

# Cannabinoids and Health

Module 10

Lecture 6: Deep Dive on Cannabis and Psychosis

Does depression or psychosis predict cannabis use (i.e., is it possible patients are self-medication)?

- As you already know, there is a clear association between schizophrenia and cannabis use leading many to conclude that cannabis use is a risk factor for schizophrenia
  - The NAS Committee concluded that there was substantial evidence of a statistical association between cannabis use and the development of schizophrenia or other psychoses, with the highest risk among the most frequent users
- The NAS Committee asked whether there is evidence that various psychiatric conditions predict cannabis use

# Self-Medication Hypothesis: Depression

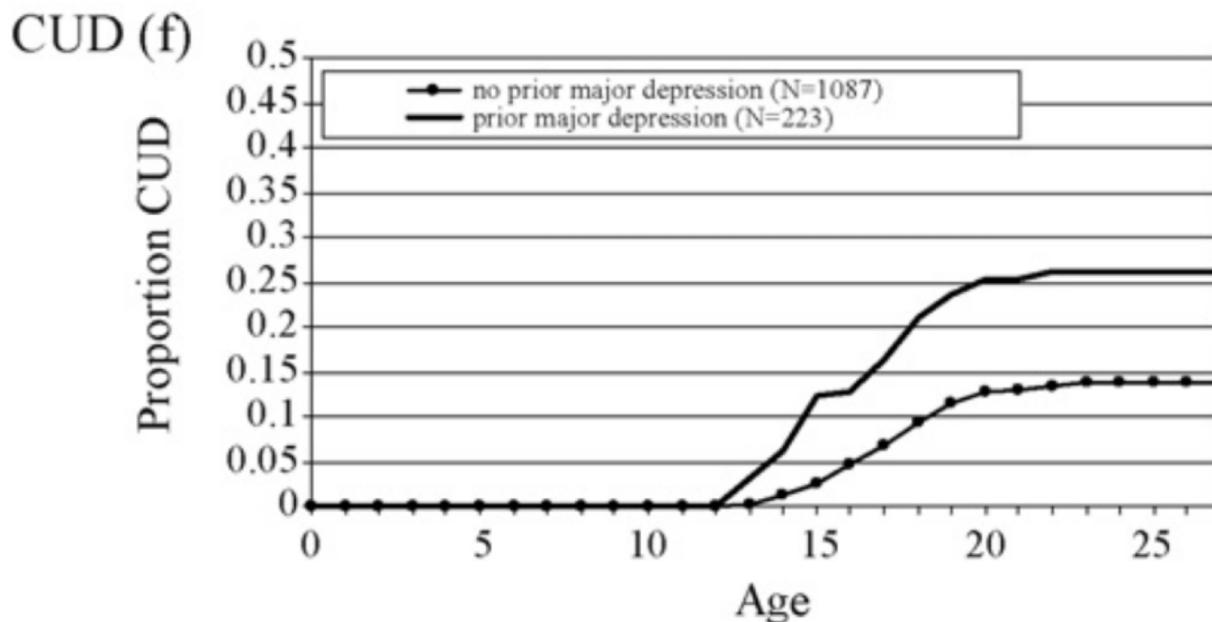
- Pacek et al studied the NESARC sample (n=34,653)
  - This is a representative adult sample in the US (18+)
  - Baseline depression was associated with greater odds of having cannabis use disorder (OR = 2.01)
  - Accounting for confounds strengthened this relationship (adjusted OR = 2.28; i.e., 2.28x greater odds for depression)

Incident AUD and CUD		Unadjusted	Adjusted <sup>a</sup>
Specific substance use disorder at follow-up		OR (95% CI)	aOR <sup>e</sup> (95% CI) <sup>f</sup>
AUD <sup>b</sup>		0.96 (0.77–1.21)	1.04 (0.82–1.32)
Alcohol abuse		0.69 (0.52–0.93)*	0.76 (0.56–1.02)
Alcohol dependence		1.39 (1.02–1.90)*	1.47 (1.06–2.03)*
CUD <sup>c</sup>		2.01 (1.09–3.68)*	2.28 (1.28–4.05)*
Cannabis abuse		2.67 (1.35–5.28)*	2.96 (1.55–5.65)*
Cannabis dependence		0.65 (0.19–2.28)	0.77 (0.22–2.64)
Co-occurring use disorders			
AUD + CUD <sup>d</sup>		1.50 (0.70–3.22)	1.51 (0.70–3.23)
Alcohol dependence + Cannabis dependence		5.23 (1.28–21.34)*	4.51 (1.31–15.60)*

