



What goes up must comedown: prevalence rates, characteristics, and coping strategies concerning MDMA aftereffects

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Abstract

Rationale MDMA is increasingly being studied for therapeutic applications, yet the prevalence and characteristics of post-acute negative effects remain debated.

Objectives We aimed to characterize MDMA's post-acute negative effects, including prevalence and symptom profile among recreational users. Given preclinical work and limited human evidence suggesting that certain supplements and antidepressants may mitigate MDMA's negative effects, we also assessed the use of these substances as coping strategies.

Methods We conducted a cross-sectional online survey of 497 MDMA-experienced participants recruited from Prolific. The survey assessed post-acute negative effects prevalence, timing, and duration; post-acute side effects; emotional changes, suicidal ideation; and intentional use of supplements or antidepressants to manage symptoms. We compared characteristics of post-acute side effects between MDMA users who self-reported ever experiencing a negative post-acute MDMA experience (colloquially known as a 'comedown') and those who did not.

Results 74.5% of participants reported experiencing a period of post-acute negative effects at least once, with onset occurring approximately 24 hours post-ingestion and lasting an average of 40 hours. The most common symptoms were fatigue (88.1%), difficulty concentrating (85.7%), restlessness (82.9%), and headache (79.7%). 14.6% of post-acute negative effects experiencers endorsed passive suicidal ideation and 6.2% endorsed active suicidal ideation. Regarding coping strategies, 30.3% reported using supplements (most commonly N-acetyl-cysteine, acetyl-L-carnitine, and magnesium) and 5.1% reported using antidepressants, with moderate perceived helpfulness.

Conclusions Post-acute negative effects of MDMA appear prevalent among recreational users in a cross-sectional sample, characterized by fatigue, negative affect, and elevated suicidal ideation. These findings highlight post-acute risks that warrant further investigation.

Keywords MDMA · Aftereffects · Mood

Introduction

3,4-Methylenedioxymethamphetamine (MDMA) is increasingly being studied for its potential therapeutic benefits, particularly as an adjunct to psychotherapy in the treatment of posttraumatic stress disorder (PTSD; for a review see, Colcott et al. 2024). Early clinical trials suggest that

MDMA-assisted therapy may reduce PTSD symptoms, resulting in a growing interest in its clinical applications (Mitchell et al. 2021, 2023; Mithoefer et al. 2011, 2018). As these interventions continue to scale and seek federal approval, it is important to better understand both their benefits and associated risks across acute, post-acute, and long-term effects.

Post-acute risks associated with MDMA have been reported in both preclinical and clinical research. In animal models, MDMA post-acute risks include neurotoxicity, marked by depleted 5-HT terminals (Schmidt 1987; Shankaran et al. 1999) following a single subcutaneous injection of MDMA, and degeneration of 5-HT axon terminals after repeated, high doses (20 mg/kg, s.c., twice daily for 4 days; O'Hearn et al. 1988). In humans, post-acute and long-term

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cognitive deficits, such as memory or executive functioning impairments (Doss et al. 2018), have been reported, and negative affective responses like depressed mood or heightened anxiety may also occur in the days following consumption (Curran and Travill 1997; Humbert-Droz et al. 2026; Liechti et al. 2001; Parrott 2013; Parrott and Lasky 1998; Verheyden et al. 2003; Vizeli and Liechti 2017; Vollenweider et al. 1998). These findings raise important questions about the clinical relevance and extent of post-acute effects in controlled studies compared to recreational use.

Recreational accounts of MDMA use often refer to a “midweek low,” “Blue Mondays,” or “Suicide Tuesdays.” These terms describe a period of low or negative affect after the acute effects of MDMA have worn off (Sessa et al. 2019). However, the prevalence, severity, and even the existence of such effects remain debated, with concerns that certain confounding factors such as poor sleep, fatigue, hydration, and polysubstance use may underlie the comedown (Blankers et al. 2025; Scott et al. 2013; Sessa et al. 2022). Mixed empirical evidence highlights the need to examine anecdotal and scientific findings to better understand the phenomenon.

Existing work on MDMA's negative post-acute effects

Empirical work of recreational MDMA use suggests that post-acute negative effects are prevalent and marked by low mood in the days following use (Curran and Travill 1997; Parrott and Lasky 1998; Verheyden et al. 2003). A study involving ecological daily assessment to longitudinally assess the European nightlife scene found a significant drop in mental well-being in the three days following ecstasy/MDMA use, controlling for co-substance use, demographics, harm reduction strategies, depression, anxiety, and sleep quality (Blankers et al. 2025).

Additionally, some laboratory MDMA studies have found similar outcomes. In a double-blind placebo-controlled study of healthy volunteers, Vollenweider et al. (1998) reported that a third of healthy participants experienced “brooding,” as well as difficulty concentrating, insomnia, restlessness, and fatigue 24 h post-MDMA. Liechti et al. (2001) and Vizeli and Liechti (2017) reported similar results in trials of healthy volunteers. Conversely, other work suggests that MDMA's post-acute negative effects either do not exist or may be due to non-pharmacological factors. Two studies involving laboratory MDMA administration observed no mood alterations in the days following use: a double-blind, placebo-controlled, within-subject design in 25 healthy, MDMA-experienced volunteers given 100 mg MDMA versus placebo, with subacute mood assessments conducted 3 days post-dose (Borissova et al. 2021); and an

open-label study in individuals with alcohol use disorder assessed mood daily for 7 days after each of two MDMA-assisted therapy sessions (Sessa et al. 2022).

Together, these studies indicate that more work considering MDMA's post-acute negative effects is needed, with the aforementioned work featuring different methodological strengths and weaknesses. Although Sessa et al. (2022) did not find decreases in mood in the 1–7 days post-MDMA (leading to a title claiming “No Evidence of Affect Drop After Taking Clinical MDMA”) they did not measure baseline mood, making it impossible to tell whether mood did or did not shift after MDMA (Flameling et al. 2022). Borissova and colleagues (2021) measured post-acute mood changes in healthy volunteers using the Beck Depression Inventory (Beck et al. 1996), which could have presented potential floor effects, with limited room for mood to decline further. Additionally, most work on the MDMA's post-acute negative effects does not assess post-acute symptoms at a longitudinally granular level, typically opting for days post-use and perhaps missing nuance in the onset, duration, and characteristics of any possible post-acute negative effects.

