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Brief Communication

Craving Reduction and Smoking Outcomes in Psilocybin-Assisted and Standard Cessation Care

Lisbeth Strandberg, Thiago Fernandes, Irina I. Shoshina, Natanael A. Santos, Nora Saether

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Craving reduction and smoking outcomes in psilocybin-assisted and standard cessation care

Running Head: Smoking Profiles and Treatment Trajectories

Lisbeth Strandberg[1], Thiago P. Fernandes [2,5], Irina I. Shoshina [3,4], Natanael A. Santos [2,5], Nora Saether[6]

[1]Department of Psychology, Masaryk University, Brno, Czech Republic.
[2]Perception, Neuroscience, and Behaviour, Federal University of Paraiba, Brazil.
[3]Faculty of Psychology, St. Petersburg State University, Saint Petersburg, Russia.
[4]Institute of Computer Science, MISIS University of Science and Technology, Moscow, Russia.
[5]Department of Psychology, Federal University of Paraiba, João Pessoa, Brazil.
[6]Department of Health, University of South-Eastern Norway, Porsgrunn, Norway.

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Abstract

Objective: Smoking cessation outcomes are heterogeneous, and factors associated with these differences are not fully understood. We examined longitudinal smoking trajectories across distinct smoking profiles and evaluated whether early craving and affective symptom changes were associated with verified abstinence.

Methods: Participants in this observational cohort were classified as dependence-predominant or affective-predominant using measures of smoking severity and affective symptoms. Abstinence was defined as 7-day self-reported abstinence verified by exhaled CO <8 ppm.

Results: Psilocybin-assisted care was associated with greater smoking reduction at week 12 (β = 5.56, 95% CI 2.18–8.94, *p* = .001) and greater urge reductions at T1 (β = -3.26, 95% CI -5.31 to -1.21, *p* = .002) and T2 (β = -2.74, 95% CI -4.85 to -0.63, *p* = .011). Psilocybin-assisted care was not associated with abstinence after adjustment (OR = 1.82, 95% CI 0.68-4.86, *p* = .233). Early craving reduction was associated with the outcome (OR = 1.54, 95% CI 1.17-2.03, *p* = .002).

Conclusions: Distinct patterns of change were observed across treatment pathways and smoking profiles, while early craving reduction was associated with abstinence. Future studies may clarify whether these profiles and early trajectories could help inform treatment stratification and individualized cessation strategies.

Keywords: Tobacco Use Disorder; Psilocybin; Smoking Cessation; Craving

1. Introduction

Tobacco use disorder remains difficult to treat despite established behavioral and pharmacological interventions. Although many smokers achieve meaningful reductions in cigarette consumption, sustained abstinence remains challenging and treatment response varies substantially across individuals [1,2]. One proposed source of heterogeneity is the relative contribution of dependence-related versus affective symptoms, which may shape smoking behavior and cessation outcomes [3].

Psilocybin-assisted treatment has emerged as a promising approach for smoking cessation and has attracted growing interest across addictive and psychiatric conditions [4-6]. However, less is known about the early clinical changes associated with treatment response, particularly whether reductions in craving and affective symptoms are similarly associated with later abstinence. Determining whether reductions in craving or affective symptoms are more closely linked to cessation may have prognostic value and inform treatment strategies [7,8].

Here, we examined longitudinal patterns of smoking reduction across cessation approaches and evaluated whether early changes in craving and affective symptoms were associated with verified abstinence at 12 weeks.

2. Methods

2.1 Study design and participants

This observational cohort study included 115 adults identified through the clinical records of a smoking cessation clinic. Participants were predominantly male (54.8%) and had a mean age of 42.17 ± 8.42 years and a mean smoking duration of 20.66 ± 9.34 years. All participants met DSM-5 criteria for tobacco use disorder. Eligibility criteria were age ≥ 18 years, daily smoking, motivation to quit, and availability for 12-week

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follow-up. Standardized clinical assessments were conducted by the smoking cessation team. Exclusion criteria included psychotic disorders, psilocybin contraindications, and clinically significant medical, neurological, or neuropsychiatric conditions affecting participation, safety, or assessment [9-11]. Participants were informed of the potential benefits and risks of both approaches. Treatment selection was non-randomized and based on clinical eligibility, team recommendation, and participant preference. Psilocybin administration was clinically monitored.

