

From Eleusis to PET scans: the mysteries of psychedelics

David Nichols, Ph.D.

WE ARE TALKING tonight about psychedelics. These are the same drugs that were

initially known as psychotomimetics. Sometime in perhaps the early to mid-1970s it became politically correct to call them hallucinogenic agents or hallucinogens, and then with the seventh and eighth editions of Goodman and Gilman*, Jaffe has told us that in fact it is now politically correct to call these drugs psychedelics in scientific contexts. I haven't actually seen that transformation occur in the formal scientific literature but psychedelics is the term by which all these drugs were known to the lay public and continues to be used by the lay press. So tonight I am going to take the liberty of using the term psychedelic and this perhaps will be one of the first presentations in quite a few decades to use this term liberally at a scientific meeting.

LET ME START OFF by suggesting that a significant number of the people in this room tonight and indeed a significant percentage of serotonin researchers worldwide first gained their interest in serotonin through some association with psychedelic agents. For some people it may have been as a participant in a legitimate scientific clinical experiment, others may have done some personal experimentation during the 1960s. Perhaps others read some of the rich and interesting literature describing the powerful effect on the psyche of these drugs and developed an academic curiosity, or perhaps still others developed an interest through the drug abuse aspect, "Why do people enjoy taking these drugs?" Whatever the motivation, I would still assert that a significant percentage of the serotonin researchers in the world today developed their research focus through some connection to psychedelic drugs. Certainly I think there would be no debate among us that the high degree of structural similarity between LSD and serotonin, the natural neurotransmitter, was a clear motivation very early on to consider that serotonin played a powerful and important role in brain behavioral states.

Psychedelics didn't just spring on us fully formed in the 1960s. They have a long, rich, and well documented history. Unfortunately, it seems as though that knowledge has not come forward to us at the present time. I guess I first became aware of this on a plane trip that I took perhaps ten or twelve years ago where I was seated next to a psychiatrist. This psychiatrist and I talked about our research interests and when I mentioned some of the earlier clinical studies that had

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* *The Pharmacological Basis of Therapeutics*, a standard reference text on the action of drugs



"Those pills you took may cause some visual distortion."

been done with LSD he was simply aghast. He just couldn't believe that LSD had ever knowingly been given to humans. What I hope to do tonight is to bring some of that ancient knowledge, if you will, into the 1990s, to give us a perspective as to why these drugs are important in the first place, why they motivated many people to do research with serotonin, and why they are still an important research area.

Psychedelics have had a profound effect on our culture. They have affected music, art and philosophy. We probably don't appreciate the extent to which psychedelics have affected our culture and our society. If you were to walk down the street and a colleague pointed to some poster or picture or article of clothing and said, "Wow, that is really psychedelic," most everyone here tonight would probably understand what he meant. Psychedelics did have a profound effect on our culture, probably in ways that we couldn't even begin to quantify today because it was so broad and widespread.

An old Playboy cartoon (above), is meant to illustrate what most people think of when they think of hallucinogens or psychedelics. Here we have a physician giving medication to a patient, telling the patient those pills he just took may produce some visual side effects. Of course what the patient is seeing is a bizarre array of hallucinated characters. His wife's head is floating, the nurse's neck is all misshapen, and this is probably what most people think about when they think of an hallucinogen. However, psychedelics or hallucinogens don't reliably produce hallucinations. I like the definition that Jaffe used for psychedelics in Goodman and Gilman. He said that they are drugs that produce changes in consciousness which normally occur only during dreaming or at times of religious exaltation. It is worth taking just a minute or two

sometime to think about the definition of a drug class like that; it is really pretty profound if you think about it.

Now, why would we be interested in psychedelics? The conventional wisdom is they are nothing but drugs of abuse. Actually, I don't think

that is the case at all. Here is a list of things that potentially would be interesting to look at or areas of study where psychedelics might be very important.

Cognitive functions and sensory processes

These drugs have a profound effect on normal cognition. How do they produce that effect? That obviously would be something very interesting to explore. Stan Grof has defined these drugs as non-specific amplifiers of unconscious processes. Normally we don't know much about the subconscious, but obviously if we have a drug that amplifies the subconscious this would be an interesting thing to study.

