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Research paper

Validation of the Swiss Psychedelic Side Effects Inventory: Standardized assessment of adverse effects in studies of psychedelics and MDMA

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ABSTRACT

Introduction: Studies of psychedelic-assisted therapy with LSD, psilocybin, MDMA, and related substances show clinical promise but inadequately assess side effects. Measuring side effects is challenging because they are not always easily differentiated from treatment effects or disease symptoms and show high heterogeneity, variable duration and impact, and sensitivity to context. A systematic questionnaire describing important characteristics of side effects of psychedelics and MDMA would greatly improve on previous methods. We aimed to create a standardized tool for recording clinically relevant side effects of psychedelics and MDMA, including their severity, duration, impact, and treatment-relatedness.
Methods: We constructed the Swiss Psychedelic Side Effects Inventory (SPSI) based on insights from previous research. It was pilot tested in 145 participants from three studies. Structured feedback from an expert panel was used to improve validity and feasibility.
Results: The final SPSI contains 32 side effects and standardized follow-up questions about their severity, impact, treatment-relatedness, and duration. It is compatible with any study design and can be administered as an interview or self-report at any timepoint after treatment with psychedelics or MDMA.
Limitations: The SPSI omits relatively unimportant side effects for brevity's sake, though space for additional symptoms is given. Future studies are needed to confirm its validity in different contexts.
Conclusions: The SPSI is available in English and German for collecting systematic data on side effects from psychedelics and MDMA. This information is vital for improving clinical decisions, informed consent, and patient safety.

1. Introduction

Recent years have seen an increase in clinical trials of psychedelic-assisted therapy (PAT) with the serotonergic psychedelics psilocybin, lysergic acid diethylamide (LSD), *N*,*N*-dimethyltryptamine (DMT), and ayahuasca, as well as the empathogen 3,4-methyl-enedioxymethamphetamine (MDMA). PAT shows clear promise in the treatment of post-traumatic stress disorder, depression, anxiety disorders, and some other mental health problems, with significant overlap in mechanisms between substances (Yao et al., 2024). Psychedelics also have favorable safety profiles (Johnson et al., 2008). However, information on the side effects of psychedelics and MDMA remains incomplete, and many studies use inadequate methods to assess them (Breeksema et al., 2022). A recent meta-analysis concluded that most studies of PAT with MDMA had high risk of bias in their data on adverse effects, mostly due to the inadequate methods (Colcott et al., 2024). Despite strong efficacy data, this has already been cited as a barrier to regulatory approval of MDMA by an advisory committee of the U.S. Food and Drug Administration (FDA) (Hardman, 2024). Better methods and more comprehensive safety data are needed for an evidence-based understanding of the side effects of psychedelics and their significance, which will facilitate clinical decision-making, informed consent, and management of risks as PAT expands.

Assessment of side effects in studies of psychedelics brings unique challenges. Firstly, both classic psychedelics and MDMA can cause a unique range of perceptual, psychological, and physical side effects

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(Breeksema et al., 2022). Secondly, side effects – like positive effects – can sometimes unfold over days and weeks even after a single dose (Evans et al., 2023). Thirdly, differentiating between side effects and therapeutic effects is not always straightforward because what looks like an adverse effect on paper may be regarded as beneficial or harmful depending on the context. For example, some ayahuasca drinkers consider vomiting ("purging") to be a desirable part of the experience (Fotiou and Gearin, 2019), and transient dysphoria can sometimes be part of a beneficial therapeutic process (Barrett et al., 2016). Finally, judgments about whether a side effect is treatment-related are complicated by the potentially long timescale and by the fact that the content of psychedelic experiences, especially challenging ones, can be related to subsequent negative effects (Calder et al., 2024a).

