

**The Effectiveness of Lysergic Acid Diethylamide to Increase Well-being and Related
Positive Mental Health Outcomes in Healthy Individuals: A Systematic Review of
Placebo-Controlled Trials**

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Abstract

There is currently a lack of research into the positive psychological properties of psychedelic substances. Although psychedelics already demonstrated the potential to elevate well-being in individuals there are currently no systematic reviews on the topic. Therefore, this systematic literature review investigates the effectiveness of lysergic acid diethylamide (LSD) in increasing well-being and related positive mental health outcomes in individuals.

Several search engines were systematically searched for peer-reviewed and placebo-controlled clinical trials, including information on the effect of LSD on well-being and on components of the PERMA model of well-being. Afterward, 8 studies were analysed, and their results were synthesised.

The results showed inconsistent positive effects of LSD on well-being. However, with an increase in dosage, the consistency of positive effects grew with the most consistent effects at 200µg. Moreover, the effect of LSD on the components *positive emotions*, *meaning*, and *relationships* from the PERMA model was positive while evidence for the components *accomplishment* and *engagement* was lacking.

Based on the results of the current study, a positive effect of LSD on well-being especially at high dosages seems likely. Regarding the components from the PERMA-model, a positive effect on concepts related to *positive emotions*, *relationships*, and *meaning* is probable. It was not possible to determine why *accomplishment* and *engagement* were not included in the literature, but a possible explanation could be the ego perception during mystical-type experiences. Nevertheless, due to a significant number of limitations of the analysed studies, such as the risk of carry-over effects and the lack of long-term measures, these conclusions need to be interpreted cautiously.

Keywords: LSD, lysergic acid diethylamide, psychedelics, well-being, PERMA model, Positive mental health, positive emotions, meaning, relationships

The Effectiveness of Lysergic Acid Diethylamide to Increase Well-being and Related Positive Mental Health Outcomes in Healthy Individuals: A Systematic Review of Placebo-Controlled Trials

Clinical applications of psychedelic substances are increasingly receiving attention within the last 15 years. The therapeutic effects of psychedelics are examined empirically, and some professionals already communicate the substances as potential breakthrough therapies for treating mental illness (Belouin & Henningfield, 2018). Recent studies have found that one to two psychedelic sessions can already have a lasting and rapid therapeutic impact (Nutt et al., 2020). For instance, Muttoni et al. (2019) claimed that psychedelics are a potential treatment for individuals suffering from depression and anxiety who cannot be helped effectively by conventional methods. Hence, the promising effects of psychedelic substances are increasingly gaining researchers' attention.

There is growing evidence that psychedelics cannot only reduce symptoms of psychopathology but also positively impact subjective well-being (Gandy, 2019). Although research examining the relationship between psychedelics and well-being is still in its early stages, there are already a variety of survey studies as well as some clinical trials indicating a link between psychedelic experiences and increased well-being (Kangaslampi et al., 2023). For instance, Mans et al.'s (2021) naturalistic observational study showed an increase in well-being up to two years after taking a psychedelic substance. Moreover, in Griffiths et al.'s (2008) clinical trial a single dose of psilocybin enhanced the well-being of 64% of the participants up until 14-month follow-up. Lysergic Acid Diethylamide (LSD), the first psychedelic which has been discovered by Western society, is one of the most widely researched psychedelic drugs (Gandy, 2019). Nonetheless, to date, critical analyses specifically focused on LSD and its effect on well-being are missing. Therefore, the current study aims to give a systematic overview of the current evidence regarding the effect that LSD has on well-being.

To gain a proper understanding of how LSD might influence well-being it is important to consider how the substance affects humans. LSD is a semisynthetic product of lysergic acid which is derived from a parasitic rye fungus (Passie et al., 2008). Moreover, it can be grouped with the classical psychedelics along with psilocybin, mescaline, and N,N-dimethyltryptamine (DMT), and has a hallucinogenic effect. As a classic serotonergic hallucinogen, LSD binds to different serotonin receptors (5-hydroxytryptamine (5-HT)), dopamine D₂ as well as α_2 adrenergic receptors (Passie et al., 2008). As an extremely potent substance LSD has its minimal recognizable dose already at 25 μ g, and 100 μ g to 200 μ g of LSD is the dosage that is recommended for a fully unfolded experience, lasting six to ten hours (Passie et al., 2008).

In recent studies, no severe adverse reactions to LSD were found. Nonetheless, some acute adverse effects can occur such as headaches, nausea, exhaustion, or lack of concentration (Dolder et al., 2016). When used in controlled medical settings LSD is viewed as relatively safe (Johnson & Griffiths, 2008). Although LSD is physically safe and not addictive, there may be psychological risks when it is consumed in unsupervised contexts. In a recreational setting when the substance is not controlled, other novel hallucinogens might be sold to consumers as LSD, further increasing the psychological risk (Rickli et al., 2015). Traumatic experiences, also called *bad trips*, can have negative long-term effects. For instance, LSD can cause flashbacks that, in rare cases, might lead to the hallucinogen persisting perception disorder (HPPD) (Halpern & Pope, 2003). Individuals suffering from HPPD reexperience perceptual symptoms they experienced under the psychedelic substance after the drug's cessation, causing clinically significant distress or impairment in functioning. Hence, although LSD does not cause severe negative effects, there is some psychological risk when consumed in uncontrolled settings.

When Albert Hofmann discovered LSD in 1943, he described his experience initially as unpleasant but on the next day he experienced “a sensation of well-being and renewed life” (Hofmann, 1980). Research showed that when administered in controlled settings, subjective effects of LSD are mainly positive. Predominantly, LSD causes changed meaning of precepts, audio-visual synaesthesia, blissful state, and positively experienced depersonalization/derealization during which the person distances from their ego or reality which is experienced as pleasant (Liechti, 2017a). Additionally, high dosages of LSD, around 200µg, can induce mystical experiences which entail a sense of unity of all things and people accompanied by a feeling of the truthfulness of this experience (Liechti et al., 2017b; Johnson et al., 2019). In studies focusing on psilocybin, researchers have related mystical experiences to positive long-term effects on personality and mood in healthy individuals as well as to positive therapeutic outcomes (Griffiths, 2011; Ross et al., 2016). This might point to the fact that mystical-type experiences could predict positive long-term effects of psychedelic drugs like LSD (Liechti et al., 2017a). Altogether, when LSD is administered in controlled settings there seem to be predominantly positive effects and few adverse reactions. Therefore, only studies in which LSD was administered in controlled settings will be included in the analysis.

To comprehend how LSD might influence well-being, it is helpful to acknowledge how the substance affects human neurobiology. The more fundamental impact on consciousness under the influence of LSD, such as ego-dissolution which encompasses distortions in one's subjective experience of the self, is shown to be connected to the disintegration of the default mode network (DMN) (Carhartt-Harris et al., 2016; Nour et al., 2016). The DMN has high

functional connectivity with other brain networks, implying that it might be the central conductor of global brain connectivity (Carhartt-Harris et al., 2014). While the DMN shuts down during the psychedelic experience, brain networks which are usually independent are connected to a greater extent, a state called *network entropy* (Carhartt-Harris, 2016). According to Shi et al. (2018), well-being is positively related to strong cross-network connectivity and weak within-network connectivity. Consequently, LSD could improve well-being by inducing an entropic brain state. This connection stresses the potential LSD might have to increase well-being, showing the importance to examine their relationship further.

