Flint A. Diagnosis and Management of Anxiety Disorders. Continuum (Minneap Minn). 2018 Jun;24(3, BEHAVIORAL NEUROLOGY AND PSYCHIATRY):893-919. doi: 10.1212/CON.0000000000000607. PMID: 29851884.

Regulation of The Threat Circuit

- Serotonin has been shown to inhibit activity in the threat circuit
  - SSRIs reduce neurobiological activity in the dorsomedial prefrontal cortex–amygdala circuit in response to aversive stimuli (McCabe C, Mishor Z, Filippini N, et al. SSRI administration reduces resting state functional connectivity in dorso-medial prefrontal cortex. Mol Psychiatry 2011;16(6):592–594. doi:10.1038/ mp.2010.138.)
- CBT may enhance cortical modulation of amygdala activity by exerting top-down cognitive control on limbic structures (Doerig N, Krieger T, Altenstein D, et al. Amygdala response to self-critical stimuli and symptom improvement in psychotherapy for depression. Br J Psychiatry 2016;208(2):175–181. doi:10.1192/ bjp.bp.114.149971.)

Conventional Treatment of Anxiety Disorders

- Depends on severity
- Education
- Avoidance of exacerbating factors
- Exercise
- Psychotherapy (e.g. Cognitive-Behavioural Therapy)
- Pharmacotherapy

Giacobbe P, Flint A. Diagnosis and Management of Anxiety Disorders. Continuum (Minneap Minn). 2018 Jun;24(3, BEHAVIORAL NEUROLOGY AND PSYCHIATRY):893-919. doi: 10.1212/CON.0000000000000607. PMID: 29851884

Commonly Prescribed Medications for Anxiety Disorders

Class/Medication	Common Side Effects
Selective serotonin reuptake inhibitors (SSRIs) (e.g. Citalopram, Escitalopram, Fluvoxamine, Fluoxetine. Paroxetine, Sertraline	Nausea, somnolence, insomnia, sexual dysfunction, loose stools, sweating, headache
Serotonin norepinephrine reuptake inhibitors (SNRIs) (e.g. Duloxetine, Venlafaxine)	SSRI side effects, hypertension
Azapirones (e.g. Buspirone)	Dizziness, nausea, insomnia, headache
Benzodiazepines (e.g., alprazolam, diazepam, lorazepam)	Sedation, psychomotor impairment, dependence, tolerance
Others (e.g. Gabapentin, Pregabalin, Propranolol Quetiapine)	Sedation, weight gain, peripheral oedema bradycardia, hypotension, metabolic effects

Giacobbe P, Flint A. Diagnosis and Management of Anxiety Disorders. Continuum (Minneap Minn). 2018 Jun;24(3, BEHAVIORAL NEUROLOGY AND PSYCHIATRY):893-919. doi: 10.1212/CON.0000000000000607. PMID: 29851884

The ECS and Anxiety

- Endocannabinoid receptors are located throughout the limbic system
- CB1 receptor agonists are reported to induce biphasic effects, with lower doses being anxiolytic and higher doses being anxiogenic (Viveros, MP, Marco, EM, File, SE (2005) Endocannabinoid system and stress and anxiety responses. Pharmacol Biochem Behav 81: 331–342.)
- The presynaptic release of GABA and glutamate, is affected by CB1 receptor activation Laaris, N, Good, CH, Lupica, CR (2010) Delta9-tetrahydrocannabinol is a full agonist at CB1 receptors on GABA neuron axon terminals in the hippocampus. Neuropharmacology 59: 121–127.
- The inhibition of GABA release by CB1 activation seems to be the cause of the anxiogenic- responses to a high dose of cannabinoids
- The inhibition of glutamate release by CB1 receptor activation, seem to mediate the anxiolytic-like effect of a low dose of cannabinoids Ruehle S, Rey AA, Remmers F, Lutz B. The endocannabinoid system in anxiety, fear memory and habituation. J Psychopharmacol. 2012 Jan;26(1):23-39. doi: 10.1177/0269881111408958. Epub 2011 Jul 18. PMID: 21768162; PMCID: PMC3267552.