2.2 Smoking profile classification

Baseline smoking profiles were derived from standardized composite scores representing dependence (CPD, FTND, QSU, and MNWS) and affective symptoms (HAM-D, HAM-A, PSS, and ISI). To calculate these scores, all measures were standardized to z-scores using the mean and standard deviation of the whole sample, followed by equal-weight averaging within each domain. Individual smoking profiles were assigned according to the relative predominance of the dependence and affective composite scores, and classification stability was assessed using bootstrap resampling. The cohort was subsequently classified into four groups according to treatment pathway and smoking profile: standard care/dependence-predominant (n = 43), standard care/affective-predominant (n = 39), psilocybin/dependence-predominant (n = 20), and psilocybin/affective-predominant (n = 13).

2.3 Smoking-cessation approaches

Participants were followed for 12 weeks with assessments at baseline (T0), week 4 (T1), and week 12 (T2). Both groups received the same weekly structured smoking cessation counselling throughout follow-up. Standard care comprised guideline-based pharmacotherapy (nicotine replacement therapy, bupropion, or varenicline). Psilocybin-assisted care comprised a single supervised oral psilocybin session (approximately 25 mg) administered after baseline assessment, preceded by two preparation sessions and followed by one integration session. Pharmacotherapy was not used in the psilocybin-assisted group. Smoking cessation support continued through T2 for both groups.

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2.4 Outcomes

The primary outcome was smoking reduction at T2, calculated as the percentage decrease in daily cigarette consumption from T0. Abstinence at T2 was defined as 7-day self-reported abstinence verified by expired CO <8 ppm. Secondary outcomes included longitudinal changes in smoking urges (QSU), expired CO, and cotinine. Associations of T0-to-T1 changes in craving and affective symptoms with abstinence at T2 were also evaluated.

2.5 Statistical analysis

Generalized estimating equations (GEE) examined smoking reduction over time, as well as longitudinal changes in smoking urges (QSU), expired carbon monoxide (CO), and cotinine, including the main effects of time, treatment condition, smoking profile, and their interactions. Regression models examined factors associated with smoking reduction and verified abstinence at T2. Linear regression was used for smoking reduction, whereas logistic regression examined the associations of early changes in craving and affective symptoms with verified abstinence. Results are presented as β coefficients or odds ratios (OR) with 95% confidence intervals. Statistical significance was set at two-sided $p < .05$, with Bonferroni correction and FDR confirmation.

3. Results

3.1 Sample Characteristics

Dependence-predominant groups showed higher baseline smoking intensity, whereas affective-predominant groups showed higher affective symptoms (Table 1).

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Table 1. Participant characteristics and smoking-related outcomes across treatment groups and study time points. Values are presented as mean ± SD unless otherwise specified.

