Cannabinoids and Mental Health

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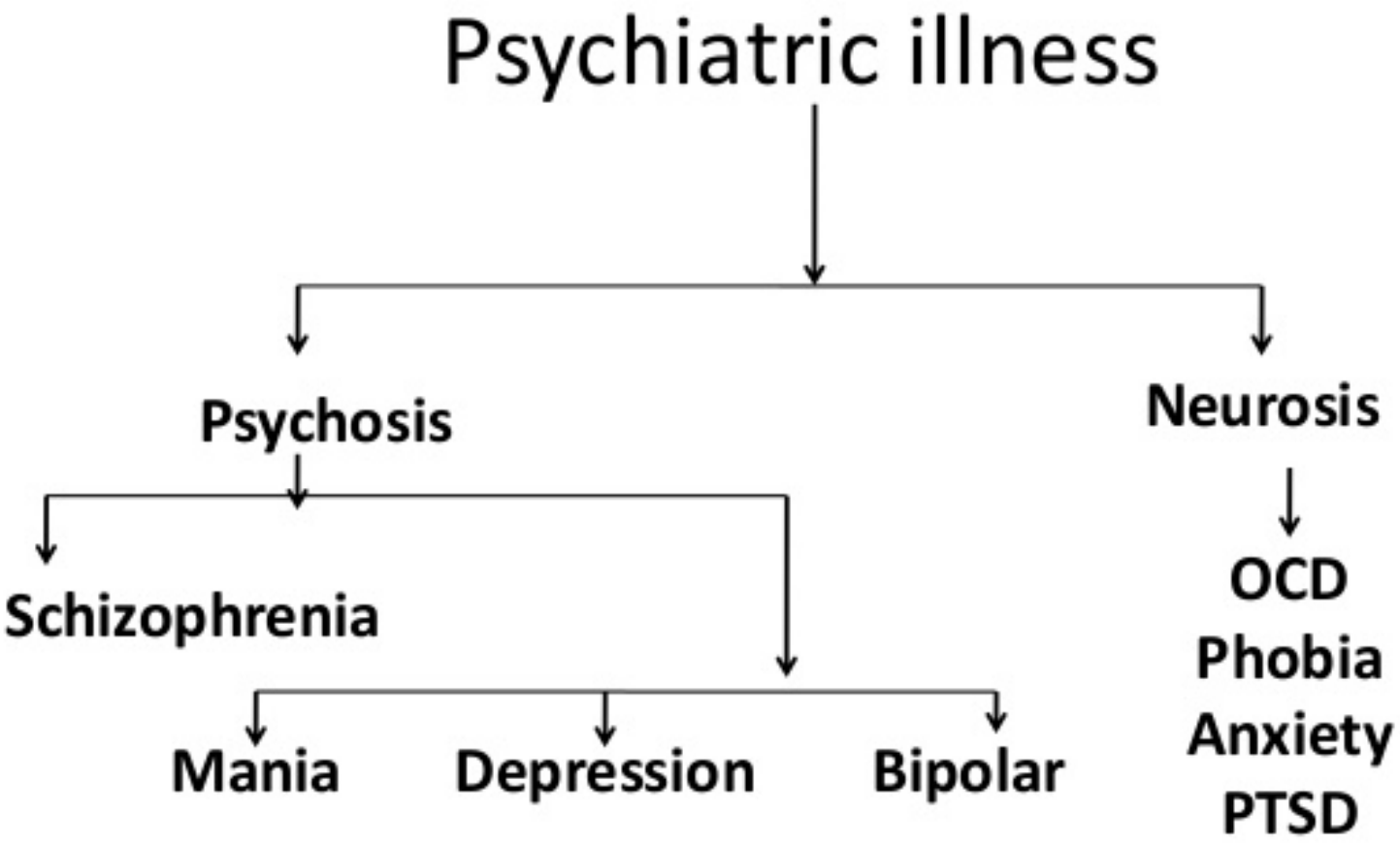
Objectives

- Describe the underlying cause of clinical depression and the primary mechanism for current treatments
- Explain the possible uses of cannabinoids or CB1 antagonists as antidepressants, and cautions
- Discuss the inconsistencies related to the effects of cannabinoids on psychoses as they relate to known antipsychotic effects
- Explain how cannabinoid receptors are involved in anxiety responses
- Outline the animal studies that support the use of cannabinoids to treat anxiety disorders
- Discuss the problems with current treatment of PTSD
- Give evidence to support the use of cannabis in treatment of PTSD



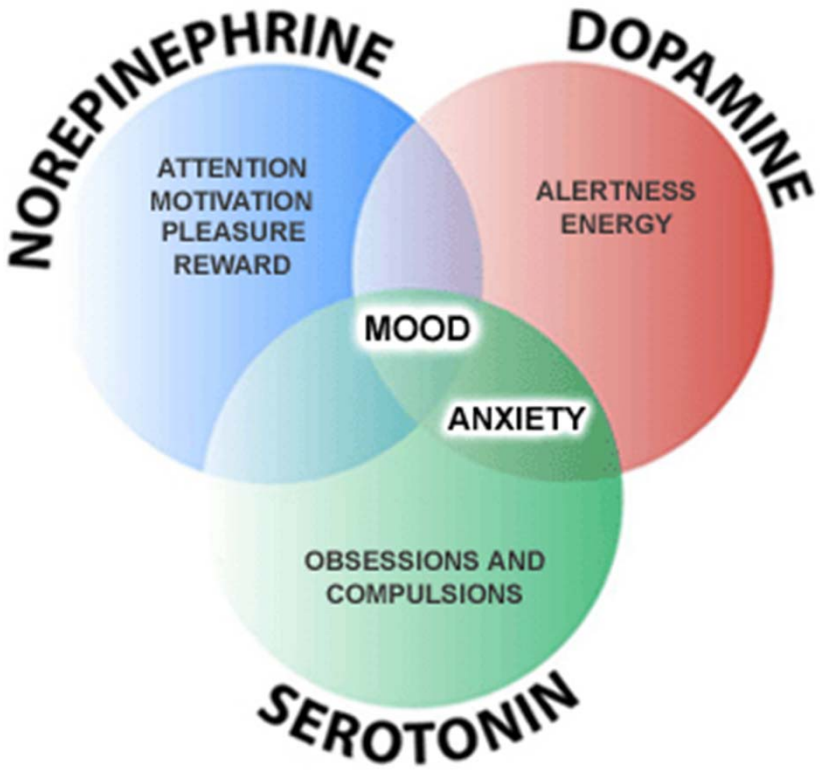
Psychosis: Pt is not aware of illness and refers to treatment

Neurosis: Less serious and insight present

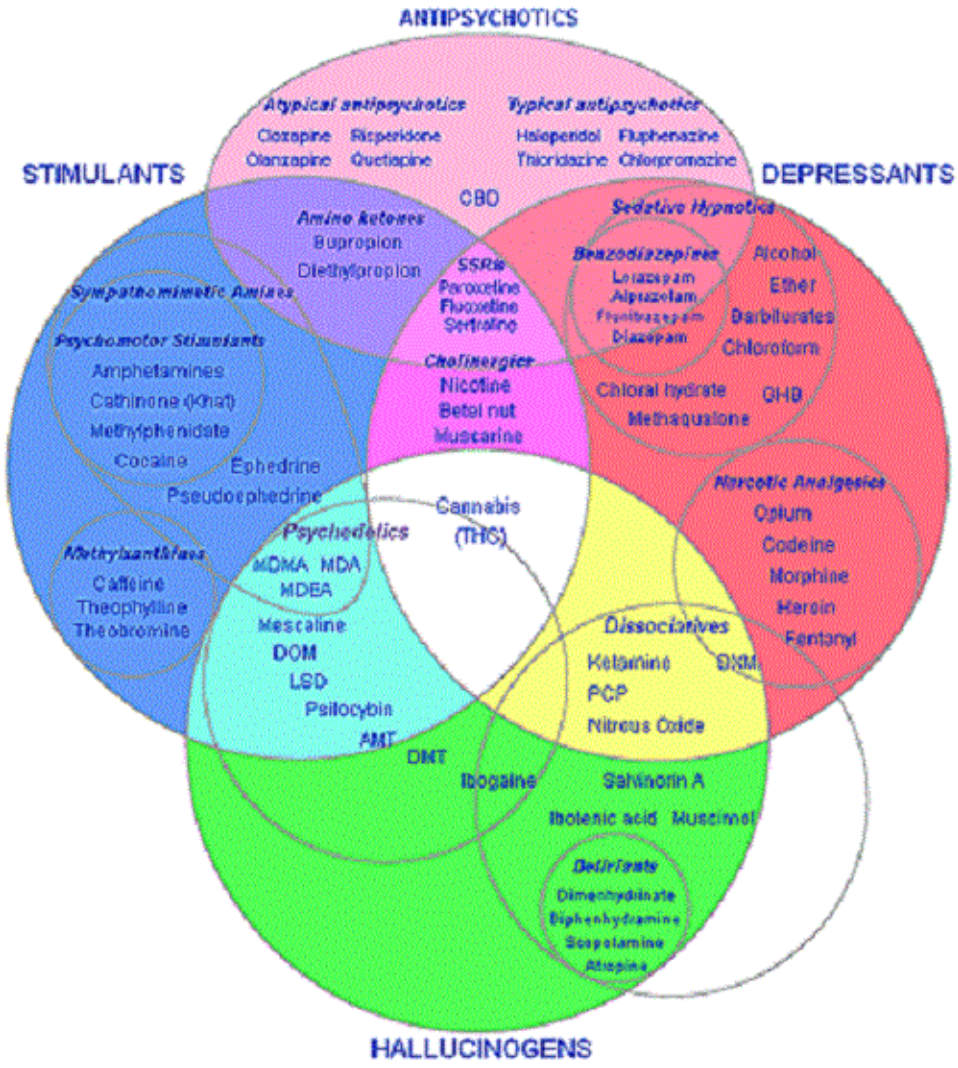
(Obsessive compulsive disorder, Post traumatic stress disorder)

