Regulatory Toxicology and Pharmacology 59 (2011) 423-429



Regulatory Toxicology and Pharmacology

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



Harm potential of magic mushroom use: A review

Jan van Amsterdam^{a,*}, Antoon Opperhuizen^a, Wim van den Brink^{b,c}

^a Laboratory for Health Protection Research, RIVM, P.O. Box 1, 3720 BA Bilthoven, The Netherlands

^b Academic Medical Center University of Amsterdam, Department of Psychiatry, P.O. Box 22660, 1100 DD Amsterdam, The Netherlands ^c Amsterdam Institute for Addiction Research, Academic Medical Center, P.O. Box 75867, 1070 AW Amsterdam, The Netherlands

ARTICLE INFO

Article history: Received 15 November 2010 Available online 21 January 2011

Keywords: Magic mushrooms Illicit drugs Risk assessment Adverse effects Recreational drugs

ABSTRACT

In 2007, the Minister of Health of the Netherlands requested the CAM (Coordination point Assessment and Monitoring new drugs) to assess the overall risk of magic mushrooms. The present paper is an updated redraft of the review, written to support the assessment by CAM experts. It summarizes the literature on physical or psychological dependence, acute and chronic toxicity, risk for public health and criminal aspects related to the consumption of magic mushrooms.

In the Netherlands, the prevalence of magic mushroom use was declining since 2000 (last year prevalence of 6.3% in 2000 to 2.9% in 2005), and further declined after possession and use became illegal in December 2008.

The CAM concluded that the physical and psychological dependence potential of magic mushrooms was low, that acute toxicity was moderate, chronic toxicity low and public health and criminal aspects negligible. The combined use of mushrooms and alcohol and the quality of the setting in which magic mushrooms are used deserve, however, attention.

In conclusion, the use of magic mushrooms is relatively safe as only few and relatively mild adverse effects have been reported. The low prevalent but unpredictable provocation of panic attacks and flash-backs remain, however, a point of concern.

© 2011 Elsevier Inc. All rights reserved.

1. Introduction

The present paper is a revised version of the technical report used in the assessment of magic mushrooms by the CAM (Coordination point Assessment and Monitoring new drugs). The CAM, an advisory board of experts that provides science-based advises about recreational drugs, was asked by the Dutch Minister of Health to assess the overall risk of psilocine and psilocybine containing mushrooms, i.e. magic mushrooms. The reason to request the assessment was the fatal accident of a French girl who allegedly had consumed magic mushrooms before the accident occurred (cf. case 8 in Section 6.5). Moreover, some other magic mushroom related incidents preceded this fatal accident, and in the same period a report from the Municipal Health Service about magic mushroom related incidents appeared. The expert panel of the CAM, consisting of toxicologists, pharmacists, pharmacologists, policy officers, clinicians, police men, and social scientist/anthropologist, assessed the acute and chronic toxicity, public health, prevalence of use, availability and public order aspects of magic mushrooms. Details on the procedure have been described recently

E-mail address: Jan.van.Amsterdam@rivm.nl (J.van Amsterdam).

(van Amsterdam et al., 2010). The first author of this review is the secretary of the CAM.

2. Methods

The thematic report of the European Monitoring Center for Drugs and Drug Addiction (EMCDDA), Hallucinogenic mushrooms: an emerging trend case study (EMCDDA, 2010), was taken as a basis for this report. In addition, two literature reviews in Dutch (Bosch et al., 1997; CAM, 2000) were available. This current report was updated with the literature retrieved using searches in the Medline database 2000–2010. Search terms were: 'magic mushrooms', 'hallucinogenic mushrooms', 'LSD', 'psilocybin', 'psilocin', 'suicide', and 'alcohol'. The present review refers to mushrooms that contain psilocybin and/or psilocin. It is explicitly indicated if other mushrooms are described.

3. Magic mushrooms products

The present report reviews psilocine and psilocybine containing mushrooms, i.e. magic mushrooms. Types of magic mushrooms most commonly sold by head or smart shops in the Netherlands are *Psilocybe cubensis* varieties, most notably the *Psilocybe*

^{*} Corresponding author. Fax: +31 30 274 4446.

^{0273-2300/\$ -} see front matter \odot 2011 Elsevier Inc. All rights reserved. doi:10.1016/j.yrtph.2011.01.006

mexicana, none of which are reported to grow wild in Europe. Taken orally, magic mushrooms have a bad taste, and therefore they are sometimes consumed as chocolate bars containing grounded mushrooms.

Magic mushrooms show a large variation in potency; their potency depends on the species or variety that is used, their origin, growing conditions and age. *P. cubensis* and *Psilocybe semilanceata* or '*Psilocybe*', commonly known as liberty caps, contain 10 mg of psylocybin per gram of dried mushroom weight (1% w/w). Some other species (e.g. *Psilocybe azurenscens and Psilocybe bohemica*) contain slightly more psylocybin. The averaged dose of psilocybin that induces hallucinogenic effects is 4–10 mg (Beck et al., 1998) or 50–300 µg/kg body weight (Hasler et al., 2004), and therefore the minimum amount of mushrooms needed to get the desired recreational effect is about 1 g of dried magic mushrooms or 10 g of fresh magic mushrooms.

The dose 'recommended' for recreational use is reported to be somewhat higher: between 1 and 3.5–5 g of dried mushrooms or 10–50 g for fresh mushrooms (Erowid, 2006). These dose ranges should be interpreted with caution, because it is difficult to estimate the dose of the active or hallucinogenic substance (e.g. psilocybin) into mushrooms (weight or number), as the concentration may vary. Furthermore, in addition to psilocybin and psilocin usually other pharmacologically active substance like indoles, phenylethylamines and baeocystin are present in magic mushrooms. However, as short-term tolerance may develop rapidly to both physical and psychological effect, dosages may have to be increased to obtain the desired effect.

