ANOREXIA NERVOSA AND CANNABINOIDS: A NARRATIVE REVIEW

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MY INSPIRATION: PATIENT CASE

- SC is a 33yo woman with hx of anorexia nervosa and multiple other comorbid psychiatric, medical, and substance use diagnoses who presented to outpatient psychiatry to establish care after recently moving to Baltimore.
- Patient had good insight into her eating disorder, after years of being in and out of psychiatric hospitals since she was a teenager. At presentation, she was at a normal BMI, but reported continued anxiety around food and the feeling of "being full". She also reported that when distressed, she would regress to using restricting behaviors as a coping skill.
- Described her motivation as "I know this could kill me. I don't want to die."
- Reported using cannabis edibles behind her family's back to help her

eat sometimes.



BACKGROUND

- Anorexia Nervosa (AN) has one of the highest mortality rates of any psychiatric disorder.
- There are still many patients who do not improve with current available treatments, which has inspired research into new therapeutic frontiers.
- The endocannabinoid system is one such target.
- I have conducted a narrative review of the literature covering primary clinical research papers conducted in human participants addressing both AN and cannabinoids, covering 18 studies spanning from 1983 to 2024 including both inpatient and outpatient settings.

QUICK DEFINITIONS

- **Anorexia nervosa:** an eating disorder (ED) defined by severe calorie restriction, fear of weight gain, and distorted body image. It has one of the highest mortality rates of any psychiatric disorder due to medical complications, substance abuse, and suicide.
- **Currently available treatments options:**
  - Conventional pharmacotherapy (e.g. antidepressants, antipsychotics) have mainly been able to target co-morbid conditions as well as using side effects to garner weight gain (especially in the case of olanzapine). These treatments have limited efficacy for core AN psychopathology.
  - Psychotherapy (e.g. Family based therapy, CBT, ACT, and DBT), may be able to better target underlying AN psychopathology. However, there are still many patients who do not improve.

QUICK DEFINITIONS



- **Cannabinoids:** Chemicals derived from the ones found in the plant cannabis sativa that exert their effect on the body by binding cannabinoid receptors.
- **Cannabinoid receptors:** G-protein coupled receptors in the body where the cannabinoids exert their effects. Mainly cannabinoid receptors 1 (CR-1) and 2 (CR-2).
    - CR-1 is present throughout the human body, including the CNS. Of specific interest is the CR-1 placement mainly in hypothalamic nuclei associated with hedonic eating as well as motivation to eat.
- **Endocannabinoids:** arachidonic acid derivatives made in the body that bind to cannabinoid receptors, the most common ones being N-arachidonoyl-ethanolamine (AEA) and 2-arachidonoylglycerol (2-AG).

