**Annotation guidelines for PsyNamic**

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# **1) Inclusion criteria for papers**

First step before starting the annotation: check whether the paper meets our eligibility criteria. All these three points need to be fulfilled in order to be included for annotation:

We will include all clinical studies which report on the use of psychedelic substances (see below) in human populations, this includes healthy volunteers (including recreational drug users) as well as individuals with medical conditions/disorders.

We will exclude:

-Clinical studies not using classical psychedelic substances including THC, CBD, cocaine, heroine, and similar substances.

-Animal studies and non-systematic reviews (including comments, editorials or similar article types). Of note, studies including animals and humans will be included.

-Corrigendums.

Exclude eligible abstract based on these criteria (no annotation required).

# **2) General rules on how to annotate:**

1) When annotating tokens:

A) **Always consider the context**: What is the population (P), intervention (I), control (C), and outcomes (O) of the text of interest. The models we train DO “learn”/”understand” context.

B) **Only annotate what is relevant for the study of interest**, e.g., when annotating species tokens: “In this study, we used LSD. To test the robustness of the findings, these experiments should be repeated using psilocybin in future studies.” Only LSD should be annotated (psilocybin is not part of this study).

2) There are 2 types of annotation tasks:

-**Text annotation**: The entire text is classified according to pre-specified labels.

-**Token annotation**: the relevant word or word span is annotated. Annotate all occurrences.

# **3) Additional rules on how to annotate:**

3) Include incorrect spelling/grammar if pertinent.

4) If possible, the labelled word string should not be a combination of terms with and without brackets. E.g. "oral appliance (OA) device" should result in two labelled words "oral appliance" and "OA". Another example: “Bone marrow stem cells (BMSC) transplantation”, no annotation of transplantation.

5) For token annotation: No annotation for cases in which an incorrect token was to be annotated (e.g., the Prodigy interface not allowing a separation), e.g., “we studied this therapy in multiple sclerosis(MS)”: Multiple sclerosis cannot be annotated without including the bracket (due to the Prodigy interface), i.e., do NOT annotate this. For sentence annotation: Annotate the whole sentence even if you have to include the first word of the following sentence due to the Prodigy interface, e.g., “We randomly assigned rats to willed movement training (WM):5 rats per …” Annotate everything including the 5 (since Prodigy will not able to exclude the “5” from the annotation).

6) Do NOT annotate punctuation at the end of the sentence (see above).