Some mushrooms may contain considerable amounts of phenylethylamine, e.g. up to $150 \mu g/g$ wet weight in *P. semilanceata* (Beck et al., 1998). Phenylethylamine is a sympathomimetic amine structurally related to amphetamines, and might be responsible for the cardiovascular effects (tachycardia) and other adverse reactions (nausea and anxiety) of magic mushrooms. Phenylethylamine is not likely to be abused. Its variability in content in mushrooms is much higher than that of psilocybin, which explains why such adverse reactions are relatively infrequent. Interestingly, the psychoactive substances psilocin and psilocybin appear to be more stable in dried mushrooms than in fresh mushrooms. For example, the Dutch Food and Consumer Product Safety Authority (VWA) could only detect traces of both compounds following 4 weeks storage of the fresh magic mushrooms (VWA, 2007).

4. Availability of magic mushrooms

4.1. Availability in the Netherlands

When magic mushrooms were still legal in the Netherlands, the users purchased their mushroom products mainly from smart shops, souvenir shops and via the internet. In a study among a representative sample conducted in 2001, 64% of the users aged 18years and older purchased their mushroom products in smart shops (Abraham et al., 2002). In 2006, when magic mushroom were still legal in the Netherlands, there some 120-150 smart shops in the Netherlands selling magic mushrooms and other legal psychoactive drugs (Dutch Association of Smart Shop Owners, 2006): about 35 in Amsterdam and a total of about 15 in four other larger towns. Since December 2008 however, the use and possession magic mushrooms has become illegal in the Netherlands, and fresh magic mushrooms are placed on List II in the Dutch Narcotic Law together with cannabis. At the same time, dried magic mushrooms were moved down from List I (hard drugs) to List II. Remarkably, the Dutch legislator did not include the truffle Sclerotia (philosopher stone) in this act of prohibition. Next to the truffle, grow sets of all kinds of mushrooms are still available at smart shops and internet shops. The purchase from internet shops is getting more and more important.

4.2. Availability in Europe

The ESPAD school surveys conducted in 2003 reviewed the accessibility of magic mushrooms to young subjects. It appeared that 4–8% of 15–16 year old school students 'obtain magic mushrooms 'very' or 'fairly' easily, whereas 'easy' access to magic mushrooms was reported by less than 10% of students in Cyprus, Finland, Greece, Hungary, Latvia, Lithuania, Romania and Turkey report and by more than 20% of students in the Czech Republic, Ireland, Italy, Poland and the UK. These levels of access are only estimates of the prevalence of use (probably overestimated). In the Netherlands, despite the lack of legal sanctions to control supply, only 16% of school students in the Netherlands report easy access to magic mushrooms.

Note that following the current trend in many consumer markets, there is a rapid diffusion of new products and brands. For example, the recent prohibition of psilocybin and psilocin containing fungi in the UK appears to have provoked an emerging interest of retailers in legal, types of magic mushroom such as *Amanita muscaria* (fly agaric) (Black Poppy, 2006).

5. Prevalence of use

Overall prevalence estimates for use of magic mushrooms in the EU are considerably lower than those for cannabis. However, life time prevalence estimates appear to equal those for ecstasy among students aged 15–16 years in some countries. Surveys in 12 EU member states indicate that, among young people aged 15–24 years old, life time use of magic mushrooms ranges from less than 1% to 8%. In the UK, almost 340,000 people aged 16–59 ever used magic mushrooms in the last year (2004/5) (Roe, 2005). In the Netherlands, life time use among 15/16 year old students was 5% (Hibell et al., 2003). In a more recent report, but still before magic mushrooms became illegal, Korf and Nabben (2007) report a decreasing trend in use of magic mushrooms. In addition, the authors suggest that the consumption of magic mushrooms is mainly initiated by the user's goal to experiment with drugs in general, and not particularly with magic mushrooms.

In the Netherlands, ever use by young adolescents (14–16 year) decreased from 5% in 1997 to 3% in 2002. The latter figure was confirmed in 2004 (Monshouwer et al., 2004). In older Dutch adolescents, life time prevalence decreased in the same period from 11% to 6%. Similar reductions were found among young visitors of Dutch pubs: last year prevalence of magic mushrooms use decreased from 6.3% in 2000 to 2.9% in 2005. Since the prohibition of magic mushrooms at the end of 2008, the prevalence of use in the Netherlands seems to have largely declined with a last month prevalence in 2009 of 0.1% (Trimbos, 2010).

6. Acute adverse effects

6.1. General side effects

The duration of a 'trip' usually lasts between 2 and 6 h. Mild adverse effects, like sleep problems generally remain present for up to about 12 h. Subjective effects range from intended feelings of relaxation (comparable to those of cannabis), giddiness, uncontrollable laughter, energy, joy, euphoria, visual enhancement (seeing colors brighter), visual disturbances (moving surfaces, waves), to mostly unintended delusions, altered perception of real events, images and faces, or real hallucinations. A survey in the UK in 2004 among 174 magic mushroom users quite high rates of anxiety (32%) and paranoia (35%) were reported (Riley and Blackman, 2008). In a recent web-based survey on hallucinogenic drugs among 600 subjects showed that the drug effects of magic mushrooms were considered as beneficial with a relatively low harm potential (Carhart-Harris and Nutt, 2010). However, sensory distortions may be coupled with negative effects, like restlessness, impaired coordination, anxiety, impaired judgment of time or distance, sense of unreality or depersonalization. In addition to the differences in psilocybin content consumed, the interpersonal variation in effects is large. A UK clubbing magazine survey conducted in 2005 found that nearly a quarter of those who had used magic mushrooms in the last year had experienced a panic attack (Mixmag, 2005). However, of 150 known cases of intoxication from magic mushrooms in Australia and New Zealand between 1934 and 1989, four subjects showed serious psychological symptoms of which one required hospital care (Allen et al., 1991). Recently, 23 case reports on acute psychiatric symptoms after consumption of magic mushrooms were reviewed by the Nordic Council of Ministers (2009).

