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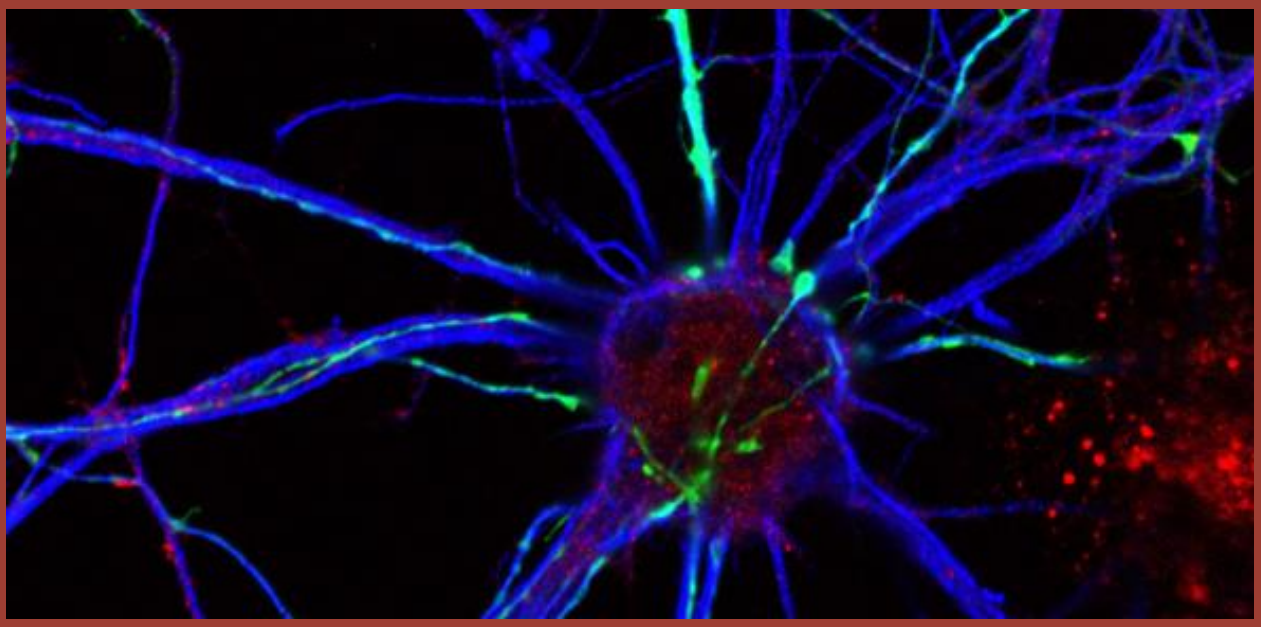

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Article

A Critical Review Investigating whether there are similarities in EEG band waves between Schizophrenic patients and participants given DMT or Ayahuasca Tea

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Abstract:
Early research suggests that the endogenous neurobiological chemical Dimethyltryptamine (DMT) may be responsible for schizophrenic symptoms [1]. This article investigates EEG band waves between participants given Dimethyltryptamine (DMT) or Ayahuasca Tea and schizophrenic patients. Evaluation of articles on EEG band wave monitoring of DMT or Ayahuasca participants was compared to articles on EEG band wave monitoring in schizophrenic patients. It is hypothesized that adult DMT and Ayahuasca participants and adult schizophrenic patients would have similar EEG oscillation-band waves. Ranlund *et al.* [2] found that schizophrenic patients produced lower band waves, and this review supported the findings that there were similarities, especially in lower band waves between the two groups. Although the reviewed Ayahuasca articles produced higher EEG wave band oscillations, the additional plant compounds added to Ayahuasca Tea may account for the resulting discrepancy in this review. The similarities in EEG band wave oscillations between the pure DMT injection and the schizophrenic patients did support the hypothesis, although, the EEG band waves only show neuron activity and not specific DMT brain chemicals. There may be a connection between the symptoms reflected in schizophrenic patients, suggestive of endogenous DMT, due to the similarities when DMT is administered.

INTRODUCTION

Endogenous Dimethyltryptamine (DMT) is a naturally occurring compound in plants, animals, and humans [3]. It is believed to help in the neuroprotection of cell death by using antioxidant properties which are involved in suppressing the apoptosis mechanism [4]. The entheogenic tea Ayahuasca contains DMT, which produces hallucinations, unlike any other psychedelic drug [5]. During schizophrenia, people have been known to experience 'realistic' alternative realities, which have the same kind of images seen with endogenous DMT [1]. This novel article investigates the established literature by linking EEG band waves, in schizophrenic patients with the band waves observed after ingesting DMT or Ayahuasca. The focus will be on adults participating in EEG monitoring after ingesting Ayahuasca [6], intravenous DMT [7], and EEG monitoring taken from schizophrenic patients [8].

This study uses quantitative data to show that DMT or Ayahuasca ingestion may produce the same EEG results seen in schizophrenic patients and that endogenous DMT may be responsible for these results. EEG oscillation-band waves can be monitored alongside subjective experiences being verbally relayed to the researchers by questionnaires on changes in consciousness while under the influence of DMT or Ayahuasca. Previous results from the subjective experience are needed to show the similarities between the EEG changes and any changes to consciousness that are experienced by the participants. This review will question some of the subjective methods, including neurophenomenology [7] and the Hallucinogen Rating Scale [6], in relation to understanding DMT or Ayahuasca participation and schizophrenia symptoms. It also reviews whether EEG methods are satisfactory given the spatial limitations in understanding what occurs in the brain during DMT or Ayahuasca ingestion and schizophrenia.

Previous research has shown a correlation between EEG band wave changes

and DMT administration [7] or ingesting Ayahuasca tea, containing DMT [6]. EEG monitoring of schizophrenic patients [8] [9] has also shown band wave changes similar to that of DMT research by Timmermann *et al.* [7]. Although using EEG monitoring for this purpose is acceptable in terms of reliability and validity, there are methodological limitations to this when confirming that these changes are due to DMT circulating within the brain.

It has been suggested that the development of some schizophrenic systems may be due to changes in endogenous DMT production in patients [1]. DMT is known to be produced in the body and may produce the same altered realities, voices, and visions experienced by schizophrenic patients [10]. Research into this phenomenon is difficult to establish due to the reliability and validity of the methods and procedures that have been used to date.

Previous studies used for mental health issues, such as schizophrenia, are predominantly defined by a psychiatric diagnosis classification system, such as the Diagnostic and Statistical Manual of Mental Disorders (DSM) or the International Statistical Classification of Diseases and Related Health Problems (ICD). Neuropsychiatry is now investigating biological differences and responses to understand schizophrenia [11], as symptom classification for the definition of health issues is becoming more controversial because the classification criteria are ever-changing [12]. Therefore, the objective of this article is not to investigate the different types of schizophrenia. Instead, it is to encourage ways of moving forward to substantiate the possibility of endogenous DMT being associated with psychotic episodes.

Electroencephalography (EEG) records high temporal resolutions of brain activity and can be presented using five different Hertz (Hz) band waves. It is useful for detecting changes in many neuropsychiatric diseases and may be considered a biomarker as the results usually show changes in specific wave bands [13]. The results explore the similarities between EEG wavebands (*delta, theta, alpha* and *beta*) between different groups of people. For example, a group drinking Ayahuasca tea containing DMT, a group intravenously injected with pure DMT and research carried out using EEG on psychotic patients. The review will also touch on various rating scales used alongside the EEG research, which provides subjective information about the various levels of consciousness experienced.

This project aims to highlight the possibility of the same EEG wavebands correlating to both psychotic episodes and when partaking of exogenous DMT. It will also address the controversies of quantitative and qualitative techniques presented in specific research papers when examining the similarities between DMT ingestion and psychotic episodes via EEG.

METHODS

It may be that the studies covered here, are based on methodological procedures that lead to inconsistent sampling due to inconsistent psychiatric classifications. For example, the DSM or ICD diagnosis of schizophrenia relies purely on symptoms rather than genetics or other biomarkers such as DMT in urine or blood [14].

There may be altered or increased endogenous DMT production in patients with schizophrenia [1] and therefore, there is merit in understanding the limitations, reliability, and validity of the core EEG research findings to date. This understanding should allow a judgment about whether these methods are suitable for investigating similar-ities between band wave changes for

DMT or Ayahuasca administration and schizophrenic patients.

This article is not a full systematic review, but a narrative literature review, consisting of English articles found initially using Google/Scholar. Manual searches were conducted from the reference lists of the initial articles. In an attempt to avoid unbiased dissemination, thesis and unpublished papers were also investigated from psychedelic blog webpages covering EEG and Ayahuasca [15]. Additional articles were found using Medline and PsycInfo with Medical Subject Headings (MeSH) terms such as N,N-Dimethyltryptamine AND Electroencephalography. Other searches included schizophrenia AND EEG AND oscillations.

Exclusions to this review were papers discussing 5-methoxy-N-N-dimethyltrypt-amine, bufotenine (toad venom), and animal studies of DMT. The inclusion criteria were defined as participants partaking in DMT or Ayahuasca administration and schizophrenia patients with any kind of EEG band wave oscillations e.g. *delta* to *gamma* on any skull location. Thus, the DMT or Ayahuasca individuals were healthy participants, and the intervention was DMT. The comparisons were DMT and schizophrenia EEG band waves, with the outcome being any similarities in oscillation-band waves.

The search criteria highlighted a scarcity of research articles that were available for this review. This lack of information may have been for several reasons, including the lack of null result publications. There was also a lack of reproduced experimental findings, which may be due to publishers unwilling to publish reproduced findings unless outcomes changed.

Many DMT research study articles were unavailable online as they were published in the 1950-1960's. Therefore, the information may be available in hardcopy but was unavailable for this review. As the interest in psychedelic compounds increases there is likely to be a steady increase in the literature produced.

The study design of EEG monitoring implemented for DMT injection consisted of a small sample of healthy male and female adult participants [7]. They were screened for psychiatric conditions along with other physical conditions.

The Timmermann *et al.* [7] research using EEG during DMT administration only highlights neural correlations, which are similarities between band wave changes due to DMT administration. There is no direct evidence that a higher level of DMT is circulating in the brain. Both Timmermann *et al.* [7] and Riba *et al.* [6] used DMT placebo during research.

Another issue arising from making comparisons between the DMT admin-istration [7] and Ayahuasca tea participants [6] is that they show inconsistencies in oscillation-band wave ranges – respectively *delta* (1-4Hz) and *delta* (1.3-3.5Hz). Thus, not using a standardized measurement range makes it difficult to ascertain which band wave the participants adhere to in general. Nayak and Anilkumar [16] raise this issue along with the fact that EEG is a specialized topic and that the methodological planning needs detailed knowledge of all the areas within EEG that would need to be considered. This is evident in the Begić *et al.* [9] study of schizophrenic patients, which used quantitative EEG (qEEG), a specialized system of algorithms providing better EEG procedures and analysis than standard EEG [17]. Some of the review articles also show inconsistent methodological procedures allowing ingestion of substances such as nicotine, alcohol and caffeine before EEG monitoring. These substances have been shown to affect EEG band waves [18] and may affect the experiment's external validity and thus results.

The unequivocal 96% EEG quantitative biomarker for paranoid schizophrenia identified by Buettner *et al.* [19] is rooted in collected computational datasets with machine learning classifiers. Thus, the importance is not so much in relying on the EEG recording but, in the methods and procedures used to investigate specific schizophrenic phenotypes. For example, other research on EEG monitoring has reached an 85% accuracy, although this was for monitoring chronic schizophrenia responding to clozapine [20]. Therefore, EEG monitoring of schizophrenia may need specific methodological algorithms for detecting specific types of schizophrenia.

Although there are nine different types of schizophrenia classified in the International Classification of Diseases (ICD-10), the Buettner *et al.* [19] EEG monitoring article focuses on paranoid schizophrenia. The EEG results on paranoid schizophrenia may have some significance. Paranoia has been known to present in both DMT [21] and Ayahuasca ingestion [22]. The schizophrenic participants in the research were defined using the DSM classification system [8] [9]. The Begić *et al.* [9] patients were hospitalized at the time, but there is no evidence to show that they were hallucinating while the research was being carried out, and there were no subjective questionnaires like in the DMT or Ayahuasca research linking EEG monitoring to any subjective experience.