# **4) Data annotation**

**Text level annotation**

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| **Parameter** | **Definition and comments** |
| **Study characteristics** | |
| Study type | **Def**: The methodological classification of research based on its design, purpose, and approach.  **Selection**: select only one (the best fitting)  Levels:  •**Randomized controlled trial (RCT):** A study where individuals are randomly assigned to one of two or more groups, with one receiving a psychedelic substance and the others receiving a placebo or standard treatment, to compare outcomes directly. I.e., the study needs to check to attributes: 1) being randomized and 2) being controlled (e.g., with a placebo or an active control).  •**Cohort study:** An observational study where a defined group of people (the cohort) is followed over time to study outcomes related to an exposure to psychedelic substance(s), comparing results within the group or with a different group not exposed to the substance. In most cases, it is explicitly mentioned that this is a cohort study.  •**Real-world study:** Examines the relationship between variables (e.g., the use of a psychedelic substance and mental health outcomes) at a single point across a real-world population. This includes real-world studies on recreational drug use, survey-based studies e.g., on MDMA use among healthy adults or studies assessing emergency department visits of people ingesting MDMA.  •**Study protocol:** A protocol of a clinical trial outlining methodology of a study still to be conducted. Annotate as if the study has been conducted.  •**Systematic review and/or meta-analysis:** A comprehensive summary of all the available primary research on a specific psychedelic-related research question. Should mention the term systematic review and/or meta-analysis in the title/abstract.  •**Qualitative study:** Explores subjective experiences, perceptions, and the impact of psychedelic substances through interviews, focus groups, or content analysis. Also includes studies focusing on religion/spirituality related to psychedelic substances.  •**Case report:** A detailed report of the symptoms, signs, diagnosis, treatment, and follow-up of one individual patient/healthy participant.  •**Case series:** A collection of case reports involving patients who were given similar interventions.  •**Other**: A study not belonging to one of the above categories or not classifiable based on the provided information. A study pooling different RCTs together belongs to this category. |
| Study purpose | **Def: T**he overall purpose of the study.  **Selection:** select zero or more, i.e., a study can have more than 1 purpose such as assessing efficacy and safety.  Levels:  •Efficacy endpoints: This item should be checked if the study measures efficacy, e.g., whether a psychedelic substance improves depression or anxiety.  •Safety endpoints: This item should be checked if the study discusses potential adverse events/side effects OF A PSYCHEDELIC SUBSTANCE (Do not annotate adverse events not necessarily linked to the psychedelic, e.g., suicide in MDMA polydrug users should not be annotated as adverse events). It is not relevant whether adverse events are reported or not, e.g., a study reporting “the adverse events were mild and transient” or “no adverse events were noted” should both be checked. This also includes neurotoxicity studies like studies looking at memory impairment after long-term MDMA use. Also includes studies assessing emergency department visits of individuals consuming e.g., MDMA.  •Pharmacokinetics Examines how the body absorbs, distributes, metabolizes, and excretes the psychedelic substance. This item should be checked if body substance levels are measured on at least one time point.  •Mechanism of action: The study assesses potential mechanisms of action of the psychedelic substance. This includes neuroimaging studies (e.g., fMRI or PET scans to see how psychedelics affect brain activity and connectivity), neuropharmacology studies (e.g., how psychedelics interact with specific neurotransmitter systems, such as serotonin 5-HT2A receptors), genetic expression studies (e.g., assessing how psychedelics affect gene expression within the brain), and electrophysiological studies (e.g., measuring changes in the electrical activity of neurons in response to psychedelic substances).  •Disease model study: The study uses the psychedelic substance to induce a model psychosis (e.g., ketamine is commonly used for that).  •Demographic study: e.g., a study assessing MDMA use among a real-world population. |
| Study control | **Def**: The control type of the study.  **Selection**: select one or more.  Levels:  •Placebo  •Active control (e.g., midazolam as a control for ketamine)  •Pre-post: A study design where measurements are taken on the same subjects at two points in time: before (pre) and after (post) a psychedelic intervention.  •Other control (e.g., non-users)  •Non-controlled  •Not applicable (e.g., for systematic reviews) |