For decades it was widely accepted that individuals are mentally healthy when they do not have a clinically diagnosed psychopathology (Westerhof & Keyes, 2010). Meanwhile, this assumption cannot by itself account for someone's optimal mental health. Nowadays it is widely recognized that the absence of psychopathology does not automatically imply complete mental health but is only one facet of it. Keyes's (2002) two continua model of mental health constitutes that a complete state of mental health is comprised of two distinct yet related dimensions, namely, mental illness and positive mental health (Westerhof & Keyes, 2009). Well-being is a crucial part of positive mental health but is often neglected in mental healthcare which focuses primarily on mental disorders (Cloninger, 2006). In psychedelic research, the focus is primarily placed on decreasing psychopathological symptoms too while the influence on positive psychological aspects like well-being is often overlooked (Jungaberle et al., 2018). This current lack of focus on positive psychological constructs highlights the need to investigate the effect of LSD on well-being.

Focusing specifically on well-being in psychedelic research has several benefits. It is particularly important as individuals possessing positive mental health report the highest psychosocial functioning, fewest missed workdays, and fewest health limitations (Keyes, 2002). Positive mental health is a protective factor when it comes to future psychopathology, making individuals more resilient (Keyes et al., 2010). Moreover, Keyes et al. (2010) showed that gains in positive mental health automatically reduce mental illness. Since only 20% of adults possess positive mental health, effective and sustainable interventions to increase well-being are called for to lift this number and LSD could be a valuable tool for this (Keyes et al., 2008; Keyes, 2005; Srivastava, 2011). Another advantage of focusing solely on the effect of LSD on well-being concerns that the whole population is considered, while only individuals suffering from psychopathology are included in clinical studies. However, individuals not diagnosed with psychopathology can also increase their mental health. Thus, an explicit focus on the effect of LSD on well-being is chosen in the current review.

To investigate the effect that LSD exerts on well-being it is necessary to conceptualise and operationalise well-being as a construct beforehand. Currently, the two dominating conceptualisations of well-being are subjective and objective well-being (Ross et al., 2020). Objective well-being can be assessed in the form of quality-of-life indicators like material resources or education. In contrast, subjective well-being, which will be the focus of this paper, concerns individual fulfilment and personal experiences (Ross et al., 2020). Furthermore, subjective well-being includes hedonic and eudaemonic well-being. While hedonic well-being is about pleasure and enjoyment, eudaemonic well-being stresses personal growth and meaning in life (Ross et al., 2020). Seligman's (2011) multidimensional conceptualisation of subjective well-being includes both hedonic as well as eudaemonic components of subjective well-being which is why it is used for the purpose of this paper. By identifying all articles that are related to these elements it is assumed that the effect of LSD on well-being can be estimated sufficiently.

According to Seligman's (2011) PERMA model, well-being consists of five building blocks, namely *positive emotions*, *engagement*, *relationships*, *meaning* and *accomplishment*. *Positive emotions* comprise hedonic components of well-being such as pleasure, happiness, and life satisfaction (Seligman, 2011). Frederickson (2004) argues that positive emotions broaden the thought-action repertoire of a person which leads them to build positive personal resources. Next, *engagement* encompasses using one's individual talents and force of character (Seligman, 2011). The component *relationships* concerns being loved, supported, and cared for by others and feeling connected to one's community. Moreover, *meaning* is about feeling a sense of purpose in one's life and experiencing a connection to something that is greater than the self. Finally, *accomplishment* includes personal achievements and fulfilling one's own goals in life. It leads to external recognition and gives individuals a sense of personal competence or mastery (Seligman, 2011).

As already stated, besides having positive effects on psychopathology and being associated with reduced psychological distress, psychedelics can also be beneficial for an individual's positive mental health (Krebs & Johansen, 2013). Specifically, evidence for the positive effect of different psychedelic substances on well-being has been accumulating in recent years (Gandy, 2019). For instance, in Agin-Liebes et al.'s (2020) crossover study, cancer patients who experienced existential distress reported increases in well-being and life satisfaction up until 4.5 years after being treated with a single dosage of psilocybin compared to placebo, both in combination with psychotherapy. Another study showed that regular ayahuasca users, compared to a control group, experienced elevated subjective well-being and increased purpose

in life which was sustained at follow-up one year later (Bouso et al., 2012). Hence, classical psychedelics have shown their potential to improve well-being in different populations.

Likewise, there are also indications that LSD has positive consequences on well-being, however, the evidence is scarcer here. In Schimmel et al.'s (2021) systematic review investigating the effect of psychedelics on the treatment of anxiety, depression, and existential distress in individuals with terminal illness the authors conclude that psychedelics seem to exert positive effects on well-being. However, using a sample only consisting of participants with terminal illnesses and psychopathological symptoms, these results cannot be generalised to the wider population. In addition, predominantly studies about psilocybin are reported in relation to well-being while there seems to be little evidence regarding LSD's effects on well-being. However, one study is described in which Gasser et al. (2015) administered two high doses of LSD and a low dose of LSD, acting as an active placebo, to individuals suffering from life-threatening diseases and illness-related anxiety. At the 12-month follow-up participants reported increased quality of life which is a concept closely related to well-being.

There is also more direct evidence of the relationship between LSD and well-being. In a recent meta-analysis on the therapeutic potential of LSD, which was conducted with healthy volunteers, moderate positive effects of LSD on well-being were observed (Li et al., 2021). However, the study objective of Li et al.'s (2021) meta-analysis was not explicitly focused on well-being but on giving an overview of the subjective and physical effects of the drug to examine its efficacy for therapy. Being also relevant for therapeutic purposes, a measure for well-being was included as a part of the subjective effects. However, the authors did not analyse the implications of the results related to well-being in detail. So, despite these promising findings, both reviews Schimmel et al. (2021) and Li et al. (2021) did not focus on well-being explicitly, primarily aiming to find out more about the therapeutic effects of LSD or psychedelics in general. Additionally, Schimmel et al.'s (2021) study was restricted to a clinical population. To fill this gap in the current literature, this review focuses solely on the effects of LSD on well-being, while concentrating on the general population.

To date, there is a lack of comprehensive understanding of positive psychological phenomena in psychedelic research. Already existing literature reviews on LSD have specifically focused on the therapeutic potential of the substance and rarely included positive psychological constructs like well-being. To gain more knowledge on the positive psychological effects of LSD and specifically on the relationship between LSD and well-being, a systematic literature review is needed. This will enable a comprehensive overview of the quality of evidence that is currently available on the topic. Hence, this paper is set out to answer

the following research question: What is the effect of LSD on well-being? Moreover, to broaden the scope of this review and gain more information on the relationship between LSD and well-being, the effect of LSD on the components of the PERMA model will also be investigated as a secondary research topic. To gather the best available causal evidence in the safest environment possible only placebo-controlled studies in controlled settings will be included.

