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ASSESSMENT OF NARCOTIC ANTAGONISTS IN THE TREATMENT OF OPIOID DEPENDENCE[1]

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Narcotic antagonists are compounds that selectively block the euphoric and physiologic effects of morphine-like drugs (opioids), such as heroin and methadone. The narcotic antagonists used for treating addiction, cyclazocine and naltrexone, are not themselves addicting and have no abuse potential or blackmarket value. When administered to an individual who is physically dependent on opioids (i.e. addicted), a narcotic antagonist will precipitate the familiar opioid abstinence syndrome. However, if one who is no longer physically dependent on opioids takes a narcotic antagonist, he will be protected against readdiction; even if heroin is used, he will experience no euphoria and will not develop opioid dependence. Having this protection, the person can return to his community, where rehabilitation can take place, despite the endemic presence of heroin or other opioids.

The potential usefulness of narcotic antagonists in helping former opioid addicts remain abstinent was first suggested by Martin et al (1) after studying the clinical pharmacology of cyclazocine. These investigators found that cyclazocine provided blockade of opioid effects for as long as 24 hr following a single oral dose and prevented the development of physical dependence from repeated injections of morphine. They suggested that maintaining a detoxified opioid addict on cyclazocine would control the

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pharmacologic actions responsible for addiction and provide an opportunity for extinction of conditioned physical dependence and drug-seeking behavior (2, 3).

In addition to its opioid-blocking action, cyclazocine produces analgesia and dysphoric side effects. The latter are characterized by sedation, visual distortions, and racing thoughts. Tolerance develops to these side effects but not to the narcotic-blocking action of cyclazocine. Abrupt discontinuation of cyclazocine after chronic administration results in characteristic withdrawal effects which include rhinorrhea, lacrimation, anorexia, and "shocks" in the neck and back, but unlike opioid withdrawal, these symptoms are not associated with drug-seeking behavior.

Early clinical trials (4–6) revealed that cyclazocine's dysphoric side effects limited its acceptability to patients. These side effects could be minimized, however, by gradual increments in daily dosages over a period of approximately 21 days, although some patients, particularly those with a history of schizophrenia, experienced the dysphoric effects anyway. Stemming from a report by Jasinski et al (7) that cyclazocine side effects were blocked by the short-acting "pure" antagonist, naloxone, Resnick et al (8) reported success in using naloxone to reduce the cyclazocine induction period from 21 to 4 days.

Cyclazocine was not acceptable for large-scale clinical trials because of its side effects. Continued interest in the potential role of narcotic antagonists in treating opioid dependence led to the synthesis of naltrexone (9) with the expectation that it would be a "pure" antagonist like naloxone but would have cyclazocine's duration of action. Initial trials in humans revealed that naltrexone has few side effects and that a single dose provides effective blockade to opiates for up to 72 hr (10, 11), such that a three-dose per week schedule would be sufficient to maintain a fairly high level of opioid blockade. The relative absence of unpleasant side effects obviates the need for a naltrexone induction period.

In response to a 1971 mandate from Congress to expand research on antagonist drugs for the treatment of heroin addiction, naltrexone was selected over other available compounds for extensive clinical testing. The responsibility and cost of this entire effort was assumed by the federal government so that naltrexone could be approved by the Food and Drug Administration for general use. Seventeen clinical programs were funded to study naltrexone using a variety of protocols. A progress report of these studies, which includes 776 patients who received naltrexone and 107 placebo controls, is contained in a NIDA Research Monograph (12). The results of these studies and others (13–15) show no evidence of toxicity from naltrexone or teratogenic effects; fertility was unaffected by naltrexone as well.

THEORETICAL BASIS

The theoretical basis for the use of narcotic antagonists in treating opiate addiction was developed by Wikler (2, 3), who postulated that conditioning factors are responsible for the relapse to heroin use in detoxified addicts. He proposed a two-factor learning theory of relapsing behavior, based upon the principles of operant (instrumental) and Pavlovian conditioning. Wikler suggested that the euphoria and relief from physical and emotional distress provided by an injection of heroin are powerful "reinforcers" that establish and maintain the opiate-using behavior through the process of operant conditioning. Pavlovian conditioning comes into play through repeated pairings between stimuli in the addict's everyday environment and withdrawal symptoms that appear in association with daily heroin use. For example, a former addict who is opiate-free for months or even years often experiences a renewed craving for heroin and physical withdrawal symptoms upon returning to an environment or meeting up with a friend that was previously associated with his opiate use. This "conditioned abstinence" response can lead to reinitiation of opiate use and eventual readdiction. According to this model, when heroin is "robbed" of its reinforcing properties by the blocking action of an antagonist, drug-seeking behavior will eventually cease as a result of extinction of previously conditioned responses. These conditioning factors partially explain why treatments without pharmacologic support for compulsive heroin use generally have not been successful; as Wikler states, there are forces operating of which neither the therapist nor patient may be aware.