6.2. Bad trips

The experience of serious negative effects is often referred to as a 'bad trip'. No exact data are available about the prevalence of a 'bad trip' among regular users. The experience of a bad trip is probably the main reason of users of magic mushroom to visit emergency care facilities. In such cases, the intoxicated individuals are usually severely agitated, confused, extremely anxious, and disoriented with impaired concentration and judgment. Acute psychotic episodes may occur in serious cases, including bizarre and frightening images, severe paranoia and total loss of reality, which may lead to accidents, self-injury or suicide attempts. A bad trip is usually followed by faintness, sadness and depression and paranoid interpretations, which may persist for days, weeks or even months. Some of these symptoms are probably associated with the use of other controlled substances. Occasionally, intermittent and chronic psychotic states due to the use of magic mushrooms are observed. In some individuals, the use of magic mushrooms can exacerbate underlying personality disorders and psychosis-like states. A report on the internet from 2007 (Shroomery, 2007) refers to more severe acute effects by extracts of mushrooms being intravenously injected (Curry and Rose, 1985; Sivyer and Dorrington, 1984). Finally, it is speculated (Satora et al., 2005) that the combined use of magic mushrooms with other psychoactive drugs, including alcohol increases the risk for bad trips.

6.3. Set and setting

The effects (intended as well as unintended, adverse effects) of magic mushrooms depend on "set" and "setting" (Zinberg, 2010). Examples of set factors are individual drug sensitivity, previous experiences, expectations and mental state of the user, whereas setting is the social-cultural environment in which the drug is used. Subjective effects vary greatly within the same person from one episode of use to the next (Jacob and Fehr, 1987; O'Brien, 1996; Pechnick and Ungerleider, 2005). In early clinical research from the 1950s and 1960s, the powerful influences of set and setting on psilocybin effects were neglected. In later studies, subjects were better prepared and interpersonal support was given during the period of drug action. These later studies found fewer adverse psychological effects (e.g. fewer panic reactions and fewer paranoid episodes) and increased reports of positively valued experiences (Leary et al., 1963; Metzner et al., 1965). However, a study by Griffiths et al. (2006) reported that 22% (8 of 36) of the volunteers treated with up to 30 mg psilocybin per 70 kg experienced a period of notable anxiety/dysphoria during the session, some times including transient ideas of reference or paranoia, despite several prior meetings with monitors, with prior contact time ranging from 8 to 24 h. Of the carefully selected volunteers treated with this high dose (30 mg/70 kg), 31% experienced significant fear and 17% had transient ideas of reference/paranoia. A recent meta-analysis of 110 healthy subjects, treated 1–4 times under controlled conditions with 45–315 μ g/kg body weight, reported no serious psychological adverse effects (Studerus et al., 2010).

6.4. Acute physical adverse effects

In general, the physiological side effects are not significant and may include dizziness, nausea, weakness, muscle aching, shivering, abdominal pain and dilation of pupils (mydriasis). A UK clubbing magazine survey conducted in 2005 found that over 25 percent of those who had used magic mushrooms in the last year had experienced nausea or vomiting (Mixmag, 2005). Tachycardia is a common finding in patients intoxicated by Psilocybe mushrooms. Mild-to-moderate increase in breathing frequency, heart rate (tachycardia of 10 b.p.m.) and systolic and diastolic blood pressure increase (+25, and +10 mm Hg, respectively) is observed at 0.2 mg/ kg psilocybin p.o. (Gouzoulis-Mayfrank et al., 1999), confirming previous data of 8-12 mg/kg p.o. psilocybin (Quetin, 1960). Generally, body temperature remains normal, but pronounced physical symptoms such as severe stomach pain, persistent vomiting, diarrhea etc. have been recorded. The latter physical complaints are not induced by psylocybin itself, but are due to the consumption of mushrooms in general. The tendency for a temporarily increased blood pressure may also be a risk factor for users with cardiovascular conditions, especially untreated hypertension (Hasler et al., 2004).

6.5. Documented fatal incidents

Fatal intoxications due to exposure to magic mushrooms are rare (Gonmori and Yoshioka, 2002; Mccawley et al., 1962) and often due to the combination of magic mushrooms with other drugs, mostly alcohol. The Rand report (Levitt et al., 2006) which refers to the use of magic mushrooms in the UK pointed out that that "National Statistics of the UK show that for death in which drug poisoning (listed on the certificate) was the underlying cause of death, between 1993 and 2000 there was one death from magic mushrooms and 5737 from heroin". Note that these figures from the UK National Statistics do not include deaths in which the misuse of drugs was a contributory factor rather than the cause of the death, and represent therefore an underestimate. The report further indicates that the lethal dose of magic mushrooms for humans is very low. As the oral LD₅₀ value of psylocybin in the rat is 280 mg/kg, 17 kg of fresh mushrooms must be consumed to reach this rate in an adult human subject. Indeed, only two fatal cases (Gerault and Picart, 1996; Bück 1961) have been described in literature which are due to overdosing with magic mushrooms (no concomitant use of other drugs). Normally, people do not die from a magic mushroom overdose, because they are not very toxic en the potential victim will spontaneously vomit keeping the final dose low.

Additional fatal cases reported in open and 'grey' literature are described below.

- 1. A 6-year old child developed hyperthermia and status epilepticus following ingestion of *Psilocybe baeocystis* (Mccawley et al., 1962).
- 2. A 31 year old English man died after leaping from a tower block window after consuming 'Hawaiian' psilocybin containing mushrooms in combination with alcohol (Manchester Evening News, 28.05.2005). A coroner confirmed the contributory role of magic mushrooms together with alcohol: the amount of alcohol consumed was two and a half times the drink drive limit.