This review's main limitation is the small number of DMT and Ayahuasca ingestion studies completed to date. Additionally, limitations lie with the initial methodological procedures of defining schizophrenia classifications, along with what the EEG is monitoring. For example, the monitoring does not show endogenous or exogenous DMT production in the brain as EEG is not equipped to monitor chemicals but finds correlations between administration of DMT and changes in brainwaves. More effective methods and procedures to address DMT administration and the brain connection may lie in carbon labeling *in vivo* animal studies enabling a detailed understanding of DMT dispersion neurobiologically [23]. It may be that advances in radioligands could be applicable and available using human participants. For example, results from tagging of DMT (or the metabolite) could be compared between labelled DMT in schizophrenics and exogenous DMT participants. This would enable any quantities and similarities to show in specific brain regions as they appeared. Additional approaches could be assays using single nucleotide polymorphisms (SNPs) to provide a plethora of chemical and metabolites that are connected to DMT and how they interact with some of the known schizophrenic gene phenotypes [21].

RESULTS

EEG Hertz frequency bands are used in the analysis and are separated into five different band waves, *delta, theta, alpha, beta,* and *gamma* [24]. Several studies show increased activity in the *delta* and *theta* band wave frequency in patients with psychosis [8] [9]. There is evidence that chronic psychosis produces increased EEG *delta* and *theta* band activity [2]. Although these results were statistically significant, they are estimated differences calculated using linear regression models, which show correlations and specific *p*-values for the wave bands were not separated in this study. Some studies have shown a decrease in *alpha* frequency in psychosis [13]. All these differing band waves are important in linking the neurological experience of psychosis to the possible experience of endogenous DMT that is produced naturally in the body [3].

Although the objective and subjective measurements complement each other by providing evidence that EEG band wave

changes record consciousness experiences, it is essential to note that the EEG monitoring cannot produce evidence of any specific chemical changes in the brain.

Riba *et al.* [6] used high and low dose Ayahuasca to show that there were changes in the EEG band waves relating to the amount of Ayahuasca taken and the effects experienced. They did this by comparing controls to participants in which it showed significant changes to EEG band waves between controls and low to high dose Ayahuasca ingestion. The *delta* and *theta* bands showed increased different ($p < 0.05$) between baseline (PRE-2) values in the absolute power (*theta* band 3.5-7.5 Hz) at low dose at 120 minutes after ingestion (-1.70 +/- 1.45 *SEM*) and (*delta* 1.3-3.5 Hz) at high dose 90 minutes after ingestion (-1.40 +/- 1.10 *SEM*). There was also a reduction in *beta* levels (-0.10 +/- 0.16 *SEM*) at a low dose and (-0.10 +/- 0.27 *SEM*) at a high dose in relative power that was also statistically significant with a *p*-value <0.05. These results suggest that DMT affects different band waves so much that the oscillations' resonance is a different frequency than baseline or controls. For example, the lower band waves increased (*delta*, *theta*), while the higher band wave (beta) was decreased.

Timmermann *et al.* [7] also endeavored to measure EEG band waves alongside the subjective experience using a rating scale during intravenous injection of DMT fumarate straight into blood system. They found reduced *alpha* (cluster $p = 5.33e-04$) and *beta* wave (cluster $p = 0.033$) bands in the time averaged component, suggesting that the higher frequency band waves showed a significant reduction from controls. In contrast, the lower frequency band waves increased for *delta* (cluster $p = 0.024$) and *theta* (cluster $p = 0.007$) bands in the oscillatory power frequency. These *p*-values show that the changes in participants from controls are statistically significant.

The rating scales measuring the subjective DMT experience complement the EEG wave band patterns found. Although subjective measures within consciousness are being debated [25], the qualitative data gathered is generally acceptable for validity and reliability [26].

Using different *p*-value measures of reporting between the research papers may elicit some controversy as it suggests that what is statistically significant in one paper will not be in another, even though the same tests may be applied. For example, Timmermann *et al.* [7] and Riba *et al.* [6] have different *p*-value targets for the subjective measures.

Rating scales are commonly used to collect and measure patients' experiences using a questionnaire, but discrepancies in rating scales may also produce problems when analyzing any correlations between papers [27]. For example, Timmermann *et al.* [7] used the neurophenomenology framework [28], which integrates the first-person subjective experience while taking psychedelics, with the objective recordings of the EEG. This framework uses an intensity rating scale, relayed verbally to the researcher, at specific times, due to DMT having an influence on key areas such as visual, emotional and bodily feelings. These scales are then coded by the researcher and are analyzed alongside the EEG's time sequences [7].

These results are based on time measured sequences of both the EEG in relation to the subjective experiences while under the influence of DMT. The results showed that visual intensity correlated with reduced *alpha* waves ($p = 2.67e-04$) (.0002.67) and *beta* ($p = 0.04$), whereas there were increases in *delta* ($p = 0.004$) and *theta* ($p = 0.01$). These results may suggest that the visual experience of DMT is related in some way to the increase of *delta* and *theta* band waves, which have been found in other neuropsychiatric conditions [8] [9].

The alternative to neurophenomenology is the Hallucinogen Rating Scale (HRS) questionnaire, specially designed for subjective experiences under psychedelic drugs [29] and was used by Riba *et al*. [6] in the Ayahuasca research. This consists of six subscales, including perception, cognition, and emotion. A one-way ANOVA with repeated measures for high and low dose ayahuasca was used. They used this method to test the mean differences between the groups of high and low, repeating each mean subscale of the HRS to find the results. The results showed that the ratings for perception, cognition, and emotion were all statistically significant, with the p-value < 0.001 on the HRS compared to controls. However, the mean score of 1.35 (SD 0.61) in decision making (Volition), was only slightly significant on a high dose with a p-value <0.05. Again, these results suggest that DMT (via Ayahuasca ingestion in this instance) may affect the body in substantially different ways by changing consciousness, like in emotional processing, as assessed using the HRS.

It is interesting to note the divergence from the HRS to neurophenomenology for subjective measures in the Timmermann *et al*. [7] research, because the reliability and validity of the HRS had already been assessed in 2001 using both Ayahuasca and DMT injections [29]. This contrasts with Winkelman [30] highlighting the lack of studies in psychedelic research using neurophenomenology. This suggests that competing techniques for qualitative data within psychedelic research can become problematic when comparing data when no official design for subjective psychedelic experiences is used as standard practice.

On the other hand, the Brief Psychiatric Rating Scale (BPRS) is used as a rating scale measurement for psychotic patients when researching EEG wave band differences [31]. This is an entirely different rating scale that is used when researching subjective Ayahuasca experiences and is analyzed differently by using a point system rated 1-7 with 18 items, but only one of these items focusing on hallucinations [32].

Future research could incorporate a standardized analysis protocol when reporting EEG band wave ranges that monitor participants under the influence of DMT. This standardized protocol should extend to qualitative measurements using one specific rating scale for measuring the subjective experience, which may extend to psychotic patients, and the DSM criteria. For example, using the HRS on psychotic patients may well highlight similarities to the subjective experience of DMT and psychotic episodes. A significant limitation to this overall review is that EEG band waves cannot measure a particular chemical present in the brain. Other limitations are the discrepancies between research papers regarding different p-value targets, EEG band wave ranges, and subjective framework methods that make it harder to properly investigate the exact similarities between them.

The overall results show that there are indeed changes to EEG wave bands under the various administrations of DMT. These changes include DMT administration when compared with controls and also the amount of DMT administered. Therefore, there is evidence that DMT affects the body and that depending on the amount residing in the body has sufficient changes to subjective consciousness ratings and correlations to EEG band waves. The measurements in psychotic episodes show the same changes to EEG wave bands, and some studies show that DMT is present in this health condition [1].

DISCUSSION

The hypothesis was evaluated by focusing on specific EEG band waves and looking for

similarities between the groups specified. The results may indicate another method for monitoring the possibility of endogenous DMT influencing any schizophrenic symptoms. This review may be a valid contribution to science by evaluating a biological mechanism for psychotic episodes in schizophrenia. This review takes ad-vantage of previous research, implying that Ayahuasca and DMT chemical composition induces schizophrenic symptoms [33].

Earlier studies suggested that the 'transmethylation hypothesis' was a disruption of metabolism that resulted in endogenous DMT, producing symptoms of schizophrenia [34]. Further investigations on urine samples confirmed that DMT levels were higher in some patients who experienced schizophrenia [1] [35]. Detection of DMT levels in blood and urine samples in schizophrenic patients has shown inconsistent results [36]. This conflicting evidence may imply insufficient methods of detection. In addressing this situation, neuroscientists incorporated EEG monitoring of schizophrenic patients finding differences to healthy controls [37].

The psychiatric condition exclusion is a double-edged sword. On the one hand, DMT administration in subjects with psychiatric conditions has been known to intensify symptoms such as changes to thought and perception [22]. Thus, it would be ethically challenging to include these patients in DMT research. On the other hand, including these subjects could shed some light on why schizophrenic phenotype people experience enhanced symptoms of schizophrenia when they participate in recreational DMT. Alternative methods to EEG monitoring may be to use genetics to associate mutations with endogenous DMT production [21], thus understanding why enhanced symptoms are experienced with DMT administration.

Research has shown that there are differences in EEG band wave oscillations in schizophrenic patients compared to controls [38] [39], although this EEG biomarker can only be assessed by using the specific methodology, which still needs to be established for different phenotypes of schizophrenia. Changes in cortical activity have not been compared between subjects under DMT or Ayahuasca influence and patients experiencing psychotic episodes. This article addresses this gap with the hypotheses that schizophrenic patients and DMT ingestion participants exhibit similar changes in EEG band wave oscillations. These findings may affirm previous studies on EEG monitoring on schizophrenic patients [40] and DMT ingestion participants [7] where oscillations were found in the lower range band waves, e.g., *delta, theta.*

Further research found changes in cortical activity and altered consciousness in subjects under the influence of DMT or Ayahuasca. This was evaluated by simultaneously using questionnaires, thus recording changes of emotional or visual experiences [6] [7]. Interest in this research area is increasing due to the cognitive similarities between the symptoms of DMT and Ayahuasca participation and schizophrenic patients [41].

Table 1 shows varied and contradictory findings for comparison. Most of the *gamma* band waves in the articles were either unmonitored or did not significantly change. The *beta* band wave increased in some of the Ayahuasca reviews, and one of the schizophrenia monitoring reviews, but decreased for the DMT study. The *alpha*

band waves decreased in two of the Ayahuasca studies and the DMT study. It, however, increased in one schizophrenia study and decreased in the other. The *theta* band waves were all reduced in the Ayahuasca studies but increased in the DMT and schizophrenia studies. The *delta* band waves decreased in one of the Ayahuasca studies but increased in both the DMT and one schizophrenia study. Although, Table 1 is a basic representation of overall findings, it does not represent differences in overall EEG techniques. For example, Hong *et al.* [8] found increased *delta* bands in resting states

Table 1:
A schematic representation of results using band wave monitoring of Ayahuasca or DMT participants and schizophrenic patients.

EEG Oscillation-Band Waves	*DELTA*	*THETA*	*ALPHA*	*BETA*	*GAMMA*
Ayahuasca Effects of Ayahuasca…[42]		▼	▼	▲	▲
Topographic pharmaco-EEG mapping ….[6]		▼		▲	
Inhibition of alpha oscillations….[43]	▼	▼	▼		
DMT Neural correlates of the DMT….[7]	▲	▲	▼	▼	
Schizophrenia A shared low-frequency…[8]		▲	▲		
Quantitative Electroencephalography… [9]	▲	▲	▼	▲	

▲ Increase in Hz. ▼ Decreased in Hz.

but reduced *delta* in sensory gating. Overall, these results were inconsistent, although there were some similarities.

It is interesting to note these similarities, especially with the pure DMT [7] and the schizophrenia participants [9]. These both showed increases in lower band wave oscillations, for example, *delta* and *theta,* and there were also similarities in the decreased *alpha* oscillations.

Also noteworthy are the articles concerning Ayahuasca participation [6] [42] [43]. These showed a reduction in *Theta* band waves compared to DMT and schizophrenic patients, while some of the Ayahuasca articles reported higher amplitude in *beta* and *gamma* ranges. These results challenge the initial hypothesis producing an opportunity to discuss why conflicting results appear.

There are a few points that may have influenced these contradictions. For example, Ayahuasca is a mixture of plants containing DMT and plants containing monoamine-oxidase inhibitors (MAOi), which allow orally taken DMT to metabolize in the body [44]. The MAO inhibitors have different psychoactive qualities [45]. The use of heterogeneous Ayahuasca plants used in the review articles may account for the differences between the Ayahuasca groups.

There were very few exogenous DMT studies as it is an illegal substance in many countries [46] and requires Home Office approval in the UK for research use [47]. Ayahuasca is legal in some countries; therefore, research is more accessible. Research studies with band wave monitoring of DMT or Ayahuasca proved to be sparse. One article had a conflict of interest [43] which may influence the results. There was a need to include Ayahuasca studies, as there was only one DMT research article exploring EEG monitoring that was relevant to this review. Therefore, there is a heterogenicity issue when comparing the studies as the Ayahuasca tea contains several plants, which may have influenced the results.