Pacek et al. , 2013, Journal of Affective disorders

# Self-Medication Hypothesis: Depression

- Wittchen (2007) conducted a prospective study
  - Baseline assessments were conducted at age 14-17
  - Three follow-ups assessments (over the next 10 years)
  - Major depression predicted problem cannabis use ( $OR = 2.4 - 2.7$ ; after adjusting for confounds)



# Self-Medication Hypothesis for Depression

- The NAS Committee concluded (13-2) that there is “limited evidence” that “childhood depression” is a risk factor for later problem cannabis use
- However, they also found moderate evidence that major depressive disorder (later in life) is a risk factor for problem cannabis use

# Self-Medication Hypothesis: Psychosis

- Hartz et al (2014, *JAMA Psychiatry*) examined psychotic disorders and cannabis use in a large, multiethnic study (n = 9-10k)
  - Individuals with chronic psychotic disorders had increased risk for “heavy” cannabis use (21 times/year)
  - Having a psychotic disorder increased the odds of heavy cannabis use by three-fold (OR = 3.5)
  - But, psychotic disorders were associated with all drug use

Table 3. Prevalence of Substance Use Measures Compared Between Cases With Chronic Psychotic Illness and Control Individuals

Substance Used	No.	Odds Ratio Estimate (95% CI) <sup>a</sup>	P Value
Alcohol: >4 drinks/d	19 878	3.96 (3.61-4.35)	$1.2 \times 10^{-188}$
100 cigarettes in lifetime	19 931	4.61 (4.31-4.94)	$<1.0 \times 10^{-325}$
Daily smoking >1 mo	19 882	5.11 (4.78-5.46)	$<1.0 \times 10^{-325}$
Marijuana >21 times/y	19 859	3.47 (3.23-3.72)	$2.6 \times 10^{-254}$
Recreational drugs >10times	19 864	4.62 (4.27-4.99)	$<1.0 \times 10^{-325}$

# Self-Medication Hypothesis: Psychosis

- While the NAS committee found evidence for the association between cannabis and psychosis, among individuals with a psychotic disorder, NAS also found
  - Moderate evidence for an association between a history of cannabis use and better cognitive performance
- What does this suggest?
- Possibility that people are using cannabis and other drugs to self-medicate symptoms

# Emerging Evidence: CBD and Psychosis

- An exploratory double-blind parallel-group trial
  - Patients with schizophrenia were randomized in a 1:1 ratio to receive CBD (1000 mg/day; N=43) or placebo (N=45) alongside their existing antipsychotic medication.
  - Participants were assessed before and after treatment using the Positive and Negative Syndrome Scale (PANSS), the Brief Assessment of Cognition in Schizophrenia (BACS), the Global Assessment of Functioning (GAF)

McGuire et al, 2018, *American Journal of Psychiatry*

Am J Psychiatry. 2018 Mar 1;175(3):225-231. doi: 10.1176/appi.ajp.2017.17030325. Epub 2017 Dec 15.

## **Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial.**

McGuire P<sup>1</sup>, Robson P<sup>1</sup>, Cubala WJ<sup>1</sup>, Vasile D<sup>1</sup>, Morrison PD<sup>1</sup>, Barron R<sup>1</sup>, Taylor A<sup>1</sup>, Wright S<sup>1</sup>.

### Author information

#### **Abstract**

**OBJECTIVE:** Research in both animals and humans indicates that cannabidiol (CBD) has antipsychotic properties. The authors assessed the safety and effectiveness of CBD in patients with schizophrenia.

**METHOD:** In an exploratory double-blind parallel-group trial, patients with schizophrenia were randomized in a 1:1 ratio to receive CBD (1000 mg/day; N=43) or placebo (N=45) alongside their existing antipsychotic medication. Participants were assessed before and after treatment using the Positive and Negative Syndrome Scale (PANSS), the Brief Assessment of Cognition in Schizophrenia (BACS), the Global Assessment of Functioning scale (GAF), and the improvement and severity scales of the Clinical Global Impressions Scale (CGI-I and CGI-S).

