Δ^9-Tetrahydrocannabinol in Depressed Patients

Joel Kotin, MD; Robert M. Post, MD; and Frederick K. Goodwin, MD, Bethesda, Md

Δ^9-tetrahydrocannabinol (THC), given under double-blind conditions to eight hospitalized depressed patients for periods of up to seven days, failed to produce significant euphoria or an antidepressant response during the period of administration. Four patients who received the drug for seven days showed little change in mood but reported considerable drowsiness. In four patients, the drug trial was shortened because of adverse reactions; two of these patients experienced severe anxiety reactions with depersonalization after a single dose. Effects on cognitive functioning and vital signs were similar to those reported by other investigators in normal subjects. We should like to emphasize that our results were obtained with a small sample of hospitalized inpatients with moderate to severe depression. Different effects might be observed in other settings or in patients with less severe depressive symptoms.

The use of various forms of cannabis (marihuana, hashish) since antiquity to induce pleasurable states' and observations of the mood-elevating properties of these drugs in normal subjects suggested the potential usefulness of cannabis derivatives in the treatment of depression. However, until the chemical synthesis of Δ^9-tetrahydrocannabinol (THC), the behavioral effects of cannabis preparations have been difficult to quantify because of the presence of several compounds in various proportions in the naturally occurring resin. Recent evidence suggests that A"-THC reproduces both the psychological and physiological actions of cannabis in man and presumably is the major psychoactive constituent of cannabis.[2-5] Almost 100 years ago an attempt was made to treat depressed patients with a hashish extract, yielding generally negative results." In the late 1940's, synhexyl, a synthetic homologue of THC, was administered to depressed patients with mixed results.[7-9] The purpose of this study was to evaluate the potential antidepressant effects of synthetic Δ^9-THC administered over a one-week period to hospitalized depressed patients. To our knowledge, this represents the first report of the effects of Δ^9-THC in depressed patients.

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From the Section on Psychiatry, Laboratory of Clinical Science, National Institute of Mental Health, Bethesda, Md.

Reprint requests to Orange County Medical Center, 101 City Drive S, Orange, Calif 92668 (Dr. Kotin).

Methods

This study was conducted on a psychiatric research ward at the National Institute of Mental Health (NIMH) designed for longitudinal psychobiological studies of patients with affective illness. All patients in the study were diagnosed by two psychiatrists and a social worker as having primary affective illness by standard criteria'": diagnostic observations were made during an initial drug-free period of several weeks, Four of the depressed patients were classified as bipolar and four as unipolar based on the presence or absence, respectively, of a prior history of mania. Patients were moderately to severely depressed at the time of the study.

On admission, informed consent was obtained for the administration of eight to ten experimental psychoactive drugs including THC; patients were told that they would receive some of these drugs during their hospitalization. Medications were administered under double-blind conditions using a design which involved one week of THC administration preceded by and followed by at least one week of placebo, Medications were in identical-appearing capsules and code numbers *were* changed at least every four days. THC and placebo capsules for this study were supplied by the National Institute of Mental Health under authorization from the Food and Drug Administration. Active drug capsules contained 5 mg of THC in a sesame oil vehicle.

THC was administered orally at a dose of 0.3 mg/kg twice a day, at 9 AM (approximately one-half hour after breakfast) and again at 10 PM; one patient received only a single daily dose at 9 AM. A single dose at this level has consistently been reported to produce psychological effects typical of cannabis in normal subjects. Because of adverse effects (described below), four out of the eight patients did not receive active drug for the full seven-day trial period. No other drugs were administered during the trial, but all patients continued in individual and group psychotherapy.