Study of personality and dreams

What is personality, where does it come from, what are the different phases and the different times in life that lead to personality development? Again, an amplifier of the subconscious or the unconscious mind might be revealing in studying personality. What about the processes involved in dreaming? I read an interesting paper many years ago by Clara Torda who had put volunteers in a sleep lab, acclimated them on one night and then the next night began an intravenous infusion a very low dose of LSD. What she observed was that the LSD produced an immediate bout of REM sleep. What kind of dreams were produced? Were they lucid dreams, were they different in any way from normal dreams? We don't know. It has been conventional wisdom that both from an EEG standpoint

AREAS OF POTENTIAL INTEREST

- Cognitive functions; sensory processes
- Processes involved in dreaming
- Structure & development of personality
- Use in obsessive-compulsive disorder
- Convict rehabilitation
- Alcohol and Substance abuse
- Pain relief in intractable pain
- Depression in terminal illness
- Parallels to near-death experiences
- Theories of "mind"

signal-to-noise ratio really needs to be examined carefully. This is in fact a problem with a lot of the studies with psychedelics. What you had were a few people in a study who had dramatic remission of symptoms but when lumped together with the whole cohort of subjects that signal, if you will, was lost in the noise and the overall study was reported as non-significant. I'll get back to that in a minute when I talk about what I think the paradigm should be for these drugs.

Pain management

Relief from intractable pain, pain relief in terminal illness, depression in terminal illness, these are all related. Many people don't realize that one of the most well documented uses for LSD was in the treatment of terminal patients. Early studies going back to those of Eric Kast in the mid 1950s showed that LSD was as effective as narcotic analgesics. Interestingly, the analgesic effect transcended the acute effect of the drug so that a comparison of LSD with a conventional narcotic like Demerol showed first of all that LSD was more effective acutely. Whereas the narcotic analgesic wore off within a period of hours, in many cases the analgesic effect of LSD went on for one or two weeks. Kast remarked on this and it eventually led into fairly extensive studies of terminal patients at the Spring Grove Hospital with Al Kurland, Charles Savage, Bill Richards, and Stan Grof. This would be a definite research area to open back up with psychedelics where effectiveness has already been well documented.

Near Death Experience

This is an area that I think is really interesting. Grof has formally pointed out this relationship but many people have commented on the parallel between the psychedelic experience and the near death experience (NDE). Probably most of you know what an NDE is but for those of you who don't let me just quickly tell you. It

and even from a descriptive, subjective standpoint that oftentimes the effect of psychedelics is like a sort of conscious dream. So here's another area where LSD might be used, to study dreaming.

Obsessive/compulsive disorder

This is a very interesting application where psychedelics might be useful. OCD is an extremely difficult disorder to treat. There are a number of anecdotal reports involving remission of OCD symptoms after psychedelics, and in one case a complete cure. I recall the report from a Scandinavian psychiatrist years ago that involved a severe obsessive/compulsive patient who was given LSD over a period of some months, in the absence of any structured psychotherapy. The paper was a report of a ten-year follow-up. The individual was completely free of obsesive/compulsive symptoms and by all accounts had a better personality than at any prior time in his life.

Convict rehabilitation

There was a tantalizing study done by Tim Leary years ago (see this issue p.10). A recent retrospective has shown that the data were not properly manipulated, shall we say. But suppose it was possible to use psychedelics in the context of convict rehabilitation. We have the highest incarceration rate of any developed nation in the world and our solution to crime seems to be to build more jails and hire more policemen. That just simply cannot go on. We need a different approach to treating social deviance. Here is a possibility that would be tremendously cost saving in our society.

Alcohol and substance abuse treatment

Although the studies with alcoholics seem to suggest that LSD was not particularly effective, some of the researchers reported that in certain patients they got dramatic recoveries. I think here is a case where the



"Here take these, I'd like to see what they do to you."

occurs when someone is pronounced clinically dead and then subsequently through some means the person is resuscitated. And it is sometimes the case that when those people are resuscitated they describe a memory of going—this would be a typical description—of going through a dark tube and emerging out into a bright light, being filled with light, being filled with a sense of ecstasy or love or often seeing heavenly messengers and hearing angelic singing, sometimes seeing long dead relatives or family members who come and greet the person. People who have this sort of NDE in many cases or most cases are convinced that they have seen the other side of death. That has demonstrated positive personality effects. These people often develop a zest for life. They have lost their fear of death. They become much more outgoing. They seem to experience life more fully. This has been very well documented in many cases and Grof has said that psychedelics can produce what he calls a "ritual encounter with death." People who have a near death experience often undergo powerful transformative changes. People who undergo a peak psychedelic experience—the type where they have a sort of drug-induced near death experience, if you will—these are the people who undergo the powerful personality changes. In the early days of psychedelic research researchers didn't fully appreciate that. They used low doses of psychedelics that produced distortions of the senses and changes in image processing and cognition. Most clinicians tried to use that state to facilitate a sort of cognitive therapy; to have people look at their pasts and introspect and so forth. But the people who had a peak experience—this parallel to the death experience—were the ones who were most often significantly helped. Certainly in the terminal cancer patient studies that was the case. I think that is the paradigm that has to be used and it is what many researchers in those earlier days failed to appreciate up until about the very end; that you have to bring about a powerful transformative experience to get personality change and a significant

