Naltrexone, an Antagonist for the Treatment of Heroin Dependence

Effects in Man

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Naltrexone (EN-1639A) is approximately 17 times more potent than nalorphine as an antagonist in man. It is virtually devoid of agonistic activity, including the ability to induce nalorphine-like dysphoric effects. Its duration of action is longer than that of naloxone, but shorter than that of cyclazocine. It is effective orally. When administered in a dose level of 50 mg/day, it produces a degree of blockade of the effects of morphine and heroin that is comparable to that obtained with 4 mg of cyclazocine per day orally. Naltrexone, thus, appears to be a relatively pure potent narcotic antagonist which is effective orally and which may have utility in the treatment of heroin and narcotic dependence.

While studying the narcotic antagonist cyclazocine, it was found that tolerance developed to its agonistic activity but not to its antagonistic activity. It was further observed that cyclazocine was orally effective and had a long duration of action. These findings suggested that it would be possible to maintain former narcotic dependent subjects on a dose of an antagonist that would prevent narcotics from exerting their euphorogenic and dependence-producing effects, and thus provide a circumstance where both physiological and conditioned behavior related to drug acquisition and to relapse could be extinguished. Early clinical studies of Jaffe and Brill and Freedman et al indicated that select patients might indeed be helped by narcotic antagonists; however, the unpleasant agonistic effects of cyclazocine made stabilization on blocking doses difficult, and the fact that an effective blockade could be maintained for only 24 hours with a daily oral dose was not only an inconvenience for the patient but allowed the effects of narcotics to become manifest by omitting a single dose. In an extensive series of studies in man, the narcotic antagonist naltrexone was found to be virtually devoid of agonistic activity; however, it had a relatively short duration of action. Zaks et al have been able, using very large doses of naloxone orally, to attain effective blockade of morphine for nearly 24 hours. It has been the consensus of opinion of investigators that for a narcotic antagonist to be optimally effective in the ambulatory treatment of narcotic addicts it must be administered in such a way that its effect would have an appreciable duration of action (one week to one month), that it should be devoid of agonistic activity, and that it should be a highly potent compound to permit its administration in a depot form.

Cyclazocine, which has an N-methylcyclopropyl substitution on the nitrogen, exhibited an exceedingly long duration of action in man. On the assumption that its long duration of action was related to the substitution on nitrogen, we felt that it would be worthwhile to study the N-cyclopropylmethyl congener of naloxone. Information concerning the synthesis of this compound, naltrexone (EN-1639A), is available from the patent literature. Blumberg et al characterized some of the pharmacological properties of naltrexone and conducted toxicologic studies in animals. Their findings indicated that naltrexone was nearly twice as potent as naloxone as an antagonist, that it had only slightly agonistic activity (e.g., analgesia), and that it had a longer duration of action than naloxone.

This communication will summarize our findings with this compound in man.

Methods

These studies were conducted in prisoner postaddicts who volunteered for and gave informed consent to all phases of the studies. Prior to participating, all patients had a recent history and physical examination and the following laboratory work-up: Chest roentgenogram, electrocardiogram, blood tests (red, white, and complete blood cell counts, differential), sedimentation rate, hemoglobin value and hematocrit reading, urinalysis (specific gravity, pH, sugar, albumin values and microscopic), serology, and serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase levels. No patient had signs or a history of psychotic behavior.

In the initial phase I studies, 13 patients participated and re-
ceived naltrexone in doses ranging from 0.01 to 80 mg subcutaneously and 0.5 to 100 mg orally. In these studies, blood pressure, pulse rate, respiratory rate, and pupillary diameter determined photographically were measured before and 1/2, 1, 2, 3, 4, 5 and 12 hours after the administration of naltrexone. An EKG was taken prior to and two hours after the drug administration. Patients and observers completed the single-dose questionnaire at each observation period.

To further determine if naltrexone had agonistic actions, five patients received, orally, 30 mg of naltrexone in a cherry vehicle or the cherry vehicle alone on alternate weeks. Observations were the same as in the preceding study, except that the patients also completed the subjective effect questionnaire. The differences between the pretreatment and treatment observations for the first five hours were summed. The differences between these sums for the naltrexone and vehicle treatment conditions were determined and their significance assessed during a t test.