The *beta* band wave increase that occurs in both schizophrenia patients [9] and Ayahuasca participants [42] (Table 1), may warrant further investigation. For example, the plant used for this Ayahuasca contains 5-Meo-DMT, another natural endogenous chemical, that may trigger psychotic symptoms [48]. This could lead to further research using exogenous 5-Meo-DMT injections and EEG monitoring.

There were differences between the schizophrenic patient band waves. Although the criteria for schizophrenia were based on the DSM-IV [49] for both studies, one patient group was drug naïve [9]. Interestingly, there are more similarities between this article and the DMT participants. Other inconsistencies in results may be due to differences in the ranges used to define the EEG band waves.

Although both Timmermann *et al.* [7] and Riba *et al.* [6] use absolute power values (e.g., *delta, theta* etc.), these results may be subject to variation, and only Riba *et al.* [6] normalize the frequencies to remove any incon-sistencies. Therefore, it is difficult to com-pare the two papers as they use different analytical approaches, which can, in some cases extend to different procedures when processing the raw data for extracting the power spectrum of frequencies [50]. Another dissimilarity between the papers is the difference in range for each wave band frequency. For example, Timmermann *et al.* [7] defines the range in *delta* as 1-4 Hz and *theta* as 4-8 Hz, which is different from the Riba *et al.* [6] ranges of *delta* as 1.3-3.5 Hz and *theta* band of 3.5-7.5 Hz. This could mean that some wave bands may be included in *alpha* as the ranges are so inconsistent throughout, and therefore, in some cases discrepancies regarding ranges to the specific band waves may produce inconsistent values. For example, Ranlund *et al.* [2] highlight inconsistent findings within EEG on psych-

otic patients, which may be influenced by the inconsistent values.

Placebos are used to validate the research conducted, although some psychedelic drug research has shown a placebo effect. For example, placebo admin-istration resulted in 61% of participants reporting drug effects following subjective questioning methods after ingestion [51]. Omitting EEG and plasma DMT baseline level recording may reduce validity, but this could be a perfect opportunity in future studies to repeat the experiment while using EEG monitoring to detect any placebo brain changes from baseline levels.

Whether these findings help answer the research question is debatable. On the one hand, there are some similarities between pure DMT and schizophrenic patient band waves, especially with the increase in lower band waves. Although, EEG monitoring does not detect specific chemical interactions, it does produce strong links to cognitive and perceptual processes that are invaluable in providing significant information when detecting changes in consciousness [52]. The results from this review suggest similarities between pure DMT and schizophrenic patient EEG band waves, unlike the Ayahuasca ingestion band waves. This may be due to different plants used in the Ayahuasca, which may have different DMT chemicals included (e.g., 5-Mexoy-DMT), or that properties of the MAO inhibitors are affecting band waves. It could also be due to different dosages.

The definition and application of specific protocols could be an invaluable opportunity for future Ayahuasca participation in EEG monitoring research. For instance, applying a diet used by Amazon tribes before ingesting Ayahuasca [53] may lead to more substantial EEG similarities with individuals with schizophrenia. Other research could investigate the DMT levels involved in circadian fluctuations within the plants [45], thus enabling control of the amount of DMT ingested from the plants. This could enable DMT quantities to be monitored and may produce similar results to schizophrenic patients' band waves if the DMT content is higher within the Ayahuasca tea. It would also be interesting to use the Buettner *et al.* [19] method to establish a precise and validated method for EEG monitoring of DMT ingestion, although this would require a very large sample size.

Ideally, reproducing each experiment, carried out using DMT or Ayahuasca, would allow other potential issues to be found. For instance, this would allow detailed information and findings to be collected in a consistent manner. Other limitations of this review are comparability. For example, Ayahuasca tea may contain different plant genus or species, and the tea may be administered in different quantities.

The Timmermann *et al.* [7] research can only assess EEG neural correlations in relation to injection of DMT. It cannot conclude any causal relationship between DMT administration and brain wave changes because it cannot monitor chemicals circulating in the brain. This warrants further investigation, perhaps using animal models to measure DMT absorption post-EEG measurement. Although, this method may also be unreliable as post-mortem asphyxiation allows many chemicals to rush to the brain [54], potentially confounding results of DMT circulating in the brain. Alternative methods to quantify the amount of DMT in blood plasma, at various times after admin-istration, may be able to provide a validated association between DMT admin-istration and blood plasma levels [7].

Building on this review, with the initial hypothesis of linking EEG band waves in schizophrenic patients and DMT ingestion participants, future study designs could move towards experimental, randomized control studies. Using schizophrenic patients under the same protocol and methods and pro-

cedures without DMT ingestion would provide better heterogenicity when comparing the two groups.

CONCLUSION

The results of this review showed similarities in EEG band waves between pure DMT injection and schizophrenic patients. Results showed increasing lower band wave frequencies within these groups. The lack of replication of results for the band waves in this group may be due to the different plants added to the Ayahuasca. It was hypothesized in this review that schizophrenic patients and DMT ingestion participants would have the same EEG band wave oscillations. The finding of this review corroborated this hypothesis. Another confounding variable to this review was the amount of DMT administered, either via injection or Ayahuasca that might account for differences in the results.

Future research could reproduce this review by incorporating a wider data base and search criteria; for example, 'hoasca' is used by the religious Uniao do Vegetal members [22]. This information was found after the initial search, so it was not included. Future studies may also include repeated protocols of EEG monitoring of DMT or Ayahuasca, reinvestigating any new results, and reviewing the inconsistencies raised in this review.

This review highlights the need for future research, for example, published studies on DMT or more chemically controlled Ayahuasca EEG band wave monitoring. EEG monitoring using other chemicals such as 5-methoxy-DMT or MAO inhibitors could contribute to the present results. This review may stimulate future research to investigate the similarities occuring in schizophrenic patients and DMT ingestion.

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A Ketamine-Induced Episode of Insight: A Case Report

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Abstract:
Schizophrenia is a chronic mental illness characterized by a constellation of symptoms, often including hallucinations, delusional thinking, and disorganization in thought and or speech, resulting in significant social or occupational dysfunction. One key factor that impairs a patient with schizophrenia to achieve and maintain wellness involves a profound lack of insight into the disease. With an improvement in insight, patients with schizophrenia are more likely to remain compliant with medication interventions and engage in active treatment modalities, including cognitive-behavioral models of change [1]. Given the predominant lack of efficacy in available long-term treatments for schizophrenia, novel mechanisms of intervention, including the use of psychedelics such as ketamine, may result in lasting improvements in insight and provide additional means of helping those with schizophrenia better understand their illness. In time it may be possible for improvements in insight to reduce the likelihood that patients with schizophrenia fail to remain compliant with medication and therapy and ultimately result in shorter and less frequent hospitalizations. The case below describes a 33-year-old male with schizophrenia who benefited from a brief and temporary improvement in insight after receiving a one-time dose of IM ketamine during a period of acute agitation shortly after being hospitalized for active psychosis.

INTRODUCTION

Schizophrenia is a psychiatric disorder characterized by chronic or recurrent psychosis, commonly associated with impairments in social and or occupational functioning [2]. Typical characteristics of schizophrenia include positive symptoms, such as hallucinations (most commonly visual or auditory) or delusions (fixed false beliefs); disorganized speech; negative symptoms (such as a flat affect or poverty of speech); and impairments in cognition (including attention, memory and executive functions). According to the DSM V, a diagnosis of schizophrenia is based on the presence of such symptoms, coupled with social or occupational dysfunction, for greater than six months in the absence of another diagnosis that would better account for one's presentation. In addition to the well-identified criteria listed in the DSM, one unique aspect of most psychotic disorders, including schizophrenia, is a lack of insight into one's illness.

Lack of insight has been traditionally viewed as a symptom, a cognitive deficit, or a defense mechanism, whereas modern accounts tend to point to impairments of metacognitive and social-cognitive abilities. These predisposing factors hinder a patients' ability to make sense of their illness in a structured and narrative manner, which may result in further distress or social impairment [3]. Ketamine, a dissociative anesthetic with a good safety profile for procedural sedation, has been used to manage the acutely agitated and violent patient in the pre-hospital and hospital settings, although studies have been relatively small [4]. Ketamine works by producing a cataleptic-like state in which a patient often dissociates from the surround-ing environment by direct action on the cortical and limbic systems. The actual mechanism of action of ketamine is as a noncompetitive NMDA receptor antagonist that blocks the binding of glutamate [2]. If the use of ketamine in the treatment of an acutely agitated patient could result in the gain of insight, it may be an avenue for future studies to explore.

CASE REPORT

The patient is a 33-year-old Hispanic male with a known history of schizophrenia who was admitted to an inpatient psychiatric hospital due to worsening psychosis. The patient was taken to the hospital by his sister after

experiencing increasing frequency and severity of command auditory hallucinations (AH), telling him to hurt himself. The hallucinations had been gradually worsening over the course of several months. Three weeks prior to his admission, he broke a mirror intending to use one of the broken shards to cut his wrists. Ultimately, he was unsuccessful with this attempt as he could not fix the shard in such a way that he deemed it appropriate to cut himself. After this plan failed, he heard AH on several occasions commanding him to jump out of a window, but he did not follow through with any of these commands. In addition to command AH, he endorsed both thought broadcasting and thought insertions at the time of presentation and identified these symptoms as significant stressors. At the time of admission, the patient was thought to be taking a regimen of medication, including Celexa 20 mg QDAY, Haldol 10 mg BID, Lithium 450 mg BID, and trazodone 100 mg QHS. The patient reported that he had been compliant with his medications, but his family reported a longstanding history of non-compliance. The patient was restarted on the above regimen at the time of admission except for lithium, which was discontinued after the patient was found to have an acute kidney injury (AKI), as evidenced by an elevated creatinine.

Soon after admission, the patient was started on mirtazapine 15 mg QHS to address active issues involving the patient's low mood and decreased appetite, and his prior to admission haloperidol dose was increased to 15 mg BID for ongoing psychotic symptoms. The patient was also started on valproic acid 1000 mg QHS for mood stabilization. The patient required restraints and "as needed" medications on several occasions during his first two days of hospitalization due to agitation. On day three of his hospitalization, the patient was transferred to the main medical center due to acute agitation, low blood pressure and muscle rigidity concerning for neuroleptic malignant syndrome (NMS).

During the patient's transfer to the medical hospital, the patient received a one-time dose of 250mg (approximately 3.7 mg/kg) IM ketamine for acute agitation. The psychiatric consultation team saw him about two hours after receiving this dose of ketamine. At the time of the consulting team's psychiatric interview, the patient was sitting up in his hospital bed singing. He was mostly alert throughout the interview and was fully oriented to person, place, time, and situation. When asked about auditory hallucinations, the patient stated that he had been hearing several different voices and responded, "oh yeah," when asked if he was hearing voices that were not his own. He confirmed that the voices had been present for several weeks and that they were one of the primary reasons he ended up in the hospital.

When asked about past substance use, the patient stated that he had never taken ketamine before, either recreationally or while in the hospital. However, the patient described experiencing life "in cheat mode" because of how he felt since receiving the IM ketamine. He was not sure if he was experienceing AH at the time of the consultation interview but worried that he would start to hear things again that were not real. He went on to describe that he was quite afraid that he would not know what to do about the voices if he did hear them in the future.

After describing his AH experience, the patient asked the interviewing provider if he could explain what it was like to have schizophrenia. The patient stated that living with schizophrenia was like being in the middle of a terrible practical joke in which the patient was the target. He noted that every day he woke up and had to reassess who was in on the joke and who might be trying to make him look foolish or try to "trip him up." He then went on to describe that "it gets

worse." He stated that amidst the joke, there is an element to life in which he has great difficulty discerning who is present in his life to help him and who may come into his life to hurt or even try to kill him as the final act of the joke. The patient stated that he had been unable to describe his experience living with schizophrenia to anyone in this manner before. He was reasonably certain that his thinking had improved because of the ketamine he had received on his transfer to the hospital. The patient remained extremely pleasant and calm for the duration of the psychiatric interview and expressed remorse for acting violently at the hospital prior to his transfer.

The patient was seen the next day after he was transferred to a floor bed and had little to no recollection of the conversation from the previous day. When he was told about various details of what was discussed, including the parts about living in a practical joke, the patient stated, "that makes a lot of sense." He was able to voice somewhat of an understanding of that metaphor and agreed that his life did feel like a practical joke at times, especially in the context of having schizophrenia. The patient continued to show significant signs of improvement and was transferred back to the acute psychiatric hospital to complete his stay. After transfer back to inpatient psychiatry, the patient continued to engage in his treatment and had no further outbursts of aggression. He was ultimately discharged home on a regimen of antidepressants and a mood stabilizer (valproic acid) and required no further "as needed" medications to address acute agitation concerns.