PATIENT SELECTION

From studies with cyclazocine, it became evident that antagonist treatment was not efficacious for all detoxified opiate addicts. Many patients discontinued cyclazocine early in treatment and became readdicted. Clinical impressions suggested that cyclazocine was beneficial to certain "types" of addicts. Resnick et al (16) presented a typological classification of opiate addicts based upon patients' self-ratings of the role opiates played in their daily lives. Two major groups were identified and found to have a differential response to cyclazocine treatment. One group appeared to use opiates as a form of "self-medication" to relieve symptoms of chronic emotional problems or stress. Heroin reportedly decreased their inhibitions, anxieties, and painful affects and they perceived themselves as feeling and functioning better with opiates in their systems than during periods when they were opiate-free. Such patients usually discontinued cyclazocine treatment prematurely. By contrast, patients in the other group experienced no symptoms

of serious affective disorders or impaired capacity to function in the absence of opiates and they tended to remain in cyclazocine treatment for relatively long periods of time. Opiate use for these individuals seemed largely attributable to environmental influences and conditioning factors. This study also revealed that patients involved in a stable relationship with a nonaddict mate were more likely to sustain cyclazocine and remain opiate-free than patients who lacked such a relationship.

In a subsequent study, Resnick et al (8) found that a patient's choice of cyclazocine over methadone maintenance, was as predictive of treatment outcome as selection criteria derived from the typological classification mentioned above. It was suggested that a patient's choice of methadone over cyclazocine reflected an awareness of his own need for opiates to feel well and function normally.

The contribution of psychosocial and drug history variables to treatment outcome with naltrexone has been examined in several clinics (17–21). The results of these studies indicate that "success" in naltrexone treatment, defined by opiate use or retention time criteria, is more likely in patients who are (*a*) involved in a meaningful relationship with a nonaddict mate; (*b*) employed full time or attending school; and (*c*) living with family members rather than with friends or alone. Additionally, patients who report longer histories of addiction, longer opiate-free periods between recurrent cycles of addiction, and less dependence on opiates just prior to detoxification, are more likely to be opiate-free one year from the start of naltrexone treatment (22).

Although it was hoped that identification of reliable predictor variables would enable clinicians to select for antagonist treatment those patients most likely to benefit from it, none of the variables isolated thus far appear powerful enough to be clinically useful for actually selecting patients. Even if such predictor variables were found, the patient's own choice of treatment modality should be the overriding consideration. When the nature of each treatment alternative is explained fully, any patient who chooses antagonists treatment should be given the opportunity to try it, since other modalities can later be used if needed.

TREATMENT OUTCOME

In early clinical trials with cyclazocine, almost all patients relapsed to opiate use within a few months. Retention rates improved, however, when investigators began to use cyclazocine within comprehensive rehabilitation programs that included psychotherapy, counseling, and various ancillary services. Reports on treatment outcome from these programs indicate that

between 30% and 60% of patients inducted onto cyclazocine were opiate-free at the time of follow-up, which ranged from 6 to 27 months (8, 23–28). The length of time patients stayed on cyclazocine varied among the different programs and no control groups were used. Chappel et al (29) attempted to assess whether cyclazocine produced any benefits beyond those that would have resulted purely from contacts with the clinical staff. Within the context of an abstinence-aftercare program, these investigators compared patients who received cyclazocine with those who elected not to take it. At twenty months after admission to the program, 33% of those who had received cyclazocine were still in abstinence-aftercare treatment, as compared to 8.5% of those who had not received cyclazocine.

In the summary of seventeen NIDA-funded studies of naltrexone (30), retention data for 883 patients showed that drop-out rates were highest during the first two months of treatment and then leveled off. Approximately 65% discontinued naltrexone within the first three months, but no outcome information was obtained. Resnick & Washton (22) reported follow-up data for 267 patients who had received naltrexone for varying periods of time before voluntarily discontinuing it. The results for patients who had been off naltrexone for at least six months at the time of follow-up revealed a clear-cut relationship between time on naltrexone and opiate-free status: 31% of those who had stayed on naltrexone for at least three months were known to be opiate-free at follow-up, as contrasted with only 2% of those who had taken naltrexone for less than three months. In a subgroup of 81 consecutive admissions for naltrexone, 33% were found to be opiate-free one year following their first naltrexone dose while the remaining 67% were readdicted. The opiate-free patients had taken naltrexone for a significantly longer period of time than those who were readdicted. Similarly, Greenstein et al (31) and Lewis et al (20) have reported that increased time on naltrexone contributes favorably to treatment outcome.

