



The Use of Classic Hallucinogens/Psychedelics in a Therapeutic Context: Healthcare Policy Opportunities and Challenges

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Abstract: Psychedelics or serotonergic hallucinogens are a group of substances that share the agonism of serotonergic 5-HT_{2A} receptors as their main mechanism of action. Its main effects include changes in perception, cognitive process, and mood. Despite being used for centuries by different cultures in ritual contexts, these substances have currently aroused the interest of science and industry for their promising antidepressant, anxiolytic, and anti-addictive effects. Considering this evidence, this article aims to explore some of the possible health policy challenges to integrate these therapeutic tools into broad and heterogeneous health systems. As a main benefit, these substances produce rapid and enduring effects with the administration of single or few doses, which could lead to new treatment possibilities for patients with severe mental disorders resistant to the usual medications. The main challenge is associated with the fact that these substances remain scheduled in most countries and are associated with social stigma related to their recreational use (especially LSD and psilocybin). This situation makes it exceedingly difficult to conduct clinical trials, although international conventions allow such research. Ethically, this could be interpreted as a violation of human rights since thousands of people are prevented from having access to possible benefits. Interestingly, ritual ayahuasca use is more acceptable to the public than the use of psilocybin-containing mushrooms or LSD. The controlled, clinical use of LSD and psilocybin seems to be less criticized and is being explored by the industry. Rigorous scientific evidence coupled with industrial interests (LSD and psilocybin), together with respect for traditional uses (ayahuasca) and international conventions, seems to be the best way for these drugs to be integrated into health systems in the next years. Which highlights the need for an urgent dialogue between science, health system, society, and politics.

Keywords: hallucinogens, psychedelics, healthcare

Introduction

Background

Psychedelics or serotonergic hallucinogens are a group of substances that have in common the agonism for serotonergic 5HT_{2A} receptors as their main mechanism of action.¹ These substances can be found in nature (such as psilocybin, present in mushrooms of the genus *Psilocybe* and many others; dimethyltryptamine/DMT, present in the botanical preparations ayahuasca and jurema; and mescaline, present in peyote and San Pedro cacti), or they can be of synthetic origins (such as the diethylamide of lysergic acid/LSD).^{2,3} Botanical psychedelics have been used for centuries as part of the traditional medicine of many cultures in the Americas.⁴⁻⁶ Mescaline has its

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traditional use based in northern Mexico (peyote) and Peru (San Pedro), and psilocybin (*Psilocybe* spp. mushrooms) in Central Mexico.⁵ DMT is the main hallucinogenic component present in jurema (traditionally used in Northeast Brazil) and ayahuasca (traditionally used in Northwestern Amazon in countries, such as Brazil, Peru, Ecuador, and Colombia).⁵

Psychedelics produce changes in sensory perception (mainly visual effects), cognitive processes (introspection, self-consciousness, mystical experiences, altered time passage) and mood (blissful state, euphoria, and joy).^{2,7} The intensity and nature of these effects are highly influenced by the set (personality and internal expectations of the subject), setting (environment in which the substance is used), and dosage.⁸ Subjects participating in clinical trials often describe mystical experiences and improved mood while under the effects of these substances.^{9–11} Although there is accumulating evidence that psychedelics are generally safe in humans,^{7,10,12} it is important to note that these substances can produce adverse effects and/or unpleasant experiences popularly known as “bad trips”, which involve transitory anxious and psychotic symptoms, confusion, dissociation and depersonalization.^{7,8} Nevertheless, careful screening of volunteers and a supportive environment seem to reduce the occurrence and severity of these experience in controlled settings.^{7,13}

Therapeutic Properties

Between the late 1950s and early 1970s several studies were conducted to investigate the possible therapeutic effects of psychedelics (especially LSD) in the treatment of anxiety, depression, and substance use disorders.^{8,13,14} Despite the promising results of these studies and the good safety profile of these drugs in controlled contexts,¹⁵ important methodological limitations in these studies (lack of placebo or control groups, absence of standardization in the monitoring of volunteers and interventions used) and the popularization of the recreational use of these drugs culminated in the prohibition of human studies until the early 1990s.^{2,8,13}

