CLINICAL TOXICOLOGY 11(4), pp. 459-472 (1977)

Peyote, a Potential Ethnopharmacologic Agent for Alcoholism and Other Drug Dependencies: Possible Biochemical Rationale*

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*This paper has been communicated at The National Drug Abuse Conference, San Francisco, California, May, 1977.

Among the drugs of abuse, none has achieved such wide popularity as alcohol (ethanol). Although this drug has been consumed by a large segment of our population, the consequences of alcohol is not readily understood by scientists actively engaged in research.

Although we have made significant progress in Western society with regard to treatment of addictive dissorders, we should not negate those primitive societies or third world cultures that also use and abuse alcohol and other drugs but subscribe to a more culturally derived holistic approach for the treatment of drug dependencies.

Folk psychiatry has been successful in the treatment of a range of physical and mental illnesses for thousands of years. Furthermore, when these ancient principles are used in a modern context, psychotherapy [33, 59]. The medicine man of Native Americans has added a pharmacologic agent to his therapy sessions to intensify his therapy, while potentiating the personal insight of the patient.

The addition of a psychedelic medication to a properly structured psychotherapeutic session has been demonstrated to be an effective technique for treating alcoholics [12, 38, 58]. Indians have used peyote for centuries [35, 41]. Recently, the United States Public Health Hospital in Clinton, Oklahoma, has incorporated peyote treatment into its alcoholic services program [1].

The ritualistic use of peyote (Lophophora williamsii) by the North American Indians in the treatment of alcoholism might shed much light on the problems resulting from the use and abuse of drugs and alcohol in more advanced communities.

Two of the authors attended peyote rituals in Oklahoma [45, 46], and over a 12-month period observed that the constituents of Arapaho congregations were rich with recovered alcoholics, many having recovered after only one meeting. The technique deserves consideration by therapists involved with the treatment of alcoholics and has been amply described elsewhere [45, 46]. The meeting consists of an orderly, constructive, and stimulating merger of three powerful psychotherapeutic modalities: the master of guide, the ritual or marathon group session, and the psychotropic drug, Lophophora williamsii, better known as peyote.

The advantage of such a therapeutic technique lies in its ability to rapidly alter the attitudes and behavior toward alcohol, long before the physical symptoms are life threatening. Through the ritual many individuals testify to unprecedented periods of mental clarity, during which they report visions of their future life as an alcoholic. It is as if the person believes they have "hit bottom" and are then ready to begin the arduous task of adjusting to a drug-free life. Later in the period of sobriety, the peyote ritual potentiates a heightened state of consciousness that once experienced in the ritual becomes incorporated in the person's lifestyle.

In previous articles our laboratory reported [45, 46] just such an experience with a 53-year-old Indian male alcoholic.

Group response is limited by permission of the roadman but often members will encourage new participants.

> A 53-year-old Wichita related his experience with peyote in the following manner: "Joseph, that's good what you said, I know how the white man's world makes you feel small and that alcohol makes you feel big. I used to drink and fight all the time, had plenty of troubles. Then John invited me to come to his meeting. So I did and I've been coming here for eleven years now, and I don't use the white man's way, alcohol, anymore. You drink that medicine, peyote, and stay with your people; it will help you feel good and make you think good."

However, we also found church members who had not been able to incorporate their heightened states of consciousness into their everyday life. Not unlike Western psychotherapy and the need for alternative modules to break through psychic blocks, the following case represents an attempt to reach troubled individuals who are not responding as well as expected.

CASE REPORT

A 29-year-old male Indian had a ten-year history of progressive and debilitating addiction to alcohol. During episodes of high-dose drinking he would have serious blockouts and commit acts of aggression and violence. His police record indicated over 20 arrests in six years. He was a skilled carpenter when sober, but unemployed prior to church membership 18 months previous to this study. Even after going to regular meetings, this man would have occasional relapses. During one ceremony, many young males recalled in detail their encounter with him during an episode of drinking. He was confronted by these members but not asked to defend himself. The emphasis was on the future, and the alcoholic accepted this counseling and criticism willingly.

