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THE EFFECTS OF CHLORDIAZEPOXIDE ON RESURGENCE IN MALE RATS: A PRELIMINARY INVESTIGATION

by

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Resurgence is defined as the recurrence of a previously but no longer reinforced behavior when a more recently reinforced behavior undergoes extinction. The present study investigated the effects of chlordiazepoxide (CDP), a member of the class of drugs known as benzodiazepines, on the resurgence of lever pressing responses emitted by male Sprague-Dawley rats. The general procedure was as follows: An operant (left lever presses) was reinforced and subsequently extinguished. Then, a second operant (right lever presses) was reinforced. Finally, 0, 1, 3, 10, and 30 mg/kg doses of CDP were administered via intraperitoneal injections to groups of nine animals each during 3 consecutive days of 1-hr exposure to concurrent extinction schedules. Slightly more left lever pressing (the resurgence response) occurred in the 1 mg/kg group than in the control group, while dose-dependent decreases in resurgence, as well as overall responding, occurred in the 3, 10, and 30 mg/kg groups relative to control levels. These results are discussed in terms of their similarity to those found in investigations of the effects of benzodiazepines on extinction.

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Marc Alden Weeden

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INTRODUCTION

Extinction is a behavioral phenomenon that allows an organism to adapt to environmental changes (Bouton, 2004). In the operant conditioning paradigm, extinction can be defined as a procedure wherein the maintaining reinforcer for a behavior of interest is withheld, causing a weakening of that behavior (Cooper, 1987). There are a large number of studies in the behavior analytic literature examining the effects of extinction and the variables that modulate those effects. For example, a May 25, 2010 search of the *Scopus* database across all available years using "The Journal of the Experimental Analysis of Behavior" and "extinction" as search terms yielded 229 results, while a search of the same database using the keywords "Journal of Applied Behavior Analysis" and "extinction" yielded 189 results. This result suggests that extinction and related phenomena have been, and continue to be, fertile ground for both basic and applied behavioral researchers.

The topic of the present research is resurgence, which is an interesting behavioral phenomenon closely related to extinction that has generated relatively little research attention (Doughty & Oken, 2008). Resurgence is defined as the recurrence of a previously but no longer reinforced behavior when a more recently reinforced behavior undergoes extinction (Catania, 1998). To provide a conceptual background for the present research, which examined the effects of a sedative-hypnotic drug, chlordiazepoxide, on resurgence in rats, subsequent sections of this document briefly overview extinction-related behavioral phenomena and extinction in applied behavior analysis (ABA).

Behavioral analyses of drug action, that is, behavioral pharmacology, is then overviewed, followed by an introduction to chlordiazepoxide, with special focus on its behavioral effects. The review section ends with a selected review of the resurgence literature.

EXTINCTION AND ITS VARIANTS

Respondent Extinction

Because respondent extinction is not closely related to the present research, it will be covered very briefly. Detailed coverage of the topic is provided by Kehoe and Macrae (1998). As a large body or research illustrates, neutral stimuli (NS) can acquire the capacity to elicit an unconditioned response (UR) through a process called **respondent conditioning** (also called Pavlovian or classical conditioning). The classic example of this type of learning is associated with the Russian physiologist, Ivan Pavlov. He observed that his dogs salivated each time his laboratory assistant approached their cages to feed them. He hypothesized that the increased salivation was under the control of a stimulus that was predictive of food (e.g., the footsteps of the assistant or the sound of the cage opening). Pavlov (1927) then conducted a series of experiments to test his hypothesis. He arranged for an auditory stimulus (the sound of a metronome) to precede immediately the delivery of meat powder. After several pairings of the auditory stimulus (NS) and the food, which was an unconditioned stimulus (US) that elicited salivation (unconditioned response, UR), the auditory stimulus elicited salivation in the absence of food. The auditory stimulus was now a **conditioned stimulus (CS)** and the salivation it elicited was a **conditioned response (CR)**.

A CS presented alone for a number of trials will lose the capacity to elicit the CR. This will also happen if the US is presented randomly in relation to the CS (Pavlov, 1927). The loss of the capacity of a formerly effective CS to elicit the CR produced by these procedures is called **respondent extinction**. So, for example, in the foregoing example, presenting the tone repeatedly without the food will cause the tone to cease to elicit salvation. If, however, during the next extinction session the response (salivation) is observed in the presence of the CS, then **spontaneous recovery** has occurred. When a previously extinguished behavior is observed when the context is changed, **renewal** has taken place. This typically occurs when the subject is returned to the conditions where the behavior was originally conditioned. If, after extinction, a behavior recovers when the subject is exposed to the US alone, then **reinstatement** has occurred. Recovery of responding that takes place when the CS and US are again paired after extinction (Bouton & Nelson, 1998) is called **reacquisition**. Reacquisition can be swift, especially if the background cues arranged during reacquisition were present during conditioning.

Operant Extinction

When a behavior no longer produces its maintaining reinforcer, the behavior ultimately ceases. This process is referred to as **operant extinction** (Byrne & Poling, 2000). Consider the following hypothetical example of a child who, when denied access to a preferred toy, engages in tantrum behavior which consists of yelling, pounding his fists on the floor, and throwing objects. His parents frequently give the child the toy after the occurrence of the tantrum and the behavior persists. After consulting with a Board Certified Behavior Analyst®, the parents decide to withhold access to the toy when the

boy is engaging in tantrum behavior, and, after a number of unsuccessful tantrums, the behavior weakens and eventually ceases completely. This is an example of operant extinction.

The use of extinction can be problematic, however. A phenomenon called **extinction-induced bursting** frequently occurs when the maintaining reinforcer for a behavior of interest is withheld. This phenomenon consists of an increase in the intensity, duration, or rate of the behavior no longer being reinforced (Miltenberger, 2004). For example, the child in the current example may yell louder, pound his fists harder, and throw objects with more force than before extinction was implemented. New topographies can occur as well. The child in the current example may kick furniture, for example, in addition to the previously mentioned behaviors that comprise a tantrum before the behavior finally decelerates. This phenomenon is typically referred to as **extinction-induced variability** (Antonitis, 1951).

