Clinical and biological predictors of psychedelic response in the treatment of psychiatric and addictive disorders: A systematic review

Bruno Romeo a, b, *, Marianne Hermand a, b, *, Amélie Pétillon a, b, Laurent Karila a, b, Amine Benyamina a, b

a APHP, Paul Brousse Hospital, Department of Psychiatry and Addictology, F-94800, Villejuif, France
b Unité Psychiatrie-Comorbidités-Addictions: Unité de Recherche PSYCOMADD 4872 Université Paris Sud-APHP, Université Paris Saclay, Le Kremlin Bicêtre, France

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ABSTRACT

Background: The use of psychedelic treatments has shown very promising results in some psychiatric and addictive disorders, but not all patients achieved a response.

Aim: The aim of this review is to explore the clinical and biological factors which could predict the response to psychedelics in psychiatric and addictive disorders.

Methods: A systematic research was performed on MEDLINE, PsycInfo, Web of science, and Scopus databases from January 1990 to May 2020. All studies investigating the predictive factors of response to psychedelics regardless of psychiatric or addictive disorders, were included.

Results: Twenty studies investigating addictive disorder, treatment-resistant depression, obsessive-compulsive disorder and depressive and anxiety symptoms in patients with life-threatening cancer were included in this review. We found that, in all indications, the main predictive factor of response to psychedelics is the intensity of the acute psychedelic experience. Indeed, we found this factor for alcohol and tobacco use disorders, treatment-resistant depression, and anxiety and depressive symptoms in patients with life-threatening cancer, but not for obsessive-compulsive disorder.

Conclusion: The intensity of the acute psychedelic experience was the main predicting factor of response. The action mechanism of this experience was not clear, but some hypotheses could be made, such as a modulation of serotonergic system by 5-HT2A receptors agonism, a modulation of the default mode network (DMN) with an acute modular disintegration of the DMN followed by a re-integration of this network with a normal functioning, or an anti-inflammatory effect of this treatment.

1. Introduction

During the 1940s, psychedelic treatments were investigated in many studies with promising results in the field of psychiatry (Sessa, 2012). This research topic stopped, in the late 1960s, when lysergide (LSD) became illegal. However, during the past twenty years, a renaissance of psychedelic research has occurred, notably in some psychiatric and addictive disorders (Sessa, 2005). Many recent studies have shown an efficacy in alcohol use disorder (AUD), with a decrease in the percentage of heavy drinking days (Bogenschutz et al., 2015), as well as in tobacco smokers, with 67% of abstinence after 12 months post-psilocybin (Johnson et al., 2017a). Psilocybin has also been studied and yielded positive results in the treatment of anxiety and depressive symptoms in patients with life-threatening cancer (Griffiths et al., 2016; Grob et al., 2011; Ross et al., 2016).

The action mechanisms of psychedelics are not totally known and some hypotheses, not mutually exclusive, could be made. The first one concerns the action on the serotonergic system by a 5-HT1A/2A/2C agonism (Halberstadt, 2015). This agonism, particularly the 5-HT2A agonism, could provoke a glutamate release leading to an activation of the fronto-cortical glutamate receptor (Halberstadt, 2015). Another trait of this 5-HT2A agonism is its link with the psychedelic effect (Madsen...
et al., 2019). Indeed, a relationship between the subjective intensity of the psychedelic experience, the neocortical 5-HT2A receptor occupancy, and the plasmatic psilocybin concentration was shown in healthy volunteers and could, in part, explain the action mechanism (Madsen et al., 2019). Another hypothesis is that psychedelics lead to a ‘regression’, allowing an improvement in psychological flexibility and cognition by inducing an acute modular disintegration of the default mode network (DMN), followed by a re-integration (Carhart-Harris and Nutt, 2017). Finally, some studies suggest that psychedelic treatments could have an anti-inflammatory effect which could restore homeostasis in the inflammatory system (Flanagan and Nichols, 2018; Garcia-Romeu and Richards, 2018; Nichols et al., 2017).

Interpreting this data is complicated by the number of variables that come into play during an efficient psychedelic experience. However, the environment in which the psychedelic session occurs plays a primordial role in the psychedelic efficacy. Most of the time, psychedelic sessions occur in a specially constructed and supportive clinical environment, with or without a psychotherapeutic intervention (Garcia-Romeu and Richards, 2018; Trope et al., 2019). In most cases, the psychedelic effects and the unfolding of the session are explained during preparatory sessions (Garcia-Romeu and Richards, 2018). The session occurs in a comfortable room with, most of the time, pleasant music. There are at least two staff members present in order to provide support to the patient (Carhart-Harris et al., 2016; Palhano-Fontes et al., 2019). In some cases, patients receiving psychedelics also benefit from a psychotherapeutic intervention, such as cognitive behavioral therapy (CBT) (Johnson et al., 2014) or motivational enhancement therapy (Bogenschutz et al., 2015). The main objective of CBT is to directly access altered cognitive and emotional states in order to challenge and replace maladaptive thoughts and behavioral patterns (Garcia-Romeu and Richards, 2018; Johnson et al., 2014).

Despite these very promising results, not all patients respond to psychedelic treatments. For example, 43% of TRD had not achieved any response by day 7 to ayahuasca (Palhano-Fontes et al., 2019) and 33% of smokers relapse during the 12-month follow-up after psilocybin treatment (Johnson et al., 2017a). Therefore, it seems important to better identify the population of patients susceptible to respond to psychedelics. The aim of this systematic review is to explore the clinical and biological factors which could predict a psychedelic response in psychiatric and addictive disorders.

2. Method

2.1. Data sources and study selection process

The study protocol is registered at PROSPERO, number CRD42020180489 and follows the PRISMA guidelines (Liberati et al., 2009). We carried out a search on MEDLINE, PsycINFO, Web of science, and Scopus databases from January 1990 to May 2020 using the keywords (ayahuasca OR psilocybin OR lysergic acid diethylamide) AND (depression OR anxiety OR major depressive disorder OR bipolar disorder OR anxiety disorder OR substance use disorder OR dependence). Studies were included if (i) they were published in English in a peer-reviewed journal, (ii) they included patients with psychiatric or addictive disorders, (iii) psychedelics were used, (iv) an evaluation of predictive factors of psychedelic response was performed. The database clinicaltrials.gov was also consulted with the same keywords to complete the search. Studies that did not fulfill these three criteria were systematically excluded from the analyses. In order to obtain additional data, the reference lists of the identified articles were reviewed for additional studies. Study selection was performed by one author (BR) and verified by another (MH).