Variable	Standard care (Dependence, n = 43)			Standard care (Affective, n = 39)			Psilocybin-assisted (Dependence, n = 20)			Psilocybin-assisted (Affective, n = 13)		
	T0	T1	T2	T0	T1	T2	T0	T1	T2	T0	T1	T2
Age (M ± SD)	43.47 ± 8.82	-	-	41.45 ± 8.32	-	-	40.02±8.07	-	-	43.38±7.90	-	-
Sex (M/F)	26/17	-	-	22/17	-	-	9/11	-	-	6/7	-	-
Years smoking (M ± SD)	22.01±9.28	-	-	19.96 ± 9.52	-	-	19.36±8.56	-	-	20.30±10.68	-	-
CPD (M ± SD)	21.49±4.35	18.18 ± 4.42	16.14±4.70	15.21 ± 3.43	13.12±3.79	11.30±4.28	20.75±3.95	16.80±4.10	14.30±4.24	14.70±3.43	11.90±4.18	10.20±4.32
FTND (M ± SD)	6.70±1.33	6.64 ± 1.35	6.32±1.38	4.92 ± 1.21	4.76±1.28	4.58±1.31	6.84±1.43	6.41±1.36	5.89±1.52	4.52±1.87	4.29±1.94	3.98±1.88
QSU (M ± SD)	54.39±3.14	47.82 ± 4.87	45.96±4.92	47.06 ± 5.50	40.88±6.21	41.20±6.08	55.60±4.84	44.78±5.10	42.64±5.49	46.39±4.97	38.12±6.03	38.74±5.82
HAM-D (M ± SD)	5.72±1.64	5.58 ± 1.80	5.33±1.99	12.33 ± 2.99	11.42±3.19	11.63±3.41	5.91±1.91	5.03±2.09	5.18±2.16	12.19±3.23	10.74±3.27	10.51±3.24
HAM-A (M ± SD)	5.62±1.93	5.31 ± 1.80	5.44±1.96	11.74 ± 2.50	10.96±2.46	11.08±2.58	6.55±1.73	5.82±1.97	5.67±2.14	10.79±2.30	9.18±2.45	9.42±2.40
MNWS (M ± SD)	11.8±4.5	12.6 ± 4.9	10.7±4.6	8.9 ± 3.8	9.8±4.2	8.7±4.0	12.1±4.6	12.9±5.1	8.8±4.1	9.2±4.0	10.1±4.4	7.9±3.7
PSS (M ± SD)	14.18±4.07	13.41 ± 4.36	13.56±4.18	22.74 ± 4.83	21.37±5.06	20.91±4.71	14.57±3.94	12.96±4.28	12.18±4.11	23.09±4.68	19.84±5.22	18.63±4.93
ISI (M ± SD)	7.24±3.18	6.58 ± 3.37	6.73±3.09	13.41 ± 3.63	12.69±3.92	12.86±3.74	7.47±3.27	6.36±3.11	6.52±3.41	13.88±3.57	11.27±3.95	10.94±3.81
CO, ppm (M ± SD)	16.82±5.02	13.76 ± 4.63	7.68±2.84	13.21 ± 4.31	10.74±3.86	7.42±2.71	16.35±4.92	14.18±4.70	6.89±2.66	12.87±4.11	10.96±3.91	6.57±2.48
Cotinine, ng/mL (M ± SD)	248.6±91.4	218.9 ± 87.2	187.4±80.6	182.4 ± 75.2	157.6±70.8	139.8±65.9	241.7±88.2	214.5±82.6	169.8±72.4	176.2±71.8	157.9±67.5	119.6±59.8
Smoking reduction (%, M ± SD)	-	15.4 ± 9.8	24.9±12.8	-	13.7±10.7	25.7±14.1	-	19.0±11.5	31.1±12.2	-	19.0±12.9	30.6±14.7

Note: Data are presented as mean ± standard deviation (SD), except sex (male/female). T0 = baseline; T1 = week 4; T2 = week 12. CPD = cigarettes per day; FTND = Fagerström Test for Nicotine Dependence; QSU = Questionnaire of Smoking Urges; HAM-D = Hamilton Depression Rating Scale; HAM-A = Hamilton Anxiety Rating Scale; MNWS = Minnesota Nicotine Withdrawal Scale; PSS = Perceived Stress Scale; ISI = Insomnia Severity Index; CO = carbon monoxide;. Smoking reduction is expressed as the percentage reduction in cigarettes smoked per day relative to baseline.

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3.2 Longitudinal Changes in Exhaled Carbon Monoxide

Exhaled CO decreased significantly over time, with reductions observed across all groups at T1 (β = -2.78, 95% CI -3.45 to -2.11, p < .001) and T2 (β = -7.55, 95% CI -8.30 to -6.79, p < .001). Psilocybin-assisted care was not associated with additional reductions at T1 (time × care pathway: β = 0.71, 95% CI -0.31 to 1.73, p = .171) or T2 (β = -0.67, 95% CI -1.73 to 0.39, p = .216). Mean CO decreased from 16.35 to 6.89 and 12.87 to 6.57 ppm in the psilocybin-assisted dependence and affective groups, compared with 16.82 to 7.68 and 13.21 to 7.42 ppm under standard care (Fig. 1A).

