**Dextromethorphan Beyond the Cough: Exploring Its Psychedelic Potential – a Systematic Review**

**Running Title: Dextromethorphan as a Psychedelic: Systematic Review**

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## Supplemental Table 1. Domain-Level Risk-of-Bias Assessment of Individual Studies

| Study | Randomization process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall (result-level) |
|---|---|---|---|---|---|---|
| **Barrett et al. (2018) [22]** | **Low Risk** — Patient population from Carbonaro et al. (2018). Within subject crossover; adequate washout | **Low risk** — Double-blind crossover, with masking of participants and staff, and no obvious deviations reported. | **High Risk**— High-dose cognitive tasks often not completed due to drug effects (outcome-related missingness). | **Low risk** — Cognitive/behavioural outcomes measured under controlled, blinded conditions. | **Some concerns**— Multiple cognitive outcomes; primary and analysis plan not clearly prespecified. | **High risk** |
| **Carbonaro et al. (2018) [23]** | **Low Risk**— Randomized crossover, balanced within-subject crossover | **Low risk** — Double-blind, controlled; no obvious deviations or protocol violations. | **Low risk** — Sample appears retained; no missing data reported. | **Some concerns** — Outcome is objective experience (self-report), which is inherently more susceptible to bias (even if blinded). | **Some Concerns** No registered analysis plan described; risk of selective reporting cannot be excluded. Also did not publish full findings in initial study | **Some concerns** |
| **Carbonaro et al. (2020) [35]** | **Low Risk**— Patient population from Carbonaro et al. (2018) Same concerns about randomization description. | **Low risk** — Interventions blinded, well-controlled crossover. | **Some concerns**— Some missing subject ratings with unclear rationale | **Some concerns** — Motivation/self-report outcomes; though blinded, subjective measures remain more prone to bias than objective measures. | **Some Concerns** — no clear pre-specified analysis plan or selective-reporting safeguards stated. Also reporting data from previously published study | **Some concerns** |
| **Carter et al. (2013) [37]** | **Some concerns / Unclear** — Randomized, but allocation generation/concealment not described. | **Low risk** — Double-blind crossover; no deviations or protocol violations reported. | **Some concerns** — Incomplete data at highest dextromethorphan doses; analyses rely on common or penultimate doses | **Low risk** — Cognitive outcomes measured under blinded conditions; objective/standardized assessments. | **Some concerns** — no explicit protocol or pre-registration described; selective reporting cannot be excluded. | **Some concerns** |
| **Mathai et al. (2023) [39]** | **Low risk**— Randomized ascending dose, but no detail on allocation concealment or sequence generation. Secondary analysis | **Low risk** — Double-blind crossover, with masking; no reported deviations. | **Low risk** — Full retention, outcomes reported. | **Some concerns** — Subjective outcome measures (hallucinogenic effects), even under blinding, are prone to measurement bias. | **Some concerns** No explicit pre-specified analysis plan or selective-reporting safeguards described. Secondary analysis | **Some concerns** |
| **Nelson et al. (1997) [36]** | **Low risk** — | **Low risk** — Double-blind, controlled; no | **Some concerns** — More withdrawals due to side effects; | **Some concern** Pain outcomes may include subjective assessments; | **High Risk** No reporting of dose-response for outcomes. | **High Risk** |

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| | Randomized, double-blind, two-period crossover with balanced order. | reported deviations from intended intervention. | dropout related to tolerability. | even if blinded, there's inherent risk of bias. | No mention of pre-specified analysis plan or selective reporting procedures. | |
| **Perry et al. (2015) [38]** | **Low risk** — Randomized, double-blind, two-period crossover with balanced order. | **Low risk** — Double-blind, interventions masked; no deviations noted. | **Low risk** — No dropouts; data complete. | **Low risk** — Objective driving or simulator measures, and standardized ratings, with blinded raters. | **Some concerns / Unclear** Absent pre-registered plan/reporting protocol; selective reporting cannot be ruled out. | **Some concerns** |
| **Reissig et al. (2012) [21]** | **Some concerns / Unclear** — Randomized ascending dose, but no detail on allocation concealment or sequence generation. | **Low risk** — Double-blind crossover, with masking; no reported deviations. | **Some concerns** — Highest dextromethorphan doses varied with tolerability, with some incomplete or zero-scored measures. | **Low risk** — Validated subjective and psychomotor measures at fixed times under blinding. | **Some concerns** Many outcomes from a single experiment without a clearly prespecified primary or preregistration. | **Some concerns** |