Coping strategies

If negative post-acute MDMA experiences are indeed a real phenomenon, it will be important to examine possible coping strategies. Preclinical work combining MDMA with alpha lipoic acid (Aguirre et al. 1999), acetyl-L-carnitine (Alves et al. 2009), N-acetyl-L-cysteine (NAC; Soleimani Asl et al. 2013), sildenafil (Puerta et al. 2012) and vitamin C (Shankaran et al. 2001) has informed harm reduction strategies among recreational MDMA users looking to mitigate possible negative post-acute experiences (Zelfand 2023). These strategies appear to be community-derived harm-reduction practices extrapolated from preclinical studies, rather than established treatments in humans. In rats, alpha lipoic acid prevented MDMA-related decreases in 5-HT and [3 H]paroxetine-labeled 5-HT transporters across several brain regions (Aguirre et al. 1999); acetyl-L-carnitine reduced mitochondrial injury markers and prevented 5-HT decreases (Alves et al. 2009); NAC reduced hyperthermia and protected against cell death markers (Soleimani Asl et al. 2013); sildenafil protected against MDMA-induced 5-HT deficits, possibly via increased MnSOD expression and reduced oxidative stress susceptibility (Puerta et al. 2012); and vitamin C suppressed striatal hydroxyl radical generation and attenuated striatal 5-HT depletion (Shankaran et al. 2001). Thus, these supplements have plausible preclinical rationales, but their efficacy for subjective post-acute MDMA symptoms in humans remains unknown.

Relatedly, limited work suggests that SSRIs given after MDMA may mitigate possible negative effects. Schmidt (1987) found that fluoxetine given to rats at the same time or 3 h after a single 10 mg/kg injection of MDMA blocked reductions in cortical serotonin one week after the MDMA dose. When fluoxetine was given 6–12 h after MDMA, cortical serotonin concentrations were reduced to 72% and 39% one week later, respectively, of those in control animals, suggesting that post-MDMA fluoxetine treatment is effective within a 6-hour window after dosing. Shankaran and colleagues (1999) demonstrated that fluoxetine given either 1 h before or 4 h after a single subcutaneous administration of MDMA ingestion (20 mg/kg) in rats reduced MDMA-induced depletion of 5-HT in the striatum. Baggott and colleagues conducted the only known empirical test of this paradigm with humans in an unpublished study, which featured a placebo-controlled, double-blind, double-dummy, within-subject design of healthy volunteers who reported prior increases in negative emotions after MDMA. Results indicated that MDMA (1.5 mg/kg) impaired probabilistic classification performance (vs. placebo) at 5 and 26 h, and that post-treatment with citalopram (20 mg given at ~3 and 26 h post-MDMA) attenuated this MDMA-related impairment; yet, self-reported mood at 26 h did not differ between MDMA alone and MDMA plus citalopram conditions. Citalopram given after MDMA yielded similar levels of peak subjective effects (e.g., closeness to others 1 h post-dose) as the MDMA alone condition, whereas pre-treatment with citalopram markedly reduced subjective effects. However, this work is unpublished; thus, results should be interpreted with caution pending peer review. Relatedly, anecdotal reports indicate that some recreational users may take SSRIs as the effect of MDMA wanes to prevent serotonergic depletion, and thus perceived negative psychological and physiological effects, but it is unclear how prevalent this technique, as well as coping strategies involving supplements, is in humans (Baggott and Mendelson 2001; Koslow, 2020; Nayak and Johnson 2023).

The present work

In summary, significant knowledge gaps exist regarding the existence of MDMA's post-acute negative effects. To expand understanding of the prevalence, characteristics, and coping strategies surrounding post-acute negative effects, we conducted an online cross-sectional survey study of psychoactive drug users. We assessed MDMA use, timing, and severity of post-acute effects, sleep quality, suicidal thoughts/behaviors, and intentional use of supplements or antidepressants to manage negative post-acute experiences. Our results from this study help inform the risks of using MDMA and possible mitigation strategies.

Methods

Participants

We recruited 497 participants residing in the US from Prolific Academic. Participants had an average age of 39 years ($SD = 10.8$). 42.5% of the sample were women. Most participants identified as White or Caucasian (79.3%), followed by Black or African American (13.1%). The most common education level was a bachelor's degree (39%), and the most frequently reported household income bracket was \$40,000 to \$59,999 (22.2%).

Procedure

An Institutional Review Board at the Johns Hopkins University School of Medicine approved all study procedures and all participants consented to joining the study after reviewing the study information. Participants on Prolific completed a cross-sectional survey about their experiences with psychoactive drugs. To mitigate selection bias and possible demand effects, the survey was not advertised as MDMA-focused. At the beginning of the survey, participants completed a question that asked which of several psychoactive drugs they had experienced before. Only those who selected MDMA were able to continue the survey; those who did not were excluded. The final sample consisted of 497 participants.

Participants reported the number of times they had taken MDMA in their lifetime with instructions to not count microdoses. Next, participants read a general description of the MDMA 'comedown' and were asked if they had ever heard of this phenomenon and whether they had ever experienced it with the following language:

Some people report experiencing a comedown after using MDMA. A 'comedown' refers to a period of low mood, low energy, emotional sensitivity, or other possibly negative experiences that some people have after the acute effects of MDMA.

With MDMA, this can happen either shortly after the drug wears off or several days later (sometimes referred to as "mid-week low," "Blue Mondays," or "Suicide Tuesdays").

Those who reported experiencing the MDMA comedown were then asked about the frequency, start, and duration of these experiences, as well as whether they had ever tried any coping strategies. Participants who indicated using either supplements or antidepressants to cope with MDMA comedown were prompted to complete several

questions asking about the specific supplements or antidepressants used, when they were taken, and how helpful they seemed to be in mitigating the comedown effects.

Regardless of whether they had or had not ever experienced an MDMA comedown, participants completed the Swiss Psychedelic Side Effects Inventory (SPSI; Calder and Hasler 2024), which was adapted to ask about “during post-MDMA comedown (i.e., after the acute effects of MDMA)” experiences or “post-MDMA (i.e., after the acute effects of MDMA)” experiences, depending on whether the participant had reported ever experiencing a comedown. The SPSI provides a standardized assessment of adverse events in studies of psychedelics and related compounds by capturing 32 side effects, their severity (*Mild, Moderate, Severe*), impact, duration, and treatment-relatedness.

Similarly, participants reported subjective changes in distinct emotions during either the comedown or the general post-MDMA experiences using the modified differential emotions scale (mDES; Fredrickson et al. 2003) on a 5-point scale (0 = *Not at all*, 4 = *Extremely*). Given that sleep quality is often discussed as a possible underlying factor when considering the existence of MDMA comedown (Blankers et al. 2025; Scott et al. 2013; Sessa et al. 2022), we also asked participants to indicate their typical sleep quality the first time they fall asleep following MDMA use (rated 0 = *Terrible* to 10 = *Excellent*) using an adapted version of the Single Item Sleep Quality Scale (Snyder et al. 2018).