In recent years, several research groups have been investigating the possible antidepressant, anxiolytic, and anti-addictive effects of psychedelics. Recent open-label studies showed that psilocybin reduced depressive and anxious symptoms in treatment-resistant depression (TRD)¹⁶ and in major depressive disorder (MDD).¹⁷ Depression and anxiety symptoms were also reduced in controlled trials in terminal cancer patients.^{18,19} Psilocybin produced positive effects in open-label trials for the treatment of alcohol and tobacco dependence.^{20,21}

Although there is less recent research with LSD, a recent meta-analysis of early studies in the 1960–70s provided evidence that it can be useful to treat of alcohol use disorder,²² and other studies indicate its possible anxiolytic properties in life-threatening diseases.²³ Regarding ayahuasca, a controlled trial showed that it reduced panic-like and hopelessness symptoms in healthy volunteers.²⁴ Furthermore, an open-label²⁵ and a placebo-controlled trial²⁶ showed that ayahuasca administration reduced depression, anxiety, and suicidality in patients with TRD.^{27,28}

In most of these clinical trials single or few doses were administered, and the beneficial effects were fast-acting (hours/days) and enduring (weeks/months).^{17–21,23,25,26} Notably, all substances showed a good safety and tolerability profile, producing mostly mild/moderate and transient effects, such as vomiting and nausea, anxiety, confusion, and headache.^{17–21,23,25,26}

In the 1980s, another type of serotonergic drugs with mind-altering and therapeutic properties appeared, the “entactogens”²⁹ These substances enhance empathy and emotional openness, and the most intensely studied drug of this class is MDMA (3,4-methylenedioxymethamphetamine), popularly known as “ecstasy”. MDMA is being researched for the treatment of social anxiety in autistic adults,³⁰ in the treatment of end-of-life anxiety (NCT00252174) and is being developed as a prescription medicine for the treatment of Post-Traumatic Stress Disorder (PTSD).³¹ Both MDMA and psilocybin have been designated by the FDA as “breakthrough therapies” and in the case of MDMA both the FDA and the Israeli Agency of Medicines have authorized its use as a compassionate medicine.³² MDMA has different mechanisms of action from those of classic hallucinogens. Instead of agonism at cortical 5-HT_{2A} receptors, MDMA inhibits monoamine (serotonin>norepinephrine>dopamine) reuptake and enhances oxytocin release.^{33,34} The therapeutic effects of MDMA on PTSD seem to be related to memory reconsolidation and fear extinction.³⁵ Although MDMA is not a truly “classical hallucinogen”, it is of interest to mention briefly here because it is in Phase 3 of clinical trials for the treatment of PTSD and is also a scheduled substance. Therefore, the challenges related to its medical use are similar to those of classic hallucinogens.

Mechanisms of Action

The therapeutic effects of psychedelics are related primarily to their agonist action at the serotonergic receptor 5HT_{2A}, and to a minor extent at 5HT_{1A} and 5HT_{2C}

receptors.^{36,37} Agonists of 5HT_{1A} receptors are thought to be responsible for passive adaptive response (tolerability to a source of stress), while 5HT_{2A} agonists are thought to be responsible for the active adaptive response (dealing with the source of the stress actively).¹⁶ Considering that psychedelics are agonists of both receptors, the increase in overall adaptability could be related to their therapeutic effects.¹⁶ Furthermore, 5HT_{2A} agonists also induce the release of glutamate, modulating the activation of the amygdala, hippocampus, and prefrontal cortex.^{38,39} The increase of glutamate in these brain areas also stimulates the synthesis of brain-derived neurotrophic factor (BDNF), increasing neuroplasticity.^{40,41} Reduced activity of the default mode network (DMN) and enhanced functional connectivity between otherwise distinct brain networks also indicate enhanced neuroplasticity induced by psychedelics.^{10,42–44}

Regarding ayahuasca, modulation of BDNF, cortisol, and inflammatory biomarkers seem to be related to its antidepressive effects in depressive patients.^{45–47} During an imagination task with the eyes closed, ayahuasca produced a brain activation pattern in occipital areas similar to the pattern observed when looking at an object with open eyes.⁴⁸ This could be related to its therapeutic effects by giving a status of reality to inner experiences, such as biographical memories.⁴⁸

