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RAPID COMMUNICATION

Concurrent Agonist-Antagonist Administration for the Analysis and Treatment of Drug Dependence

JED E. ROSE[1] AND EDWARD D. LEVIN

Nicotine Research Laboratory, VA Medical Center, Durham, NC and Department of Psychiatry, Duke University, Durham, NC

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ROSE, J. E. AND E. D. LEVIN. *Concurrent agonist-antagonist administration for the analysis and treatment of drug dependence*. PHARMACOL BIOCHEM BEHAV **41**(1) 219–226, 1992.—Two key strategies for the treatment of drug dependence involve the use of agonists to substitute for the abused drug and the use of antagonists to block the reinforcing actions maintaining drug self-administration. A different strategy for the treatment of drug dependence is outlined, comprising the concurrent administration of an agonist and an antagonist. Concurrent administration of an agonist with an antagonist, in the proper ratio, should produce maximal occupancy of receptors and attenuation of the reinforcing actions of the abused drug. The addict would be relatively "insulated" from the reinforcing effects of the abused drug; at the same time the balance of agonist and antagonist effects is predicted to prevent withdrawal symptoms or intoxication resulting from an under- or over-stimulation of drug receptors. Advantages over the use of agonists alone and antagonists alone, and over mixed agonist-antagonist molecules, are discussed. Application of concurrent agonist-antagonist administration to the analysis of mechanisms underlying nondrug reinforcement and to the treatment of disorders involving receptor disregulation is also described.

Drug dependence Self-administration Addiction Agonist Antagonist Nicotine Opioid Cocaine Reinforcement Behavior Regulation Sustained release

TWO of the main strategies proposed in the treatment of drug dependence involve the use of agonists to substitute for the abused drug, and the use of antagonists to block the reinforcing actions maintaining drug self-administration (20). Thus, methadone, an opioid agonist, is commonly used in the treatment of opiate dependence (e.g., heroin addiction). Likewise, nicotine, a potent agonist at nicotinic cholinergic receptors, is used in the treatment of tobacco dependence (16). Conversely, naltrexone, an opioid receptor antagonist, has also been utilized in the treatment of heroin addiction (17), and mecamylamine, a nicotinic antagonist, has been used to promote smoking cessation (49). While agonist substitution treatment and antagonist treatment each have potential advantages, they have usually been discussed as though they are mutually exclusive. A notable exception is the use of mixed agonist-antagonist drugs, such as buprenorphine, which have received increasing attention in the treatment of opiate and cocaine dependence (19, 21, 24, 26, 31).

However, the concurrent use of a combination of an agonist with an entirely different antagonist, in order to treat drug dependence, may have several advantages in clinical treatment (41,42). These include greater flexibility in titrating agonist and antagonist effects and greater generality of application to different drugs of abuse, as will be discussed below. Agonist-antagonist combinations may also be useful in the analysis of neurotransmitters involved in mediating drug reinforcement. The general thesis is that concurrent administration of an agonist with an antagonist, in the proper ratio, has the advantages of both types of treatment, while minimizing the disadvantages of treatment with agonists or antagonists separately. Agonists and antagonists share one property in common, namely, they both occupy receptors or receptor-coupled effectors critical for the action of the abused drug. The combination treatment should produce maximal attenuation of the reinforcing actions of the abused drug. In addition, many side effects resulting from overstimulation or understimulation of receptors can be diminished by the opposing balance of an agonist with an antagonist. The addict receiving a combination of an agonist and an antagonist would be predicted to be relatively "insulated" from the reinforcing effects of the abused drug; at the same time that individual is predicted to be relatively comfortable, i.e., neither in a state of withdrawal nor intoxication from an under- or overstimulation of drug agonist receptors.

WHAT ARE THE UNIQUE ASPECTS OF CONCURRENT AGONIST-ANTAGONIST ADMINISTRATION?

A great number of studies in pharmacology have coadministered an agonist and an antagonist; in fact, the simple demon-

[1]Requests for reprints should be addressd to Dr. Jed E. Rose, Nicotine Research Laboratory (151-S), VA Medical Center, 508 Fulton St., Durham, NC 27705.

stration that a compound is an antagonist requires coadministration to block the actions of an agonist. However, in the context of treating drug dependency it is counterintuitive to administer both an agonist and an antagonist at the same time as part of the treatment. When antagonists have been administered in the context of drug self-administration, they have usually been administered alone to demonstrate that the agonist is maintaining self-administration behavior by virtue of acting at receptors known to be blocked by the antagonist. It is true that the subject will have both the agonist and antagonist in the system at a given time. However, the typical procedure would require that the subject continue self-administering the drug in order to maintain the agonist/antagonist drug combination in their systems.