All participants were also asked several questions regarding the prevalence and content of suicidal ideation (SI) following MDMA, participants’ certainty that such thoughts were due to MDMA, and their onset and duration. These questions were asked using a modified version of the Columbia-Suicide Severity Rating Scale (C-SSRS), adapted such that we could measure aspects of SI in an online, survey-based sample using self-report measures. Passive suicidal ideation was assessed with: “After the acute effects of MDMA have worn off, have you ever wished you were dead or wished you could go to sleep and not wake up?” Active suicidal ideation was assessed with: “After the acute effects of MDMA have worn off, have you ever actually had any thoughts of killing yourself?” Both items were rated from “No” to “Yes.” Participants endorsing passive or active suicidal ideation were asked parallel follow-up items assessing certainty that the thoughts were due to MDMA, “Approximately how certain are you that these thoughts/feelings [thoughts of killing yourself] were due to MDMA?” rated from 0% to 100%; onset, “In hours, how long after taking MDMA have these thoughts/feelings [thoughts of killing yourself] typically started for you?”; duration, “In

hours, how long have these thoughts/feelings [thoughts of killing yourself] typically lasted for you?”; and frequency, “Approximately what percent of the times that you have taken MDMA have you had these thoughts/feelings [thoughts of killing yourself]?” rated from 0% to 100%. Participants endorsing either passive or active suicidal ideation were also asked whether, after the acute effects of MDMA had worn off, they had experienced an interrupted attempt, aborted attempt, or preparatory act, each rated from “No” to “Yes (please describe).”

To capture coping strategies involving antidepressants or supplements, participants who indicated experiencing the comedown were asked if they had “ever taken steps to intentionally try to reduce, prevent, or cope with an MDMA comedown (e.g., taking another substance, doing a specific activity, or using another strategy)?”. The listed options were: vitamins or supplements (e.g., 5-HTP, magnesium, vitamin C, multivitamins), benzodiazepines (e.g., Xanax, Valium), cannabis, alcohol, antidepressants (e.g., SSRIs, SNRIs, TCAs, MAOIs) started or adjusted specifically for this, opioids (e.g., codeine, oxycodone, morphine), over-the-counter medication (e.g., ibuprofen, acetaminophen), relaxation techniques (e.g., meditation, yoga, mindfulness, breathing techniques), sought professional help (e.g., therapist, doctor), and ate specific foods. Participants who indicated intentionally using antidepressants and/or supplements were then asked questions regarding the type, frequency of use to treat comedown, timing relative to MDMA dose, overall perceived helpfulness (1 = *Not at all*, 5 = *Extremely*), and intent to use again to treat comedown (“Given the opportunity, would you take [specific antidepressant/supplement] again as a method to reduce, prevent, or cope with a post-MDMA comedown?”; *Yes, No, Unsure*).

Analytic strategy

Analyses were descriptive and exploratory. Participant characteristics and survey responses were summarized using frequencies and percentages for categorical variables and means and standard deviations for continuous variables. Participants were descriptively grouped according to whether they reported ever experiencing post-acute negative effects following MDMA use. Group values and mean differences are presented to characterize the sample and contextualize symptom patterns, but no inferential hypothesis tests were conducted. This approach was chosen because the study was designed to estimate self-reported prevalence, timing, symptom profiles, and coping strategies in a retrospective cross-sectional sample rather than to test causal or confirmatory group differences.

Results

Out of 497 participants who indicated they had experience with MDMA, 74.45% ($n=370$) reported ever experiencing a comedown. Demographics between those who did and did not ever experience a comedown were similar (Table 1).

Table 1 Demographics

	Comedown ($n=370$)	No Comedown ($n=127$)
Age, M (SD)	38.5 (10.1)	40.6 (12.5)
Sex, n (%)		
Male	209 (56.8%)	68 (54.8%)
Female	159 (43.2%)	56 (45.2%)
Gender, n (%)		
Man	207 (55.9%)	67 (53.2%)
Woman	156 (42.2%)	55 (43.7%)
Non-binary	5 (1.4%)	0 (0%)
Genderqueer/GNC	1 (0.3%)	1 (0.8%)
Transgender, n (%)		
Yes	8 (2.2%)	2 (1.6%)
Sexual orientation, n (%)		
Heterosexual	273 (75%)	106 (84.1%)
Homosexual	18 (4.9%)	3 (2.4%)
Bisexual/Pansexual	68 (18.7%)	13 (10.3%)
Queer	1 (0.3%)	2 (1.6%)
Asexual	2 (0.5%)	2 (1.6%)
Race/Ethnicity, n (%)		
American Indian/Alaskan Native	4 (1.1%)	2 (1.5%)
Asian	23 (6.1%)	9 (6.8%)
Black or African American	47 (12.4%)	18 (13.5%)
Middle Eastern/North African	1 (0.3%)	0 (0%)
Native Hawaiian/Pacific Islander	0 (0%)	1 (0.8%)
White or Caucasian	296 (77.9%)	98 (73.7%)
Other	0 (0%)	0 (0%)
Education, n (%)		
Some high school or less	3 (0.8%)	0 (0%)
High school graduate/equivalent	47 (12.7%)	23 (18.3%)
Some college, no degree	82 (22.2%)	18 (14.3%)
Associate/Technical degree	25 (6.8%)	14 (11.1%)
Bachelor's degree	148 (40.1%)	45 (35.7%)
Master's/Professional degree	53 (14.4%)	23 (18.3%)
Doctorate degree	10 (2.7%)	3 (2.4%)
Household income, n (%)		
Less than \$10,000	16 (4.4%)	6 (4.8%)
\$10,000 to \$19,999	22 (6.1%)	9 (7.3%)
\$20,000 to \$29,999	28 (7.7%)	11 (8.9%)
\$30,000 to \$39,999	47 (13%)	17 (13.7%)
\$40,000 to \$59,999	80 (22.1%)	28 (22.6%)
\$60,000 to \$79,999	51 (14.1%)	15 (12.1%)
\$80,000 to \$99,999	36 (9.9%)	11 (8.9%)
\$100,000 to \$149,999	50 (13.8%)	17 (13.7%)
\$150,000 to \$199,999	20 (5.5%)	8 (6.5%)
\$200,000 to \$249,999	9 (2.5%)	0 (0%)
\$250,000 or greater	3 (0.8%)	2 (1.6%)

¹Participants could select multiple races/ethnicities

Participants who reported experiencing comedowns reported using MDMA 17.20 ($SD=24.29$) times, on average, throughout their lives; those who never experienced a comedown reported 8.16 ($SD=18.86$) lifetime uses, on average. Among those who reported experiencing comedowns, participants estimated that an average of 63% ($n=342$, $SD=29.8\%$) of their lifetime MDMA use was followed by a comedown. Participants reported that the onset of comedown experiences typically started 23.75 h ($SD=17.86$) after taking MDMA, and they lasted 39.74 h ($SD=29.18$). Regarding sleep quality following MDMA use, participants who experienced comedowns reported a mean sleep quality of 3.5 ($SD=2.52$), whereas those who did not experience comedowns reported a mean sleep quality of 4.87 ($SD=2.63$).