The potency of naltrexone relative to nalorphine was assessed in five patients by its ability to precipitate abstinence in subjects dependent on 15 mg of morphine sulfate administered four times daily. This method has been previously described. Briefly, a crossover design was employed in which patients received either 0.07 or 0.14 mg/70 kg of naltrexone or 1.5 or 3.0 mg/70 kg of nalorphine hydrochloride at weekly intervals and the intensity of abstinence was assessed. The relative potency and its 95% confidence limits were calculated.

A comparison of the duration of action of naltrexone with nalorphine, both administered subcutaneously, was made in nine subjects. Pupillary diameter was measured photographically at 0700 and 0730 in 3.5 foot-candles of light, and 25 mg of morphine sulfate were administered subcutaneously at 0800. Naloxone (1 mg) or naltrexone (0.5 mg) was administered together with the morphine or 3, 6, and 12 hours before the morphine. As a placebo control, saline was administered five hours before morphine. Patients received one of these nine treatment conditions at weekly intervals. The order of the treatments was randomized, and each patient received all treatment conditions according to a Latin-square design. Following the administration of morphine, pupillary diameter was again determined at 0900, 1000, 1100, 1200, 1300, and 2000. At these times, patients and observers completed the single-dose opiate questionnaire and patients completed a subjective effect questionnaire. All medications were administered subcutaneously in a 0.5-mL volume under double-blind conditions.

To assess the duration of action of orally administered naltrexone, a cherry vehicle was administered orally at 0800, 1400, 2000, and 0200 at weekly intervals over a five-week period to five subjects. At 0800 patients received 30 mg of morphine. For four weeks the patients received 15 mg of naltrexone in one of each of the four cherry vehicles. On the fifth week none of the four vehicles contained naltrexone. On the sixth week the subjects received 15 mg instead of 30 mg of morphine and no naltrexone was administered. Doses of naltrexone were randomized and a Latin-square design employed. Observations were the same as in the previously described studies.

The efficacy of chronically and orally administered naltrexone in antagonizing the effects of single doses of morphine and preventing the development of physical dependence to chronically administered morphine was assessed in nine subjects. In six subjects naltrexone was administered orally at 0600 and 1800 in a dose level of 15 mg twice daily. In one additional subject, the dose level was 25 mg twice daily. In two subjects, naltrexone was administered orally once daily in a dose level of 50 mg at 1200. During the control period, a cherry vehicle was administered and the effects of 15 and 30 mg of morphine on pupils and subjective state were assessed. Naltrexone in cherry syrup was substituted for the vehicle and patients were brought to their maintenance dose within several days. When patients had achieved their maintenance dose levels, two or more test doses of morphine were administered subcutaneously at 0800 and their effects on pupillary diameter and subjective state were assessed as described in the preceding study. Patients were then given morphine four times daily in increasing dose levels until a stabilization dose of 240 mg/day was attained. They attained their stabilization dose by the sixth day, were maintained on this dose level for 11 days and then abruptly withdrawn from morphine while continuing to receive naltrexone. Ten days after withdrawal from morphine, naltrexone was discontinued by the substitution of the cherry vehicle. The intensity of the abstinence syndrome was assessed using the method of Himmelsbach. During this phase of the study, routine observations of vital signs as well as signs of abstinence were made three times daily, and patients and observers completed chronic-dose questionnaires (Figs 1 and 2) daily. Responses to question 5 have not been analyzed and sign and symptom scale scores have not been developed; thus, these data will not be reported.

**Results**

**Dose Ranging of Naltrexone.** Most of the 11 subjects who received naltrexone subcutaneously (0.01 to 80 mg) identified it as a "blank" and reported that it produced either no subjective changes or relaxation, which is a common response following the administration of a placebo. A few subjects reported that they stretched or yawned following its administration. One subject had symptoms and signs such as scratching, tautiveness, and "coasting" following 2 and 25 mg of naltrexone, and both observers and the subject thought that an opiate had been administered. Another patient who received 70 mg of naltrexone became nauseated and irritable, had racing thoughts, and saw Disney-like characters when his eyes were closed. He slept well the night after he had received the drug; however, the following night he had a panic reaction which was related to a chest pain. Findings of a physical examination and EKG were normal at this time except for an increase in respiratory rate and some tremulousness. The panic reaction subsided after the administration of 100 mg of pentobarbital sodium intramuscularly. Another 50-year-old patient who had received, at weekly intervals, 0.1 and 0.2 mg doses of naltrexone suffered a coronary 5½ days after receiving his last dose. Most patients who received naltrexone orally reported no change; however, two patients became sleepy and identified naltrexone as a barbiturate. No EKG changes were seen following naltrexone administration. There was a trend for blood pressure to be elevated and pupils to be constricted.