In contrast, we are proposing to maintain the agonist/antagonist combination via a route other than the habitual route of drug self-administration. This difference is absolutely crucial, for three reasons. First, if we suppose that a patient is administered an antagonist as part of treatment, but self-administers the drug of abuse by the route and method to which he is accustomed, then at the end of treatment the patient will still be in the habit of self-administering the abused drug on a regular basis. This would predispose the individual to relapse after treatment is terminated, as compared with a treatment program in which abstinence had been maintained for the same length of time. It is necessary to recognize that any effective drug treatment may need to be implemented over a considerable period of time, e.g., several months, in order to have a significant probability of producing sustained success (abstinence) in the long term.

A second problem with the standard paradigm, when viewed from a clinical perspective, is that unless the antagonist dose is sufficiently high to completely block the reinforcing effects of the abused drug, it provides a direct reward for drug self-administration. In fact, the patient may increase self-administration of the abused drug to overcome the effects of the antagonist (36,43). If patients temporarily stop self-administering the abused drug, they may suffer the aversive effects of the antagonist remaining in their systems, unopposed by the agonist. Hence, the patient is implicitly encouraged to continue self-administering the abused drug. In contrast, we are proposing to maintain a comfortable balance of agonist and antagonist in the patient's system even when the patient does not self-administer the abused drug by the habitual method. Ideally, the patient would have abstained from the abused drug and a technique completely unrelated to the usual act of self-administration would be used to deliver the agonist/antagonist combination in a continuous fashion. Occasional "slips," taking the abused drug occasionally, would produce little pleasure due to the blockade caused by the agonist and antagonist in the system. Of course, the presence of the combination would render the patient comfortable and minimize the number of slips during this period, as compared with an antagonist alone treatment (see discussion below). At the end of the period, the patient would have had considerable practice in resisting the abused drug in many situations. Indeed, psychologically patients will have made the subtle but important distinction of viewing themselves as nonusers. Hence, when the treatment is ended, patients should have a much better chance of remaining permanently abstinent than if they must continue to self-administer the drug in order to maintain the agonist-antagonist combination in the system. By delivering the agonist and antagonist with a transdermal skin patch (33,52) or some vehicle other than the usual delivery system employed with the abused drug, it would be possible to maintain the agonist and antagonist in the system continuously, even during the night. To the extent that any transient changes in drug levels provided subtle rewards, it would tend to reinforce the act of patch self-administration, not the act associated with self-administering the abused drug (e.g., self-injection or smoking).

As a third drawback, the standard procedure of administering an antagonist to a subject engaged in self-administration of a drug also fails to maintain a constant ratio of agonist to antagonist concentrations in the system. Because self-injection or inhalation of an abused drug produces rapidly changing blood levels, and the rate of elimination of the abused drug or agonist is generally different from that of the antagonist, any desirable ratio of agonist levels to antagonist levels that might be attained immediately after drug self-administration would soon change to become an undesirable ratio over time. In contrast, by using a continuous delivery system such as a skin patch, it should be possible to adjust the rates of agonist and antagonist infusion to maintain a constant ratio of concentrations in the bloodstream.

Thus, the paradigm used often in research studies to explore the effects of the concurrent presence of agonist and antagonist in the body has little therapeutic potential. In situations where antagonists have been used clinically and agonist administration has been discouraged, there is no programmed concurrent administration of agonist and antagonist; the case of antagonist-alone treatment will be discussed in a subsequent section.

THEORETICAL BASIS OF COMBINED AGONIST-ANTAGONIST ACTION

In general, the term antagonist can refer to any drug that counteracts the effect of an agonist, and the following types of antagonists have been described (50): 1) chemical antagonists, which do not interact directly with the organism but rather react with the agonist to inactivate it; 2) competitive antagonists, which interact with the same receptor site as the agonist; 3) noncompetitive antagonists, which interact with different receptor sites than the agonist, yet block the actions of the agonist; and 4) functional or physical antagonists, which produce an independent effect at a different effector system which cancels out the effect of the agonist. The actions of sympathetic and parasympathetic responses at the pupil would be an example.