Post-MDMA side effects. Among participants who reported experiencing comedowns, the most commonly reported side effects on the SPSI were fatigue, tiredness (88.1%), difficulty concentrating or thinking clearly (85.7%), feeling restless or irritable (82.9%), headache (79.7%), and feeling sad, mournful, or depressed (76.9%). On average, SPSI side effects began 23.2 h ($SD=4.1$) after taking MDMA. The average reported onset (in hours after taking MDMA) for each of the top 5 side effects was as follows: fatigue, tiredness (22.3 h), difficulty concentrating or thinking clearly (21 h), feeling restless or irritable (23.2 h), headache (21.4 h), and feeling sad, mournful, or depressed (24.6 h). Figure 1 depicts side effect rates by group.

Post-MDMA emotions. Among those who experienced comedowns, the most common emotions that participants indicated they typically felt were sad, downhearted, or unhappy ($M=1.79$, $SD=1.22$), stressed, nervous, or overwhelmed ($M=1.6$, $SD=1.21$), and angry, irritated, or annoyed ($M=1.32$, $SD=1.18$). Between the comedown and no-comedown groups, the largest differences in emotions typically felt (framed as either “during post-MDMA comedown” or “post-MDMA”, respectively) were among the following emotion categories: sad, downhearted, or unhappy (higher in comedown group; $M_{\text{difference}} = 0.97$), stressed, nervous, or overwhelmed (higher in comedown group; $M_{\text{difference}} = 0.84$), and angry, irritated, or annoyed (higher in comedown group; $M_{\text{difference}} = 0.63$). Figure 2 depicts mean emotions by group.

Post-MDMA Suicidal ideation. Among participants who reported experiencing comedowns, 14.6% ($n=54$) endorsed passive suicidal ideation (i.e., wishing to be dead or not wake up) and 6.2% ($n=23$) endorsed active suicidal ideation (i.e., thoughts of killing oneself) following MDMA use. Participants reporting passive SI estimated they were 64.1% ($SD=34\%$) certain these experiences were attributable to MDMA. These thoughts typically began 39.3 h ($SD=36.8$) after ingestion and lasted 66.4 h ($SD=46.1$). Passive SI occurred after an estimated 60.5% ($SD=33\%$) of

Swiss Psychedelic Side Effects Inventory rates

By comedown status (Comedown: n=370, No comedown: n=127)

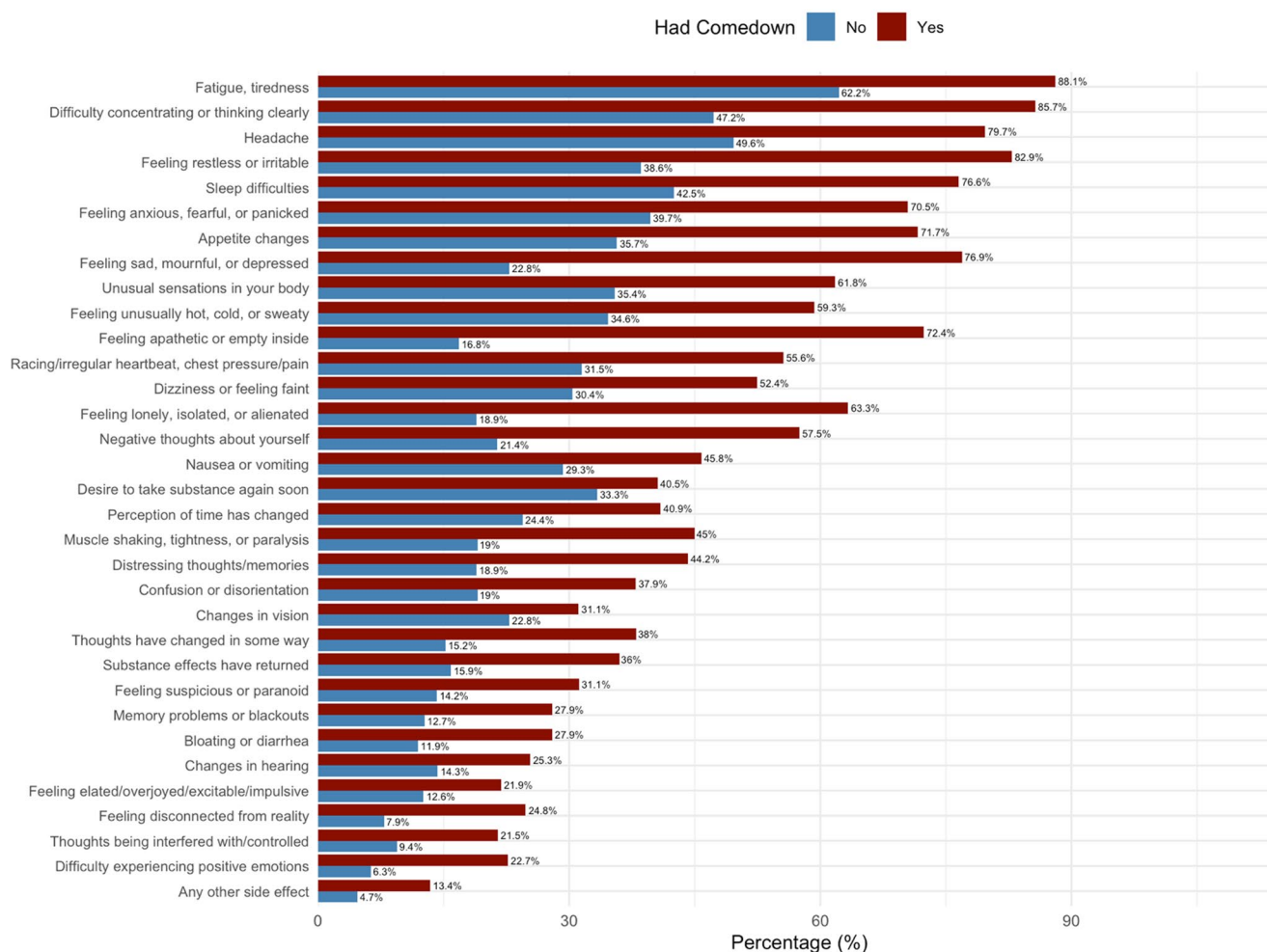


Fig. 1 Descriptive SPSI rates by comedown status

participants' lifetime MDMA use. Among those endorsing active SI, certainty of MDMA attribution averaged 52.8% ($SD=35.1\%$). Onset was 57.8 h ($SD=46.8$) post-ingestion, with an average duration of 75 h ($SD=53$). Active SI followed an estimated 58% ($SD=33\%$) of MDMA users. Among comedown experiencers, participants estimated that active SI occurred 58.0% ($SD=33.0\%$) of their lifetime MDMA use occasions. Regarding suicidal behaviors, 1.35% ($n=5$) reported an interrupted attempt, 0.81% ($n=3$) reported an aborted attempt, and 1.08% ($n=4$) reported preparatory acts toward a suicide attempt. Overall, 1.35% ($n=5$) of comedown experiencers endorsed at least one suicidal behavior following MDMA use.