- 3. A 33 year old Irish man died after falling from the fourth floor of a building after consuming magic mushrooms and alcohol (Irish Independent, 02.03.2006).
- 4. A young French girl died after trying 'to fly' from the window of her room on the second floor after taking magic mushrooms (Asselborn et al., 1999). The autopsy revealed a traumatic cause of death, and post-mortem toxicological analysis indicated consumption of psilocybin and cannabis. Psilocybin concentrations were 0.06 mg/l for venous blood and 0.22 mg/l for heart blood. Moreover, her blood contained three cannabinoids (THC: 30 µg/l; 11-OH-THC: 8 µg/l and THC-COOH: 90 µg/l).
- 5. A 27-year-old Frenchman was found dead in an irrigation canal in winter time. The toxicological examination confirmed the ingestion of a large amount of mushrooms (*Psilocybe subcubensis*). It was concluded that he died of cold temperature in winter time (Gonmori and Yoshioka, 2002).
- 6. In 2004 one suicide was reported in the Czech Republic, in which the presence of magic mushrooms was confirmed by autopsy (European Monitoring Centre for Drugs and Drug Addiction (EMCDDA).
- 7. An 18-year old male on Hawaii allegedly died after consumption of ten magic mushrooms. Later it was shown that the victim died of an overdose of heroin; no psilocybin was detected in the stomach (Allen, 1988).
- 8. A young French girl who had allegedly used magic mushrooms jumped from a building in Amsterdam (CAM, 2007). Blood tests were, however, not performed to ascertain use of magic mushrooms.
- 9. Two young foreign male tourists died after they jumped out of the window of an Amsterdam hotel after the consumption of magic mushrooms (Buster and van Brussel, 2007).
- 10. A 18-year old Dutch male died after he jumped out of the window. According to the police he had used magic mush-rooms (De Telegraaf, 2008).
- 11. A 20-year old Dutch male died after he became sick following the use of magic mushrooms, ecstacy and alcohol (De Gelderlander, 2008).

6.6. Interaction of magic mushrooms with other drugs

Both psilocine and psilocybine are dimethyltriptamines (DMT's), which are rapidly metabolized (inactivated) by the enzyme MAO (mono amine oxidase, which catalyses the oxidative deamination of biogenic amines). As such, MAO-inhibitors inhibit the metabolization of DMT's. Acetaldehyde, the primary metabolite of ethanol, reacts in vivo with endogenous biogenic amines thereby producing the MAO-inhibitors tetrahydroisoquinolines (TIQs) and β -carbolines (tryptolines). Thus, it is speculated that alcohol may enhance the trip (and adverse effects!) induced by magic mushrooms. Though chocolate also contains MAO-inhibitors, the amount of MAO-inhibitors in regular chocolate is clinically not relevant. Finally, tobacco use is associated with lowered levels of MAO in the brain and peripheral organs (prolonged effects; recovery following smoking cessation) (Fowler et al., 1996; van Amsterdam et al., 2006). Tobacco smokers may therefore experience more pronounced desired and adverse effects of magic mushrooms as compared to non-smokers.

7. Chronic toxicity

7.1. Flashbacks

Flashbacks are spontaneous recurrences of a previous psilocybin experience (perceptual alterations, pseudo-hallucinations) without renewed intake of the drug. Flashbacks may occur long

(days, weeks or even years) after having used magic mushrooms (Benjamin, 1979). A critical review (Halpern and Pope, 2003) of 20 quantitative studies about the so-called Hallucinogen Persisting Perception Disorder (HPPD; Flashbacks) concluded that the current knowledge is very limited. HPPD appears to be an existing, but uncommon disorder, sometimes persisting for months or years after hallucinogen use. HPPD is reported mostly after LSD use, but less commonly with the use of magic mushrooms or LSD administered in research or treatment settings (Halpern and Pope, 2003). Indeed, in the study of Carhart-Harris and Nutt (2010), based on 600 forms submitted via the web, 38 out of the 174 subjects who used all drugs reported symptoms of hallucinogen persisting perceptual disorder (flashbacks). When those 38 subjects were asked which drug was most responsible for the flashback, 55% answered LSD and 22% psilocybin. In most reports on flashbacks the subject was a poly-drug user or a psychiatric patient at the time of use.

7.2. Psychosis and other psychiatric diseases

In a series of studies about the acute subjective, psychological, and perceptual effects of psilocybin it was shown that psilocybin induces a psychotic state that mimics certain aspects of acute and incipient stages of schizophrenia (Carter et al., 2005; Hasler et al., 2004; Vollenweider et al., 1998; Gouzoulis-Mayfrank et al., 1998; Vollenweider et al., 1998; Vollenweider and Geyer, 2001). Though these reports do not establish a causal relation between psilocybin and psychiatric disease, the possible role of hallucinogens in precipitating or exacerbating enduring psychosis, other psychiatric conditions, and long-lasting visual perceptual disturbances should be assessed more closely (Abraham et al., 1996; Halpern and Pope, 1999). A similar association has been claimed with respect to the use of cannabis, which is also assumed to exacerbate psychosis in vulnerable subjects (van Amsterdam and van de Brink, 2004). It is, therefore, advocated, that psychiatric patients and genetically susceptible subjects i.e. those with a family history of psychiatric disease should fully abstain from the use of any recreational drug. In schizophrenic patients the consumption of magic mushrooms may induce an acute psychotic state that necessitates hospitalization (Nielen et al., 2004).

8. Physical and psychological dependence

The authors could not find any evidence that magic mushrooms can lead to physical or psychological dependence. Tolerance to the psychedelic effects of psilocybin develops rapidly, but withdrawal symptoms and psychological dependency do not occur (Abramson and Rolo, 1965; Isbell et al., 1961) or are very rare compared to all other (illegal) drugs (Anthony et al., 1994; Stone et al., 2006; Stone et al., 2007).