Methods

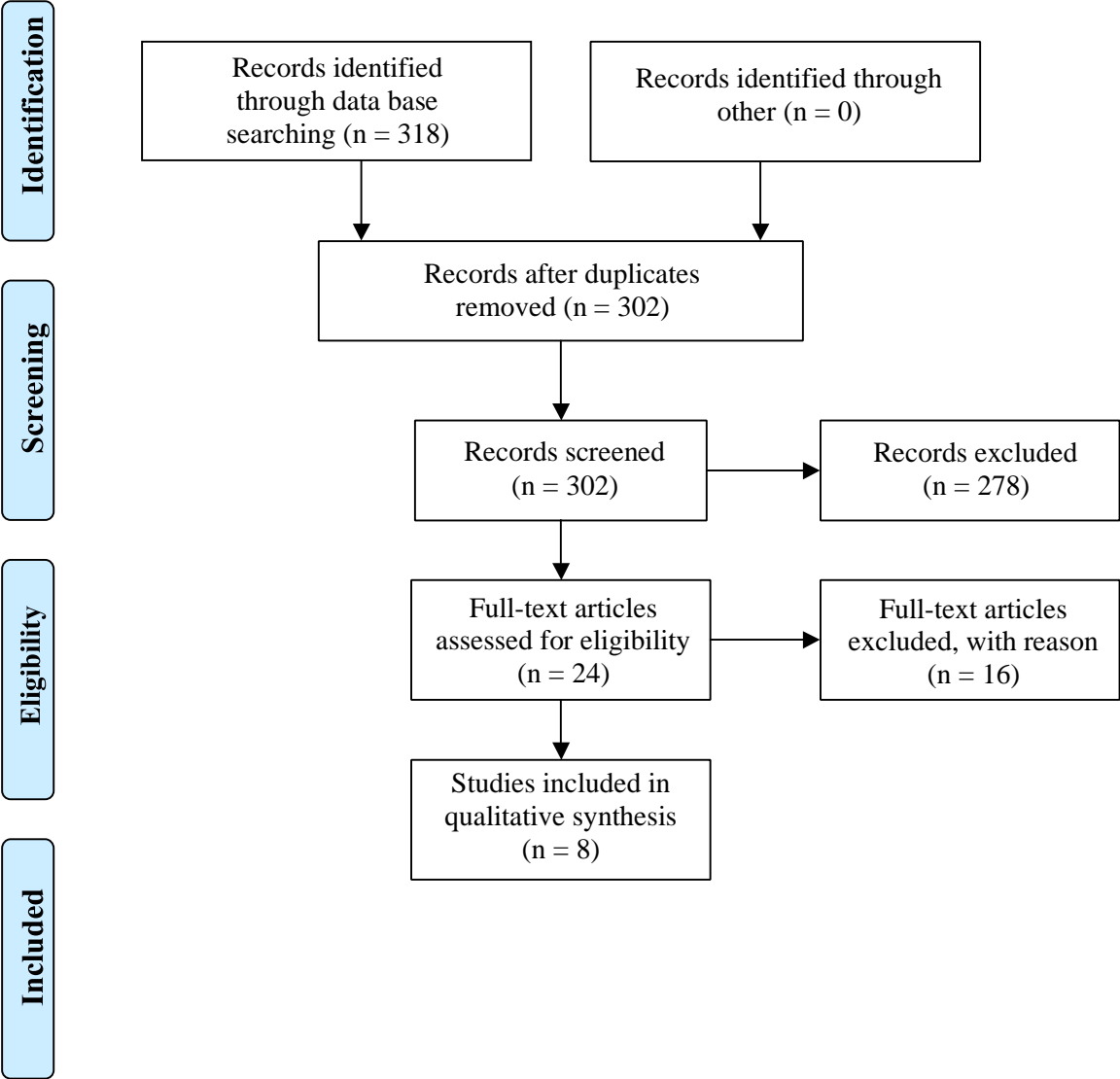
Search Process

The search, as well as the selection method, were designed according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines (Shamseer, 2015). Scopus, PsycNet, and PubMed were systematically searched for peer-reviewed articles between December 2022 and January 2023. To identify relevant literature, different variations of the term LSD were combined with well-being and its synonyms. Since the research in this field is still scarce, sub-concepts from the PERMA model of well-being were included in the search string as well. This should ensure that also secondary evidence for the relationship between LSD and well-being can be included in the analysis. The following search string was finally used: (LSD OR “lysergic acid diethylamide”) AND (wellbeing OR well-being OR “well being” OR flourishing OR happiness OR “quality of life” OR “positive emotions” OR engagement OR “positive relationships” OR meaning OR accomplishment OR PERMA).

In total, the search gave 318 hits. After removing duplicates, the 211 remaining articles' titles and abstracts were screened, and irrelevant studies were excluded. Afterward, 40 articles were assessed for eligibility by their full text. To ensure literature saturation, a secondary search was conducted by manually screening the references of the identified articles and thereby one more article was identified. Moreover, with the remaining articles a snowballing approach was used to check if any relevant literature was missed but no additional sources were found (Greenhalgh & Peacock, 2005). In the end, eight studies were included in the systematic literature review (see Figure 1).

Figure 1

PRISMA Flow Chart



Inclusion Criteria

To be included in the qualitative analysis of the following review, studies had to include information about the effect of LSD on well-being or on at least one of the components of the PERMA model of well-being. Only peer-reviewed randomized clinical trials were included to ensure high quality. Moreover, LSD had to be administered in a controlled setting to ensure that the trials are comparable as well as to minimise psychological risk for participants. To ensure this, studies needed to report that a physician or psychologist/psychotherapist was present during the whole procedure and that a standardized setting was used, for instance, a hospital room. Furthermore, studies needed to be published after 2010 as the first wave of psychedelic research is known to be methodologically weak (Wheeler & Dyer, 2020). Finally,

in the results of the studies it needed to be clear that only LSD and no other substances impacted well-being.

Extracted Data

For the purpose of analyzing the included studies, important information was extracted from each of the studies to check which aspects differed between studies (see Table 2). Basic information included the authors' names, the study design, a description of the study conditions, the mode of blinding the participants, the sample size as well as the study objectives. In addition, I checked the studies for well-being or PERMA model-related outcome measures and the outcomes of these measures. The classification of the extracted outcome measures according to the PERMA model can be seen in Table 1. In the absence of available criteria in the literature, the classification was done by the researcher. Moreover, some additional information was extracted from the studies to check for possible moderators of the treatment effect (see Table 3). This included the mean age of the participants, the gender ratio, the percentage of participants who were naïve to psychedelics, so who never consumed psychedelics before, as well as at what point in time the questionnaires were filled in.

Table 1

Classification of outcome measures according to the PERMA Model

PERMA model component	Outcome measure	Item of outcome measure
Positive emotions	5-D ASC	Blissful state
	VAS for subjective mood effects	Happy
	MEQ	Positive mood
	PEQ	Positive mood changes Positive attitudes about life/self
Engagement	-	-
Relationships	VAS for subjective mood effects	'Feeling close to others' 'I want to be with other people'

	PEQ	Altruistic/positive social effects
Meaning	5-D ASC	Changed meaning of percepts
	PEQ	Meaningfulness of the LSD experience
Accomplishment	-	-

Risk of bias assessment

All included studies were assessed for their quality with the help of the Cochrane risk of bias tool for randomised trials (Higgins et al., 2011). Seven aspects were used to evaluate the studies. Namely random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other forms of bias. To score the categories, low, unclear, or high risk of bias was assigned to each of them. Low risk was assigned to studies in which it could be proven that there is no risk of the assessed type of bias, unclear risk was given to studies in which information is lacking about the type of bias and finally high risk was used when a category is violated. However, four of the studies (Dolder et al., 2016; Holze et al., 2019; Holze et al., 2020; Schmid et al., 2015) were already assessed with the Cochrane risk of bias tool in Li et al.'s (2021) meta-analysis and hence their results for the assessment were transferred to this study.

