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The Novel-Response Procedure in Humans

BRANDI J. SMITH AND WARREN K. BICKEL

Departments of Psychology and Psychiatry, University of Vermont, Burlington, VT 05401

SMITH, B. J. AND W. K. BICKEL. *The novel-response procedure in humans*. PHARMACOL BIOCHEM BEHAV **64**(2) 245–250, 1999.—The novel-response drug discrimination procedure is one of several three-choice procedures developed to address interpretational difficulties that can occur under standard two-response procedures. The novel-response procedure is unique among three-choice discrimination procedures by using instructions, rather than explicit training procedures. With the novel-response procedure, participants are trained under a standard two-response (drug vs. placebo) discrimination, and then instructed that in the presence of a drug stimulus unlike either of the training drugs, responses should be made on the novel-response alternative. Several studies have assessed the utility of the novel-response procedure by comparing effects under a standard two-response and the novel-response procedure in participants trained to discriminate triazolam from placebo. Results indicate that the novel-response procedure can increase the selectivity of both placebo- and drug-appropriate responding, and in this way, allows for finer distinctions to be made among sedatives than a standard two-response procedure. © 1999 Elsevier Science Inc.

Triazolam Benzodiazepines Novel-response procedure Drug discrimination Humans

THE results of drug discrimination studies are an integral part in the investigation of drug-taking behavior because the effects of drugs may serve as discriminative stimuli in drug-seeking, and thus, may play a role in the inception of such behavior (25). In standard two-response DD procedures, drug effects serve as discriminative stimuli such that in the presence of one drug stimulus (a training drug), responses on a particular lever are reinforced; and in the presence of another drug stimulus (usually placebo), responses on the alternative lever are reinforced. Thus, left and right responses are discriminated operants based on drug vs. placebo discriminative stimuli. After training and the acquisition of the discrimination, novel drugs are tested and results are interpreted based on the distribution of responding between the two levers.

Drug discrimination studies are useful for characterizing pharmacological mechanisms because drugs that act through similar mechanisms of action tend to substitute (i.e., occasion >80% training-drug appropriate responding) for one another (19). This specificity comes, in part, from the fact that the training procedure of differential reinforcement used in drug discrimination means subjects can be trained to discriminate relatively low doses of drugs. This is an advantage because at lower doses, the observed effects are likely those of a specific system, whereas with higher doses the observed effects could be manifestations of nonspecific interactions with multiple CNS systems.

Despite these positive aspects of drug discrimination procedures, the standard two-response (drug vs. placebo) procedures can cause interpretational difficulties. For example, placebo-appropriate responding to a test drug can be interpreted as either the test drug was dissimilar to the training drug or an inactive dose of the test drug was administered (5). Another interpretational difficulty occurs when a test drug occasions a mix of placebo- and drug-appropriate responding, known as partial substitution. Among the many possible interpretations of this result are: 1) the test drug shares the discriminative stimulus effects of the drug, but at a lower intensity; or 2) the discriminative stimulus effects of the test drug overlap with, but are not identical to those of the training drug (12). Thus, while drug discrimination procedures provide a sensitive and specific assay of pharmacological effects, the results can sometimes be difficult to interpret.

Recently, three-choice discrimination procedures have been applied in human studies of drug discriminative stimulus effects to increase the selectivity of placebo- and drug-appropriate responding. In one series of studies, three-way discrimination were trained among opioid agonists, antagonists, and placebo (20,21), and among opioids with different receptor subtype selectivities and placebo (6,22). The three-choice training procedure used in these studies increased the selectivity of drug-appropriate responding compared to two-choice procedures (23). In another effort to increase selectivity of responding, healthy volunteers were trained in three-choice discriminations among triazolam, zolpidem and placebo, and among diazepam, buspirone, and placebo (7,16). These studies demonstrated increased selectivity of placebo- and drug-

Requests for reprints should be addressed to Brandi J. Smith, Ph.D., Department of Psychiatry and Behavioral Science, Behavioral Biology Research Center, 5510 Nathan Shock Drive, Suite 3000, Baltimore, MD 21224.

appropriate responding. Finally, we developed a novel-response procedure in which participants were trained under standard two-choice conditions (drug vs. placebo) and then during testing were offered a response alternative appropriate for novel drug effects.