2.2. Quality of assessment

Quality assessment of the included studies was performed with the modified Newcastle-Ottawa Scale (Deeks et al., 2003) for open-label uncontrolled trial, with the Cochrane Collaboration’s Tool to assess the risk of bias (Higgins et al., 2003) for randomized doubled blind clinical trials and with the checklist for retrospective databases for retrospective studies (Moher et al., 2003). This assessment was performed by one author (BR) and was verified by another (MH). Any disagreements were discussed with a third author (AB).

3. Results

3.1. Article identification process

The article-selection process is described in Fig. 1 and Tables S1–S5, according to the PRISMA guidelines (Liberati et al., 2009). Twenty studies fulfilled the inclusion criteria (Agin-Liebes et al., 2020; Bogenschutz et al., 2015; Carhart-Harris et al., 2017, 2018; Carrillo et al., 2018; Davis et al., 2017; de Almeida et al., 2019; Erritzoe et al., 2018; Garcia-Romeu et al., 2014, 2019, 2020; Griffiths et al., 2016; Johnson et al., 2017a, 2017b; Mertens et al., 2020; Moreno et al., 2006; Palhano-Fontes et al., 2019; Roseman et al., 2018a, 2018b; Ross et al., 2016). Among these studies, two studies investigated AUD (Bogenschutz et al., 2015; Garcia-Romeu et al., 2019), three studies investigated tobacco smokers (Garcia-Romeu et al., 2014; Johnson et al., 2017a, 2017b) but only two studies used the same population with a follow-up at six months (Garcia-Romeu et al., 2014) and twelve months (Johnson et al., 2017a), and two studies investigated cannabis, opioid and stimulant misusers according to the fifth version of the Diagnostic and Statistical Manual of Mental disorders (DSM-5) (Davis et al., 2017; Garcia-Romeu et al., 2020). One study investigated obsessive-compulsive disorder (OCD) (Moreno et al., 2006). Nine studies investigated treatment-resistant depression (TRD) (Carhart-Harris et al., 2017, 2018; Carrillo et al., 2018; de Almeida et al., 2019; Erritzoe et al., 2018; Mertens et al., 2020; Palhano-Fontes et al., 2019; Roseman et al., 2018a, 2018b). Many of these studies investigated different characteristics of the same population (Carhart-Harris et al., 2017, 2018; Carrillo et al., 2018; Erritzoe et al., 2018; Mertens et al., 2020; Roseman et al., 2018a, 2018b). Roseman et al. (2018b) focused on whether the intensity of the acute psychedelic experience was predictive of longer-term clinical outcomes. Erritzoe et al. (2018) investigated pre-existing state or trait markers. Carrillo et al. (2018) analyzed the components of speech. The last three studies (Carhart-Harris et al., 2017, 2018; Mertens et al., 2020; Roseman et al., 2018a) performed imagery analyses. Palhano-Fontes et al. (2019) and de Almeida et al. (2019) used the same population, but de Almeida et al. (2019) focused on the serum Brain-Derived Neurotrophic Factor and cortisol levels. The last three studies investigated depressive and anxiety symptoms in patients with life-threatening cancer (Agin-Liebes et al., 2020; Griffiths et al., 2016; Ross et al., 2016). Concerning the type of psychedelics, most of the studies used psilocybin with a relative similarly dosage, between 20 and 30mg/70 kg (Bogenschutz et al., 2015; Carhart-Harris et al., 2018; Garcia-Romeu et al., 2014; Griffiths et al., 2016; Johnson et al., 2014; Ross et al., 2016). Only one study (Moreno et al., 2006) used psilocybin with a different dosage, ranging from 25 to 300 µg/kg. Two other studies (de Almeida et al., 2019; Palhano-Fontes et al., 2019) used ayahuasca...
Fig. 1. Article identification process.

Table 1  
Addictive disorders Included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Psychedelic (dose)</th>
<th>Nb Patients</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bogeneschutz et al. (2015)</td>
<td>AUD</td>
<td>Open label</td>
<td>Psilocybin (0,3 mg/kg)</td>
<td>9</td>
<td>Associations between Alcohol consumption change (PDD; PHDD at W8; PACS, AASE at W5) and HRS; MEQ; ASC intensity after session.</td>
</tr>
<tr>
<td>Garcia-Romeu et al., 2019</td>
<td>AUD</td>
<td>Retrospective online survey</td>
<td>All type</td>
<td>343</td>
<td>Associations between change AUDIT-C at M3 and AUD severity (Pre-AUDIT-C, Alcohol distress, number of DSM5 symptoms; years of problematic drinking); quality of psychedelic session (MEQ; Experience meaningful, insightful); dose of psychedelic.</td>
</tr>
<tr>
<td>Garcia-Romeu et al. (2014)</td>
<td>Adults smokers</td>
<td>Open label</td>
<td>Psilocybin (20–30 mg/70 kg)</td>
<td>15</td>
<td>Higher SOCQ, personal meaning, spiritual significance, impact on Wellbeing after sessions in quitters patients. Associations between change of consumption (SASE, craving, urinary cotinine, breath CO, TLFB) at M6 and quality of psychedelic session (SOCQ, personal meaning, Spiritual significance, wellbeing)</td>
</tr>
<tr>
<td>Johnson et al., 2017a b</td>
<td>Adults smokers</td>
<td>Open label</td>
<td>Psilocybin (20–30 mg/70 kg)</td>
<td>15</td>
<td>Differences between quit, reduce and relapse groups for age of first psychedelic experience, confidence to abstain from smoking, alexithymia and numbers of cigarettes/d, before psychedelic experience and craving after psychedelic experience. Differences were also found for personal meaning, spiritual significance.</td>
</tr>
<tr>
<td>Johnson et al., 2017b</td>
<td>Quit or reduce smoking</td>
<td>Retrospective online survey</td>
<td>All type</td>
<td>358</td>
<td>Associations between DUDIT-C change score and age, substance distress, craving, Pre-DUDIT-C, age at time of experience, ratings of the experience as personally meaningful and insightful.</td>
</tr>
<tr>
<td>Garcia-Romeu et al., 2020</td>
<td>Quit or reduce poly-substance use</td>
<td>Retrospective online survey</td>
<td>All type</td>
<td>444</td>
<td>Associations between DUDIT-C change score and age, substance distress, craving, Pre-DUDIT-C, age at time of experience, ratings of the experience as personally meaningful and insightful.</td>
</tr>
<tr>
<td>Davis et al., 2017</td>
<td>Problematic opioid consumption</td>
<td>Retrospective online survey</td>
<td>Iboigaine (15 mg/kg)</td>
<td>88</td>
<td>Better response in patients who consumed prescription opioids than heroin. No differences for acute subjective effects except that the responder subgroup agreed more strongly with the degree to which their ibogaine experiences contributed to gaining insight.</td>
</tr>
</tbody>
</table>