IMPLICATIONS FOR RESEARCH

The possible interaction of both agonist and antagonist compounds with the recently discovered endogenous opioids (32, 33) should be carefully evaluated. Comparisons of the effects of antagonists in ex-addicts with those who have never been addicted to opioids may provide valuable insight into the biological functions of the endogenous opioids, the physiological substrates of addiction and, perhaps, the clinical indications for opioid and antagonist maintenance (34).

Concerning the clinical efficacy of opiate antagonists there are at least three major areas that need further investigation. These are (*a*) detoxifica-

tion from opiates; (*b*) the development of new antagonist compounds; and (*c*) the treatment milieu in which antagonists are used.

Detoxification

Facilitation of the opioid detoxification process calls for concentrated research efforts, since the ineffectiveness of current methods limits the applicability of postdetoxification treatment. High dropout rates characterize the final stages of detoxification and subsequent opioid-free period required before an antagonist can be administered. For example, 42% of the 1536 patients in the NIDA-funded naltrexone studies (30) failed to receive even a single dose of medication, presumably because of inability to detoxify completely. In our treatment facility, 35% of 191 consecutive applicants for naltrexone were unable to complete the prerequisite detoxification from opiates (35).

In an effort to compress the detoxification period and minimize dropout rates, Resnick et al (36) explored naloxone-precipitated withdrawal as a means for facilitating induction onto naltrexone. It was hoped that by precipitating withdrawal directly, the duration of the abstinence syndrome could be reduced significantly, without increasing its severity to unacceptable levels. As it turned out, patients who participated in this study found the procedure preferable to the more gradual detoxification procedures routinely employed. Patients dependent on low doses of methadone were able to start naltrexone within 48 hr. The findings that naloxone-precipitated withdrawal poses no significant risk to patient well-being has also been reported by Blachly et al (37) and Kurland & McCabe (38), but its usefulness as a routine detoxification procedure is limtited because inpatient care is required. Washton, Resnick & Rawson (39) showed facilitation of opiate detoxification in an outpatient setting when abstinence symptoms were treated with the nonopiate drug, clonidine hydrochloride. Further research is needed to develop methods that minimize the stress of opioid detoxification without requiring hospitalization so that more patients who want to try an antagonist can be treated by this modality.

New Antagonists

It is generally believed that antagonists would be more efficacious if their duration of action were extended. The desirability of a longer-acting antagonist became evident in studies with cyclazocine; it had to be taken daily at a clinic or dispensed for self-administration, since its opioid blocking action was limited to 24 hr. Daily clinic visits sometimes imposed a hardship on patients, particularly those who were employed or traveled long distances to get to the clinic. Take-home doses, on the other hand, often compromised

compliance; patients were tempted to skip one day's medication to get "high" on heroin, using the rationalization that it would be "just for that one time." Instead of being an isolated instance of opiate use, however, that "one time" often initiated increased craving for opiates and eventual readdiction.

The problem of noncompliance was solved, in some cases, by having a reliable family member be responsible for administering take-home medication on those days when the patient could not come to the clinic (8). However, this approach is impractical for implementation on a large scale and current FDA regulations do not permit antagonist medication to be taken home.

Another way to deal with noncompliance is to extend the duration of an antagonist's narcotic-blocking action, thereby eliminating the need for a patient's daily cooperation in taking medication. In one such attempt (40) the opiate-blocking action of cyclazocine was extended to 72 hr by means of gradual dosage increments, but patient acceptability was reduced by the resultant dysphoric side effects. Although naltrexone provides 72-hr blockade without dysphoric side effects, it is thought that an even longer-acting preparation would be more efficacious. Current animal research (41, 42) is exploring depot implants of naltrexone that extend opioid-blocking action to as long as 60 days, but these preparations are not yet ready for use in humans.

While the concept of a depot antagonist is appealing, it is unrealistic to think that it will solve rather than postpone the problem of noncompliance. Moreover, before depot preparations can be used effectively in treatment, the question of which patients should receive it and at what stage in their treatment must be considered. A depot preparation may be contraindicated for patients just starting treatment or for those who need the structure provided by frequent clinic visits and the opportunity to be engaged in a therapeutic relationship. On the other hand, patients who have already made significant progress toward rehabilitation may be especially good candidates for a depot implant, such as those who detoxify from long-term methadone maintenance or leave a drug-free therapeutic community.