Among participants who did not report experiencing comedowns, 2.4% ($n=3$) endorsed passive suicidal ideation and 1.6% ($n=2$) endorsed active suicidal ideation following MDMA use. Participants reporting passive SI estimated they were 48.7% ($SD=46.3\%$) certain these experiences

were attributable to MDMA. These thoughts typically began 23.7 h ($SD=24$) after ingestion and lasted 40.7 h ($SD=29.3$). Passive SI occurred after an estimated 65% ($SD=26\%$) of participants' lifetime MDMA use. Among those endorsing active SI, certainty of MDMA attribution averaged 5.5% ($SD=7.8\%$). Onset was 115 h ($SD=75$) post-ingestion, with an average duration of 11.5 h ($SD=14.8$). Among those who did not report experiencing comedowns, participants estimated that active SI occurred 58.5% ($SD=58.7\%$) of their lifetime MDMA use occasions. Regarding suicidal behaviors, 0% reported an interrupted attempt, 0% reported an aborted attempt, and 0.79% ($n=1$) reported preparatory acts toward a suicide attempt.

Antidepressants and supplements taken to reduce the comedown. Table 2 depicts comedown coping strategies endorsed by participants who reported experiencing them. Of participants who experienced comedowns, 5.14% ($n=19$) reported intentionally using antidepressants, and

Emotion Profile: Comedown vs No Comedown

Scale: 0 = Not at all, 4 = Extremely

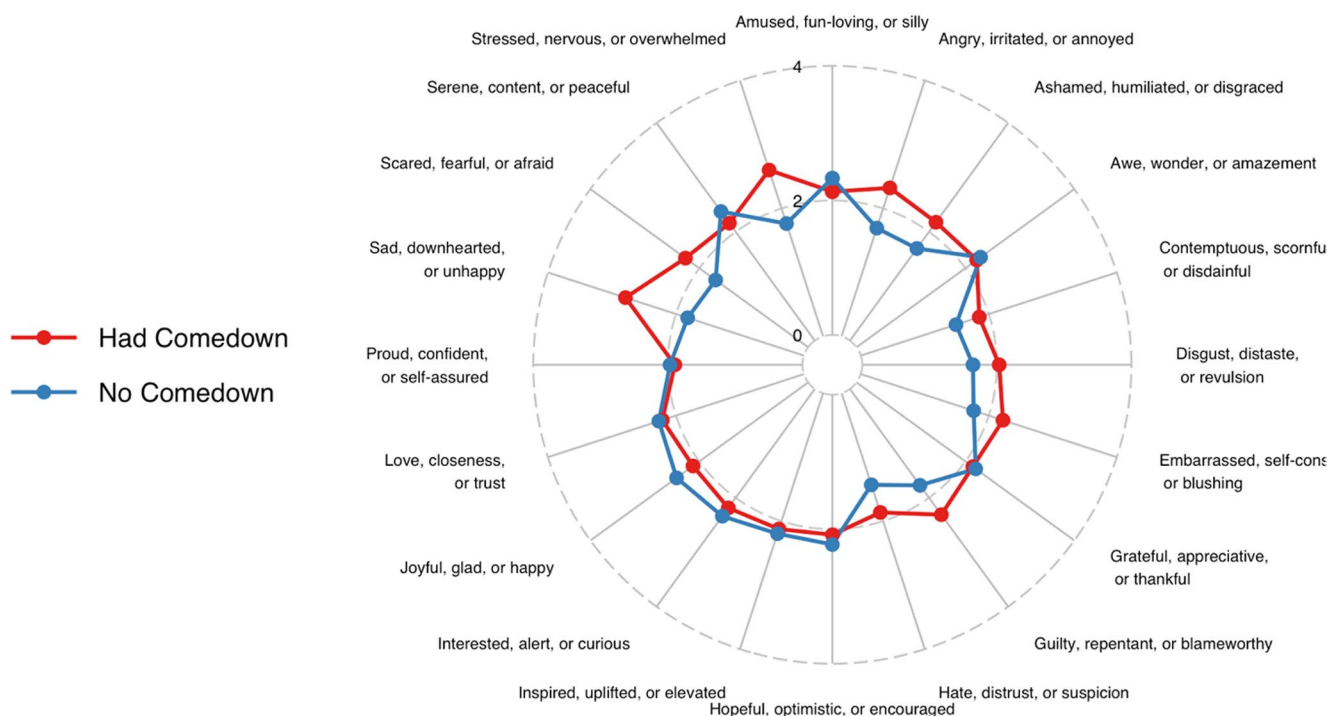


Fig. 2 Average modified differential emotions scale scores by comedown status

Table 2 Coping strategies used for comedown

Coping Strategy	n (% of comedown experiencers)
Vitamins or supplements	112 (30.3%)
Cannabis	118 (31.9%)
Alcohol	78 (21.1%)
Relaxation techniques	69 (18.6%)
Benzodiazepines	57 (15.4%)
Over-the-counter medication	47 (12.7%)
Ate specific foods	28 (7.6%)
Opioids	25 (6.8%)
Antidepressants	19 (5.1%)
Other	19 (5.1%)
Sought professional help	11 (3.0%)

30.27% ($n=112$) reported using supplements to cope with the comedown. Among those who used antidepressants, the most reported were sertraline (52.6%), fluoxetine (47.4%), and escitalopram (36.8%). Among those who used supplements, the most common were N-Acetyl-Cysteine (NAC) (59.8%), Acetyl L-Carnitine (48.2%), and Magnesium (43.8%).