AUD: Alcohol use disorder; HRS: Hallucinogen Rating Scale; MEQ: Mystical Experience Questionnaire; ASC: Altered state of consciousness; SOCQ: States of Consciousness Questionnaire; PDD: percent of drinking day; PHDD: percent of heavy drinking days; PACS: Penn Alcohol Craving scale; AASE: Alcohol Abstinence self-efficacy Scale; AUDIT-C: Alcohol Use Disorders Identification Test – Consumption score; DUDIT-C: Drug use Disorders Identification Test-Consumption; SASE: smoking abstinence self-efficacy; TLFB: timeline follow-back (self-report cig/d); DSM5: Diagnostic and Statistical Manual of Mental Disorders 5; d: day; W: Week; M: month; cig: cigarettes.

a Correlations only with PDD and PHDD.
b Same population than Garcia Romeu 2015 but follow up at M12.
with a dosage of 1 ml/kg. The last three studies were based on three retrospective online survey studies which investigated the impact of all types of psychedelics in alcohol, opioid, cannabis and stimulant use disorders, as well as in tobacco smokers (Garcia-Romeu et al., 2019, 2020; Johnson et al., 2017b). However, it is important to note that, in these three studies, more than 70% of the patients used psilocybin or LSD (87.8% in Johnson et al. (2017b); 74.1% in Garcia-Romeu et al. (2019) and 72.3% in Garcia-Romeu et al. (2020)). The last one investigated the efficacy of ibogaine (15 mg/kg) in opioid use disorder (Davis et al., 2017). The main characteristics and results are reported in Tables 1–3.

### 3.2. Alcohol use disorder

In the two studies (Bogenschutz et al., 2015; Garcia-Romeu et al., 2019) investigating the impact of psychedelics in AUD, an association was found between the intensity of the acute psychedelic experience (evaluated by the mystical experience questionnaire (MEQ) in the two studies, by the 5-Dimensional altered states of consciousness scale (5D-ASC) and by the hallucinogen rating scale for Bogenschutz et al. (2015)) and the improvement in addictive behaviors. Indeed, results showed that the intensity of the mystical experience (Bogenschutz et al., 2015; Garcia-Romeu et al., 2019), the hallucinogen rating scale and the altered state of consciousness (Bogenschutz et al., 2015) during a psychedelic session were associated with a decrease in AUDIT-C after three months (Garcia-Romeu et al., 2019), a decrease in the percentage of drinking days and of heavy drinking days four weeks after the psychedelic session (Bogenschutz et al., 2015), a decrease in craving and an increase in alcohol abstinence self-efficacy one week after the psychedelic session (Bogenschutz et al., 2015).

The severity of AUD pre-psychedelic treatment (pre-AUDIT-C, alcohol distress, number of DSM 5 symptoms, and years of problematic drinking) was associated with a decrease in AUDIT-C three months after the psychedelic session (Garcia-Romeu et al., 2019). Moreover, the dose of psychedelic intake was also correlated with the decrease in AUDIT-C three months after the psychedelic session (Garcia-Romeu et al., 2019). It is important to note that the dose of psychedelics administered was correlated with the intensity of the acute psychedelic experience, notably the mystical experience, as well as with the insight experience; those two variables were also associated with the AUDIT-C at three months (Garcia-Romeu et al., 2019).

We did not find any relation between AUDIT C changes at three months and sex, age, time since experience, spiritually significant experience, challenging experience and age of the first drink (Garcia-Romeu et al., 2019).