9. Public health effects

9.1. Availability of adequate user information

Many young tourists visit the Netherlands (especially Amsterdam) to use magic mushrooms which until recently were easy available in legal smart shops. Most incidents with magic mushroom occur in foreign tourists and not in Dutch users. Therefore, retailers from the smart shops provide warnings in English about the use of magic mushrooms. These leaflets warned specific groups to refrain from using magic mushrooms. The groups at risk are: persons under the age of 18, pregnant women, patients who use pharmaceutical drugs or suffer from a mental illness, and people who drive or operate machines. They also warned not to use magic mushroom in combination with alcohol, and to start mushrooms consumption by taking small portions, because the aimed effect is delayed due to slow uptake into the blood using this route of dosing. Occasionally, the number of a UK Drug Help line is displayed on the label. However, the quality of the information provided by those selling the product varies (CAM, 2000). Most leaflets provide some information about the maximum shelf life, the nature of possible side-effects and the amount of active substances (psilocybin and psilocin). In 2006, most of the online shops warned against the use magic mushrooms when taking medication and/or in combination with alcohol or other drugs such as stimulants, but only two thirds warn against the use of magic mushrooms when the user suffers from depression or psychosis. Many o these internet sites of the online shops provide information on the intended use, but only few provide information on the safe use and the possible adverse effects of magic mushrooms. In general, the information from the retailers is biased towards the positive effects.

9.2. Emergencies related to the use of magic mushrooms

In Europe, the reported number of people seeking medical assistance for magic mushrooms intoxication is very low. In Toxicological Information Centers of the Slovak Republic the number of intoxications with all natural drugs increased 5-fold between 2001 and 2002 and poisonings due to mushrooms (not specified) was 4.3% of all poisonings (Kresanek et al., 2005). Mushroom poisonings are also common in Poland, especially in summer and autumn and are associated with traditional wild-mushroom picking and cookery. However, very few (2-4 psilocybe intoxications are reported annually by the Polish toxicological center (Satora et al., 2005). A data summary from the Swedish Poison Information Centre collected over 15 years in the period 1980–1995 reported only 25 cases of patients with Psilocybe mushroom intoxication (Beck et al., 1998). Of these patients, 10 showed anxiety; 4 agitation; 3 flushing; 3 nausea/vomiting; and 2 flashbacks. A more recent report from this source indicates that in the last 5 years the number of cases increased considerably to around 30-40 calls annually. though this is still relatively low. The Dutch National Poisoning Information Center (NVIC) reported 60 requests for information about magic mushroom poisoning per year, and this number was stable over the years 2001-2006 (NFI, 2007). Since the prohibition of magic mushrooms in the Netherlands in December 2008, the number of such information requests decreased (in 2007, 2008 and 2009 the number was 67, 57, and 14, respectively).

In 2005, the Amsterdam Municipal Health Service registered 2837 calls for ambulance service assistance related to recreational drug use (Buster and van Brussel, 2007). Alcohol intoxication was the most frequent reason of an emergency call (2056 times; 72.5%), whereas for magic mushroom use it was 70 times (2.5%). Most of the calls referred to ambulance services given to tourists: 92% of magic mushroom 'victims' were foreigners. In contrast to incidents related to cocaine, heroin and ecstasy, magic mushroom related incidents were relatively harmless: treatment in an intensive care unit was needed for 11-20% of the group who had used cocaine, heroin or ecstasy, and for 1.5% of those who had used magic mushrooms. More importantly, it is highly probable that the combined use of magic mushrooms with either alcohol or cannabis was the major cause of the incidents (no exact data available). Finally, magic mushroom incidents occurred mainly (95%) in public places (street, bars, hotels), which is considerably higher as compared to incidents related to the use of the cocaine, heroin, XTC and alcohol (60-70%). Since the prohibition of magic mushrooms in December 2008, the number of calls for ambulance assistance related to the use of magic mushrooms has declined from 117 in 2008 to 53 in 2009.

In the period 2004–2006, the Dutch National Forensic Institute (NFI) investigated the presence of psilocybin in urine of subjects deceased under suspicious circumstances, including unnatural death, use of drugs in traffic, and criminal cases where subjects were doped. Psilocybin was probably involved (detected in urine) in only 4 of the 4636 cases investigated (NFI, 2007).

10. Public order and safety

Theoretically, a magic mushroom user could behave recklessly during a mushroom trip, and panic attacks during a 'bad trip' could evoke aggressive behavior. Forensic physicians in Amsterdam have registered 30–36 lock-ins at police stations related to magic mushroom intoxications per year. Main reasons to lock the subjects in were public nuisance (71%) and violation of traffic rules (27%). For comparison: the number lock-ins for alcohol was 1846 (Buster and van Brussel, 2007). It should be noted that psilocybin (100– $250 \mu g/kg$ p.o.) affects the subjective perception of time, synchronization and tapping tempo, working memory and subjective changes in conscious state (Hasler et al., 2004), which largely impairs car driving and handling of machines (Wittmann et al., 2007).

11. Criminal involvement

The Dutch National Criminal Intelligence Service found no evidence of public nuisance as a result of sale or use of magic mushrooms. The 2007-briefing of the Dutch National Police Forces (KLPD, 2007) reports no criminal acts related to magic mushrooms, no relations between magic mushroom growers and criminals, no offenders of law related to magic mushrooms, except for two offences in one shop for selling dried magic mushrooms (the shop is temporarily closed). Occasionally, the police receives postal mailings containing illegal dried magic mushrooms with destinations abroad (which were undeliverable). The border police at the Belgium border regularly observed the export of dried mushrooms to France, Belgium and Luxembourg, which are confiscated. The customs at the national airport (Amsterdam Schiphol) occasionally confiscated small amounts (some kilograms) of magic mushrooms. In 2006-2007, the German customs found and confiscated one large mailing of 27 kg magic mushrooms.

12. Conclusion

It is concluded, that the use of magic mushrooms rarely (if ever) leads to physical or psychological dependence, that acute and chronic adverse effects are relatively infrequent and generally mild, that public health and public order effects are very limited and that criminality related to the use, production and trafficking of magic mushrooms is almost non-existent. However, attention should be paid to the infrequent occurrence of flashbacks and accidents. More specifically, in the absence of proper surveillance of the user the panic attacks evoked by magic mushroom use may lead to severe and sometimes fatal accidents.