Although this mode of treatment is not widely accepted and has not been conclusively proven to be effective; nevertheless, it seems important to consider the mechanism of ethnopsychedelic therapy for alcoholics. It is tempting to speculate that the observed positive effects of the peyote ritual and its integral involvement in the recovery rate of alcoholics may possibly be due to a present state of enhanced self-awareness, a detachment from the ego-anchors of anxiety that are more common to factors inherent in the past and future. The participant floats steady, level, as in an oceanic sense of oneness.

An alternate hypothesis regarding the mechanism of action of the

usefulness of peyote in the treatment of alcoholism may reside not only in its profound effects on the psyche but in the biomedical nature of the cactus itself. Further consideration into the biochemical nature of peyote is warranted since there is evidence that supports the biochemical approach to alcohol addiction [47]. Simply, what is the magic in the peyote?

Along the lines of alcohol addiction as a biochemically linked disorder, an attractive new approach has emerged from three centers in the United States [14, 18, 49], postulating the formation of addictive alkaloid derivatives from the interaction between biogenic amines and the ethanol metabolite, acetaldehyde.

β-Phenylethylamines are known to condense nonenzymatically with aldehydes through a Picet-Spengler mechanism to produce a class of compounds called tetrahydroisoquinoline (TIQ) alkaloids. Pictet-Spengler condensations are probably important for the biosynthesis of alkaloids in plants [54] and are being actively investigated for their role in animal physiology. Recent demonstration of the endogenous formation of TIQ alkaloids in vivo during ethanol intoxification [17], and identification by Sandler and co-workers [52] of urinary excretion of salsolinol (TIQ derivative) in Parkinson patients receiving L-dopa and ethanol supports the hypothesis that the formation of endogenous alkaloids might be responsible for the addictive properties of ethanol in vivo. Hence, O'Neil and Rahwan [44] have not been able to identify salsolinol in the brains of mice exposed to ethanol vapor, thus making the above hypotheses less plausible. However, other work from our laboratory [25] supports the work of Collins and Bigdeli [17], and argues with the report by O'Neil and Rahwan [44].

Since norepinephrine (NE) and dopamine (DA) constitute the major catecholamines in the CNS, it is obvious that their TIQ derivates formed in vivo following ethanol consumption would contribute to some pharmacologic response to ethanol by interfering with catecholaminergic mechanisms in the brain and in the periphery. These alkaloids have been shown by Cohen and his group [16] to have some properties in common with the catecholamines. They probably compete for the same uptake and storage mechanisms, and perhaps they act as false transmitters. Under certain experimental conditions, they are norepinephrine-like in action and they are secreted in a similar manner as NE [15, 22, 27]. Since they have already been shown to be formed in vivo following alcohol consumption [17, 25], it would not be surprising if they were shown to contribute to the acute alterations in sympathetic and central nervous system activity usually associated with ethanol ingestion.

These properties of the TIQs raise an interesting speculation as proposed by Cohen [16] which may be paraphrased in the following manner: The "hangover" obtained from alcohol ingestion occurs as the general sedative and depressant actions of alcohol are wearing off.

Still others, such as tremulousness, hyperexcitability, hallucinosis, and seizure, are seen after particularly heavy or long-term drinking; they occur when blood alcohol levels have either declined considerably or are absent. The TIQ alkaloids may be either secreted or leaked from nerve terminals and contribute to the behavioral actions of alcohol [28].

These characteristic neurologic disturbances could be due to the persistent physiologic action of the TIQ alkaloids. In this way, the actions of these alkaloids could indeed be responsible for the process of physical dependence or addiction in alcoholism. Much research [4, 8, 9] has already supported this hypothesis by Cohen and coworkers. There is evidence of similar biochemical effects of ethanol and salsolinol [50], TIQ-induced alterations in core body temperature [10], as observed in withdrawal from alcohol in humans [37], TIQ-induced convulsions in mice [2], potentiation and/or suppression of alcohol-induced withdrawal reactions in mice, depending on the dose employed [4, 8, 9].