Dichotomic CB1R function in glutamatergic and GABAergic neurons

- While there has been found to be a low cannabinoid receptor type 1 (CB1R) expression in glutamatergic neurons, high CB1R expression was found in GABAergic neurons.

- In mice that are deficient in CB1R on glut neurons, spine density and dendritic branching are increased, while it is decreased in mice that are deficient in CB1R on GABA neurons.

- Moreover, the two mutant-mouse lines show opposite behaviour phenotypes in anxiety related behaviours, such as, neophobia, exploration, fear relief and habituation.

- The authors have concluded that "CB1R in cortical glutamatergic and forebrain GABAergic neurons calibrates excitatory synaptic balance and consequently regulates fear and anxiety-like behaviours"

Lutz B, Marsicano G, Maldonado R, Hillard CJ. The endocannabinoid system in guarding against fear, anxiety and stress. Nat Rev Neurosci. 2015;16(12):705-718. doi:10.1038/nrn4036

The ECS and Anxiety

- CB1R-deficient mice show increased anxiety-like behaviour when exposed to aversive conditions only
- CB1 activation also influences:
  - The hypothalamic pituitary adrenal (HPA) axis
  - Immune system activation
  - Neuroplastic mechanisms

Sarris, J., Sinclair, J., Karamacoska, D. et al. Medicinal cannabis for psychiatric disorders: a clinically-focused systematic review. BMC Psychiatry 20, 24 (2020). https://doi.org/10.1186/s12888-019-2409-8

Phytocannabinoids and Anxiety

- Cannabis has been used across most ancient civilizations for its medicinal, relaxing and mood-enhancing properties (Tambaro S, Bortolato M. Cannabinoid-related agents in the treatment of anxiety disorders: current knowledge and future perspectives. Recent Pat CNS Drug Discov. 2012;7(1):25-40. doi:10.2174/157488912798842269)
- However, epidemiological evidence shows a relationship between cannabis use and anxiety symptom levels.
- This association has been found to be weak and mainly derived form cross sectional data (Kedzior KK, Laeber LT. A positive association between anxiety disorders and cannabis use or cannabis use disorders in the general population--a meta-analysis of 31 studies. BMC Psychiatry. 2014;14:136.)
- It is unknown whether individual with anxiety seek cannabis treatment, rather than a anxiety occurring as a result from cannabis use
- A stronger positive association was revealed between anxiety and cannabis use disorder, however another study elucidated that when controlling for baseline confounders, no significant relationship was found with cannabis use and a greater frequency of anxiety (Feingold D, Rehm J, Factor H, Redler A, Lev-Ran S. Clinical and functional outcomes of cannabis use among individuals with anxiety disorders: a 3-year population-based longitudinal study. Depress Anxiety. 2018;35(6):490–501.)

Cannabidiol and Anxiety

- CBD has agonist properties at the serotonergic 5-HT1A receptor (Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res. 2005;30(8):1037–43)
- This may explain its anxiolytic effect
  - Serotonin has been shown to inhibit activity in the threat circuit
- CBD has been found to also activate $GABA_A$ receptors
  - This may contribute to its anxiolytic effect (Bakas T, van Nieuwenhuijzen PS, Devenish SO, McGregor IS, Arnold JC, Chebib M. The direct actions of cannabidiol and 2-arachidonoyl glycerol at $GABA_A$ receptors. Pharmacol Res. 2017 May;119:358-370. doi: 10.1016/j.phrs.2017.02.022. Epub 2017 Feb 27. PMID: 28249817.)

Animal Studies

- Overall showed that the administration of CBD reduced anxiety, depression, and stress-related behaviours.
- Some negative results:
  - Anxiolytic properties of CBD depend on the species/strain, age, gender, doses, route of administration and time course (acute less effective than chronic).