| Data type | **Def**: Whether the data are collected longitudinally or cross-sectionally.  **Selection**: select only one  Levels:  • Longitudinal short: Outcomes are measures during at least two different time points ≥ 24 hours apart but the total follow-up time is < 3 months.  • Longitudinal long: Outcomes are measures during at least two different time points ≥ 24 hours apart and the total follow-up time is ≥ 3 months.  • Cross-sectional: Outcomes are measured during one single time point (or more than one time point within < 24 hours).  • Unknown: Data type is unknown  • Not applicable (e.g., for systematic reviews or for studies pooling a variety of other studies together without providing information about data type) |
| Data collection | **Def**: The approach how the data are collected.  **Selection**: select only one  Levels:  • Retrospective: Data has been collected retrospectively (case reports are always retrospective)  • Prospective: Data has been gathered prospectively (always select prospective for study protocols)  • Unknown: Data collection unknown.  • Not applicable (e.g., for systematic reviews)  Additional information:  •Important is when the actual OUTCOME was measured, i.e., an abstract describing a patient receiving ketamine over 4 weeks, but the outcome was only measured twice within 2 hours = cross-sectional. |
| Number of participants | **Def**: The number of participants studied. Include all study participants (including the ones not receiving psychedelics).  **Selection**: select only one.  Levels:  • 1-20  • 21-40  • 41-60  • 61-80  • 81-100  • 100-199  • 200-499  • 500-999  • ≥1000  • Unknown  • Not applicable (e.g., for systematic reviews) |
| Sex of participants | **Def**: The sex of participants studied.  **Selection**: select only one.  Levels:  • Male  • Female  • Both sexes (We assume both sexes if nothing reported and ≥ 5 included subjects)  • Unknown (check this if neither the number of participants nor their sex is reported  • Not applicable (e.g., for systematic reviews) |
| Age of participants | **Def**: The age of participants studied.  **Selection**: select only one.  Levels:  • Pediatric (< 18 years old)  • Adult (≥18 years) (We assume adults if nothing reported)  • Unknown  • Not applicable (e.g., for systematic reviews) |
| **Substance(s)** | |
| Substances | **Def**: The psychedelic substance(s) studied. Of note, include enantiomers, chemical analogues, or organic substances under the respective class (e.g., Esketamine would go under Ketamine, emp-01 would go under MDMA, “magic mushrooms” would go under psilocybin).  **Selection**: select one or more.  Levels (substances:  • Ketamine (not further specified)  • S-Ketamine  • R-Ketamine  • MDMA (Ecstasy)  • LSD  • Psilocybin (or psilocin)  • Psychedelic mushrooms (as organic compound, including psychedelic truffles).  • Ayahuasca (DMT plus MAO-inhibitor, also 5-MeO-DMT plus MAO-inhibitor)  • DMT  • 5-MeO-DMT  • Mescaline  • Ibogaine  • Salvinorin A  • Combination therapy: One or more of these substances combined with any other non-psychedelic substance or any other type of therapy (e.g., electroconvulsive therapy or psychotherapy)  • Analogue (check this and the respective substance if it is not the exact substance listed above but closely related [claimed by the study authors], e.g, MDE is an analogue of MDMA 🡪 check “MDMA” and “analogue”)  • Unknown (e.g., when just mentioning psychedelics without further specification) |
| Application form | **Def:** The form of substance application.  **Selection:** select one or more.  Levels:  • Oral  • Nasal  • Intravenous  • Smoking  • Subcutaneous  • Other  • Unknown  • Not applicable (e.g., for systematic reviews) |
| Regimen | **Def:** What therapeutic regimen did the study use?  **Selection:** select zero or more (a study could have both single and multiple applications potentially)  Levels:  • Microdosing (as defined by the study authors)  • Application at multiple times points (e.g., LSD given on at least 2 time points or ketamine weekly for 3 months)  • Single dose (substance is only applied once, also counts as single dose if substance is applied more than once over up to 1 hour)  • Unknown (e.g., in a cross-sectional study on psychedelic use among the general population and it is not clear how many times the participants consumed psychedelic substances)  Additional information:  • Could potentially be annotated for systematic reviews.  • PER substance (i.e. once DMT and once ketamine in the same study is single dose). |
| Setting | **Def**: The setting in which the psychedelic substance is applied.  **Selection**: select one or more.  Levels:  •Clinical: the substance is applied in a clinical setting, e.g., a room of a clinic (this will be the large majority).  •Naturalistic: the substance is applied in a naturalistic setting, e.g., within a traditional ayahuasca ceremony in nature.  •Party setting  •Other setting  •Unknown: Select only if it is very unclear from the context.  •Not applicable (e.g., for most systematic reviews, except systematic reviews which look at naturalistic settings of psychedelic substances)  Additional information  •Select clinical if no particular setting is mentioned. Select unknown only if it is very unclear from the context in which setting the substance was applied. |