Under certain circumstances, extinguished behavior recurs in the next extinction session (Catania, 1998). This is called **spontaneous recovery**. In our example, following extinction the tantrum behavior disappears one day, but appears the next at a level comparable to that before the extinction procedure was implemented. When a previously extinguished behavior is observed when the context is changed, **renewal** has taken place (Welker & McAuley, 1978). This typically occurs when an organism is returned to the circumstances where the behavior was originally conditioned. Reinstatement also is used to refer to the recurrence of previously emitted behavior produced by response-independent reinforcer delivery (Reed & Morgan, 2006).

RESURGENCE

As stated previously, resurgence is defined as the recurrence of a previously, but no longer, reinforced behavior when a more recently reinforced behavior is extinguished (Catania, 1998; Epstein, 1983, 1985). In studies that examine resurgence, an operant (R1) is reinforced then subsequently extinguished. Next, a second operant (R2) is reinforced then extinguished (the resurgence condition) and any increase in the first response (R1) is termed resurgence (Da Silva, Maxwell, & Lattal, 2008).

In an early demonstration of resurgence, Epstein (1983) used a concurrent schedule arrangement with pigeons. Two response keys were active throughout the experiment. Pecking on one key was reinforced under a variable-interval (VI) 60-s schedule until a moderate, steady rate of responding occurred. Reinforcers were withheld for 1 or more sessions (determined at random) for a maximum of 15 sessions. All extinction sessions were 1 hr in length. Next, while a response incompatible with key pecking (e.g., wing raise, quarter turn right, head turn right) was reinforced 20 times, each pigeon was observed on a video monitor while the feeder was operated with a hand switch. Reinforcers were withheld after the alternative response was reinforced 20 times, after which pecking resumed on the key correlated with a history of reinforcement. Few pecks occurred on the key on which responses were never reinforced, which indicated that pecking on the key correlated with reinforcer delivery was not simply the result of extinction-induced variability.

In 1985, Epstein described a three-condition study wherein a pigeon's pecks on the right key of a typical 3-key chamber produced access to food on a VI 1-min schedule.

All three keys were white and illuminated during this condition. In the second condition, only pecks on the center key were reinforced under the VI 1-min schedule and, predictably, responding shifted to the center key. The rate of responding on the right key decreased as pecking rates stabilized on the center key. There were no pecks on the right key by the end of the 10th 1-hr session. In the third condition, no reinforcers were delivered. There was little responding on the left key (the one with no associated history of reinforcement), while responding on the center key (the key that most recently produced access to food) was high for the first 40 minutes of the extinction session. At this point, responding on the right key (the key with the more distal history of reinforcement) resumed at high rates. The results of this study are noteworthy because resurgence was observed when the reinforcer for the first response was withheld while reinforcers were available concurrently for the second response. These results have been replicated elsewhere (e.g., Lieving & Lattal, 2003, Experiments 2, 3, and 4). To date, behavior analysts have simply construed resurgence as a behavioral outcome of extinction and have only recently attempted to delineate the behavioral principles that account for, or affect, the phenomenon (e.g., Lieving & Lattal, 2003).

Resurgence in Problem Solving

Skinner (1953) defined a problem as a circumstance where a highly probable response cannot be emitted. Resurgence may be a potential mechanism for creativity and problem solving (Lieving & Lattal, 2003; Shahan & Chase, 2002). Epstein (1987) trained a pigeon to engage in a number of separate responses including pushing a box toward targets, climbing onto a box, and pecking a plastic banana that hung within reach. The

plastic banana was then presented out of reach, while only pecks to the banana were reinforced. Epstein then arranged extinction of all responses with the exception of pecks to the banana. Under these conditions (the problem situation), the previously trained behaviors reappeared and combined. The pigeon pushed the box under the banana, climbed onto the box, and then stood on the box and pecked the banana. After the novel combination was reinforced, the chain of responses occurred again when the problem conditions were presented on subsequent occasions.

Resurgence and Relapse

Although more research in the area is required, resurgence may provide the framework necessary to explain behaviorally problems of social significance such as clinical relapse of undesirable behavior (Lieving & Lattal, 2003; Mace et al., 2010). Problem behavior such as self-injury and the consumption of illegal drugs (discussed in greater detail later) may be able to be explained under some circumstances by resurgence. Consider the example of a young man diagnosed with autism who engages in head banging. After a functional analysis (Iwata, Dorsey, Slifer, Bauman, & Richman, 1982/1994), it is determined that the maintaining reinforcer for his problem behavior is attention from his parents. He is then taught to mand for attention via sign language and attention for head banging is minimized. After learning and using the mand for attention, head banging decreases to a near-zero level and his parents' vigilant responding to the mands wanes. Head-banging then increases to pretreatment levels. This increase in the previously, though not currently, reinforced behavior can be explained by resurgence and not simply by a hypothetical construct like "frustration." With its mechanism apparent,

the response can be treated more effectively. For example, parents could be re-trained to ensure that they are attending to the mand in a timely manner, thus increasing reinforcer density and weakening the establishing operation (EO) for the problem behavior. In addition, a program to teach the young man to wait for attention or to occupy himself with other activities could be implemented.

Lieving, Hagopian, Long, and O'Connor (2004) examined the resurgence of problem behavior in two children diagnosed with developmental disabilities. The first was Christine, a 7-year-old girl diagnosed with severe mental retardation and autism. She reportedly engaged in disruption (banging, throwing, and kicking objects), self-injury (head banging, self-biting, and body hitting against walls), and aggression (hitting, kicking, pushing, and chin-pressing). Christine was ambulatory, nonverbal, and communicated via gestures. The second participant was Sam, a 9-year-old boy diagnosed with mild mental retardation, mood disorder, oppositional defiant disorder, and attention deficit hyperactivity disorder. He reportedly engaged in disruption (banging, throwing, and kicking objects), aggression (hitting, kicking, pushing, grabbing and throwing objects within 2 ft of a person), dangerous acts (standing on furniture, touching electrical outlets, throwing objects to ceiling, and turning over heavy objects), and inappropriate language (cursing). Sam was verbal and ambulatory.