Moreover, LSD and psilocybin reduce the recognition of negative emotions through amygdala modulation, while increasing positive affect and mood.⁴⁹ The anxiolytic and antidepressant effects reported in the literature seem to be related to this mechanism of action in brain areas related to emotional processing.^{49,50} Psychological mechanisms also seem to be involved in the therapeutic effects of hallucinogens. Decentering and mindfulness-related processes have been associated with positive therapeutic outcomes in studies of acute drug administration^{51–54} and in long-term users.⁵⁵ Positive change in personality, such as increases in the traits of openness to experience and self-transcendence, is also related to the therapeutic effects of these compounds.^{7,56,57}

It is still not clear what is the role of psychotherapy in clinical trials with psychedelics. Psychological interventions may or may not be used combined with psychedelics. In the open-label and controlled ayahuasca trials of ayahuasca for TRD, no psychotherapy was used,^{25,26} while in the open-label trials of psilocybin for TRD,¹⁶ MDD,¹⁷ and alcohol²⁰ and tobacco²¹ dependence, and in the LSD²³ and psilocybin^{18,19} trials for anxiety and depression in cancer patients, more elaborate techniques were used. Further

research is needed to better understand the possible beneficial role of different types of psychotherapy in trials with psychedelics.

Considering the initial evidence presented of the potential therapeutic uses of psychedelics in mental health, we will now explore some of the possible and most relevant health policy opportunities and challenges that may be associated with the integration of the therapeutic use of these compounds in a broad and heterogeneous health system.

Healthcare Policy Opportunities

Most medications used for the treatment of psychiatric disorders, such as antidepressants and anxiolytics, are used daily and for long periods (months to years). This increases the treatment costs for the individual and the health care system. The daily and prolonged use of these drugs is also associated with significant adverse effects,⁵⁸ which also reduces treatment adherence. Moreover, most prescribed antidepressants and anxiolytics need several weeks to reach their therapeutic effects.

The paradigm of the treatments using hallucinogens/psychedelics is different since instead of being primarily pharmacologically oriented, it is both pharmacologically and psychologically oriented. Importantly, the usual method involves only one or few doses associated with a psychological treatment. For instance, in all current studies with these drugs only 1–3 doses are being used, and sometimes therapeutic effects are observed weeks to months afterwards.^{7,10,59} This is perhaps one of the most important benefits associated with these drugs since it would be cheaper for individuals and society in the long term. Although in the short term it will be necessary to invest time and resources in the treatment sessions (which may or may not include psychotherapeutic processes), only one or few treatment sessions would be performed, and benefits would last longer than current pharmacotherapy and/or standard psychotherapy. This could allow healthcare systems to prevent long-term costs. Furthermore, the good safety and tolerability of these treatments^{7,10} could increase treatment adherence and reduce social and individual costs in managing serious adverse effects.

Hallucinogens/psychedelics could also be one more opportunity for patients who do not respond to traditional/available medications. Treatment-resistant patients usually have tried at least two different medications (often more) without benefit and are a challenge to health professionals since treatment failure also increases symptoms overtime. Thus, any new treatment options that could

have a significant impact on these individuals, their families, and society would be warranted. Chronic, treatment-resistant patients also have comorbid disorders and/or diseases and low quality of life. By reducing part of the psychological suffering in terms of anxiety and depressive symptoms, psychedelics could indirectly reduce the overall disease burden and increase quality of life, especially in the long term.

Hallucinogens/psychedelics are also related to novel mechanisms of action in relation to traditional medications, which are often based on the monoaminergic imbalance theory. The modulation of cortical 5-HT_{2A} receptors and the subsequent increase in glutamatergic tone and the associated neuroplasticity are novel mechanisms of action.^{7,41,60} The psychological effects of these drugs, which often include mystical experiences, increased empathy and sociality, ego dissolution, and increased acceptance, openness, and psychological flexibility, are also new therapeutic mechanisms considering that they are drug-induced and both acute and enduring, thus possibly enhancing the psychotherapeutic processes. Those new pharmacological and psychological perspectives are relevant to clinical practice and to psychopharmacological and psychological theories of psychiatric disorders.