therapeutic effect. That is what I referred to earlier about the signal-to-noise ratio. This transformative experience is the "signal" that you need to find, but it was obscured in the "noise" of all the subjects who did not experience this effect of the drug. In all the early studies, one wonders what the results would have been if subjects who experienced this "peak experience" had been analyzed separately from those who did not.

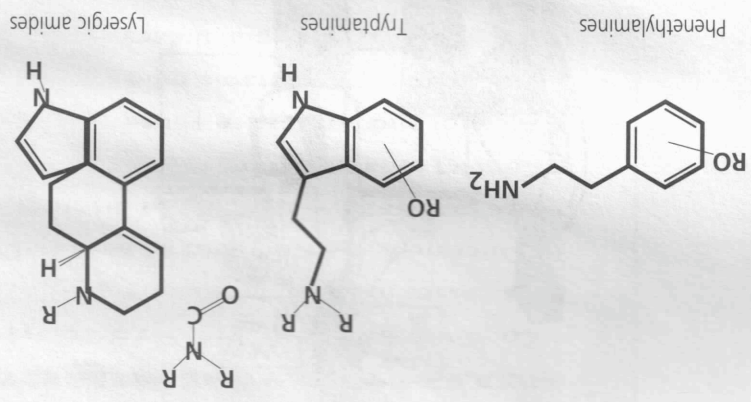
Study of the mind

A final use for psychedelics is simply to study the mind and to develop theories about mind and the mind-brain relationship. I have a humorous cartoon—these are often sent to me by colleagues—in which the physician gives medication to the patient saying, "Here take these, I would like to see what they do to you." This represents the wishes of psychedelic researchers like myself. We really don't have a good model for understanding the clinical effects of these drugs.

Available research model

The best animal model we have right now is probably the two lever drug discrimination. In this model a rat is trained to discriminate between an injection of saline and a drug like LSD, for example. After the animal reliably learns to discriminate LSD from a saline injection he is administered some new experimental drug and by observing which lever the animal presses one concludes that the animal is saying this drug was either like the training drug, that is, like LSD or was not like LSD. I have sort of a comparison between the rat and the human experience. In the rat "dialogue" the researcher says to the rat, "What does it feel like?" and the rat can only say, "It feels like LSD," or "It doesn't feel like LSD." The human experience on the other hand is quite different. When the researcher says, "What does it feel like?" the human subject is just as likely to reply, "I was a witness to the Creation, I died and was reborn, it changed my life." You

Three Basic Types of Hallucinogen Molecules



can see that the type of animal data we have is a pale, pale reflection of what we would like to see in clinical studies of psychedelics.

What I am really focusing on are what I would call

the classical psychedelic agents. These are compounds that

fall into these three chemical categories that are all

serotonin agonists. On the left [above] we have the simple

phenethylamines, the prototype of these would be

mescaline. In the center we have the tryptamines,

N,N-dimethyltryptamine and 5-methoxy-N,N-dimethyl-

tryptamine. Psilocybin and psilocin would be the compo-

nents of "magic mushrooms." They are hydroxylated or

oxygenated. Then on the right are the lysergic amides,

which are the most potent class and of course where the

"R" groups are two ethyl groups, you have lysergic acid

diethylamide or LSD. These are the classical psychedelics

and for those of you that follow the 5HT_{2A} receptor

literature, these are all believed to exert their effects

primarily by stimulating serotonin 5HT_{2A} receptors.

PET scan research

I did promise in the title to talk about PET scans. Unfortunately there isn't much of this work being done but there is one laboratory right now in the world where

cutting edge research is

taking place. It is the

laboratory of Dr. Franz

Vollenweider at the

University of Zurich

Psychiatric Hospital. This

slide is from some of his

work showing a fluorine-

18 fluorodeoxyglucose

(FDG) PET experiment.