The novel-response procedure, in contrast to the trained three-choice procedures described above, relies on an instructed response. A series of studies in humans trained to discriminate triazolam, a short-acting benzodiazepine, from placebo demonstrated that the novel-response procedure is useful for making distinctions among drugs that cannot be made under standard two-response procedures (5,12,13,18,24). The following is a review of the methods, results, and implications of these studies.

GENERAL METHODS

We have completed five studies using the novel-response procedure (5,12,13,18,24). In all five studies, volunteers were trained to discriminate triazolam from placebo. Three of these five studies were conducted using crossover designs comparing results under a standard two-response and a novel-response procedure (5,13,24). Two studies were conducted under the novel-response procedure only (12,18).

The general method used in the crossover studies is as follows. Participants first completed a training (or sampling) phase in which they were told at the time of ingestion which capsules they were receiving (e.g., drug A or drug B). Participants completed four such training sessions in which they had two exposures to each training stimulus on alternate sessions. Next, participants completed a test-of-acquisition phase in which they demonstrated the ability to discriminate the two training drugs by responding >80% capsule-appropriately on a fixed interval (FI) 1-s schedule of point presentation for four consecutive sessions within eight sessions. On the FI, the number of points accumulated is displayed continuously on the video screen. The schedule lasts 3 min, and the number of points earned on each key are recorded and converted to monetary reinforcement at the end of the session. Then, those participants meeting the acquisition criterion entered either the two-response or the novel-response test phase. After completing all test sessions under one procedure, participants completed all test sessions under the alternate procedure. The first two to four sessions of each testing phase were acquisition sessions. The purpose of this phase was to ensure that the instructions describing the testing conditions did not disrupt the stimulus control of the training drugs. Testing of novel drugs and various doses of the training drug began after successful completion of this second acquisition phase. On test

TABLE 1

INSTRUCTIONAL SETS

Training Instructions
For this part of the experiment, you will be administered one of two drugs, either __or __. You will be immediately told which drug you are receiving. After the drug is administered, you will complete the computer tasks according to which drug you received. In proceeding with the computer tasks, you have the opportunity to make one of two responses for indicating the drug you received. Use the left button to indicate drug __and the middle button to indicate drug __. At the end of the session you will earn up to $12.00, depending upon your performance during the tasks.
Test-of-Acquisition Instructions
For this part of the experiment, you will be administered one of two drugs, either __ or __ without being informed of which drug you are receiving. After the drug is administered, you will complete the computer tasks and indicate which drug you received. In proceeding with the computer tasks, you have the opportunity to make one of two responses for indicating the drug you think you received. Use the left button to indicate drug __ and the middle button to indicate drug_. At the end of the session you will be told which drug you received. If you indicated correctly, you will earn up to $12.00.
Novel - Response Procedure Test Phase
For this part of the experiment, you may have a __ day, a __ day or a test day. On a test day, the drug you receive may be precisely __, precisely __ or may not be precisely like __ or __. You will not be given any information at the beginning of the session to indicate which drug you received, or if it is a test day. You will proceed with the computer tasks and indicate which drug you received. Use the left button to indicate drug __, the middle button to indicate drug __, and the right button (N) when you believe the drug is not precisely like __ o r__. At the end of the session, you will be told which drug you received or whether it was a test day. BONUS: If you had a test day and the drug was __ or __ you will earn the average amount you received on the last four __ and __ days only if you responded on either the __ or __ buttons. If it was a test day and the drug you received was neither __ nor __, then you will earn the amount you responded on the __button. On every test day you will not be told whether you received __, __, or __ until the end of the study. Thus, you will not be told how much you earned on each test day until the study is completed.
Two-Response Procedure Test Phase
For this part of the experiment, you may have a __ day, a __ day or a test day. On a test day, the drug you receive may be precisely __, precisely __ or may not be precisely like __ or __. You will not be given any information at the beginning of a session to indicate which drug you received, or if it is a test day. You will proceed with the computer tasks and indicate which drug you received. Use the left button to indicate drug __ and the middle button to indicate drug __. At the end of the session, you will be told which drug you received or if it was a test day. On a test day, you will earn the average amount you received on the last four __ and __ days.