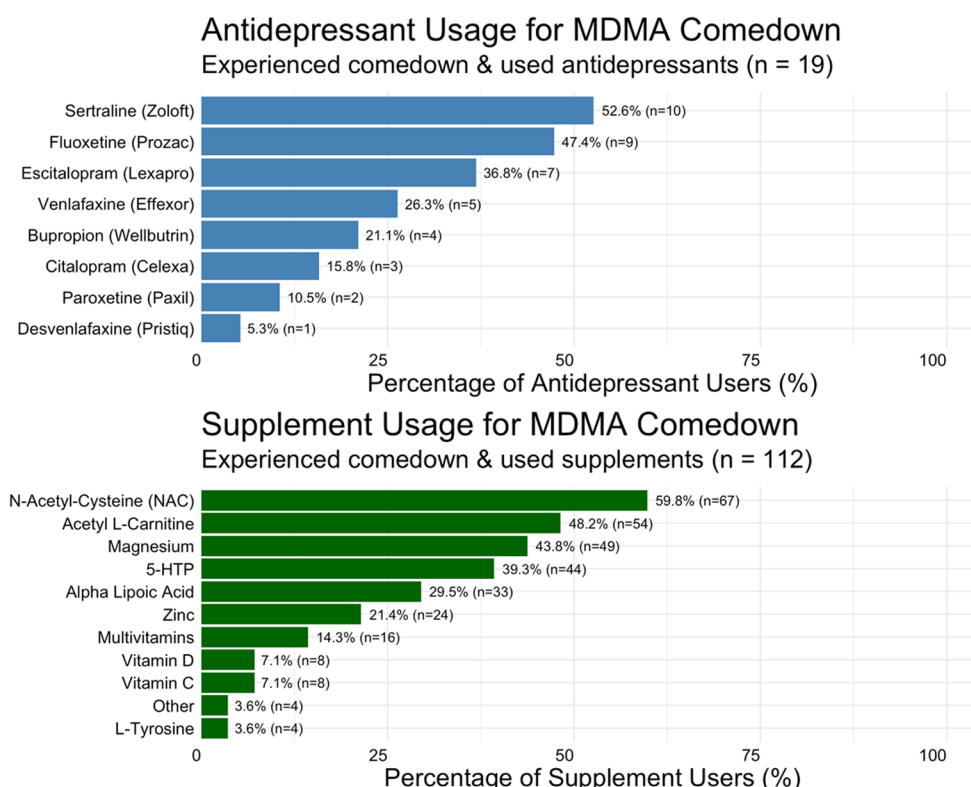
When taken before MDMA use, antidepressants were intentionally taken an average of 19 h ($SD=9.6$) prior to ingestion, and when taken after, they were taken 28.6 h ($SD=14.8$) post-MDMA use. Supplements taken before

MDMA were used an average of 33.9 h ($SD=47.9$) prior to ingestion, and when taken after, they were used 29.2 h ($SD=35.1$) post-MDMA use. Figure 3 depicts antidepressant and supplement use.

Collapsed across all antidepressants, the overall perceived helpfulness for managing comedown symptoms was 3.22 out of 5 ($SD=1.13$). For supplements, the overall perceived helpfulness was 2.83 out of 5 ($SD=1.06$), with largely even distribution of average helpfulness scores across the different supplements (Fig. 4). Figures 5 and 6 depict mean helpfulness of each antidepressant and supplement for each SPSI symptom. When asked whether they would use these substances again for comedown management, 70.7% of antidepressant use instances were rated as “would use again”, with 22% indicating “no” and 7.3% indicating “unsure.” For supplements, 74.2% of use instances were rated as “would use again”, with 7.7% indicating “no” and 18.1% indicating “unsure.”

Among antidepressant users ($n=19$), willingness to use again for comedown was highest for desvenlafaxine (100%, 1/1) and citalopram (100%, 3/3), followed by escitalopram (85.7%, 6/7), fluoxetine (77.8%, 7/9), sertraline (70%, 7/10), paroxetine (50%, 1/2), bupropion (50%, 2/4), and venlafaxine (40%, 2/5). Among supplement users ($n=112$), L-tyrosine

Fig. 3 Rates of antidepressant and supplement use for treating comedown



had the highest rate of reuse willingness (100%), followed by N-acetyl-cysteine (80.6%, 54/67), 5-HTP (77.3%, 34/44), vitamin C (75%, 6/8), multivitamins (75%, 12/16), acetyl L-carnitine (73.6%, 39/53), alpha lipoic acid (72.7%, 24/33), magnesium (69.4%, 34/49), zinc (66.7%, 16/24), vitamin D (62.5%, 5/8), and other supplements (50%, 2/4).

Discussion

The present study provides a systematic characterization of MDMA's post-acute negative effects by assessing associated symptoms, emotional correlates, and coping strategies in a sample of recreational users. We estimate the prevalence of self-reported post-acute negative effects—defined for participants as “comedown” experiences—in a large online sample while detailing their timing and symptom profiles, which include elevated rates of passive and active suicidal ideation. Furthermore, we report real-world coping strategies, such as supplement and post-use antidepressant use, identifying their frequency and self-reported effectiveness among recreational users.

Prevalence and characteristics of the MDMA's post-acute negative effects

Our results suggest that the MDMA's post-acute negative effects are prevalent phenomena. Our sample was drawn

from a Prolific cross-sectional drug-use survey and was not advertised as MDMA-focused, reducing self-selection biases. Nearly three-quarters (74.5%) of participants reported experiencing a comedown at least once. Moreover, among participants who reported ever experiencing a comedown, respondents estimated that, on average, 63.0% of their lifetime MDMA use occasions had been followed by a comedown. This participant-level retrospective estimate suggests that, among those who experience comedowns, comedowns are relatively common post-MDMA occurrences. These findings align with earlier observational work documenting post-acute impacts on mood following MDMA use (Curran and Travill 1997; Parrott and Lasky 1998; Verheyden et al. 2003) and ecological momentary assessment research showing significant drops in mental well-being days after MDMA (Blankers et al. 2025). The most commonly reported symptoms (fatigue, difficulty concentrating, restlessness, headache, and depressed mood) may reflect serotonin depletion (Johnson et al. 1986; Vollenweider et al. 1998). Together, the temporal profile of negative post-acute experiences in our sample (with onset approximately 24 h post-ingestion and duration averaging 40 h), coupled with questions about specific side effects and emotions, expands prior research on the comedown with greater granularity.