Cannabinoids and Depression

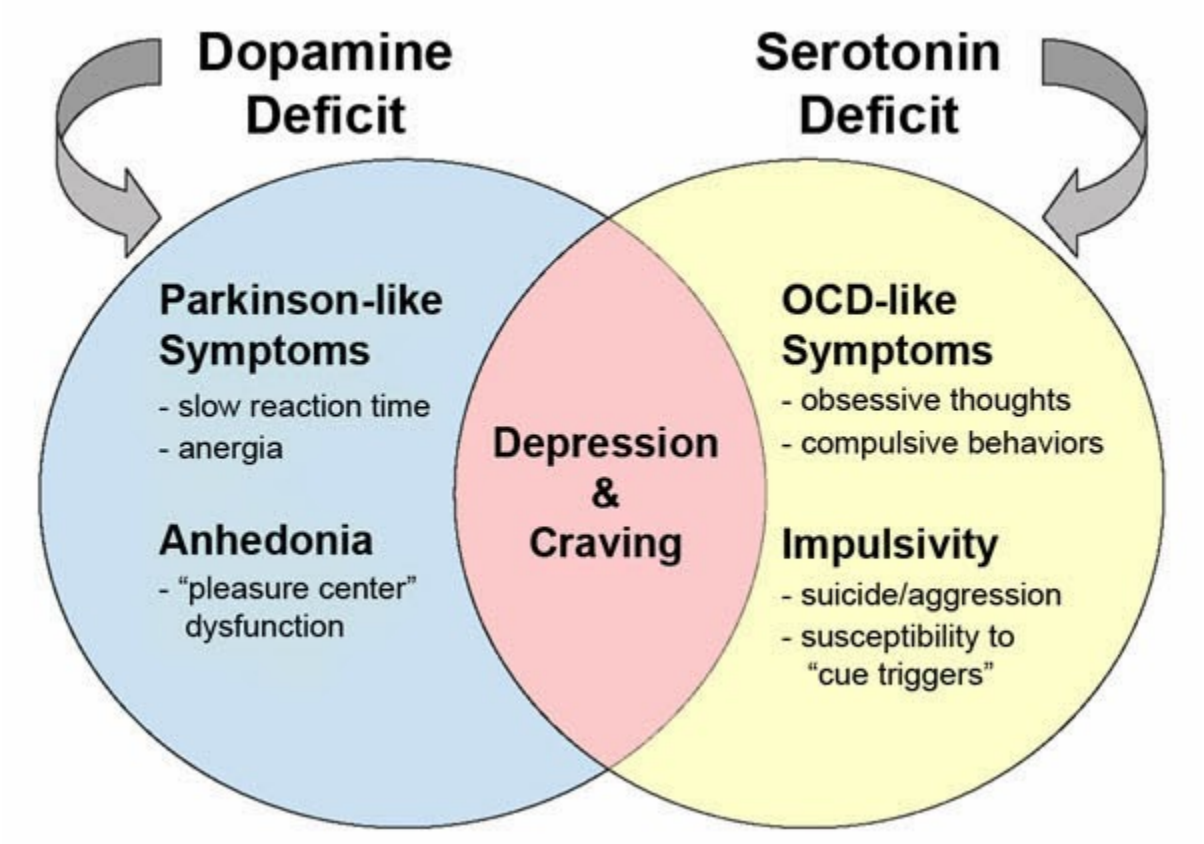
Normal Mood Requires a Balance between Several Neuronal Signaling Pathways



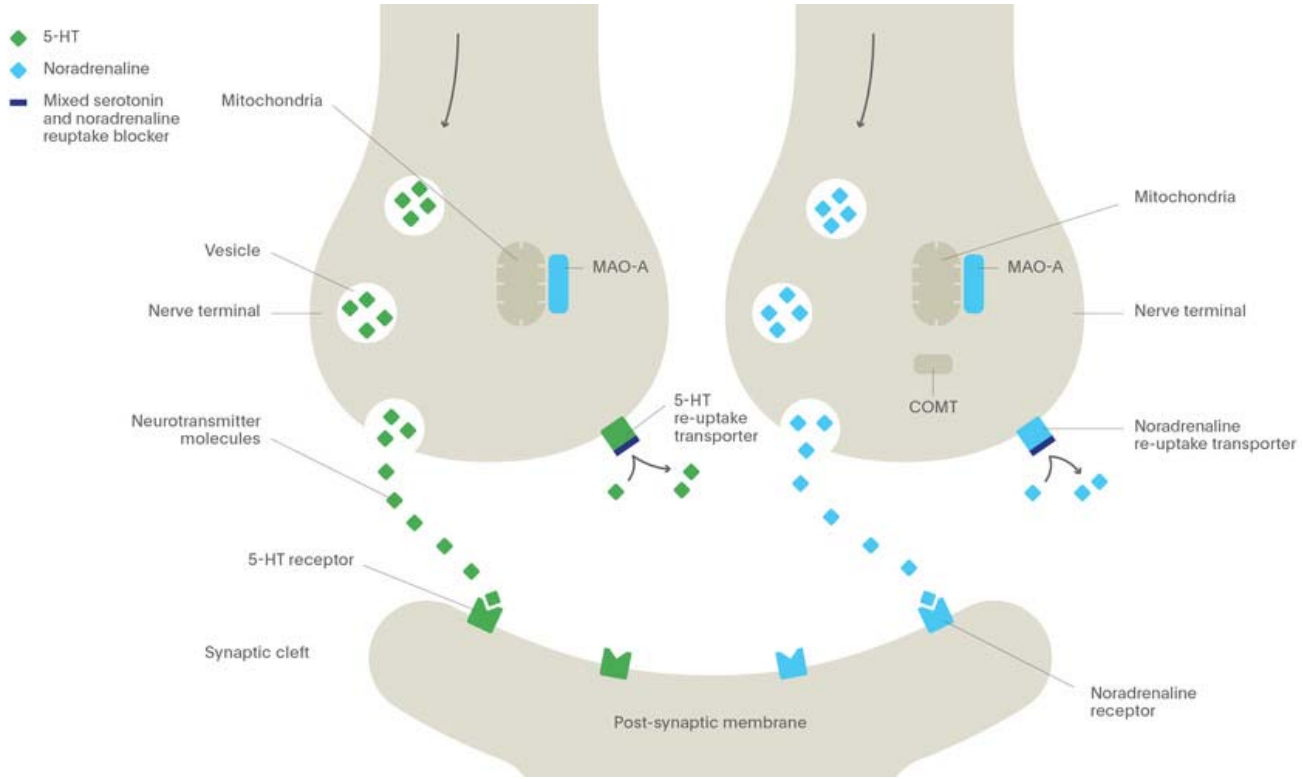
Cannabis Effects Overlap with Treatments for Mental Disorders and Drugs of Abuse



