Progress in Neuropsychopharmacology & Biological Psychiatry 81 (2018) 1–10

Contents lists available at ScienceDirect

Progress in Neuropsychopharmacology & Biological Psychiatry

journal homepage: www.elsevier.com/locate/pnp

Serotonergic hallucinogens in the treatment of anxiety and depression in patients suffering from a life-threatening disease: A systematic review

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ARTICLE INFO

Keywords:
Hallucinogen
LSD
Psilocybin
Anxiety
Life-threatening disease
Cancer

ABSTRACT

Anxiety and depression are some of the most common psychiatric symptoms of patients suffering with life-threatening diseases, often associated with a low quality of life and a poor overall prognosis. 5-HT_{2A}-receptor agonists (serotonergic hallucinogens, 'psychedelics') like lysergic acid diethylamide (LSD) and psilocybin were first investigated as therapeutic agents in the 1960s. Recently, after a long hiatus period of regulatory obstacles, interest in the clinical use of these substances has resumed. The current article provides a systematic review of studies investigating psychedelics in the treatment of symptoms of existential distress in life-threatening diseases across different periods of research, highlighting how underlying concepts have developed over time. A systematic search for clinical trials from 1960 to 2017 revealed 11 eligible clinical trials involving a total number of N = 445 participants, of which 7 trials investigated the use of lysergic acid diethylamide (LSD) (N = 323), 3 trials investigated the use of psilocybin (N = 92), and one trial investigated the use of dipropyltryptamine (DPT) (N = 30). The 4 more recent randomized controlled trials (RCTs) (N = 104) showed a significantly higher methodological quality than studies carried out in the 1960s and 1970s. Evidence supports that patients with life threatening diseases associated with symptoms of depression and anxiety benefit from the anxiolytic and antidepressant properties of serotonergic hallucinogens. Some studies anecdotally reported improvements in patients´ quality of life and reduced fear of death. Moreover, low rates of side effects were reported in studies that adhered to safety guidelines. Further studies are needed to determine how these results can be transferred into clinical practice.

1. Introduction

Receiving a diagnosis of a life-threatening physical disease is usually a shocking event, associated with a significant degree of emotional suffering including fear, anger, despair, and social withdrawal. While some patients are capable of coping effectively with the challenges of their disease and the associated 'existential distress', others develop a broad range of psychological problems (Teunissen et al., 2007; Van Lancker et al., 2014), with a high prevalence of anxiety and depressive symptoms (Mitchell et al., 2011; Watts et al., 2015, 2014; Wilson et al., 2007). *Existential distress* includes core phenomena like feelings of hopelessness, a loss of will to live, a loss of meaning and sense of dignity, and a sense of being a burden to others and a desire for a hastened death (Boston et al., 2011; Boston and Mount, 2006; Chochinov et al., 2005a; Jaiswal et al., 2014; Kissane et al., 2001). These problems are often associated with poor treatment adherence (Arrieta et al., 2013) and higher mortality rates (Brown et al., 2003). In palliative care, there is a growing consensus that existential distress is a core determinant of

Abbreviations: 5HT, 5-hydroxytryptamine (= serotonin); 5-HT_{2A}, 5-hydroxytryptamine (serotonin) receptor 2A; ASC, altered states of consciousness; BDI, Beck Depression Inventory; DMT, *N,N*-dimethyltryptamine; DPT, *N,N*-dipropyltryptamine; DSM-IV, Diagnostic and Statistical Manual of Mental Disorders, 4th edition; ECRS, Emotional Condition Rating Scale; HADS, Hospital Anxiety and Depression Scale; HAM-A, Hamilton Rating Scale for Anxiety; HAM-D, Hamilton Rating Scale for Depression; HPPD, Hallucinogen Persisting Perception Disorder; LSD, lysergic acid diethylamide; MEQ30, Mystical Experience Questionnaire; SAP, Substance-assisted psychotherapy; STAI, State-Trait Anxiety Inventory; PDT, psychedelic (peak) therapy; POI, Personal Orientation Inventory; POMS, Profile of Mood States; QoL, Quality of life