Previous studies of psychedelics and MDMA have measured side effects using spontaneous patient reporting, open questions, or general adverse effect scales, all of which have disadvantages (Breeksema et al., 2022; Colcott et al., 2024). Spontaneous reporting relies on patients to volunteer information about side effects, and open questions, such as "Have you noticed any side effects?", avoid mentioning specific symptoms. Neither fulfills a high standard of evidence for evaluating safety because for various reasons, patients may not volunteer information even about even relatively troubling side effects if not specifically asked (Allen et al., 2018; Junqueira et al., 2023). The general adverse effect scales used in previous studies of psychedelics and MDMA, such as the List of Complaints (Zerssen, 1976) or the UKU Side Effect Rating Scale (Lingjaerde et al., 1987), do ask specific questions. However, they are not tailored to the unique side effect profile of psychedelics, making them inefficient because they miss some side effects of interest and include some irrelevant ones. They also do not assess side effect duration or impact on patients, and some also lack simple ratings of severity.

Many scholars have called for systematic assessment of side effects from psychedelics and MDMA to facilitate quality assurance in clinical settings and evidence-based communication about risks (McNamee et al., 2023; Breeksema et al., 2022; Colcott et al., 2024). A psychedelic-specific side effects questionnaire which also records side effect duration, subjective impact on patients, and likelihood of treatment-relatedness would greatly improve on existing methods in several ways. Systematic assessment is the most reliable method for recording side effects (Junqueira et al., 2023), and it would allow easier comparability between substances, patient groups, and contexts of psychedelic use, which is especially important because psychedelic drug effects – adverse or otherwise – are highly sensitive to context (Carhart-Harris et al., 2018). Reliable, quantitative, and validated safety data would also facilitate comparisons with other potential treatments for the same disorders, improving clinical decision-making. Furthermore, data could be more easily pooled across studies, improving statistical power and allowing for analyses of risk factors for adverse effects (Ioannidis, 2009). Standardized assessment of side effects could also be used in research on the use of psychedelics outside of controlled settings, which has been rising for the past decade and is an important focus of harm reduction research (Winstock et al., 2021). Side effects questionnaires specific to particular classes of drugs have a precedent, for example in the Liverpool University Neuroleptic Side-Effect Rating Scale (Jung et al., 2005), the Antidepressant Side-Effect Checklist (Uher et al., 2009), and the Ketamine Side Effect Tool (Short et al., 2020). However, there is currently no specific and standardized tool for assessing side effects of psychedelics or MDMA.

1.1. Aims

Here, we present the development of the Swiss Psychedelic Side Effects Inventory (SPSI), a standardized tool for measuring side effects from psychedelics and MDMA. We aimed to develop a questionnaire that would 1) include the most clinically important side effects, 2) record the severity and timing of symptoms, 3) assess subjective impact on patients' lives, 4) standardize judgments of treatment-relatedness, and 5) be feasible to use in any clinical or research context as either a clinician-administered interview or patient self-report.

2. Methods

The SPSI was developed using previous research, pilot studies, and expert feedback. The English and German versions were developed in parallel (see supplementary materials for translation procedures). First, we collected a pool of potential items based on clinical experience and existing literature. Next, we piloted the SPSI in three independent samples and improved it based on this data. Finally, we used a structured questionnaire to collect and incorporate feedback from experts regarding the SPSI's validity, content, and feasibility. These steps are described in more detail below.

2.1. Development of initial item pool

We first compiled a list of potentially relevant side effects from existing literature, as well as clinical experience with PAT. We began with 44 items from the List of Complaints which were sensitive to psychedelics and MDMA in previous studies (Holze et al., 2022; Vizeli and Liechti, 2017). We used a recent systematic review of adverse effects in clinical trials of psychedelic and MDMA to identify 10 more items (Breeksema et al., 2022). Because this review concluded that side effects may be under-reported, we used literature on side effects outside of controlled studies to identify another 18 possible side effects (Carbonaro et al., 2016; Strassman, 1984; Halpern et al., 2018; Bouso et al., 2022; Aixalà, 2022). We also composed follow-up questions to assess relevant details about the timing and duration of symptoms, and presence of any functional impairment or need for treatment. Because negative feelings and symptoms might be part of a beneficial therapeutic process, for example as seen in exposure therapy, participants were also asked to rate the valence and impact of each side effect as positive, neutral, or negative on a 5-point scale from "very negative" to "very positive". Likelihood of treatment-relatedness was rated based on recommendations from the World Health Organization, which classifies treatment-relatedness on a 4-point scale from "unlikely" to "certain" when enough information is available (WHO, 2018). Finally, we integrated informal feedback on the SPSI's validity from two colleagues with PAT experience. The initial version of the SPSI consisted of 66 side effects and 11 follow-up questions, plus an "other" category allowing additional symptoms.