### Table 2

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Design</th>
<th>Psychedelic (dose)</th>
<th>Nb Patients</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moreno et al., 2006</td>
<td>OCD</td>
<td>Phase I</td>
<td>Psilocybin (25–300 μg/kg)</td>
<td>9</td>
<td>No association between severity of OCD (YBOCS or VAS) and HRS score</td>
</tr>
<tr>
<td>Carhart-Harris et al., 2017a</td>
<td>Moderate to severe unipolar TRD</td>
<td>Open-label</td>
<td>Psilocybin (10 and 25 mg, 7 days apart)</td>
<td>20</td>
<td>Negative association between QIDS-SR16 changes at W5 and the quality of psychedelic session: experience of unity, spiritual experience and blissful state (ASC) Association between ASC score and psilocybin doses</td>
</tr>
<tr>
<td>Carhart-Harris et al., 2017b</td>
<td>Moderate to severe unipolar TRD</td>
<td>Open-label</td>
<td>Psilocybin (10 and 25 mg, 7 days apart)</td>
<td>19</td>
<td>An increase of ventromedial prefrontal cortex-bilateral inferior lateral cortex RSFC and a decrease in parahippocampal-prefrontal cortex RSFC at day 1 after psilocybin were predictive to response at W5.</td>
</tr>
<tr>
<td>Roseman et al., 2018a</td>
<td>Moderate to severe TDR</td>
<td>Open-label</td>
<td>Psilocybin (10 and 25 mg, 7 days apart)</td>
<td>20</td>
<td>Negative association between QIDS-SR16 changes at D1, W1 and W3 post-treatment increases in amygdala responses to fearful &gt; neutral faces, with greater activations relating to better outcomes</td>
</tr>
<tr>
<td>Carrillo et al., 2018</td>
<td>Moderate to severe unipolar TRD</td>
<td>Open-label</td>
<td>Psilocybin (10 and 25 mg, 7 days apart)</td>
<td>17</td>
<td>Speech analytics (average positivity of a text as the mean positive score over all words in the text, and did the same for its average negativity) before psilocybin permit to identify responders from non-responders with a significant level of 85% accuracy</td>
</tr>
<tr>
<td>Erritzoe et al., 2018</td>
<td>Moderate to severe unipolar TRD</td>
<td>Open-label</td>
<td>Psilocybin (10 and 25 mg, 7 days apart)</td>
<td>20</td>
<td>Negative association (at trend level) between Neuroticism scores at baseline and depression improvement at 3 months. No difference between responders and non responders at M3 for Neuroticism, extraversion, openness to experience, agreeableness and conscientiousness.</td>
</tr>
<tr>
<td>Roseman et al., 2018b</td>
<td>Moderate to severe unipolar TRD</td>
<td>Open-label</td>
<td>Psilocybin (10 and 25 mg, 7 days apart)</td>
<td>20</td>
<td>Negative association between QIDS-SR16 changes at W5 and quality of psychedelic session: high OBN and low DED (ASC). OBN is better predictor of reductions in depression than both VRS and AUA. Association between complete » OBN and anxiety, anhedonia, optimism and pessimism (STAI, SHAPS, LOT-R, DAS) at different time points (D1, W1, W5, M3, M6)</td>
</tr>
<tr>
<td>Mertens et al., 2020</td>
<td>Moderate to severe TDR</td>
<td>Open-label</td>
<td>Psilocybin (10 and 25 mg, 7 days apart)</td>
<td>20</td>
<td>Association between vmPFC and occipital-parietal functional connectivity and BDI scores at W1. Association between ruminations changes at 1W and ventromedial prefrontal cortex-right amygdala functional connectivity during face processing post- (versus pre-) treatment. No association between BDI, RRS, STAI (in-scanner anxiety levels) and amygdala FC after treatment at 1W and 3M. Negative association between MADRS score changes at D7 and quality of psychedelic session (with the MEQ subscale « transcendence of time and space » and with the HRS subscale « perception » for subgroup of ayahuasca responders only).</td>
</tr>
<tr>
<td>Palhano-Fontes et al., 2019</td>
<td>Unipolar TRD</td>
<td>RCT</td>
<td>Ayahuasca (1 ml/kg)</td>
<td>29</td>
<td>Negative association between MADRS score changes at D7 and quality of psychedelic session (with the MEQ subscale « transcendence of time and space » and with the HRS subscale « perception » for subgroup of ayahuasca responders only).</td>
</tr>
<tr>
<td>Nóbrega de Almeida et al., 2019</td>
<td>Moderate to severe TRD</td>
<td>RCT</td>
<td>Ayahuasca (1 ml/kg)</td>
<td>28</td>
<td>Association between the number of previous unsuccessful antidepressant treatments and D2 remission rate (MADRS)</td>
</tr>
</tbody>
</table>

OCD: Obsessive-Compulsive disorders; TRD: treatment resistant depression; RCT: randomized double blind trial; HRS: Hallucinogen Rating Scale; MEQ: Mystical Experience Questionnaire; ASC: Altered state of consciousness; SOOCQ: States of Consciousness Questionnaire; YBOCS: Yale Brown Obsessive Compulsive scale; VAS: Visual analog scale; QIDS-SR16: 16 item Quick Inventory of Depressive Symptoms; MADRS: Montgomery-Asberg depression rating scale; OBN: Oceanic Boundlessness; DED: Dread of ego-dissolution; VRS: Visionary restructurization; RSFC: resting state functional connectivity; AU: Auditory alterations; BDI: Beck depression inventory, DSM5: Diagnostic and Statistical Manual of Mental Disorders 5; fMRI: functional magnetic resonance imaging; d: day; BDI: Beck depression inventory; W: Week; M: month.

* Same population than Carhart-Harris et al., 2017a.

* Same population than Palhano-Fontes et al., 2019.
self-efficacy (SASE) score at six or twelve-month follow-up and the levels of experience, were associated with a decrease in urinary cotinine at six and/or twelve-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2017a). Indeed, in a population of tobacco smokers that have reduced or quit smoking after a psychedelic experience, patients who stopped smoking showed a higher personal meaning score at one-year follow-up. The spiritual significance score was also higher in patients who quit or reduced smoking than in relappers (Johnson et al., 2017b). Moreover, Garcia-Romeu et al. (2014) found that quitters had a higher personal meaning, spiritual significance and impact on wellbeing score after session than still smokers. The decrease of TLFB at six months was associated with higher personal meaning and wellbeing scores after the psychedelic sessions only at six-month follow-up (Garcia-Romeu et al., 2014). No association was found between TLFB and the spiritual significance score after session at six or twelve-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2017a). The increase of SASE, reflecting the confidence to abstain from smoking and temptation to smoke at six months, was associated with higher personal meaning, spiritual significance and wellbeing scores after psychedelic sessions (Garcia-Romeu et al., 2014). The craving was not associated with the personal meaning, spiritual significance and wellbeing scores (Garcia-Romeu et al., 2014). Higher spiritual significance and wellbeing score after one psychedelic session were associated with a decrease in urinary cotinine at six and/or twelve-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2017a). A higher personal meaning score, but not spiritual significance and wellbeing scores, after one psychedelic session was associated with a decrease in carbon monoxide (CO) rate at six-month but not at twelve-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2017a). Additionally it seems that other baseline assessments could also be useful in predicting the psychedelic efficacy, such as the alexithymia score, which was higher in relapers than in patients maintaining abstinence (Johnson et al., 2017b).