For the present purposes we consider only those antagonists which either act competitively, noncompetitively, or functionally (mechanisms 2, 3 or 4).

Competitive Antagonists

As a first class of agonist-antagonist interactions, let us consider the result of combining an agonist with a competitive antagonist, i.e., one that binds to the same receptor site and can be displaced to some extent by increasing doses of agonist. Let us assume that the agonist administered as part of the treatment is comparable to the abused drug in terms of affinity for the receptors in question and efficacy in stimulating the receptors upon binding. At the extreme, we can imagine the agonist and antagonist to be present at a sufficiently high dose that almost all of the receptors are occupied with either the agonist or the antagonist. The ratio would need to be chosen so that the net stimulation of the receptors involved would be in a desirable range (resulting in neither withdrawal nor intoxication). If the individual subsequently self-administers an abused drug acting as an agonist at these receptors, it must compete for receptors with the agonist and antagonist already present. This will result in an attenuation of the response and a rightward shift of the dose-response curve for the abused drug. This shift in the dose-response curve will be more extreme than that caused by administration of the same doses of agonist alone or antagonist alone, which leave more receptors available for stimulation by the drug of abuse. Moreover, the net level of receptor activation will be

maintained closer to its optimal level by the combination agonist-antagonist treatment, in between a level corresponding to aversive withdrawal symptoms on the one hand and intoxication on the other.

The effective ratio of agonist to antagonist doses would vary according to whether there is a significant number of "spare receptors" (4), in which case an agonist would produce a maximal response even when a small fraction of the total number of receptors is occupied. In that case, the ratio of antagonist to agonist doses would need to be much higher to produce the desired result.

Although there is the possibility of overcoming blockade to some extent by self-administering a large dose of the abused drug, it would be more difficult to do so than if the same dose of agonist alone had been used, or a lower dose of agonist which had a comparable effect in terms of net receptor activation. Also, in the case of some abused substances, such as cigarettes, most relapses begin as slips, e.g., the smoking of part or all of one cigarette. If the reinforcing effects of these slips could be blocked, the readdiction may be prevented. It is unlikely that a smoker motivated to quit would smoke several cigarettes in a row to attempt to overcome blockade. Moreover, the fact that some agonist stimulation is present at the outset would be expected to reduce the patient's motivation to attempt to overcome the antagonist effect. This is because the individual would not be suffering withdrawal symptoms and may be deriving from the agonist at least some of the psychological effects sought from the abused drug.

Noncompetitive Antagonists

The use of a noncompetitive antagonist may provide further advantages over competitive blockers. This is due to the fact that a noncompetitive antagonist cannot be overcome by increasing the dose of the abused drug. Nonetheless, a balanced level of net activation can be provided by the agonist-antagonist combination, because by acting at different receptor sites the agonist could offset the actions of the antagonist (see Fig. 1). Once the system is saturated with agonist and antagonist coadministered as part of the treatment, with few unoccupied receptor sites available, the abused drug would have little or no effect. The displacement of agonist binding would lead to little effect (assuming comparable efficacies of the agonist and the drug of abuse), and the antagonist could not be displaced, so there would be virtually no effect of even a large dose of the abused drug. In essence, the noncompetitive antagonist lowers the maximal response "ceiling" possible when the abused drug is taken. Likewise, the agonist raises the "floor" by providing an increased baseline of stimulation that reduces the maximal reinforcing effect produced by the abused drug. Together, agonist and antagonist eliminate the window available for a response to the abused drug (see Fig. 2).

Functional Antagonists

If two functions mediated by different receptor sites are antagonistic, it may be possible to provide a balanced state of activation while attenuating the effects of an abused drug at one of the sites. Examples would include the balance between sympathetic and parasympathetic branches of the autonomic nervous system, and in the CNS the balance between muscarinic cholinergic and dopamine D_1 receptor activation (27). In essence, the dose-response curve for an agonist acting at one of the systems would be in an asymptotic region and would not be responsive to the abused drug. However, the feasibility of this approach would hinge on the two systems being functionally antagonistic at all relevant sites. This criterion is not fully met even in the example of sympathetic-parasympathetic antagonism cited. Although many responses are affected oppositely (e.g., pupil dilation, heart rate), some responses are not offset, e.g.,