The data from functional analyses (Iwata et al., 1982/1994) for both participants suggested that the problem behavior for both individuals was maintained by access to tangibles. In the first condition of the experiment, all instances and topographies of aggression were reinforced. Next, all topographies of interest were measured while extinction was implemented for one specific topography after another. For example, in

the case of Sam, reinforcers were withheld for disruption, then for disruption and dangerous acts, and finally for disruption, dangerous acts, and cursing. Resurgence was observed for both participants across conditions. That is, each participant emitted different topographies of aggression following exposure to extinction for some other topography of aggression.

These results suggest that practitioners should consider resurgence when assessing and treating challenging behavior. It is important for practitioners to program for alternative, appropriate responses to be reinforced in the target setting in an effort to prevent the resurgence of problem behavior. It may even be practical to train multiple desirable responses in the event that reinforcers for one topography of appropriate behavior are not available. This may delay or, perhaps, prevent problem behavior from resurging.

Resurgence and Infant Caregiving Responses

A recent study by Bruzek, Thompson, and Peters (2009) was conducted in an effort to ascertain the conditions under which the resurgence of infant caregiving responses was likely to occur in human participants. In their study, the recorded crying of an infant was terminated dependent upon the emission of a targeted caregiving response (e.g., rocking, feeding, playing) towards a baby doll in a room which included materials designed to simulate that of a typical infant (e.g., blankets, a bottle, toys). Approximately 2 min prior to each experimental session, participants (undergraduate students at the University of Kansas who were given extra credit for their participation in the study) were

given vocal instructions that advised them to “do what comes naturally” in response to the simulated crying and not to touch the data recording devices.

In Experiment 1, the simulated infant cry was played at the beginning of the session and was terminated dependent upon the emission of the target response (response 1) for 3 s. If the target response ceased for 3 s, the cry was turned on again. This experimental condition was repeated until the acquisition criteria were met (5 consecutive min of engagement in the target response). In the extinction phase of response 1, the cry was presented for the duration of the session independent of responding. Criterion for extinction was the absence of the target response for 5 min. During the next phase, a second response was negatively reinforced, and after engaging in the response for 5 continuous min, was then no longer reinforced (i.e., the response no longer produced the termination of the simulated crying).

Resurgence was observed in 6 of the 7 participants in Experiment 1. This is noteworthy for two reasons: (a) the results were consistent with prior findings by Epstein (1983) and Lieving and Lattal (2003), who found that resurgence occurred when the initial target response was exposed to traditional extinction, and (b) because resurgence was demonstrated in human participants in a negative reinforcement preparation, the first of its kind. In addition, the results of Experiment 1 were consistent with Epstein and Lieving and Lattal in that the magnitude of resurgence was not affected by the degree of exposure to extinction.

Experiment 2 was conducted to examine the effects of length and recency of reinforcement on responding during the resurgence condition. Play responses were those under investigation in this experiment. Response 1 was shaped using the same procedures

described in Experiment 1. However, the participants were required to complete three sessions. Next, a second play response was reinforced for a single session, giving the participant a more recent, but shorter history of reinforcement for response 2. During the extinction phase, both responses 1 and 2 were not reinforced in the same manner as in Experiment 1. In the resurgence condition, a third response was reinforced and then subsequently exposed to extinction. Results indicated that no participants engaged in a higher level of the most recently reinforced response during the resurgence condition. These results are consistent with those obtained in pigeons by Lieving and Lattal (2003), who found that the recency of exposure to the reinforcement contingency had no effect on the degree to which responses resurged. Taken together, these two studies suggest that how recently a behavior is reinforced has little effect on the magnitude of resurgence.

The results of the study by Bruzek et al. (2009) do suggest, however, that the length of reinforcement history may affect resurgence. In their study, responses with a longer, but more temporally distant, history of reinforcement were more likely to resurge than those with shorter, more temporally proximal histories of reinforcement. A limitation of this study is that response 1 was always associated with the longer history of reinforcement. A study involving rats by Reed and Morgan (2006) suggested that resurgence shows a primacy effect. The experimenters trained rats three sequences of responses and found that after the most recently reinforced response sequence resurged when exposed to extinction, the more recently trained response sequences were more likely to resurge. Thus, primacy may be a confound in the study by Bruzek et al. (2009).

Resurgence and Functional Communication Training (FCT)

Volkert, Lerman, Call, and Trosclair-Lasserre (2009) evaluated resurgence during treatment with FCT in two experiments. In FCT, the reinforcer for an undesirable behavior is withheld and is delivered dependent upon the emission of an alternative appropriate communication response. Failure to implement procedures with integrity in the natural environment may lead to an increase in the rate of problem behavior (Mace & Roberts, 1993).

The participants in this study were children diagnosed with developmental disabilities, each with a history of self-injury, aggression, or disruption maintained by social reinforcers. This was verified through functional analysis (Iwata et al., 1982/1994). In Experiment 1, functionally equivalent communication responses were trained across three children and subsequently exposed to extinction. In Experiment 2, three children (one child participated in both experiments) were exposed to thin schedules of reinforcement rather than strict extinction. Overall, results of both studies showed a robust resurgence of problem behavior. Noteworthy is that the results of Experiment 2 are consistent with those obtained by Lieving and Lattal (2003), who observed resurgence of previously reinforced behavior in pigeons (albeit at low levels) when exposed to a thin schedule of reinforcement.

Summary and Conclusions Regarding Resurgence

Although it was first demonstrated nearly 30 years ago, for many years resurgence generated little research interest. Recent studies have shown, however, that resurgence is

a robust outcome of extinction that has significant applied implications. Basic and applied researchers have begun to explore the variables that influence resurgence and considerable progress has been made. To date, however, no one has examined whether drugs affect it. For four decades, behavioral pharmacologists (e.g., Thompson & Schuster, 1968) have emphasized that the research methods and analytical concepts characteristic of behavior analysts provide a solid foundation for isolating and explaining the behavioral effects of a wide range of substances. The present study used this approach, summarized below, to study the effects of chlordiazepoxide.