To further determine whether naltrexone had agonistic activity, 30 mg/70 kg was compared with the cherry vehicle. The results of this experiment are summarized in Table 1. As can be seen, naltrexone significantly increased diastolic blood pressure and decreased body temperature. Pups were slightly constricted. Subjective changes that were reported were not different from those reported under the placebo condition.

**Relative Antagonistic Activity.** Naltrexone is approximately 17 times more potent than nalorphine in precipitating abstinence in patients dependent on 60 mg of morphine a day (Fig 3).

**Duration of Action.** Figure 4 compares the duration of action of subcutaneously administered naltrexone (0.5 mg) and naloxone (1.0 mg) in blocking the effects of 25 mg of
### Chronic Dosage Attitude Questionnaire

**Name**

**No.**

**Drug**

**Study**

**Date**

**ANSWER ALL QUESTIONS ACCORDING TO HOW THIS DRUG IS AFFECTING PATIENT TODAY.**

1. Has the patient shown a drug effect today?  
   Yes______  No______

2. Does its effect resemble any of the following drugs? Check one or more.
   a. Dope (heroin)
   b. Barbiturate (goofball)
   c. Cocaine
   d. Amphetamines (speed, benny, Methedrine)
   e. Marihuana (pot)
   f. LSD
   g. Thorazine
   h. Miltown and Librium

3. Does the patient like its effects? (Check one)
   a. Dislike
   b. Don't care one way or the other
   c. Slightly
   d. Moderately
   e. A lot

4. Is the patient hooked?
   Yes______  No______

5. Have you observed any of the following signs in the patient today?
   a. Relaxed
   b. Tired
   c. Anxious
   d. Nervous
   e. Drunk
   f. Depressed
   g. Disheveled
   h. Unfriendly
   i. Primping
   j. Vomiting
   k. Soapboxing or rapping
   l. Stays to himself
   m. Driving
   n. Coasting
   o. Nodding
   p. Sleepy
   q. Scratching
   r. Uncooperative
   s. Rides the bed
   t. Complaining
   u. Can't sleep
   v. Irritable
   w. Moody
   x. Stays close to ward
   y. Room disorderly

6. Is the patient kicking?
   Yes______  No______

7. How do you think the patient feels?
   a. Very good
   b. Good
   c. Average
   d. Slightly bad
   e. Moderately bad
   f. Bad
   g. Very bad

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Fig 1.—Chronic dosage attitude questionnaire (aide's rating).
ANSWER ALL QUESTIONS ACCORDING TO HOW THIS DRUG IS AFFECTING YOU TODAY.

1. Have you felt a drug effect during the last 24 hours? Yes______ No______

2. Does its effects resemble any of the following drugs? Check one or more
   a. Dope (heroin)  
   b. Barbiturate (goofball) or alcohol  
   c. Cocaine  
   d. Amphetamines (speed, benny, Methedrine)  
   e. Marijuana (pot)  
   f. LSD  
   g. Thorazine  
   h. Miltown and Librium

3. Do you like the effects? Check one
   a. Dislike  
   b. Don’t care one way or the other  
   c. Slightly  
   d. Moderately  
   e. A lot

4. Are you hooked? Yes______ No______

5. Have you had any of the following feelings or symptoms during the last 24 hours? Check the ones you have had.
   a. Relaxed  
   b. Tired  
   c. Anxious  
   d. Nervous  
   e. Drunk  
   f. Pins and needles  
   g. Rush or flush  
   h. Cold or chills  
   i. Joint, bone, muscle or back pains  
   j. Soapboxing or rapping  
   k. Nausea or vomiting  
   l. Feel hot or cold
   m. Driving  
   n. Coasting  
   o. Nodding  
   p. Sleepy  
   q. Skin itchy  
   r. Stomach cramps  
   s. Diarrhea  
   t. Gooseflesh  
   u. Can’t sleep  
   v. Irritable  
   w. Weak  
   x. Nervous or jumping stomach