García-Gutiérrez MS, Navarrete F, Gasparyan A, Austrich-Olivares A, Sala F, Manzanares J. Cannabidiol: A Potential New Alternative for the Treatment of Anxiety, Depression, and Psychotic Disorders. Biomolecules. 2020;10(11):1575. Published 2020 Nov 19. doi:10.3390/biom10111575

Clinical Trials

- The first clinical trials were conducted in 1974 and 1982
  - CBD alleviates THC-induced anxiety in healthy male volunteers

Karniol I.G., Shirakawa I., Kasinski N., Pfeferman A., Carlini E.A. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. Eur. J. Pharm. 1974;28:172–177. doi: 10.1016/0014-2999(74)90129-0

Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects.Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG Psychopharmacology (Berl). 1982; 76(3):245-50.

- 300mg oral CBD administration decreased anxiety in healthy subjects exposed to the simulated public speaking test in a double-blinded study (Effects of ipsapirone and cannabidiol on human experimental anxiety.Zuardi AW, Cosme RA, Graeff FG, Guimarães FS J Psychopharmacol. 1993 Jan; 7(1 Suppl):82-8)
- CBD significantly reduced subjective anxiety, evaluated by the Visual Analogue Mood Scale (VAMS), and increased mental sedation.
  - Reduced activity on the medial temporal cluster (left amygdala-hippocampal complex, extending into the hypothalamus), and the left posterior cingulate gyrus, and with high activity on the left parahippocampal gyrus Crippa J.A., Zuardi A.W., Garrido G.E., Wichert-Ana L., Guarnieri R., Ferrari L., Azevedo-Marques P.M., Hallak J.E., McGuire P.K., Filho Busatto G. Effects of cannabidiol (CBD) on regional cerebral blood flow. Neuropsychopharmacology. 2004;29:417–426. doi: 10.1038/sj.npp.1300340.)

CBD Cont.

- In individuals diagnosed with anxiety disorders 400mg oral CBD reduced subjective anxiety and induced changes in regional cerebral flow (Crippa J.A., Derenusson G.N., Ferrari T.B., Wichert-Ana L., Duran F.L., Martin-Santos R., Simoes M.V., Bhattacharyya S., Fusar-Poli P., Atakan Z., et al. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: A preliminary report. J. Psychopharmacol. 2011;25:121–130. doi: 10.1177/0269881110379283. [PubMed] [CrossRef] [Google Scholar] [Ref list])

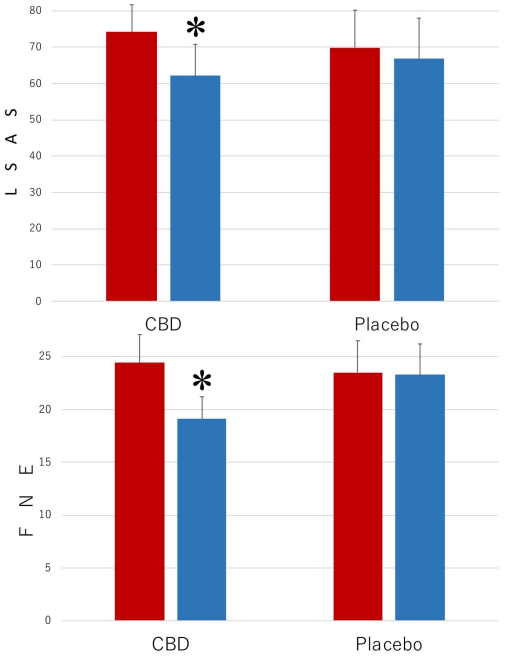
- Psychiatric patients with primary concern of anxiety or poor sleep
  - 25 mg/day to 50–75 mg/day; capsule; 1–3 months- ↓ Anxiety and Improved sleep disturbances (Shannon S., Lewis N., Lee H., Hughes S. Cannabidiol in Anxiety and Sleep: A Large Case Series. Perm. J. 2019;23:18–041. doi: 10.7812/TPP/18-041.)