**RESULTS:** After 6 weeks of treatment, compared with the placebo group, the CBD group had lower levels of positive psychotic symptoms (PANSS: treatment difference=-1.4, 95% CI=-2.5, -0.2) and were more likely to have been rated as improved (CGI-I: treatment difference=-0.5, 95% CI=-0.8, -0.1) and as not severely unwell (CGI-S: treatment difference=-0.3, 95% CI=-0.5, 0.0) by the treating clinician. Patients who received CBD also showed greater improvements that fell short of statistical significance in cognitive performance (BACS: treatment difference=1.31, 95% CI=-0.10, 2.72) and in overall functioning (GAF: treatment difference=3.0, 95% CI=-0.4, 6.4). CBD was well tolerated, and rates of adverse events were similar between the CBD and placebo groups.

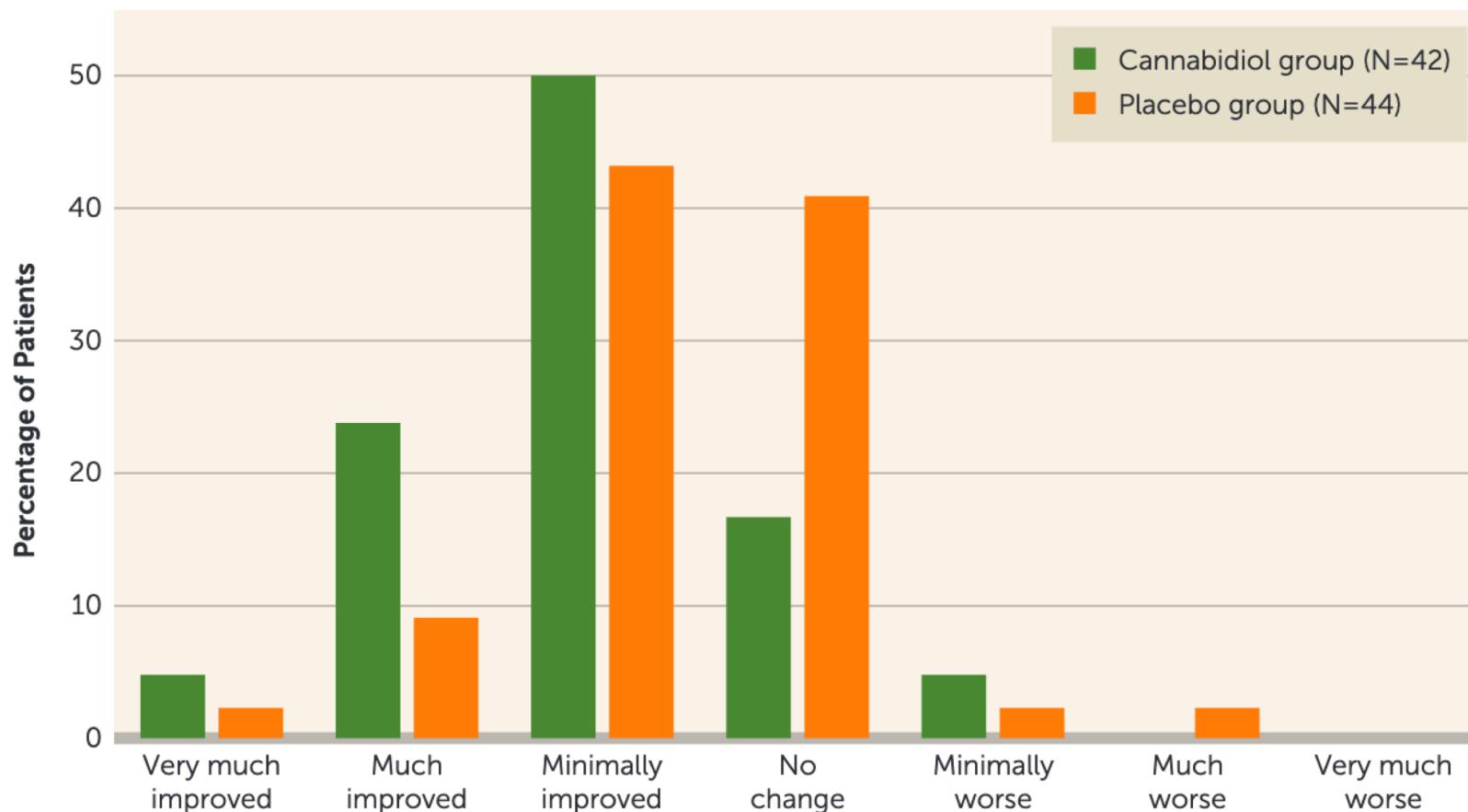
**CONCLUSIONS:** These findings suggest that CBD has beneficial effects in patients with schizophrenia. As CBD's effects do not appear to depend on dopamine receptor antagonism, this agent may represent a new class of treatment for the disorder.

