The Influence of Cannabis and Nicotine Co-Use on Neuromaturation – A Systematic Review of Adolescent and Young Adult Studies

Supplement 1

Study Selection

A systematic review was carried out following the recommendations of The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement (1). A search strategy was designed that limited study selection to youth/adolescent animal studies or human studies with adolescent and young adult participants. PubMed and PsycInfo databases were systematically searched from August 27 through August 31, 2020. Reference sections from papers that met inclusion criteria were also reviewed for possible studies that may have otherwise been missed. Unpublished manuscripts were not considered given the variability in the quality of preprints and unpublished studies. The following Key Medical Subject Headings (MeSH) search terms were identified a priori and included "(cannabi* OR marijuana OR THC) AND (nico* OR tobacco OR cigar*) AND (cognit* OR Neuropsych* OR memory OR attention* OR executive function* OR functional brain imaging OR Diffusion tensor imaging OR Structural MRI OR MRI OR PET OR Positron Emission Tomography OR magnetic resonance imaging OR brain imaging) AND (co-use OR simultaneous OR concurrent OR polysubstance OR co-administration OR co-occurring OR combined OR concomitant OR (marijuana AND tobacco))".

Screening Review and Inclusion/Exclusion Criteria

Four authors independently reviewed titles and abstracts (MHM, NEW, RB, VGD) before determining inclusion in the review. All the titles and, when potentially appropriate, abstracts were screened based on the eligibility criteria and classified as "relevant" or "not relevant." Studies for

which eligibility criteria were unclear were read in full to determine relevancy. All authors agreed upon the final list of studies that met the *a priori* inclusion criteria:1) the study had to report on neurocognitive outcomes, structural neuroimaging (e.g., MRI, diffusion tensor imaging[DTI]), or functional neuroimaging (e.g., blood-oxygen-level-dependent signal[BOLD]) finding as an outcome measure; 2) have a user group where cannabis/cannabinoids and nicotine/tobacco are jointly considered; 3) the study had to have an age range of 13-35 or, for preclinical studies, non-adult subjects; and 4) the study had to be data-based as review articles were not included. All studies with a scientific aim of examining both cannabis and nicotine use on outcomes measures were deemed eligible based on the present selection criteria. Thus, there was no minimum level of substance use required for inclusion. If age range was not explicitly stated, corresponding authors were contacted to request age information; if no response were received and the average age and age range appeared to fit criteria and all other inclusion criteria met based on rater agreement, the study was included. Studies that only investigated the main effects of either tobacco or cannabis, studies whose primary aim was outcomes from prenatal use, major psychopathology, neurological condition, case studies, or electroencephalogram (EEG) studies were not included.

Data Extraction

The search yielded 1,107 studies, and 53 met initial criteria for further consideration (see Figure 1). Fifteen were duplicates, and 26 did not meet the inclusions/exclusion criteria. This process yielded twelve studies for the final review. Data extraction from each study included participant demographics (age, sex), sample size, cognitive, structural, and functional imaging findings, abstinence period before testing, covariates, and co-use results (see Table 1). The primary results of interest for the qualitative synthesis of cannabis and nicotine co-use were findings associated with the neurocognitive and neuroimaging outcomes.

Risk of Bias Assessment

All included studies were rated for risk of bias using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) scale (2, 3). Ratings were then combined to indicate a summary of findings based on overall quality of evidence (see Table S1). Per GRADE guidelines, outcomes based on studies are rated as high when there is great confidence that the effect is close to the true effect. Moderate reflects confidence that results are accurate, but acknowledges results may be substantially different. Low indicates the true effect may be significantly different. Very low reflects that the true effect is likely to be substantially different. In the present review, individual studies were rated as low to high quality. Outcomes of interest for this systematic review included major neurocognitive and neural health domains, with overall evidence suggesting low to high certainty in findings.

Table S1. Evidence Profile and Summary of Findings Based on GRADE Review of Studies.

# Studies	Inconsistency of Results	Indirectness of Evidence	Imprecision	Reporting Bias	Overall Certainty of Evidence
Outcome: Influence of co-use on cognition in humans					
4	Serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ Moderate
Outcome: Influence of co-use on neural health as measured by structural imaging					
1	Not serious	Not serious	Serious	Undetected	⊕⊕◯◯ Low
Outcome: Influence of co-use on functional imaging					
5	Serious	Not serious	Not serious	Undetected	⊕⊕⊕◯ Moderate
Outcome: Influence of co-use on cognition in preclinical samples					
3	Not serious	Not serious	Not serious	Undetected	⊕⊕⊕⊕ High

Supplemental References

1. Moher D, Shamseer L, Clarke M, Ghersi D, Liberati A, Petticrew M, et al. (2015): Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev*. 4:1.

2. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. (2008): GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. *BMJ*. 336:924-926.

3. Goldet G, Howick J (2013): Understanding GRADE: an introduction. *J Evid Based Med*. 6:50-54.