It is remarkable to us that the TIQ alkaloids discussed by Cohen and Collins [14] and others [18], are similar in structure to a number of naturally occurring simple alkaloids that are found in desert cacti [55] and which exhibit pharmacologic actions such as excitation, narcosis, blood pressure changes, and convulsions. Of great interest is that these naturally occurring alkaloids are pharmacologically similar to the neuroamine-derived alkaloids found in the brain during alcohol intoxication [48]. These facts take on even greater significance when one considers the chemistry of peyote, a drug described in this and other papers [45, 46] to be a potential effective therapeutic deterrent to alcoholism. According to Friedberg [19], peyote contains at least 15 β-phenethylamine and isoquinoline alkaloids, and Schultes [55] reported that all the alkaloids are pharmacologically active. Furthermore, the TIQ alkaloids found in peyote are hallucinogenic and are responsible for differences between intoxication states produced by pure mescaline, the active ingredient, and that produced by the peyote cacti. For reviews of the pharmacology of isoquinolines see Refs. [24, 28].

It has been observed that in both mice [35] and humans [23], administration of ethanol will ameliorate alcohol-induced withdrawal symptomatology, and this is true also for low doses of the TIQ derivative salsolinol in mice [4, 8, 9]. This phenomena may be viewed as replacement therapy if indeed ethanol and/or TIQ alkaloids are responsible for alcohol addiction and subsequent physical dependence. In this regard, it is tempting to speculate that the beneficial effects of peyote in the treatment of alcoholism may in part be due to the alcohol-like or replacement properties of the TIQ alkaloid constituents in peyote. An analogy of this in the addiction field is methadone as replacement or maintenance therapy for heroin or other opiates. In support of this thesis is the use of peyote as a maintenance drug in alcohol treatment programs [1].

The recent findings of Myers and associates [42] showing that small doses of isoquinolines administered into the central nervous system maintains ethanol drinking, at first glance, is evidence against the addictive property of the isoquinolines. However, similar findings are obtained with ethanol itself and thus the notion of ethanol-like effects are somewhat strengthened.

Furthermore, there is some evidence that salsolinol is addictive, [4, 8, 9, 43], and other alkaloids have been considered along similar lines. In the context of the present discussion, the benzyl tetrahydropapaveroline (THP) possesses high pharmacologic activity in its own right [36] with many of the properties of a β-adrenergic agonist [30, 34, 53, 56]. Its in vitro formation is promoted both by ethanol and by acetaldehyde [61]. The structure of THP bears a surprisingly close resemblance to that of certain naturally occurring alkaloids of the opiate type and is the requisite intermediate in morphine biosynthesis in the opium poppy Papaver somniferum. Because of this likeness, Davis and Walsh [18] proposed that the in vivo formation of such a compound might form the basis of ethanol addiction. Thus, it is conceivable that the isoquinoline derivative could yield effects similar to those seen after morphine administration. In this regard, Ross et al. [11, 50] reported that morphine, ethanol, and a TIQ alkaloid, salsolinol, deplete calcium in regional areas of the brain. This effect is selectively antagonized by the stereospecific narcotic antagonist, naloxone. This work suggested a common chemical action for morphine and ethanol.

How these alkaloids might serve to mediate the biochemical, behavioral actions of ethanol and opiates is speculative; nevertheless, there is considerable evidence in the literature indicating a relationship between opiates and ethanol [6-8].

Acute administration of salsolinol to mice undergoing withdrawal from ethanol vapor was found in our laboratory (depending upon the dose) to either ameliorate (10 μg/i.c./animal) or exacerbate (100 μg/i.c./animal) ethanol-induced withdrawal symptoms [4, 8, 9].

Sinclair [57] has shown that morphine suppresses voluntary alcohol consumption (VAC) in hamsters, and Ho et al. [29] have demonstrated that a single injection of an opiate agonist significantly suppresses VAC in both mice and rats. Ross et al. [51] have described the same effects in hamsters and have also shown that dextrorphan had no significant effect on alcohol consumption indicating the necessity for an active opiate enantiomer. In recent unpublished preliminary experiments we have found that naloxone or naltrexone at 5 mg/kg can inhibit ethanol narcosis in mice, while higher doses of the narcotic antagonist (10 mg/kg) potentiate the narcosis. However, Harris [26] found no effect of naloxone on ethanol-induced narcosis in mice. Additionally, Jones and Spratto [31] have recently demonstrated that concurrent administration of ethanol can effect morphine withdrawal in rats, and Uyeno [60] has observed that withdrawal of ethanol after

chronic administration increases morphine self-administration in monkeys. Furthermore, Blum et al. [3] have shown that the ethanol-withdrawal syndrome in mice is significantly suppressed by a single injection of 10 mg/kg morphine at the fifth hour post-ethanol exposure.