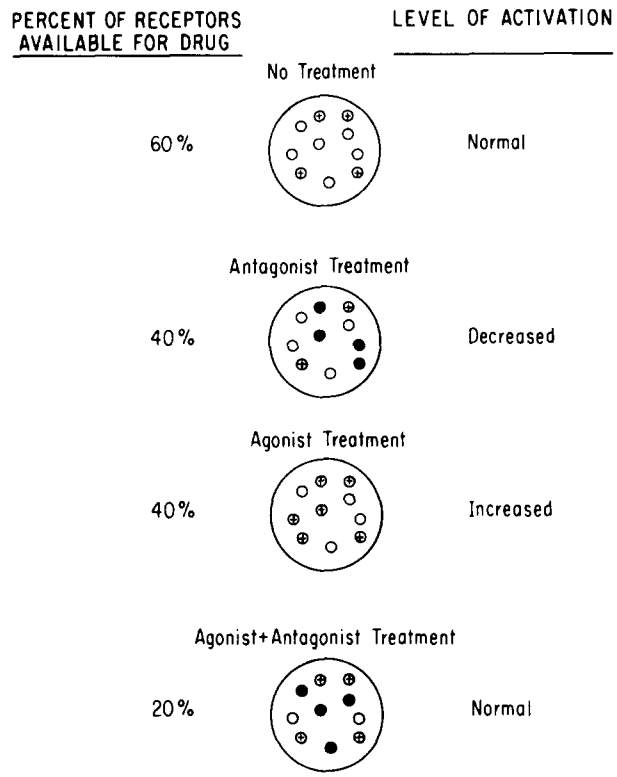

FIG. 1. Depiction of neuronal receptors mediating reinforcing actions of an abused drug, with open circles indicating unoccupied receptors available for stimulation. The plus signs indicate receptors stimulated by an administered agonist or by an endogenous neurotransmitter. Filled circles represent receptors blocked by a noncompetitive antagonist. The net level of neuronal activation corresponds to the total number of plus signs. Combined agonist-antagonist administration produces the greatest reduction in receptors available for stimulation by a drug of abuse, while maintaining a normal level of stimulation.

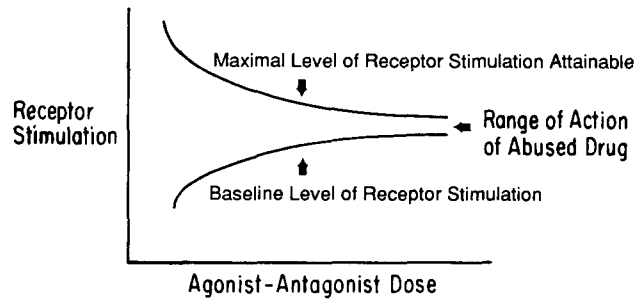

FIG. 2. Diagram showing the effect of increasing doses of an agonist and a noncompetitive antagonist on level of receptor stimulation and on the response to an abused drug. As the doses of agonist and antagonist increase, the window of action for the abused drug shrinks, while a desired level of receptor stimulation is maintained.

sympathetically mediated skeletal muscle arteriole vasodilation (30). The use of competitive and highly selective antagonists described in the previous section would be more likely to ensure a balanced state of activation at a given receptor subtype, and is predicted to be more effective in blocking the reinforcing actions of an abused drug with a minimum of side effects.

Effect on Indirect-Acting Agonists

It is predicted that the effect of fluctuations in the release of a neurotransmitter would be attenuated, as in the case of exogenously administered agonists. If so, the reinforcing effects of both directly acting and indirectly acting drugs of abuse would be attenuated. For example, the effects of a direct agonist such as nicotine would be attenuated by a nicotine-mecamylamine combination. With an indirect agonist, such as cocaine, which blocks uptake of dopamine (15) and also directly releases dopamine (45), thereby increasing dopamine levels in the nucleus accumbens (13), agonist-antagonist combinations may be used that target dopamine receptors. Additionally, serotonergic agonist-antagonist combinations merit evaluation because cocaine has been shown to facilitate serotonin release (5, 6, 15, 44). With an indirectly acting agonist, even a competitive antagonist for the released transmitter can lower the maximal response, due to the limited pool of available transmitter (22). Therefore, in this situation a competitive antagonist would have the key advantage that noncompetitive antagonists have with abused drugs that are direct acting agonists.