# Emerging Evidence: CBD and Psychosis

## Cannabidiol (CBD) as an Adjunctive Therapy in Schizophrenia: A Multicenter Randomized Controlled Trial

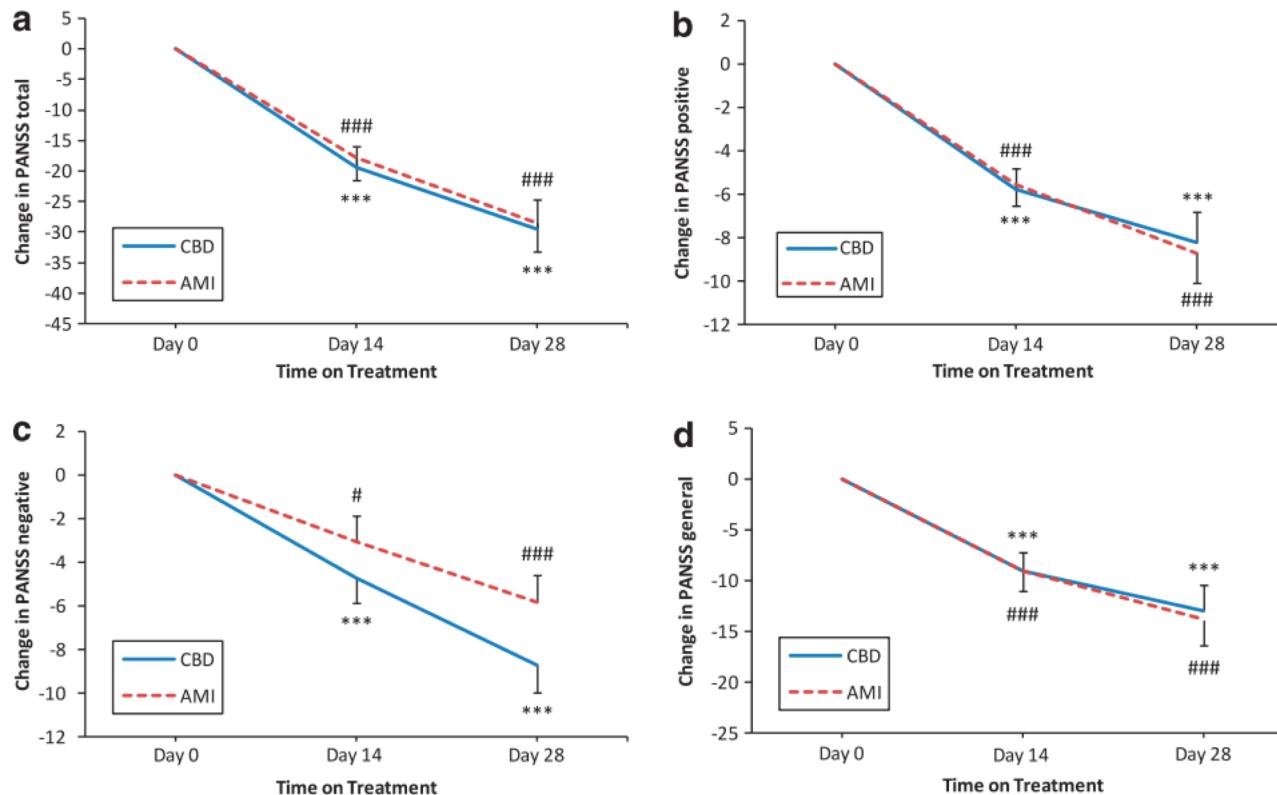
Philip McGuire, F.R.C.Psych., F.Med.Sci., Philip Robson, M.R.C.P., F.R.C.Psych., Wieslaw Jerzy Cubala, M.D., Ph.D., Daniel Vasile, M.D., Ph.D., Paul Dugald Morrison, Ph.D., M.R.C.Psych., Rachel Barron, B.Vet.Med., M.R.C.V.S., Adam Taylor, Ph.D., Stephen Wright, F.R.C.P.(Edin), F.F.P.M.