Psychological and behavioral effects of THC were monitored in several ways: (1) Patients were rated twice daily throughout the placebo-THC-placebo period by a consensus of a trained psychiat-

ric research nursing team using a 15-point scale which focused on the global items of depression, mania, psychosis, anger, and anxiety." (2) One nurse rated each patient individually under double-blind conditions every two hours; for this purpose a 15-item scale was specifically designed to measure the effects of THC. Items rated included the following: depression, anxiety, anger, elation, talkativeness, restlessness, drowsiness, somatic complaints, grandiosity, psychosis, mania, retardation, agitation, sadness, and others. (3) Each patient rated himself every two hours on a similarly constructed scale. Items on this scale included many of the nurse-rated items but were phrased in terms of feeling: feel depressed, feel alert, feel uncomfortable physically, feel uncomfortable mentally, feel hungry, have feeling of unreality, my body feels different. (4) A psychiatrist who was aware of the medication received interviewed each patient daily. For all behavioral ratings, a two-point change during active drug administration and a change of similar magnitude in the opposite direction following placebo substitution were required before any effect was considered a pharmacological response to THC. A two-point change on the scale, in our experience, reflects a measurable clinical change since in practice the upper and lower regions of the 15-point scale are rarely used.

To measure cognitive and motor function during the trial, patients were tested daily with a short psychological test battery which included the digit span and digit symbol substitution subscales of the WAIS. (Ten different digit-symbol versions were used to avoid a learning effect.) Both of these scales have been reported to show decreases in performance after THC or cannabis administration to normal subjects.[12,13] To assess subjective effects, a modified version of the Hollister symptom sign questionnaire was also administered.[3,14] The above tests were administered daily, three to five hours after administration of the morning capsules, during both the THC and placebo periods by an observer who was blind to the study conditions.

Temperature, pulse, blood pressure, and respiratory rate were obtained on a routine four times a day basis throughout the trial: however, no attempt was made to obtain time-course data on pulse or blood-pressure effects of THC, since this would have required some restriction of the patients' normal activities. Renal, hepatic, and hematopoietic function were monitored repeatedly, and each patient was weighed daily. In all women pregnancy tests were performed immediately prior to the trial. In five patients sleep was monitored using all-night EEG recordings.

The risk of psychic dependence was minimized by careful patient selection, administration of the drug over a relatively short course under strict double-blind conditions, the concomitant use of other therapeutic modalities (group and individual psychotherapy), and prior and subsequent administration of other psychoactive drugs.

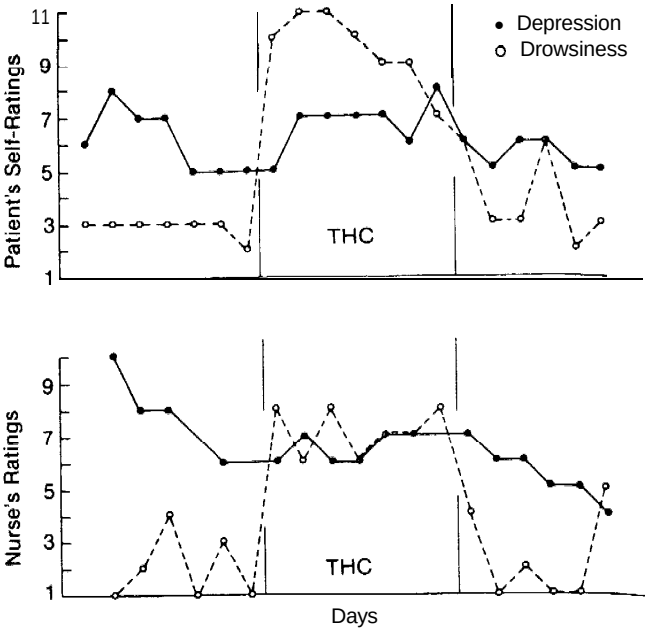
Results

None of the eight moderately to severely depressed patients who received THC manifested an antidepressant response to the drug. There were no significant changes in global depression ratings, individual two-hourly depression ratings, or self-ratings. Although a few patients experienced brief periods of well-being associated with relaxation and some giddiness, none of these reactions persisted and on the whole patients did not experience the effects of THC as pleasant or mood elevating.

The most common effect, manifested in both verbal reports and rating changes, was an increase in drowsiness.

The case of a 39-year-old depressed woman is typical of the four who received the full one-week trial of THC.