BEHAVIORAL PHARMACOLOGY

Behavioral pharmacology is a discipline that uses the research tactics of the experimental analysis of behavior (EAB) to study the behavioral effects of drugs. These methods, popularized by B. F. Skinner (1938) and explained in detail by Sidman (1960), have been used to study drug abuse and the effects of many different substances on what laypeople term learning, memory, and motivation. Consistent with the philosophy of radical behaviorism, behavioral pharmacologists look for the locus of behavioral control in the environment and reject hypothetical constructs (e.g., the mind, the self) as causes of behavior, preferring instead to operate under the assumptions that (a) behavioral effects of drugs are lawful and subject to scientific analysis, and (b) behavioral effects of drugs are worth studying in their own right (Poling & Byrne, 2000). To behavioral pharmacologists, drugs are simply stimuli that can affect behavior.

The main areas studied by behavioral pharmacologists are the behavioral loci of drug action (i.e., actual changes in behavior produced by a drug), the behavioral

mechanisms of drug action (i.e., the stimulus properties of the drug or the effects of the drug on behaviors controlled by other stimuli), and the variables that modulate drug effects (i.e., the pharmacological and behavioral variables that influence a drug's effects) (Byrne & Poling, 2000). Through research in these areas, behavioral pharmacologists endeavor to gain a knowledge base sufficient to predict and control the behavioral effects of drugs.

As stated earlier, behavioral pharmacologists view drugs as stimuli that lawfully affect behavior. Drugs have been demonstrated by behavioral pharmacologists to function as motivational operations (e.g., Northup, Fusilier, Swanson, Roane, & Borrero, 1997), discriminative stimuli (e.g., Kamien, Bickel, Hughes, & Higgens, 1993), negative reinforcers (e.g, Hoffmeister, 1975) and positive reinforcers (e.g., Meisch & Lemaire, 1993).

One of the most important contributions of behavioral pharmacologists is their demonstration that learning can powerfully modulate the effects of a given drug. For example, in organisms that are physically dependent on a drug, pairing environmental stimuli with drug abstinence (which produces a set of signs and symptoms known as withdrawal) can establish those stimuli as CSs that elicit conditioned withdrawal (Laraway, Snycerski, Byrne, & Poling, 2000). The presentation of such CSs to a person for which they had been paired with heroin abstinence would produce vomiting, sweating, yawning, diarrhea, hyperalgesia, and dysphoria. It would also serve as an establishing operation for heroin as a reinforcer, increasing the likelihood of drug-craving and drug-seeking. Therefore, any treatment package for a heroin abuser should include a procedure that decreases the strength of the CR (symptoms of withdrawal) elicited by the CS

(environmental stimuli associated with a withdrawal syndrome), thereby reducing the value of a drug and decreasing the likelihood of potentially dangerous drug-seeking behavior. The necessity of such a procedure is obvious only to those aware of conditioning principles as they relate to drug effects.

Results of a study involving rats by Podlesnik, Jimenez-Gomez, and Shahan (2006) suggested that resurgence may play a role in drug relapse. The experimenters arranged alcohol administration as the reinforcer for right-lever pressing by rats. Then, in the second condition, they discontinued alcohol administration for right-lever presses while chain pulling was reinforced with the delivery of food pellets. In the final condition, when food delivery was terminated, chain pulling weakened while right-lever pressing resurged. Responding on the left lever (a control manipulandum that never produced programmed consequences) was minimal.

While perhaps an oversimplification, Podlesnik et al. (2006) proposed that food-reinforced chain pulling in rats was analogous to a socially appropriate alternative behavior in humans (e.g., securing gainful employment, improved relationships with friends and family) established through treatment, while the discontinuation of food delivery could be viewed as the onset of undesirable events (e.g., loss of employment, family conflicts). Further research in this area is required to strengthen their position.

As of this writing, no study has investigated the effects of drugs on resurgence. The present study did so with respect to chlordiazepoxide, a well-studied drug with a range of behavioral effects, including the capacity to selectively increase punished responding. Insofar as both punishment and extinction are response-weakening operations, it is possible that chlordiazepoxide will increase resurgence, as well as

punished responding. Studies showing anti-punishment effects of chlordiazepoxide, as well as other effects of the drug, are summarized in the following section.

CHLORDIAZEPOXIDE

Chloridiazepoxide (CDP) is a benzodiazepine. Benzodiazepines are a class of drugs that have anxiolytic (anti-anxiety), sedative, anticonvulsant, amnestic, and relaxant properties (Julien, 2008). They are sometimes called selective central nervous system (CNS) depressants because they are agonists of the neurotransmitter gamma-amniobutryic acid (GABA), meaning they facilitate the binding of GABA (Schroeder et al., 1998). As a result of this enhanced effect, an influx of chloride ions occurs, causing hyperpolarization of the postsynaptic neuron, depressing its excitability (Charney, Mihic, & Harris, 2006). The limbic system, which consists of the hippocampus, amygdala, anterior thalamic nuclei, and limbic cortex, is a group of brain structures that support a number of functions including behavior, emotion, olfaction, and long-term memory (Carlson, 2009). The anxiolytic effects of benzodiazepines are produced through their effects on this system. It should be noted that the side effects of benzodiazepines (e.g., muscle relaxation, increased seizure threshold, sedation) occur as a result of their interactions at other regions of the brain including, but not limited to, the brain stem and cerebral cortex. For a more in-depth coverage of the preceding information, please see Charney et al. (2006).