APPLICATION OF AGONIST-ANTAGONIST COMBINATIONS TO THE TREATMENT OF DRUG DEPENDENCE

Importance of Controlling Ratio of Agonist to Antagonist

Maintaining a relatively constant ratio of agonist to antagonist concentrations is expected to be important in blocking drug reinforcement while maintaining receptor activation within a desirable range. This might be difficult to achieve with oral dosing, due to differences in rates of absorption, distribution and elimination of the agonist and antagonist. A ratio of concentrations which is initially desirable would change over time, tending to cause an imbalance of agonist and antagonist effects. However, transdermal drug delivery systems would circumvent this problem. Transdermal patches are currently used to deliver a wide variety of therapeutic agents, including scopolamine, nitroglycerin, clonidine, estrogen, and nicotine (37–39, 46, 52). Transdermal delivery systems can provide constant rates of drug delivery over a 24-h period or longer. The rates of agonist and antagonist release would be adjusted depending on the elimination rates of the two drugs, and thus a constant ratio of drug concentrations could be maintained in the body. Limitations on the applicability of transdermal delivery systems may be posed by the skin's permeability to different drugs and by the total dose that needs to be delivered; generally drugs with which less than 100 mg/24 h is required would be ideal (46). This would include many agonists and antagonists, and, therefore, may not prove to be a serious limitation. Skin permeation is best with small lipophilic molecules, but progress has been made in delivering larger or more polar molecules with the use of skin penetration enhancers and with techniques such as iontophoretic delivery (7, 9, 46).

Related techniques that could potentially be used to maintain a constant ratio of agonist to antagonist concentrations are implantable osmotic mini-pumps, subcutaneous implants or depot injections with known rates of drug release (9).

Predicted Advantages of Agonist-Antagonist Combination Treatment Over Agonist-Alone Treatment

Agonist-antagonist combination treatments are predicted to have a key advantage over agonist-alone treatment, in that some of the side effects of the agonist might be attenuated by the antagonist. Moreover, the abuse liability of the combination should be less than that of the pure agonist. In a similar vein, naloxone or small amounts of naltrexone have been added to sublingual buprenorphine preparations used in the treatment of pain in order to reduce the likelihood of abuse by opiate addicts who might inject the preparation intravenously (29).

Agonist-alone treatment is only partially effective at blocking reinforcement from the abused drug, unless high doses are used. Methadone administration, for example, does not completely prevent the euphoric response to opiate injections (2). Similarly, nicotine replacement in doses usually employed has little effect on the reinforcing effects of cigarette smoke, as judged by ongoing rates of smoking behavior (1). The combined administration of an agonist and an antagonist can potentially provide much more effective blockade of reinforcement than the agonist alone, especially if a noncompetitive antagonist is utilized. In principle, this would make it less likely for a "slip," i.e., a single self-administration of the abused drug following a cessation attempt, to lead to a full-blown relapse.

Interestingly, in the presence of agonist-antagonist blockade of drug reinforcement, continuing to engage in the behavior of self-administering the abused drug is actually an extinction treatment. Thus, in the case of a behavior like cigarette smoking, which is strongly associated with situational cues and which itself presents many conditioned reinforcing sensory cues (40), the act of smoking in the face of agonist-antagonist treatment may lead to a gradual extinction of learned associations maintaining the behavior. Similarly, cocaine and opiate use are triggered by stimuli associated with prior use, and perhaps also by cues associated with abstinence (10,35). Extinction of situational cues can, in principal, be accomplished by exposure to these cues while abstaining from drug use. In practice, this is difficult to achieve, because without "protection," pharmacologic or otherwise, addicts trying to abstain may feel too threatened by these cues to voluntarily expose themselves. In fact, most drug treatment programs stress the importance of avoiding cues that can elicit craving and lead to relapse.

Extinction of conditioned reinforcing cues surrounding the act of drug self-administration is even more difficult to achieve because it requires a convincing placebo drug self-administration procedure. Some promising results have been obtained with heroin and cocaine users (10), but such treatment could be conducted more intensively if pharmacologic blockade were employed (32). In fact, naltrexone treatment has been viewed as a method of extinguishing conditioned reinforcing cues (17). Unfortunately, there are problems with antagonist-alone treatment that severely limit its usefulness, which are discussed below.