Mental Disorders are Associated with Dysfunctional Neurotransmitters



Antidepressant Mechanism

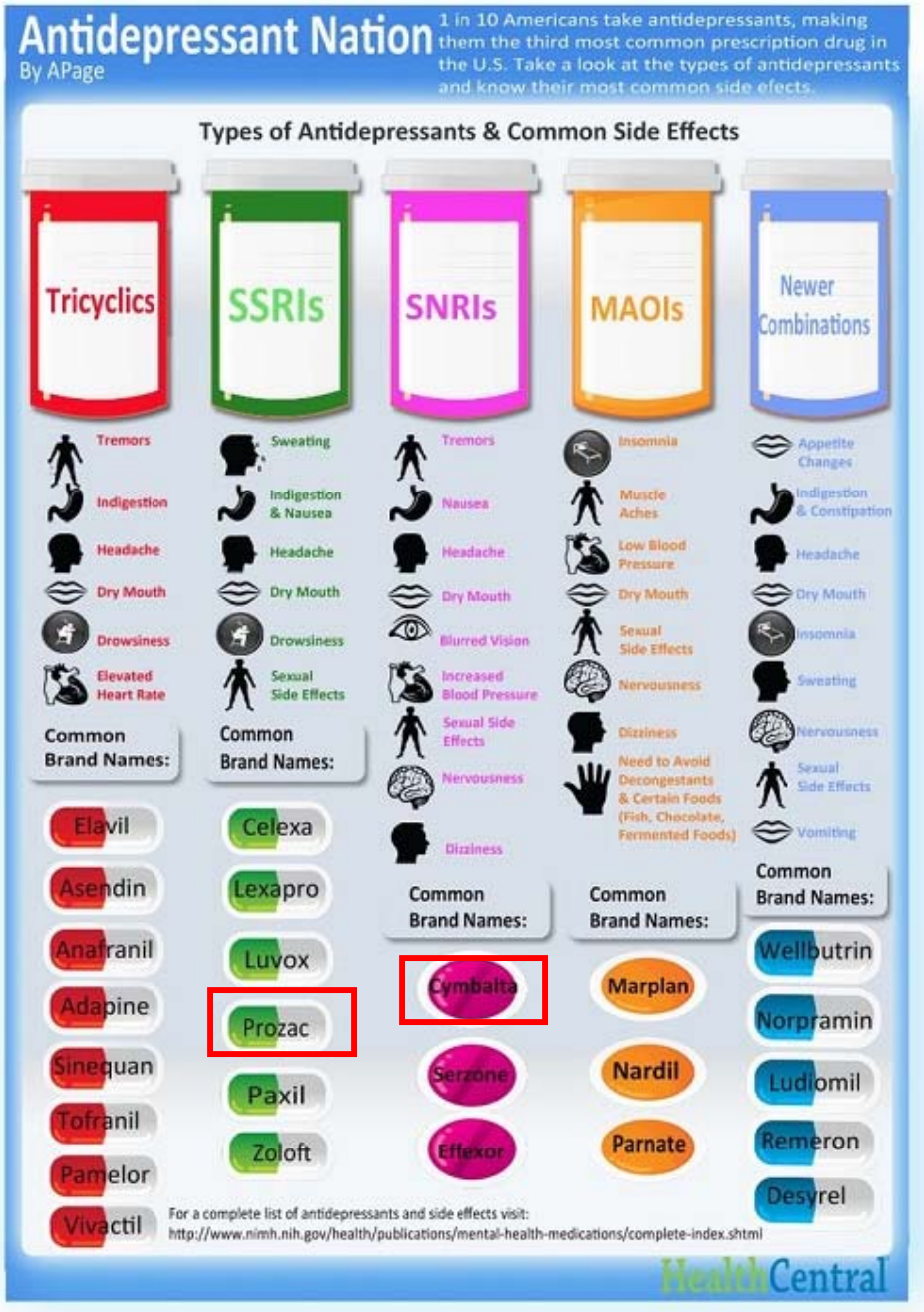


- Problem: too little NE and 5-HT (primarily 5-HT1 receptor activity)
- Most effective agents block reuptake of serotonin and/or norepinephrine
- **Fluoxetine (Prozac™)**
  - SSRI (selective serotonin reuptake inhibitor)
- **Duloxetine (Cymbalta™)**
  - SNRI (serotonin norepinephrine reuptake inhibitor)

Many Classes of Antidepressants

- Most Antidepressants act by raising levels of Serotonin, Norepinephrine, or Dopamine

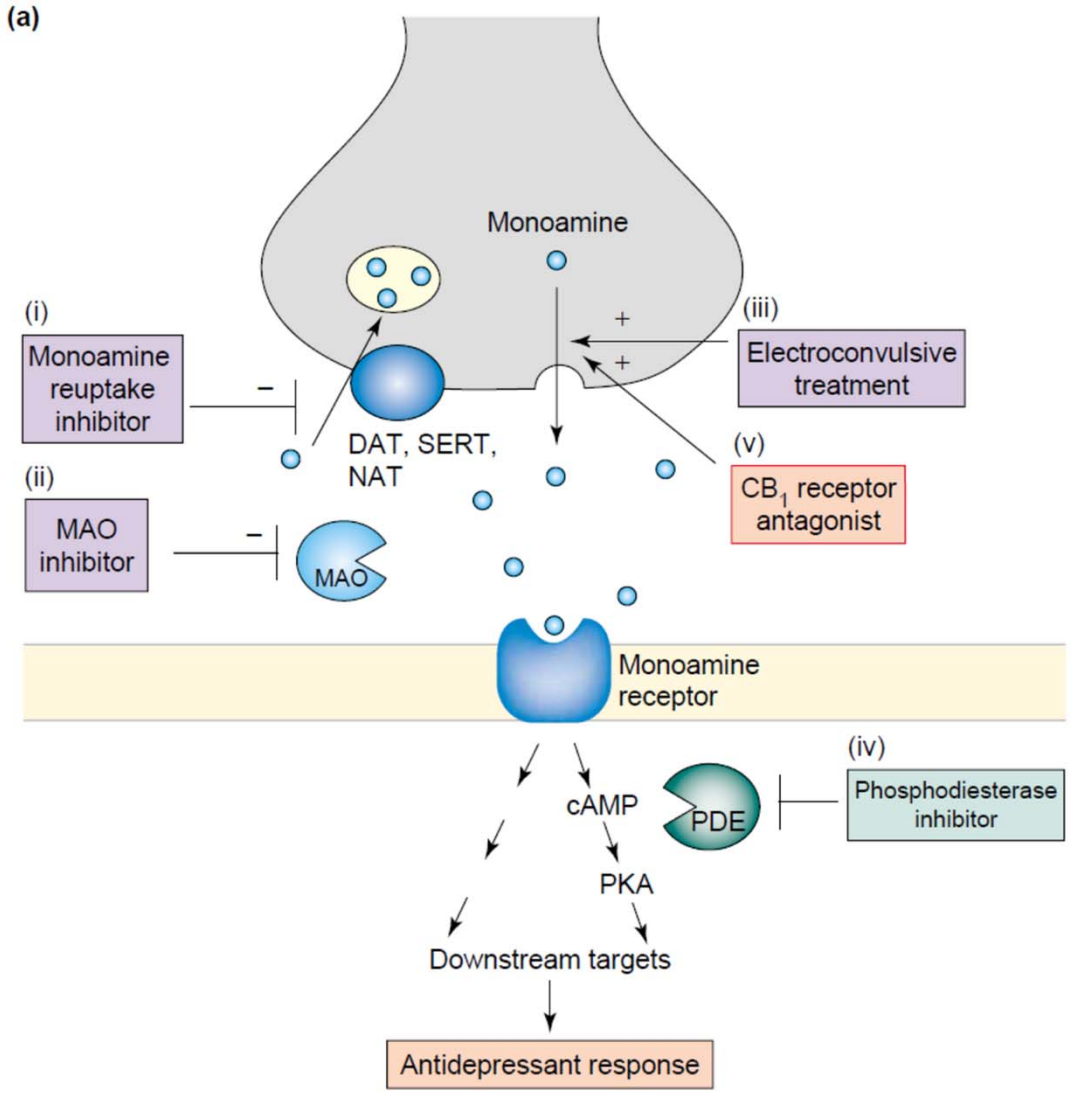
- They are NOT receptor agonists that could result in tolerance
- Side effects mostly mild: nausea/headache and reduced libido



Do Cannabinoids have Antidepressant Effects?

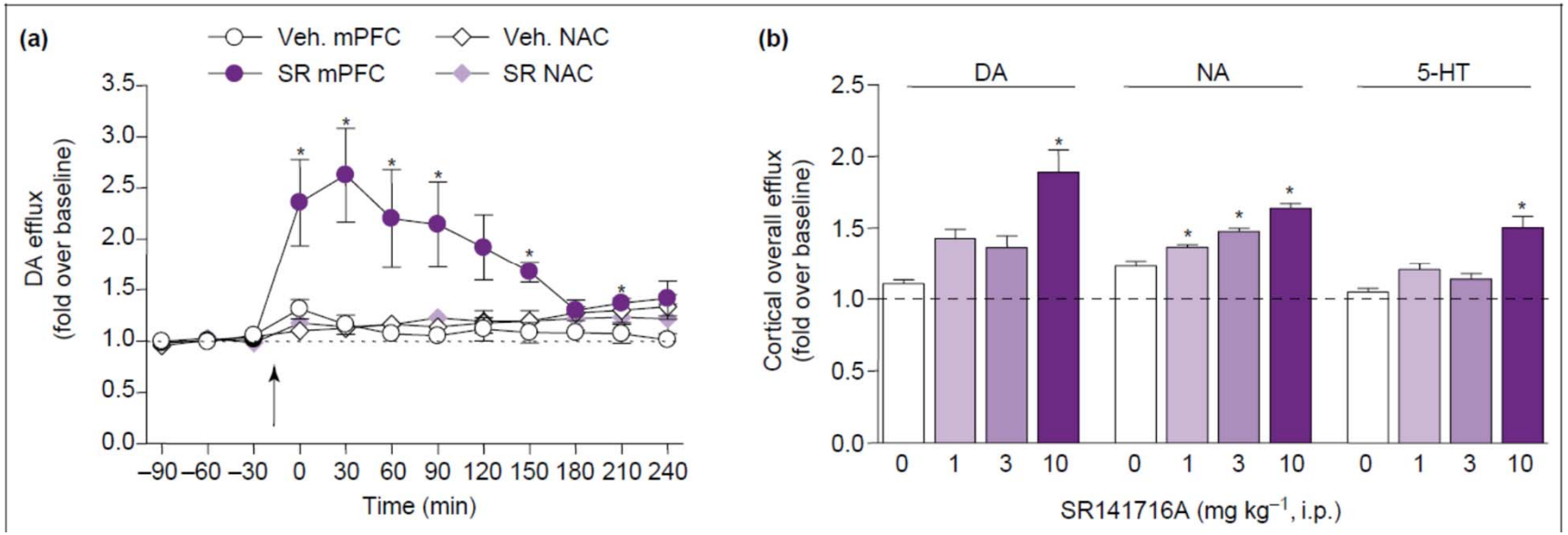
- CB1 receptor antagonist activity
- Direct agonist effects on 5-HT1 receptors
- Effects on other receptor signaling