In addition to continued work on depot preparations, other antagonist compounds should be explored. It often has been assumed that a desirable characteristic for a clinically useful antagonist is the lack of agonist activity, but this assumption has not been tested experimentally. Clinical experience with cyclazocine, a mixed agonist/antagonist, and naltrexone, a pure antagonist, suggests that each of these compounds has unique advantages. Unlike cyclazocine, naltrexone is devoid of unpleasant side effects, thus obviating the need for an induction period and making it more acceptable to patients,

but because it is also devoid of withdrawal effects, it can be discontinued abruptly without discomfort before the patient has developed internalized controls over impulsive opiate use. Cyclazocine can be discontinued without discomfort, but only by gradual dose reductions over a number of days. Because of the necessity to make prior arrangements for cyclazocine dosage decrements so as to avoid unpleasant withdrawal effects, patients are more likely to discuss with the clinic staff their plans to stop the medication. These discussions provide patients with an opportunity to explore their reasons for wanting to stop medication and to carefully evaluate whether or not it is in their best interest to do so at that particular stage of treatment.

Based on the foregoing considerations, an antagonist compound that is without unpleasant side effects but does produce some withdrawal effects when discontinued abruptly, might be more efficacious than those currently available. Preliminary findings (43) suggest that oxilorphan may be one such compound but further research is needed to assess its clinical efficacy. Another possibility is the combined use of cyclazocine and naltrexone. For instance, naltrexone could be given initially in order to establish immediate opioid blockade followed by the gradual introduction of cyclazocine. After a full maintenance dose of cyclazocine is reached, the naltrexone could be withdrawn and the patient would remain on cyclazocine alone. Introduced in this way, cyclazocine may prove to be more acceptable since the previously administered naltrexone would be expected to block cyclazocine's dysphoric side effects.

Treatment Milieu

There is a prevailing view among clinicians that psychotherapeutic intervention plays an important role in the retention and rehabilitation of patients in narcotic antagonist treatment. This view is supported by the observations that (*a*) cyclazocine retention rates improved when patients were seen regularly for individual counseling and (*b*) patients who received naltrexone in conjunction with individual therapy remained in treatment significantly longer than those who received naltrexone alone (44). These observations do not seem surprising in light of the fact that narcotic antagonists change neither the intrapsychic, environmental, or lifestyle problems of which opiate use is symptomatic. Unless these problems are ameliorated, the individuals will be predisposed to terminate treatment and become readdicted. Antagonist medication is only one component of a comprehensive rehabilitation program; the medication, in itself, is not the whole treatment (45).

Since the efficacy of antagonist medication seems to be interrelated with nonpharmacologic variables of treatment, it is unreasonable to conduct

efficacy studies without identifying and controlling for the most important of these other variables. The relative contributions of antagonist medication and individual therapy outcome of treatment needs to be assessed systematically. Information obtained from such studies may provide a rational base for the design of future treatment programs and the allocation of funds.

IMPLICATIONS FOR PREVENTION AND TREATMENT

The pharmacologic actions of antagonists uniquely provide prophylaxis against readdiction, so these compounds are particularly well suited for individuals who have progressed in another modality, such as methadone maintenance or a therapeutic community, but who wish to leave that form of treatment. Patients coming off methadone maintenance should be encouraged to use naltrexone during the postdetoxification period, when protracted abstinence symptoms often lead them to reinitiate opiate use. When naltrexone was introduced into a methadone maintenance program, it generated optimism toward attempts to detoxify and provided a reason for patients to remain in abstinence treatment (46). For residents of a drug-free therapeutic community who wish to return to their home environment, naltrexone treatment may help them continue the process of gaining self-control over opiate use, when the structured life-style and peer support of the therapeutic community are no longer present. Naltrexone can be used prophylactically for all individuals who are likely to reinitiate opiate use after a long period of abstinence. For example, cyclazocine and naltrexone have been used in a work release program with inmates (47) and for previously addicted parolees who are released to the community (48, 49).

In response to spreading heroin addiction, public health policies have ranged from severe legal penalties such as incarceration of the opiate user, to treatments that sanction opioid dependence through methadone maintenance programs or that proscribe the use of any medications, as in therapeutic communities. Narcotic antagonists provide another approach that appears sufficiently efficacious to warrant making them available for use in all addiction treatment programs. Pending the final results of studies on the safety of naltrexone and its subsequent approval by the Food and Drug Administration, there seems at present no valid reasons for excluding naltrexone from any addiction treatment setting.

Although heroin addicts are often perceived in a stereotypic manner, addicted individuals have, in fact, widely different underlying pathologies and life situations. Thus, within any one facility, a variety of modalities should be available so that treatment can be tailored to the individual. No

single treatment approach is best for all patients and moreover, the preferred modality for any one individual may change with the passage of time. Incorporating antagonists into existing programs would provide greater flexibility of treatment: Patients could have the option of moving from one modality to another as their needs dictate, without compromising continuity of care.

When the single modality concept of treatment is dispensed with, more patients will get the kind of help they need. Drug abuse policies that affect the design of treatment programs should be based on these considerations. Unfortunately, current program planning policies often perpetuate the existing polarity among treatment modalities. The wisdom of such policies should be seriously reconsidered.

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