Results

Table 2

Study Characteristics and Outcomes

Authors	Study design	Study conditions/ number of dosages	Blinding	Sample size	Study Objective	Well-being related Outcome Measures	PERMA model component	Outcome
Carhart-Harris (2016)	Placebo- controlled within-subjects cross-over design, balanced order	(1) 75µg LSD (2) Placebo → 1 time LSD	Single-blind, inactive placebo	N = 20	Acute and mid-term (2 weeks after dosing) psychological effects of LSD in healthy subjects	5D-ASC: Blissful state Changed meaning of precepts	Positive emotions Meaning	Increase under LSD compared to placebo Increase under LSD compared to placebo
Dolder et al. (2016)	Randomised placebo- controlled within-subjects crossover designs	(1) LSD: 200µg N = 16, 100µg N = 24 (2) Placebo → 1 time LSD	Double-blind, inactive placebo with opaque capsules	N = 40	Acute effects of LSD on emotion processing in healthy subjects	AMRS: well-being VAS for subjective mood effects: 'Happy'	Positive emotions	Marked increase under LSD compared to placebo ($F_{1,38} = 11.49, p < .01$); no difference between 100µg (Cohen's $d =$ 3.54) and 200µg (Cohen's $d = 3.89$) Increase under LSD compared to placebo → peak effects greater at 200µg than 100µg

						‘Feeling close to others’ & ‘I want to be with other people’	Relationships	Increase under LSD compared to placebo → peak effects greater at 200µg than 100µg
Holze et al. (2020)	Placebo-controlled within-subjects crossover design	(1) Placebo (2) 25µg LSD (3) 50µg LSD (4) 100µg LSD (5) 200µg LSD (6) 200µg LSD 1 h after ketanserin administration → 4 times LSD	Double-blind, inactive placebo with opaque capsules	N = 16	Acute dose-dependent effects of LSD (1h before and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, and 24 h after dosing) in healthy subjects	AMRS: well-being 5D-ASC: Blissful state Changed meaning of precepts	Positive emotions Meaning	No effect for 25µg, 100µg and 200µg of LSD compared to placebo; Marked increase at 50µg of LSD compared to placebo ($p < .05$; Cohen’s $d = 3.89$) No effect at 25µg and 50µg of LSD; Increase at 100µg and 200µg of LSD compared to placebo No effect at 25µg and 50µg of LSD; Increase at 100µg and 200µg of LSD compared to placebo
Holze et al. (2019)	Placebo-controlled within-subjects cross-over design	(1) 100µg LSD (2) MDMA (3) D-amphetamine (4) Placebo → 1 time LSD	Double-blind, inactive placebo	N = 28	Describe and compare acute subjective effects and acute effects on autonomous nervous system of LSD, MDMA and D-amphetamine in healthy subjects	AMRS: well-being 5D-ASC: blissful state changed meaning of precepts MEQ: positive mood	Positive emotions Meaning Positive emotions	No effect compared to placebo Increase under LSD compared to placebo Increase under LSD compared to placebo Increase compared to placebo
Preller et al. (2020)	Randomized placebo-controlled	(1) 100µg LSD (2) Placebo	Double-blind, inactive placebo	N = 22	Acute effects of LSD on personal relevance processing	5D-ASC: Blissful state	Positive emotions	Increase under LSD compared to placebo

	within-subject cross-over design	(3) Ketanserin + 100µg LSD → 1 time LSD			with/without pre- treatment of ketanserin (5-HT _{2A} antagonist) in healthy subjects	Changed meaning of precepts PANAS: Music paradigm (question 1-3 of subjective experience of musical excerpts)	Meaning Meaning	Increase under LSD compared to placebo Increase in positive affect under LSD compared to placebo Music rated more meaningful in LSD condition compared to placebo; Meaning of previously meaningless and neutral music increased under LSD
Schmid et al. (2015)	Randomized placebo- controlled within-subjects cross-over design	(1) 200µg LSD (2) Placebo → 1 time LSD	Double-blind, inactive placebo	N = 16	Acute effects of LSD in healthy subjects	AMRS: well-being 5D-ASC: blissful state Changed meaning of precepts	 Positive emotions Meaning	Marked increase under LSD compared to placebo ($F_{1,15} = 8.2, p < .05$; Cohen's $d =$ 3.66) Increase under LSD compared to placebo Increase under LSD compared to placebo
Schmid & Liechti (2017)	Randomised placebo- controlled within-subjects cross-over design, balanced order	(1) 200µg LSD (2) Placebo → 1 time LSD	Double-blind, inactive placebo	N = 16	Long-lasting (12 months after dosing) subjective effects of LSD in healthy subjects	PEQ: well-being/life satisfaction positive attitudes about life/self positive mood changes	 Positive emotions Positive emotions	Increase under LSD at 1- and 12-month follow-ups compared to baseline Increase under LSD at 1- and 12-month follow-ups compared to baseline Increase under LSD at 1- and 12-month follow-ups compared to baseline

					altruistic/positive social effects	Relationships	Increase under LSD at 1- and 12-month follow-ups compared to baseline	
					meaningfulness of the LSD experience	Meaning	Increase under LSD at 1- and 12-month follow-ups compared to the assumption that the experience will be as meaningful as an everyday experience	
Wießner et al. (2021)	Randomized placebo-controlled crossover design	(1) 50µg LSD (2) Placebo → 1 time LSD	Double-blind, inactive placebo	N = 24	Exploring the suitability of LSD as a psychosis or therapy model (acute, 7 hours after dosing) in healthy subjects	5D-ASC: blissful state Changed meaning of precepts MEQ: positive mood	Positive emotions Meaning Positive emotions	Increase under LSD compared to placebo Increase under LSD compared to placebo Increase under LSD compared to placebo

Scales: Adjective Mood Rating Scale (AMRS), Altered States of Consciousness (5D-ASC), Visual Analog Scale (VAS), Positive and negative Affect Scale (PANAS), Persisting Effects Questionnaire (PEQ), Mystical Experiences Questionnaire (MEQ)

Table 3

Additional Information to Check for Possible Moderators of Treatment Effect

Authors	Mean age & standard deviation	Participant gender	Naivety to psychedelics	Point of measurement
Carhart-Harris (2016)	30.9 ± 7.8	4 female, 16 male	0% naïve	5D-ASC: end of dosing day

Dolder et al. (2016)	33 ± 11 (100µg) 29 ± 6 (200µg)	20 female, 20 male	72,5% naïve	AMRS: 1 hour before & 3, 10, 24 hours after administration VAS: 1 hour before and 0, 0.5, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 16, 24 hours after administration
Holze et al. (2020)	29 ± 6.4	14 female, 14 male	62,5% naïve	AMRS: 1 hour before & 1.5, 4, 11 hours after administration 5D-ASC: 24 hours after administration
Holze et al. (2019)	28 ± 4	8 female, 8 male	68,75% naïve	AMRS & MEQ: 1 hour before & 1.5, 4, 11 hours after administration 5D-ASC: 11 hours after administration
Preller et al. (2020)	25.7 ± 3.7	5 female, 17 male	63,46% naïve	5D-ASC & PANAS: 10 minutes before & 12 hours after administration
Schmid et al. (2015)	28.6 ± 6.2	8 female 8, male	56,25% naïve	AMRS: before administration and 3, 10, 24 hours after administration 5D-ASC: 24 hours after administration
Schmid & Liechti (2017)	28.6 ± 6.2	8 female, 8 male	56,25% naïve	PEQ: 1, 12 months after administration
Wießner et al. (2021)	35 ± 11	8 female, 16 male	29,17% naïve	5D-ASC & MEQ: 7 hours after administration