CB1 receptor antagonists may stimulate neurotransmitter release



CB1 antagonist stimulates neurotransmitter release in Rat brains

- CB1 antagonist induced DA release in the prefrontal cortex (mPFC)
- Cortex levels of DA, NA and 5-HT were also increased



SR, CB1 antagonist; DA, dopamine; NA, norepinephrine; 5-HT, serotonin

TRENDS in Pharmacological Sciences Vol.26 No.12 December 2005

CB1 receptor antagonists

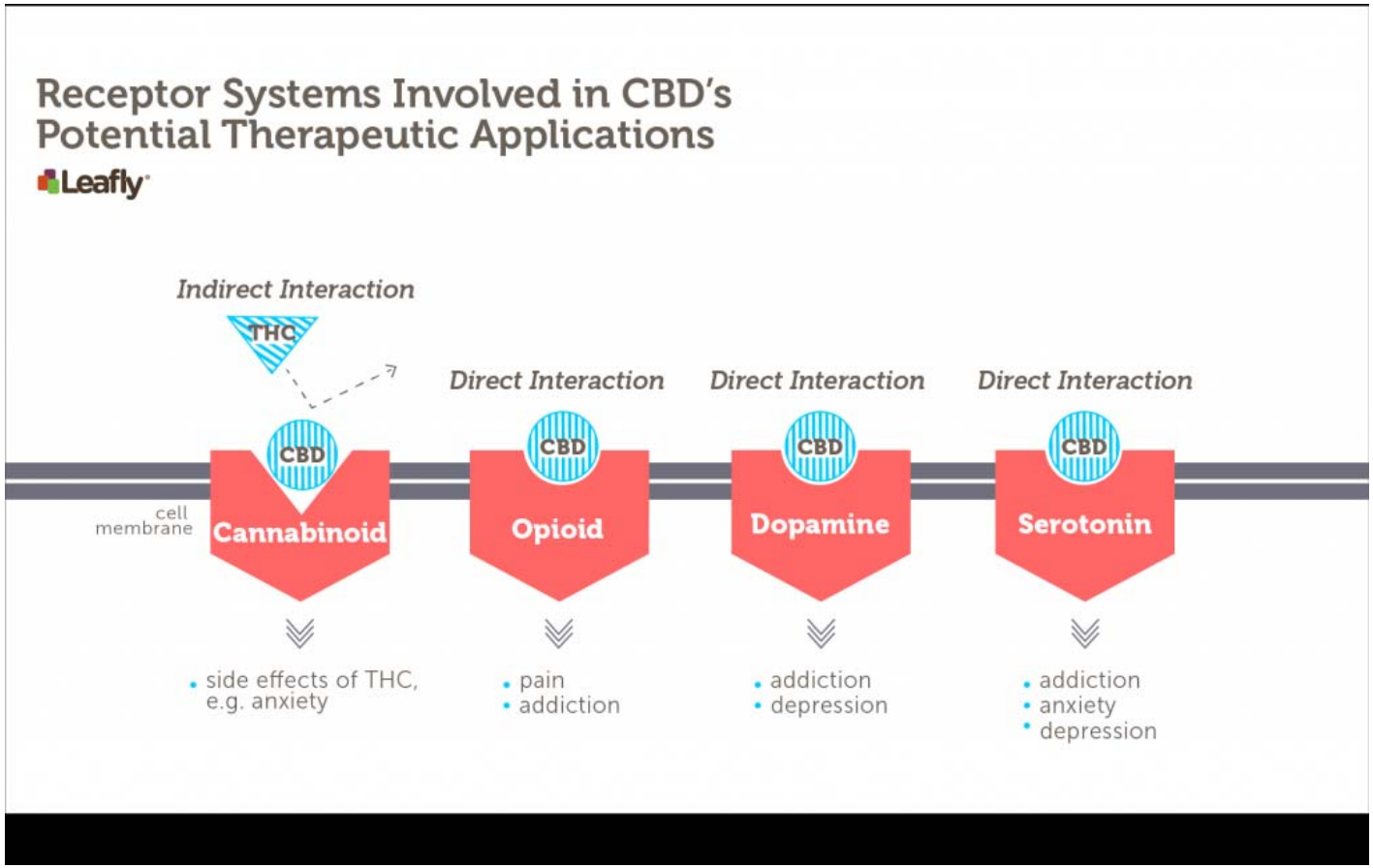
- CB1 receptor antagonists show changes in neurochemicals similar to other antidepressants
- CB1 receptor antagonists show effects in animal models of depression
- What about CBD? It’s not a great antagonist (low binding affinity).

A Cautionary Tale

Clinical CB1 antagonist: Rimonabant

- Rimonabant is a selective CB1 blocker
  - Developed by Sanofi-Aventis
- Clinically approved for treatment of obesity in Europe in 2006…..withdrawn in 2008
  - Never approved by US FDA
- Caused depressive symptoms in 10% of patients, 1% with suicide ideation

CBD has slight antagonist activity at CB1 receptors and potential agonist activity at other receptors



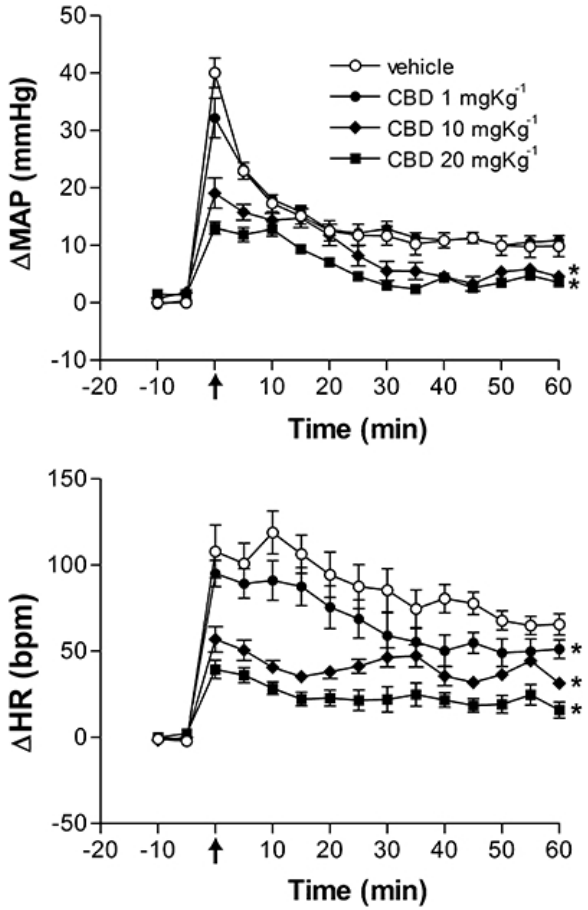
Could these interactions explain the effects of CBD and cannabis on mental health?

CBD is a weak agonist at 5-HT1 receptors

- CBD displaced the 5-HT1 agonist 8-OH-DPAT from 5-HT_{1A} receptors in cultured cells transfected with the receptor.
- CBD caused an increase in Gi activity and a decrease in cAMP formation.

Neurochem Res. 2005 Aug;30(8):1037-43.
Agonistic properties of cannabidiol at 5-HT1a receptors.
Russo EB[1], Burnett A, Hall B, Parker KK.