sessions, participants were told only that it was a test, and that the drug letter code would not be revealed until the end of the study. Test-of-acquisition sessions were interspersed among the test sessions to assure that participants maintained the ability to discriminate the training conditions. In studies not using the crossover design, the testing phase consisted of the novel-response testing only.

As mentioned above, instructions are an important component of the novel-response procedure (Table 1). The novel-response test phase instructions indicated that 1) on a test session, if the drug a participant received were one of the training stimuli, then responses on either training key will be nondifferentially reinforced; and 2) on a test session, if the participant receives a drug that is not like either of the training stimuli, only responses on the novel-response alternative will be reinforced. Importantly, the two-response instructions only indicate the former and not the latter contingency. The two-response test phase instructions do not indicate a response appropriate to a stimulus that differs from either of the training stimuli. Reinforcement for test sessions under both procedures was withheld until the completion of the study (5).

In addition to testing the discriminative stimulus effects, several self-report questionairres and a measure of psychomotor performance were assessed. The ARCI consisted of 49 true/false questions that were scored as five subscales: a morphine–benzedrine group (MBG), a pentobarbital–chlorpromazine–alcohol group (PCAG), a lysergic acid diethylamide group (LSD), a benzedrine group (BZ), and an amphetamine group (A) (10,14). The adjective rating scale presented 32 adjectives that participants rated on a five-point scale from 0 (not at all) to 4 (extremely). The items were grouped into two subscales: a sedative scale consisting of adjectives describing stimulant effects (5,12,18), and a stimulant scale consisting of adjectives describing stimulant effects. The VAS consisted of 100-point horizontal lines anchored with "not at all" on one end and "extremely" on the other. Participants rated the strength of drug effect, drug-liking, good drug effects, bad drug effects, drug-induced high, drug-induced anxiety, the similarity of the drug to each training conditions and, under the novel-response procedure, the similarity of the drug to a novel drug condition. A computerized version of the DSST was used (15). Participants responded on a numeric key pad to reproduce a geometric pattern associated with a digit according to the code presented continuously across the top of the screen. Data collected were the number of trials correctly completed and the number of trials completed.

RESULTS AND DISCUSSION

Table 2 provides a summary of the drugs tested under the novel-response procedure. As shown in the table, drugs similar to and dissimilar to triazolam have been tested using the novel-response procedure. The following discussions of the results is broken down by general drug classes. To determine which drugs were tested as part of which study, refer to Table 2.

Drugs Dissimilar to Triazolam

One of the disadvantages of two-response procedures is the overinclusiveness of placebo-appropriate responding. That is, placebo-appropriate responding can occur when an inac-

TABLE 2

THE MAXIMUM AVERAGE PERCENTAGES OF TRIAZOLAM-APPROPRIATE AND NOVEL RESPONDING UNDER THE TWO-RESPONSE AND THE NOVEL-RESPONSE PROCEDURES