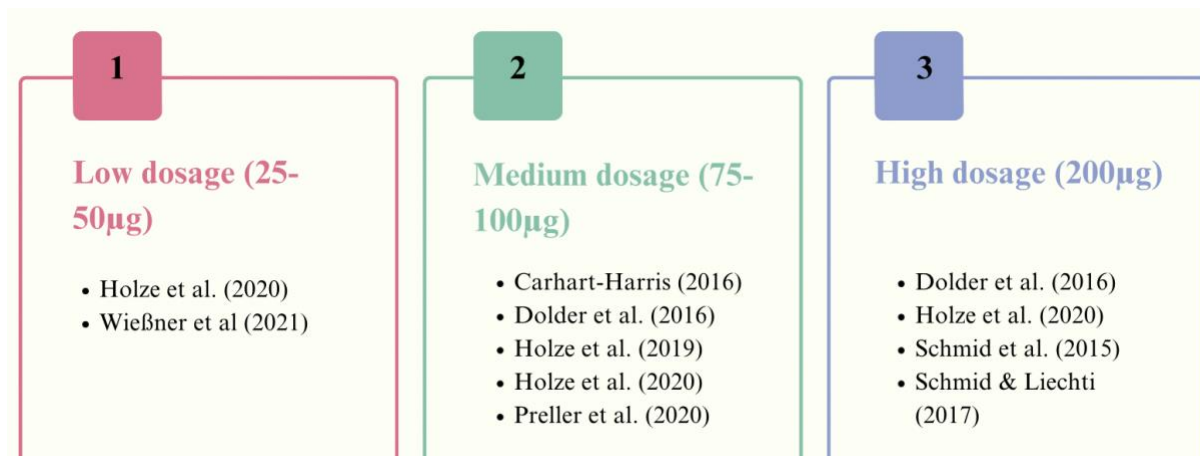
Study Characteristics

There are several aspects that are similar in all analysed studies. Generally, it occurred that all studies made use of a placebo-controlled within-subjects cross-over design. Moreover, each study employed a relatively small sample size between 16 and 40 participants. Remarkably, only healthy subjects were included in all eight studies. In total, 180 subjects participated in all studies. In none of the studies, adverse events occurred. Additionally, all studies used an inactive placebo. Finally, the primary study objective was not about the effect of LSD on well-being in all the trials but mostly about the acute subjective effects of LSD more generally.

When looking at the study characteristics one can identify three different clusters based on the LSD dosage that was administered namely low, medium, and high dosage (see Figure 2). According to these groups, I will present the results. The first cluster, which includes studies with a low dosage of LSD (25-50µg), consists of 2 studies (Holze et al., 2020; Wießner et al., 2021). Holze et al.'s (2020) study has 6 study conditions including different doses of LSD, ketanserin which is a 5-HT_{2A} receptor antagonist plus LSD and placebo. With administered LSD dosages being 25, 50, 100, and 200µg, the study is included in each cluster but will only be described in detail in this section. In contrast, Wießner et al.'s (2021) study only consists of a 50µg LSD condition and placebo. Moreover, both studies were double-blind while Holze et al. (2020) additionally utilising opaque capsules through which the participants could not see what substance is inside. Holze et al.'s (2020) aim was to investigate the acute dose-dependent subjective and autonomous effects of LSD. These effects were among others measured with the Adjective Mood Rating Scale (AMRS) which includes a measure of well-being and the Altered States of Consciousness Questionnaire (5D-ASC) which includes a question related to positive emotions (blissful state) and a measure related to meaning (changed meaning of precepts) from the PERMA model. In Wießner et al. (2021) the primary objective was to explore whether LSD is a suitable therapy tool or a useful psychosis model due to the phenomenological similarities to schizophrenic symptoms. In addition to the 5D-ASC they included the Mystical Experiences Questionnaire (MEQ) which encompasses a measure related to positive emotions (positive mood).

Figure 2

Study Clusters According to LSD Dosage



Next, the cluster with medium dosages of LSD (75-100µg) contains five different studies (Carhart-Harris, 2016; Dolder et al., 2016; Holze et al., 2019; Holze et al., 2020; Preller et al., 2020). All studies besides Holze et al. (2019) and Holze et al. (2020) had two conditions, namely LSD and placebo. Holze et al. (2020) included 2 additional conditions, besides 100µg of LSD and placebo they added a MDMA and a D-amphetamine condition. The MDMA and D-amphetamine conditions could be seen as an active placebo to some degree due to the substances' partially overlapping effects with LSD. Additionally, two of the studies used opaque capsules which increases blinding (Dolder et al., 2016; Holze et al. 2020). Furthermore, Carhart-Harris et al. (2016) was the only study included in the systematic analysis that was single-blind while all others used double-blinding. The primary objective of the studies in this cluster was more general in some studies, examining acute and mid-term subjective/psychological effects of LSD (Carhart-Harris, 2016), or more specific on acute effects of LSD on emotion or personal relevance processing (Dolder et al., 2016; Holze et al., 2019; Preller et al., 2020). Four of the studies made use of the 5D-ASC (Carhart-Harris et al., 2016; Holze et al., 2019; Holze et al., 2020; Preller et al., 2020) and three of the AMRS (Dolder et al., 2016; Holze et al. 2019; Holze et al., 2020). Holze et al. (2019) further utilised the MEQ. Moreover, Dolder et al. (2016) additionally included a Visual Analog Scale (VAS) for subjective mood effects including the item 'happy' which is related to the sub-concept positive emotions of the PERMA model. Finally, Preller et al. (2020) used the Positive and Negative Affect Scale (PANAS) encompassing the sub-scale positive affect which is also related to positive emotions. They additionally added a music paradigm in which the meaning of previously meaningful, meaningless, and neutral music under the influence of LSD was investigated.

The final cluster with the high dosages (200µg) includes four studies (Dolder et al., 2016; Holze et al., 2020; Schmid et al., 2015; Schmid & Liechti, 2017). Besides Holze et al. (2020) all studies from this cluster had two study conditions, LSD and placebo. The primary study objective of the studies which were not yet included in the previous conditions was to investigate the acute (Schmid et al., 2015) and long-term (Schmid and Liechti, 2017) effects of LSD. The measures which were related to well-being in these remaining two studies were the AMRS, the 5D-ASC (Schmid et al., 2015), and the Persisting Effects Questionnaire (PEQ) (Schmid & Liechti, 2017). In the PEQ well-being is included directly in addition to questions related to positive emotions, meaning, and positive relationships.

Possible Moderators of Treatment Effect

The additional information, which was obtained from the studies to check for possible moderators of the treatment effects, showed that the mean age of the studies was between 25.7 and 35 years. Moreover, in most studies, the ratio between female and male participants was balanced except in three studies that included more men than women (Carhart-Harris, 2016; Preller et al., 2020; Wießner et al., 2020). Next, in most of the studies, at least half of the subjects never consumed psychedelics before and were thus naïve to LSD. Carhart-Harris (2016) only included individuals who had used the substance before, and in Wießner et al. (2021) about 70% of participants used psychedelics prior to the study. Finally, in most studies, the questionnaires were filled in during the session or closely afterward while the exact time points and frequencies at which they were administered varied between studies and the type of measure that was obtained.