Some other characteristics also seem to be relevant, such as the confidence to abstain from smoking, a trait that was more important in patients who stopped than in relappers or in patients who reduced their use (Johnson et al., 2017b). We can also note that the age at the time of the psychedelic experience could have an impact on the prognosis, with a better prognosis for late experiences (Johnson et al., 2017b). No difference in prognosis was noted for the variables of age, race, education, sex, age at onset of smoking, years of smoking, number of previous attempts to quit, smoking dependence, premeditated intention to quit or intention to take psychedelics, type of psychedelics, location of the psychedelic experience, negative effects experienced during the psychedelic session, other toxic substances used, or psychiatric antecedents (Johnson et al., 2017b).

### 3.3. Tobacco smokers

The intensity of the acute psychedelic experience seems associated with better outcomes in tobacco smokers (Garcia-Romeu et al., 2014; Johnson et al., 2017a). Indeed, Garcia-Romeu et al. (2014) performed a direct comparison between quitters (n = 12) and still smokers (n = 3) and found that quitters had a higher alteration of consciousness after the psychedelic session. No association was found between the decrease in self-reported cigarettes consumption (TLFB), smoking abstinence self-efficacy (SASE) score at six or twelve-month follow-up and the levels of consciousness alteration, mystical experience and hallucinogen intensity scores right after the session (Garcia-Romeu et al., 2014; Johnson et al., 2017a). The decrease in craving was associated with a higher consciousness alteration during the session but not with mystical experience or hallucinogen intensity (Garcia-Romeu et al., 2014). We can note that the craving score after the psychedelic experience leading to a cessation or a reduction of consumption was significantly lower in patients who maintained their abstinence than among patients who reduced their consumption or relapsed. Relapsers also had a higher craving score than patients who reduced their consumption (Johnson et al., 2017b). No difference was found between these three groups regarding the craving score before the psychedelic experience (Johnson et al., 2017b). A higher consciousness alteration or intensity of mystical experience, but not a higher hallucinogen intensity of the psychedelic experience, were associated with a decrease in urinary cotinine at six and/or twelve-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2017a). Urinary cotinine is a reflection of the amount of nicotine absorbed. No association was found between CO rate and consciousness alteration, mystical experience or hallucinogen intensity (Garcia-Romeu et al., 2014; Johnson et al., 2017a).

Other markers of the psychedelic experience, such as the personal meaning, the spiritual significance and the impact on wellbeing, seem to be associated with better outcomes in tobacco smokers (Garcia-Romeu et al., 2014; Johnson et al., 2017a, 2017b). Indeed, in a population of tobacco smokers that have reduced or quit smoking after a psychedelic experience, patients who stopped smoking showed a higher personal meaning score at one-year follow-up. The spiritual significance score was also higher in patients who quit or reduced smoking than in relappers (Johnson et al., 2017b). Moreover, Garcia-Romeu et al. (2014) found that quitters had a higher personal meaning, spiritual significance and impact on wellbeing score after session than still smokers. The decrease of TLFB at six months was associated with higher personal meaning and wellbeing scores after the psychedelic sessions only at six-month follow-up (Garcia-Romeu et al., 2014). No association was found between TLFB and the spiritual significance score after session at six or twelve-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2017a). The increase of SASE, reflecting the confidence to abstain from smoking and temptation to smoke at six months, was associated with higher personal meaning, spiritual significance and wellbeing scores after psychedelic sessions (Garcia-Romeu et al., 2014). The craving was not associated with the personal meaning, spiritual significance and wellbeing scores (Garcia-Romeu et al., 2014). Higher spiritual significance and wellbeing score after one psychedelic session were associated with a decrease in urinary cotinine at six and/or twelve-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2017a). A higher personal meaning score, but not spiritual significance and wellbeing scores, after one psychedelic session was associated with a decrease in carbon monoxide (CO) rate at six-month but not at twelve-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2017a). Additionally it seems that other baseline assessments could also be useful in predicting the psychedelic efficacy, such as the alexithymia score, which was higher in relapers than in patients maintaining abstinence (Johnson et al., 2017b).

Some other characteristics also seem to be relevant, such as the confidence to abstain from smoking, a trait that was more important in patients who stopped than in relappers or in patients who reduced their use (Johnson et al., 2017b). We can also note that the age at the time of the psychedelic experience could have an impact on the prognosis, with a better prognosis for late experiences (Johnson et al., 2017b). No difference in prognosis was noted for the variables of age, race, education, sex, age at onset of smoking, years of smoking, number of previous attempts to quit, smoking dependence, premeditated intention to quit or intention to take psychedelics, type of psychedelics, location of the psychedelic experience, negative effects experienced during the psychedelic session, other toxic substances used, or psychiatric antecedents (Johnson et al., 2017b).

### 3.4. Other substance use disorders

Two studies have investigated other substance use disorders, such as opioid use disorder (Davis et al., 2017), or a combination of patients with cannabis, opioids and stimulant use disorders (cannabis, opioids and stimulant substances) (Garcia-Romeu et al., 2020). In the first study (Davis et al., 2017), a better response was found in patients using prescribed opioids (56%) than in patients using heroin (44%) after ibogaine treatment. As far as the acute subjective effect of ibogaine is concerned, the study shows that the “responders” subgroup reported a stronger contribution of the ibogaine experience in the improvement of their insight regarding the cause of their addiction (Davis et al., 2017). Moreover, the responders subgroup had higher spiritually meaningful experiences than non-responders (Davis et al., 2017). No difference was found between responders and non-responders in socio-demographic characteristics (age, gender, ethnicity, education level, relationship