Study	Doses (mg/70 kg)	Drugs Tested	Maximun% Two-Response	Maximun% Novel-Response	
			TRZ	TRZ	Novel
Bickel et al., 1993	0.32	triazolam	100	100	0
	5, 20	amphetamine	25	0	87.5
Kamien et al., 1994	0.32	triazolam	N/A	100	0
	0.75–3.0	lorazepam	N/A	80	17
	7.5–30	buspirone	N/A	40	58
Oliveto et al., 1994	0.32	triazolam	N/A	90	0
	7.5–30	diazepam	N/A	100	0
	1–6	hydromorphone	N/A	25	57
Kamien et al., 1997	0.32	triazolam	100	100	0
	56–177	secobarbital	100	33	100
	320, 560	caffeine	0	0	33
Smith and Bickel, under review	0.35	triazolam	87.5	100	0
	0.25–1.75	alprazolam	100	100	0
	2.5–35	zolpiden	100	75	50
	75–525	caffeine	8.3	0	38

Results are reported for the training dose of triazolam, and any dose of the test drugs. Test doses are listed with "," when only two doses were tested and "–" when three or more doses were tested. Under the two-response procedure, placebo-appropriate responding can be deduced from subtracting the percent triazolam-appropriate responding from 100. Under the novel-response procedure, the maximum percentages of triazolam-appropriate and novel responding are not necessarily from the same dose, and therefore, percentages may add to >100%, and placebo-appropriate responding cannot be inferred. "N/A" indicates not applicable.

tive dose of a drug is tested, or when a drug with dissimilar effects to the training drug is tested (5). The novel-response procedure was originally developed to specifically address this issue. By offering a response alternative appropriate for novel stimulus effects, the selectivity of the placebo-appropriate response could be increased.

Opioids and stimulants do not substitute for benzodiazepine training stimuli in either nonhumans or humans (8,11). Two stimulants, *d*-amphetamine and caffeine, have been tested using the crossover design comparing two-response and novel-response procedures (Table 2). Both drugs occasioned mostly placebo-appropriate responding under the two-response procedure, and dose-related increases in novel responding under the novel-response procedure. These results clearly indicate increased selectivity of placebo-appropriate responding; that is, with the novel response present, the placebo response was no longer a default response for effects dissimilar to the training drug.

Hydromorphone, a μ-opioid agonist, was tested only under the novel-response procedure (Table 2). Similar to the findings with the stimulant drugs, hydromorphone produced dose-related increases in novel responding. Interestingly, hydromorphone also occasioned a small amount of triazolam-appropriate responding (25%). These results suggested only a small degree of overlap between the discriminative stimulus effects of hydromorphone and those of triazolam.

Nonbenzodiazepine Anxiolytics/Hynotics

To test for increased selectivity of triazolam-appropriate responding under the novel-response procedure, three nonbenzodiazepines with varying degrees of sedating and anxiolytic effects were tested.

Several doses of secobarbital, a barbiturate with similar sedating effects as triazolam, were tested under both a two-response and a novel-response procedure using the crossover design (Table 2; (13)]. Consistent with two-response procedure studies conducted with nonhuman subjects [e.g., (17)], secobarbital completely substituted for triazolam when tested under the two-response procedure; however, when tested under the novel-response procedure, secobarbital produced predominantly novel-appropriate responding (13). Thus, the discriminative stimulus effects of secobarbital, a drug that binds to a different site on the $GABA_A$ receptor complex than triazolam, were distinguished from those of triazolam under the novel- but not under the two-response procedure.

In a more recent study, the discriminative stimulus effects of zolpidem were compared to those of two traditional benzodiazepines, triazolam and alprazolam (24). Zolpidem is a nonbenzodiazepine hypnotic that is selective for the BZ-I receptor subtype. The effects of triazolam, alprazolam, and zolpidem were assessed under a two-response and under the novel-response procedure. Under the two-response procedure, triazolam, alprazolam, and zolpidem substituted for triazolam. Under the novel-response procedure, triazolam, alprazolam, and zolpidem produced dose-dependent increases in triazolam-appropriate responding; however, zolpidem also produced novel-appropriate responding at intermediate doses. Neither triazolam nor alprazolam produced any novel-appropriate responding. These results suggested that the discriminative stimulus effects of zolpidem were similar, but not identical, to those of triazolam and alprazolam. These results are consistent with another three-choice discrimination study in humans in which healthy volunteers were successfully trained to discriminate among triazolam (0.5 mg/70 kg), zolpidem (20 mg/70 kg), and placebo (16). The doses of triazolam and zolpidem produced similar ratings of overall drug effect, and similar decreases on psychomotor performance measures suggesting that the doses were comparable. The fact that zolpidem and triazolam could be distinguished suggests at least some nonoverlapping discriminative stimulus effects between the two drugs.