In the early 1960s, the benzodiazepine known as CDP (Librium) was introduced and quickly became a popular treatment for anxiety. Due to its anticonvulsant effects, the drug was also used to treat chronic alcohol withdrawal syndrome. It is noteworthy that the effects of all benzodiazepines are very similar in humans (McKim, 2007). However, their

relative potency differs. For example, some are more potent as sedative-hypnotics (e.g., flurazepam), while others are more potent as anxiolytics (e.g., alprazolam). It is for this reason that, in 1963, diazepam (Valium) was marketed specifically for the treatment of anxiety. Benzodiazepines continue to be used to this today as a short-term treatment of insomnia and stress-related anxiety. Among the reasons for this are that they are easy to use, act quickly, and have relatively low toxicity (Julien, 2008). However, due to the potential for producing dependency, benzodiazepines are contraindicated for long-term use. For conditions that require long-term treatment (e.g., panic disorder, phobias, and posttraumatic stress disorder), behavioral interventions and antidepressant drugs are generally recommended.

Untoward effects of benzodiazepines in humans can include confusion, fatigue, increased reaction time, and motor impairment (McKim, 2007). A study by Betts, Clayton, and MacKay (1972) showed significant driving impairments in participants who were administered a 50-mg dose of CDP divided over the course of 36 hours. Further, the effects of benzodiazepines are potentiated by alcohol. This effect was demonstrated by Linnoila and Hakkinen (1974), who showed that increased collisions occurred in participants given a 10-mg dose of diazepam (Valium) prior to a simulated driving task.

Pharmacokinetics

Route of Administration and Absorption

In humans, benzodiazepines are typically administered parenternally (by injection) or orally. The route of administration varies depending on the drug's intended use. For

example, if an immediate effect is desired, as in the case where the drug is used to quell a seizure, an intravenous injection (IV) may be necessary. In the case where anxiety is to be treated over the course of a 2-week period, the oral route is more appropriate.

Benzodiazepines are readily absorbed from the digestive system. However, the speed at which each is absorbed varies across compounds and individuals. To illustrate this point, consider a study by Garattini, Mussini, Marcucci, and Guaitani (1973), who found that the blood level (the amount of drug present in the bloodstream) of one person was 20 times higher than that of another person given the same dose of the same dose of diazepam. One of the fastest acting benzodiazepines, diazepam, reaches a peak in approximately 30 to 60 minutes, whereas others, including CDP, may take up to several hours to peak (McKim, 2007).

Distribution

Once a benzodiazepine enters the bloodstream, its duration of action is determined by the lipid solubility of the drug. Lipid solubility refers to the extent to which a drug will dissolve in fat tissue in the body (McKim, 2007). In general, drugs vary in the level of lipid solubility. Highly lipid-soluble compounds like benzodiazepines cross the blood-brain barrier, a mechanism that protects the brain from harmful substances, and produce their effects on the brain quickly (Poling & Byrne, 2000). These effects can also dissipate quickly as benzodiazepine molecules have a tendency to be redistributed outside the CNS in the body fat. Most drugs do not have any effect in the body fat. Put differently, drugs absorbed in fat are generally inactive. The drug then is released in small amounts back into the bloodstream where it is metabolized by the liver (McKim, 2007).

Biotransformation

While in the liver, benzodiazepines are broken down by enzymes into new compounds called metabolites (Poling & Byrne, 2000). These new compounds are generally inactive. That is, they do not affect biological processes. However, in the case of CDP, the metabolites are active, which influences the duration of action of the drug. The metabolites have an even longer half-life (the time it takes for half the amount of drug to be broken down and eliminated) than that of the original substance. According to Julien (2008), the mean elimination half-life of CDP in humans is 10 hours (range 8-24 hr). It is noteworthy that the elderly have a reduced capacity to metabolize benzodiazepines and their active metabolites. In fact, it may take an elderly patient 1 month or longer to be completely drug free after a single dose of a long-acting benzodiazepine (Julien, 2008). In addition, the metabolism of benzodiazepines can be slowed by alcohol. In fact, Desmond, Patwardham, Schenker, and Hoyumpa (1980) demonstrated that even a small drink of alcohol can increase the half-life of CDP by 60%. Readers interested in more extensive coverage of the biotransformation of benzodiazepines are directed to Charney et al. (2006).

Excretion

A two-phase excretion curve results from the aforementioned redistribution of drug molecules in body fat (Charney et al., 2006). First, the blood level drops quickly as the drug is redistributed. Second, the remaining drug in the bloodstream is metabolized as the drug stored in the body fat is released. This second phase is generally far longer than

the first, and the time it takes for the drug to be inactivated and removed from the body varies from individual to individual.

Drugs or their metabolites are typically removed from the body in the urine. However, it is not uncommon for substances to be excreted through feces, saliva, exhaled air, or breast milk (Poling & Byrne, 2000). In fact, benzodiazepines easily cross the placental barrier and appear in the milk of mothers who are breastfeeding their children (McKim, 2007).

RATIONALE FOR THE PRESENT STUDY

In the behavioral pharmacology literature, the term **anti-punishment** has been used to describe a drug-induced increase in behavior that has been specifically punished (Rasmussen, 2006). In a typical investigation of the anti-punishment effects of a drug, a baseline response rate of an operant of interest, usually lever-pressing, is established under a schedule of food reinforcement. Next, the operant of interest is exposed under some schedule to a stimulus (e.g., electric shock, timeout) which has been demonstrated previously to decrease responding (e.g., van Haaren & Anderson, 1998). Anti-punishment effects are demonstrated when, in the presence of the drug, the punished behavior increases.

Anti-punishment effects are typically demonstrated in studies involving benzodiazepines, barbiturates, and ethanol, all GABA agonists (Rasmussen, 2006). Sometimes referred to as “disinhibitory” effects, increases in punished responding have been observed in studies with rats (e.g., Koob, Braestrup, & Britton, 1986), humans (e.g., Carlton, Siegel, Murphee, & Cook, 1981), and a number of other species including

squirrel monkeys (e.g., Barrett, Brady, & Witkin, 1985), cats (e.g., Masserman & Yum, 1946), and pigeons (e.g., Brocco, Koek, Degryse, & Colpaert, 1991).