The list mentioned in Section 6.5 is partly based on newspaper articles and will probably not be complete. On the other hand, fatal accidents were sometimes (e.g. case 8–11) attributed to the use of magic mushrooms although the evidence was not available (no autopsy or blood test report). Furthermore, the reported fatal accidents and suicides will not always appear as mushroom related deaths in the official statistics. Still, the infrequent but severe adverse effects are often associated with overdosing and the combined use with other drugs, including alcohol. When using magic mushrooms, many, if not all, accidents can be prevented by a supporting setting, such as surveillance by a 'sober' person. An attractive option is to make psilocybin available for use only on premises, e.g. in specially designed environments for this purpose. The results of this review have been used in a recent study to rank the relative harm of magic mushrooms compared to a selection of 19 illicit drugs, including heroin, cocaine, ecstasy and cannabis. Based on the rating of 19 experts for 19 recreational drugs for dependence potential, acute and chronic adverse health effects, prevalence, social harm and criminality, magic mushrooms were ranked as the illicit drug with the lowest harm (van Amsterdam et al., 2010). Similar low harm ratings for magic mushrooms were reported by two expert groups in the UK (Nutt et al., 2010, 2007; van Amsterdam et al., 2010).

Based mainly on the content of the expert CAM report, the overall risk potential of magic mushrooms use was judged to be very low and the CAM advised the Minister of Health to maintain the legal status of magic mushrooms. However, because the generation of panic attacks by magic mushrooms is unpredictable, and the panic attacks have resulted in the (fatal) accidents observed among some tourists, the Dutch Minister of Health prohibited the possession, use, production and trafficking in December 2008 (Expatica Communications B.V., 2008). Like cannabis, magic mushrooms are now classified as a 'List II drug' in the Dutch Narcotic Law. This decision was taken despite the advice of the CAM expert panel.

Conflict of interest

The authors declare that there are no conflicts of interest.

Acknowledgment

The present study was supported by the Dutch Ministry of Health, Welfare and Sports.

References

- Abraham, H.D., Aldridge, A.M., Gogia, P., 1996. The psychopharmacology of hallucinogens. Neuropsychopharmacology 14, 285–298.
- Abraham, M.D., Kaal, H.L., Cohen, P.D.A., 2002. Licit and illicit drug use in the Netherlands 2001. CEDRO/Mets en Schilt, Amsterdam.
- Abramson, H.A., Rolo, A., 1965. Lysergic acid diethylamide (LSD-25). 38. Comparison with action of methysergide and psilocybin on test subjects. J. Asthma Res. 3, 81–96.
- Allen, J.W., 1988. A private inquiry into the circumstances surrounding the 1972 death of John Gomilla, Jr., who died after allegedly consuming ten hallucinogenic mushrooms while residing in Hawaii. J. Psychoact. Drugs 20, 451–454.
- Allen, J.W., Merlin, M.D., Jansen, K.L., 1991. An ethnomycological review of psychoactive agarics in Australia and New Zealand. J. Psychoact. Drugs 23, 39–69.
- Anthony, J.C., Warner, L.A., Kessler, R.C., 1994. Comparative epidemiology of dependence on tobacco, alcohol, controlled substances, and inhalants: basic findings from the National Comorbidity Survey. Exp. Clin. Psychopharmacol. 2, 244–268.
- Asselborn, G., Wennig, R., Yegles, M., 1999. Tragic Flying Attempt Under the Influence of "Magic Mushrooms". Laboratoire National de Santé, Division Toxicologie, CRP-Santé. Centre Universitaire, Luxembourg.
- Beck, O., Helander, A., Karlson-Stiber, C., Stephansson, N., 1998. Presence of phenylethylamine in hallucinogenic psilocybe mushroom: possible role in adverse reactions. J. Anal. Toxicol. 22, 45–49.
- Benjamin, C., 1979. Persistent psychiatric symptoms after eating psilocybin mushrooms. Br. Med. J. 1, 1319–1320.
- Black Poppy., 2006. The Fly Agaric Mushroom, Black Poppy: a drug users health and lifestyle magazine, issue 11. Website: http://www.blackpoppy.org.uk/science_flyargaric.html (retrieved November 2010).
- Bosch, J.A., Pennings, E.J.M., de Wolff, F.A., 1997. Psychoactieve paddestoel and plantproducten; toxicologie en klinische effecten. Report to the Ministry of Health.
- Bück, R.W., 1961. Mushroom poisoning since 1924 in United States. Mycologia 53, 537–538.
- Buster, M, van Brussel, G., 2007. Acute medische hulp in verband met incidenten door het gebruik van roesmiddelen in Amsterdam, 2007. Een stijgende trend van paddo-incidenten. GG&GD Amsterdam (Amsterdam Municipal Health Service). Website: http://www.gezond.amsterdam.nl/GetDocument. ashx?DocumentID=2371&name-Acute-medische-hulp-paddo-incidenten& rnd=634246864103392254">http://www.gezond.amsterdam.nl/GetDocument.
- CAM., 2000. Risk Assessment report relating to paddos (psilocin and psilocybin). Coordination Centre for the Assessment and Monitoring of New Drugs (CAM),

Den Haag, The Netherlands. Website: <www.rivm.nl/bibliotheek/digitaaldepot/ cam_paddo_advies.pdf> (retrieved November 2010).