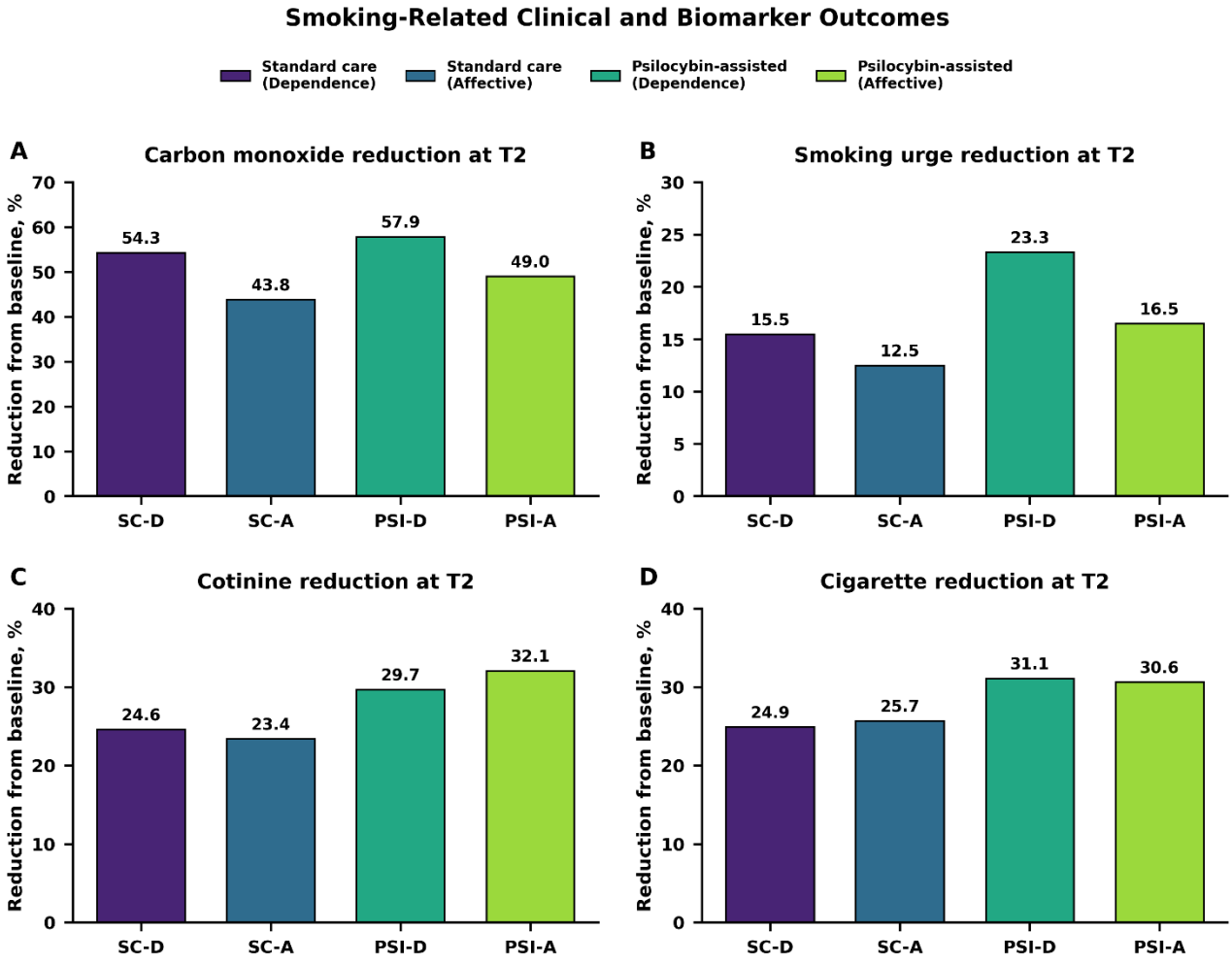


Fig 1. Smoking-related clinical and biomarker outcomes according to treatment condition and baseline smoking profile. (A) Percentage reduction in exhaled carbon monoxide (CO) from baseline to the final follow-up (T2). (B) Percentage reduction in smoking urges, assessed using the Questionnaire on Smoking Urges (QSU), from baseline to T2. (C) Percentage reduction in

cotinine concentrations from baseline to T2. (D) Percentage reduction in cigarette consumption (cigarettes/day) from baseline to T2. Overall, psilocybin treatment was associated with larger reductions in smoking-related outcomes than standard care, although the magnitude of improvement varied across outcome domains and baseline smoking profiles. **Note:** CO, exhaled carbon monoxide; QSU, Questionnaire on Smoking Urges; SC-D, standard care (dependence-predominant profile); SC-A, standard care (affective-predominant profile); PSI-D, psilocybin treatment (dependence-predominant profile); PSI-A, psilocybin treatment (affective-predominant profile); T2, final follow-up.