2.2. Pilot testing

Participants in three separate studies completed the SPSI at various timepoints after taking psychedelics or MDMA (Fig. 1). Participants could give open-ended feedback about the questionnaire's content and ease of use, and three investigators also gave feedback from the interviewer's perspective. All participants provided written, informed consent and all studies were conducted according to the Declaration of Helsinki. The three studies are described below and more details can be found in the supplementary materials.

2.2.1. Patient sample: open-label psychedelic-assisted therapy

We used the SPSI in an open-label study of 18 patients, most diagnosed with treatment-resistant depression, who received a total of 31 PAT sessions with LSD or psilocybin at the Fribourg Network of Mental Health, Fribourg, Switzerland. Details of the study are described elsewhere (Calder et al., 2024b). The use of LSD and psilocybin was approved by the Swiss Federal Office of Public Health as part of the limited medical use program allowing PAT in Switzerland (Calder and Hasler, 2023). Doses ranged from 100 to 200 μg LSD base (Dr. Hysek Pharmacy, Biel) or 10-25 mg psilocybin dihydrate (Dr. Hysek Pharmacy, Biel). The treating psychiatrist (GH) administered the SPSI as an interview at an integration therapy session 1–2 days after PAT. Patients were

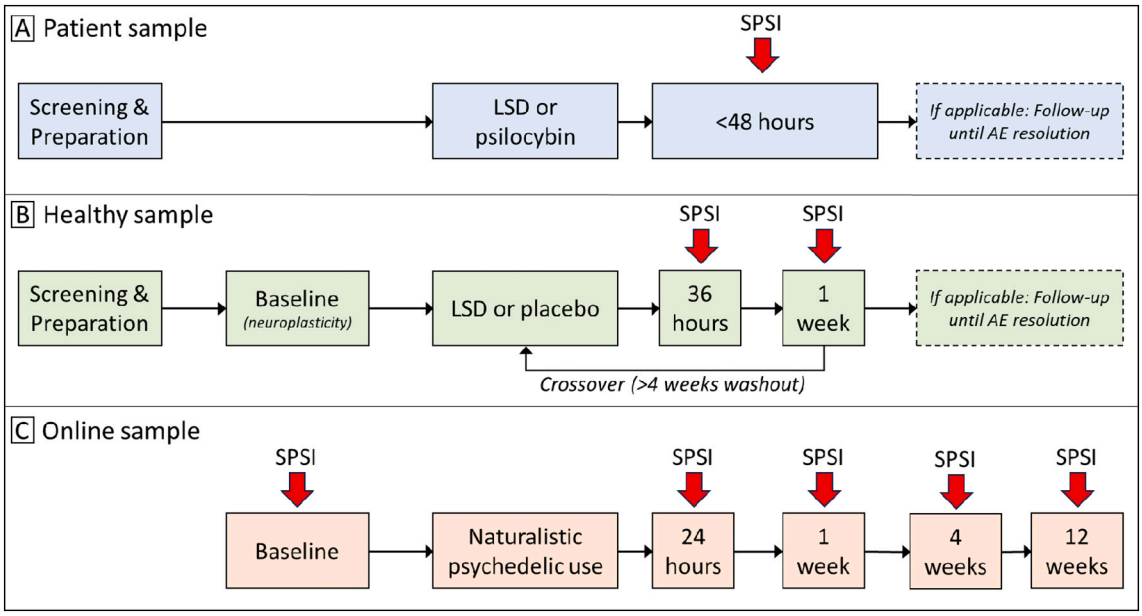

Fig. 1. Overview of three studies piloting the Swiss Psychedelic Side Effects Inventory (SPSI).
A) Patients undergoing psychedelic-assisted therapy with LSD or psilocybin completed the SPSI within 48 h of treatment. B) Healthy volunteers completed the SPSI one day and one week after receiving LSD or placebo. C) Participants in a prospective online study of naturalistic psychedelic use completed the SPSI before and at four timepoints after taking psychedelics.

asked to report all side effects experienced at any time during or after the acute drug effects. The treating psychiatrist followed up on any lasting side effects until they resolved.