DISCUSSION

Ketamine is a highly controversial medication that has been in clinical use since the late 1960s. Although it is best known for its dissociative anesthetic properties, ketamine also exerts analgesic, anti-inflammatory, and antidepressant actions, all of which have been studied in somewhat limited capacity [5]. In addition to these known properties, several small studies have shown ketamine as a viable treatment of acute agitation in patients with psychotic disorders, including schizophrenia. Furthermore, in the prehospital setting, specifically, when patients are being taken to the ED for further evaluation, ketamine has been shown to reduce agitation and may provide a safer environment in which staff and patients can coexist [6]. Given the various complications in establishing rapport with and successfully treating any agitated patient, including those with psychotic disorders, it seems logical that treatment modalities successful in reducing acute agitation could be considered for use in other novel ways to improve patient outcomes during one's hospital stay.

It is well understood that a lack of insight into one's illness serves as a significant barrier to achieving patient compliance and remission of disease in various illness processes. This generalization is aptly true in cases of schizophrenia and other psychotic disorders [3]. Put most simply; insight may be defined as a patient's ability to recognize and accept his illness and engage in subsequent treatment. Those who lack insight may be at higher risk of nonadherence to treatments, impaired social and or occupational functioning, or ultimately adverse clinical outcomes. In a clinical climate seeking more definitive treatment models for long-term remission of psychotic disorders such as schizophrenia, novel approaches, such as the use of ketamine, for temporary improvement in insight may be helpful. Without current evidence of ketamine's use as a monotherapy in treating the psychotic symptoms of schizophrenia, it is inadvisable to suggest that it be used as a reliable approach to treating the non-agitated psychotic patient when existing medication and

therapeutic models have shown reliable and reproducible results, especially in treating the positive symptoms of schizophrenia (hallucinations, delusions, and disorganized speech and thoughts) [7]. However, given that in the above case, ketamine was shown to bring on temporary improvement in insight and an overall reduction in active psychotic symptoms, future studies could seek to investigate further the implications of ketamine as a novel augmenting or adjuvant agent in the treatment of psychotic disorders including, but not limited to, schizophrenia.

AUTHOR INFORMATION

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Ethical Guidelines for Ketamine Clinicians

Raquel G Bennett, PsyD

Republication of The KRIYA Institute's *Ethical Guidelines for Ketamine Clinicians* for reference:

- The ethical ketamine clinician recognizes that therapeutic ketamine is a mental health treatment. In this document, "therapeutic ketamine" refers to ketamine that is administered to a patient primarily for a psychiatric indication, psycho-spiritual exploration, and or psychological work. Therapeutic ketamine does not include ketamine that is administered primarily for anesthesia or pain management, which are considered separate fields (specialties) from therapeutic ketamine.
- The ethical ketamine clinician recognizes that ketamine is a powerful psychoactive medicine with prominent dissociative and psychedelic properties. The ethical ketamine clinician recognizes that therapeutic ketamine patients require specialized psychological care before, during, and after receiving ketamine.
- There are three roles in every therapeutic ketamine treatment: (1) a mental health professional; (2) a medical professional; and (3) the patient. In some cases, one person may be able to fulfill both professional roles, such as a psychiatrist who has substantial psychotherapy training.
    - The responsibilities of the mental health professional include: doing the clinical intake interview and assessment; doing integrative treatment planning; providing psychological preparation before the ketamine administration; providing psychological support during the ketamine administration; and providing psychological support following the ketamine administration (a/k/a "integration"); and managing any psychological or psychiatric emergencies during the course of ketamine treatment.
    - The responsibilities of the medical professional include: assessing the patient's physical condition before ketamine treatment; attending to the physical and medical safety of the patient during ketamine treatment; and assessing and treating any adverse reactions during the course of ketamine treatment.
    - The responsibilities of the patient include: communicating clearly and honestly with the clinical team; and actively participating in the integrative treatment plan as much as possible.
- The ethical ketamine clinician recognizes that there are different approaches to ketamine treatment, and that each approach has advantages and drawbacks. The ethical ketamine clinician is skillful with the specific treatment(s) that they offer. In addition, the ethical ketamine clinician is familiar with all of the major routes of administration, different dosing strategies, and different conceptual paradigms for therapeutic ketamine treatment.
- The ethical ketamine clinician understands and appreciates the importance of integrative psychiatric and psychological care for therapeutic ketamine patients (i.e., using multiple strategies to get better and stay well). The ethical ketamine clinician takes the time to explain this to each patient and helps patients to connect to these resources in their community.
- The ethical ketamine clinician practices within the scope of their professional license, and they recognize their limitations with respect to their professional training and experience. They actively seek consultation as needed, and they make referrals to other professionals as needed.
- The ethical ketamine clinician upholds all of the responsibilities of their professional license with respect to all aspects of their clinical practice, including informed consent, record-keeping, professional boundaries, confidentiality, and general professional conduct.

- The ethical ketamine clinician aspires to be compassionate, thoughtful, honest, and forthright in all of their personal and professional communications.
- The ethical ketamine clinician actively tries to make therapeutic ketamine accessible to members of the community who do not have the financial resources to pay for the treatment that they need.
- The ethical ketamine clinician is honest and transparent in marketing their services. They rigorously adhere to the FDA guidelines about advertising, and their clinical and advertising claims are supported by the research literature.
- The ethical ketamine clinician has received special training and or mentorship in working with therapeutic ketamine. A comprehensive training includes substantial education in the following domains: medical, psychological, and psychedelic. Additionally, the ethical ketamine clinician regularly reads the newly published literature and participates in continuing education to stay abreast of the latest developments in this rapidly growing field.

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Commentary

Wesley C Ryan, MD

The use of ketamine for psychiatric and mental health indications has grown exponentially in recent years [1]. A growing number of studies have established a consensus regarding clear benefit in the treatment of unipolar and bipolar depression [2], which was further validated by the recent FDA approval of esketamine**,** a stereoisomer and component of racemic ketamine, for treatment of treatment-resistant depression [3]. These clinical data are being translated into practice by a variety of professionals, some with a high degree of rigor and others without. It is in this current zeitgeist where we reside: certain academics are clearly skeptical of this practice as it plays out in broader clinical practice [4] and for good reason. The majority of ketamine providers draw from limited, if any, formal psychiatric or psychological training or experience, and provide in-office ketamine without psychiatric treatment planning or psychotherapy [5]. A not insignificant minority of clinics offer "package deals" on ketamine, grossly mis-represent the treatment by suggesting it is a "cure" for depression or make unsubstantiated and exaggerated claims about efficacy [6, 7]. Such abuses are un-fortunately prevalent and undermine the real but measured benefits possible with ketamine.

It is particularly timely then that Bennett, who is the founder of one of the first organizations seeking to clarify the many unknowns in the use of ketamine [8], has sought to articulate not so much a manual on how to effectively utilize ketamine in clinical work, but rather a set of guidelines and expectations for competent provision of such care [9]. Notably, this document is by the author's definition constrained to the use of ketamine for mental health indications ("therapeutic ketamine" as it is termed), apart from those well-established uses in anesthesia or emergency department practice, or those lesser studied but hopeful such as high dose use in the treatment of refractory pain disorders [10]. Indeed, while anesthesiologists are arguably the most qualified in the provision and monitoring of high dose ketamine for and monitoring of high dose

ketamine for pain management and sedation, the nuances of subanesthetic ketamine for mental health conditions are driven by psychiatric pathology rather than supporting adequate ventilation and perfusion of vital organs. The safety profile of such subanesthetic ketamine in terms of somatic concerns is largely benign [11]. The greater concern in such patient populations is mental health sequelae and suicide, as evidenced by the "black box warning" for esketamine [12]. The importance of longitudinal experience in working with such individuals, and of suicide risk assessment in particular, cannot be understated. While studies have demonstrated ketamine to have anti-suicidal benefit [13], cases with such tragic outcomes unfortunately still do exist and are actually increasing in frequency [14] arguably in part as a consequence of subpar provider qualification.

This concern over practitioner training and scope of practice is well founded; it is simply not possible to provide a *truly* informed consent, including risks, benefits, and alternatives, if the provider does not have psychiatric training [15]; it is un-realistic for anesthesiologists, for example, to meaningfully comment upon the use of monoamine oxidase inhibitors, tricyclic antidepressants, electroconvulsive therapy (ECT), or various psychotherapy modalities, because it is outside of the scope of their training. Indeed, for this very reason ECT is typically performed either jointly by a psychiatrist and anesthesiologist, or occasionally solely by a psychiatrist. A multiple year post graduate medical specialization, psychiatry residency, is arguably the best physician qualification for work with this challenging patient population, where concepts such as the biopsychosocial model [16] are introduced to providers to help them appreciate a more nuanced view of a given individual's strugglees. The reality, however, is residency programs are only beginning to teach trainees about such "therapeutic ketamine," while related emerging treatments with psychedelic effects, such as MDMA and psilocybin assisted psychotherapies, appear to be covered in only a cursory manner. This is not unexpected, however, given recent renewed interest amongst academics in exploring therapeutic benefit and—in time—medicalizeing psychedelics [17].

The psychedelic effects of ketamine, sometimes dismissed as a side effect, or simply "dissociation," warrant a closer look [18,19]. These effects do not simply provoke distortions in the auditory or visual or proprioceptive senses, but also may occasion mystical experiences [20], a sense of awe [21], and changes in the way intrapsychic conflicts—and possible solutions to them—are perceived [22]. Ego defenses are altered, and with the expertise of a skilled psychotherapist, the experience may yield insights and improvement in maladaptive patterns of behavior [23]. The guidelines are arguably most important in this regard: in pointing out the need and advocating for not simply a prescriber, but also a clinician well versed in psychotherapy and the nuanced process of maintaining a therapeutic frame for preparation, support, and, ultimately, growth [24]. Without attention to these components—as is done in other psychedelic assisted psychotherapies currently in clinical trials —the beneficial effects of ketamine are not fully realized, and overall efficacy probably suffers [25].

Is psychotherapy training "enough" for work with this and other psychedelics? Some form of additional specialized training is helpful if not required, but how to best provide it to budding clinicians? The Multidisciplinary Association for Psychedelic Studies (MAPS), the study sponsor for the clinical trials seeking FDA approval for MDMA-assisted psychotherapy [26], for example, has established a rigorous clinician training program as a requirement to provide

that treatment. Ketamine on the other hand has long been generic, now being used off-label, and is without any formal FDA requirement for psychotherapy. In absence of such a sponsor, training programs of various duration, depth, and quality have emerged, which attempt to address such topics as set and setting, the therapeutic container, effects unique to ketamine, and generally attempt to familiarize clinicians with the process of working with psychedelics. These efforts are laudable, and while not a substitute for formal psychotherapy training, as the guidelines suggest, another important nuance to consider in the provision of therapeutic ketamine.

More practically, these guidelines make an initial attempt to address the thorny issue of decreased patient access stemming from high cost. The vast majority of providers offering ketamine do not contract with insurance companies, and thus are "out-of-network" providers, which typically translates into high out-of-pocket costs and low—if any—insurance reimbursement for patients; in this sense ketamine is one of the latest treatment that highlight long standing problems with mental health parity [27]. The lack of formal FDA approval for ketamine in the treatment of any mental health condition hinders such health insurance coverage, but there is cause for hope: results from a recent clinical trial suggest ketamine is non-inferior to esketamine in the treatment of depression [28] and provides such benefit at a cost several orders of magnitude less ($1-2 per dose of ketamine in contrast to $600-900 per dose of esketamine) [29]. Perhaps with time and further study, insurers will decide to instead cover the much less expensive generic parent compound, a policy that several large health care organizations including the Veterans Affairs [30] and Northern California Kaiser Permanente have tried [31].

Ultimately, these guidelines reiterate how important rigor is in this new era of "therapeutic ketamine." As more data emerges, clinical use—and expectations of providers—will evolve. For the time being, however, these guidelines are useful starting point in shaping community use, holding it to the highest standard, and ensuring best outcomes—both in individual patients, and in the burgeoning field of psychedelic psychiatry.

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Ketamine-Hypnosis Package (KHP): A Clinical Case Study for the treatment of depression and addiction administering Ketamine with Hypnotherapy

Sophie-Charlotte Adler, M.Sc., Mario Schieb, MD

Background. There are few studies on ketamine and its properties to work with addiction (alcohol, opioid, cannabis, and cocaine use disorder). The studies show that ketamine treatment can help reduce craving and support abstinence [14]. Hypnotherapy is an evidence-based treatment gaining popularity for treating addiction, but not everybody can be hypnotized due to different levels of suggestibility. Our clinical practice has observed that people who are not highly hypnotizable, such as patients with obsessive-compulsive disorders, become more suggestible accompanied by our newly developed method called "Ketamine-Hypnosis package" (KHP). In this case report and study, we want to explore and evaluate the potential of KHP in working with addiction. Diagnostic and a qualitative content analysis should give profound insights into the treatment process and method.