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**Table 3** Depression and anxiety in patients with life-threatening cancer Included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Psychedelic (dose)</th>
<th>Nb Patients</th>
<th>Main results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Griffiths 2016</td>
<td>RCT</td>
<td>Psilocybin (22–30mg/70 kg)</td>
<td>51</td>
<td>Associations between Depressive and anxiety (HAM-D, HADS total/dep/ anxiety, HAM-A, STAI trait anxiety, ISI) or outcomes evaluating the living with a poor cancer prognosis (MQOL, LAP-R Death acceptance scale, Purpose in life test) at W5 and MEQ after psychedelic session.</td>
</tr>
<tr>
<td>Ross et al., 2016</td>
<td>RCT</td>
<td>Psilocybin (0,3 mg/kg)</td>
<td>29</td>
<td>Associations between change depressive and anxiety score at W6 (HADS total; BDI; STAI-Trait and state) and MEQ after psychedelic session. No association between change depressive or anxiety scores at M38 and MEQ and the mystical-type experience scores (MQE-30) at baseline</td>
</tr>
<tr>
<td>Agin-Liebes et al., 2020</td>
<td>RCT</td>
<td>Psilocybin (0,3 mg/kg)</td>
<td>15</td>
<td>Higher personal meaning, spiritual significance and wellbeing scores after psychedelic sessions (Garcia-Romeu et al., 2014). The craving was not associated with the personal meaning, spiritual significance and wellbeing scores (Garcia-Romeu et al., 2014). Higher spiritual significance and wellbeing score after one psychedelic session were associated with a decrease in urinary cotinine at six and/or twelve-month follow-up (Garcia-Romeu et al., 2014; Johnson et al., 2017a).</td>
</tr>
</tbody>
</table>

RCT: randomized double blind trial; HRS: Hallucinogen Rating Scale; MEQ: Mystical Experience Questionnaire; ASC: Altered state of consciousness; SOQC: States of Consciousness Questionnaire; STAI: Spielberger’s Trait Anxiety Inventory; SHAPS: Snaith-Hamilton Pleasure Scale; LOT-R: Life Orientation Test Revisited; DAS: Dysfunctional Attitudes Scale; HAMD: Hamilton depression scale; HADS: Hospital Anxiety and Depression scale; HAM-A: Hamilton Anxiety rating scale; STAI: State Trait Anxiety Inventory, BSI: Brief Symptom Inventory, MQOL: McGill Quality of Life; LAP-R: Life Attitude Profil-revised; BDI: Beck depressive inventory, DSM5: Diagnostic and Statistical Manual of Mental Disorders 5; d: day; W: Week; M: month.

* Same population than Ross et al., 2016 but follow up at M54.
to explore this component, this study used patients and, in addition, the authors noted that oceanic boundlessness (OBN) outcomes. The same results were obtained at week 5 after psilocybin psychedelic experience was predictive of better longer-term clinical consciousness was associated with higher psilocybin doses. In order to explicitly linked to Stace between responders and non-responders at month 3 for neuroticism, all words in the text. The same procedure was followed in order to obtain meaningful association with the DUDIT-C.

3.5. OCD

Only one study (Moreno et al., 2006) has investigated the response prediction to psychedelic treatment in patients with obsessive-compulsive disorders. In this study, the authors did not find any association between the severity of OCD (measured by the Yale Brown Obsessive Compulsive scale or a visual analog scale) and the intensity of the session (measured by the hallucinogen rating scale).

3.6. Treatment resistant depression

The intensity of the acute psychedelic experience was also associated with a higher improvement in depressive symptoms, without any difference between the types of psychedelics used. More precisely, the improvement in depressive symptoms at day 7 was correlated with the MEQ subscale “transcendence of time and space” in the ayahuasca group and with the hallucinication rating scale (HRS), subscale “perception” in ayahuasca responders (Palhano-Fontes et al., 2019). Within the same population, the number of previous unsuccessful antidepressant treatments was associated with a decrease in the remission rate at day 2 after a psychedelic session (de Almeida et al., 2019).

The improvement in depressive symptoms at week 5 after psilocybin was associated with the alteration of consciousness during a psychedelic session, notably the items: experience of unity, spiritual experience and transcendence of time and space in the ayahuasca group and with the hallucination rating scale (HRS). The intensity of the mystical experience during the psychedelic treatment was found to be associated with a decrease in the remission rate at day 2 after a psychedelic session (de Almeida et al., 2019). The same results were obtained at week 5 after psilocybin and, in addition, the authors noted that oceanic boundlessness (OBN) was the best predictor of a reduction in the depressive symptoms. OBN is explicitly linked to Stace’s “mystical experience”, negatively associated with anxiety, anhedonia and pessimism and positively associated with optimism at different time points: day 1, week 1, week 5, month 3, month 6.

Interestingly, one study (Carrillo et al., 2018) investigated the emotional component of speech in patients with treatment-resistant depression. To explore this component, this study used patients’ responses to an autobiographical memory test and assigned a positive or a negative emotional connotation to each word. They then assessed the average positivity of a text by calculating the mean positive score across all words in the text. The same procedure was followed in order to obtain the average negativity. Through this speech analysis, the authors showed that they could identify responders from non-responders with a significant level of 85% accuracy (Carrillo et al., 2018).

One study has investigated the pre-existing state or trait markers in patients with TRD (Erritzoe et al., 2018). No difference was found between responders and non-responders at month 3 for neuroticism, extraversion, openness to experience, agreeableness and conscientiousness (Erritzoe et al., 2018).

Finally, three studies have investigated predictive factors through imaging. (Carhart-Harris et al., 2017; Mertens et al., 2020; Roseman et al., 2018a). These three studies used functional magnetic resonance imaging (fMRI) in order to analyze functional connectivity during resting state sequence (Carhart-Harris et al., 2017), functional connectivity (Mertens et al., 2020) or only local BOLD activity (Roseman et al., 2018a) during emotional processing. Cahart Harris et al. (2017) found a relation between an increase in ventromedial prefrontal cortex-bilateral inferior lateral cortex resting state functional connectivity, or a decrease in parahippocampal-prefrontal cortex resting state functional connectivity at day 1 after psilocybin, and the rate of response at week 5. An increase in amygdala responses to fearful versus neutral faces at day 1 after psilocybin was associated with response and remission rates at day 1, weeks 1 and 3 but not at weeks 2 and 5 (Roseman et al., 2018a). Similarly, responders and remitters at week 1 significantly differed from healthy controls, with an increase in vmPFC and occipital-parietal cortex functional connectivity (and particularly the areas in the visual cortex) during an emotional face paradigm at day 1 after psilocybin use. An association between a change at week 1 in the intensity of rumination and a decrease in vmPFC cortex-right amygdala functional connectivity was also found. These results could underline an increased task engagement as well as changes in emotional stimulus recognition and processing post-treatment which were predictive of an improvement in depressive symptoms. Nevertheless, amygdala functional connectivity did not correlate with BDI change, ruminative response scale or Spielberger’s Trait Anxiety Inventory score at week 1 and month 3 (Mertens et al., 2020).