The finding that morphine attenuates the ethanol withdrawal syndrome [3, 5]; that naloxone inhibits the development of dependence to ethanol [4, 8, 9]; that biochemical cross-tolerance exists between morphine and ethanol [51]; and that naloxone partially reduces salsolinol-induced convulsions in mice [4, 8, 9] suggests that ethanol, or some metabolite, affects the opiate receptor. Hamilton et al. [25] recently found that salsolinol behaves as a weak opiate agonist-antagonist on the guinea pig ileum. Additionally, salsolinol depletes regional brain Ca^{2+}, as does morphine, when administered peripherally [50]. Both of the above effects of salsolinol are inhibited by naloxone, suggesting that the site of action is the opiate receptor. Furthermore, in Goldstein's laboratory (personal communication), salsolinol was found to stereospecifically bind to the opiate receptor in guinea pig brain. Salsolinol was found to be ten times less potent than normorphine in this preparation. In this regard, salsolinol was found to inhibit binding of calcium to synaptic membranes. The potency of this action is similar to the opiate agonist levorphanol. Naloxone was found to partially block this response but did not reverse it once it was initiated [52]. Marshall et al. [40] found that 3-carboxysalsolinol produces analgesia itself and potentiates morphine analgesia. Both of these effects are inhibited by naloxone. Intracerebral administration of salsolinol has also been found to affect morphine analgesia in mice [62]. These results support a partial agonist role for salsolinol with regard to opiate receptor interaction. The findings that salsolinol and 3-carboxysalsolinol prolong ethanol-induced narcosis supports an agonist role for ethanol actions [39].

Additional support for ethanol-like actions of the isoquinolines and for beta carbolines is derived from the profound effects of these agents in ethanol preference studies [20], following continuous intraventricular infusion [42] and from the work of Church et al. [13] showing induction of sleep by salsolinol.

These speculations, while intriguing, require the demonstration that TIQ alkaloids are formed in vivo during ethanol intoxication and that there may be formation of significant amounts of these alkaloids to produce physical dependence. The term "significant" is relative in this application, because localized formation of these compounds in synaptic nerve endings could provide physiologic, active concentrations which might be below the detectable limit for current techniques.

Although there is evidence which refutes the common mechanism theory [21], if the common link between opiates and alcohol is the neuroamine derived alkaloids (TIQ derivatives) and if these alkaloids were

pharmacologically active agents that have replacement value (as the addictive component), then it would not be surprising to find that peyote, a source rich in these alkaloids, acts as an equally effective deterrent for both alcohol and opiate abuse.

The following case histories are representative of peyote use for opiate abusers in a non-Indian community.

Superficially, these non-Indian church members looked no different from other farmers of the area. They were short-haired, conservatively dressed, hard-working family people with neither visible signs of nor kind words for the counter-culture. Of 46 active members, 18 reported a history of daily excessive alcohol intake, six had been addicted to heroin, and 11 had psychological problems associated with polydrug use. Their regular use of peyote is confined to their intimate, all-night services and is thought to lend them sensitivity and insight into the everyday life of sobriety. Their personal experiences are rarely shared, but there is often reference to extreme clarity and increased self-worth. They seldom report ecstatic revelations or dramatic hallucinations, but often refer to the abstract spiritual powers of the cactus and its incompatibility to other drugs and alcohol.

CASE 1

This is a 28-year-old black male with a four-year history of heroin addiction in a large midwestern city. He was raised by an overprotective, loving mother with six siblings. Much of his youth was marked by acting out, behavioral problems, poor school performance, alienation, and loneliness. He was attracted to the Native American Church and ate of the peyote six years ago and soon embraced their doctrines of brotherly love, self-reliance, and sobriety. He is now a well-respected leader of his church with a stable family and small independent farm.