2.2.2. Healthy sample: effects of LSD on neuroplasticity in healthy volunteers

The SPSI is the main safety outcome in a double-blind, randomized, placebo-controlled crossover trial investigating the effects of 100 µg LSD on neuroplasticity in healthy volunteers (NCT05177419). Details and results will be published elsewhere. The study was approved by the Cantonal Ethical Committee Bern (BASEC-ID: 2021-01322). The use of LSD base (>99 % purity, Lipomed AG, Arlesheim, Switzerland) was approved by the Swiss Federal Office of Public Health (Ref-Nr: 2022/016797). Participants were 21–55 years of age and psychologically and physically healthy. One day after receiving LSD and placebo, participants were asked to report all acute and post-acute side effects experienced since drug ingestion. One week later, they were asked about all side effects occurring since the previous appointment. If any side effects remained unresolved at one week, investigators followed up until they subsided.

2.2.3. Online sample: prospective survey study of naturalistic psychedelic use

Finally, the SPSI was used in a prospective online pilot study in psychiatrically healthy adults who were planning a "trip" with any of several psychedelics, including MDMA (Table 1). The study was approved by the Cantonal Ethical Committee Bern (BASEC-ID: 2022-01529) and recruited participants for approximately ten months. The study consisted of five surveys, all of which included the SPSI: one before psychedelic use, then four more up to 12 weeks after. In the first survey, participants were asked to indicate which side effects they had experienced in the past week (without psychedelics) to establish a baseline. The second survey assessed side effects within the first 24 h after dosing. Surveys at one week, four weeks, and twelve weeks post-dosing all asked participants to indicate which side effects they had experienced in the past week. The time period of one week was kept consistent in order to

Table 1
Descriptive statistics for the three samples in which the SPSI was piloted, including doses of the psychedelic drugs consumed and subjective intensity of drug effects in the online sample. Data are shown as mean (SD). Doses for the online sample are self-reported and are thus only approximate.

Sample	N	% male	Age Mean (SD)	Drug information								
					LSD	Psilocybin mushrooms	MDMA	Ayahuasca	DMT	Mescaline	2C-B	5-MeO-DMT
Online	96	66.67 %	32.16 (10.31)	Dose	202.27 (140.30) µg	4.81 (8.92) g	195.02 (148.38) mg	2.57 (0.53) cups	23.67 (20.07) mg	700 g, 2 pups	24.5 (0.71) mg	15 mg
				N	26	32	18	9	6	2	2	1
				Intensity (0–100)	73.82 (18.09)	70.83 (23.37)	72.36 (20.27)	87.43 (10.81)	58.67 (22.69)	42.5 (45.96)	66 (1.41)	94
Patients	18 (31 PAT sessions)	29.41 %	47.29 (17.04)	Dose	131.25 (45.81) µg	19.35 (4.60) mg						
				N patients (sessions)	5 (8)	13 (23)						
Healthy	31	51.61 %	28.74 (7.65)	Dose	100 µg							
				N	31							
Total N	145				62	45	18	9	6	2	2	1

improve comparability to baseline.

2.3. Revision using pilot data

We aimed to reduce the initial item pool to include the most clinically relevant side effects while ensuring a reasonable length. Using pilot data, we identified the most frequent and distressing side effects which were likely to be treatment-related. Predefined criteria were used to identify side effects which were rare (<5 % of entire sample) and had little negative valence or impact (average ratings of >−0.25 on a scale from −2 to 2), which became candidates for removal or consolidation with similar items. We also considered side effects added under "other", as well as participant and interviewer feedback on wording and potential redundancies in both side effects and follow-up questions. Finally, we considered newly published literature describing a detailed list of lasting adverse effects attributed to psychedelics and MDMA (Evans et al., 2023).