During the baseline evaluation period her depression was characterized by "low feelings," apathy, and social withdrawal; prior



Depression and drowsiness ratings while receiving THC.

to admission she frequently spent entire days in bed. In her fourth week of hospitalization she received 20 mg of THC at 9.4~ daily for one week. On the first active drug day at 3 PM she told the nurse rater she felt drowsy, relaxed, and that her feet felt far away from her body. She also complained of a dry mouth. These feelings lasted until after dinner, waning about 7 PM. On successive days she had similar feelings but these occurred earlier in the day, within one hour after taking her pills the last three days. There were short periods of giddiness noted as well. She complained of drowsiness throughout the seven days on THC, and stated she tried to remain alert. In response to a question by the nonblind observer she stated she felt "more unpleasant than pleasant." Her therapist, who was blind to the medication, noted increased lability of mood, but did not feel the basic course of therapy was altered. On the first placebo day following THC she felt somewhat tired but by the second day felt more "herself.' Throughout the THC period her depression ratings remained essentially unchanged, but both her self-ratings and individua nurse's ratings reflected her drowsiness. The figure illustrate: these data.

Because of adverse reactions, two patients received THC for only five days and two received only a single dose. These patients are presented individually.

A 29-year-old female lab technician was admitted with moder ately severe retarded depression. After four weeks in the hospita she was given THC, 10 mg twice a day. This was increased to 2(mg twice a day by the third day of the trial. That evening she complained of "flooding thoughts" and inability to remember re cent events, such as the plot of a movie she was watching on tele vision or what she had said in conversation five minutes previ ously. She feared she was "going crazy." In spite of reassurance that she was experiencing side effects of a drug, she continued t report unpleasant experiences. The fourth day of active drug (2(mg twice a day) she complained of dizziness at noon and continuer flooding thoughts. Although her anxiety had lessened somewhat it was decided to substitute placebo after the morning dose on th fifth day. Her unpleasant experiences promptly ceased by tha evening.

A 61-year-old unipolar depressed man was admitted to th NIMH because of increasingly severe depression; he spok

monosyllabically, refused to eat, and slept poorly. Over the first five weeks in the hospital his condition gradually worsened to a near-mute, psychotic state. During the first five days of THC (20 mg twice a day) this downward course continued, so the trial was terminated.

A 52-year-old depressed woman with a bipolar history was given 20 mg of THC at 9 AM. At noon she lay down, feeling weak and dizzy. She told a nurse, "My head and arms feel heavy, my legs too, I can't lift them. My mouth is so dry." Her anxiety rapidly increased and she complained of nausea and her body "twisting and pulling." At one point she said she had "death chills ... I want to go home to my children." She had racing thoughts and felt she could read off the back of her eyelids what was on her mind. She said she feared she was going to die. Her anxiety lessened with continued reassurance and she slept intermittently over the next three hours. By 5 PM she was no longer in distress. She reported that she had experienced "words running through her head without control." When asked if the experience was similar to her previous manic periods she said, "No, there's nothing pleasant about this." Because of this reaction it was decided to substitute placebo that evening and discontinue the trial. The patient spent an uneventful night.

A 43-year-old woman with unipolar depression also had distressing symptoms after receiving 20 mg of THC at 9 AM. At 9:20 AM, the patient became panicky and complained of shortness of breath and "tightness" in her chest. She reported her arms and legs felt heavy, numb, and cold. She had feelings of unreality and during a therapy session at 11 AM she reported "things seem far away and in compartments ... it's like I'm not really talking to you ... as though we're on a different level." Time sense was distorted. She felt the events of the morning "happened yesterday." She felt tired, but was "afraid to go to sleep, afraid of what might happen." By early afternoon she felt in better control and by 5 PM all effects of the drug had disappeared.

None of the eight patients who received **THC** showed consistent changes on global ratings of depression, mania, psychosis, anxiety, or anger during the active drug period. The only exceptions were the two women who experienced panic reactions after a single dose, reflected in a higher anxiety and psychosis ratings for that eight-hour period.

On the nurses' individual two-hour ratings only two items (increased drowsiness and decreased restlessness) were noted to change during the active drug period in three out of the six patients who received the drug for five days or more.

Patients self-ratings failed to show any consistent pattern of change except for drowsiness ratings which increased during THC administration in four patients. The self-rating items of "feel depressed," "feel hungry," and "feel uncomfortable physically" increased during active drug administration in two cases.