Buspirone is a nonbenzodiazepine anxiolytic that exerts its effects through interactions with the $5HT_{1A}$ receptor. Under a two-response procedure in humans, buspirone partially substituted (71% drug-appropriate responding) for a diazepam training stimulus (11). These results suggested either overlap in the discriminative stimulus effects of buspirone and diazepam or a lack of selectivity, and were inconsistent with studies conducted with nonhuman subjects (2,9). Under the novel-response procedure, buspirone produced a dose-related increase in novel responding, reaching a maximum of 58% (Table 2). Buspirone occasioned approximately 20% triazolam-appropriate responding at this highest test dose. These results indicate that buspirone's discriminative stimulus effects are largely dissimilar to triazolam's. In this case, the addition of the novel response distinguished among two interpretations of partial generalization that are indistinguishable from results under two-response procedures—that the discriminative stimulus effects of buspirone are similar to those of a benzodiazepine, but at a lower intensity, or that the discriminative stimulus effects overlap with, but are not isomorphic with, those of a typical benzodiazepine. The dose-dependent increase in novel responding after buspirone favors the latter interpretation. As with zolpidem, buspirone has been studied using a trained three-choice discrimination procedure in humans (7). In that study, volunteers were trained to discriminate between placebo, buspirone (15 mg/70 kg) and diazepam (10 mg/70 kg). Ten of 12 volunteers were able to acquire this three-way discrimination, suggesting distinct discriminative stimulus effects of buspirone compared to a typical benzodiazapine.

Together, these three studies described above suggest that the novel-response procedure can distinguish drugs with different mechanisms of action and different selectivities at the same receptor, even when therapeutic effects may be similar (i.e., anxiolytic, or hypnotic).

Benzodiazepines

Several benzodiazepines have been tested under the novel-response procedure (Table 2). Triazolam, diazepam, and alprazolam all fully substituted for the triazolam training drug (5,18,24), and none of these drugs produced any novel responding. In contrast, lorazepam produced 17% novel responding, as well as 80% triazolam-appropriate responding (Table 2). The novel responding to lorazepam was not unexpected in light of the findings from nonhuman primates in which lorazepam did not produce a typical benzodiazepine-like profile of discriminative stimulus effects. When a lorazepam vs. placebo discrimination in baboons and rats was trained, pentobarbital did not fully substitute for lorazepam, but when trained to discriminate pentobarbital from placebo, lorazepam did fully substitute for lorazepam (1–3). This asymmetrical substitution profile does not occur when other benzodiazepines (e.g., diazepam) are tested (4). Thus, the results from the novel-response procedure in humans are consistent with the nonhuman drug discrimination literature in suggesting that lorazepam's discriminative stimulus effects are not identical to those of other benzodiazepines. Importantly, the re-

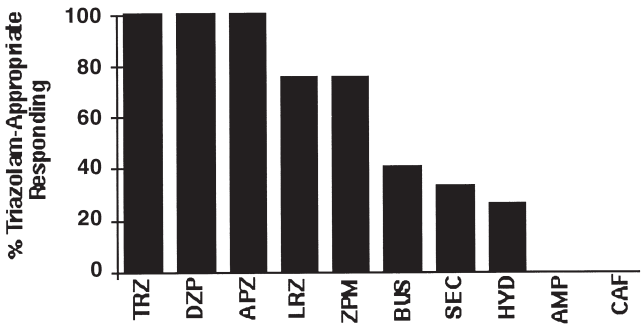

FIG. 1. Rank ordering of drugs tested under the novel-response procedure by the maximal percentage of triazolam-appropriate responding in the presence of the novel-response option. TRZ: triazolam; DZP: diazepam; APZ: alprazolam; LRZ: lorazepam; ZPM: zolpidem; BUS: buspirone; SEC: secobarbital; HYD: hydromorphone; AMP: *d*-amphetamine; CAF: caffeine.

sults from tests with benzodiazepines demonstrate that the novel-response procedure did not increase selectivity to the point of disrupting generalization to the training drug class.