2.4. Expert evaluation of face and content validity

After refining the SPSI using pilot data, we contacted 28 international experts who had experience administering psychedelic substances and/or studying their side effects. We identified experts based on their experience with administering psychedelics in the context of therapy and/or research studies, and we aimed make the pool of experts as international as possible. We also aimed to include experts with a variety of relevant backgrounds, include in psychotherapy, neuroscience, psychiatry, and psychedelic harm reduction. Experts were invited via e-mail and given eight weeks to provide feedback via a structured Qualtrics survey. They were asked to comment on the SPSI's ease of use and face validity, including whether any side effects should be added, consolidated, or subtracted and whether the follow-up questions about severity, impact, and duration were appropriate. Experts were also asked about the feasibility of the SPSI as a self-report questionnaire, as well as whether they would use such a questionnaire in their research or practice. An open-ended section allowed for any other comments. Once feedback had been collected, it was de-identified, collated and reviewed in order to identify repeated comments. Decisions about which suggestions to implement were agreed upon by all authors in discussion rounds. Comments made by at least three experts were automatically integrated.

2.5. Statistical analysis

Statistical analyses were performed in RStudio, Version 2023.06.1. In the healthy and online samples, differences in the total number of side effects reported after psychedelics compared to placebo or baseline, respectively, were analyzed using Wilcoxon's signed rank tests at each timepoint. Differences in the frequency of specific side effects were analyzed using McNemar's test. The Benjamini-Hochberg procedure was applied to reduce the false positive rate.

3. Results

3.1. Results of pilot studies

Side effects data was collected from 145 participants in the three studies (Table 1). The patient and healthy samples had no dropouts. The online study included 96 participants who completed the questionnaire 24 h after a psychedelic experience, and 53 of them completed the surveys one and four weeks later. The final survey at twelve weeks had a high drop-out rate (N = 6) and was dropped from the analysis.

3.1.1. Feedback from participants and investigators

Both investigators and study participants could give open-ended feedback on the SPSI. The most common critique was that the questionnaire was too time-consuming. Both investigators and participants felt that some side effects and follow-up questions were either unimportant or so similar that they could be combined. All three investigators suggested changes to the wording of items to improve their clarity and content validity. Several participants left positive remarks about including ratings of subjective impact rather than assuming all side effects are negative.

3.1.2. Most frequent and distressing treatment-related side effects

To refine the SPSI, we identified the most frequent and distressing treatment-related side effects at different timepoints. We first determined which side effects were significantly more likely to occur after psychedelics than control conditions in the healthy and online samples. The healthy sample reported significantly more side effects after LSD than placebo one day after treatment ($W = 496$, $p < 0.001$), but not one week later ($W = 201.5$, $p = 0.98$). One day after treatment, 15/66 side effects were reported significantly more often after LSD than placebo (Table 2). No side effects occurred statistically more often one week after LSD than placebo. In the online sample, we examined differences from baseline for each timepoint. No timepoint showed significantly more side effects overall than baseline, but vision changes and four somatic side effects (feeling warm, sweating, balance problems, heaviness) were reported more often within the first 24 h after drug ingestion than at baseline (Table S1).

We next identified the most frequent side effects judged as likely to be psychedelic-related (i.e., "probably" or "certainly" related). Within the first 48 h after drug intake, the most frequent side effects across all samples were vision changes, tiredness, appetite changes, nausea, sleep problems, and headaches (Table S2). In the first week after dosing, the most frequent side effects were sleep problems, headaches, trouble concentrating, flashbacks, and tiredness. Online participants from the four-week follow-up most often reported vision changes, derealization, emotional blunting, flashbacks, and sleep problems. Two healthy volunteers and one patient reported treatment-related side effects that resolved after the final follow-up (see supplementary materials). "Other" treatment-related side effects were reported by 18 participants, each only once (see supplementary materials).

Next, we investigated which treatment-related side effects had the most negative ratings of valence and impact at different timepoints (Table S3). In the first 48 h post-dosing, the most negative valence ratings were given to suicidal ideation, sense of impending doom, panic attacks, nightmares, and anxiety. The most negative impact was seen for intrusive thoughts and memories, nightmares, emotional blunting, bladder problems, and bruxism. For post-acute side effects lasting up to four weeks, the most negative valence ratings were given to impulsivity,

Table 2
Results of McNemar's test for side effects reported significantly more frequently one day after LSD than after placebo in the healthy sample. Benjamini-Hochberg correction was applied to reduce the false error rate. N = 31. *$p < 0.05$, **$p < 0.01$.

