What are the safety and efficacy considerations for potential approval? Drawing from ongoing trials and existing clinical experience

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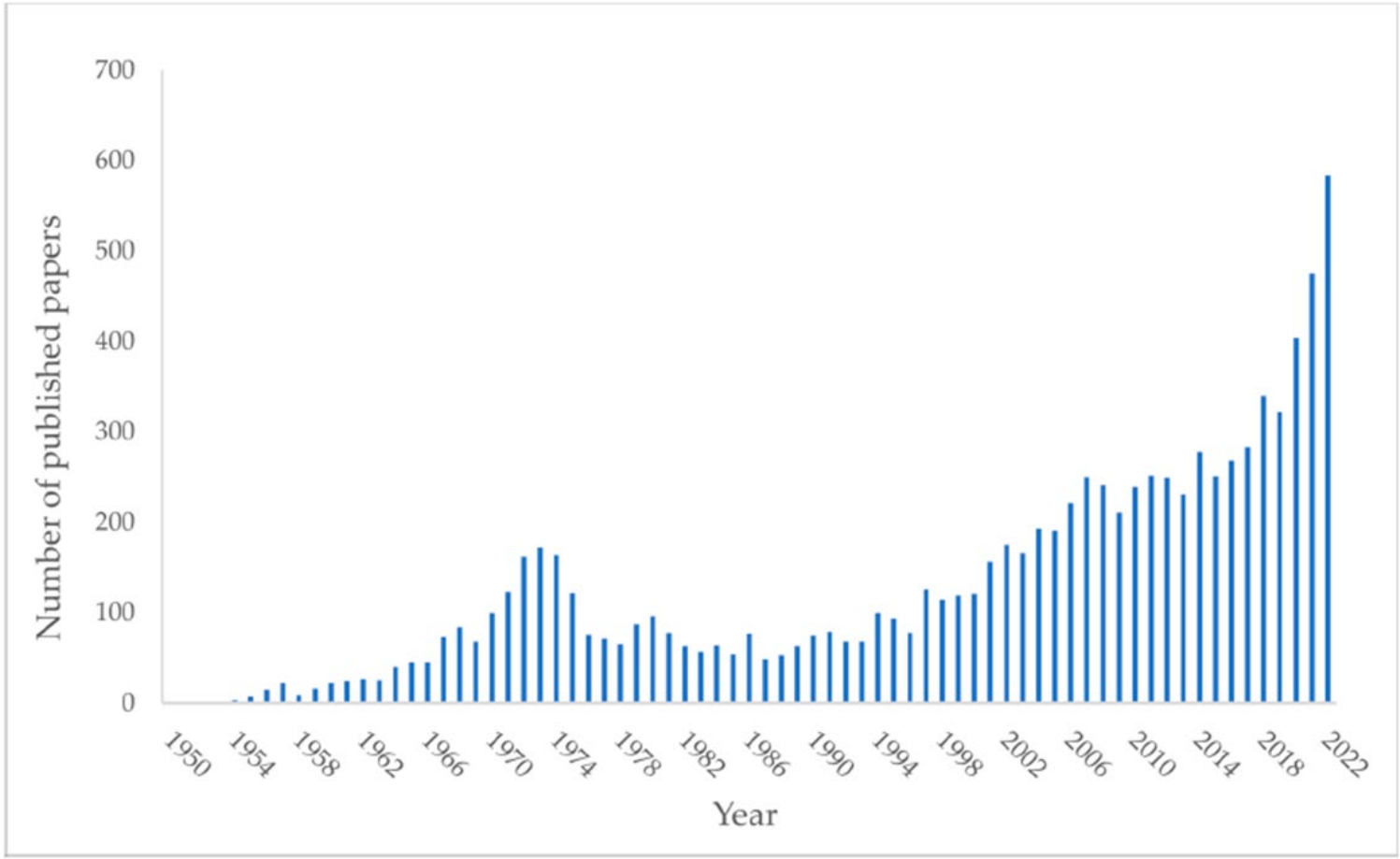
Number of papers published per year from 1952 to 2022 reported on PubMed by searching for “psychedelic therapies”.