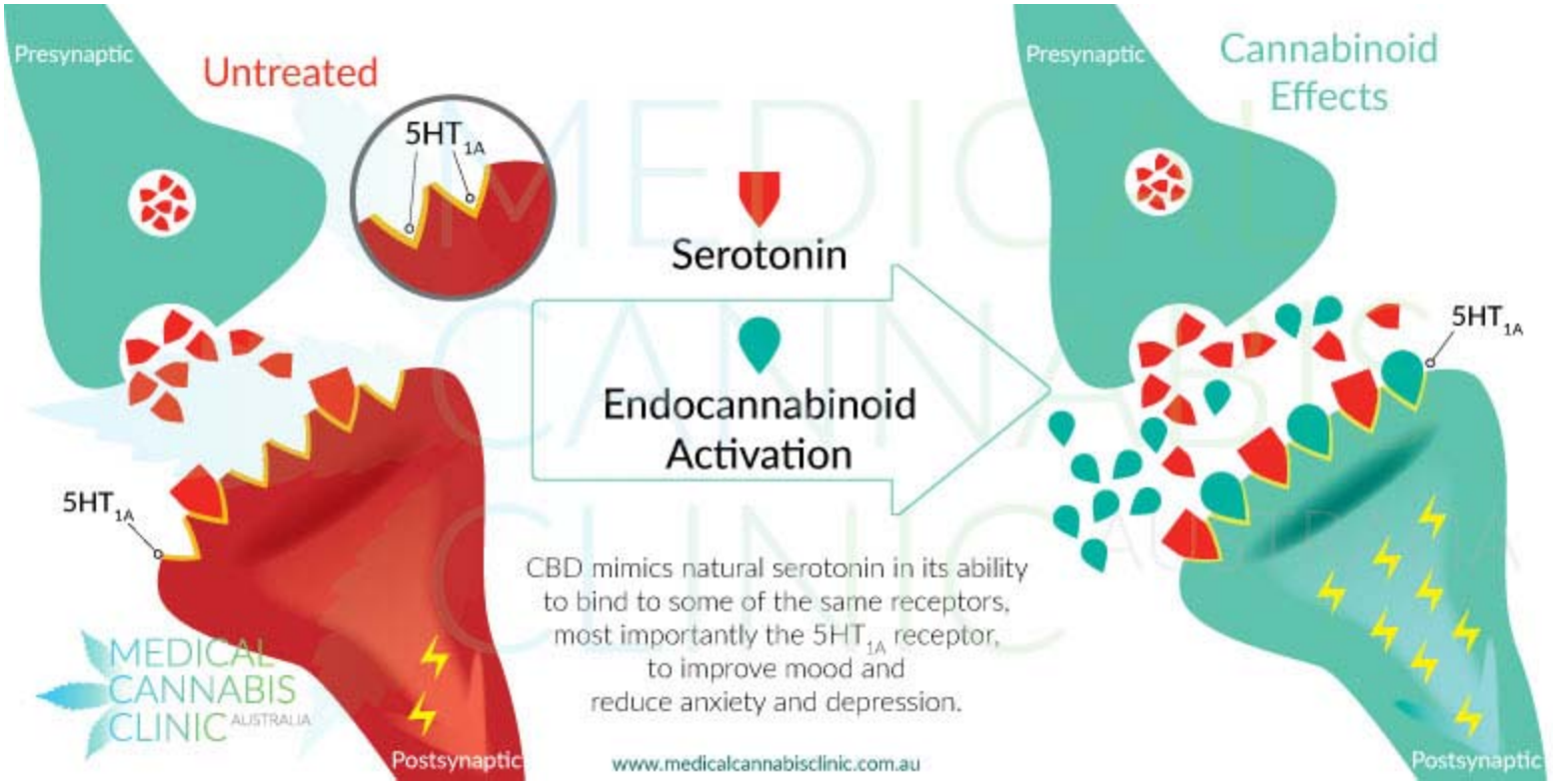
Increasing CBD reduces restraint stress response in animals



- Animal restraint leads to increased blood pressure and heart rate
- CBD reduced these responses
- CBD effect was reversed by a 5-HT1 receptor antagonist

Br J Pharmacol. 2009 Jan; 156(1): 181–188.

CBD antidepressant effects through 5-HT1 receptors



CNS Neurol Disord Drug Targets. 2014;13(6):953-60.

Clicker Question: What would be a primary concern in using CBD as a 5-HT1 agonist to treat depression?

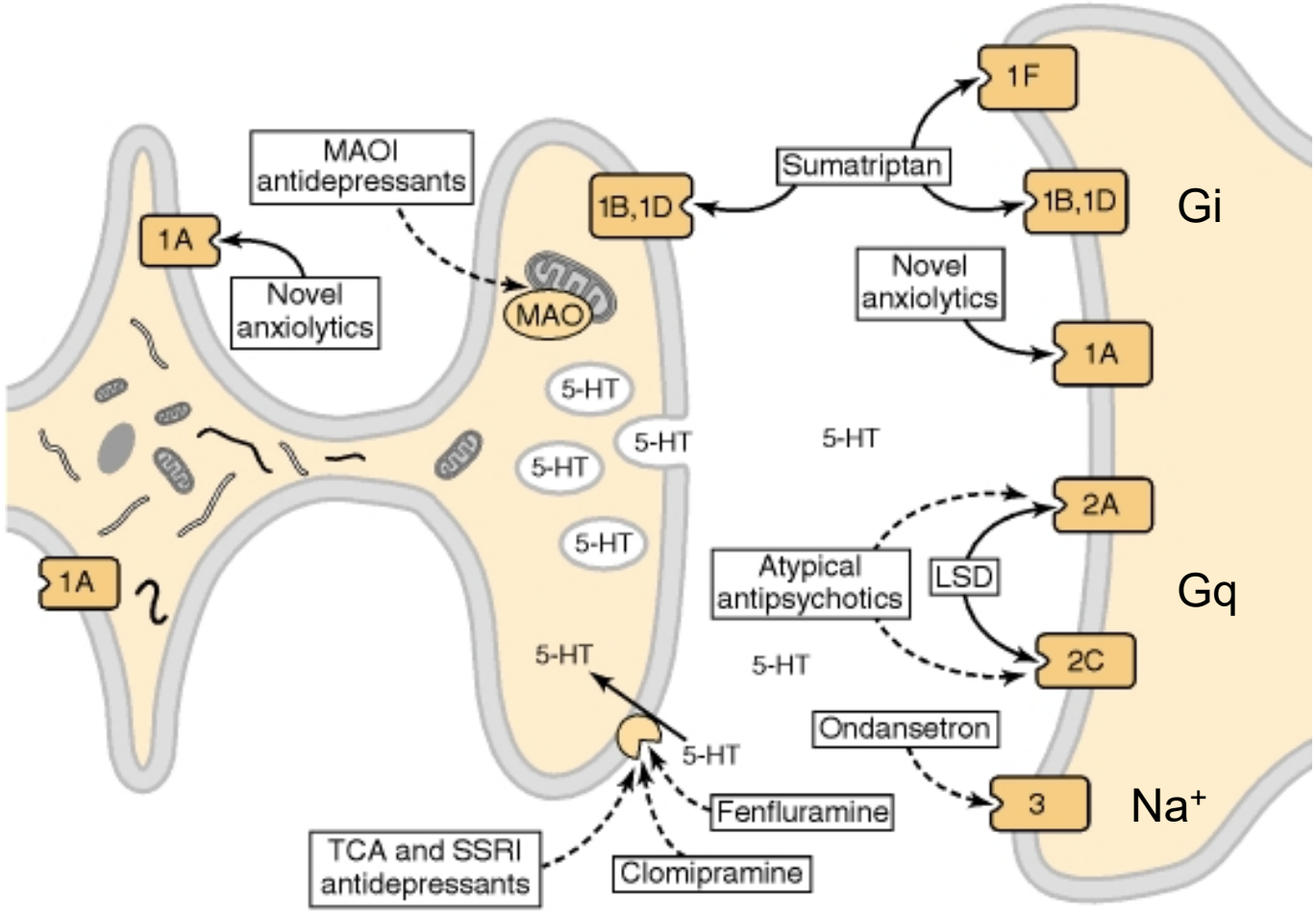
A. It might cause psychoses like LSD

B. It might cause downregulation of receptors resulting in tolerance

C. It might cause migraine headache

D. It might cause nausea

Serotonin Actions on CNS Neurons



Anti-migraine

Anxiolytic

Anti-psychotic

Anti-nausea

Block reuptake: antidepressant

Clinical Trials for CBD in Depression: Systematic reviews

- CBD trials (Nabiximols)
  - Three separate trials, none favored treatment over placebo

Table 2. Summary Estimates From Meta-analyses of Parallel-Group Studies and Results for Primary Outcomes With Associated GRADE Ratings (continued)

Indication[a]	No. of Studies (No. of Patients)	Cannabinoid (No. of Studies)	Comparator	Outcome[b]	Summary Estimate	Favors	I^2, %	GRADE Rating[c]
Depression	1 (66)	Nabiximols	Placebo	Depression Hospital Anxiety and Depression Scale (0-52) Follow-up 5 weeks	Mean difference (95% CI), 0.15 (−1.0 to 1.31)	Placebo	NA	Very low
	1 (182)	Nabiximols	Placebo	Depression assessed using the Montgomery-Åsberg Depression Scale (0-54) Follow-up 9 weeks	Mean difference (95% CI), 1.90 (−0.22 to 4.02)	Placebo	NA	Very low
	1 (160)	Nabiximols	Placebo	Depression Beck Depression Inventory Scale (0-63) Follow-up 6 weeks	Mean difference (95% CI), 0.69 (−0.76 to 2.14)	Placebo	NA	Very low