Case Report. The subject is a 48-year-old male German Social Worker with treatment-resistant depression, suicidal thoughts, obsessive behavior, and several forms of addiction. The patient received a 10-day treatment at Instituto Dr. Scheib, with Diagnostic, rTMS, neurofeedback, and four sessions of KHP. Every Ketamine infusion remained with a standard dose of 0.5 mg/kg *R*-Ketamine for about 45 minutes.

Results. Primary outcome measures included change in depression as measured by the BDI-II with a reduction from 44, highly depressed, to a score of 3, no depression, and change of symptoms measured by the SCL-90 R that showed a clear reduction in almost every factor vs. baseline. The qualitative content analysis of the KHP sessions identified nine categories; Setting, Intervention, Body, Control, Feelings, Insights/Realizations, Addiction, Depression and Imagery. QEEG measurements before and after treatment showed a pattern of over-representation of slow brain activity with closed eyes, which can be observed in fluctuating concentration and volatile impulse control. Follow-Up Data with BDI-II one week after treatment showed factor 3 and 5 weeks after treatment factor 15.

Conclusions. The 10-day-treatment program improved numerous important treatment outcomes in one substance-dependent adult engaged in hypnotherapeutic modification, including promoting less substance abuse, diminishing craving, and reducing the risk of relapse. Further research is needed to replicate these promising results in a larger sample.

INTRODUCTION

There is much research related to psychedelic substances and their ability to treat alcoholism and addiction [1]. Almost every psychedelic was studied for treating sub-stance abuse: LSD, Ayahuasca, Peyote, Ibogaine, and Psilocybin [2]. These treatments involving mind-altering substances show promising results in reducing cravings and withdrawal syndromes [3, 4, 5, 6]. As Ketamine (off-label usage) is the only legally available psychedelic medicine at the moment [7], we can hereby gain important information for the therapeutic work with psychedelics in an emerging field.

The study "Ketamine reduces alcohol consumption in hazardous drinkers by interfering with the reconsolidation of drinking memories: preliminary findings [8]" shows a new way of treating alcohol addiction with ketamine as the scientists cue-alcohol memories and used ketamine as a blockade for reconsolidation of memories. Blood concentrations of ketamine and its metabolites during the critical 'recon-solidation window' predicted beneficial changes only following MRM reactivation. Results show that this treatment reduced

hedonic and motivational properties in the participants' drinking behavior (N=90) [8].

The side effects of ketamine that have been discovered since 1970 include hallucinations, psychotic experiences, changes in sensory perception, and body image. Often people feel detached from their body and surroundings [9]. Perception of time and space changes completely. Many people describe the experience of ketamine as weird, fascinating, scary, strange, frightening, disorienting, and very different from anything they have experienced before. The effects of ketamine are strongly dependent on the dosage. Krupitsky developed the KPP, a ketamine-treatment for alcohol and heroin dependence, almost 30 years ago and demonstrated very effective outcomes [10].

One can observe that more and more therapists in the world are beginning to work therapeutically with ketamine [11]. For example, in the USA, there are no common or ethical rules related to this work.

We combine ketamine infusions (0.5 mg/kg) with hypnotherapeutic guidance, influenced by a psychoanalytic and Ericksonian approach, to work with the material coming up during a ketamine infusion. The study *Ketamine as a possible moderator of hypnotizability: a feasibility study* [12] shows promising results for ketamine as an augmenting agent for hypnotizability and supports our predictions for this case study. This study shows that on the day ketamine was administered to the participants (N=11), they were significantly more able to be hypnotized as measured with the Clinician-Administered Dissociative Scale (CADSS) [12].

We wanted to explore our Ketamine-Hypnosis Package (KHP) as a new treatment for reducing addiction. The "Alcoholic Anonymous" fellowship dedicated to the 12-step program is still one of the lowest costs and most successful programs. Here the primary goals are sobriety and abstinence [13]. Our goal was not to reach as Ms. Adler has been guiding the ketamine journeys for almost three years, she has gained significant experience, and we decided to try working with addiction as a pilot project for interlacing clinical work and science at Instituto Dr. Scheib.

CASE CONTEXT

The Clinic

The Instituto Dr. Schieb is an international therapy and training center specialized in mental and psychosomatic illnesses, with its headquarters in Palma de Mallorca at Clinica Luz and in Berlin. We are an international, multi-professional team of specialists in psychiatry, psychosomatic medicine, psychotherapy, psychologists, and therapists. At the Clinica Luz in Palma, we treat patients with burnout, depression, anxiety disorders, OCD, addictions, and eating disorders in particular. Our therapy concept consists of intensive individual psychotherapy, hypnotherapy, relaxation, individualized sports therapy, as well as modern neuromodulation and training procedures, supplemented by advanced pharmacotherapy, if necessary. Due to the intensity and multimodality of the therapeutic approaches, we have an average treatment time of only two to a maximum of three weeks. Patients can be accommodated in our spacious single rooms and suites at the clinic, as well as in a hotel opposite the hospital.

Ketamine-Hypnosis Package (KHP)

We have a comfortable, safe setting for our ketamine infusions. Our Institute is located inside "Clinica Luz," which secures clinical safety and the presence of physicians at all times. The lounge stands underneath a window giving a wonderful view into nature. There are pillows and blankets provided for a

cozy feeling. Indirect light compliments the setting.

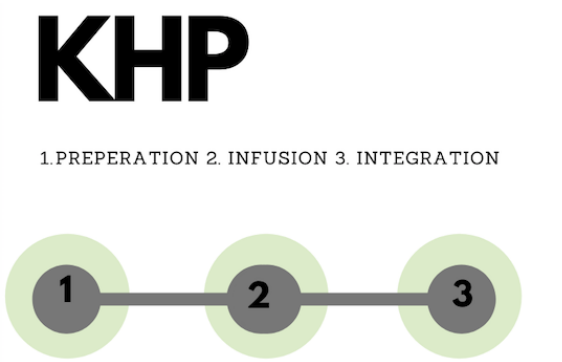

Figure 1

Our KHP creates a therapeutic experience around the ketamine infusion. KHP includes psychological preparation, hypnotherapeutic guidance during the ketamine-journey, and an integration session after the experience. The effectiveness of KHP is likely to be caused by different factors, which will be examined in the following.

Indirect hypnosis is a subtle, respectful method utilizing metaphors, stories, body language, and a feeling of relaxation and safety to improve treatment effectiveness. Direct hypnosis would explicitly order a person to enter the trance state, which could be comparable to the ketamine effect. The mind-altering substance Ketamine changes everyday consciousness and brings one into a dream-like state comparable to a trance state [10]. We can see that depending on dose and set, these internal journeys have a large variety and can lead to significant shifts in overall well-being.

In our combination of hypnotic therapy during the ketamine infusion, we form a contract with the patient to support their goals and secure their safety. With KHP, patients can explore their minds in a new way; open up more easily as defense mechanisms are relaxed - memories, feelings, old patterns and beliefs, history, trauma, anxieties, and sadness can appear vividly and intensely. Also, the beauty of life, lightness, wonder, and a feeling of ego loss can be experienced in this space. With hypno-therapeutic guidance, ketamine can be understood as an effective medical tool to help patients overcoming dysfunctional thoughts, beliefs, and emotions. So, the mindset and body set can be experienced in a new frame of reference. Some describe it as a reset. In our clinic, the patient receives ketamine intravenously and will be on a ketamine journey for about 50 minutes. Every session is different; patients never know what will happen on the journey into the unknown. So, this needs a lot of trust, safety, and therapeutic background. Depending on the effect, the patient may require repeated administrations over their treatment.

Repetitive Transcranial Magnetic Stimulation (rTMS)

With this procedure, strong magnetic impulses are given to certain parts of the brain. This enables the activity of these areas to be activated or reduced. This procedure is particularly effective for depressive disorders, sleep disorders, post-traumatic stress disorders, obsessive-compulsive disorders, addiction disorders, eating disorders, and after brain damage. The procedure is largely free of side effects and is increasingly used in large clinics to treat depression. The latest generation of devices is used, enabling even more precise localization of the stimulation area by synchronous measurement of physiological parameters.

Brain Mapping and Neurofeedback

The electrical waves derived from the brain provide information on the function and cooperation of some regions of the brain (EEG). Brain mapping shows brain activity in the form of a "map" of the brain, from which conclusions can be drawn about certain disorders. Many of these disorders

can be treated through neurofeedback. The EEG signals are correlated with an animation on a screen. The patient learns to reduce or increase the activity of certain areas of the brain. This procedure is ideal for treating ADHD and convulsions, and for anxiety, depression, sleep, and concentration disorders.

Heart Rate Variability

The heart rate variability shows the influence of the vagus nerve on the control of the heart. It is significantly reduced in depression. Our patient shows an increased stress index in HRV; the other parameters are mainly within the normal range.

The patient got all treatments for free in our private clinic as he confirmed to be a study patient. We were also allowed to record and film the whole treatment for the purpose of this study. Furthermore, he signed a letter of acceptance for publishing the video records. On this base, our sources of data are case notes, audio- and videotaped sessions, patient self-report measures (BDI-II, SCL), patient notes, therapist notes, and reflections, as well as qEEG screenings at the beginning and the end of treatment.

CASE REPORT

The patient is a 48-year-old educator who has completed various training courses in order to be able to work with young people who have a tendency to resort to violence. He has been on sick leave for 18 months. He sought evaluation due to depression, in which he had treated himself with the aid of various substances.

Even in his primary school days, he was probably depressed and had no desire for life. He also had suicidal thoughts with concrete ideas for implementation but would finally decide against it, as he had a 12-year-old daughter and his knowledge about the dramatic emotional consequences it can have when relatives commit suicide.

At the age of 13, he drank his first beer, and then he tried out just about everything in material and non-material, legal and illegal addictive substances: THC, codeine, cocaine, amphetamines, and psilocybin. However, he kept changing substances, which is probably why he never really became addicted. He had also engaged in extreme sports and had finally run away from depression.

In 2013 and 2014 he failed at a project in his profession and suffered burnout. He was no longer able to cope with the world and compensated with drugs. Depression was diagnosed for the first time in his life during this period.

After his burnout, he had not taken any drugs for six weeks, and he was getting worse and worse. He had turned to a psychiatric-psychosomatic acute consultation to get help for his depression. They refused to offer him treatment because he first would have had to undergo detoxification.

A drug counseling center then placed him in a six-month long-term therapy program within a clinical setting. There he had one on one 30-minute individual therapy every two weeks. Additionally, he attended numerous group sessions, almost exclusively addressing alcohol addiction, which did not feel beneficial to him. He felt as if he was under a glass bell and restricted in his independence. After two months, he was discharged with the consent of the clinic. His depression persisted.

After another excessive demand in his job, he was put on sick leave again. After a year, he repeatedly sought admission to a clinic, where he reported he sometimes smoked cannabis to get to sleep. Because of this self-disclosure, he was refused admission. The clinic's preconditions re-

quired him to stay clean for at least six months before being admitted.

In the meantime, his health insurance company had referred him to a day clinic, the same clinic he visited to treat his addiction - but this time, he was directed to a different ward. There he managed to get involved in the groups caused in some part by the proximity of the groups to his former department. However, after this six-week clinic stay, he had a complete breakdown.

He was prescribed various antidepressants, e.g., doxepin, mirtazapine, and duloxetine, which increased his suicidal thoughts. Pregabalin reportedly helped him, but he had underestimated its addictive potential. He subsequently weaned himself of all medications.

CASE FORMULATION

The patient shows impressively how the differentiation between addiction therapy and psychotherapy or psychosomatic-psychiatric treatment prevented the patient from receiving adequate help in time. Most patients with harmful or dependent substance abuse, or addictive behavior, have an underlying psychiatric disease that must be treated in parallel to the addiction. In most cases, these are depressive disorders or anxiety disorders.

TREATMENT

Treatment Plan and Goals

Therapy is multimodal and uses psychotherapeutic, pharmacological, and technical procedures in the treatment.

After a detailed anamnesis and examination, a psychological examination is performed, and a quantitative EEG and measurement of heart rate variability are obtained.

The quantitative EEG shows which areas of the cerebral cortex are active at which wavelength. This can provide important information for the neurofeedback training program. Our patient shows increased alpha activity in the frontal brain area, particularly in depression with brooding compulsion and difficulty falling asleep.

The heart rate variability shows the influence of the vagus nerve on the control of the heart. It is significantly reduced in depression. Our patient showed an increased stress index in HRV; the other parameters are largely within the normal range.

The following is the course of the first week of therapy for the patient at the clinic.