Predicted Advantages of Agonist-Antagonist Combination Treatment Over Antagonist-Alone Treatment

Combined agonist-antagonist treatment would also have advantages over antagonist-alone treatment. The latter, while having the potential of completely blocking the reinforcing effects of the abused drug, would also have a high chance of producing many adverse side effects. These would include withdrawal symptoms as well as other side effects resulting from an underactivation of the neurotransmitter system involved. Mecamylamine, for instance, is effective at blocking nicotine reinforcement

in animals and humans (11, 34, 43, 47), but also produces dysphoria and other side effects, leading to a high patient dropout rate (48,49). This has limited the enthusiasm for applying mecamylamine to smoking cessation treatment.

Naltrexone, the opiate antagonist, does not seem to produce many side effects, providing treatment is not initiated until after successful withdrawal from opiates (17). Of course, if naltrexone treatment is begun before withdrawal an acute abstinence syndrome will be precipitated. Thus an initial barrier to treatment is the requirement of withdrawing from opiates before treatment. The agonist-antagonist combination treatment would avoid this difficulty, because sufficient agonist effects could be maintained to prevent withdrawal symptoms.

An additional problem with antagonist-alone treatment is that there is an absence of desired effects of the abused drug. Drugs such as nicotine, for instance, may be used in part to achieve absolute enhancements in pleasure, mood regulation, cognitive performance and weight control (51). This is suggested in part by evidence that nicotine has some of these effects in nonsmokers and in naive animal subjects. Thus, apart from the alleviation of withdrawal symptoms, some positive benefits of drug self-administration may be sought by the user (18). Antagonist-alone treatment would not provide any of these perceived benefits, and hence long-term compliance with treatment tends to be poor, except in highly motivated subjects (17). Combined agonist-antagonist treatment might give the patient some of the long-term desired effects of the abused drug, and thus improve compliance with treatment.

Predicted Advantages of Agonist-Antagonist Combination Treatment Over Mixed Agonist-Antagonist Drugs

Although promising results have been obtained with the mixed agonist-antagonist buprenorphine in the treatment of heroin and cocaine abuse (19,31), the general approach proposed here has both more generality and more specificity of action. That is, by selecting from the large number of relatively selective agonists and antagonists, there is great flexibility in the choice of drugs and neurotransmitter systems. Therefore, it would not be necessary to develop new drug molecules having mixed agonist-antagonist effects in order to achieve the beneficial effects of combined agonist-antagonist actions. By targeting any one of several specific neurotransmitter systems, the approach could potentially be applied to many drugs of abuse, including cocaine, heroin and nicotine.

A second advantage of combining different agonists and antagonists is the great flexibility in the selection of the ratio of agonist effects to antagonist effects. Using two different molecules allows a titration of the ratio of agonist and antagonist effects not achievable with a single molecule. Early in treatment it might be desirable to have a higher net agonist effect, with a gradual tapering of these actions over time. Nonetheless, full blockade of the reinforcing actions of the abused drug could be maintained throughout treatment by having a sufficient dose of both agonist and antagonist present at all times. Mixed agonist-antagonist drugs, as well as partial agonists acting at a particular receptor, will not necessarily have the desired level of agonist activity at a dose sufficiently high to block the actions of the abused drug. For example, high doses of buprenorphine which might be advantageous in terms of competing with and thereby attenuating the reinforcing effects of heroin, produce a limited agonist effect. In fact, high doses of buprenorphine have been shown to precipitate abstinence symptoms in morphine-dependent animals (12,14). Even in nondependent subjects, some responses to buprenorphine exhibit a biphasic dose-response curve which cannot be accounted for by a simple partial agonist effect at μ opioid receptors and may involve actions at other receptors.

Lewis (28) has described the combination of 2–8 mg daily buprenorphine with naltrexone for treating heroin addiction, and proposes that it may provide more effective blockade of heroin's reinforcing effects than naltrexone alone. However, he reports that buprenorphine does not attenuate the abstinence syndrome precipitated by naltrexone, and hence addicts cannot be given the combination treatment until after a period of 1–4 weeks on a daily dose of 2–8 mg buprenorphine alone. Moreover, it is not clear that a sufficient level of agonist effects can be maintained by this dose of buprenorphine in the presence of naltrexone, and whether that combination would yield a much better clinical outcome than the use of naltrexone alone after a period of buprenorphine administration [cf. (25)]. We predict that a methadone-naltrexone combination should be able to maintain a higher agonist effect in the initial phase of treatment, while at the same time achieving more effective blockade of heroin's effects. Alternatively, it is predicted that patients on 2–8 mg buprenorphine alone would benefit from a combination of naltrexone with a much higher dose of buprenorphine in the second phase of treatment in order to maintain sufficient agonist effects in the presence of naltrexone (14).