Novel drugs and treatments could be derived from the use of these compounds in the future.⁶¹ These new treatments and advances could not only reduce social and individual disease-related burden by treating symptoms but also could prevent the development of psychiatric disorders. Indeed, populational studies did not find associations between psychedelics and mental health problems in most users,^{22,62} but did find that their use was associated with some mental health benefits.^{63–65}

Similar advances are currently being observed with the use of the N-methyl-D-aspartate (NMDA) glutamate receptor antagonist ketamine in TRD. Ketamine also has psychedelic/hallucinogenic effects and induces fast and enduring antidepressant effects.⁶⁶ However, the prolonged safety of ketamine is still poorly investigated, and this drug has potential for tolerance (resulting in increasing dosing and toxicity), abuse/dependence (increased by tolerance), and bladder toxicity.⁶⁷ Such effects are not observed with classic psychedelics/hallucinogens. Regarding tolerance, although LSD and psilocybin induce a fast (and cross-) tolerance with repeated doing (with the possible exception of ayahuasca/DMT⁶⁸) since their effects are prolonged with few doses there is no need to increase those doses. Besides, as previously mentioned,

only few doses are usually used in current studies. Psychedelics/hallucinogens do not have a high abuse potential, and in controlled trials any such effects are reduced by using few doses. Previous observational studies with ritual ayahuasca users reported absence of social and psychological measures associated with drug abuse/dependence. Instead, significant reductions in previous drug use/problems were observed.⁶⁹

The social contexts and culturally mediated effects related to some of these drugs are also relevant in discussing the opportunities and benefits offered by them. In the case of ayahuasca, its traditional indigenous and syncretic religious use is often related to increases in social bonds and improvements in community health.^{70–74} Ayahuasca is usually used in group ceremonies or sessions, and previous studies among ritual users have observed improvements in mental health measures including reduced anxiety and depression, less use of prescription medications, better quality of life, psychosocial adjustment, stress coping strategies, and indicators of perceived social support.^{63,64} In these traditional contexts, ayahuasca is already a medicine, although it is important to acknowledge that the conceptions of diseases and their treatments are often quite different between traditional and non-traditional users.^{72,73} For instance, indigenous and syncretic religious users often have different worldviews and perspectives on health, which are also different for less religiously/ritually inspired users. In any case, it is quite interesting that ayahuasca is almost always used ritually and in groups, be it in the remote Amazonian tribes or in big urban centers.

In this sense, ayahuasca is different of other classic hallucinogens/psychedelics such as LSD and psilocybin regarding cultural acceptance. LSD and psilocybin are usually associated with recreational use, which may limit their acceptance by a community that for decades have associated these drugs with mental health problems. Perhaps the example of ayahuasca use and regulation in South America could help to reduce the prejudice with other psychedelics. The public perception can change by the acceptance that a powerful mind-altering drug can be used respectfully by young and old community members, if used carefully. The recognition that psilocybin also has a deep history of medicinal and traditional use in Mexico could also help reducing the prejudice against its use. The mystical-type experiences that these compounds may produce help our understanding of their traditional medicinal

uses and point to new, more respectful uses and perceptions of such uses.

The popularization and globalization of practices involving ayahuasca and other ethnobotanicals (like peyote, San Pedro or iboga – an African plant containing ibogaine) that occur outside of biomedical or culturally oriented settings and that are led by non-health professionals or unprepared individuals brings some important challenges that will be discussed in the next section.

Healthcare Policy Challenges

The opportunities offered by psychedelics/hallucinogens are accompanied by several challenges. One of the most relevant is the legal status of these compounds worldwide. Psilocybin, DMT, LSD, and MDMA are in the Schedule I of the United Nations Convention on Psychotropic Substances from 1971. This means that they lack therapeutic effects and have a high potential for abuse/dependence and to cause serious adverse effects. This often translates in costly and time-consuming bureaucratic processes to perform both preclinical and human studies with these drugs (if the studies are allowed at all to be performed at the end of this process). In this scenario, some researchers suggested that these drugs should be reclassified so that their therapeutic potentials can be fully investigated like any other drug with therapeutic potentials.^{75,76} But although re-schedule would be desirable, the Convention already established that scheduled substances are only allowed precisely for scientific and medical purposes. Thus, these substances should be re-scheduled not only because their risk do not correspond with the specific schedule list where they are located but because the Convention already guarantees its medical and scientific uses. Indeed, there are already some interesting and practical possibilities to explore their medical uses. The most immediate way is allowing its medical use under compassionate use conditions. This is already happening with LSD, psilocybin, and MDMA in Switzerland, the United States, Canada, and other countries.⁷⁷