Mastinu et al., 2023

Efficacy considerations: Existing literature data

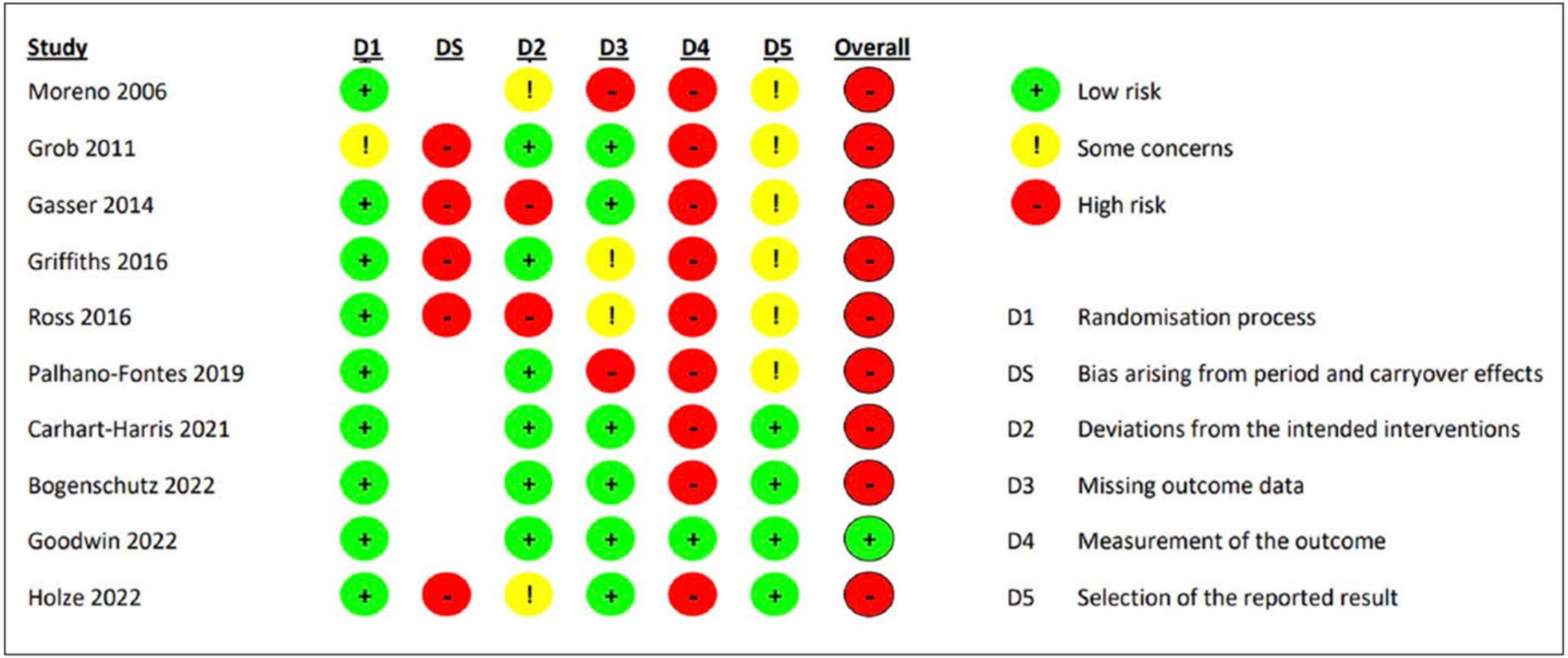
- Psychedelics have been evaluated in the treatment of a wide variety of mental disorders, **including major depressive disorder (MDD), treatment-resistant depression (TRD), end-of-life anxiety, anorexia nervosa, bulimia nervosa, PTSD, alcohol-use disorder, nicotine dependence, migraine and cluster headaches.**
- The available studies are mostly of **limited size** (from 30 to 176 patients in AUD studies, from 6 to 104 patients in MDD, from 8 to 233 patients in TRD) in a highly selected population (percentage of prescreened to randomized below 10%), including subjects with previous psychedelic experience (Holze et al., 2024).
- **Different doses of psychedelics** were evaluated in the available studies.
- **PK variability** has been described, which affects interpretation of the available efficacy data (Holze et al., 2023).
- **Heterogeneity of therapeutic response** limits conclusions regarding efficacy of psychedelics.
- Many of the studies were **open-label design, non-randomized.**

Efficacy considerations - risk of bias in randomized clinical trials on psychedelic medicine

Study	Design	Sample size (*n* randomized)	Diagnostic group	Intervention/control	Prior psychedelic use (% use)	Expectancy/therapeutic alliance	Allocation concealment (correct guesses)	Protocol/SAP
Moreno et al. (2006)	WSD	9 (–)	OCD	Psilocybin/psilocybin (LD)[a]	(100%)	–/–	–	–/–
Grob et al. (2011)	WSD	12 (–)	C-R anxiety disorders	Psilocybin/niacin[a]	(67%)	–/–	Reported narratively as unsuccessful	–/–
Gasser et al. (2014)	PGD	12 (12)	Life-threatening illness and an anxiety disorder	LSD/LSD (LD)[a]	(8%)[d]	–/–	Participants (100%) Study staff (92%)[e]	–/–
Griffiths et al. (2016)	C	51 (56)	C-R anxiety and depression disorders	Psilocybin/psilocybin (LD)[a]	(45%)	–/–	Reported narratively as unsuccessful	–/–
Ross et al. (2016)	C	29 (31)	C-R anxiety and depression disorders	Psilocybin/niacin[a]	(55%)	–/–	Participants – Study staff (97%)	+/+
Palhano-Fontes et al. (2019)	PGD	29 (35)	TR unipolar major depressive disorder	Ayahuasca/placebo liquid[b]	(0%)	–/–	Participant (81%)[f] Study staff –	–/–
Carhart-Harris et al. (2021)	PGD	59 (59)	Moderate-to-severe major depressive disorder	Psilocybin + microcrystalline[c]/psilocybin (LD)[a] + escitalopram	(92%)	–/+	–	+/+
Bogenschutz et al. (2022)	PGD	95 (95)	Alcohol use disorder	Psilocybin/diphenhydramine[c]	–	–/–	Participant (94%) Study staff (93%)	+/+
Holze et al. (2022)	WSD	39 (44)	C-R or generalized anxiety disorders	LSD in ethanol/solely ethanol[c]	–	–/–	Participants in active group (95%) Study staff –	–/–
Goodwin et al. (2022)	PGD	233 (233)	Moderate-to-severe major TR depressive disorder	Psilocybin/psilocybin (LD)[a]	(6%)	–/–	–	+/+