Buprenorphine has also shown some promise in the treatment of cocaine abuse (31), but unfortunately it has been shown to potentiate some of cocaine's effects (8). Thus it is not likely that reductions in cocaine self-administration following buprenorphine administration are due to a blockade of cocaine reinforcement. With the agonist-antagonist approach suggested here, dopamine receptor antagonists which have been shown to attenuate cocaine's reinforcing actions could be employed in conjunction with an appropriate dopamine agonist. This approach would seem more likely to block the reinforcing effects of cocaine.

A final, and perhaps key advantage of the approach suggested here is that a noncompetitive antagonist can be employed. On theoretical grounds, the combinatation of an agonist with a noncompetitive antagonist would provide the most complete blockade of drug reinforcement, at relatively moderate doses of each, as discussed in the Theoretical Basis of Combined Agonist-Antagonist Action section.

APPLICATION OF AGONIST-ANTAGONIST COMBINATIONS IN ANALYZING DRUG REINFORCEMENT AND BEHAVIORAL MECHANISMS

The method described here can potentially be used to better understand the role of particular neurotransmitter systems in drug dependence as well as nondrug-reinforced behaviors. By insulating the postsynaptic receptor from the endogenous neurotransmitter, it would be possible to evaluate the role of that system in drug self-administration, cognitive performance, or other behaviors. This may shed more light on the effects of a given neurotransmitter than studies using agonists alone, because an agonist causes a substantial change in the baseline level of activity of the system and would not prevent fluctuations in neurotransmitter stimulation. The combined agonist-antagonist approach could "lock in" a specified level of activity, preventing fluctuations due to varying presynaptic release of the transmitter. This is analogous to the voltage-clamp method used to regulate membrane potential in studies of neuronal function (23). In the voltage-clamp method, a source of external current (analogous to the high concentration of agonist and antagonist) is used to maintain a constant membrane potential and cancel out fluctuations in voltage that would otherwise occur due to changing ion conductances. This allows the behavior of the system to be studied

without confounding changes in membrane potential. Similarly, the agonist-antagonist system may buffer the postsynaptic neuronal membrane from changes in potential due to phasic changes in transmitter release from nerve terminals, maintaining a relatively constant potential determined by the ratio of agonist to antagonist concentrations.

The use of antagonists alone in analyzing drug dependence has the problem that in addition to blocking reinforcement, antagonists can induce a withdrawal state which reproduces the effects of extreme deprivation. Thus, after receiving high doses of the nicotinic antagonist mecamylamine, cigarette smokers show a dramatic increase in smoking behavior, despite the fact that most of the reinforcing effects of nicotine are blocked. Presumably, the withdrawal state produced by mecamylamine elicits a strong drive to engage in smoking. Combined agonist-antagonist administration, in varying ratios, can maintain the drive state at a range of levels while blocking the reinforcing effects of the self-administered drug. Conceivably, the agonist-antagonist method described could be used to assess the role of a given neurotransmitter system in reinforcement by nondrug stimuli, such as food or sex.

With certain transmitter systems, it may present serious or even fatal consequences to administer the antagonist alone. Thus, with GABA blockers, convulsions may result from antagonist administration (3). However, if a combination of a GABA agonist and a GABA blocker is administered, serious side effects might be avoided. The effects of endogenous GABA release would be attenuated, so the effects of insulating the receptor system from that transmitter could be examined. Specifically, the role of transient vs. tonic levels of receptor stimulation could be investigated. An agonist-antagonist combination would prevent fluctuations in receptor stimulation, while any particular level of receptor stimulation could be maintained by using different ratios of agonist to antagonist. In general, systems involved in phasic information transfer may show serious disruption from this type of manipulation, whereas systems which principally serve as tonic modulators would not show dysfunction.

APPLICATION OF AGONIST-ANTAGONIST COMBINATIONS TO PROBLEMS OF DISREGULATION

The strategy of concurrent agonist-antagonist administration might also have application to the treatment of disorders involving disregulation of a neurotransmitter system needed for a tonic level of activation. Numerous diseases are thought to result from disregulation of neurotransmitter systems, including schizophrenia, affective disorders, manic-depression, and autonomic hyperreactivity. The potential application of agonist-antagonist combinations to the treatment of these and other disorders would be expected to have advantages over agonist-alone and antagonist alone approaches, because the latter often produce unwanted shifts in tonic functions in addition to modulating reactivity.