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http://dx.doi.org/10.1016/j.pnpbp.2017.09.012
Received 17 August 2017; Received in revised form 13 September 2017; Accepted 16 September 2017
Available online 22 September 2017
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poor well-being and quality of life (QoL) in patients with a life-threatening disease, determining the effectiveness in coping with the challenges of the disease (Breitbart et al., 2005, 2000; Edwards et al., 2010; Jones et al., 2003; Kandasamy et al., 2011; McClain et al., 2003; Puchalski, 2012; Rodin et al., 2009). Thus, an increasing number of psychotherapeutic interventions are approaching existential distress by meaning-enhancing interventions like the 'Meaning-centered Group Psychotherapy' (Breitbart et al., 2015, 2010), 'Dignity Therapy' (Chochinov et al., 2005b) or 'Supportive-expressive Group Therapy' (Reuter, 2010) (for a review see LeMay and Wilson, 2008). In contrast, there are currently no specific pharmacological treatment options regarding this particular type of distress (Breitbart et al., 2010). So far, treatment strategies mainly focus on reduction of symptoms like pain or sleep disturbances. Recently, the interest in the therapeutical potential of classic serotonergic hallucinogens (5-HT_{2A} receptor agonists; 'psychedelics') has resumed, and there is some evidence for efficacy in certain indications (Majić et al., 2017). In the following we will give an overview over this group of substances and outline the history of using these substances in the treatment of anxiety and depression in patients suffering from life-threatening diseases.

1.1. Substance class and historical background

The naturally occurring alkaloid psilocybin (4-phosphoryloxy-*N,N*-dimethyltryptamine) and the semisynthetic lysergic acid diethylamide (LSD) belong to the group of the classic or serotonergic hallucinogens ('psychedelics'), which can be divided into phenethylamines and tryptamines, including its subset of ergolines (Nichols, 2004). Besides mescaline (3,4,5-trimethoxyphenethylamine) and DMT (*N,N*-dimethyltryptamine), LSD and psilocybin constitute the most representative compounds of this substance class (Nichols, 2016; Passie et al., 2008, 2002). The chemical structure of the tryptamines resembles the neurotransmitter and tissue hormone serotonin (5-hydroxytryptamine, 5-HT) (Nichols, 2004) (see Fig. 1). Moreover,

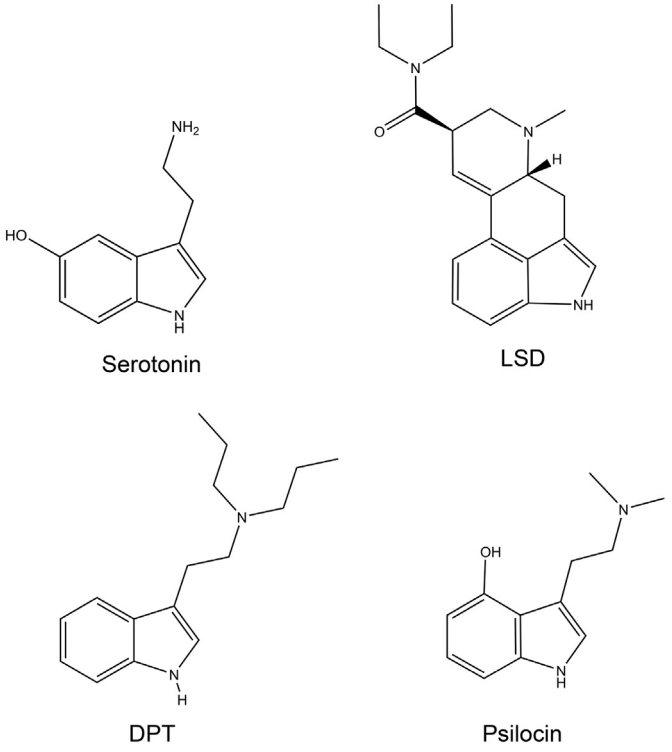

Fig. 1. Structural formula of serotonin (hydroxytryptamine, 5-HT) and related tryptamines psilocin (*N,N*-dimethyl-4-hydroxytryptamine, active metabolite of psilocybin), DPT (*N,N*-dipropyltryptamine) and LSD (lysergic acid diethylamide).

psychedelics share a common mechanism of action at different 5-HT receptors, primarily the 5-HT_{2A} receptor (Geyer and Vollenweider, 2008), which appears to be crucial for the specific psycho-vegetative effects, probably by activating a complex signal cascade (Halberstadt, 2015; Vollenweider and Kometer, 2010).