Hovmand et al., 2023

Efficacy considerations - risk of bias in randomized clinical trials on psychedelic medicine



Hovmand et al., 2023

Efficacy considerations – major drawbacks of the available studies

- The lack of control group
- Not well-defined study population (inclusion and exclusion criteria – e.g. age, comorbidities, concomitant medications, severity of disease, prior response to the authorised treatment - treatment resistant population, prior experiences with psychedelics)
- Selection bias
- Statistical analysis (sample size, studies not sufficiently powered, missing data etc)
- Primary and secondary endpoints, treatment duration, time of the primary analysis
- The lack of long-term treatment effects
- Placebo effect
- The breaking blind issue, in psylocybin trials the failure of masking is estimated at 95% (Bogenschutz et al., 2022).

Efficacy considerations – what issues need to be further addressed

- Mechanism of action
- Secondary pharmacodynamic effects
- Dose selection
- PK evaluation, including target population
- DDI
- Additional evaluation of the breaking blind issue
- The role of psychotherapy in achieving the beneficial effects (high costs of psychotherapy, need for standardisation of psychotherapy, if proposed to be used in combination), a drug-assisted psychotherapeutic process ?
- It cannot be expected that all study participants will respond equally – recommendations for repeated treatment (dose, time interval, definition of a partial response, evaluation of efficacy/safety after repeated administrations).

Main safety findings/issues

- LSD, psylocybin, mescaline – moderate increases in blood pressure and heart rate, anxiety, nausea, headache. Several acute serious adverse events, including acute delusions and anxiety.
- Acute psychedelic states (challenging experience/bad trip)– described as transcendent and transformative moments (involving feelings of fear, anxiety, dysphoria), which may correlate with clinical benefits need to be further evaluated both in terms of efficacy and safety.
- The safety and tolerability appear to be dependent on the dose and route of administration.
- Small safety database size, not in line with the ICH E1 (The Extent of Population Exposure to Assess Clinical Safety for Drugs Intended for Long-Term Treatment of Non-life-threatening conditions). In this guideline, the minimal requirements for safety evaluation of an investigational drug are as follows: 100 patients treated for at least 1 year, 300-600 patients treated for at least 6 months and 1500 individuals treated in total.

Main safety findings

Frequently Reported AEs in Psychiatric Patients					
	Psilocybin	LSD	DMT	Mescaline	5-MeO-DMT
Acute[h,i,j,k,l,m]	Psychological discomfort Anxiety Fear Nausea or vomiting Paranoia Headaches/ migraines Gastrointestinal discomfort/ diarrhea Thought disorder Lightheadedness Sore muscles Acute hypertension	Anxiety Nausea Headache Feeling cold Feeling abnormal Emotional distress Anxiety Illusion Abnormal thinking Dysphoria	Anxiety Headache Tingling Nausea Dysphoria	No modern data available; for historical data, see a comprehensive review by Vamvakopoulou *et al.* (113).	Abdominal discomfort Feeling abnormal Muscle spasms Muscle discomfort Dizziness Headache Paresthesia Sensory disturbance Anxiety Flashback Nausea Depressive symptoms
Subacute[h,i,j,k,l,m]	Headache Fatigue Insomnia Anxiety Migraine attack Visual distortion Tenseness Nausea	Feeling cold Feeling abnormal Emotional distress Illusion	Back pain		None reported
SAEs[j,k,l,m]	Suicidal ideation Suicidal behavior Intentional self-injury Hospitalization due to lack of improvement of depression	Acute anxiety and delusions	Hypotension[n] Bradycardia[n]	None reported	None reported

Holze et al., 2024

Safety consideration

- Safety should be evaluated systematically
- All adverse events should be reported
- Evaluation of safety/adverse events should be included as secondary outcomes
- Safety in elderly should be carefully addressed
- Long-term safety, including safety after repeated use should be addressed
- Adverse events of special interest, including psychotic episodes and suicidality
- Tolerance, withdrawal symptoms, abuse/dependence potential should be properly addressed
- Specific safety considerations relevant to target populations

Conclusions

- Psychedelics can be considered promissing products for the treatment of mental disorders, however, large, multicentre, well-designed and properly conducted studies in representative populations are needed to substantiate the efficacy and safety in a well-defined target population of patients.
- Guidelines recommendations should be followed.
- Research groups/developers shall consider seeking Scientific Advice to discuss in detail the planned development program (quality, non-clinical and clinical issues).
- PRIME designation can be considered an available option to facilitate interactions with regulators.


Thank
you!