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Self-Administration of Nalbuphine, Butorphanol and Pentazocine by Morphine Post-Addict Rats[1]

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STEINFELS, G. F., G. A. YOUNG AND N. KHAZAN. *Self-administration of nalbuphine, butorphanol and pentazocine by morphine post-addict rats.* PHARMAC. BIOCHEM. BEHAV. **16**(1)167–171, 1982.—The purpose of the study was to define possible self-administration of nalbuphine, butorphanol and pentazocine by morphine post-addict rats. Rats were prepared with permanent EEG and EMG electrodes and indwelling IV cannulae, made tolerant to and physically dependent on morphine, then trained to lever press for morphine IV self-injections on a fixed ratio (FR) 20 schedule of reinforcement. Rats were then spontaneously withdrawn from morphine. When these morphine post-addict rats were returned to the experimental cages three to four weeks later, they were found to reestablish self-administration of morphine as well as to establish self-administration of nalbuphine, butorphanol and pentazocine. Suppression of REM sleep for at least 30 min was apparent following self-injections of these agents. After the stabilization of self-injection patterns, withdrawal from morphine and pentazocine was found to be associated with intense abstinence symptoms. However, withdrawal from nalbuphine and butorphanol was not. It can be concluded that while drug-seeking behavior for the above narcotics in morphine post-addict rats was analogous as measured by self-administration, nalbuphine and butorphanol appeared to produce lower levels of physical dependence.

Morphine Nalbuphine Butorphanol Pentazocine Self-administration Post-addict rats Physical dependence

THE therapeutic efficacy of the narcotic drugs in the treatment of pain has been found to be unsurpassed by drugs from other pharmacological classes. While this effect has been utilized for centuries, the euphoric and other psychological effects of narcotics have made them candidates for abuse. This has prompted scientists to search for compounds that possess similar therapeutic efficacies to that of a narcotic agent such as morphine but devoid of abuse potential.

One general class of compounds that has resulted from this intensive search is the mixed agonist-antagonist analgesics. Three of these compounds, pentazocine, nalbuphine and butorphanol are currently available for therapeutic use as potent analgesics. Original clinical studies demonstrated that these three compounds produce significant analgesia [3, 8, 10, 11]. Pentazocine was reported to possess a lower abuse potential than that of morphine [11] and nalbuphine to possess a low abuse potential similar to that of pentazocine [10]. It has been further suggested that the dependence liability of butorphanol may be lower than that of most other mixed agonist-antagonist narcotics [3,8].

Moreover, clinical studies have demonstrated that pentazocine abuse is more predominant in humans with histories of narcotic abuse [1, 2, 19]. Similarly, monkeys with a history of codeine self-administration self-administered greater amounts of several opiates and opioids than monkeys with a history of cocaine self-administration [9]. It was also demonstrated that morphine post-addict rats relapsed to the self-administration of morphine [7, 18, 23, 27]. Therefore, post-addict rats with a history of morphine self-administration were used in the present study to assess the abuse potentials of nalbuphine, butorphanol and pentazocine.

METHOD

Female Sprague-Dawley rats (250–300 g) were used. For drug injections, a chronic silicone rubber cannula was implanted under ketamine anesthesia (100–150 mg/kg, IP) into the right external jugular vein [21,22]. For ipsilateral bipolar

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electroencephalographic (EEG) recordings, stainless steel screws were implanted over the frontal (2 mm anterior and 2 mm lateral to bregma) and parietal (3 mm posterior and 2 mm lateral to bregma) cortices. An additional screw was placed 6 mm posterior and 2 mm lateral to bregma and served as the indifferent electrode. For electromyographic (EMG) recordings, stainless steel wires were inserted into the temporalis muscles. Electrodes were soldered to a miniature Continental connector which was attached to the skull with dental acrylate and Eastman Kodak 910FS adhesive [12,15].

Throughout the study each rat was maintained in an individual cage that was equipped with a response lever, a swivel cabel connector for EEG and EMG recordings, and a feed-through cannula for drug administration. Lighting conditions consisted of a timer-regulated period of darkness from 10 p.m. to 6 a.m. EEG and EMG activities were recorded continuously on a Grass Model 7D polygraph. The EEG was filtered to pass frequencies between 1 and 35 Hz. Lever presses and drug injections were recorded on an Esterline-Angus event recorder as well as on the event marker channels of the Grass polygraph.

The drugs used were: morphine sulfate, pentazocine lactate, nalbuphine hydrochloride and butorphanol tartrate. All drugs were dissolved in isotonic saline (0.9%), and a 0.1 ml volume was administered by a Harvard infusion pump over six sec for intravenous drug administration. Doses are expressed as the salt.