A major problem of anxiolytic and sedative-hypnotic drugs, including ethanol, is engaging in behavior that should be suppressed. Consider the following hypothetical situation wherein a person has consumed too much alcohol and, because of the obvious signs of intoxication, the individual's love interest may withhold attention. As a result, resurgence of a previously extinguished, or perhaps punished, inappropriate behavior (e.g., calling a former lover) may occur. Further, Gray and McNaughton (2000) concluded in a recent review that anxiolytic drugs increase resistance to extinction. There are other mechanisms that could contribute, but sedative-facilitated resurgence may also play a role. As stated earlier, both punishment and extinction are response-weakening operations. It may be the case that CDP will facilitate resurgence, which is a prominent behavioral result of exposure to extinction. The purpose of the present study was to investigate this possibility and to see if a drug that increases responding suppressed in one way (i.e., via punishment) also increases responding suppressed in another way (i.e., via extinction, currently [R2] or previously [R1]).

METHODS

Subjects

Forty-five pharmacologically naïve male Sprague-Dawley rats, purchased from Charles River (Portage, MI) and approximately 270 days old at the beginning of the study (mean weight = 394 g) were used. The rats had histories of water deprivation and lever

pressing to earn access to water. They were housed individually in plastic cages (24 cm long × 31.5 cm wide × 21 cm high) located in a colony room maintained on a 12-h light/12-h dark schedule and kept at a relatively consistent temperature (20-22 C). The rats were maintained at 80-85% of their free-feeding weight throughout the study and had unlimited access to water. The rats were fed Purina Rat Chow (Ralston-Purina, St. Louis, MO) after each experimental session. This study was conducted in accordance with the *Guide for the Care and Use of Laboratory Animals* promulgated by the National Research Council (1996) and was approved by the Institutional Animal Care and Use Committee (IACUC) at Western Michigan University (Appendix A).

Apparatus

Experimental sessions were conducted in commercially available operant conditioning chambers, each 31.5 cm long × 25.5 cm wide × 25 cm high (Med Associates, St. Albans, VT). Each chamber contained two retractable response levers located 6 cm above the floor on the right and left sides of the front wall. An aperture located 2 cm above the floor in the middle of the front wall allowed access to food. When scheduled, 45 mg food pellets (BioServ, Frenchtown, NJ) were delivered into the aperture. An overhead 28-V light provided ambient illumination throughout experimental sessions. Each chamber was housed in a sound- and light-attenuating shell equipped with an exhaust fan that provided masking noise and ventilation. Experimental events were controlled and data were recorded by MED-PC software operating on an IBM-compatible personal computer located in an adjacent room.

Procedure

As Cleland, Foster, and Temple (2000) pointed out, to conduct investigations of resurgence where the levels of the independent variable are manipulated in a within-subject design, many reinforcement and extinction procedures would have to be repeated. The results of a number of studies (e.g., Bullock, 1960; Bullock & Smith, 1953; Clark, 1964; Schaeffer, Salzburg, Birkle, & Ryan, 1967) have suggested that over successive extinction and retraining conditions, responding in extinction progressively weakens. In addition, resurgence has been demonstrated to be repeatable only across two exposures to the resurgence procedure (Lieving & Lattal, 2003). For these reasons, a between-groups experimental design was deemed appropriate for this experiment. Although the effects of each level of the independent variable are not assessed across each subject and, therefore, the variables controlling the behavior of individual subjects are not isolated (Sidman, 1960), a between-groups design allows for the tentative generalization of results across a population. In the present study, separate groups of 9 rats were exposed to 5 pharmacological conditions of interest with behavioral procedures held constant.

Initially, magazine training was conducted by exposing each animal to a fixed-time (FT) 60-s schedule of reinforcement. Under this schedule, a single food pellet was delivered independent of responding every 60 s for 1 hr. At the end of the session, cages were inspected to ensure that the animals had consumed all pellets. Next, the animals were exposed to FR 1, 3, 5, 7 and 10 schedules of reinforcement on the left lever (R1). Because the rats had a history of lever pressing prior to this study, no training was required to engender responding. Under the FR schedules, a food pellet was delivered as

soon as the specified number of responses (e.g., 5 under FR 5) was emitted. Responses on the right lever produced no reinforcers. Sessions ended when the animals completed 60 ratios (cf. Lieving & Lattal, 2003). The FR 10 schedule on the left lever was in effect for 10 consecutive days, while responses on the right lever produced no reinforcers. Next, in the response elimination condition, 1 hr extinction sessions were conducted. This condition was in effect for a minimum of 10 sessions and until the each rat had emitted 60 or fewer responses (less than one response per min) for a total of 6 sessions. This criterion was based on response elimination procedures described by Da Silva et al. (2008). Across all subjects, this took between 7 and 12 days.

In the following condition, all subjects were exposed to FR 1, 3, 5, 7, and 10 schedules of reinforcement on the right lever (R2). The FR 10 schedule was in effect on the right lever for 10 consecutive days while no reinforcers were available for responses on the left lever. While the FR 10 schedule was in effect, intraperitoneal (IP) saline injections (dose) were given on day 1, 3, 5, 7, and 9 to control for the effects of the injection itself. Finally, 0, 1, 3, 10, and 30 mg/kg doses of chlordiazepoxide (CDP, Sigma, St. Louis, MO) were administered via IP injections to groups of nine animals each during 3 consecutive days of 1 hr exposure to concurrent extinction schedules. The drug was administered in a volume of 1 ml/kg, 15 min prior to the start of the experimental sessions. Chlordiazepoxide hydrochloride was dissolved in an isotonic sodium-chloride solution approximately 4 hrs prior to administration. This allowed the drug to attain room temperature prior to injection.