3.7. Depressive and anxiety symptoms in patients with life-threatening cancer

An association between the intensity of the acute psychedelic experience and the improvement in depressive and anxiety symptoms was found at short-term (Griffiths et al., 2016a; Ross et al., 2016) but not at long-term follow-up (Agin-Liebes et al., 2020). Indeed, associations were only found at week 5 (for Griffiths et al., 2016) and week 6 (for Ross et al., 2016)) between the intensity of mystical experience (evaluated by MEQ) during the psychedelic session and the improvement in depressive and anxiety symptoms (evaluated by the Hamilton depression scale, the Hospital anxiety and depression scale, the Hamilton anxiety rating scale and the state trait anxiety inventory), but not after 4.5 years (Agin-Liebes et al., 2020). Moreover, another association was found between the intensity of the mystical experience during the psychedelic session and the improvement in different outcomes evaluating living with a poor cancer prognosis at week 5. Indeed, at week 5, an association was found between the intensity of the mystical experience during the psychedelic session and the improvement in quality of life, meaningful existence during the life-threatening illness, anxiety-/positive attitudes about death, measure of life meaningfulness and a self-rated scale assessing logically integrated understanding of self, others, and life in general (Griffiths et al., 2016).

4. Discussion

In this systematic review, we found that the main predictive factor of a response to psychedelics is the intensity of the acute psychedelic experience, in any indication. Indeed, we found this factor in alcohol and tobacco use disorders, treatment-resistant depression, and anxiety and depressive symptoms in patients with life-threatening cancer. We did not find any association in obsessive-compulsive disorder, however this indication was only investigated in a very small study. Other predictive factors were the severity of AUD, the confidence to abstain from tobacco smoking and the age at the time of the psychedelic experience. In patients with TRD, the quality of speech, notably the allocation of...
positive connotations to a text, seems to be a predictive factor of response, whereas the number of previous unsuccessful antidepressant treatments seems to predict a poorer prognosis. Some regions of interest known as being implicated in depression pathophysiology, such as the amygdala or vmPFC, could also be of interest in predicting a response to psychedelics.

It seems important to note that several factors could modulate the quality of a psychedelic session. The first one is the environment in which the session takes place. For example, the modality of psychedelics administration could influence the quality of a session. The course of the psychedelic protocol seems to have an impact on the safety and the efficacy of psychedelics (Garcia-Romeu and Richards, 2018). Indeed, the environment could influence the patients’ anxiety levels and impair cognition during the psychedelic session, which was found to be predictive of less positive clinical outcomes in TRD (Roseman et al., 2018b). Moreover, a specific environment creates the safest conditions to use psychedelics, especially as the access to such molecules can also be a source of recreational use. The dose of psychedelics administered is another factor affecting the psychedelic effect, since this factor has been associated with the intensity of the acute psychedelic experience, as well as with the insight experience (Garcia-Romeu et al., 2019, 2020).

Expectations and other relevant state and trait factors could also play an important role in modulating the effect of psychedelics, notably on personal meaning, spiritual significance and impact on wellbeing, as well as on the acute effect of psychedelics. In line with this argument, several studies have underlined the importance of pre-existing state or trait markers. Thus, the religious or spiritual interests of the participants may increase the likelihood that the psilocybin experience is interpreted as having a substantial spiritual significance, thus promoting the effectiveness of the experiment (Russ et al., 2019). Conversely, the level of preoccupation, rigidity and absence of openness prior to a psychedelic session could diminish the effect of psychedelics (MacLean et al., 2011; Russ et al., 2019). However, only one study investigated pre-existing state or trait in patients with TRD (Erritzoe et al., 2018) and did not show any difference between responders and non-responders. In addition, some psychotherapeutic interventions may have a synergistic effect on the psychedelic experience by decreasing anxious apprehension and by focusing attention. Meditation, for example, seems to enhance psilocybin’s positive effects while counteracting possible dysphoric responses (Smigielski et al., 2019). In a more global way, the therapists’ competencies and therapeutic alliance-building have been shown to greatly influence clinical outcomes (Phelps, 2017). These results suggest that the setting as well as psychological insight are, therefore, very important in achieving a high-quality psychedelic experience.

It is particularly interesting to note that the intensity of the acute psychedelic experience was a common predictive factor of response without any distinction between psychiatric and addictive disorders. One possible explanation for this association is that the action mechanisms are similar, since the intensity of the session was directly associated with the intensity of the acute psychedelic experience, as well as with the insight experience (Garcia-Romeu et al., 2019, 2020).

Moreover, a specific environment creates the safest conditions to use psychedelics, especially as the access to such molecules can also be a source of recreational use. The dose of psychedelics administered is another factor affecting the psychedelic effect, since this factor has been associated with the intensity of the acute psychedelic experience, as well as with the insight experience (Garcia-Romeu and Richards, 2018; Nichols et al., 2017).

The use of psychedelics could temporally reverse the process of network integration and segregation that characterize the development of the brain (Carhart-Harris and Nutt, 2017; Wylie et al., 2014). This ‘regression’ could in turn facilitate the openness of mind and the psychological flexibility and cognition (Carhart-Harris and Nutt, 2017) necessary to the clinical improvement of patients with psychiatric and/or addictive disorders. Furthermore, the anti-inflammatory effects of psychedelics may also contribute to their therapeutic effect, by restoring homeostasis in the inflammatory system (Flanagan and Nichols, 2018; Garcia-Romeu and Richards, 2018; Nichols et al., 2017).