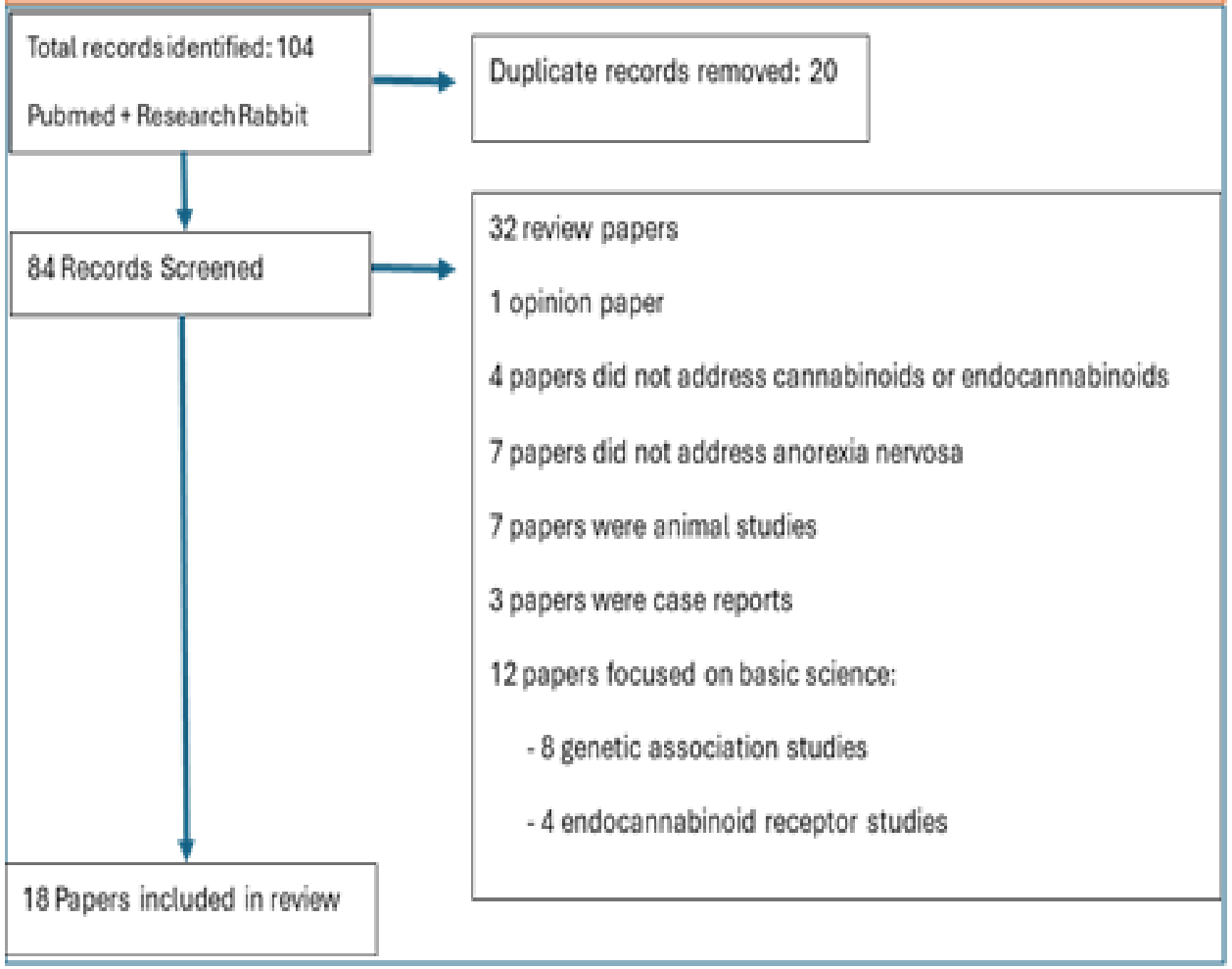
PURPOSE

- With recent legislation throughout the country increasingly liberalizing cannabis use, patients with AN are increasingly exposed to recreational cannabinoids, and as in the example of my patient SC, may be seeking to use this as self-medication (of AN or of comorbid symptoms such as anxiety).
- I aimed to better understand how these substances interact with the psychiatric illnesses we treat clinically and how to advise patients.
- A secondary aim was to understand if the endocannabinoid system may be a viable target of treatment for this population.

METHODS

- A literature review was conducted through an electronic search of PubMed and Research Rabbit using the key terms “anorexia nervosa”, “cannabis”, and “cannabinoids”.
- Papers were screened and only papers with primary human studies that studied both anorexia nervosa and cannabinoids were included.
- Papers that couldn't be found in English or Turkish, as well as case reports, and basic science papers referring to receptor and genetic association studies were excluded.

Figure 1: Methods: Identification of Studies



METHODS

18 articles were included in this review:

- 4 RCTs ,
- 5 cross-sectional comparative,
- 1 longitudinal prospective cohort study,
- 1 longitudinal retrospective cohort study,
- 1 longitudinal controlled pilot study,
- 1 cross-sectional interventional pilot study,
- 5 cross-sectional controlled studies.



Figure 2- Map of Study Sites and Years

These studies were from 1983 to 2024. Studies happened to be from 9 different countries.

RESULTS

The 18 studies fell into 3 distinct study types:

- ones that administered cannabinoids (x5),
- ones that measured endocannabinoids (x6),
- ones that surveyed regular cannabinoid use of the participants (x7).

DEMOGRAPHICS

All (N=2617)	Substance use survey (N=2148)	Exogenous cannabinoids (N=44)	Endocannabinoids (N=425)
Age			
Mean	25.5	30.3	20.6
SD	11.3	11.1	6.4
Gender			
% female	95%	100%	99%
Race			
% Caucasian	76%	At least 79% (1 study didn't specify)	No studies specified but all in Europe
ED			
% AN	36%	100%	43%

STUDIES THAT SURVEYED SUBSTANCE USE IN ED PATIENTS

Reference	Design	Participants	Interventions	Outcomes
Wiederman & Pryor (1996)	Cross-sectional	454 F adults: 134 AN, 320 BN	Lifetime substance use survey	BN substance use> AN substance use
Wiederman & Pryor (1996)a	Cross-sectional	117 F adolescents: 59 AN, 58 BN	Lifetime substance use survey	BN substance use> AN substance use
Haug et al. (2001)	Cross-sectional	100 F, inpatient ED w/ AN vs BN	Lifetime substance use survey	Cannabis use rates were comparable between groups.
Jordan et al. (2003)	Cross-sectional	Outpatient F: 40 AN vs 58 MDD	Lifetime substance use survey	Cannabis use rates were comparable between groups.
Herzog et al. (2006)	Longitudinal cohort	246 Fs: 136 AN, 110 BN	Lifetime substance use survey	Cannabis use rates were comparable between groups.
Mann et al. (2014)	Cross-sectional	290 adolescents w/ EDs	Lifetime substance use survey	Increasing age (p=0.001), non-white race (p=0.002), and male gender (p=0.024) were predictors of cannabis use
Laliberte et al. (2024)	Longitudinal	843 adults w/ ED	Lifetime substance use survey	AN binge/purge and BN cannabis use> other ED groups. Cannabis use ↑ 2014<2020

DISCUSSION

- Studies in **all 3 groups** were limited in patient diversity.
- The **studies surveying participant cannabinoid use** found a correlation between binge-purge behaviors. This association was not consistent over the years.
- Regular recreational substance use other than cannabis consistently correlated with regular cannabis use.
- There was a noted increase in cannabinoid use among ED patients after legalization liberalizing legal use of cannabinoids. (Laliberte et al.)
- Other **Limitations**:
  - Studies did not differentiate between different strains or method of consumption of exogenous cannabinoids.
  - Reporting bias due to reliance on self-reports.