- However, in non-clinical volunteers with high paranoid traits, 600mg oral CBD increased anxiety and had no effects on persecutory ideation (Hundal H., Lister R., Evans N., Antley A., Englund A., Murray R.M., Freeman D., Morrison P.D. The effects of cannabidiol on persecutory ideation and anxiety in a high trait paranoid group. J. Psychopharmacol. 2018;32:276–282. doi: 10.1177/0269881117737400.)

Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers with Social Anxiety Disorders

- 37 Japanese teenagers with SAD and avoidant personality disorder
- Received cannabis oil (n = 17) containing 300 mg CBD or placebo (n = 20) daily for 4 weeks
- CBD significantly decreased anxiety measured on the Fear of negative Evaluation scale and the Liebowitz Social Anxiety Scale (LSAS)

Masataka N. Anxiolytic Effects of Repeated Cannabidiol Treatment in Teenagers With Social Anxiety Disorders. Front Psychol. 2019 Nov 8;10:2466. doi: 10.3389/fpsyg.2019.02466. PMID: 31787910; PMCID: PMC6856203.



Δ^9-Tetrahydrocannabinol and anxiety

- THC is a CB1 receptor agonist
  - May explain its bi-directional effect on anxiety
  - May also be influenced by genetic, developmental and contextual factors
- Modest doses of cannabis and other CB_1 receptor agonists results in euphoria, relaxation, heightened perception, sociability and creativity
- Moderate to high doses have been reported to elicit phobia, agitation, panic, dysphoria, psychotic manifestations and cognitive impairments (Tamabaro et al. 2012)
- No studies to date have investigated the role of THC in anxiety disorders directly
- Ongoing study at the University of Colorado looking at the anxiolytic effects of different ratios of THC and CBD (1:0, 1:1, 0:1) in people with mild-moderate anxiety (Hitchcock L. 2018. Available from https://clinicaltrials.gov/ct2/show/NCT03491384?cond=Anxiety&intr=Cannabis&rank=2.)

THC may be effective in reducing anxiety in other conditions

- A randomised, double-blind study in healthy volunteers (n=42) subjected to a Trier Social Stress Test and non-stressful test, after receiving no oral THC (n=13), 7.5 mg THC (n=14), or 12.5 mg THC (n=15) 2.5 hours before the test showed that low dose of THC produces subjective stress-relieving effects in line with those commonly reported among cannabis users, but that higher doses may non-specifically increase negative mood. (Childs E, Lutz JA, de Wit H. Dose-related effects of delta-9-THC on emotional responses to acute psychosocial stress. Drug Alcohol Depend. 2017 Aug 1;177:136-144. doi: 10.1016/j.drugalcdep.2017.03.030. Epub 2017 May 30. PMID: 28599212; PMCID: PMC6349031.)
- An open-label study of nabilone (synthetic THC) as monotherapy or adjuvant therapy with first-line gabapentin in patients with neuropathic pain Nabilone provided subjective benefit in reducing anxiety in patients with painful peripheral neuropathy showed significant improvement in Hospital Anxiety and Depression Scale-A scores (Bestard JA, Toth CC. An open-label comparison of nabilone and gabapentin as adjuvant therapy or monotherapy in the management of neuropathic pain in patients with peripheral neuropathy. Pain Pract. 2011 Jul-Aug;11(4):353-68. doi: 10.1111/j.1533-2500.2010.00427.x. Epub 2010 Nov 18. PMID: 21087411.)
- In a study that analysed Data from the app Strainprint TM using multilevel modeling, medical cannabis users perceived a 50% reduction in depression and a 58% reduction in anxiety and stress following cannabis use Cuttler C, Spradlin A, McLaughlin RJ. A naturalistic examination of the perceived effects of cannabis on negative affect. J Affect Disord. 2018 Aug 1;235:198-205. doi: 10.1016/j.jad.2018.04.054. Epub 2018 Apr 6. PMID: 29656267.