Sleep disruption may be an important contributor to, and in some cases a competing explanation for, the post-acute negative effects reported in this study. Averaged reported typical sleep quality following MDMA use for both

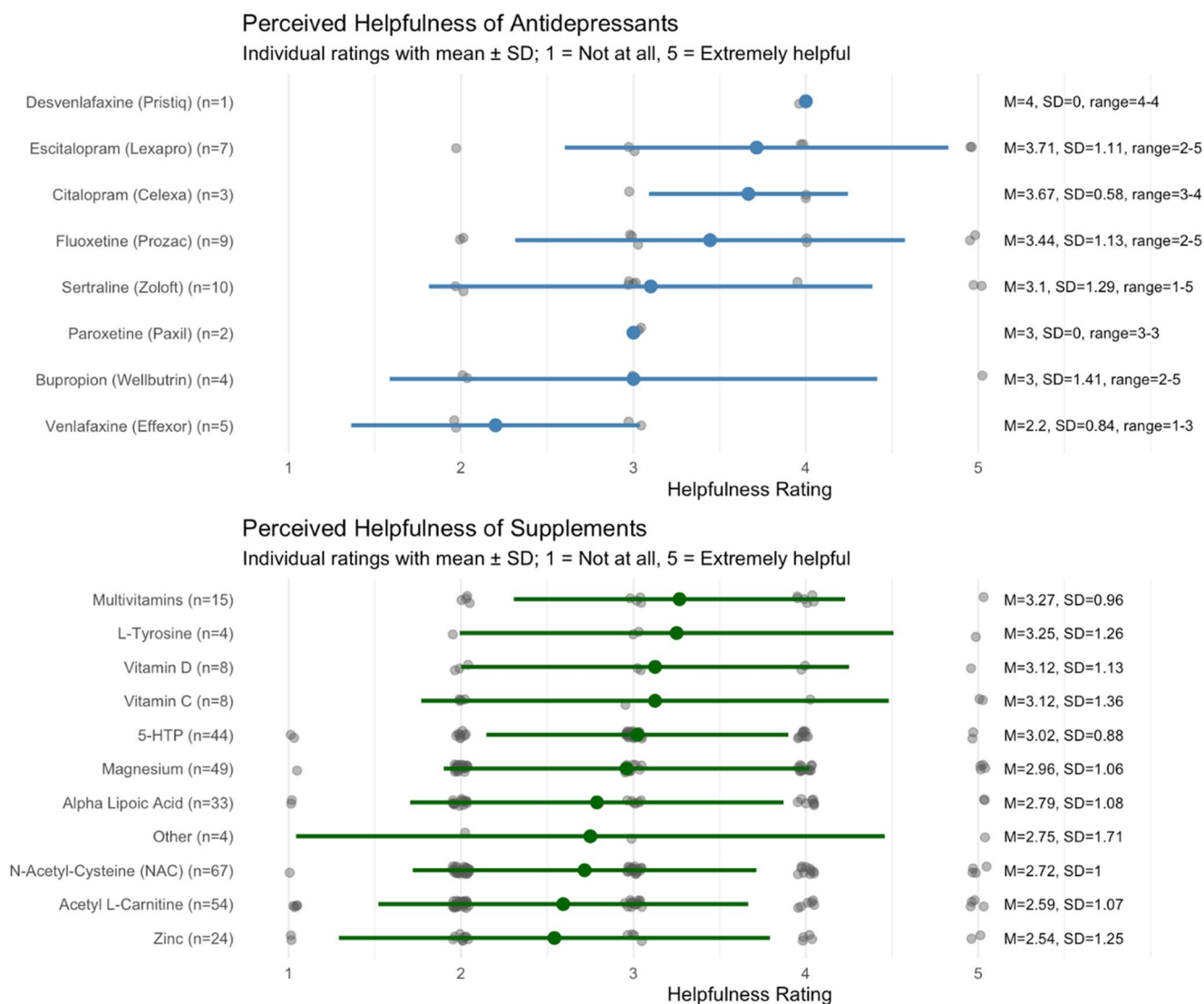


Fig. 4 Perceived helpfulness of antidepressants and supplements for comedown. Horizontal bars represent SD

comedown experiencers and non-experiencers was below the scale's midpoint, explicitly labeled "Fair", with comedown experiencers reporting an average 1.37 points lower than non-experiencers. Whether sleep quality may explain negative effects after recreational MDMA use remains an open question. Findings in prior work are mixed: Pirón and Morgan (2010) reported non-significant differences in sleep quality between ecstasy users and non-users ($N=32$), but found that controlling for sleep quality led to non-significant group differences in mood (after dropping 2 with missing sleep data). Huxster and colleagues (2006) found significant differences in restless sleep between ecstasy users and non users ($N=38$), yet when controlling for sleep, group differences in mood remained significant. Similarly, Blankers et al. (2025) found that post-MDMA reductions in well-being remained after controlling for sleep quality and covariates. Thus, sleep quality should be treated as an

important interpretive factor rather than a definitive explanation: poorer sleep may contribute to or amplify some reported comedown symptoms, but current evidence does not establish whether sleep disruption fully accounts for post-acute negative effects after MDMA use.

Perhaps the most clinically meaningful finding from our study concerns post-MDMA suicidal ideation. Among comedown experiencers, 14.6% endorsed passive suicidal ideation (wishing to be dead or not wake up) and 6.2% endorsed active suicidal ideation (thoughts of killing oneself) following MDMA use. These rates were markedly higher than among non-comedown experiencers (2.4% and 1.6%, respectively). Participants attributed these thoughts to MDMA with moderate certainty (averaging 64% for passive SI and 53% for active SI), and a small proportion (1.35%) reported engaging in suicidal behaviors following MDMA use. Still, these results should be interpreted with caution,