6. Are you kicking? Yes______ No______

7. How do you feel?
   a. Very good  
   b. Good  
   c. Average  
   d. Slightly bad  
   e. Moderately bad  
   f. Bad  
   g. Very bad

Fig 2.—Chronic dosage attitude questionnaire (patient’s rating).
Table 1.—Effects of Naltrexone (30 mg orally) on Physiologic Changes and Subjective State*

<table>
<thead>
<tr>
<th></th>
<th>Vehicle</th>
<th>Naltrexone</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic blood pressure</td>
<td>23.4</td>
<td>51.1</td>
<td>27.7</td>
</tr>
<tr>
<td>Diastolic blood pressure</td>
<td>1.6</td>
<td>31.6</td>
<td>30.0**</td>
</tr>
<tr>
<td>Pupillary diameter</td>
<td>2.6</td>
<td>1.0</td>
<td>- 1.6</td>
</tr>
<tr>
<td>Temperature</td>
<td>2.1</td>
<td>1.0</td>
<td>- 1.1**</td>
</tr>
<tr>
<td>Pulse rate</td>
<td>9.6</td>
<td>12.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Respiratory rate</td>
<td>6.2</td>
<td>1.0</td>
<td>- 5.2</td>
</tr>
<tr>
<td>Opiate signs</td>
<td>4.6</td>
<td>3.2</td>
<td>- 1.4</td>
</tr>
<tr>
<td>Opiate symptoms</td>
<td>0.2</td>
<td>2.0</td>
<td>1.8</td>
</tr>
<tr>
<td>Liking—observers</td>
<td>1.2</td>
<td>1.2</td>
<td>0</td>
</tr>
<tr>
<td>Liking—patients</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>LSD†</td>
<td>26.4</td>
<td>27.3</td>
<td>0.9</td>
</tr>
<tr>
<td>MBG†</td>
<td>0</td>
<td>1.2</td>
<td>1.2</td>
</tr>
<tr>
<td>PCAG†</td>
<td>25.6</td>
<td>23.2</td>
<td>2.4</td>
</tr>
</tbody>
</table>

* Each value is the mean, for five subjects, of the sum of the differences between the mean control value and the treatment values or the sum of observations for the first 5 hours after drug administration. The superscripts indicate those differences that were statistically significant at the .05 level.
† LSD is the LSD scale; MBG is the morphine-benzadrine group scale which measures feelings of euphoria and well-being; and PCAG is the pentobarbital-chlorpromazine-alcohol group scale which measures feelings of apathetic sedation.7

Fig 3.—Potency and 95% confidence limits of naltrexone relative to nalorphine in precipitating abstinence in six subjects dependent on 60 mg of morphine daily. Relative potency and confidence limits are expressed as mg naltrexone equivalent to 1 mg of nalorphine.

Fig 4.—Comparison of time-action courses of naloxone and naltrexone in antagonizing pupillary constrictive and subjective changes produced by morphine. Solid dots and horizontal lines indicate effects of 25 mg/70 kg of morphine. Triangles indicate effects of naloxone (1 mg) administered with morphine, and 3, 6, and 12 hours before. Crosses indicate alterations in morphine effect produced by naltrexone (0.5 mg), administered with or 3, 6, or 12 hours before morphine. Each point represents mean of sum of responses or differences between responses obtained during first five hours after administration of morphine.
differences

Fig 5.—Effects of orally administered naltrexone (15 mg) on response to 30 mg of morphine administered subcutaneously. Naltrexone was administered 6, 12, 18 and 24 hours before morphine. Open circles on ordinate indicate effects of 30 mg; closed circles, of 15 mg of morphine. Each point represents mean of sum of scores or differences obtained for first five hours after administration of morphine in five subjects.