Week plan		
Day	Time	Treatment
22.02.2020	18:00-19:00	First assessment with Dr. Mario Scheib
24.02.2020	11:00-12:00	Diagnostic
	12:00-13:00	rTMS
	14:00-15:00	Anamnesis interview
	15:00-16:00	QEEG
	17:00-17:30	rTMS
	18:00-19:00	Planned Ketamine Infusion but not possible because of blood pressure
25.02.2020	11:00-11:30	rTMS
	14:00-15:00	Relaxation
	16:00-16:30	rTMS
	17:30-19:30	KHP: 1st Ketamine-Infusion
26.02.2020	11:00-11:30	rTMS
	12:00-12:45	KHP: Integration and preparation
	17:00-18:00	rTMS
	18:00-19:30	KHP: 2nd Ketamine-Infusion
27.02.2020	10:00-10:30	rTMS
	12:00-13:00	KHP: Integration
	13:00-13:30	Yoga / Meditation
	13:30-14:00	rTMS
	15:00-16:00	Neurofeedback
28.02.2020	10:30-11:00	rTMS
	14:00-14:50	KHP: preparation
	15:00-15:30	rTMS
	15:30-16:30	Neurofeedback
	18:00-19:00	KHP: 3. Infusion
02.03.2020	10:30-11:00	rTMS
	13:00-14:00	Neurofeedback
	14:00-14:30	rTMS
	14:30-16:00	KHP: preparation, 4. Infusion, Integration
03.03.2020	10:30-11:00	rTMS
	12:00-13:00	Final Integration and last therapy session with Mrs. Adler
	14:00	Neurofeedback
	16:00	2nd Diagnostic

Table 1

The aim is not primarily abstinence, but rather a higher self-efficacy and satisfaction of the patient, leading to a change in substance use and addictive behavior. It is, therefore, a matter of regaining autonomy. Autonomy in the sense of self-determination, not to be dominated by drugs but to make conscious decisions with a clear conscience, without having to criticize oneself, which would trigger a downward spiral in thoughts.

Regarding drugs, the following substances were identified due to their effect on the patient's mood. Table 2 summarizes the importance and the experienced effect of the drugs reported by the patient.

Alcohol -> main companion	Availability as a gap filler. Dangerous because of its availability, regularity, acceptance.
Amphetamine -> main companion	To stimulate, good effects. In lower doses rather calming.
Crystal	Concentration
Heroine	One can take a rest. Feeling good.
Codeine / Tramadol	Island. Don't have to think anything. Finally turn off your head.
Cannabis (THC)	To fall asleep. Shy of people. Prefers taking it alone.
Hallucinogens	Time Out and Joy

Table 2

Therapist and Relational Factors

Sophie-Charlotte Adler is a psychologist and trained hypnotherapist. In her masters thesis, she examined the potential of the mind-altering substance psilocybin considering its usage in modern psychotherapy in research and practice [1]. She is an active researcher in the field of the actual worldwide happening "psychedelic renaissance." Her research about "substance assisted therapy" and the interdisciplinary "drug-science" form the basis for her work today as a "Ketamine assisted Hypnotherapist." Since she completed her bachelor's degree at a psychoanalytic university, psychoanalysis forms the background of her work. After her studies in Germany and Austria, Sophie Adler discovered not psilocybin but another mind-altering substance, ketamine, is offered as a psychotherapeutic treatment in Mallorca, and she started working as a psychologist for Dr. Scheib.

Since June 2018, Sophie has been in charge of ketamine infusions at Instituto Dr. Scheib. Over time and with the support of her direct supervisor Dr. Scheib she developed her own method, the Ketamine Hypnosis Package (KHP). This package consists of preparing the ketamine journey, hypnotherapeutic support during the infusion, and subsequent integration. Relaxation, suggestions, and posthypnotic orders are used a lot. The three units of KHP can also be extended over several days, depending on the patient's treatment plan. Single hypnosis sessions between the KHP sessions support the long-term effects and enhance the therapy process.

One of the key elements of KHP is to work with the feelings of controlling and learning how to let go of control. The experience of letting go and feeling well simultaneously can bring profound changes. Hypnosis and Ketamine both have to do with a change of everyday consciousness. This is often frightening for people with control issues. The KHP has proven to be very advantageous for depression, anxiety, PTSD, and pain. In 2019, four patients suffering from treatment-resistant obsessive-compulsive disorders were successfully treated with the help of this program.

Due to her psychological and neuroscientific research on psilocybin, Ms. Adler is very familiar with numerous substances and their mechanisms. As a result, she could approach the patient's addictive experience with an open and value-free attitude. At the same time, her background enables her to provide a profound basis for discussion in the patient's process of finding a healthier relationship to drugs. In order to lead an addicted patient under ketamine, essential factors have to be clearly considered. It is important that the patient does not add the pleasant ketamine experience to

his collection as a new drug but clearly recognizes the treatment as a therapeutic method. For this reason, therapeutic guidance here has a novel role in comparison to common therapeutic methods. Especially the creation of the setting supports the professional treatment frame and should never be underestimated. The KHP approach considers the importance that the patient can feel safe and comfortable. To achieve this, the development of a sustainable relationship is the first priority.

In 2019 she attended the KRIYA Conference in California and was part of the first KRIYA Consultation Group, a ketamine-therapist group.

COURSE OF TREATMENT AND MONITORING

The patient arrived on the 21st of February 2020 in Mallorca. Saturday the 22nd, he had his first assessment with Dr. Mario Scheib.

On Monday the 24th of February, our clinic program started with Diagnostic and rTMS (1 HZ, right, 20 minutes). In repetitive transcranial magnetic stimulation, a pulsating magnetic field increases or decreases the activity of certain areas of the brain. This can be used to treat both depressive symptoms and the tendency to addictive behavior. We stimulate the dorsolateral prefrontal cortex on the right side with one hertz, then on the left side with 10 hertz.

Later he had his first interview with the psychologist and hypnotherapist Mrs. Adler summarized as follows. Even as a child, the patient experienced himself as thoughtful, sad, and felt the desire to live no longer necessary. “To have control” and “to be able to defend oneself” are very important for the patient. As a child, he was physically abused by his father. He had problems with hierarchies and power all his life; he does not take orders from anyone. The patient is continually struggling with his past and wants to put an end to his old story.

“There's hardly a situation that I don't associate with a substance.” At the beginning of the therapy, the patient states that he likes to live with drugs. His goal in dealing with substances is: “I want to control them and not be controlled by the drugs!”. He reports about early experiences of smoking cannabis, "it is not my thing, because I don't control the situation anymore, I don't like to give up control!”. Working with the topic of control is vital for the patient's therapy on many levels and will run through every session. Especially within ketamine-hypnosis the handling and working with control and substance in one psychotherapy session can be exceedingly multifaceted. The sensual perceptions are altered on various levels. The typical way of thinking and receiving is not comparable to the ketamine state. It is essential to understand that ketamine can be a catalyst for bringing up unconscious psychological material, presenting new psychotherapy opportunities.

The patient wished to be able to switch off his head and certain sorts of thoughts. A loud inner critic resided inside himself “that stands at the edge of the stage and comes over every now and then.” He describes this critical voice as *the* problem. “I can't get out – that's the problem. Thoughts spiral.” These thought patterns and a loud inner critic voice is prevalent in depression. One of the patient’s goals is “dealing with feelings.” It became clear that the patient uses substances to control and navigate his mood, feelings, thoughts and behavior. He has no real connection to his inner world anymore. Mind and body are not in touch. So, it becomes one goal to find back to what he lost one day – his inner safety.

The patient’s ambivalent situation becomes apparent through his political statement: “Drugs for work contradicts my political views! Destroying yourself for

capitalism…". This patient showed a strong resentment toward the state and capitalism. The drugs are ruining his life. During the therapy process, it became clear that the relationship to the drugs was not the same as he dreamed it to be. He found himself lost and inactive. He was very depressed and lost any sense of living a happy life.

That evening he should have received his first ketamine infusion, but his blood pressure was too high. He received medication to lower the blood pressure from Dr. Scheib.

Tuesday the 25th, he started with rTMS (twice daily for 20 min per session) in the morning and late afternoon for the entire duration of the treatment.

KHP

Then he had a preparation talk (50 min) for his first ketamine infusion, which took place at 6 pm. The first ketamine hypnosis session turned out to circled around the past of the patient. It looks as though the camera became a trigger for memories from challenging experiences in his former political activist days. This camera setting influenced the first session (and all the others) mainly because the patient struggled with being filmed. Feelings of rage, aggression, wonder, and memories of lost persons came to the surface. Under these circumstances, the creation of a genuine, safe setting becomes even more important. The patient described problems regarding sharing emotions and especially doing this with an unknown person. The camera led to feelings of fear and suspicion that the material could be used against him. The first session consisted of vivid arguments and discussing confusing thoughts. It became clear to the patient that the way he was being perceived from the outside is more important to him than he would like it to be.

Here the therapeutic relationship is particularly challenging when accompanying a patient struggling with letting go of control, substance abuse and fighting with enemies during a ketamine infusion. The mind-altering substance Ketamine changes the everyday consciousness and brings one into a dream-like state comparable to a trance state. A trustful relationship supports patients to open up more easily as defense mechanisms are relaxed, memories, feelings, old patterns and beliefs, history, trauma, anxieties, and sadness can appear vividly and intensely. Imagine the therapist who always keeps the thread to guide the patient safely and help them to walk through the opening doors. In doing so, the therapist always weaves the emerging insights into the client's beliefs and dysfunctional thinking. The neuroplasticity introduced through ketamine allows the creation of new ways of thinking, realizing, and feelings -experiencing another way of being for around 45 minutes.

This session was a lot about the inner resistance fight. With hypnotherapeutic support, the patient can overcome dys-functional thoughts, beliefs, and emotions. So, the mindset and body set can be experienced in a new frame of reference. All this allows him to let go of the past and create space for new perspectives.

These insights will be integrated and practiced in everyday consciousness during the next days and influence the following process. Wednesday the 26th in the morning, the patient had an integration session to talk about the ketamine journey. It became clear that in the past he only acted, fended off, "zoned out," dissociated, took a passive attitude towards life, and refused to live by tripping out. He was radicalized. He was ticked off from the very beginning and felt part of the rebellious attitude. However, in the end, this also made him unfree because a rebel always has an opponent whom he fights, on whom he stares and holds responsible for his own actions. Who is in control here? To whom one is subordinated

to, control is fought, and constantly observed and through this one, becomes a controller. The patient carries an image of the enemy within himself, which was projected onto the camera, for example. He rationalizes incredibly.

Infusion

The second ketamine hypnosis treatment began with a focus on the treatment setting and the patients' uncertainties regarding the outer world. By shifting the patient's awareness and anxieties from the external to his internal state through calming and stabilizing interventions, emotions and bodily sensations came into the patient's focus. Again, the therapist applied a reinforcing and reassuring intervention allowing the patient to feel secure enough to fantasize and to create the image of a secure cave corresponding to increased feelings of unity and security. The image could then be reflected on by the patient as a desire that he was previously unaware of: "I'm familiar with it when it's presented to other people, but I've never found or seen or had one for myself."

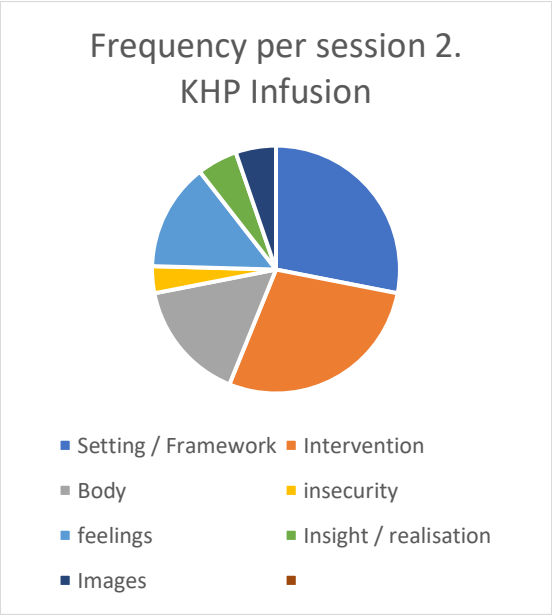

Table 3

KHP Integration Thursday the 27th

It could be speculated that the security established in the last session encouraged the patient to engage in further self-reflection. During the integration session, he noticed differences in his way of relating to himself and his compulsive and addictive behaviors, as well as noticing a decrease in ruminating thoughts: "without falling back into self-accusatory thinking."