POSSIBLE PROBLEMS

Several practical problems need to be taken into account in implementing the agonist-antagonist combinations discussed above. First, there may be only imperfect cancelling of side effects due to differing potencies of an agonist and antagonist at different receptor subtypes. Antagonists in particular are often less specific than agonists (4). However, combined administration should usually produce some benefit, relative to agonist-alone or antagonist-alone treatment. An exception would be if both agonist and antagonist have the same side effects and if their effects are additive or synergistic. Alternatively, if an agonist produces rapid desensitization, as with nicotine, then there may be antagonist-like actions which summate with those of the antagonist employed. In general, though, there should be many cases where acceptable cancelling of side effects occurs through combined agonist-antagonist effects. Even in the case of nicotine, it has been shown that smokers can tolerate extremely high plasma nicotine levels in the presence of mecamylamine (36).

TABLE 1

AGONIST-ANTAGONIST COMBINATIONS FOR DIFFERENT DRUG DEPENDENCIES

Drug Dependence	Agonist-Antagonist Combination
Nicotine	Nicotine-Mecamylamine
Cocaine	D_1: SKF 38393-SCH 23390
	D_2: LY 171555-Raclopride
	D_1 and D_2: Pergolide-Fluphenazine
Heroin	Methadone-Naltrexone

Another practical difficulty may be that the patient experiences toxic effects from attempting to overcome the blockade of reinforcement by administering an enormous dose of the abused drug. Of course, this is a possibility even with antagonist-alone treatment, and we predict that combined agonist-antagonist treatment would make this eventuality less likely because the patient would be less motivated to attempt to obtain agonist effects due to the presence of those effects at some level in the combined treatment.

Perhaps the most serious practical problem with the suggested approach would be its effect on endogenous neurotransmitter efficacy. The actions of neurotransmitters would be blocked like those of other agonists, resulting in a functional disconnection of the receptor normally activated by that neurotransmitter. Of course, this is an advantage in studying the role of different neurotransmitter systems in behavior, as described in the Application of Agonist-Antagonist Combinations to the Treatment of Drug Dependence section. However, for clinical application, it may pose a problem for systems whose activation is phasic and responsive to stimulus conditions. In this case, combined agonist-antagonist administration may induce a functional impairment. However, for systems which provide a relatively tonic influence, or for systems not normally engaged to a significant extent (e.g., those involved in pain transmission), clinical applications would be quite feasible. Also, systems requiring slow circadian fluctuations could be accommodated relatively easily by drug delivery systems which allow a temporal pattern of drug delivery to be programmed (9).

A related problem arising from the chronic insulation of neural systems from endogenous transmitter stimulation might be an increase in sensitivity to phasic changes upon withdrawal of the agonist-antagonist treatment. This could have the advantage, in the case of the dopamine reward system, of making the patient more reponsive to mildly rewarding cues, conceivably counteracting the anhedonia following a period of cocaine abuse. On the other hand, the response to the drug of abuse could be potentiated. In any event, it may be possible to avoid this hyperreactivity by gradually withdrawing the patient from the agonist-antagonist treatment in a dose-weaning program, and allowing sensitivity to recover slowly.

CONCLUSIONS

A novel research and treatment approach has been described involving concurrent administration of an agonist with an antagonist for the analysis and treatment of drug dependence. While this approach may initially seem counterintuitive, the likely ad-

vantages become clear upon a detailed consideration of the pharmacologic actions of receptor agonists and antagonists. The potential of insulating an individual from the desired effects of an abused drug, while at the same time minimizing withdrawal symptoms and side effects, is sufficiently important that it deserves careful testing and evaluation. Apart from its application to treatment, the technique described here may be a valuable research tool in analyzing drug reinforcement by functionally and reversibly lesioning a given neurotransmitter receptor system. It is analogous to the voltage clamp methodology used so successfully by neurophysiologists to elucidate mechanisms of neuronal function. The method may also have applications in the analysis of neurotransmitter receptor systems mediating the response to many kinds of nondrug reinforcing stimuli, and potentially to the understanding and treatment of disorders involving disregulation of receptor activity. The hypotheses presented concerning particular drugs of abuse, including cocaine, heroin and nicotine, are specific and testable, and can be evaluated with specific drugs and populations of patients (as listed in Table 1).

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