- CAM. 2007. Report of Coordination point Assessment and Monitoring new drugs (CAM). Aanvullende informatie paddoincidenten in Amsterdam. Website: http://www.rivm.nl/bibliotheek/digitaaldepot/cam_paddo_aanvulling.pdf (retrieved November 2010).
- Carhart-Harris, R.L., Nutt, D.J., 2010. User perceptions of the benefits and harms of hallucinogenic drug use: a web-based questionnaire study. J. Subst. Abuse 15, 283–300.
- Carter, O.L., Pettigrew, J.D., Hasler, F., Wallis, G.M., Liu, G.B., Hell, D., Vollenweider, F.X., 2005. Modulating the rate and rhythmicity of perceptual rivalry alternations with the mixed 5-HT2A and 5-HT1A agonist psilocybin. Neuropsychopharmacology 30, 1154–1162.
- Curry, S.C., Rose, M.C., 1985. Intravenous mushroom poisoning. Ann. Emerg. Med. 14, 900–902.
- De Gelderlander. 2-10-2008. Website: http://www.gelderlander.nl/voorpagina/nijmegen/3913766/Waarschuwing-na-xtcdode-in-Nijmegen.ece (retrieved November 2010).
- De Telegraaf. 3-8-2008. Website: http://www.telegraaf.nl/binnenland/1611897/ Weer_dodelijke_paddo-sprong__.html> (retrieved November 2010).
- Erowid., 2006. Erowid. Website: http://www.erowid.org>. Dated: 25.03.2006.
- European Monitoring Centre for Drugs and Drug Addiction (EMCDDA). Hallucinogenic mushrooms: an emerging trend case study. Website: http://www.emcdda.europa.eu/html.cfm/index31208EN.html (retrieved November 2010).
- Expatica Communications B.V., 2008. <http://www.expatica.com/nl/news/ local_news/Netherlands-bans-magic-mushrooms_47271.html>. Retrieved November 2010.
- Fowler, J.S., Volkow, N.D., Wang, G.J., Pappas, N., Logan, J., MacGregor, R., Alexoff, D., Shea, C., Schlyer, D., Wolf, A.P., Warner, D., Zezulkova, I., Cilento, R., 1996. Inhibition of monoamine oxidase B in the brains of smokers. Nature 379, 733– 736.
- Gerault, A, Picart, D., 1996. Intoxication mortelle a la suite de la consommation volontaire et en groupe de champignons hallucinogenes [Fatal Poisoning After a Group of People Voluntarily Consumed Hallucinogenic Mushrooms]. Bull. Soc. Mycol. Franc 112, 1-14. Website: http://www.lycaeum.org/leda/docs/10488.shtml?ID=10488> (retrieved January 2011).
- Gonmori, K., Yoshioka, N., 2002. Fatal Ingestion of magic mushroom: a case report. Ann. Toxicol. Anal. 14, 350.
- Gouzoulis-Mayfrank, E., Heekeren, K., Thelen, B., Lindenblatt, H., Kovar, K.A., Sass, H., Geyer, M.A., 1998. Effects of the hallucinogen psilocybin on habituation and prepulse inhibition of the startle reflex in humans. Behav. Pharmacol. 9, 561– 566.
- Gouzoulis-Mayfrank, E., Thelen, B., Habermeyer, E., Kunert, H.J., Kovar, K.A., Lindenblatt, H., Hermle, L., Spitzer, M., Sass, H., 1999. Psychopathological, neuroendocrine and autonomic effects of 3,4-methylenedioxyethylamphetamine (MDE), psilocybin and d-methamphetamine in healthy volunteers. Results of an experimental doubleblind placebo-controlled study. Psychopharmacology (Berl) 142, 41–50.
- Griffiths, R.R., Richards, W.A., McCann, U., Jesse, R., 2006. Psilocybin can occasion mystical-type experiences having substantial and sustained personal meaning and spiritual significance. Psychopharmacology (Berl) 187, 268–283.
- Halpern, J.H., Pope, H.-G.J., 1999. Do hallucinogens cause residual neuropsychological toxicity? Drug Alcohol Depend. 53, 247–256.
- Halpern, J.H., Pope, H.-G.J., 2003. Hallucinogen persisting perception disorder: what do we know after 50 years? Drug Alcohol Depend. 69, 109–119.
- Hasler, F., Grimberg, U., Benz, M.A., Huber, T., Vollenweider, F.X., 2004. Acute psychological and physiological effects of psilocybin in healthy humans: a double-blind, placebo-controlled dose-effect study. Psychopharmacology (Berl) 172, 145–156.
- Hibell, B, Andersson, B, Bjarnasson, T, Ahlström, S, Balakivari, O, Kokevi, A, Morgan, M., 2003. The 2003 ESPAD Report; Alcohol and Other Drug Use Among Students in 35 European Countries. Stockholm. Website: http://www.sedqa.gov.mt/pdf/information/reports_intl_espad2003.pdf>.
- Isbell, H., Wolbach, A.B., Wikler, A., Miner, E.J., 1961. Cross tolerance between LSD and psilocybin. Psychopharmacologia 2, 147–159.
- Jacob, M.R., Fehr, K.O.B., 1987. Drugs and drug abuse: a reference text, second ed. Toronto, Addiction Research Foundation, quoted through Neuroscience of psychoactive substance use and dependence, (2004) WHO, Geneva: pp. 104–105.
- KLPD. 2007. Briefing J. van der Klein, N. de Bruin, Korps Landelijke Politiediensten, May 2007.
- Korf, D.J., Nabben, T., 2007. Briefing of Bongers Institute, University of Amsterdam. Kresanek, J., Plackova, S., Caganova, B., Klobusicka, Z., 2005. Drug abuse in Slovak Republic, Przegl. Lek. 62, 357–360.
- Leary, T., Litwin, G.H., Metzner, R., 1963. Reactions to psilocybin administered in a supportive environment. J. Nerv. Mental Dis. 137, 561–573.
- Levitt, R, Nason, E, Hallsworth, M., 2006. The Rand Corporation. The evidence base for the classification of drugs. Website: http://www.rand.org/pubs/technical_reports/2006/RAND_TR362.pdf (retrieved November 2010).
- Mccawley, E.L., Brummett, R.E., Dana, G.W., 1962. Convulsions from psilocybe mushroom poisoning. Proc. West. Pharmacol. Soc. 5, 27–33.
- Metzner, R., Litwin, G.H., Weil, G.M., 1965. The relation of expectation and mood to psilocybin reactions: a questionnaire study. Psychedelic Rev. 5, 339.
- Mixmag., 2005. Mixmag Drug Survey 2000–2005 evidence includes personal communication from Dr. Luke Mitcheson. Reference cited in EMCDDA report. Website: http://www.emcdda.europa.eu/attachements.cfm/att_31215_EN_TP_Hallucinogenic_mushrooms.pdf> (retrieved November 2010).