	Placebo	LSD	χ^2	p
Vision changes or hallucinations	32.26 %	93.55 %	15.43	0.005**
Nausea	12.90 %	74.19 %	15.43	0.005**
Appetite changes	9.68 %	74.19 %	18.05	0.002*
Sleep problems	29.03 %	70.97 %	8.47	0.037*
Concentration problems	22.58 %	67.74 %	8.45	0.037*
Feeling euphoric, excited, energetic	12.90 %	64.52 %	14.06	0.006**
Change in speed of movements/speech	3.23 %	58.06 %	15.06	0.005**
Muscle shaking or trembling	3.23 %	54.84 %	14.06	0.006**
Thoughts racing	0.00 %	51.61 %	14.06	0.006**
Crying	6.45 %	51.61 %	12.07	0.010*
Sweating	3.23 %	48.39 %	12.07	0.010*
Anxiety	3.23 %	48.39 %	12.07	0.010*
Balance problems	3.23 %	45.16 %	11.08	0.014*
Derealization	0.00 %	41.94 %	11.08	0.014*
Depersonalization	0.00 %	41.94 %	11.08	0.014*

stomach pain, nausea, feeling uneasy, and fear of going insane. Side effects with the most negative impact were racing thoughts, vision changes, fear of going insane, sweating, and memory problems.

Based on insights from pilot data, we distilled the SPSI to its most relevant items in order to optimize comprehensiveness while keeping the length reasonable (see supplementary materials for details). Decisions about which items to combine, remove, and add were made based on combining information from participant and investigator comments with data on frequency, valence, impact, duration, and treatment-relatedness. We also added items from a newly published list of lasting difficulties after psychedelics and MDMA (Evans et al., 2023). Finally, we amended the clinician's instructions to improve inter-rater reliability, which was a possible source of differences in side effect frequency between samples in this study.

3.2. Results of expert evaluations

Seven invited experts agreed to give structured feedback on the revised SPSI (25 % response rate). Experts were based in Switzerland, Germany, the United States, and the United Kingdom and had backgrounds in psychiatry, clinical psychology, and neuroscience. Most stated that the SPSI was understandable and feasible for use as an interview or self-report, and nearly all said they would consider using it in their research or practice. Experts praised the specificity for psychedelic-specific side effects, the inclusion of subjective impact, the differentiation between acute and post-acute effects, the ability to track changes in side effects over time, the clear guidelines for assessing treatment-relatedness, and the focus on systematic assessment of side effects.

After reviewing all comments, we implemented 73 % of suggestions for improvement. To summarize, improvements included changing the wording of some items and instructions to improve content validity and clarity for laypeople, adding details to the instructions, masking impossible answers to avoid confusion, and adding a total score based on severity and impact to facilitate statistical analysis of overall side effect burden. Additionally, an important discussion about the optimal number of items arose because some experts had contradictory opinions. Though some favored shortening the SPSI for practical reasons, others suggested adding side effects, and balancing thoroughness with brevity was challenging. We strove for an optimal balance by combining some closely related side effects into symptom clusters (e.g. muscular effects), which allowed us to sensibly include most of the suggested additional side effects. Finally, we added a rating of tolerability similar to that found on the Ketamine Side Effects Tool (Short et al., 2020) in order to inform decisions about the dose in any future psychedelic sessions, for example in PAT with repeated dosing (Calder et al., 2024b). Table S4 contains an overview of decisions about keeping, changing, adding, and removing items for each item at each of the three development steps (literature review, data analysis, and expert feedback).

4. Discussion

4.1. The Swiss Psychedelic Side Effects Inventory: strengths and applications

The final version of the SPSI can be found in the supplementary materials in both English and German. The SPSI is a standardized questionnaire for systematically assessing important side effects from psychedelics and MDMA in any clinical or research setting. It typically takes <15 min and can be given as an interview or patient self-report in paper or digital format at any timepoint of interest after acute psychedelic effects have subsided. It specifies 32 side effects with blank fields for adding others, as well as structured follow-up questions assessing severity, adverse or beneficial impact, treatment-relatedness, timing, and duration for each side effect endorsed. Instruction pages for clinicians and patients provide guidelines for completion. The SPSI's strengths include its systematic assessment of side effects, specificity for psychedelics and MDMA, consideration of both adverse and beneficial impact, standardized criteria for determining treatment-relatedness, adaptability to diverse study designs, and data-driven and expert-informed development.