Table 2.—Effects of Chronically Administered Naltrexone (15 mg Twice a Day Orally) on Subcutaneously Administered Morphine*

<table>
<thead>
<tr>
<th>Dose of Morphine (mg)</th>
<th>Control 15</th>
<th>Control 30</th>
<th>Control 50</th>
<th>Control 100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feel effect—patients</td>
<td>2.4</td>
<td>4.9</td>
<td>0.4</td>
<td>0.7</td>
</tr>
<tr>
<td>Feel effect—observers</td>
<td>5.9</td>
<td>5.7</td>
<td>5.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Identification—patients</td>
<td>1.3</td>
<td>3.5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Identification—observers</td>
<td>5.6</td>
<td>5.7</td>
<td>5.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Symptoms</td>
<td>2.6</td>
<td>19.6</td>
<td>0.3</td>
<td>0.7</td>
</tr>
<tr>
<td>Signs</td>
<td>12.7</td>
<td>20.4</td>
<td>15.7</td>
<td>11.4</td>
</tr>
<tr>
<td>Liking—patients</td>
<td>2.5</td>
<td>9.7</td>
<td>0</td>
<td>0.7</td>
</tr>
<tr>
<td>Liking—observers</td>
<td>6.6</td>
<td>11.6</td>
<td>7.3</td>
<td>4.9</td>
</tr>
<tr>
<td>MBG scale</td>
<td>4.3</td>
<td>14.0</td>
<td>2.9</td>
<td>2.6</td>
</tr>
<tr>
<td>Pupils</td>
<td>8.6</td>
<td>9.8</td>
<td>1.9</td>
<td>4.2</td>
</tr>
</tbody>
</table>

* Each value represents the mean, for six subjects, of the sum of responses for the first five hours after the administration of morphine for subjective responses. For pupils the mean is for the sum of the differences between the mean control value and the observations for the five-hour period following the administration of morphine.

morphine. These dose levels were adjudged to be equipotent on the basis of their ability to precipitate abstinence. In subjects dependent on 240 mg of morphine, naloxone was seven times as potent as nalorphine. Recent estimates of naloxone's potency relative to nalorphine in subjects dependent on 60 mg of morphine indicate that it is ten times as potent as nalorphine; thus, naloxone would be estimated to be 0.6 times as potent as naltrexone. As can be seen, the degree of blockade produced by naltrexone was greater than that of naloxone at all times and the half life of naltrexone blockade was at least twice that of naloxone.

The blockade produced by a single 15-mg oral dose of naltrexone is evident six hours after administration, becomes maximal by 12 hours, and persists for over 24 hours (Fig 5).

Blocking Action of 15 and 25 mg of Naltrexone Administered Chronically.—As can be seen from Table 2, by all means the effects of 100 mg of morphine in subjects receiving naltrexone, 15 mg twice a day orally, were less than those of 15 mg of morphine in these subjects prior to receiving naltrexone. Observers and subjects were not able to differentiate 50 and 100 mg of morphine in patients receiving naltrexone; however, the effect of these doses was distinguishable on pupils. Similar observations were made in subjects receiving 50 mg of naltrexone daily. The pupillary data suggest that 15 mg of naltrexone administered twice daily attenuates the effects of morphine by a factor of 20. Fig 6 illustrates the effects of chronically administered morphine (240 mg/day) in patients receiving naltrexone (30 and 50 mg a day orally) as assessed by the modified chronic-dose questionnaire. Only one subject identified his medication as a narcotic and then only on two occasions. Six of the patients did not recognize or identify effects of the medication, while the other three on various occasions identified their medication as a barbiturate, amphetamine, chlorpromazine, or a minor tranquilizer (meprobamate or chloralhydrate). On some days these patients made several different identifications. In contrast, the observers commonly identified the drug as a narcotic even through the third day of withdrawal. Whereas the observers thought the patients liked the medication and that it made the patients feel good, the patients reported a mild aversion toward morphine.

At least a partial explanation of this disparity was due to the fact that some patients experienced mild abstinence symptoms shortly following the ingestion of naltrexone and thought they were "kicking." When morphine was withdrawn, about 50% of the patients recognized that they were abstinent. Although the observers thought all patients were "hooked" and abstinent when morphine was withdrawn, they did not recognize that the patients were kicking until the third day of abstinence. Although patients reported that they felt slightly to moderately bad when they were withdrawn, they did not appear sick.