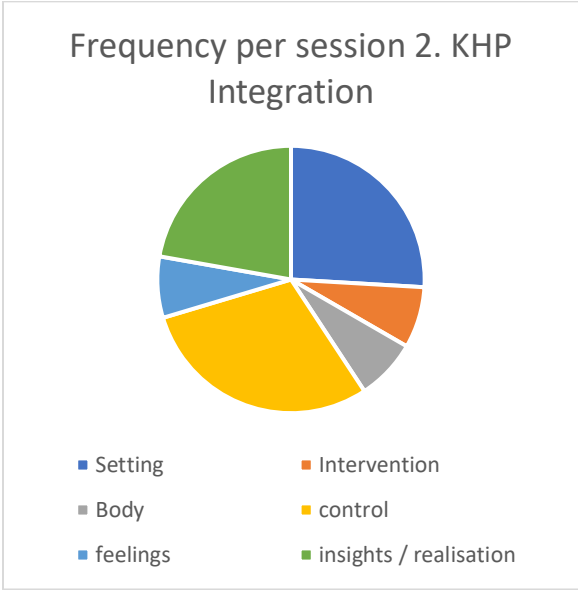

Table 4

Neurofeedback

In neurofeedback training, brain activity is linked to an animation. Through experiences of success, the brain learns to be more or less active in certain areas. This is called operant conditioning. In our patient, the increased alpha activity in the frontal brain was reduced, and the beta activity increased during training.

Yoga and Meditation

We complemented the treatment of the patient with an intervention combining meditation and the gentle practice of physical

yoga. It seemed apt to apply such an intervention since both meditation and physical yoga strengthen abilities that seemed particularly useful in this case.

Not only do these practices ease symptoms of stress and anxiety, which the patient was suffering from, but they are also especially powerful at strengthening the connection of mind and body and teaching the practitioner to be aware of his own physical state of being. Given that a feeling of disconnection between mind and body and a carelessness towards the body were recurring themes during therapy, the intervention was indicated, and it was received very well by the patient. In the following days, he reported a newly found sense of ease in times of little to no external stimulation - something the patient experienced as particularly stressful before the intervention.

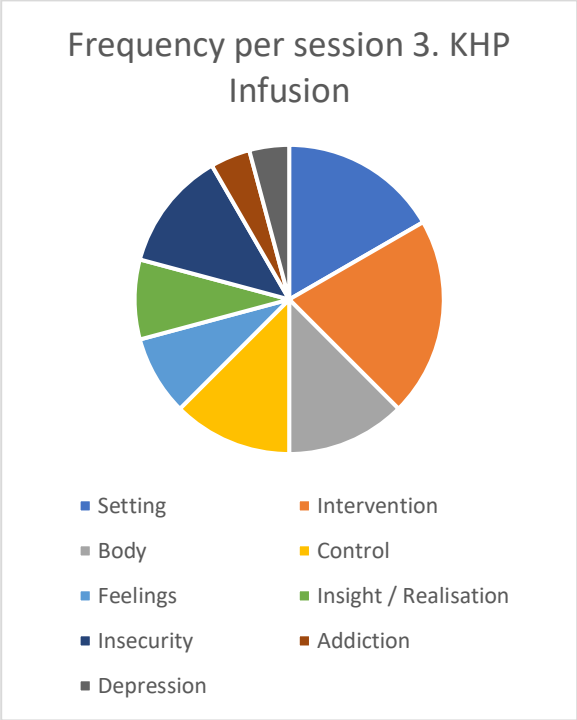

Table 5

KHP Preparation Friday the 28th

In this preparation session, plenty of time was devoted to establishing the patient's trust in the further progression of the treatment as well as to sketching out a plan for further treatment by discussing set and setting and addressing the patients insecurities in regard to his status as "research patient." The topic of a „simple life" that was established during the ketamine intervention was resumed, and it was reflected upon the "multi-problematic" nature of human beings.

KHP Infusion #3

The 3rd ketamine infusion dealt with various topics, perhaps hinting at the patient feeling more at ease during the intervention and, therefore, freer to let his mind wander. It was again commenced with a discussion of set and setting (a long discussion on whether or not to lie down during the infusion), followed by an episode focused on the bodily sensations. The patient's more open conduct led

Table 5

to him expressing a wish for music, which led to an emotional reaction. "sound triggers me incredibly." The patient was then able to reflect on his emotionally open and vulnerable state, expressing his wish to gain the therapist's approval: "really, what I am trying to do here is trying to convince you that my way of life is okay." This admission led to a focus on the therapeutic relationship and the patient's interest in the person of the therapist, as well as insight into some norm-oriented patterns of thought in the patient and that's why I can't get over that"

KHP Infusion #4 March 2nd

During the 4th infusion, strong bodily sensations overcame the patient. Feelings of pain related to current but also past injury and bodily trauma rose up and could, by careful intervention, be used to start a process of regression into childhood memories of vulnerability and feelings of inadequacy. Reflecting on his entire lifespan, the patient came to the conclusion that he disregarded his body

all his life, leading to the realization that he wants to pay more attention to his bodily needs in the future:" I can't ignore this (any longer), it's impossible."

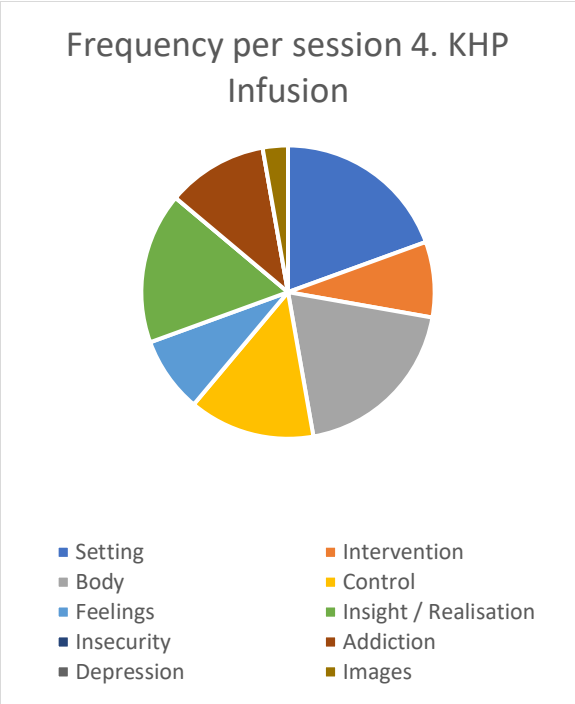

Table 6

KHP Final Session

The final discussion revolved around extensively, reflecting again on the impact of set and setting on treatment outcomes. The patient characterized the treatment as enabling him to access both his emotions and his sense of self-worth. He experienced a new will to tackle life, as opposed to the "hole of depression" that he felt trapped inside before. Reflections on the question of how to stabilize the experienced improvements in mood and motivation were followed by reflecting the key issues of the treatment: the patient's insecurities and the relationship between the patient and the therapist, while also acknowledging the patient's intuition that there are still multiple problems remaining. He then reiterated the insight gained during the final ketamine intervention, that urged him to pay more attention to his bodily needs.

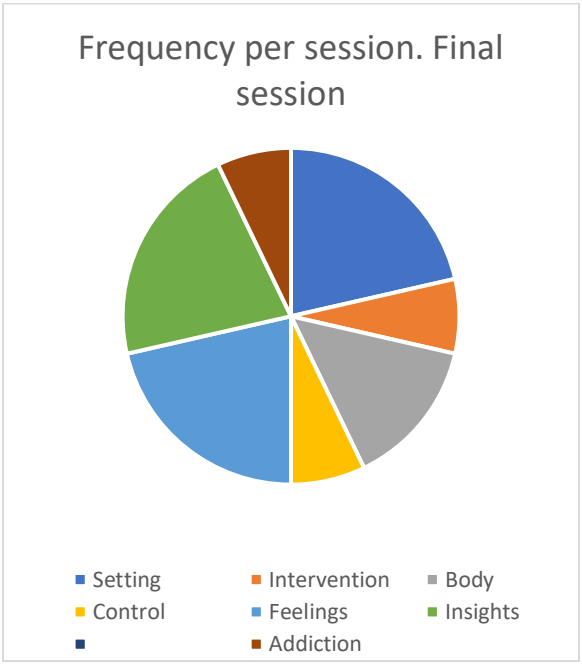

Table 7

In summary, the patient noticed a blatant difference concerning the time span before and after the 10-days treatment. "This change and rotation in 10 days is no comparison to previous therapies". How long these changes will persist must still be determined. The patient felt as if he was gaining access to himself again. "I will deal with my own history and the difference is that I want to do so!". The patient said that the effect comes from the combination of Ketamine and Hypnotherapy. "Ketamine alone does not work." The KHP opens doors, and the patient has to walk through. The patient recognizes self-worth as the linchpin and develops strategies to work with that in conjunction with the therapist. Acceptance gains more and more value. The patient's evaluation of his problems was changing. They were no longer all-encompassing. He felt more relaxed and more serene. A new quality of safety was experienced by the patient, who felt safer by himself now. The session ended with the patient stating: "If this is the key, I

find it disgusting not to make it available to a wider audience."

Treatment Outcome

In the following, the diagnostic results from before and after treatment are presented. The Beck Depression Inventory (BDI-II) is a self-report inventory with 21 multiple choice questions to measure the severity of depression. The data shows a reduction from 44, highly depressed, to a score of 3, no depression after 10 days of treatment compared to baseline.

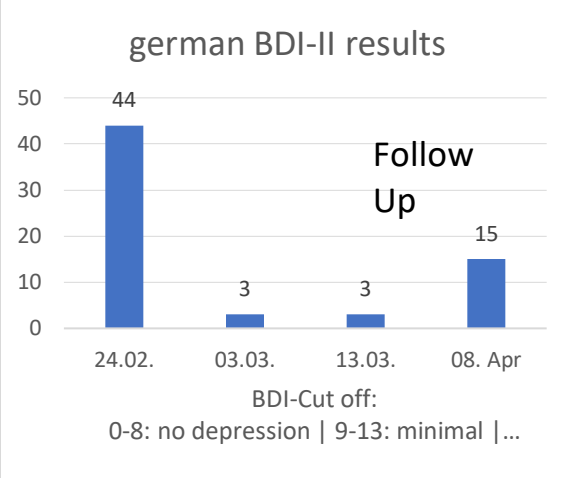

Figure 2

The "Symptom Checklist 90-R" (SCL-90-R) consists of 90 items and evaluates symptoms of psychopathology and a range of psychological problems through self-report. It is often used to measure the progress and outcome of treatments for research. As shown in Figure 3, the patient shows reductions in all symptoms except somatization. In the following, it can be seen how the symptom dimensions changed in the amount of reduction in numbers. The higher score ofsomatizations (from 5 to 8) might be explained by the back pain of the patient that occurred some days before the end of treatment. Obsessive-compulsive (from 24 to 3), interpersonal sensitivity (from 24 to 5), depression (from 41 to 2), anxiety (from 19 to 4), hostility (from 11 to 2), phobic anxiety (from 7 to 1), paranoid ideation (from 18 to 4), psychoticism (from 11 to 2), additional items (from 23 to 13).

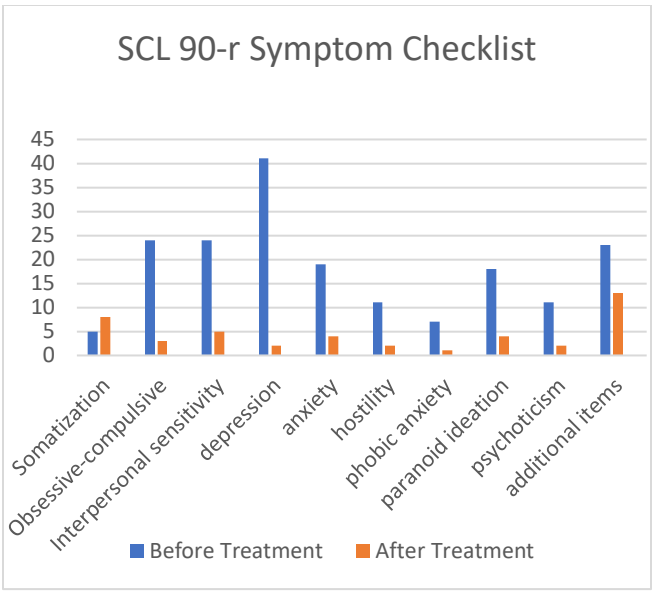

Figure 3

QUALITATIVE RESULTS

First EEG Measurement

There is a clear increase in the slow frequency range when the eyes are closed. This is particularly evident in the increased prominence of alpha activity (8-12 Hz) in the frontal region. With open eyes, the picture is largely inconspicuous. The present pattern of over-representation of slow brain activity with closed eyes can be seen in fluctuating concentration and volatile impulse control. It can be seen that there is a substantial slowdown due to too much alpha activity in the frontal area. This is often associated with compulsive brooding, thought circles, and depressive episodes. This pattern can also lead to agitating thoughts during relaxation and falling asleep and can be characterized by worry or self-doubt. It is difficult to stop the train of thought or direct it to other topics. This "thought carousel" can be caused by slowing down the frontal area and can be

improved by various mental exercises, such as neurofeedback.