DATA ANALYSIS

Responses on the lever for which extinction was just arranged, R2, or the **extinction lever**, were recorded each session during which extinction was arranged for that lever. Responses on the other lever, R1, or the **resurgence lever**, also were recorded. Two measures were used to quantify resurgence. One was the absolute number of responses on the resurgence lever. The other was the number of responses on the resurgence lever expressed as a proportion of responses on both levers. Two-way repeated measures analysis of variance (ANOVA), with dose (or group) and extinction day as factors was performed to examine possible differences in responding among the five groups during the resurgence sessions. The Bonferroni test (a conservative posttest) was used for the post hoc analyses of differences in responding between individual groups relative to control. All statistical tests were run with GraphPad Prism statistical software with alpha set at $p < 0.05$.

In addition to examining the effects of CDP on resurgence, the drug's effects on the response currently undergoing extinction, R2, also were assessed. This was done by conducting a two-way repeated measures analysis of variance (ANOVA), with dose (or group) and extinction day as factors and number of responses on the extinction lever as the dependent variable.

RESULTS

The presence of resurgence was confirmed by examining performance of the control group (which received 0 mg/kg CDP). Figure 1 shows for this group the mean proportion of right-lever presses (no associated history of food reinforcement) emitted during the first extinction session compared to the mean proportion of responses emitted on the left lever (the lever with an associated history of food reinforcement) during the first day of the resurgence condition. Statistical analysis via a paired (or correlated samples) *t* test revealed that the proportion was significantly higher for right-lever responses ($t = 3.445$, $df = 8$, $p < 0.01$), indicating that resurgence, not simply extinction-induced variability, affected responding.

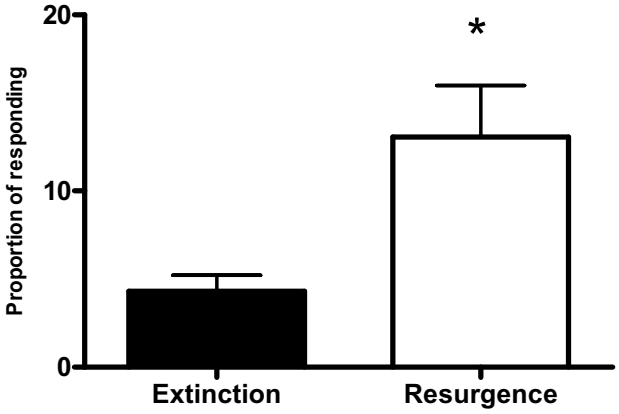

Figure 1. Confirmation of resurgence via a paired *t* test.
The presence of resurgence was confirmed by examining performance of the control group. The mean proportion of right-lever presses (no associated history of reinforcement) emitted during the first extinction session compared to the mean proportion of responses emitted on the left lever (the lever with an associated history of food reinforcement) during the first day of the resurgence condition. Statistical analysis via a paired *t* test revealed that the proportion was significantly higher (indicated by an asterisk) for right lever presses ($t = 3.445$, $p < .01$), indicating that resurgence affected responding.

Figure 2 shows the mean number of resurgence responses across each group per day. On Day 1, the mean for the 1 mg/kg group (M = 40.33) was slightly higher than that of the control group (M = 34.44), with dose-dependent decreases in responding occurring across the 3, 10, and 30 mg/kg groups with means of 27.89, 5.56, and 4.89 responses per day, respectively. On Day 2, the mean for the control group was highest (M = 20.33), followed in descending order by the 1 (M = 12.89), 10 (M = 12.22), 3 (M = 8.56), and 30 mg/kg (5.22) groups. On Day 3, the mean for the control group was highest (M = 14.33), followed by dose-dependent decreases in the 1 (M = 12.89), 3 (M = 9.11), 10 (M = 4.56), and 30 mg/kg (3.56) groups. The effect of CDP was analyzed by two-factor ANOVA (dose and day as repeated factors). This analysis showed a significant effect of dose [$F(4, 40) = 11.00$, $p < .05$] and day [$F(2, 40) = 16.00$, $p < .05$], as well as a significant

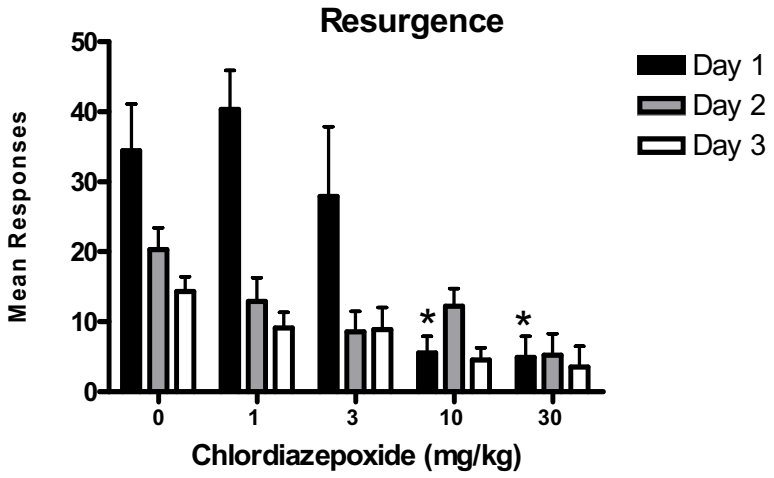

Figure 2. Effects of cholordiazepoxide on mean resurgence responding.
Effects of chlordiazepoxide (CDP) on responding on the left lever (R1) during 1 hr exposure to concurrent extinction schedules. Each bar represents the mean ± SEM of nine rats. Significant differences ($p < .05$, Bonferroni test) from vehicle control values are represented by an *asterisk.*

interaction of dose × day [$F(8, 40) = 3.56$, $p < .05$]. Bonferroni posttests revealed significant differences from vehicle control values during Day 1 in the 10 and 30 mg/kg groups.