The specificity of the SPSI for psychedelics and MDMA is an advantage over passive reporting, open questions, and general side effect scales used in previous studies. General questionnaires like the List of Complaints (Zerssen, 1976) include side effects which are relatively uninteresting because they are unnecessarily specific, easily tolerated, and/or have no known relationship to psychedelics (e.g. heavy legs, urge to urinate, increased pigmentation). They also miss many relevant side effects, including some of the most common lasting side effects, such as derealization and depersonalization, perceptual disturbances, and feeling lonely or isolated (Evans et al., 2023). The SPSI also screens for uncommon side effects that are nevertheless of interest to clinicians and regulatory bodies, including manic and psychotic symptoms, suicidality, and abuse potential. Lack of data on side effects and specifically on abuse potential was recently cited by an FDA advisory committee as a reason against approving MDMA for the treatment of PTSD (Hardman, 2024).

The most frequent side effects observed using the SPSI were consistent with previous research, supporting the SPSI's validity. Frequent short-term side effects were comparable to results from previous studies of LSD, psilocybin, and MDMA, which identify fatigue, concentration problems, appetite changes, headaches, muscle tightness, and symptoms of sympathomimetic activation as the most common side effects (Holze et al., 2022; Vizeli and Liechti, 2017; Straumann et al., 2024; Breeksema et al., 2022; Colcott et al., 2024). Regarding post-acute side effects, controlled studies report flashback phenomena, anxiety, panic symptoms, and depressed mood, with varying severity (Breeksema et al., 2022; Muller et al., 2022). Outside of controlled studies, the most common persisting negative effects include anxiety, depression, derealization, depersonalization, feeling lonely or isolated, perceptual disturbances, and "existential struggle", which is operationalized on the SPSI as "distress related to one's understanding of reality or the meaning of life" (Evans et al., 2023; Bremler et al., 2023; Carbonaro et al., 2016). These were not the most common in our data, perhaps due to differences in sample selection. Notably, however, sleep problems were the most common persisting side effect in our data and also among the most frequent in other studies (Simonsson et al., 2023; Bremler et al., 2023).

The SPSI is unique for collecting data on subjective severity and impact, which are important for a complete understanding of psychedelic side effects. Many potentially uncomfortable side effects received positive average impact ratings, such as anxiety and crying. In PAT, some unpleasant effects can be part of a beneficial therapeutic process and are poorly described as "side" effects (Gasser et al., 2015). Most respondents in studies of people who experienced distressing side effects from psychedelics report benefitting from those experiences (Carbonaro et al., 2016). At other times, the same unpleasant drug effects may be harmful, warranting both their inclusion in side effects questionnaires and assessment of their subjective severity and impact. Both study participants and the expert panel found the inclusion of subjective impact ratings valuable.

Side effects from psychedelics and MDMA, as well as their severity and impact, can change over time. Though most side effects emerge before the drug is eliminated from the body, some can appear weeks later (Evans et al., 2023), possibly as part of a stress response to extremely frightening psychedelic experiences (Calder et al., 2024a). Additionally, some side effects are usually benign in the acute phase but become worrisome when they last longer, and the reverse can be true when effects that initially seem negative were part of a beneficial therapeutic process in retrospect. For these reasons, we recommend using the SPSI to follow side effects for at least several weeks or even months after psychedelic treatments to ensure complete understanding of how they develop.

It is sometimes unclear whether changes in symptoms are due to the natural course of an illness or to a treatment. The SPSI standardizes judgments of treatment-relatedness based on existing WHO guidelines, improving their transparency compared to previous studies. Importantly, judgments of treatment-relatedness require special considerations with psychedelics and MDMA. One is the relatively long timescale over which side effects may emerge. Additionally, it can be difficult to disentangle drug-related from therapy-related adverse effects when both are combined (Klatte et al., 2023). Finally, in addition to clinicians' professional judgment, there is clear rationale for incorporating patients' views on treatment-relatedness because the content of their psychedelic experiences is sometimes clearly connected to changes in symptoms, whether positive or negative (Breeksema et al., 2024). For example, one patient undergoing psilocybin-assisted therapy described an existential confrontation with suffering during her "trip" which greatly exacerbated her depressive symptoms (Evans, 2024).