From a legal and ethical point of perspective, when the scientific and medical uses allowed by the Convention are not guaranteed by individual countries, the Convention has been violated. This violation confronts directly with several human rights, including the Right to science, the Right to enjoy the highest attainable standard of physical and mental health, and the Right to enjoy the benefits of scientific progress and its applications.⁷⁸ Such violations usually happen for socio-political reasons, since in our

society these drugs are associated with the stigma of recreational misuse, health problems, and limited therapeutic value.^{79,80} This is especially relevant for LSD, psilocybin, and MDMA. As described above, these compounds can be safely administered in controlled settings, and several therapeutic potentials do exist.^{7,10} Even recognizing their potential for abuse in the recreational context, populational studies have not found that they are related to mental health problems in most users.^{22,62} Instead, their use was associated with mental health benefits.^{63–65} The re-scheduling of these drugs could lead to an increase in both research and public acceptance if such research finds beneficial effects.

Moreover, since the Convention allows the medical use of psychedelics, medical doctors should also gain (indeed, regain) the control and capacity to use the medicines that they consider the best option for their patients according to their clinical criteria. It could also be understood as unethical that some patients need to wait to fail in several treatments before being treated with psychedelics. By re-scheduling these compounds and following the already approved uses according to the Convention, many patients could obtain benefit from the treatment with these substances administered under medical conditions. Meanwhile, clinical trials will continue to be developed and performed to improve efficacy and safety.

The legal situation is also complex with ethnobotanicals. The only plants that are scheduled in the 1971 Convention are cannabis (*Cannabis sativa*), poppy (*Papaver somniferum*) and coca (*Erythroxylum coca*). Ayahuasca, peyote, iboga, and *Psilocybe* mushrooms are not scheduled.⁸¹ However, some countries have specific laws for controlling them, which often lead to criminal accusations against people carrying or using these plants. This controversial legal situation has been contested by several international social movements that demand that the Convention should be respected and that people carrying or using these plants should not suffer criminal accusations. Moreover, such social movements also demand the decriminalization of scheduled plants. For instance, some US States like Oregon and Colorado, and cities, such as Oakland or Denver, have already passed bills decriminalizing psychoactive plants. Furthermore, countries like Canada have already approved medical compassionate use with these plants and fungi.

In the specific case of ayahuasca, its ritual and therapeutic use by indigenous groups in several South American countries including Brazil, Colombia, Peru,

and Ecuador is not scheduled and, indeed, is protected by local legislation.⁷⁴ The same type of legal and cultural acceptance is observed among non-indigenous populations in these countries, including local healers from jungle/rural areas and organized groups in urban centers such as the Brazilian syncretic religions that use ayahuasca as their sacrament (Santo Daime, União do Vegetal, and Barquinha). Over the past 20 years, these Brazilian syncretic religions have spread throughout Latin America and to several countries, including the US, Canada, Japan, South Africa, Australia, and several European countries.⁷⁴ In several of these places these groups have achieved some form of legal authorization for the ritual/religious use of ayahuasca. Therefore, ayahuasca is different from LSD and psilocybin both regarding regulation and cultural acceptance, which can be more challenging in the case of LSD, psilocybin, MDMA, and other synthetic drugs related to drug abuse/misuse. Furthermore, specifically in the case of Brazil, the regulation that allows the Brazilian ayahuasca religions to use ayahuasca ritually also allows (and indeed stimulates) preclinical and clinical research with ayahuasca.⁷⁴

This more permissive context in Brazil and South America with ayahuasca could probably facilitate its integration in broader healthcare systems. Maybe in the near future a dynamic and collaborative continuum ranging from the ritual and therapeutic uses in indigenous and religious groups to the psychiatric and psychotherapeutic uses in non-indigenous/-traditional societies could be achieved.