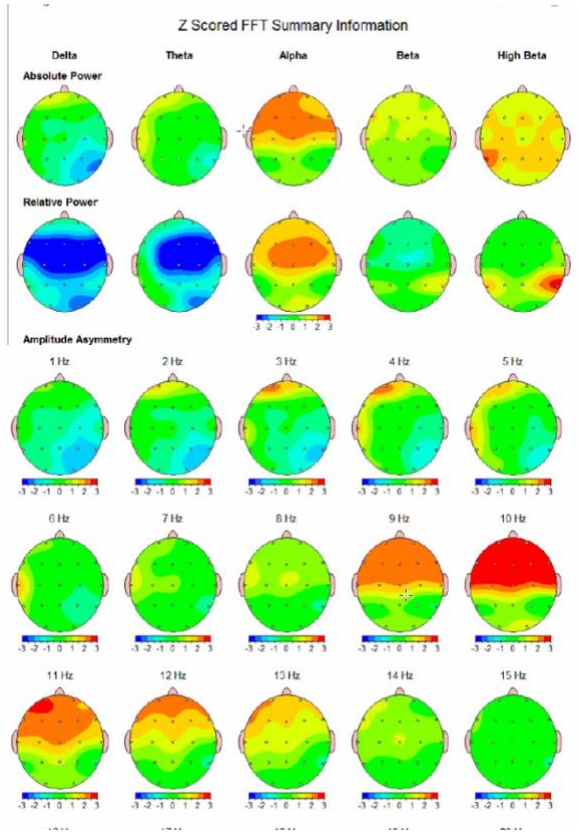

Figure 4

Second EEG Measurement

The second measurement did not show prominent differences from the first measurement. This could have different reasons. First, a qEEG measurement depends on the quality of the recording and the current condition of the patient. Therefore, the exact comparability is subject to interfering variables. Possibly our patient would have needed more training, or it was not trained properly.

Interpretation

By means of qualitative content analysis and an inductive approach, different categories could be developed, including all except the first KHP, the entire material and demonstrate both clear similarities and systematic differences between the KHP sessions. These are the categories we defined: Setting, Intervention, Body, Control, Feelings, Insights/Realization, Addiction, Depression, Imagery. The exact distribution can be seen in the graphs above. On the basis of the qualitative content analysis, it can be seen that the topics and the frequency of these vary with each session. It becomes clear that there are more topics per session. One could assume that the patient gains more confidence from session to session, can allow more, and thus becomes more honest.

The following table 8 illustrates the individual ketamine infusions with a normal dose and summarizes the topics from the sessions, which have been evaluated with qualitative content analysis.

KHP Summary

Date	Session number	Dose	Theme
25.02.2020	1	0.5	Anger, Political Past, Activism, Control, vicious, blame, fault, "Into the Lion Mouth", "Warrior"
26.02.2020	2	0.5	Inwards, Feelings, Trust, cave, safe place, Island, calming
28.02.2020	3	0.5	Music, Control, memories
02.03.2020	4	0.5	Body, Childhood memories, Drugs, Addiction, Control, letting go, happiness
10.03.2020	5	0.5	Addiction, Control, letting go, happiness

Table 8

Follow Up

Because of his exceptional progress within the 10-day study period, it was decided together with the patient to expand his stay by 10 more days to continue the neurofeedback training and the rTMS treatment. Furthermore, Eye Movement Desensitization and Reprocessing psychotherapy (EMDR) was conducted for five hours to consolidate the success and secure the safety of the patient. Especially traumatic experiences can be processed through EMDR. In this case, there were traumatic experiences in the patient's life, which promoted depression and drug abuse. Here, as in hypnosis, a lot of work was also done with the inner safe place.

Furthermore, new resources were installed to find new ways of regulation. By the end of the study, the patient felt he now had enough resources to cope with his life.

The patient filled out the BDI-II scale one month after treatment. Because of the "corona crisis," the situation to come back home, integrating and adjusting his therapeutic fruits into daily life was challenged highly. The score of the follow-up achieved was 15, which correlates to mild depression.

In addition to psychological testing, a follow up telephone interview was conducted to see how the patient was doing five weeks after completing the treatment. The patient came back from Mallorca to the big city and was confronted with the worldwide "Corona Crisis." Accordingly, the validation of the therapy process was a particular challenge. "Actually, the state prescribes depressive behavior. To stay at home, not to meet anyone, not to do anything big and not to be able to talk to anyone". It is precisely these circumstances that are a major risk factor for a relapse into uncontrolled consumption. The patient was stable, confident, and committed to helping people who cannot shop for themselves. The patient openly reported that he drank alcohol (up to 1 bottle of wine), but not every day. It, therefore, remains to be seen how things will develop in these extraordinary times. We keep on staying in contact with the patient.

DISCUSSION

The present case study explores the use of ketamine combined with hypnotherapy within a unique therapeutic framework. Results from the preserve report provide preliminary evidence that ketamine combined with hypnotherapeutic preparation, guidance and integration effectively reduces depression, suicidal thoughts, obsessive behavior connected with the theme of control and addiction in 10 days. In this patient KHP improved mood and behavior compared to previous treatments in the patient's life.

Ketamine administration without psychological guidance can be problematic. Depending on the set, setting, and dose, a ketamine infusion can be overwhelming, frightening, and patients can experience bad trips. Adding hypnotherapy as a framework and guidance has excellent potential to reduce psychological symptoms with more insights and a feeling of safety. Hypnotherapy helps the patient to relax, and posthypnotic suggestions support the desired changes.

However, the study was not randomized and was limited by several factors. By introducing innovative techniques, case studies can be crucial to the research process. Nevertheless, they have some disadvantages which should be discussed in the following. As a clinical case study, the data and results cannot be replicated and are only valid for this patient. Therefore, generalizability cannot be applied.

This presentation cannot lead to causal conclusions but might offer inspiration for new treatment models.

Due to the filming and documentation of everything, and the patient knowing that he was a research patient this case report might also confront the "Hawthorne-effect."

This study aimed to explore new ways in the treatment of addiction and depression and to evaluate the KHP method for the first time. The author wanted to give insights into the work as she developed the KHP method one and a half years ago. Researcher bias must be expected, especially in data interpretation. To reduce this bias somewhat, Ms. Adler worked closely with her intern, who transcribed, commented, and evaluated each session, and afterward a discussion about opinions and observations occurred. This was an attempt to evaluate the subjective perception of the researcher. The intern came precisely at the beginning of the

research project and finished the internship at the end of the study. So little personal bias is to be expected here. The case was also discussed and critically debated with colleagues in team meetings.

To enable objectivity, specific measurement techniques, quantitative diagnostics, and qualitative content analysis were selected as research methods. The BDI-II is a validated and reliable measuring instrument for monitoring depressive disorders, and it is well suited to follow the pace of therapy even with only one week in between.

Qualitative content analysis is time-consuming, and the formation of appropriate categories can be complex, considering the claim of objectivity. It is possible that other categories or frequencies might appear if other researchers would conduct a content analysis for the same case.

One significant advantage is the transcription of each session, which enables anyone at any time to track the patient's progression through treatment. With this report, researchers can examine how subjective effects in perception and motion change in relation to the ketamine state, considering the time before, during and after receiving ketamine IV through a standard dose (0.5 mg/kg).

It should be mentioned that additional addiction diagnostics to compare before and after were not conducted. However, access to the patient's previous addiction diagnostic results were available for review. Thinking prospectively, measuring abstinence rates after 3 and 6 months could bring interesting results. More data would be desirable here.

From an ethical point of view, it should be noted that the complete treatment was provided at no expense to a person who no longer wanted to live. The patient got out of his depression and regained motivation and confidence to lead his life.

However, one must critically examine what it means to give ketamine to a person with a substance use disorder. It is mostly advised against treating people with ketamine who have a history of drug abuse. It can be argued that ketamine in anesthesia is administered to numerous people with a drug history. It is also necessary to weigh the risks of leading an unhappy life up that could possibly culminate in suicide which could be mitigated against with a change of consciousness using therapeutic guidance in a unique framework. Additional research on how to reduce excessive drug consumption is needed.

Another point of discussion is the use of different methods. It is difficult to clearly differentiate which method is responsible for which treatment effect. Whether from rTMS, neurofeedback, the ketamine alone, the KHP or everything together. This would have to be divided experimentally and statistically in future studies.

IMPLICATIONS AND RECOMMENDATIONS

The Ketamine-Hypnosis Package is an innovative method. The goal of this case study was to give an example of how to work with ketamine combined with hypnotherapy to treat depression and addiction.

Implications for Clinical Practice and Theory

The study has shown what can be achieved through our treatment program within just 10 days. Depression, suicidality, compulsion, and addiction can be clearly reduced within a short time.

The patient wished to be able to live a normal life. Through the program, he more and more learned to accept himself with his own history. One notable aspect of ketamine treatment is that patients can observe and meet themselves. Under the influence of ketamine, they encounter themselves and

their consciousness in a new way. The client experienced himself through himself, outside of his habitual thinking. With the help of appropriate guidance, the patient was able to meet his inner self in a very short time compared to other treatment methods. Psychedelic substances can be door openers to the unconscious. For practitioners who would like to try this method, it is strongly recommended that they prepare themselves thoroughly beforehand so that they feel as comfortable as possible. Their demeanor has a significant influence on the sessions and experiences of the patient. One should never use ketamine or hypnosis without having completed appropriate training.

Furthermore, Ms. Sophie Adler has a psychoanalytic background. Sigmund Freud described the dream as "via regia into the unconscious" and thus founded psychoanalysis. Now the ketamine state is a dream-like state. One could draw an analogy here; the therapeutic accompaniment of the ketamine experience offers the possibility of actively guiding, shaping, and interpreting a dream state. The patient often cannot remember the content of the journey and forgets what happened already during the infusion. At the same time, however, memories and feelings come to light from the unconscious. This work cannot be compared with ordinary psychotherapy, and it should be investigated which therapy methods are suitable and which are not. There exists an enormous potential in the combination of Psychoanalysis and Hypnotherapy and maybe influences of Systemic Therapy regarding the integration process. The combination of ketamine and hypnotherapeutic guidance allows a type of "meta-work" where the therapist holds the safe space where the patient can directly recognize himself and meet his real being outside of the normal context. It could be assumed as an emotional experience according to the principle of the dominant effect if this experience is so powerful that it virtually overwrites the past experiences, maybe like a positive trauma generation that leads to a change of character and behavior.

A lasting stabilization through intensive short-term therapy is the foundation for intensive psychotherapy, which should follow the treatment to fortify the results. This psychotherapy can be conducted at the place of origin of the patient, online or at the Instituto Dr. Scheib. Additionally, patients are encouraged to stay in contact with us after the treatment via the internet, phone, or in-person at the Instituto Dr. Scheib.

Implications for Future Research

The results from the case report should provide some insight as to whether KHP improves the therapy process for depressed and addicted patients in a short amount of time. What if it is possible to treat addiction much faster and safer? Future research is needed to give further information about hypnosis´ efficacy in ketamine treatments.

A hypnotic guided Ketamine experience tends to offer up the possibility for transformation of the self in a short amount of time. Could KHP be a more efficient treatment method with shorter treatment duration, subjectively better feeling and lower costs? Long-term results can maybe positively encourage.

It would be very interesting to include psychoanalytical research to investigate which methods of dream interpretation fit ketamine therapy. Typically, psychoanalysis is a very lengthy procedure, but the current trend goes more and more towards the shortest possible treatment duration. Ketamine is a catalyst for the therapy process - presenting the potential to conduct psychoanalysis in a shorter time. Following these thoughts, the teachings of C.G. Jung concerning the interpretation of symbols and the

work with archetypes could also provide promising starting points.

It would be beneficial if scientists could agree on questionnaires to measure the degree of consciousness change and its influence on the success of therapy [1]. For example, HSC, 5D-ASC and MEQ-30 are used fairly consistently across psychedelic studies and scores on the MEQ-30 questionnaires seem to correlate fairly well with outcomes.

The results indicate a wider field of research possibilities. Studies could compare brain areas and network connectivity under the influence of ketamine and hypnosis. It would be very interesting to evaluate metabolic similarities and differences between KHP, Ketamine without guidance, and hypnosis without ketamine. Especially the Default Mode Network might gain significant interest here.

The utility of hypnotherapeutic interventions as adjuvants to ketamine in depression and addiction treatment is understudied. However, additional research is needed to examine hypnotherapeutic interventions that may help integrate the ketamine experience and enhance long-term treatment outcomes.

Furthermore, collaborative efforts to develop ethical guidelines for working with psychedelic substances should be encouraged.

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