Neuroinflammation in Anxiety

- Increased blood levels of TNF-α induce anxiety behaviour in anxiety rodent model of chronic mild stress
- Inhibition of TNF-α by infliximab reduces anxiety in rodent models
- Mice that over ex-press IL-6 or TNF-α show anxiogenic behaviour
- Individuals with anxiety have higher levels of IL-6
- Healthy medical students that take nationwide examination have increased anxiety levels and a significantly increased levels of pro-inflammatory cytokines

An **Integrative Approach** to **Neuroinflammation** in **Psychiatric disorders** and **Neuropathic Pain** Diana I Luri J Exp Neurosci. 2018; 12: 1179069518793639. Published online 2018 Aug 13. doi: 10.1177/1179069518793639

Neuroinflammation

- Both THC and CBD may have a role in reducing neuroinflammation
- This may contribute to their anxiolytic effect

Cheung KAK, Peiris H, Wallace G, Holland OJ, Mitchell MD. The Interplay between the Endocannabinoid System, Epilepsy and Cannabinoids. Int J Mol Sci. 2019;20(23):6079. Published 2019 Dec 2. doi:10.3390/ijms20236079

Conclusion

- More clinical evidence is needed
- Most evidence currently for CBD-dominant or purified CBD products
- THC may also have a role in a dose dependent manner- further research is needed

Choosing Cannabis Product for anxiety

- MC is second line treatment when conventional treatment is not effective or has cause intolerable side effects
- Consider the preferences of the patient, age and clinical condition
- More evidence for CBD predominant formulations
- THC can have a biphasic effect and can be anxiogenic
- CBD rich formulation - minimal adverse events

Maccallum and Russo, 2018

Dosing and administration

- High safety profile
- THC median lethal dose is estimated to be >800mg/kg
- CBD tolerated at more 1000mg daily
- Consider polypharmacy and drug interactions
- “start low, go slow”

Maccallum and Russo, 2018

Dosing and administration considerations

- Due to the psychoactive component of cannabis, dosing is based on the amount of THC in each product
- Starting dose of THC: 2.5 mg daily
- 1.25 mg for elderly and naive patients
- Increased by 2.5mg or 1.25 mg every 4-5 days until optimum results are achieved, or adverse effects develop

- CBD only products- starting dose 5mg-25mg daily

- Vaping- 1 inhalation every 15 min PRN, max 1g daily

Maccallum and Russo, 2018

Dosing and administration considerations

- For most patients, starting with a CBD predominant formulation, will minimise side effects
  - For example, start with 0.25ml-1ml nocte of 1:20 THC:CBD
  - Consider comorbidities- e.g., cardiac disease
  - Starting on a CBD predominant formulation will minimise potential anxiogenic effects of THC
  - Can use as one combined product or a split protocol of CBD/THC
  - CBD only formulations should be used with a history of psychosis- 5mg BD as a starting dose is usually appropriate

Dosing and administration considerations

- For experienced patients, a formulation that contains equal THC:CBD may be the most effective (remember that recreational marijuana is usually very high in THC)
- Start with 2.5mg THC nocte- for example 0.25ml nocte of 10:10 THC:CBD formulation
- Vaping for management of breakthrough symptom can be extremely beneficial due to quick onset: 1 inhalation every 15 min PRN, max 1g daily
- Sativa dominant strains may worsen anxiety- preference to indica dominant in most cases
- Consider terpene profile- calming terpenes, e.g., Linalool and myrcene can be beneficial

A Wholistic Approach

- Consider other factors that would contribute to inflammation, anxiety and agitation
- Diet and lifestyle
  - Anti-inflammatory, nutrient dense diet
  - Gut health
  - Stress management
  - Exercise
- Micronutrients and supplements
  - Omega 3s
  - PEA
  - Vitamin D
  - B vitamins