Fig. 5 Average perceived supplement helpfulness by SPSI side effect

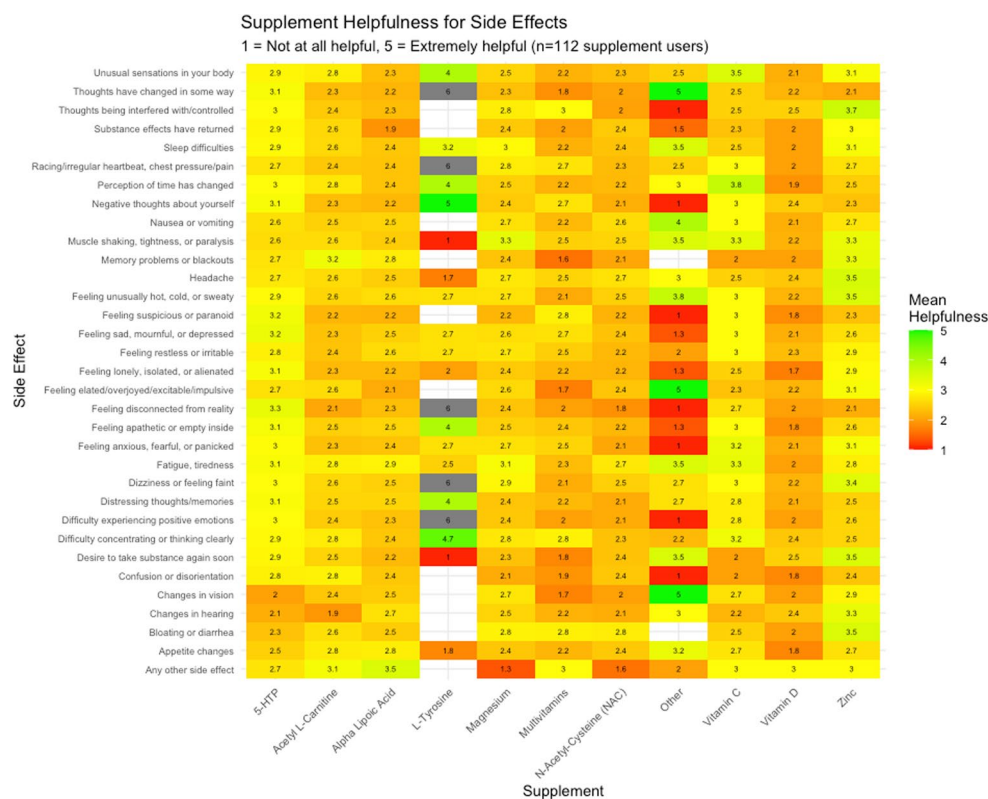


Fig. 6 Average perceived antidepressant helpfulness by SPSI side effect



as retrospective reports cannot establish whether MDMA caused suicidal ideation or whether such thoughts reflected pre-existing vulnerability, contextual factors, sleep disruption, polysubstance use, or other influences.

Nevertheless, the timing of these reports, with average onset of active and passive suicidal thoughts approximately 40–60 h after ingestion and duration averaging 66–75 h among comedown experiencers, is consistent with the time-frame described colloquially in recreational drug communities as “Suicide Tuesday.” These findings should therefore be interpreted as an important safety signal warranting prospective investigation.

Coping strategies: supplements and antidepressants

Our findings provide the first empirical snapshot of how recreational users attempt to mitigate MDMA’s post-acute negative effects. Approximately 30% of comedown experiencers reported using supplements, with N-acetyl-cysteine (NAC), acetyl-L-carnitine, and magnesium being the most common. These choices align with harm reduction recommendations circulating in online communities and are informed by preclinical research suggesting neuroprotective effects of these compounds (Aguirre et al. 1999; Alves et al. 2009; Soleimani Asl et al. 2013). A smaller proportion (5.14%) reported using antidepressants, most commonly the SSRIs sertraline, fluoxetine, and escitalopram.

Perceived overall helpfulness of antidepressants and supplements was middling (approximately 3 out of 5), but most participants indicated they would use these substances again for treating the comedown. The dosing window of recreational users’ antidepressant use surrounding MDMA (about 19 h before or 29 h after) is much wider than preclinical dosing paradigms (Schmidt 1987; Shankaran et al. 1999) and may play a role in perceived efficacy. Still, these self-reported helpfulness ratings should be interpreted with caution, given the lack of controlled comparisons and potential placebo effects.

Limitations

Our results had important limitations. Most notably, we used a cross-sectional survey for data collection, which limits causal inferences. Retrospective self-reports are subject to recall bias, and participants’ use of MDMA, dosage, purity, contextual factors (e.g., alone vs. with others, use setting, physical activity), and attributions of symptoms to MDMA cannot be verified. These factors may contribute to or underlie reported post-acute negative effects. The Prolific sample may not be representative of all MDMA users, and selection bias could have influenced who chose to

participate, despite our efforts to mask the study’s focus on MDMA. Prevalence estimates of post-acute negative effects should be interpreted in light of possible expectancy and demand effects. Although defining the comedown experience enabled us to ask participants about specific symptoms and intentional coping strategies for such experiences, it is possible that defining the experience may have prompted participants to reevaluate prior MDMA experiences and inflated endorsement of the comedown. Still, among participants who endorsed not having comedown experiences, top SPSI symptoms showed moderately high rates (e.g., fatigue: 62.2%, headache: 49.6%, difficulty concentrating: 47.2%) among a subsample who would not interpret these as comedown experiences. Additionally, as participants in our sample were recreational users, it is also unclear whether the observed negative post-acute experiences would occur in laboratory contexts, where compound purity, dosage, and polysubstance use could all be controlled. Finally, our data do not capture whether participants’ lifetime MDMA experiences involved polysubstance use, which may contribute to, but not fully explain, post-acute negative effects (Blankers et al. 2025; Pirona and Morgan 2010).

Future directions

Given mixed evidence concerning the existence of MDMA’s post-acute negative effects and the different methodological approaches in existing research, future work is needed to clarify these phenomena. In particular, a randomized, placebo-controlled trial of MDMA administration in which participants are followed at a granular level with measures designed to be sensitive to possible negative post-acute effects would provide the most rigorous design. Such studies should incorporate ecological momentary assessment to capture real-time symptom fluctuations and standardized sleep quality assessments. Additionally, controlled research examining the efficacy and safety of proposed harm reduction strategies, particularly those involving supplements and post-MDMA SSRI administration, is needed before such approaches can be recommended. Finally, future work is needed to better determine prevalence of serious adverse post-acute outcomes such as suicidal ideation, as well as the mechanisms that might underlie such outcomes.

Conclusion

This study contributes to the growing empirical literature on MDMA’s post-acute negative effects. Among recreational users, such effects are a prevalent phenomenon characterized by fatigue, cognitive difficulties, negative affect, and elevated rates of suicidal ideation. These findings highlight

potential risks that should inform both harm reduction efforts and the development of MDMA-assisted psychotherapy protocols. While recreational users commonly employ supplements and, less frequently, antidepressants to alleviate negative post-acute symptoms, the efficacy of these strategies remains unestablished. As interest in therapeutic applications of MDMA continues to grow, understanding and mitigating post-acute adverse effects will be essential for ensuring patient safety and optimizing treatment outcomes.

Author contributions SPG and SMN designed and conducted the research. All authors wrote the manuscript.

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Data availability The data are available from the authors upon request.

Declarations

Competing interest SPG reports a relationship with Palo Santo that includes: consulting or advisory. DBY has received research support from the NIH, the Gracias Family Foundation, the Heffter Research Institute, and philanthropic donors to the Johns Hopkins Center for Psychedelic and Consciousness Research. He co-directs the Hub at Oxford for Psychedelic Ethics (HOPE), which has received a small anonymous donation to support travel for underrepresented workshop participants; DBY does not personally receive financial support for this role. DBY has received consulting a fee from Soneira and educational speaking fees from the Integrative Psychiatry Institute. SMN reports a relationship with Resilient Pharmaceuticals that includes: consulting or advisory.

Clinical trial number Not applicable.

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