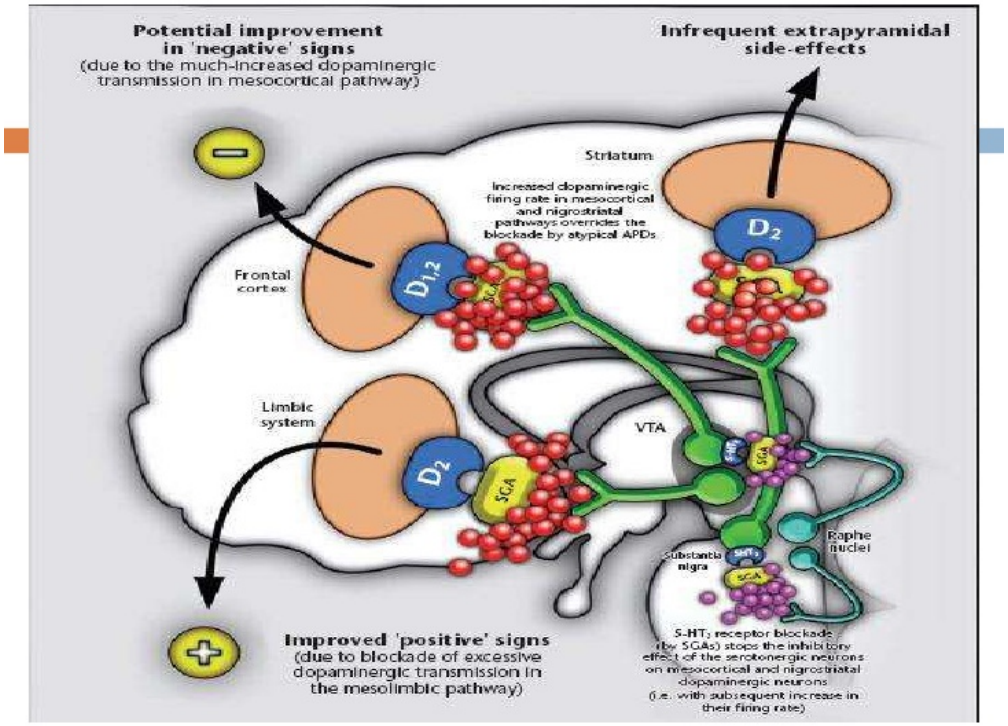
Not much known about whole plant cannabis and depression except Negative Associations

- Heavy cannabis consumers more likely to report thoughts of suicide
- Cannabis consumers are more likely to complete suicide
- Regular cannabis use is associated with an increased risk of developing social anxiety

Cannabinoids and Psychosis

Psychosis: Schizophrenia

- **Positive Effects**
  - Delusions
  - Excess D2 receptor signaling
- **Negative Effects**
  - Depression and withdrawal
  - Excess 5-HT2 receptor signaling or too little 5-HT1 signaling
- **Treatment**
  - D2 receptor blockers
  - Selective 5-HT2 receptor blockers



Current Antipsychotic

- Aripiprazole (Abilify™)
  - Newest antipsychotic (FDA 2002)
  - D2 and 5HT-1 receptor partial agonist/antagonist
  - Also approved for mania and major depression
  - #1 drug in sales in 2014: heavily marketed for depression.

Endocannabinoid System in Psychoses

- Endocannabinoids affect neural development
- CB1 receptors are altered in psychotic patients
- Anandamide levels are higher in psychotic patients

CBD treatment for Psychosis: Systematic Review

- CBD: 2 trials vs. amisulpride, huge variability in responses, so no significance

Psychosis	1 (35)	Cannabidiol	Amisulpride	Mental health Brief Psychiatric Rating Scale Follow-up 4 weeks	Mean difference (95% CI), −0.10 (−9.20 to 8.90)	CBM	NA	Low
	1 (35)	Cannabidiol	Amisulpride	Mood Positive and Negative Syndrome Scale (30-210) Follow-up 4 weeks	Mean difference (95% CI), 1 (−12.60 to 14.60)	Amisulpride	NA	Low
Tourette syndrome	1 (17)	THC capsules	Placebo	Tic severity Shapiro Tourette Syndrome Severity Scale (0-6) Follow-up 6 weeks	Mean difference, −0.70 *P* value = .03	THC	NA	Low
	1 (17)	THC capsules	Placebo	Tic severity Tourette syndrome symptom list (tic rating) Follow-up 6 weeks	Mean difference, −16.2 *P* value < .05	THC	NA	Low
	1 (18)	THC capsules	Placebo	Tic severity Yale Global Tic Severity Scale (0-100) Follow-up 6 weeks	Mean difference, −12.03 *P* value = .061	THC	NA	Low
	1 (17)	THC capsules	Placebo	Tic severity Tourette Syndrome Clinical Global Impression Scale (0-6) Follow-up 6 weeks	Mean difference, −0.57 *P* value = .008	THC	NA	Low

Note: Amisulpride is an antipsychotic. It is not a US drug; acts by blocking D2/D3 and possibly 5-HT7 receptors

Cannabis Negative Effects on Psychoses

- Cannabis produces symptoms of psychoses
- Heavy use in young adolescents is associated with increased risk of developing schizophrenia

There is no evidence to support or refute a statistical association between cannabis use and:

- Changes in the course or symptoms of depressive disorders (12-6)
- The development of posttraumatic stress disorder (12-10)

Evidence against Negative Effects of Cannabis on Psychoses

There is moderate evidence of *no* statistical association between cannabis use and:

- Worsening of negative symptoms of schizophrenia (e.g., blunted affect) among individuals with psychotic disorders (12-2c)

There is limited evidence of a statistical association between cannabis use and:

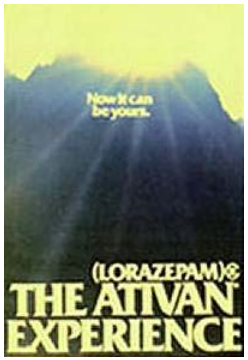
- An increase in positive symptoms of schizophrenia (e.g., hallucinations) among individuals with psychotic disorders (12-2b)
- The likelihood of developing bipolar disorder, particularly among regular or daily users (12-3)
- The development of any type of anxiety disorder, except social anxiety disorder (12-8a)
- Increased symptoms of anxiety (near daily cannabis use) (12-9)
- Increased severity of posttraumatic stress disorder symptoms among individuals with posttraumatic stress disorder (12-11)

Cannabinoids and Anxiety

Anxiety symptoms can overlap with depression symptoms

- More sympathetic responses
- More role for the amygdala—worrying
- More overall increase in neuronal activity
- Treatment is with SSRI or with benzodiazepines

Most prescribed anxiolytics are Benzodiazepines



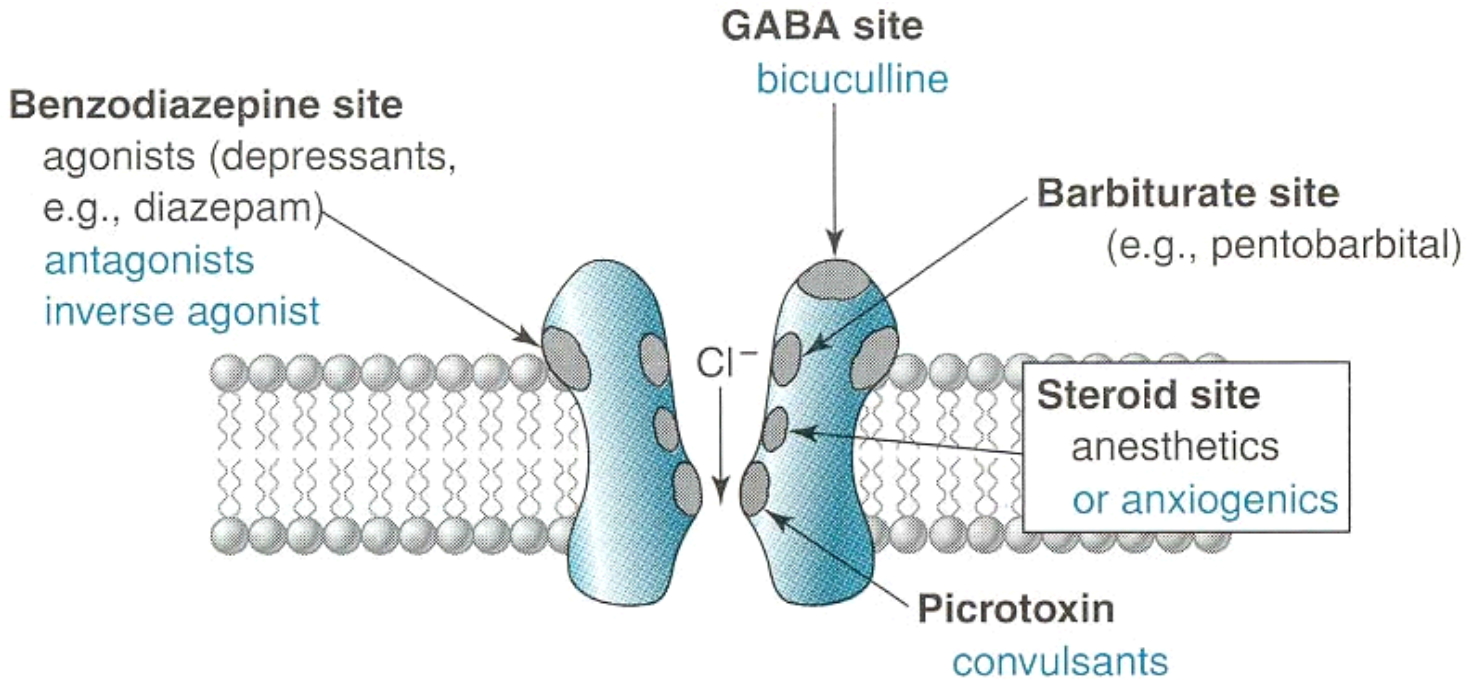
- **Diazepam** (Valium)
- Lorazepam (Ativan)
- Clonazepam (Klonopin)
- Triazolam (Halcion)
- Chlordiazepoxide
- Alprazolam
- Clorazepate=>nordiazepam
- Halazepam
- Oxazepam
- Prazepam