| Substance naivety | **Def:** Whether the study participants are naïve to psychedelic substances. A study could involve both naïve and experienced users.  **Selection:** select one or more.  Levels:  • Substance-naïve participants  • Substance-non-naïve participants  • Unknown (this should also be checked for studies where it is not clear whether study participants have consumed such substances, e.g., in surveys on drug use).  • Not applicable (e.g., for systematic reviews) |
| **Clinical measures** | |
| Condition | **Def**: The overarching conditions of the study participants under investigation.  **Selection**: select zero or more.  Levels:  • Psychiatric condition (e.g., PTSD, depression, anxiety disorder, addiction such as smoking addiction. Check this and the corresponding disorder below e.g, in case of depression: check both “psychiatric condition” and “depression”.).  • Depression  • Anxiety  • Post-traumatic stress disorder (PTSD)  • Alcoholism  • Other addictions (includes addictions like smoking and others)  • Anorexia  • Alzheimer’s disease  • Non-Alzheimer dementia  • Substance abuse (e.g., when the study participants are polydrug users/abusers of certain substances and the effect of one or more psychedelics is studied on an outcome DIFFERENT to treating the addiction to drugs)  • (Chronic) pain (e.g., cluster headache)  • Palliative setting (end of life)  • Recreational drug use  • Healthy participants (will also include larger population-based studies for e.g., recreational drug use where we can assume that most participants do not have major medical conditions. Is commonly checked together with recreational drug use)  Additional information:  •Of note, this only applies to the condition being treated, i.e., if a study assesses whether chronic recreational MDMA use is causing depression, do NOT annotate depression as condition. |
| Outcomes | **Def:** Does the study measure/use/report certain specified outcomes?  **Selection**: select zero or more.  Levels:  •The ability to drive a car  •Suicide (incl. suicidal ideation or related questionnaires)  •Functional MRI (fMRI)  •MRI (e.g., arterial spin labelling. Note: check this and the fMRI box if fMRI has been used)  •PET, SPECT (or similar imaging approaches)  •Physiological functions (e.g., heart rate, blood pressure, body temperature, pupillary diameter)  •Electroencephalography (EEG/MEG), Of note: includes MEG  •Mental functions (physiological mental functions, e.g., ability to recognize faces, form language, mindfulness, memory)  •Psychedelic experience, e.g., mystical experience questionnaire or visual scale for psychedelic experience.  •Soluble biomarker (e.g., proteins in blood or CSF or also in non-liquid body compartments such as hair)  •Surveys (e.g., questionnaires about how commonly psychedelic substances are consumed in a recreational setting)  •Interviews (person-to-person)  •Neurotoxicity (measuring biological neurotoxicity more or less directly, e.g., MR-spectroscopy to measure toxicity metabolites or cell assays of patients. This does NOT include indirect measures of neurotoxicity such as adverse events of MDMA use)  •Emergency department visits (e.g., studies assessing reasons for emergency department visits of users of psychedelic substances). |
| Clinical trial phase | **Def:** stages in which scientists conduct experiments with a therapeutic intervention to obtain sufficient evidence for a process considered effective as a medical treatment (phase 0-4), i.e., considering efficacy and/or safety of the therapeutic intervention. NOTE: Medical devices and behavioural therapies (like meditation or psychotherapy) do not have phases.  **Selection:** select zero or more (could be a phase 1/2 for example).  Levels:  •Phase 1  •Phase 2  •Phase 3  •Phase 4  •Unknown: fulfilling above definition but phase not explicitly (or implicitly) mentioned.  •Not applicable: Not fulfilling the above definition, e.g., an fMRI study assessing the changes upon lsd or a survey among MDMA users or a systematic review.  Additional information:  •Of note: the exact phase is rarely being reported, i.e., most studies will either be unknown or not applicable. |
| Study conclusions | **Def:** The overarching finding of the study. Only applies to studies testing a therapeutic impact of psychedelic substances on medical conditions (e.g., psychiatric conditions, headache) or on overall quality of life (e.g., increasing well-being in healthy volunteers via increased mindfulness).  **Selection:** select only one.  Levels:  • Positive (e.g., if a study reports: “lsd might decrease suicidal ideation in depression”)  • Negative (e.g., if a study reports: “ketamine worsened neuropathic pain in patients”)  • Neutral (e.g., if a study reports: “we did not observe an effect of MDMA on avoidance behaviour”)  • Mixed: both negative and positive conclusion  • Unknown: no conclusion  • Not applicable (e.g., for a study assessing fMRI changes of lsd or for a study protocol)  Additional information:  •Information is mostly found in the last 2 – 3 sentences of the abstract. |