Rats were first made tolerant to and physically dependent on morphine by a series of automatic intravenous injections delivered every hour. On the first day, rats received a dose of 1.25 mg/kg/hr of morphine. The dose was then increased to 2.5, 5.0, 10.0 and 20.0 mg/kg/hr on successive days. Each rat was then trained to lever press in order to receive morphine on a fixed ratio (FR) schedule of reinforcement. An FR of one lever press was initially required per injection, and the FR was gradually increased to 20 over a period of several days. After the rats had stabilized self-adminstration patterns for morphine (10 mg/kg/inj), they continued to self-administer morphine for two weeks.

These morphine-addict rats were then removed from their experimental cages and placed in individual plastic home cages for the next three to four weeks. Previous studies have shown that overt signs of morphine withdrawal have dissipated in less than three weeks [26,28]. The rats were then divided into five groups of four rats each. During the initial morphine self-administration the mean daily morphine intake of these five groups of rats were not significantly different ($p<0.05$). The five groups of morphine post-addict rats were placed back into their experimental cages for relapse to the self-administration of morphine and for possible establishment of self-administration of the three mixed agonist-antagonist narcotics studied. The dose used per self-injection of nalbuphine, butorphanol or pentazocine was that which resulted in periodic single and occasionally double self-injections, similar to the self-administration pattern reported to occur in morphine-addict rats self-administering 10 mg/kg/inj of morphine [14, 15, 17]. Thus, the first group of morphine post-addict rats was given access to morphine (10 mg/kg/inj); the second group, pentazocine (1 mg/kg/inj); the third group, nalbuphine (5 mg/kg/inj) and the fourth group, butorphanol (0.5 mg/kg/inj). A control group of four morphine post-addict rats was given access to saline self-administration (0.1 ml/inj). In all cases, rats had continuous access to the drug solution for self-administration. The EEG was continuously recorded along with the daily drug intake

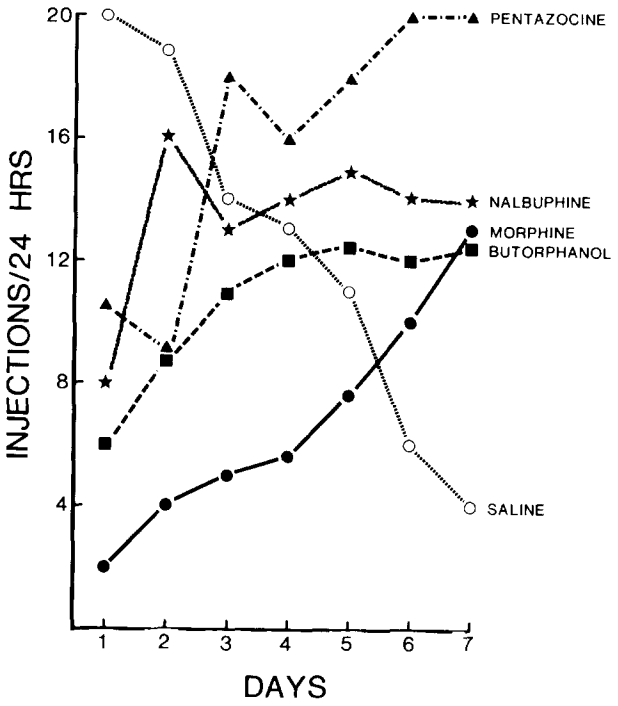

FIG. 1. Mean daily numbers of self-injections are shown over seven days of self-administration of morphine, pentazocine, butorphanol, nalbuphine and saline in morphine post-addict rats. Each group was comprised of four rats.

for seven days. On the eighth day, saline was substituted for each of the narcotics.

Studies of rapid eye movement (REM) sleep times and distributions during self-maintained dependence on narcotics in the rat have delineated additional similarites and differences in the general pharmacodynamic profiles among several narcotics [17, 20, 24]. Moreover, the degree of REM sleep suppression has been demonstrated to be a reliable measure of severity of withdrawal from narcotics [26,28]. Thus, REM sleep times and distribution were also assessed in the present study.

RESULTS

The mean daily number of morphine self-injections for all 20 rats used during the initial morphine self-administration period was 13.6. In the group of morphine post-addict rats relapsing to morphine self-administration, self-injections gradually increased to an average of 12.9 self-injections per 24 hr by the seventh day (Fig. 1). During self-administration of pentazocine, nalbuphine and butorphanol in morphine post-addict rats the mean daily number of self-injections similarly increased over the seven days studied. In contrast, a pattern of extinction emerged when morphine post-addict rats were allowed to self-administer saline. The mean number of saline self-injections was very high on the first day, then steadily declined for the following six days.