**FIGURE 2. Clinical Global Impressions Severity Scores at End of Treatment in a Study of Adjunctive Cannabidiol in Schizophrenia (Intention-to-Treat Analysis Set)**



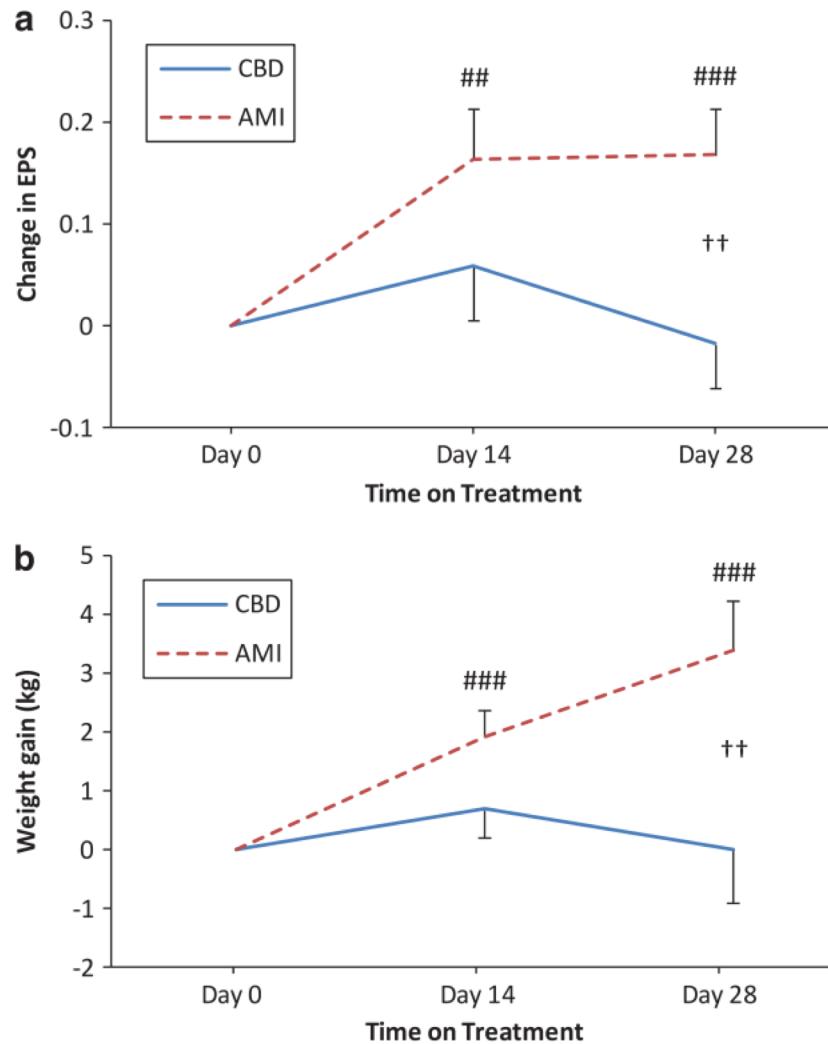
# In 2012 trial, CBD equals or exceeds treatment as usual