Another important healthcare policy challenge involves funding. Since these drugs were described several decades ago and/or are natural compounds (psilocybin, DMT, mescaline) they are usually considered off-patent. Furthermore, the paradigm of using single or few doses during treatment is often not considered financially attractive. Thus, until recent years, the pharmaceutical industry usually gave little support for such studies. Indeed, most of the current research with these drugs is funded by private and charitable donations.⁷⁶ However, this scenario is rapidly changing, with several pharmaceutical companies being created and funding clinical trials with these drugs. For instance, several pharmaceutical companies are investing in developing psychedelics as prescription medicines.⁸² Examples of this increasing interest include the breakthrough therapy designation granted by the US Food and Drug Administration for the trials of psilocybin for major depression funded by the Usona Institute and for treatment-resistant depression funded by Compass Pathways/Atai.⁸³ Again, ayahuasca is

an exception. To the best of our knowledge, Brazil is not only the single country that is currently running clinical trials with ayahuasca but all these trials are funded by national and/or local public agencies that give financial support for research in the country.

Paradoxically, pharmaceutical companies are now using the knowledge accumulated in the preclinical and Phase 1 studies with LSD, psilocybin, and DMT/ayahuasca to develop their products. It is important to acknowledge that substances like psilocybin and ayahuasca/DMT were discovered and extracted from indigenous communities. Psychedelic pharmaceutical companies should think in terms of reciprocity to return both to society and to indigenous communities the benefits of their sales when psychedelic substances become prescription medicines. That would mean, for example, to facilitate these drugs for free to those medical doctors using them under the umbrella of compassionate use programs, and to invest and develop programs in indigenous and other traditional communities. Moreover, since the ritual and therapeutic use of ayahuasca is traditionally spread in South America and the plants used in its preparation are native to these countries, each country needs to follow its specific rules regulating the use of traditional knowledge and endemic genetic material.⁶³

Another significant challenge is related to the different medical systems involved in psychedelic practices. While biomedical practices are validated by the means of clinical trials, traditional practices have already been validated by the long history of traditional use. Currently, we are in an unusual situation where the medicalization of psychedelics co-exists with community/traditional uses. For instance, the therapeutic use of ethnobotanicals by a mixture of mental health professionals, lay persons that have learned how to use them in traditional contexts, and a myriad of other practitioners and providers, are emerging all over the world. Due to globalization, traditional medical systems and scientific biomedical approaches already co-exist. Not only Western medical systems are exported to indigenous communities but traditional medical systems are gaining popularity in Western societies. Indigenous doctors are coming to Western countries to perform ayahuasca/iboga rituals, while Westerners are traveling to Amazonian/African countries in search of spiritual enlightenment and healing. Contemporary research is starting to show how traditional medical systems involving ayahuasca are helping Westerners to improve their mental and physical conditions.^{51,84} Moreover, the paradigm of the Right to science is also starting to recognize traditional knowledge

as a special kind of scientific knowledge.⁷⁸ In the future, the co-existence of such different systems will face the challenge of regulation. Ethical standards will need to be defined, professionals will need to be trained, and long-term safety will need to be monitored. The traditional use of ayahuasca could serve as an example of regulatory rigor while respecting traditional knowledge.

Other important challenges are the costs to implement such therapies and the feasibility and adherence of long therapeutic sessions. In the case of LSD and psilocybin, most therapeutic models being currently investigated involve a series of preparatory and integration sessions and the actual session, which is usually performed by several therapists. While this structure surely increases the safety of the process and may indeed increase its efficacy, it could be unrealistic to implement in society, especially in less economically developed countries.

Moreover, culturally adapted settings will need to be developed, since the therapeutic settings in studies made in the US and Europe are not necessarily efficient and accessible in other countries. Further, several therapy sessions will certainly increase treatment costs and reduce adherence, and the professionals involved in implementing those therapies will need to be trained. Thus, the scientific community could try to investigate more accessible forms of implementing those therapies.

Conclusions

Psychedelics or classic hallucinogens are promising substances to treat depression, anxiety, and substance-related disorders. The available evidence suggests that these drugs will be incorporated in health systems worldwide in the following years. Complex situations need complex solutions. Thus, more than ever it will be necessary a dialogue between scientists, policy and decision makers, community agents, social and health professionals, spiritual leaders, ethnobotanical ceremony providers, and activists.⁷⁸ There is no way to avoid the incorporation of psychedelics into Western societies both in the medical and in the social levels, so only progressive and regulating-oriented approaches (rather than repressive and persecution oriented) will be of benefit for society.

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