However, the modalities of psychedelics administration cannot explain the different psychedelic experiences reported within the same study (thus with the same conditions). Another explanation is a putative interpersonal expression variability for 5-HT2A receptors (Carhart-Harris and Nutt, 2017; Jokela et al., 2007). 5-HT2A receptors signaling has been found to be highly influential during key developmental periods, especially as far as intense learning is concerned (Lambe et al., 2011). However, 5-HT2A receptors polymorphisms could be influenced by environmental elements (Carhart-Harris and Nutt, 2017; Jokela et al., 2007) such as early-life stress and maternal deprivation (Benkireddy et al., 2010). Hence, this variation could account for the differences found in sensitivity to psychedelic drugs.

Brain imaging studies (BIS) have also allowed to detect some predictive factors of response to psychedelics. It is important to note that all these studies (Carhart-Harris et al., 2017; Mertens et al., 2020; Roseman et al., 2018a) were performed in the same TRD open label study population. These findings could underline a difference in the action mechanisms between psychedelics and classic antidepressants. Indeed, an increased vmPFC bilateral inferior-lateral parietal cortex (iPFC) resting state functional connectivity at day 1 after psilocybin was found to be predictive of a better response at week 5. This result could be similar to results obtained after electroconvulsive therapy, in which the default mode network (DMN) integrity is decreased acutely and increased post-acutely, but not after administering antidepressants (Carhart-Harris et al., 2017). This result could thus suggest a ‘reset’ mechanism caused by psychedelics, in which an acute modular disintegration of DMN is followed by a re-integration of this network with a normal functioning (Carhart-Harris et al., 2017). The two other BIS (Mertens et al., 2020; Roseman et al., 2018a) showed that an increase in amygdala responsiveness and a decrease in functional connectivity (FC) between the amygdala and the ventral striatum, or an increased FC between the vmPFC and occipital and parietal cortices during face processing (for depressive symptoms) at day 1 after psilocybin, were predictive of a response to this psychedelic. These different results could be interpreted as a decreased inhibitory input from the vmPFC region to these different regions. This would in turn lead to a disinhibitory influence in these regions, as well as on the amygdala responsiveness. These findings could thus suggest that psilocybin and antidepressants have different action mechanisms, notably in the regulation of emotional processing.
Conventional antidepressants down-regulate the emotional responsiveness (Goodwin et al., 2017), whereas psychedelics allow patients to fully experience their emotions (Carhart-Harris et al., 2018b; Roseman et al., 2018). The disinhibitory influence of vmPFC on amygdala responsiveness could indicate a potential emotional reconnection reported in successful psychedelic therapy (Watts et al., 2017).

As far as other predictive factors are concerned, it is interesting to note that the confidence to abstain from tobacco smoking and the age at the time of the psychedelic experience were also predictive of a better psychedelic efficiency in smokers. Moreover, the severity of substance use disorder could be predictive of a better psychedelic response (Garcia-Romeu et al., 2019, 2020) as opposed to TDR, since the number of previous unsuccessful antidepressant treatments seems to be a predictor of a poorer prognosis (Palhano-Fontes et al., 2019). This difference could be explained, firstly, by specific psychological mechanisms potentially at play in psychedelic use, such as increased self-efficacy and motivation to change, as well as decreased craving, leading to a reduction in alcohol use (Garcia-Romeu et al., 2019). Secondly, it seems plausible that serotonin 2A agonist psychedelics may possess some inherently anti-addictive properties (Bogenschutz et al., 2015; Garcia-Romeu et al., 2014). The specific effects of psychedelics on AUD could be mediated by their effects in altering emotional processing and social cognition (Dolder et al., 2016; Garcia-Romeu et al., 2014; Kometer et al., 2012; Kraehenmann et al., 2016; Mueller et al., 2017; Preller et al., 2016; Stroud et al., 2018), which constitute well-described risk factors for relapse (Rupp et al., 2017). Another hypothesis that could explain this efficacy is the presence of a dual pathology in many patients, notably patients with severe AUD who are at an increased risk of having a comorbid psychiatric disorder, such as mood or anxiety disorders (Grant et al., 2015; Hasin et al., 2018; Lai et al., 2015). It is possible that psychedelic treatments have a very quick efficacy on depressive and anxiety symptoms, thus facilitating remission in these patients. Furthermore, it is interesting to note that the presence of first-degree AUD antecedents is also associated with a better response to ketamine (Romeo et al., 2017) in unipolar (Phelps et al., 2009) and bipolar depression (Luckenbaugh et al., 2012), with a longer anti-depressive efficacy (Niciu et al., 2014). Personal AUD was also found to predict a better ketamine response in bipolar depression (Luckenbaugh et al., 2012) but not in unipolar depression (Phelps et al., 2009).

This review has several limitations. The first one is the low number of studies included and the fact that many studies used the same population, making it difficult to generalize the results. The second limitation is that the number of patients included in most studies was very low, thus lowering the power of the different statistical analyses. Third, some included studies were retrospective online surveys, which could cause a memory bias (Davis et al., 2017; Garcia-Romeu et al., 2019, 2020; Johnson et al., 2017b). Fourth, in some studies, the follow-up after psychedelic treatment was relatively short. For example, in the OCD study (Moreno et al., 2006), only a 24-h follow-up was performed. Finally, studies with very different methodologies were included in this review, which makes it difficult to compare the obtained results.

In conclusion, it can be advanced that the efficacy of psychedelics has been demonstrated in some psychiatric and addictive disorders, but not all patients responded to these treatments. In this review, we found that the intensity of the acute psychedelic experience, principally imputable to the action of the serotonergic system, was the main predicting factor of response. This association could be explained by the presence of a probable overlap in the two action mechanisms, involving the agonist of the 5-HT2A receptors, which can account for the clinical efficacy and the physiology of the psychedelic experience. Further clinical studies are needed to clarify the importance of predictive factors, firstly, in order to confirm these results and, secondly, in order to expand research towards other fields of investigation, such as the impact of different psychotherapeutic methods on psychedelic efficacy.

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Appendix A. Supplementary data

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References