Figure 7 illustrates the intensity and time course of abstinence in patients dependent on 240 mg/day of morphine who had been treated with naltrexone and cyclazocine, as well as a group of untreated patients. As can be seen, both the 30 and 50 mg daily doses of naltrexone markedly attenuated the degree of abstinence and dependence. The
30-mg dose level was less efficacious than the cyclazocine (2 mg twice daily); whereas, 50 mg of naltrexone produced a comparable degree of blockade.

**Comment**

Naltrexone is a potent narcotic antagonist. In man it appears to be 17 times more potent than nalphorine, which would make it approximately twice as potent as naloxone. These findings agree well with those reported by Blumberg et al.\(^{10,11}\) in rats, mice and rabbits. In the morphine-dependent dog, naltrexone is 2.5 (1.8 to 3.8) times more potent than naloxone in precipitating abstinence. Further, its duration of action is appreciably longer than that of naloxone in man. Blumberg and Dayton\(^{11}\) reported that naltrexone had a slightly longer duration of action than naloxone in rodents. The fact that the methycyclopropyl substitution on the nitrogen markedly enhances the duration of antagonistic action of this oxymophore antagonist is similar to the observations made with the similarly substituted benzomorphan cyclazocine,\(^{2}\) suggesting that the congeners with the N-methycyclopropyl moiety are metabolized or distributed quite differently in man than they are in rodents and the dog.\(^{11}\) Finally, naltrexone is effective orally in man as an antagonist in modest dose levels (30 to 50 mg/day). Much larger doses of naloxone (up to 3,000 mg/day) are required to produce a comparable level of blockade.\(^{6}\) Indeed, 50 mg of naltrexone a day orally produces a level of antagonism in preventing the development of physical dependence on morphine in man that is comparable to that produced by 4 mg orally a day of cyclazocine.\(^{2}\)

If naltrexone has agonistic activity of either the nalorphine type or morphine type, they are minimal. In dose levels that are adequate for blockade, patients have not reported subjective changes that are different than those seen under placebo conditions. On the other hand, 30 mg orally of naltrexone produced a significant increase in diastolic blood pressure and perhaps some pupillary constriction.

Blumberg and Dayton\(^{11}\) have reported that naltrexone has liminal analgesic action in the rat, but not the mouse, using the phenylquinone writhing test. We have not been able to detect significant agonistic actions of naltrexone in the chronic spinal dog and if they are present, they are highly variable. As indicated, only one patient who received 70 mg of naltrexone subcutaneously exhibited a syndrome which resembled in any way the type of psychotomimetic and dysphoric reactions seen with cyclazocine and nalorphine. It is within the realm of possibility that naltrexone can be partially metabolized to an active compound by some species and individuals.

In some patients, the administration of naltrexone, particularly large doses, evoked reports of yawning and stretching. It is not known whether these signs and re-
ports are meaningful actions of naltrexone or are signs of precipitated protracted abstinence.

No change in signs or symptoms was seen when naltrexone was discontinued following its chronic administration at either the 30 or 50 mg daily dose level. When patients were stabilized on both naltrexone and morphine, the patients indicated an unpleasant state to which they expressed a slight aversion. This observation demonstrates that the chronic administration of naltrexone effectively antagonizes the euphorogenic effects of morphine. Two factors may contribute to the patients' negative reaction to the administration of both naltrexone and morphine chronically: (1) When subjects were stabilized on morphine, the ingestion of naltrexone would precipitate mild signs and symptoms of abstinence which would become manifest within 15 to 30 minutes and would subside over the following hour. (2) The fact that the patients did not experience euphoria with the administration of morphine was a disappointment to them.

It would appear that a single daily dose of naltrexone does not provide quite the same sustained level of blockade that is attained with cyclazocine; however, this probably would be of little clinical significance since it is unlikely that patients would wish or be able to use the quantity of narcotics chronically on the street that were employed in this study. Further, the lack of agonistic effects of naltrexone may be in most treatment conditions more than an offsetting advantage. Because of its potency and longer duration of action and oral effectiveness, naltrexone has definite advantages over naloxone in the treatment of heroin dependence.

A preliminary report of these data was presented at the 74th annual meeting of the American Society for Clinical Pharmacology and Therapeutics, New Orleans, March 23, 1973."