The SPSI can be used in a variety of clinical and research contexts, including clinical practice, clinical trials, observational studies, and online surveys. This is an important feature because the risks of psychedelics and MDMA vary by context and communication about side effects sometimes needs to be specific to particular drugs, patient groups, or settings (Schlag et al., 2022). The SPSI is versatile enough to gather comparable data from different settings, including PAT, controlled use in healthy people, and recreational use.

4.2. Limitations

Future studies will be needed to confirm the SPSI's validity in different types of study designs, including content validity, inter-rater reliability, and concurrent validity with other measures covering negative acute effects, for example the Challenging Experiences Questionnaire (Barrett et al., 2016) or the Hallucinogen Rating Scale (Strassman, 2005). The potential impact of contextual variables on SPSI scores should also be investigated, including the effect of diagnoses, study setting (e.g. in clinical trials vs. online surveys), and clinician- vs. self-report, as our data suggest that these variables may affect the results. Additionally, we aimed for the SPSI to be as comprehensive as possible, yet also brief enough to be useful in clinical studies, meaning that some very rare or clinically less relevant side effects are not included but can be added under "other" side effects. The SPSI does not include side effects detected with medical instruments, such as blood pressure changes. Items screening for certain psychiatric symptoms, particularly mania and psychosis, are important to include but must always be interpreted with caution when self-reported, as clinical judgment is essential for accurate assessments. Additionally, the SPSI does not assess the specific consequences of side effects, though these are an important aspect reported in previous studies. For some, side effects like anxiety, paranoia, or delusional states can become severe enough to lead to social difficulties, functional impairment, or even accidents and dangerous behavior (Evans et al., 2023). The SPSI's questions on severity and impact cover this to some degree, but we encourage adding relevant details in the open comment section. We also recommend assessing side effects for longer time periods than those used in the pilot studies. Finally, the three studies described here were designed to pilot and refine the SPSI rather than make meaningful statistical comparisons between the drugs, participant groups, and contexts included. However, such comparisons are an essential area for future research.

4.3. Conclusions and outlook

A clear next step for future research with the SPSI is creating detailed, longitudinal safety profiles for different substances, dose ranges, patient groups, and contexts. This would facilitate comparisons of risk between psychedelics, but also between PAT and other treatments for the same conditions, helping to optimize clinical decisions. Further studies on prevalence, risk factors, and prognosis of prolonged adverse effects would also be valuable for mitigating harms and supporting affected patients.

As interest in psychedelics and PAT grows, accurate and detailed information on side effects benefits anyone in contact with psychedelics or those who use them. Because of the unique challenges of understanding side effects from psychedelics, this should include systematic information on side effect prevalence, duration, severity, subjective impact, and likelihood of treatment-relatedness. In clinical practice, reliable side effects data can improve the quality of treatment decisions, informed consent, and patient safety. It can also allow researchers to evaluate how side effects vary between drugs, patient groups, and treatment contexts, facilitating evidence-based communication about the risks and benefits of psychedelics.

When evaluating the safety of new treatments, systematic assessment of side effects helps satisfy a high standard of evidence. The SPSI could form an important component of strategies for collecting transparent, reliable data on psychedelic side effects and their risk factors in various contexts, including PAT. Ultimately, better methods for studying side effects can help us make serious negative effects from psychedelics and MDMA even rarer than they already are.

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CRediT authorship contribution statement

Abigail E. Calder: Writing – review & editing, Writing – original draft, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Gregor Hasler:** Writing – review & editing, Supervision, Resources, Methodology, Conceptualization.

Declaration of competing interest

GH has received advisory or speaker honoraria from Gilgamesh Pharma, Lundbeck, Janssen, und OM Pharma. The authors have no further competing interests to declare.

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