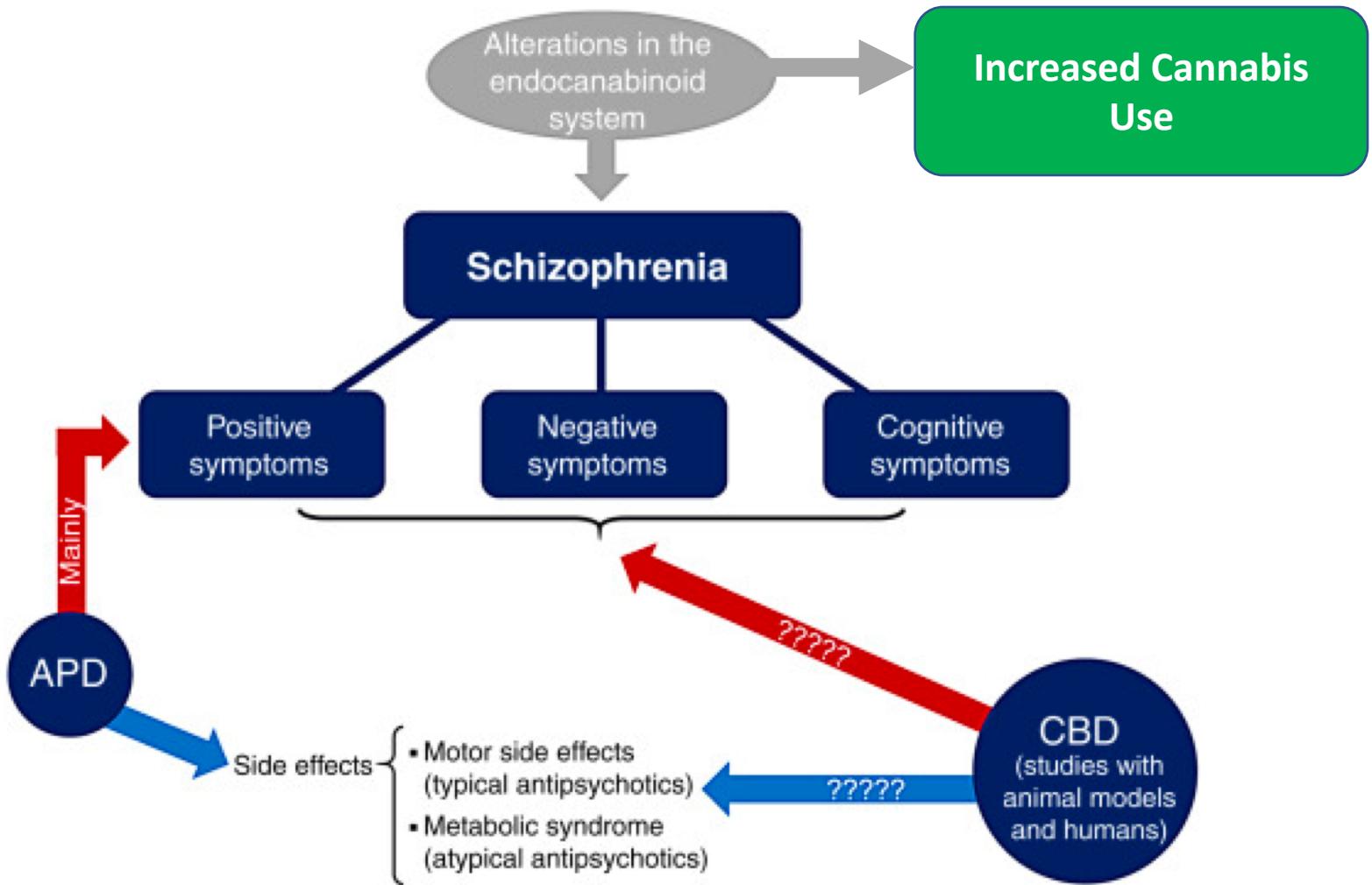
Enhanced anandamide activity ameliorates psychosis  
FM Leweke et al



**Figure 2** Changes from baseline in Positive and Negative Symptoms Scale (PANSS) scores determined using mixed effects repeated measures model analysis (adjusted for baseline). (a) PANSS total score. (b) PANSS-positive score. (c) PANSS-negative score. (d) PANSS general score. Data show predicted means and s.e. at each weak. Statistical significance is calculated between groups ( ${}^{\dagger}P \leq 0.05$ ,  ${}^{\ddagger}P \leq 0.01$  and  ${}^{\ddagger\ddagger}P \leq 0.001$ ) and vs baseline (that is, 0; \*CBD, #AMI; \*\*/## $P \leq 0.05$ , \*\*/# $P \leq 0.01$ , \*\*# $P \leq 0.001$ ).

# In 2012 trial, CBD has fewer side effects





# Conclusions

- As noted previously, there is strong evidence of an association between cannabis use and psychosis
  - not so much with depression or bipolar disorder
- It is possible that cannabis use early in life plays a causal role in the development of schizophrenia
- It is possible that there is a factor (genetic? Alterations in the endocannabinoid system) that causes both
- It is possible that individuals who have a preexisting risk and early symptoms are beginning to self-medicate
- Early clinical trials suggest that CBD (600-1000 mg) has considerable promise
- While CBD may be helpful, THC may be detrimental