During subsequent saline substitution for each narcotic on day 8, mean daily numbers of saline self-injections significantly increased over narcotic self-administration values to 34.1, 50.0, 40.7 and 38.6 saline self-injections for the mor-

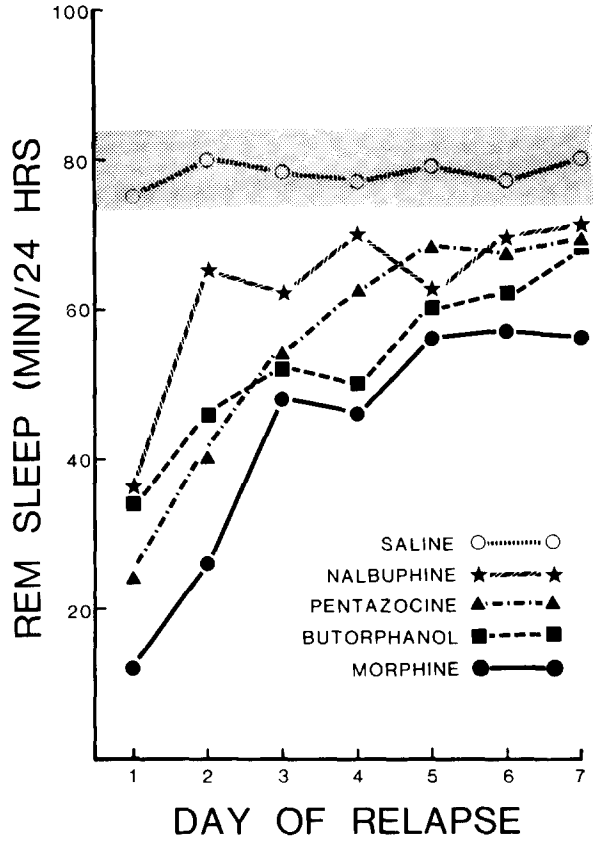

FIG. 2. Mean REM sleep times in min per 24 hr are shown over seven days of self-administration of morphine, pentazocine, butorphanol, nalbuphine and saline in morphine post-addict rats. Each group was comprised of four rats. The shaded area represents the mean±SEM for five consecutive days prior to any narcotic exposure.

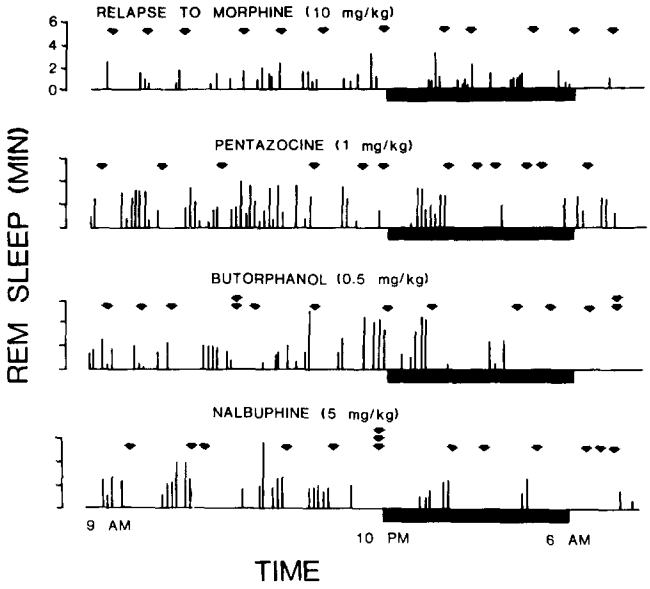

FIG. 3. REM sleep distributions for individual rats during the seventh day of self-administration of morphine, pentazocine, nalbuphine and butorphanol in morphine post-addict rats. Self-injections are indicated by the filled arrows.

phine, pentazocine, nalbuphine and butorphanol groups, respectively.

As shown in Fig. 2, self-administration of morphine, nalbuphine, butorphanol and pentazocine suppressed mean daily REM sleep times during the first two or three days. Thereafter, REM sleep times gradually increased and stabilized at nearly normal values on days 5–7. Upon saline substitution on day 8, mean REM sleep times were significantly suppressed to 20.4 and 30.6 min in morphine and pentazocine rats, but not for nalbuphine (98.0) and butorphanol (92.2).

Further similarities and differences during self-administration of these narcotics emerged following the study of the pattern of distribution of REM sleep episodes in relation to drug self-injections. Such data for individual rats during day 7 of self-administration are shown in Fig. 3. The pattern of morphine self-injections similar to that reported earlier [23] is presented in the top row of Fig. 3. The individual rat in this figure, for example, took single injections of morphine (10 mg/kg/inj) at intervals of about two hr. Furthermore, each morphine self-injection usually suppressed REM sleep episodes for 30 min or more, after which occurrences of REM sleep reappeared and persisted until immediately before subsequent morphine self-injections. Figure 3 also shows that on the seventh day of self-administration of pentazocine, nalbuphine and butorphanol in morphine post-addict rats drug self-injection patterns and distributions of REM sleep episodes were similar to those during relapse to morphine. Single and, occasionally, multiple self-injections were relatively equally spaced, and REM sleep occurrences were usually suppressed following self-injections.