Risk of bias

Looking at the results of the risk of bias assessment, Carhartt-Harris et al. (2016) got assigned a high risk of bias for blinding of participants and personnel as they only used a single-blind design, not blinding the researchers but only the participants (see Figure 3). As the other studies in this category used double-blinding and were placebo-controlled they got assigned a low risk of bias. However, it is necessary to stress that blinding studies with psychedelic drugs is generally difficult because of the strong and noticeable effects that the substances exert and the current lack of suitable active placebos. Next, Schmid et al. (2015) were assigned reporting bias because they only reported autonomic and endocrine effects at expected peak periods of LSD while full documentation of the effects needs to be reported in the results (Li et al., 2021). Moreover, the categories of allocation concealment and blinding of outcome data could not be assessed adequately due to a lack of information in most studies. Therefore, only a few studies could be scored with a low risk of bias in these categories which poses an additional risk to the

Outcomes Related to Well-being

Primary Evidence

The AMRS measures well-being directly and can thus be seen as primary evidence in this systematic literature review. When it comes to primary evidence for well-being, in the low dosage studies, it can be observed that only at 50µg and not at 25µg of LSD a significant marked increase occurred (Holze et al., 2020). In fact, 50µg was the only dosage at which an increase in this measure was found in Holze et al.'s (2020) study. Hence the evidence for increases in well-being is mixed among studies using a low dosage of LSD.

Next, in the second cluster with the medium dosage studies, the findings were contradictory. Regarding the AMRS, Dolder et al. (2016) found a significant marked increase for well-being at 100µg of LSD while Holze et al. (2019) and Holze et al. (2020) did not find a significant effect at the same dosage. So, the primary evidence for the effect of LSD on well-being was heterogeneous in the medium-dosage studies.

Finally, among the high-dosage studies, the evidence for the influence of LSD on well-being was inconsistent as well, with one study finding no effect and 3 studies finding a positive effect. The results of the AMRS, similar to the medium dosage studies, showed conflicting outcomes. Dolder et al. (2016) and Schmid et al. (2015) both reported a significant marked increase for the 200µg LSD condition, whereas Holze et al. (2020) did not find a significant effect at this dosage. In Schmid and Liechti's (2017) study the PEQ showed a significant increase at 1- and 12-month follow-up for well-being/life satisfaction at the 200µg dosage compared to the assumption that no change would occur. Between the two follow-ups, there was no significant difference in well-being, indicating that the increase in well-being is stable and long-lasting. Furthermore, the authors stressed that no participant reported a decrease in well-being after the LSD treatment. Consequently, the findings on whether LSD increases well-being at a dosage of 200µg are mixed.

Secondary evidence

The secondary evidence encompasses measures related to the PERMA model components and thus is also associated with well-being. The components *engagement* and *accomplishment* could not be identified in any of the included studies.

Positive Emotions.

In the 5D-ASC *blissful state* is included. This measure belongs to the sub-concept *positive emotions* from the PERMA model. For *blissful state*, Wießner et al. (2021) found a significantly elevated score for 50µg of LSD compared to placebo. However, for the exact same dosage, Holze et al. (2020) did not find a significant increase in the LSD condition compared to placebo.

In line with this, they did not find an effect at the lower dosage of 25µg too. Finally, looking at the MEQ's section on *positive mood*, also belonging to the sub-concept *positive emotions* of the PERMA model, Wießner et al. (2021) did find a significant increase under LSD compared to placebo. Hence, evidence for an increase in *positive emotions* is mixed in the low-dosage studies.

In the medium-dosage studies, the evidence for an increase in *positive emotions* was more consistent. Research in which the 5D-ASC was employed shows significantly higher scores for *blissful state* in the LSD condition versus in the placebo condition indicating a consistent acute effect at 75 to 100µg (Carhart-Harris, et al., 2016; Holze et al., 2019; Holze et al., 2020; Preller et al. 2020). Moreover, in Holze et al. (2019), the item of the MEQ about positive mood increased under LSD compared to placebo. In Preller et al. (2020) the outcome of the PANAS showed an increase in *positive affect* compared to baseline in the LSD condition versus placebo. Moreover, the VAS for subjective mood effects showed significant increases for the item *happy* at the 100µg LSD dosage compared to the placebo, indicating an increase in *positive emotions* (Dolder et al., 2016). Thus, among the middle-dosage studies, the measures related to *positive emotions* are all affected positively by the substance.

Looking at the studies with high dosages, outcomes are positive as well. In Schmid and Liechti (2017), subjects experienced a significant increase in *positive attitudes about life and self* as well as *positive mood changes* at both follow-ups. Moreover, the 5D-ASC showed consistently significant increases for *blissful state* at the 200µg dosage compared to placebo (Holze et al, 2020; Schmid et al., 2015). Hence, in the high dosage cluster, effects on *positive emotions* are consistently positive.

Meaning.

In the 5D-ASC there is also a measure related to *meaning* from the PERMA model included, namely *changed meaning of precepts*. For this measure Wießner et al.'s (2021) study showed an increased score at 50µg of LSD compared to placebo. Like in the previous section, Holze et al. (2020) did not find an elevated score for *changed meaning of precepts* at 25µg and 50µg of LSD. Thus, in the low dosage studies the findings for *meaning* are heterogenous.

Looking at the medium dosage studies, scores for *changed meaning of precepts* were increased in the LSD condition compared to the placebo suggesting a consistent acute effect at 75 to 100µg (Carhart-Harris, et al., 2016; Holze et al., 2019; Holze et al., 2020; Preller et al. 2020). In Preller et al.'s (2020) study the music paradigm in which the meaning of previously meaningful, meaningless and neutral music was explored showed that the participants rated music as significantly more meaningful under 100µg of LSD compared to placebo. Especially

music that was previously meaningless or neutral to the subjects was judged as more meaningful. Accordingly, a consistently positive effect of LSD on *meaning* can be observed in the medium dosage range.

In the high-dosage studies, the 5D-ASC showed consistently significant increases in *changed meaning of precepts* compared to placebo as well (Holze et al, 2020; Schmid et al., 2015). Furthermore, compared to the assumption that experiencing LSD will be as meaningful as an everyday experience, ratings on the meaningfulness of the LSD experience significantly increased at the study's follow-ups (Schmid & Liechti, 2017). On top of that, 10 out of the 14 subjects rated the LSD experience as among the ten most meaningful events of their lives. So, the influence LSD had on *meaning* was consistently positive at 200µg.

Relationships.

Related to *relationships* from the PERMA model, Dolder et al. (2016) included *feeling close to others* and *I want to be with other people* in their VAS for subjective mood effects. These measures showed significant increases at the 100µg LSD dosage compared to placebo. Hence, the component *relationships* was increased by a medium dosage of LSD.

Regarding the high-dosage studies, subjects experienced a significant increase in *altruistic and positive social effects*, being connected to *relationships* (Schmid and Liechti, 2017). Furthermore, *feeling close to others* and *I want to be with other people* on the VAS did also increase at 200µg of LSD (Dolder et al., 2016). While the baseline effects were similar, it is noticeable that the peak effects of the substance in these categories are significantly higher at the 200µg dosage compared to the 100µg dosage. Thus, LSD influenced *relationships* positively with more intense peak effects at the higher dosage.

Discussion

This systematic literature review collected available evidence on the effect of LSD on well-being while also looking into the relationship between LSD and the components of the PERMA model. This was done by screening different search engines for peer-reviewed placebo-controlled trials which include evidence on the influence of LSD on well-being and/or the PERMA model components. In total, 8 studies were found that fulfilled all inclusion criteria which were then analysed further. The relevant information from these articles was gathered and a risk of bias assessment was performed for each study.