KLONOPIN® clonazepam

Clicker Question: Benzodiazepines affect the $GABA_A$ Chloride channel receptor. To treat anxiety, which mechanism would be most beneficial?

A. Inhibit GABA activity
B. Stimulate GABA activity

Benzodiazepines increase activity of the $GABA_A$ Chloride Channel



Benzodiazepines like **diazepam** cause an increase in the frequency of the GABA channel openings, resulting in inhibition of action potentials and sedation

Side Effects of Benzodiazepines

- Related primarily to the CNS depression and include: drowsiness, excess sedation, impaired coordination, nausea, vomiting, confusion and memory loss. Tolerance develops to most of these effects.

- Dependence with these drugs may develop.
- Serious **withdrawal syndrome** can include convulsions and death.
- Patients are often prescribed an SSRI first

Clicker Question: What effect does CB1 receptor activation have on GABA secreting neurons?

A. Inhibits GABA release

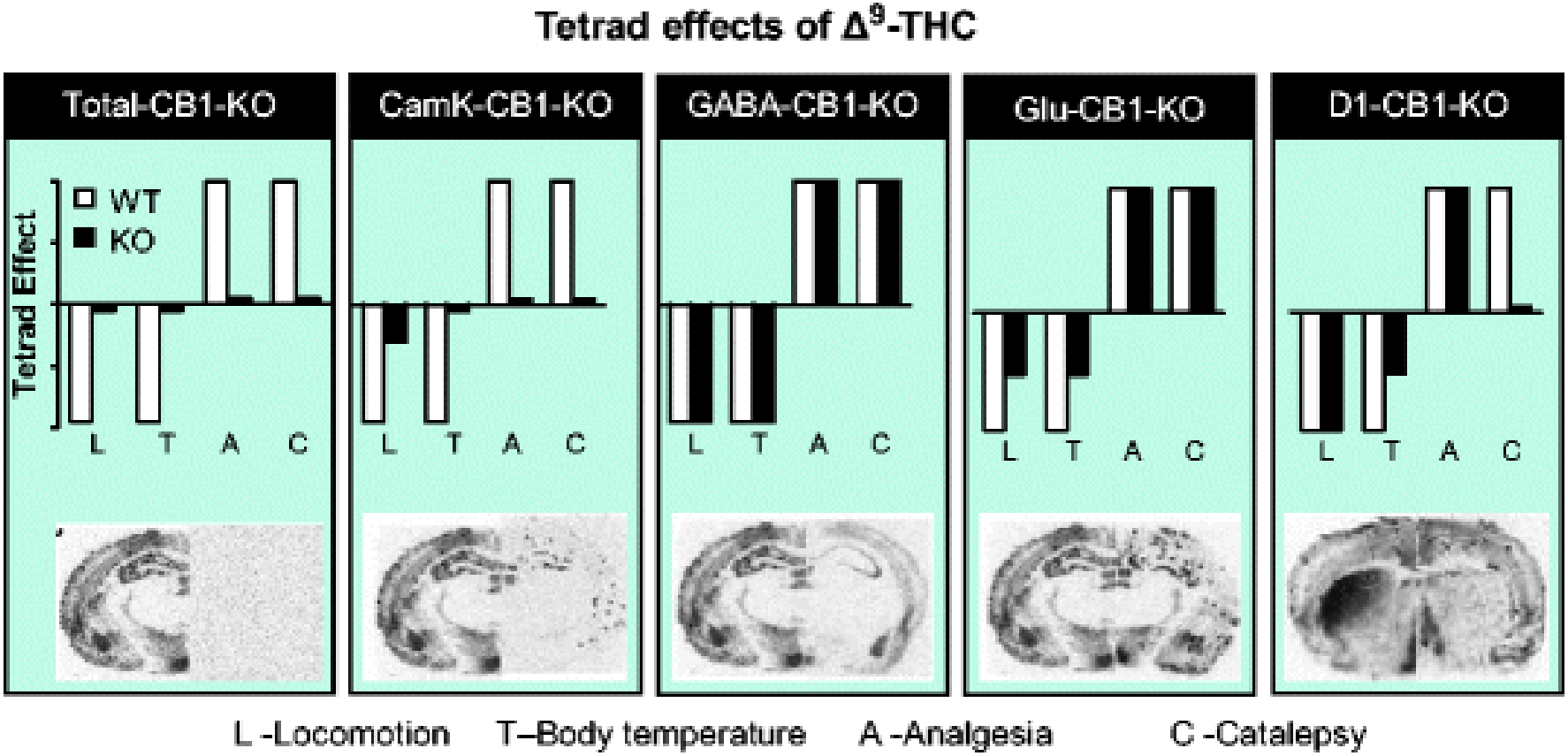
B. Stimulates GABA release

C. No effect on GABA release, not found on GABA receptors

Cannabinoids and Anxiety: Animal models

- Preventing anandamide breakdown by FAAH reduces anxiety in animal models
- CB1 receptor knockout has higher anxiety
  - Knockout in selective neurons changes behavior
- TRPV1 activation causes anxiety--opposite of CB1 receptor activation
  - TRPV1 knockout shows less anxiety

Effects of THC change when CB1 receptors are deleted from specific neuron types



http://link.springer.com/chapter/10.1007/7854_2009_16/fulltext.html

Distinct subpopulations of neurons are responsible for different behavioral effects

Effects of Cannabinoids on Anxiety in Humans

- Clearly a complex patient-specific response
- Low doses are anxiolytic
  - Sedation?
- High doses cause anxiety
  - Paranoid feelings
  - More intense with edibles

Anxiety: Systematic Reviews

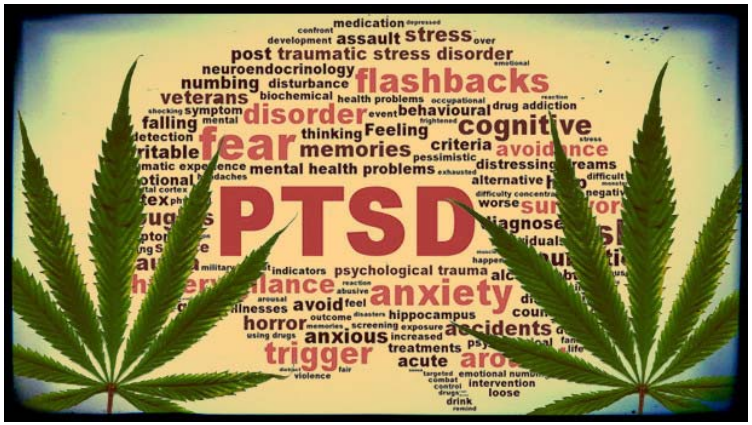
- THCs, Dronabinol, Nabilone: greater short-term benefit for anxiety and sleep disorders (high risk of bias)
- CBD: greater improvement in anxiety score than placebo (randomized, p=0.01)
- Cannabis: no good trials

- Overall conclusion is that cannabinoids have good potential as anxiolytic agents

Anxiety disorder	1 (24)	Cannabidiol	Placebo	Anxiety Visual Analogue Mood Scale (anxiety factor scale; 0-100) Follow-up 107 minutes	Mean difference, −16.52 *P* value = .01	CBM	NA	Very low
Sleep disorder	1 (22)	Nabilone	Placebo	Sleep apnea/hypopnea Apnea Hypopnea Index Follow-up 3 weeks	Mean difference, −19.64 *P* value = .02	CBM	NA	Low
	8 (539) In other indications	Nabiximols (7), THC/CBD (1)	Placebo	Sleep quality NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.58 (−0.87 to −0.29)	CBM	33	Very low
	3 (1637) In other indications	Nabiximols (3)	Placebo	Sleep disturbance NRS (0-10) Follow-up 2-15 weeks	WMD (95% CI), −0.26 (−0.52 to 0.00)	CBM	64	Very low

Anxiety: Negative effects

- Daily cannabis use is associated with increased anxiety
- Heavy use is associated with social phobias.