CASE 2

This is a shy, reticent white male in his late twenties who acquired an addiction to heroin following years of polydrug abuse. He was the third of five siblings raised by stern, religious parents, with a long history of interpersonal difficulties. During a five-year period of addiction, his wife deserted him, leaving with his mother their only child. His treatment included out-patient counseling and methadone maintenance with only limited success. He met a leader of the Native American Church while hitchhiking and attended a meeting "to get high." During his first experience with peyote, he visualized the dramatic

seriousness of his addiction. Following a progressive resocialization, his self-confidence improved, his inner fears and conflicts diminished, and he has abstained from heroin for three years. He is now remarried, united with his daughter, and works his own small farm while being heroin free.

We also found a few Indian participants who became members not through the alcoholic route but because of a drug dependency. The authors interviewed one Indian member who had just this problem and subsequently solved it with the aid of the peyote ritual.

CASE 3

A 36-year-old Indian male confined to a wheelchair because he sustained a spinal cord injury in an auto accident while in the army. He had recovered from the initial reactive depression after a year or so, but continued on Dilaudid for recurrent bouts of pain. After several years, he began using the Dilaudid intravenously and became a seriously withdrawn, hostile, passive, aggressive addict, five years post-trauma. He then became interested in and joined the Native American Church; since that time he has had no need or desire to use Dilaudid or any other potential psychoactive drug.

Whether the stimulus is social, psychological, or pharmacologic, many members of the Indian and non-Indian groups reported rapid and noticeable improvement in drug-seeking behavior and anxiety producing thought processes following their use of peyote as members of the Native American Church. While the selection process and skill of the medicine man are important factors, this report documents the use of peyote in structured healing ceremonies useful to chemical-dependent people (opiate and alcohol alike) of many races.

In summary, this paper describes an alkaloid-based hypothesis concerning the biochemical rationale for the use of peyote as an ethnopsychedelic tool for the treatment of alcoholism and other drug dependencies. Although this speculation is at its best very tentative, it is the hope of these authors to stimulate research and test its validity and thereby uncover further problems associated with the possible etiology of addictive disorders.

If, in fact, our theory is borne out, coupled with the proof of an alkaloid-based biochemically linked common denominator for chemical dependence of both the alcohol and opiate type, then it would not be surprising if a common modality of treatment be advocated. This treatment may include the use of synthetic tetrahydroisoquinolines or possibly plants high in the source of these alkaloids—namely

peyote or other desert cacti or agents that may antagonize the formation of certain endogenously formed alkaloids. As an alternative, if the isoquinolines are responsible for maintaining the desire to drink, then one would want to develop substances that antagonize the formation of certain endogenously formed isoquinoline alkaloids. The potential therapeutic value of peyote may reside in chemicals (possible isoquinolines) that may inhibit the neuropharmacologic actions of other isoquinolines such as THP or salsolinol. Support for this suggestion is derived from the work of Karniol and Carlin [32], showing that certain substances in cannibis inhibit behavioral effects of tetrahydrocannibinol.

SUMMARY

The authors examine folk psychiatry among Native American Church members from an enthnopharmacologic viewpoint. Alcohol and opiate abuse among Indian and non-Indian are presented in case histories proving to be asymptomatic under Indian guidance and through participation in the peyote ritual.

The biochemical alkaloids common in the peyote cactus, rather than just the psychoactive substances (mescaline), are purported to be pharmacologically similar to the neuroamine-derived alkaloids found in the brain during alcohol intoxification. Evidence is reviewed that points out possible common features of alcohol and opiate dependence leading to the speculation for a common mode of treatment may reside in plants rich in isoquinoline alkaloids.

ACKNOWLEDGMENTS

This research was supported by NIDA Grant #1-T01-DA00290-01 to Dr. Kenneth Blum and National Institute on Alcohol Abuse Grant #5-T01-AA07006-02 to Dr. Paul Pascarosa. The authors are grateful to Mr. Mark M. Halsweig for work done in the field. Both Dr. Blum and Dr. Pascarosa are Career Teachers in the Drug and Alcohol Addiction Field. Sanford Futterman is a graduate student, Department of Psychology, Antioch College West, and this paper is in partial completion of studies for the M.A. degree.

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