Overall, a positive effect of LSD on well-being seems more likely than no effect. A negative effect was found in none of the studies and is thus very unlikely. The findings are not fully consistent but especially at higher dosages, positive effects are more frequent. At medium and lower dosages, the effect is less clear as the results are more inconsistent. Regarding the low

dosage studies, 25µg LSD is unlikely to affect well-being (Holze et al., 2020). However, at 50µg a marked increase in well-being was found in the only study that examined well-being at this dosage, despite the small sample size (Holze et al., 2020). This inconsistent finding of low LSD dosages is in line with other literature reviewing the effects of *microdosing* which entails taking low doses of psychedelics regularly. Earlier reviews also concluded that some studies find positive effects of *microdosing* while others do not (Bornemann, 2020). To examine whether the effects of *microdosing* go beyond placebo, more large-scale placebo-controlled trials are necessary (Kuypers, 2019). Hence, at this point, evidence is still insufficient to determine whether such low doses of LSD have a positive effect on well-being.

Regarding the medium dosages, two studies did not find an effect at 100µg (Holze et al., 2020; Holze et al. 2019) while one study did find a marked effect of LSD on well-being at the same dosage (Dolder et al., 2016). It is impossible to determine a trend here since the evidence is still scarce. Moreover, it is not possible to draw any conclusions based on the risk of bias rating as all three studies had the same rating. However, Dolder et al. (2016) made use of the largest sample out of all included trials, giving the most statistical power to this study. The smaller sample sizes of the other studies might explain why they did not find a significant effect. Nevertheless, with the current evidence base, it is still not possible to draw any conclusion on whether medium dosages of LSD improve well-being. However, some of the results imply potential, stressing the necessity to conduct further research in this area.

The final cluster, consisting of studies with high dosages, includes the largest number of trials and has thus the largest evidence base. Compared to the low and medium-dosage studies positive results occurred more consistently. Three out of the four studies found marked effects of LSD on well-being (Dolder et al, 2016; Schmid et al., 2015; Schmid & Liechti, 2017) with only one study that found no effect (Holze et al., 2020). It should be considered that three out of the four studies have small sample sizes and Schmid et al.'s 2015 study has a considerable risk of bias. Nevertheless, the increase in significant results indicates that higher dosages of LSD are more likely to elevate well-being in individuals. Dolder et al.'s (2016) study offers further support for this hypothesis as peak effects on well-being were especially high at 200µg compared to 100µg. This is in line with previous studies measuring the effects of psilocybin on well-being which also found that higher dosages improved well-being more (Griffiths, 2011; Griffiths, 2018).

That higher dosages of LSD are more likely to increase well-being could be explained by the finding that mystical experiences elicited by LSD lead to improvements in well-being. Research already found that ratings of mystical-type experiences predicted increases in well-

being after taking psychedelics, indicating that mystical experiences might be a working mechanism of substances like LSD (Haijen et al., 2018; Kangaslampi, 2019). Mystical experiences occur in a dose-dependent manner with higher dosages being more likely to trigger them (Barrett & Griffiths, 2018). Therefore, if mystical-type experiences are (partly) underlying the positive changes in well-being this would explain why well-being increases more consistently at higher doses of LSD when mystical experiences occur more frequently. In line with this, Griffiths et al. (2018) suggest in their study that the greater positive effect of high psilocybin dosages on well-being is influenced by the intensity of mystical experiences. To gain more clarity, future research is needed examining whether mystical experiences mediate the effect LSD possibly exerts on well-being.

Regarding the related concepts from the PERMA model, *positive emotions*, *meaning* and *relationships* could be identified in the studies, but not *engagement* and *accomplishment*. The former three concepts were consistently positively influenced by LSD while there is no information about the remaining two concepts. Only Holze et al. (2020) did not find any significant effects at the dosage of 25µg and 50µg for measures related to *positive emotions* and *meaning*. However, at higher dosages of 100µg and 200µg, they did find a significant positive effect of LSD on these measures. In comparison, Wießner et al. (2021), having a larger sample size, also administered the same questionnaire to their participants with a 50µg dose of LSD and found a significant effect on both, *meaning* and *positive emotions*. Looking at these results, one can put the absent positive effect in Holze et al.'s (2020) study in perspective. They did observe insignificant increases in *meaning* and *positive emotions* at of 25µg and 50µg. Hence, it should be considered that they only used a sample size of 16, resulting in low statistical power. In comparison, all other analysed studies which examined the relationship between LSD and well-being-related components did find positive effects of the psychedelic substance at all dosages (Dolder, 2020; Holze, 2020; Preller, 2020; Schmid, 2015; Schmid & Liechti 2017; Wießner, 2021). Therefore, it seems likely that LSD influences *positive emotions*, *meaning* and *relationships* positively but further studies are needed to gain more certainty on these findings.

With the previous findings in mind, the question emerges as to why only three out of the five PERMA components could be identified in the studies. There were no studies found that investigated the effect of LSD on *engagement* or *accomplishment* in the literature. Therefore, it can be assumed that the relationship between LSD and these components has not been studied yet. When LSD is described in the literature, subjective effects like changed *meaning*, *positive emotions*, as well as feelings of closeness to others (*relationships*) are regularly referred to (Liechti, 2017a). Moreover, these concepts are often included in questionnaires assessing the

psychedelic experience like the Altered States of Consciousness Questionnaire (5D-ASC) or the Mystical Experiences Questionnaire (MEQ). This might indicate that LSD works and affects well-being primarily through these components and not as much through the other components. More precisely, that researchers most frequently selected to study *positive emotions* and *meaning* and *relationships* in connection to LSD might imply that these concepts are closely related to the working mechanisms of LSD while the remaining concepts are not.

Referring to mystical experiences as a working mechanism in psychedelics again, Griffiths et al. (2006) found that mystical experiences had sustained personal meaning for their participants. Moreover, positive emotions and social connectedness are also known to be experienced during mystical experiences (Kangaslampi et al., 2020). Accordingly, mystical-type experiences, as a working mechanism of psychedelics, seem to be closely connected to *meaning*, *positive emotions*, and *relationships*. That concepts like *engagement* or *accomplishment* are not experienced during mystical experiences might be explained by the nature of this state of mind. The perception of the self or ego dissolves during mystical experiences (MacLean et al., 2012). However, feeling accomplishment or engagement presupposes that one perceives oneself as an individual which is not natural in a state of unity and transcendence. For instance, accomplishment involves feeling a sense of personal achievement and goal-directedness which is inherently egocentric. To gain more clarity on this hypothesis, more studies on the effect of LSD on all the PERMA components, especially on *engagement* and *accomplishment*, are necessary. At this point, it is impossible to conclude why only part of the PERMA components could be identified in the literature but the ego state during mystical experiences could be a possible explanation.

To get an insight into the reasons why some studies did, and some studies did not find a significant positive effect of LSD on well-being and the PERMA components, possible moderators of the treatment effect were considered. However, when comparing the studies that did find and that did not find positive effects and looking into potential moderators, no patterns could be identified. The same result occurred when comparing the only study that did not consistently find positive effects of LSD on *positive emotions* and *meaning* with the other studies. So, the moderators we considered, which were mean age, gender, naivety to psychedelics, and time of measurement, did not show any effect on the treatment outcome.

As there is still significant uncertainty regarding the effects of LSD on well-being it is not possible at this point to recommend the substance for mental health care. This does not mean that the potential of LSD to improve well-being should be underestimated. However, research is still in an early phase. To authorise LSD for official use more certainty on the beneficial

effects of the drug as well as evidence-based guidelines for practitioners are needed (Torres, 2021). Nonetheless, the findings of this systematic review are also relevant to mental health care in non-psychedelic settings. Although it is currently not feasible to use psychedelics as a therapeutic tool to increase well-being, the therapeutic potential of its probable working mechanisms like mystical experiences could be integrated into therapies. One possibility proposed by Kalzuna et al. (2022) could be to integrate mindfulness into therapies. Through reducing self-focused cognitions this might have, although weaker, comparable effects to the ego dissolution in mystical experiences. Moreover, the findings of this study stress the importance of positive emotions, relationships, and meaning in life for well-being. The study shows that a lack of these concepts is a source of suffering in our society which urgently needs to be addressed in mental health care. Hence, research on the effect of psychedelics on well-being could not only be seen as an intervention itself. Especially in times in which psychedelics are not a feasible intervention (yet), the research could be seen as a tool to understand how we can influence well-being more generally.

