

L-5-Hydroxytryptophan for LSD-Induced Psychosis

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The serotonin precursor L-5-hydroxytryptophan reversed the symptoms of a 23-year-old man suffering from LSD-induced psychosis who participated in a randomized, double-blind crossover study of the drug and a placebo. This finding is compatible with the speculation that some LSD-induced psychotic disorders may be caused by a relative deficiency of CNS serotonin. (Am J Psychiatry 140:456-458, 1983)

Lysergic acid diethylamide, a potent hallucinogen, causes in humans a characteristic toxic state lasting 6 to 12 hours. However, in certain individuals the use of LSD, not necessarily in large doses, has also been associated with the development of psychosis preceded by a lucid interval of weeks or months (1). Such psychoses related to psychostimulants may evolve over years (2, 3) and have a poor prognosis (4).

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In the 1950s, Gaddum (5) and Woolley and Shaw (6) suggested that serotonin mechanisms might have a role in the pathogenesis of certain mental disorders. This hypothesis was based on the idea that the mind-altering capabilities of LSD were possibly related to the drug's ability to antagonize serotonin-dependent neuronal systems. Since then, CSF from patients with hallucinogen-related psychoses has been found to have a low level of 5-hydroxyindoleacetic acid, a primary metabolite of serotonin (7). In addition, a therapeutic trial of the serotonin precursor L-5-hydroxytryptophan (5-HTP) in 11 chronic schizophrenic subjects was related to an improvement in 6 (8). It follows that if LSD is associated with a psychosis based on a serotonin deficiency in the CNS, 5-HTP may have therapeutic value in this disorder. The following study tested this hypothesis.

CASE REPORT

Mr. A, a 23-year-old former college student, was psychotic when he was seen at the age of 20. The disorder was characterized by auditory and visual hallucinations and by grandiose delusions. He had taken LSD five times between the ages of 18 and 21, and he had a paternal great aunt who had been psychotic. Before the onset of his present illness, he had been a high school honors student, athlete, and editor of the school's yearbook. Following the first use of LSD in his freshman year of college, his work had deteriorated, and he had dropped out. Psychotic symptoms emerged 11 months later.

A medical evaluation at the onset of his illness included a physical examination, routine chemistries, urinalysis, hemogram, determination of serum copper and lead levels, skull films, sleep EEGs, and a computerized tomography (CT) scan of the cerebrum, all of which were unremarkable.

For the 29 months after the onset of his illness, Mr. A was treated continuously with large doses of antipsychotic agents, including trifluoperazine, chlorpromazine, and lithium carbonate, without clinical remission. The onset of tardive dyskinesia occurred during this time.

With the informed consent of Mr. A and his parents, a double-blind crossover trial of 5-HTP was begun; the aromatic-L-amino-acid decarboxylase inhibitor carbidopa, 25 mg q.i.d., was also given to increase the amount of active agent reaching the CNS. During control periods the carbidopa was continued but the 5-HTP was replaced with an inert, identical placebo of lactose. Measures of psychosis included evaluations by psychiatrists two to seven times a week; taped interviews; the MMPI; the Brief Psychiatric Rating Scale (BPRS) (9); a follow-up scale for prognosis in hallucinogen-induced psychosis (4); and the Fourteen-Symptom Behavior and Mood Rating Scale for Longitudinal Patient Evaluation by Nurses (10).

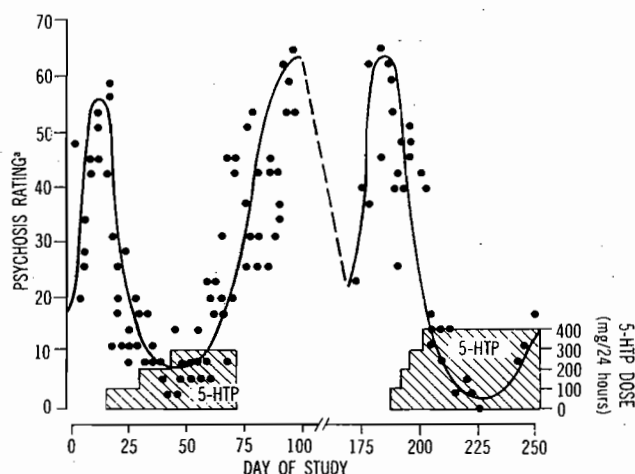
The follow-up scale measures prognosis in chronic psychosis with scores for hospitalization, treatment, symptoms, social adjustment, vocational performance, and overall outcome. The scale score varies directly with favorable prognosis.

The behavior and mood scale was administered daily by one to five observers, who were nurses and psychologists involved in Mr. A's treatment. This 14-point scale had been used to measure psychosis during a previous trial (8) of 5-HTP in chronic schizophrenic patients but was modified to score 10 items (false beliefs, appears delusional, suspicious/distrustful, paranoia, senses imaginary things, hallucinating, unexplainable euphoria, great self-opinion, mentally ill, and psychiatric sickness). To increase interrater reliability a reference manual was prepared by assigning to each item of the scale the most appropriate description of each from the Present State Examination (11) (Present State Examination symptom numbers 72, 73, 125, 74, 61, 118, 41, 76, 107, and 4, respectively).