The treatment strategies presented in the current article originally emerged in the 1950s and 1960s. The idea of treating existential anxiety and depression in terminally ill patients with serotonergic hallucinogens was first suggested in an interview by the physician Valentina Wasson after participation in a ceremony involving 'magic mushrooms' containing psilocybin in 1957 and then some years later by the writer Aldous Huxley (Halifax and Grof, 1977). Subsequently, clinical trials evaluating psychedelic-assisted therapy in this indication have been carried out by different research groups in the U.S., however, initiating in the 1960s until the mid 1970s, when research on psychedelics came to a halt due to regulatory restrictions. However, after a hiatus period of > 30 years, LSD and psilocybin are currently being re-evaluated for the treatment of anxiety and depression, or 'existential distress' in patients with a life-threatening disease (Griffiths and Grob, 2010; Grob et al., 2013).

1.2. Studies in healthy volunteers

Scientific interest in serotonergic hallucinogens emerged due to the observation that a dosis of 200 to 500 µg of LSD may be capable of inducing 'unique, profound, overwhelming, otherworldly and impressive' (Sherwood et al., 1962) altered states of consciousness (ASCs), sometimes labelled as 'peak experiences'. Effects are sometimes followed by profoundly positive and potentially therapeutic after-effects (Maslow, 1962, 1959; Osmond, 1957) termed as 'psychedelic afterglow' (for a review see Majić et al., 2015) and described as 'elevated and energetic mood with a relative freedom from concerns of the past and from guilt and anxiety' (Pahnke, 1969a). One study administered a relatively high dose of psilocybin (30 mg) to a group of 20 students of theology before they attended a religious service in a private chapel ('Good Friday Experiment', Pahnke, 1963). When compared to the control group that received nicotinic acid as an active placebo, the psilocybin group experienced a high rate of profound experiences (30–40%), similar to the characteristics of nondrug-related 'mystical-type' experiences, described in the literature of theology (Hood, 1975; Pahnke, 1969b, 1967; Pahnke and Richards, 1966) (see Table 1). In a more recent study, psilocybin (30 mg/70 kg) or methylphenidate (40 mg/70 kg, as active control) were administered to a sample of healthy hallucinogen-naïve subjects in a double-blind, cross-over design (Griffiths et al., 2006). Out of the 36 subjects who received each substance in individual sessions conducted in specific setting, 22 subjects fulfilled Pahnke's criteria for having a 'mystical' peak experience. Positive after-effects were measured at 14-month follow-up with an observation of increased well-being or life satisfaction in 64% of the subjects (Griffiths et al., 2008). Respectively, 58% of subjects rated the experience as one of the most personally meaningful and 67% rated the

Table 1
Phenomenological features of a mystical-type experience—either naturally occurring or occasioned by a classical hallucinogen.
(Pahnke, 1963; Pahnke and Richards, 1966; Adapted from Grob et al., 2013).

- *Unity*: A core feature—a strong sense of the interconnectedness of all people and things—All is one—sometimes a sense of pure consciousness or a mind all things are alive
- *Transcendence of time and space*: A sense of timelessness, when the past and future collapse into the present moment—an infinite realm with no space boundaries
- *Deeply felt positive mood*: Universal love, joy, peace, tranquillity
- *Sense of sacredness*: Reverence, awe, or holiness
- *Noetic quality*: A sense of encountering ultimate reality
- *Ineffability and paradoxicality*: The feeling that the experience cannot be adequately described in words—a sense of the reconciliation of paradoxes
- *Transient experience with persisting positive changes in attitude and behavior*

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