Strengths and Limitations

Strengths and Limitations of the Analysed Studies

There are some important points that need to be considered when interpreting the analysed studies and drawing conclusions from them. A limitation that applies to all studies concerns that only healthy subjects were included although an explicit focus of the study was to include healthy as well as clinical populations. In all studies, individuals were excluded who suffer from diagnosed psychiatric illnesses. Moreover, having an immediate family history of psychotic disorder or sometimes a first-degree family member with any psychiatric disorder was an exclusion criterion in all trials. Additionally, participants had to undergo a health screening and needed to be declared as physically and mentally healthy by a psychiatrist/physician. For instance, people with chronic illnesses were often excluded from the trials. Several studies also excluded individuals who consumed illicit drugs more than 10 times throughout their life. Due to these restrictions, the results are not representative of the whole society and specifically cannot be extended to clinical populations. Although the safety of the participants needs to be the highest priority, to gain a more representative picture of the influence LSD has on well-being, future studies need to integrate more varied individuals, also including or focusing on clinical populations.

A limitation that was already mentioned shortly in the risk of bias assessment concerns the study design of the analysed studies. A within-subjects design was utilized in every study which is problematic as this is only suitable to examine treatments that do not have persistent effects

(Charness et al., 2012). However, there might be the risk that if participants get the LSD treatment first, this may have carry-over effects to the next session, distorting the results (Lieberman & Shalev, 2016). Especially when it comes to psychedelics, it is highly likely that participants notice they are in the experimental group. The substance's mind-altering effects are strong and can easily be identified, weakening the placebo effect (Aday et al., 2022). With the current lack of suitable active placebos in psychedelic research, this problem is amplified putting serious limits to the conclusions of the current literature search. This problem could be solved by utilising between-subject designs in future trials or by researchers testing whether the effects found in the first round of administration are any different from subsequent rounds.

Another limitation connected to the previous one is that the studies which were analysed mostly did not focus on well-being explicitly and were therefore not constructed to measure it in the best way possible. This might have, for instance, contributed to the choice of the within-study design in many studies. When it comes to well-being, treatment should have a long-term impact on the participants. However, most of the trials focused on short-term outcomes and did not include long-term follow-ups. Accordingly, whether the studies measure well-being sustainably is questionable since it is mostly treated as a state, and it is not known whether the results endure further. Although it is already promising to know that LSD possibly improves well-being or its related sub-concepts acutely, to benefit our society sustainably, these findings need to be extended over longer periods. Hence, there is a strong need to create studies that are tailored to measuring the long-term effects of LSD on well-being, including the number of sessions necessary to achieve lasting effects.

Strengths and Limitations of this Systematic Review

Besides considering the strengths and limitations of the analysed studies it is important to acknowledge some important aspects regarding the literature review itself. When interpreting this study, the exclusive focus on controlled experimental studies needs to be addressed. A disadvantage of this choice is that other types of evidence were automatically excluded. By choosing strict exclusion criteria important information might be missing from the current analysis. Especially as there are not many studies yet on the effect of LSD on well-being, a broader scope could have been beneficial to gather as much information as possible. For instance, including longitudinal or cohort studies could have broadened the perspective on the topic by adding more naturalistic evidence and sustained effects. However, the same point of utilising strict exclusion criteria simultaneously is a strength of this systematic review. By focusing on controlled experimental studies only placebo-controlled studies were included which is a major strength of the current review, adding to the strength of the evidence. Thereby

it was possible to gather the most rigorous evidence on the topic and to identify important gaps as well as problems regarding the current state of research regarding the influence of LSD on well-being.

The risk of bias assessment can also be seen as a strength and limitation to this study. On the one side, it was helpful because it revealed that all studies suffer from bias and need to be treated with care. On the other hand, the two-level classification which was based on the risk of bias assessment did not add value to the analysis. Studies with contradicting results were always categorised at the same level so no pattern emerged which favoured an effect direction based on better study quality. Moreover, due to time constraints, only the study reports could be used to rate the different criteria from the risk of bias assessment, and it was abstained from contacting the authors for missing information. With a considerable amount of relevant information missing in the reports, not all sections of the risk of bias assessment could be rated, putting its accuracy into question (Jørgenson et al. 2016). For instance, allocation concealment was only addressed in two out of the eight studies and therefore had to be rated with unclear risk of bias in the remaining studies. Due to this, the question emerges whether the risk of bias rating might have painted an inaccurate picture of the studies' quality. If all categories could have been rated, this might have impacted the conclusions differently, putting a limitation to the current study. Therefore, future reviews should contact trial authors in case of missing information to gain more certainty on the risk of bias assessment (Jørgenson et al. 2016)

Finally, a major strength of the systematic literature search is the inclusion of the PERMA model into the search string of the literature search. As the effect of LSD on well-being is a topic that is only starting to be researched, not many studies have been published yet on the direct effect of LSD on well-being. Including the sub-components of the PERMA model in the search made it possible to include more indirect evidence as well. However, as the sub-components from the PERMA model are framed broadly there also emerged problems. For example, search terms like *meaning* or *relationships* generated a significant amount of irrelevant hits during the search process. Moreover, it needs to be considered that the items found in the studies often are not fully congruent with the sub-components from the PERMA model and thus cannot account for them completely. For instance, *blissful state* was categorized into the component *positive emotions*, but it is only one positive emotion among many. Since the PERMA model is formulated broadly, it was necessary to take decisions on how to operationalize it for the purpose of this study. As no standardised approach to this was found in the literature there is no evidence of the validity of our categorization. Creating a valid classification to utilise the PERMA model in psychedelic research is an important topic for

future studies. So, although there might be limitations to the current categorisation, adding the sub-components of the PERMA model to the search generated valuable secondary evidence on the effect LSD has on well-being that would have been missed otherwise.

Conclusion

There is a strong need to find new interventions that increase well-being in society, so understanding whether LSD positively impacts well-being is of interest. By systematically searching the current literature, this study found that evidence in favour of a positive effect of LSD on well-being is emerging but still not conclusive. It seems likely that higher dosages of the substance more consistently increase well-being while medium and low dosages affect well-being less consistently. This is in line with earlier research about the importance of mystical experiences as a possible working mechanism of psychedelic therapy since these occur more often at higher dosages of the substances. Regarding the sub-concepts from the PERMA model of well-being, the evidence shows positive effects of LSD on *positive emotions*, *meaning*, and *relationships*. This suggests that while positive effects of LSD on well-being seem possible, especially at high doses (200µg), it is also essential to consider what parts of well-being are especially tackled by LSD and why. The outcomes of this study can only be seen as preliminary evidence for the relationship between LSD and well-being, highlighting the importance of conducting further research to gain certainty on the nature of the effect and its working mechanisms. However, future trials need to include long-term follow-ups, larger sample sizes and need to control for carry-over effects. Currently, we are still a long way from any large-scale use of LSD in the public mental health domain but focusing more on aspects related to well-being, specifically on *positive emotions*, *meaning* and *relationships* in mental health care and getting inspiration from psychedelics' probable working mechanisms could be a first step for current practitioners.

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