The drug trial was preceded by a 10-day washout period. The assignment of order of drug and placebo was made randomly by the pharmacist. 5-HTP was given twice, first while Mr. A was an outpatient, then while he was an inpatient; the doses and results are shown in figure 1. During the last 7 days (days 9–15) that Mr. A was taking placebo as an outpatient, his mean (\pm SD) behavior and mood scale score was 51.0 ± 6.0 ; during the last 7 days (days 59–65) of the subsequent trial of 5-HTP, his score was 18.2 ± 6.7 ($t=9.58$, $p<.001$; two-tailed t test). His follow-up scores during these two periods were 1.60 ± 1.34 and $2.80 \pm .84$ ($t=1.70$, $p=.128$). During Mr. A's inpatient treatment, his behavior and mood scale score for the last 7 days of the placebo period (days 180–186) was 55.7 ± 6.3 and for the last 7 days of the 5-HTP trial (days 202–208) it was 13.5 ± 13.6 ($t=7.44$, $p<.001$); his follow-up score rose from $1.40 \pm .89$ to $3.40 \pm .55$ ($t=4.26$, $p=.003$).

While Mr. A was taking placebo, his condition rapidly deteriorated in a week, but this process was reversed when he was treated with 5-HTP. Following a return to placebo on the 66th study day, Mr. A relapsed into a marked psychosis, again with bizarre and erratic behavior, which interrupted the protocol until the 173rd day, when the crossover was replicated in an inpatient setting. While he was taking

FIGURE 1. Psychosis Ratings of a Man With LSD-Induced Psychosis Treated With L-5-Hydroxytryptophan (5-HTP)



*10-item version of the Fourteen-Symptom Behavior and Mood Rating Scale for Longitudinal Patient Evaluation by Nurses (10).

placebo, Mr. A's mental status again deteriorated in a matter of a few days to the point that he required four limb restraints, suffered continual hallucinations and delusions, and was unable to hold logical discourse beyond sentence fragments. After the reinstatement of 5-HTP, the number and intensity of psychotic symptoms rapidly decreased. During both trials of 5-HTP the BPRS score fell, from 33 to 18 and from 63 to 6. The MMPI showed reduced paranoia and more control over hypomania. As of this writing, Mr. A continues to take 400 mg/day of 5-HTP and 100 mg/day of carbidopa, is out of the hospital, works full-time, lives independently, is involved in his first stable heterosexual relationship, and remains at the most functional level since the onset of his illness 46 months ago. Tardive dyskinesia remitted with the prolonged avoidance of phenothiazines.

DISCUSSION

5-HTP improved the condition of this patient to a more functional level than that achieved with any other treatment during his illness. The hypothesis that his illness represents an LSD-induced psychosis, however, is not proven. Deception in illicit drug use is common. The lucid interval between the time of drug use and the onset of symptoms has not been widely described. The mechanism by which LSD may exert chronic effects on the CNS is not known, and the relevance of the LSD state as a model psychosis is controversial (12). On the other hand, an experience with a major hallucinogen is unique and not easily confused with the effects of nonhallucinogenic agents (H.D. Abraham, "Visual Disturbances in a Population of LSD Users," presented at the 134th annual meeting of the American Psychiatric Association, New Orleans, May 9–15, 1981). In a chemical analysis of illicit drugs (13), the likelihood that a drug claimed to be LSD was actually LSD was 80.3%. In addition, a number of other chronic LSD effects have been found, including

flashbacks (14), thought disorder (15), EEG abnormalities (16), decrease in cortical functions (17), abnormal MMPI scores (18), deviant scores on the Reitan trail making test (19), and a defect in color vision (20).

It is widely hypothesized (21) that the therapeutic mechanism of conventional antipsychotic agents such as the phenothiazines involves the blockade of post-synaptic receptors for dopamine. Such agents were not effective for this patient, however, suggesting that his illness was resistant to such an effect. In a follow-up study of patients with hallucinogen-related psychoses (3), half had poor prognoses despite phenothiazine treatment, and 2 of 15 committed suicide. The fact that 5-HTP was helpful for this patient adds credence to the speculation that such an illness may represent a relative serotonin deficiency. It is noteworthy that when 5-HTP was effective in the treatment of chronic schizophrenic subjects (8) the mean effective dose was more than 12 times the therapeutic dose for this patient, raising the possibility that 5-HTP for some LSD-induced psychoses represents a chemotherapeutic specificity. It remains to be shown whether chronic administration of 5-HTP is effective for this disorder and whether in a crossover with conventional antipsychotic agents it is clinically superior.

The public health consequences of LSD use may not be small. A 1980 survey (22) of American high school seniors representative of the nation found that 35.3% of the boys reported that LSD was "very easy to get," and 7.2% of the same group had used the drug at least once in each of the preceding 5 years.

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