3.3 Longitudinal Changes in Smoking Urges

QSU scores decreased significantly over time, with lower scores at T1 (β = -6.48, 95% CI -7.34 to -5.62, p < .001) and T2 (β = -7.92, 95% CI -8.84 to -7.00, p < .001) relative to baseline. Reductions were greater under psilocybin-assisted care at T1 (β = -3.26, 95% CI -5.31 to -1.21, p = .002) and T2 (β = -2.74, 95% CI -4.85 to -0.63, p = .011), indicating greater decreases in smoking urges throughout follow-up compared with standard care (Fig. 1B).

3.4 Smoking Reduction at T2

Cotinine declined from T0 to T2 across groups (β = -49.8, 95% CI -63.5 to -36.1, *p* < .001), without a significant difference between care pathways (β = -18.9, 95% CI -42.7 to 4.9, *p* = .120; Fig. 1C). Mean smoking reduction at T2 was 24.9% and 25.7% in the standard-care groups versus 31.1% and 30.6% in the corresponding psilocybin-assisted groups. Psilocybin-assisted care was associated with 5.56 percentage points greater reduction (95% CI 2.18 to 8.94, *p* = .001), whereas smoking profile was not (β = 0.18, 95% CI -3.84 to 4.20, *p* = .931) (Fig. 1D).

3.5 Factors Associated with Smoking Abstinence

Adjusted logistic regression showed that greater reductions in smoking urges between T0 and T1 were associated with higher odds of verified abstinence at T2 (OR = 1.54, 95% CI 1.17-2.03, p = .002). Changes in affective symptoms were not associated with abstinence (OR = 1.06, 95% CI 0.70-1.61, p = .772). Psilocybin-assisted care (OR = 1.82, 95% CI 0.68-4.86, p = .233) and smoking profile (OR = 1.18, 95% CI 0.41-3.42,

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p = .759) were not independently associated with abstinence. The final model demonstrated good discriminative performance (AUC = 0.78, 95% CI 0.69-0.87).

4. Discussion

In this 12-week observational study, smoking reduction was observed in both treatment pathways, although greater reductions in cigarette consumption were associated with psilocybin-assisted care over follow-up. Dependence- and affective-predominant participants displayed partially distinct trajectories across smoking-related measures, although baseline smoking profile was not associated with abstinence. Reductions in craving between T0 and T1 were associated with biochemically verified abstinence at T2, whereas changes in affective symptoms were not. Together, these findings suggest that reductions in craving between T0 and T1 may be associated with subsequent smoking cessation outcomes.

Previous psilocybin-assisted smoking cessation studies have focused primarily on feasibility, safety, and clinical outcomes, with limited examination of processes associated with treatment response [4-6]. These results indicate that the smoking profiles captured differences in baseline clinical presentation but did not distinguish the likelihood of subsequent abstinence [12,13]. Psilocybin-assisted care was associated with greater reductions in smoking urges and cigarette consumption, although not with additional cotinine reductions or independently higher odds of verified abstinence. Early craving reduction, rather than changes in affective symptoms, was associated with subsequent abstinence, consistent with its potential relevance as an early indicator of smoking cessation outcomes [2,3,14].

The divergence between self-reported cigarette reduction and biochemical measures also warrants attention. Although psilocybin-assisted care was associated with greater reductions in cigarette consumption, corresponding differences in CO and cotinine were not statistically supported. This pattern may reflect differences in measurement sensitivity, exposure timing, or unmeasured sources of nicotine and reinforces the need for cautious interpretation of treatment-specific associations.

Several limitations should be considered, including the non-randomized design and modest subgroup sizes, which limit conclusions about the durability of acute

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changes and their relationship with longer-term outcomes. However, abstinence was biochemically verified rather than based on self-report alone. Other unassessed participant- and treatment-related factors may also have contributed to the observed differences. Accordingly, the findings characterize response patterns within this population rather than definitive treatment-specific responses or smoking phenotypes.

Overall, smoking reduction may follow different longitudinal trajectories across clinical profiles and treatment approaches, while early craving reduction may provide clinically relevant information about subsequent abstinence.

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Data statement: The data analyzed during the current study are available from the corresponding author on reasonable request.

Ethical statements: This study adhered to the principles of the Declaration of Helsinki for research involving human participants and received ethical clearance from the IRB of the participating institution (EKV-2024-109). All participants provided written informed consent before inclusion.

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Data curation, Visualization, Formal analysis, Writing - original draft. All authors reviewed and approved the final manuscript.

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