Daily psychological testing was performed in five patients during the three-week trial period. Digit span (forward and backward) and performance on the digit-symbol substitution test decreased during active drug administration in three patients, and was unchanged in two. These responses displayed a rebound with placebo substitution. Those who complained most of drowsiness had the greatest impairment of performance on these tests. An increased number of items was checked during the active drug period on the Hollister Symptom Sign Questionnaire by four patients.

Temperature, pulse, respiration, and blood pressure all measured on a four times daily basis showed considerable variation from patient to patient and from day to day during THC administration. With this large degree of variability (presumably related to the fact that the patients were freely ambulatory during the study period), no consistent pattern of vital-sign changes on THC was discernible for the majority of the patients. One patient showed a mean increase of ten points in the 1 PM lying and standing pulse.

Four of the six patients who received THC for five to seven days showed an increase in weight during the active drug period, Two of these four lost weight when placebo was substituted. Our clinical impression was that these patients increased their foot intake during the THC period. The mean weight increase for the total group was 2.2 lb, which in this small population did not achieve statistical significance.

There were no changes in indicators of renal, hepatic, or hematopoietic function during the trials in any of the patients.

Although two patients said they slept better while receiving THC, EEG recordings during sleep tended to show an increase in sleep latency and a decrease in REM time and REM percentage during THC administration.'"

One patient received a lumbar puncture at 2 PM on the seventh day of THC administration (20 mg daily at 9 AM). Cerebrospinal fluid metabolites of serotonin, dopamine, and norepinephrine showed no clear change with THC compared to a prior drug-free lumbar puncture under similar conditions. Baseline vs THC determinations (in ng/ml were: 13 vs 15 for 5HIAA, 3 vs 5 for HVA, and 15 vs 17 for MHPG.

Comment

The data presented here strongly suggest that THC is not an effective antidepressant when given to hospitalized, depressed patients for one week in a double-blind trial. Although responses to the drug varied considerably and there were occasional intermittent periods of giddiness associated with a sense of well-being, overall depressed mood did not change. The most common effect was drowsiness and a feeling of heaviness in the limbs. No mania ratings were recorded in any of the four bipolar depressed patients during THC administration. This is in contrast to our previous observations that, compared to unipolar patients, bipolar patients show an increased tendency to "switch" into mania or hypomania while receiving activating drugs such as tricyclic antidepressants, monoamine oxidase inhibitors or levodopa.[16]

In four of the eight patients, the drug was discontinued because of adverse effects, including severe anxiety reactions following a single 20-mg dose in two patients. These panic reactions included elements of depersonalization, derealization and distortions of body image. Several patients, including the two who had panic reactions, also reported "flooding thoughts," "words racing through my head without control," or difficulty concentrating. This state, frequently described in psychosis, seems to reflect a lack of ability to structure internal and external stimuli, to ignore some thoughts or feelings in order to pursue a logically related train of thought, Our depressed patients experienced this state as dysphoric. Fortunately, both pa-

tients who experienced panic reactions responded to reassurance with some diminution of anxiety.

Psychotherapy did not appear to be altered during the THC trial. One patient was noted by her therapist to have increased lability of affect while she was receiving THC, but on the whole, few differences were apparent from either the patients' or therapists' points of view,

In three patients, THC appeared to cause progressive changes over the drug trial. One patient experienced increasing "flooding of thoughts" and dysphoria over five days of constant (20 mg) dosage THC administration. Another experienced no symptoms initially while receiving 5 and 10 mg of THC, but at the end of the trial felt markedly fatigued and dizzy when receiving these doses after THC had been reduced because of side effects occurring at 15 and 20 mg. A third patient experienced the onset of drug-related drowsiness increasingly earlier in the day as the trial progressed. These progressive changes may indicate either increasing tissue levels of drug over time or the phenomenon of reverse tolerance. The lower performance on the digit span and digit-symbol substitution subscales of the WAIS, similar to reports of others[12,13] was consistent throughout the trial and did not show evidence of an increasing drug effect over time.