The self-injection pattern of saline and distribution of REM sleep episodes during morphine abstinence (day 8) are shown for an individual rat in the top row of Fig. 4. After the last morphine self-injection, saline self-injections increased in number and peaked within 6 to 8 hr. REM sleep was severely suppressed for 18 to 20 hr. During abstinence from pentazocine, saline self-injections also increased in number and reached a peak at the end of the first day of saline substitution; REM sleep was also suppressed but to a lesser degree than during abstinence from morphine. Following abstinence from nalbuphine and butorphanol, saline self-injections also increased in number. However, in contrast to abstinence from morphine and pentazocine, abstinence from nalbuphine and butorphanol was not associated with similar suppression of REM sleep episodes.

DISCUSSION

Relapse to intravenous morphine self-administration in morphine post-addict rats has been previously reported [7, 18, 23, 27]. In the present study we found that morphine post-addict rats similarly self-administered pentazocine, nalbuphine and butorphanol. In this procedure the continuous access to drug solutions allows rats to define their daily drug intake through lever pressing. Our present findings suggest

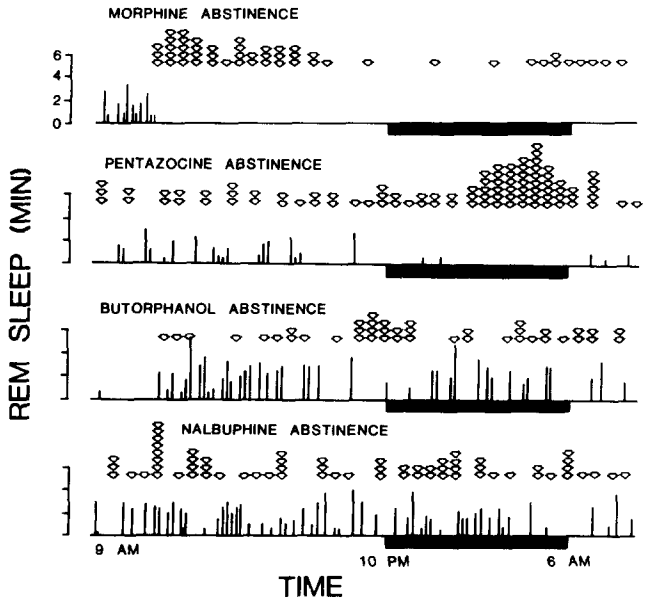

FIG. 4. REM sleep distributions during saline substitutions in individual rats previously self-administering morphine, pentazocine, nalbuphine and butorphanol. Saline self-injections are indicated by the unfilled arrows.

that, in rats with a history of morphine addiction, the abuse potentials of the mixed agonist-antagonists analgesics, pentazocine, nalbuphine and butorphanol, were analogous to that of morphine.

Previous studies have shown that the administration of morphine suppresses REM sleep in the naive rabbit [13], rat [15] and cat [5,6]. In dependent rats each morphine self-injection delayed the onset of REM sleep episodes [15,17]. Since naloxone was found to block this suppressant effect of morphine on REM sleep in the rat, the effect is drug related [4,16]. Self-injections of morphine and of the mixed agonist-antagonist analgesics by morphine post-addict rats produced significant suppression of REM sleep time during the first two or three days of self-administration. Reestablishment of partial tolerance to the REM sleep suppressant effects of morphine, pentazocine, nalbuphine and butorphanol was observed by the gradual increases of daily REM sleep times toward control values. However, REM sleep episodes continued to be suppressed immediately following self-injections of these narcotics.

Following saline substitution for each of the narcotics, the number of self-injections significantly increased and, in the cases of morphine and pentazocine, REM sleep occurrences were severely suppressed. Similar effects of morphine abstinence on lever pressing behavior and REM sleep time have been previously reported [25, 26, 28]. During butorphanol and nalbuphine abstinence, however, REM sleep time was not affected. The degree of REM sleep suppression has been considered to be a measure of severity of withdrawal from narcotics and has been shown to co-vary with frequency of head shakes [26,28]. Thus, one may argue that a considerable degree of physical dependence existed in rats self-administering morphine and pentazocine; on the contrary, a relatively lower degree of physical dependence prevailed with butorphanol and nalbuphine. Therefore, while differences in degree of physical dependence were produced by morphine and pentazocine on the one hand and butorphanol and nalbuphine on the other hand, analogous abuse potentials in rats with a history of morphine self-administration were demonstrated for all four narcotics studied. The data suggest that self-administration studies using morphine post-addict rats may represent an additional experimental tool for the assessment of abuse potentials of psychoactive drugs.

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