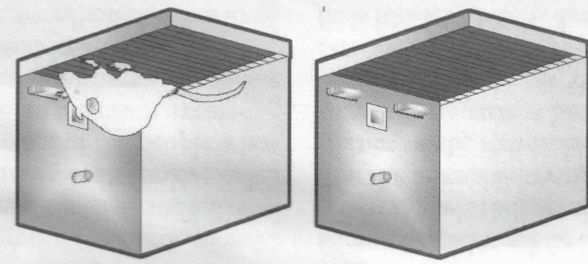
On the left (facing page),

we have a PET scan of a

normal human and on

the right a PET scan of

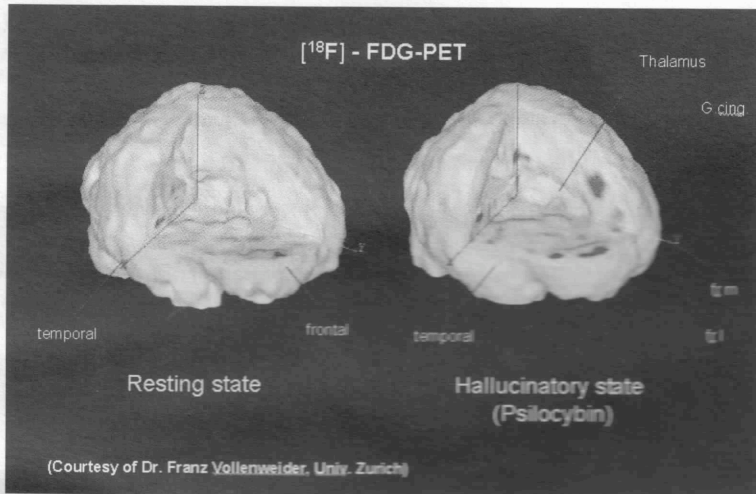
Two-Lever Drug Discrimination Paradigm



the brain of a subject who is taking psilocybin. What you can see is the areas where the fluorodeoxy glucose has been taken up, where higher brain metabolism is occurring, and with psilocybin in the frontal cortex and thalamus it is a really high level of FDG uptake. As you can see, it is possible to do some really interesting research with psychedelics, just not too many people seem to be interested in doing it for some reason.

Finally, another cartoon sent to me by a psychiatrist friend: In this case we have the physician with a whole desk full of boxes and bottles of medication telling the patient, "One of these should make you feel better, be sure and let me know which one it is." This is the kind of situation we are faced with now. Due to the chemistry and pharmacology work in a number of laboratories we have quite a number of these molecules that have, at least in the animal model, LSD-like effects. What we don't know is what their clinical effects would be, or which of these might be useful for particular therapeutic indications. We have a plethora of different molecular structures and we really don't have a clue as to what value they might have or what effects they might produce.

I would like to end with an e-mail message that was sent to me by a colleague of mine a couple of weeks ago. He is a fellow that goes around giving workshops on herbal medicine. At one workshop he had a fellow come up to him and relate this story to him. This is what he said, "One of the fellows at the workshop had been afflicted with severe dyslexia when he was a child. He described to me how the letters would just seem to float off the page and get all mixed up in his



head. He had a lot of social problems because of this. He was considered the dummy and was outcast because of this. He started taking LSD when he was around 15 or 16 and he described how over the course of a series of sessions he was able to 'look inside his brain.' He had been formally diagnosed as being brain damaged and while under the effects of LSD 'understood how things were wired' and those were his words. Then in one particularly high dose and harrowing session he described to me how he had discovered 'all these unused filing cabinets in a different part of his brain.' He said he was able by an act of will to somehow download the language software from the damaged language centers and transfer the functions to this unused newly discovered or understood part of his brain. After that he said he had no more problems.

Suddenly, words on a page made sense, they stayed put and no longer floated away." Well, I realize that isn't the report of a double blind placebo controlled clinical study but the literature is replete with anecdotal first person accounts just like that. And if only a small percentage of those accounts represent the real potential of psychedelic drugs, aren't we missing out on something very profound and fundamentally important by not pursuing a more extensive research effort with these fascinating compounds? •

David Nichols, Ph.D. is President of the Heffter Research Institute.
E-mail: drdave@pharmacy.purdue.edu



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