The fact that the expected pulse increases were not observed in these patients appears to be related in part to the relatively large variations in pulse, which were secondary to normal variations in activity and psychic state. These patients were part of an intensive community-living experience in an active research ward milieu throughout the trial, compared with the relatively controlled laboratory settings used by other investigators. Thus, any increases in pulse which may have been produced by THC would have been "washed out" by pulse fluctuations associated with other variables. In addition, the timing of the pulse measurements (9 AM, 1 PM, 6 PM, 9 PM) was not optimal for picking up pulse changes which might have been produced by a 9 AM oral dose of THC.

The failure of all eight depressed patients to experience the effects of THC as pleasurable may reflect several different factors. The clinical state of depression itself may involve a basic impairment of one's ability to experience pleasure. Effects such as relaxation, giddiness, and amplification of sensory input, which are often interpreted as pleasant by nondepressed cannabis users, may be interpreted negatively by a depressed patient as a lack of bodily control and inability to concentrate, From our data, it does not appear that the administration of THC under double-blind conditions produces an improvement in the basic mood, psychomotor, or cognitive features of depression. The effect of set and setting on the experience and interpretation of cannabis effects is of great importance as has been emphasized by other investigators.","[1] The administration of THC under double-blind conditions in this trial precluded the establishment of any positive expectation in the patient. The fact that the patients could not have prepared themselves for the experience of an altered state of consciousness may also have contributed to the predominantly negative effects of the drug in these depressed patients. Finally, the relatively brief duration of the trial (one week) must be kept in mind, since standard antidepressants require two to three weeks to produce clinical improvement.

Jane Weisenberg and Paulette Bachorick assisted with psychologic testing.

Nonproprietary and Trade Names of Drug

Levodopa—*Larodopa, Dopar, Bendopa, Levopa, Bio-dopa.*

References

1. Pillard RC: Marihuana. *N Engl J Med* 283:294-303, 1970.
2. Isbell H, et al: Effects of (-) Δ^9-transtetrahydrocannabinol in man. *Psychopharmacologia* 11:184-188, 1967.
3. Hollister LE, Richards RK, Gillespie HK: Comparison of tetrahydrocannabinol and synhexyl in man. *Clin Pharmacol Ther* 9:783-791, 1968.
4. Mechoulam R, et al: Chemical basis of hashish activity. *Science* 169:611-612. 1970.
5. Holtzman D, et al: 1-Δ^9-tetrahydrocannabinol: Neurochemical and behavioral effects in the mouse. Science *163: 1464-1466*, 1969.
6. de Tours JM: Lypemanie avec stupeus: tendance à la démencetraitement pars d'extrait (principle résineux) de cannabis indica. Guerison *Lancette Gazette Hôpital* 30:391-396, 1857.
7. Stockings GT: A new euphoriant for depressive mental states. *Br Med J* 1:918-922, 1947.
8. Pond DA: Psychological effects in depressive aatients of the marijuana homologue synhexyl. *J Neurol Neurosurg Psychiatry* 11:271-279, 1948.
9. Parker CS, Wrigley F: Synthetic cannabis preparations in psychiatry: I. Synhexyl. *J Ment Sci* 96:276-279, 1950.
10. Winokur G, Clayton PJ, Reich T: *Manic Depressive Illnes* St. Louis, CV Mosby Co, 1969.
11. Bunney WE Jr, Hamburg DA: Methods for reliable longitudinal observation of behavior. *Arch Gen Psychiatry* 9:280-29 1963.
12. Weil AT, Zinberg NE, Nelsen JM: Clinical and psychological effects of marihuana in man. *Science* 162:1234-1242, 1968.
13. Tinklenberg JR, et al: Marijuana and immediate memor *Nature* 226:1171-1172, 1970.
14. Weiss JL, et al: Cardiovascular effects of Δ^9-tetrahydr cannabinol in man. *Clin Pharmacol Ther* 13:671-684, *1972.*
15. Gillan JC, et al: Sleep during one week of administration Δ tetrahydrocannabinol to psychiatric patients. Read before th 11th Annual Meeting of the Association for the Psychophysiolog Study of Sleep. New York, 1972.
16. Murphy DL, et al: L-DOPA: Regular induction of hyp mania in bipolar manic-depressive patients. *Nature* 229:135-13 1971.
17. Waskow IE, et al: Psychological effects of tetrahydrocann binol. *Arch Gen Psychiatry* 22:97-107, *1970.*