STUDIES THAT ADMINISTERED EXOGENOUS CANNABINOIDS

Reference	Design	Participants	Interventions	Outcomes
Gross et al. (1983)	Crossover RCT	11 adult F w/ AN	Δ9-THC vs diazepam	No significant differences in weight gain or hunger.
Andries et al. (2014)	Crossover RCT	24 adult F w/ AN	Dronabinol vs placebo	Weight gain dronabinol> placebo (p=.03)
Andries et al. (2015)	Crossover RCT	24 adult F w/ AN	Dronabinol vs placebo	No significant change in total IGF-I, bioactive IGF, or IGFBPs.
Andries et al. (2015)a	Crossover RCT	24 adult F w/ AN	Dronabinol vs placebo	Ave activity intensity was higher on dronabinol.
Avraham et al. (2017)	Pilot	9 adults w/ AN, inpatient	Δ9-THC (no controls)	Patients gained weight and their ED attitudes improved.

DISCUSSION

- The **studies administering cannabinoids** (Δ9-THC and dronabinol) found only modest, though statistically significant, differences in weight gain compared to control groups.
- In RCT, Δ9-THC didn't show a significant increase of weight, though that study issues of low tolerability doses that led to dropouts causing study to possibly be underpowered.
- Exogenous cannabinoid administration did not result in improved attitudes towards eating compared to controls.
- When using higher doses, side effects caused dropouts in already limited sample sizes. (Gross et al.)
- Large doses causing dysphoric effects did not appear to be required to get the weight gain effect.



STUDIES THAT MEASURED ENDOCANNABINOID LEVELS

Reference	Design	Participants	Interventions	Outcomes
Monteleone et al. (2005)	Cross-sectional	53 Outpatient F w/ EDs	Blood and urine collection for endocannabinoids.	fasting AEA: AN>HC ($p<.02$), BED> HC ($p<.005$) Plasma AEA ∝ 1/leptin
Monteleone et al. (2015)	Cross-sectional	21 adults in ED inpatient	Hedonic eating vs not. Blood collection.	2-AG and PEA had differing trends between AN vs HC
Piccolo et al. (2019)	Longitudinal pilot	Adults: 15 AN vs. 9 HC	Blood collection before and after meal.	HC AEA> AN AEA HC reported more hunger.
Tam et al. (2021)	2 arms: longitudinal and cross-sectional	F: 67 acute AN, 27 recovered AN, 84 HCs	Blood and hair samples collected.	Higher AEA, PEA, OEA in acute AN Phys activity ∝ SEA, PEA, OEA
Baenas et al. (2023)	Cross-sectional	113 adult F (29 HCs, 27 AN)	Blood collection and metabolic measures.	AEA: AN< HC< OB
Miranda-Olivos et al. (2023)	Cross-sectional	36 adult F: 18 AN, 18 HC	Blood measurements and f-MRI brain.	In AN, decreased NAcc–right insula and NAcc–left supp. motor area connectivity

DISCUSSION

- The **studies measuring endocannabinoid levels** were varied and innovative but only measured blood, urine, and hair endocannabinoid levels.
- Their results were inconsistent with each other, though each study had differing uncontrolled variables.
- What remained consistent was that endocannabinoid responses differed between AN participants and HCs.



CONCLUSIONS

- The studies reviewed in this paper offer **limited evidence** towards supporting the connection between endocannabinoid system derangements and AN pathophysiology.
- Similarly, limited evidence showed administering **exogenous cannabinoids at low/tolerated dosages** conferred **minimal but statistically significant increases in weight gain** in AN.
- While there is biological plausibility to a connection between the endocannabinoid system and AN treatment, given the limitations of the studies reviewed in this paper, **there is not sufficient evidence at this time to recommend cannabis as a treatment for AN.**

RECOMMENDATIONS FOR FUTURE STUDIES

- For surveys of cannabis use: Studies focusing more specifically on cannabinoid use and ask about specific types of cannabinoids are needed. Including more male and non-Caucasian race patients will make the data more generalizable.
- For administering cannabinoids: Larger study populations, with more diversity, and longer durations of follow up after administration. RCTs with matched controls to ideally differentiate from standard of care baseline. Appears that lower doses are adequate for weight gain effect in the short term.
- For endocannabinoid measurements: Larger sample sizes, more diversity with matched controls, more frequent measurements of levels to control for natural daily fluctuations of hormone levels, control for activity levels. CSF endocannabinoid levels would be an interesting addition but may be too invasive to justify.

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QUESTIONS?



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