Rank Ordering

Kamien et al. (13) previously reported that rank ordering the drugs tested under the novel-response procedure by the maximum percentage of triazolam-appropriate responding that occurred in the presence of the novel response demonstrated three categories of drugs—benzodiazepines anxiolytics/hypnotics (≥75% triazolam-appropriate responding), nonbenzodiazepine sedatives (20–74% triazolam-appropriate responding), and drugs with no similarity to triazolam (<20% triazolam-appropriate responding). Interestingly, zolpidem, tested since that report, alters these categories. Figure 1 gives the most up-to-date rank ordering of drugs tested under the novel-response procedure. As shown in the figure, zolpidem produced a maximum of 75% triazolam-appropriate responding in the presence of the novel-response procedure, indicating that zolpidem, a nonbenzodiazepine hypnotic, and lorazepam, an atypical benzodiazepine, are equally similar to triazolam. Thus, the group of drugs occasioning ≥75% triazolam-appropriate responding now includes a nonbenzodiazapine hypnotic.

Relationship of Discrimination to Self-Reported Drug Effects

Subjective drug effects and discriminative responding often covary, although whether subjective effects underlie discriminative stimulus effects is not known. In certain cases, the novel-response procedure distinguished drugs that could not be distinguished based on subjective effects (i.e., self-reports) alone. Recall that both secobarbital and zolpidem fully substituted for triazolam under the two-response procedure, but not under the novel-response procedure (13,24). In both cases, the self-reported effects were consistent with the two-response drug discrimination results; that is, just as the two-response procedure did not distinguish each drug from triazolam; neither did the self reports. For example, triazolam, secobarbital, and zolpidem produced similar dose-related effects on several self-report measures (e.g., on measures of sedation such as the PCAG subscale of the ARCI and visual analog ratings overall feelings of drug effect and drug-induced high) and on the DSST. Thus, the drug discrimination measure appears to have greater selectivity than the drug self-report measures used in these particular studies. However, in another three-choice study, zolpidem was distinguished from triazolam by its discriminative stimulus effects and certain subjective effects [e.g., measures of somatic symptoms; (7)]. This study points out that the lack of selectivity of subjective effects can be due to the particular measures used.

SUMMARY AND FUTURE DIRECTIONS

The novel-response procedure is one of several three-choice drug discrimination procedures developed for humans in an effort to increase the selectivity of drug and placebo responses. Among three-choice procedures developed for human drug discrimination, the novel-response procedure in particular is based on principles from the experimental analysis of behavior. Via instructions, including the differential reinforcement contingency for novel-appropriate responding, novel responding to drugs with discriminative stimulus effects unlike either training condition is occasioned. The procedure was initially developed to further understanding of the over-inclusiveness of placebo-appropriate responding; however, the procedure has also addressed the selectivity of drug-appropriate responding and contributed to understanding of partial substitution.

Thus far, the novel-response procedure has only been applied to sedative/hypnotics. Future research should extend the use of the novel-response procedure to other classes of drugs, such as opioids. The ability of the novel-response procedure to distinguish among drugs selective for different subtypes of opioid receptors could be compared to other three-choice procedures [e.g., (20,21)] that make finer distinctions among drugs than standard two-choice studies. The novel-response procedure could also be applied to determine the discriminative stimulus effects of more complex drug discriminations, such as those involving antagonism and drug mixtures.

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