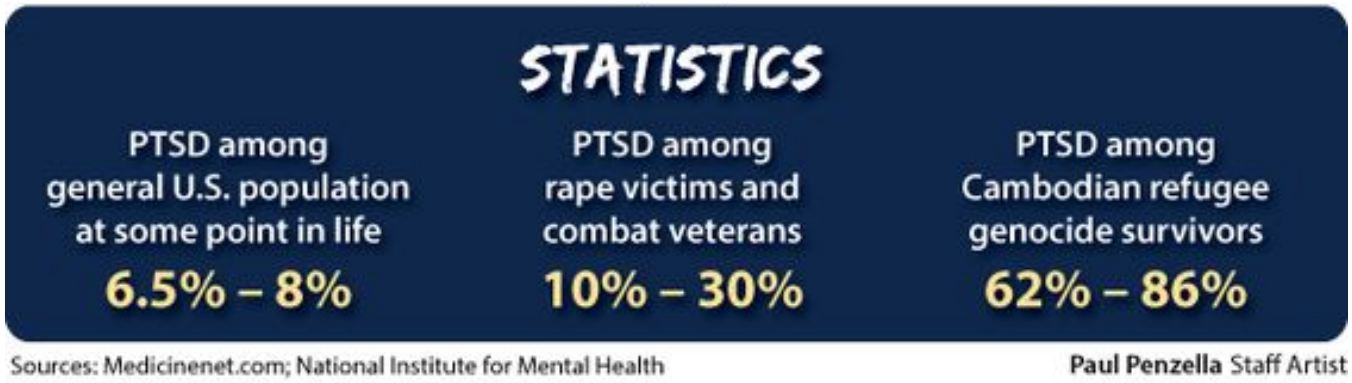
Cannabinoids and PTSD

PTSD (post-traumatic stress disorder)

- A physiological and behavioral response to exposure to emotional trauma
- To be diagnosed with PTSD, an adult must have all of the following for at least 1 month:
  - At least one re-experiencing symptom
  - At least one avoidance symptom
  - At least two arousal and reactivity symptoms
  - At least two cognition and mood symptoms

Highest Risk

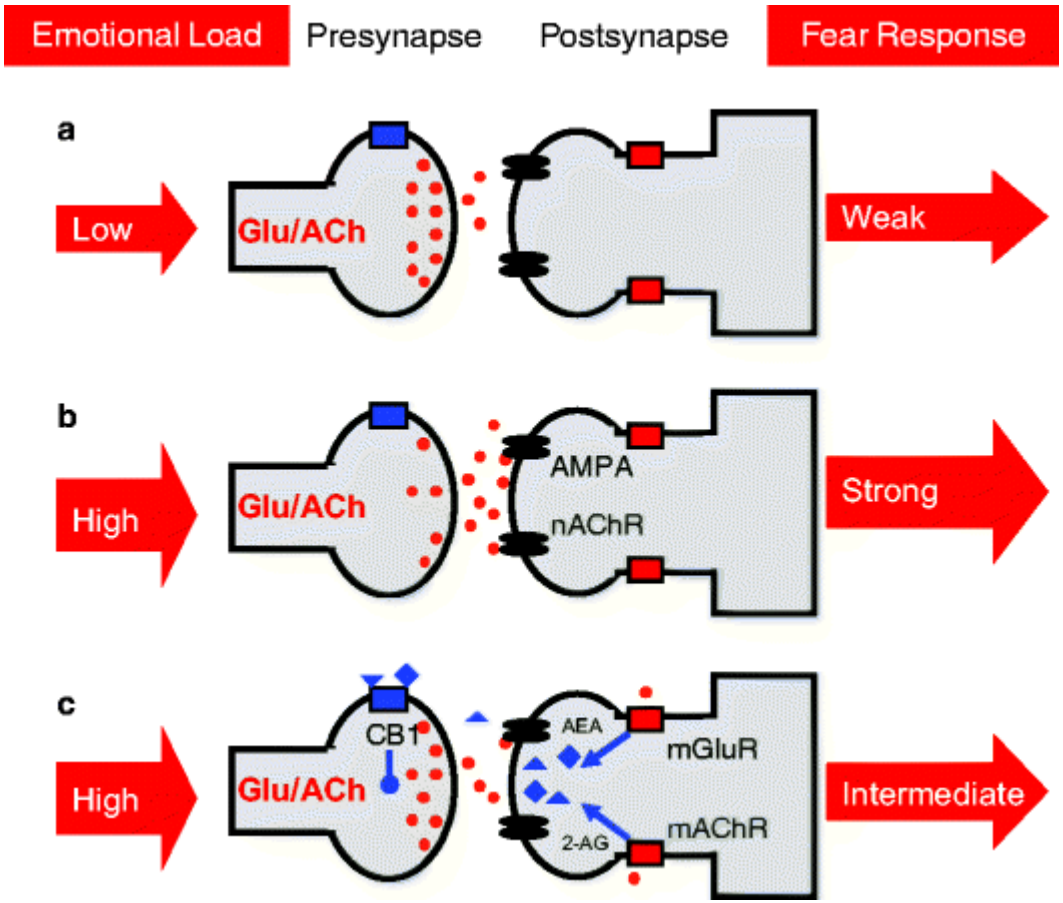
- High intensity: Combat veterans, Rape victims, Refugees
- Vulnerable age: Childhood trauma
- Preexisting mental disorder or substance abuse



Treatments for PTSD

- Refractory to treatment
- Most patients treated with antidepressants or anxiolytics, with poor success
- Behavioral therapy has some benefit

A cellular model of endocannabinoid-controlled fear relief

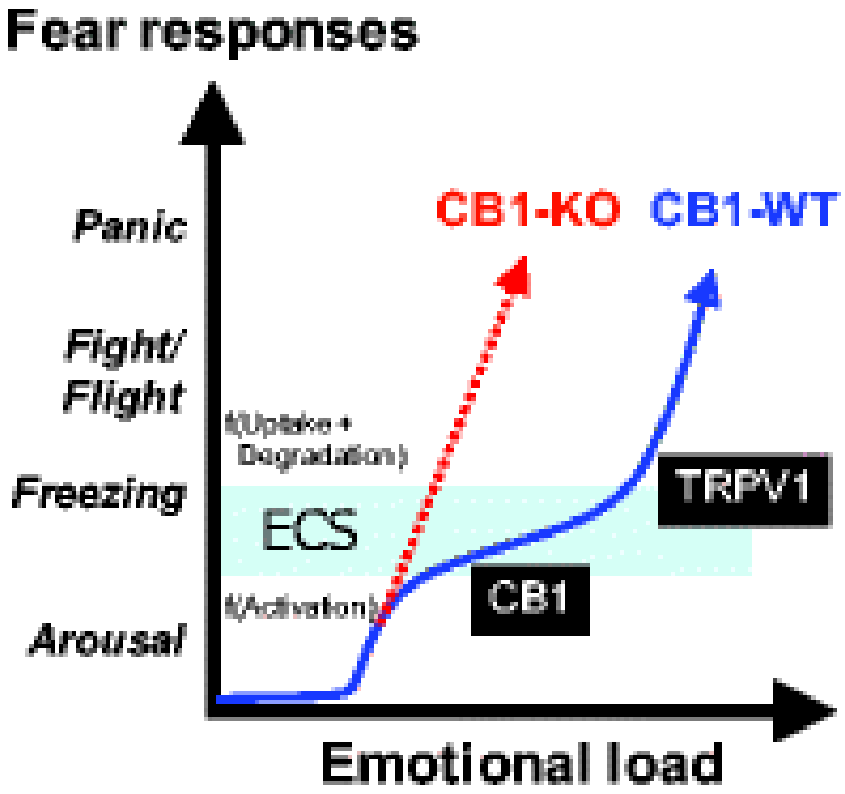


Excess signaling by neurons leads to activation of mGluR triggering the formation of enoocannabinoids

Negative emotional load triggers the endocannabinoid response

2 stages: CB1 and TRPV1

CB1 reduces fear response
TRPV1 enhances fear



http://link.springer.com/chapter/10.1007/7854_2009_16/fulltext.html

A malfunctioning endocannabinoid system leads to excess fear conditioning or PTSD

Cannabinoids in PTSD: Animal models

- CB1 agonists reduces recurrent fear in animal models of PTSD (reconsolidation)
  - Very time-dependent, needed signal at time of fear
- FAAH inhibitors to increase endocannabinoid levels reduced PTSD

Testimonial: Medical Marijuana for PTSD

- https://www.youtube.com/watch?v=M_GDFoJE0gA

Future Directions:

- CBD Clinical Trials
  - 39 clinical trials using CBD in mental health disorders
  - Mostly related to anxiety and psychosis
- Altering Endocannabinoids
- CB1 receptors agonists and antagonists
- Medical Marijuana Testimonials
  - Clinical trials for cannabis in PTSD