- Monshouwer, K, Dorsselaer, S, Gorter, A, Verdurmen, J., Vollebergh, W., 2004. Jeugd en riskant gedrag; kerngegevens uit het peilstationsonderzoek 2003. Trimbos instituut Utrecht.
- NFI 2007. Personal communication. Briefing by Nederlands Forensic Instituut (NFI; Dutch Forensic Institute). May 2007.
- Nielen, R.J., van der Heijden, F.M., Tuinier, S., Verhoeven, W.M., 2004. Khat and mushrooms associated with psychosis. World J. Biol. Psychiatry 5, 49–53.
- Nordic Council of Ministers 2009. Occurrence and use of hallucinogenic mushrooms containing psilocybin alkaloids. Copenhagen. Website: http://www.norden.org/en/publications/publications/2008-606/at_download/publicationfile (retrieved November 2010).
- Nutt, D.J., King, L.A., Saulsbury, W., Blakemore, C., 2007. Development of a rational scale to assess the harm of drugs of potential misuse. Lancet 369, 1047–1053.
- Nutt, D.J., King, L.A., Phillips, L.D., 2010. Drug harms in the UK: a multicriteria decision analysis. Lancet 376, 1558–1565.
- O'Brien, CP., 1996. Drug addiction and drug abuse. In: Hardman, J.J., Limbird, L. (Ed.), Goodman and Guilman's the pharmacological basis of therapeutics, ninth ed., pp. 557–577.
- Pechnick, R.N., Ungerleider, J.T., 2005. Hallucinogens, In: Lowinson, J. H., Ruiz, P., Millman, R. B., Langrod, J. G. (Ed.), Substance Abuse A Comprehensive Textbook, fourth ed. pp. 313–323.
- Quetin, A.M., 1960. La psilocybine en psychiatrie clinique et experimentale. Paris: Medical dissertation.
- Riley, S.C., Blackman, G., 2008. Between prohibitions: patterns and meanings of magic mushroom use in the UK. Subst. Use Misuse 43, 55–71.
- Roe, S., 2005. Drug Misuse Declared: findings from the 2004/05 British Crime Survey, HOSB 16/05 (London: Home Office). Website: http://rds.homeoffice.gov.uk/rds/pdfs05/hosb1605.pdf> (retrieved November 2010).
- Satora, L., Goszcz, H., Ciszowski, K., 2005. Poisonings resulting from the ingestion of magic mushrooms in Krakow. Przegl. Lek. 62, 394–396.
- Shroomery. 2007. The Shroomery <http://www.shroomery.org>.
- Sivyer, G., Dorrington, L., 1984. Intravenous injection of mushrooms. Med. J. Aust. 140, 182.

- Stone, A.L., O'Brien, M.S., De La Torre, A., Anthony, J.C., 2007. Who is becoming hallucinogen dependent soon after hallucinogen use starts? Drug Alcohol Depend. 87, 153–163.
- Stone, A.L., Storr, C.L., Anthony, J.C., 2006. Evidence for a hallucinogen dependence syndrome developing soon after onset of hallucinogen use during adolescence. Int. J. Methods Psychiatr. Res. 15, 116–130.
- Studerus, E., Kometer, M., Hasler, F., Vollenweider, F.X., 2010. Acute, subacute and long-term subjective effects of psilocybin in healthy humans: a pooled analysis of experimental studies. J. Psychopharmacol. doi:10.1177/0269881110382466.
- Trimbos., 2010. Monitor drugsincidenten. Fact sheet 2009. Website: http://www.drugsincidenten.nl/documents/PDFs/Factsheet%20monitor%20drugs incidenten%20.pdf> (retrieved November 2010).
- van Amsterdam, J.G.C., Opperhuizen, A., Koeter, M., van den Brink, W., 2010. Ranking the harm of alcohol, tobacco and illicit drugs for the individual and the population. Eur. Addict. Res. 16, 202–207.
- van Amsterdam, J.G.C., Talhout, R., Vleeming, W., Opperhuizen, A., 2006. Contribution of monoamine oxidase (MAO) inhibition to tobacco and alcohol addiction. Life Sci. 79, 1969–1973.
- van Amsterdam, J.G.C., van de Brink, W., 2004. Cannabis als risicofactor van schizofrenie. Tijdschr. Psychologie 46, 515–524.
- Vollenweider, F.X., Geyer, M.A., 2001. A systems model of altered consciousness: integrating natural and drug-induced psychoses. Brain Res. Bull. 56, 495–507.
- Vollenweider, F.X., Vollenweider-Scherpenhuyzen, M.F., Babler, A., Vogel, H., Hell, D., 1998. Psilocybin induces schizophrenia-like psychosis in humans via a serotonin-2 agonist action. Neuroreport 9, 3897–3902.
- VWA 2007. Briefing of VWA (Dutch Food and Consumer Product Safety Authority). Wittmann, M., Carter, O., Hasler, F., Cahn, B.R., Grimberg, U., Spring, P., Hell, D., Flohr, H., Vollenweider, F.X., 2007. Effects of psilocybin on time perception and
- temporal control of behaviour in humans. J. Psychopharmacol. 21, 50–64. Zinberg, N.A., 2010. Drug, Set, and Setting: The Basis for Controlled Intoxicant Use. Yale University Press, London.