**Token level annotation**

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| **Parameter** | **Definition and comments** | **Examples** |
| Application area | **Def**: The condition or disease of interest studied under the impact of the psychedelic substance in the present paper.  Additional information:  •Our working definition for the **Application** is any "state labeled as diseases by virtue of consensus on prevalent sociocultural and medical values". It has to have "clearly identifiable diagnostic features and disease progression, and response to specific treatment."  •As a general guideline, annotated entities should be conditions that have an ICD-11 code.  •**Annotate only in title and/or the introductory part of the abstract, i.e., when the problem or objective of the study is discussed (including abbreviations)**. Do NOT annotate outcomes, such as “the Hamilton Depression Scale” should not be annotated. Similarly, “antisuicidal response” should not be annotated. Or: “among participants, depression was reduced”, do NOT annotate depression.  •Do not annotate over brackets: “…or bipolar disorder (BD) type 1 and type 2”, only bipolar disorder and BD should be annotated as two entities.  •Do NOT annotate very generic concepts like “psychiatric condition”  •Annotate sweeping statements like “…with major depressive and bipolar disorder” as one entity.  •Annotate the reasonably necessary string, e.g., “active suicidal ideation”, active suicidal ideation should be annotated. However, adjectives could be annotated, “Depressed patients”, annotate Depressed but not patients. “depressive symptoms” should both be annotated (also symptoms of depression). In “refractory anxiety disorder”, annotate the entire string.  •Further defining characteristics should be included: Acute/Chronic; Active/Inactive; Mild/Moderate/Severe; End Stage/Early Stage; Drug-resistant; Total/Partial; Intermittent/Relapsing and others. Similarly, "Post-stroke" should be annotated instead of only "stroke" because it refers to the phase after the acute stroke.  •Annotate abbreviations. Abbreviations should be annotated separately. For instance,“Huntington disease (HD)”should be separated into two annotations: “Huntington disease” and “HD.  •Of note, in “Managing dissociative symptoms following esketamine”, dissociative symptoms are NOT the treatment target but the target of the study and should NOT be annotated (context is relevant).  •Cigarette addiction is a disorder but not smoking cessation.  •Can be empty, i.e., no annotation per abstract. |  |
| Dosage | **Def:** The applied dosage(s) of the psychedelic substance(s) in the present study.  •Only annotate for studies testing not more than 1 psychedelic substance (e.g., do not annotate in a study testing lsd and psilocybin, BUT annotate in a study testing psilocybin against midazolam)  •Do NOT annotate doses of other substances or of the psychedelic substance in other studies (e.g, mentioned by referencing other studies)  •Do not annotate concentrations of solutions but dosages, i.e., do NOT annotate 500mg/10 ml, but annotate 2mg/kg.  •Annotate the number and the corresponding unit.  •Annotate all reported doses for the respective psychedelic substance.  •Annotate only for single substance studies (i.e., do not annotate in abstracts which report the dosage of two or more psychedelic substances).  •Annotate the number including the unit.  •Annotate also the term “between” if pertinent, similarly “or” and “and” should be annotated. Do not annotate “per device”.  •Annotate also relative dosages (e.g., 1 mg/kg), do not annotate the terms “bw” or “body weight” or similar if pertinent  •Do NOT annotate doses measured in e.g., plasma (like 4 mg/ml)  •Can be empty, i.e, no annotation per abstract. | Lsd was used in this study (100-150 mg).  In our study, between 15 and 20 mg of psilocybin was used.  Here, 0.4 mg/kg bodyweight DMT was used.  The patient received 56 or 84 mg ketamime.  The patient received 40 mg or 120 mg MDMA |

Regular expressions for NCTS to identify linked registries.