Figure 3 shows the mean proportion of resurgence responses across each group per day. On Day 1, the mean for the 1 mg/kg group ($M = 14.01$) was slightly higher than that of the control group ($M = 13.13$), with dose-dependent decreases in responding occurring across the 3, 10, and 30 mg/kg groups with means of 7.2, 4.23, and 2.0 responses per day, respectively. On Day 2, the mean proportion for the control group was highest ($M = 24.60$), followed in descending order by the 10 ($M = 17.06$), 1 ($M = 14.21$), 3 ($M = 9.71$), and 30 mg/kg (7.74) groups. On Day 3, the mean for the control group was highest ($M = 36.04$), followed in descending order by in the 1 ($M = 21.34$), 10 ($M = 19.34$), 3 ($M = 17.35$), and 30 mg/kg (1.72) groups. The effect of CDP on this measure

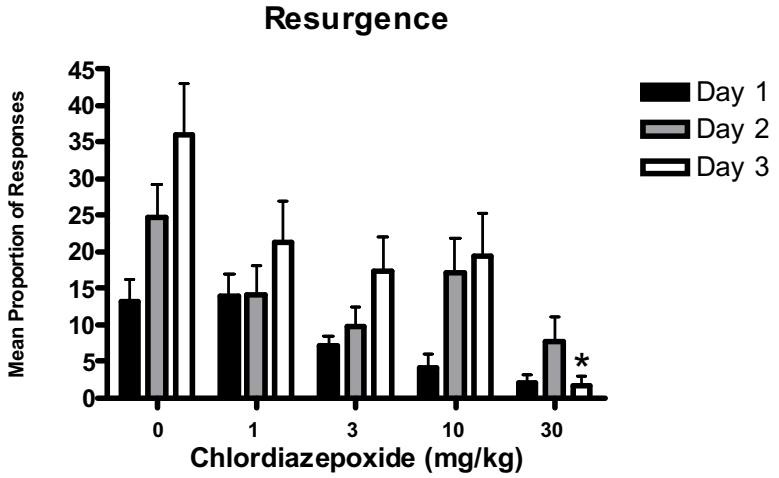

Figure 3. Effects of cholordiazepoxide on mean proportion of resurgence responding. Effects of chlordiazepoxide (CDP) on responding on the left lever [R1] during 1 hr exposure to concurrent extinction schedules. Each bar represents the mean proportion of responding ± SEM of nine rats. Other details as in Figure 2.

was analyzed by two-factor ANOVA (dose and day as repeated factors). This showed a significant effect of dose [$F(4, 40) = 10.85$, $p < .05$], day [$F(2, 40) = 9.74$, $p < .05$], but not a significant interaction of dose × day [$F(8, 40) = 1.58$, $p > .05$]. Bonferroni posttests indicated that, relative to control, the mean proportion of resurgence responding in the 30 mg/kg group was significantly lower on Day 3.

Figure 4 shows the mean number of extinction responses across each group per day. On Day 1, the mean for the 3 mg/kg group ($M = 313.3$) was highest, followed by the control ($M = 282.4$), 1 ($M = 280.7$), 30 ($M = 87.11$), and 10 mg/kg ($M = 85.56$) groups. On Day 2, the mean for the 1 mg/kg group was highest ($M = 102.8$), followed in descending order by the 3 ($M = 92.89$), 10 ($M = 91.89$), control ($M = 77.56$), and 30 mg/kg (67.11) groups. On Day 3, the mean for the 3 mg/kg group was highest ($M = 55.00$), followed by the 1 ($M = 52.89$), control ($M = 51.89$), 30 ($M = 47.33$), and

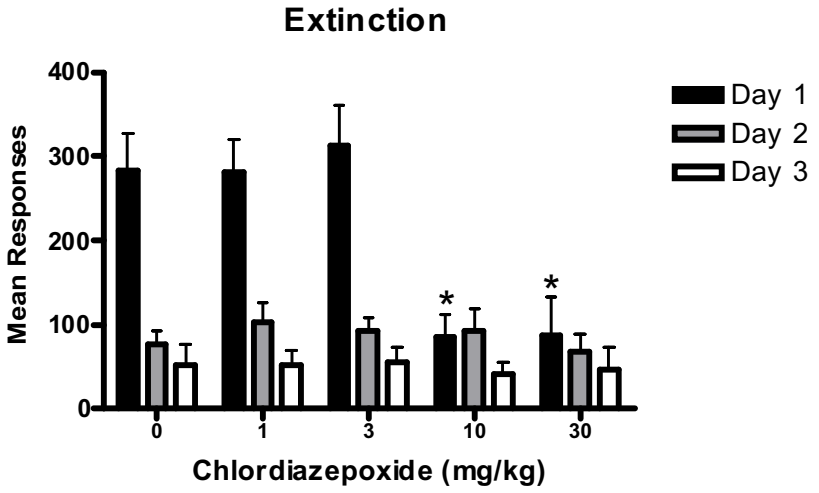

Figure 4. Effects of chlordiazepoxide on mean extinction responding.
Effects of chlordiazepoxide (CDP) on responding on the right lever [R2] during 1 hr exposure to concurrent extinction schedules. Each bar represents the mean proportion of responding ± SEM of nine rats. Other details as in Figure 2.

10 mg/kg (M = 41.11) groups. The effect of chloridazeposixe on this measure was analyzed by two-factor ANOVA (dose and day as repeated factors). This showed a significant effect of dose [$F(4, 40) = 6.10$, $p < .05$] and day [$F(2, 40) = 40.93$, $p < .05$], as well as a significant interaction of dose × day [$F(8, 40) = 4.57$, $p < .05$]. Bonferroni posttests revealed significant differences from vehicle control values during Day 1 in the 10 and 30 mg/kg groups

Figure 5 shows the mean proportion of extinction responses across each group per day. On Day 1, the mean proportion for the 30 mg/kg group (M = 97) was highest, followed by the 10 (M = 95.77), 3 (M = 92.8), control (M = 86.87), and 1 mg/kg (M = 86.00). On Day 2, the mean for the 30 mg/kg group was highest (M = 91.30), followed in descending order by the 3 (M = 90.29), 1 (M = 85.79), 10 mg/kg (M = 82.94), and control (M = 75.4) groups. On Day 3, the mean for the 30 mg/kg group was highest (M = 93.4),

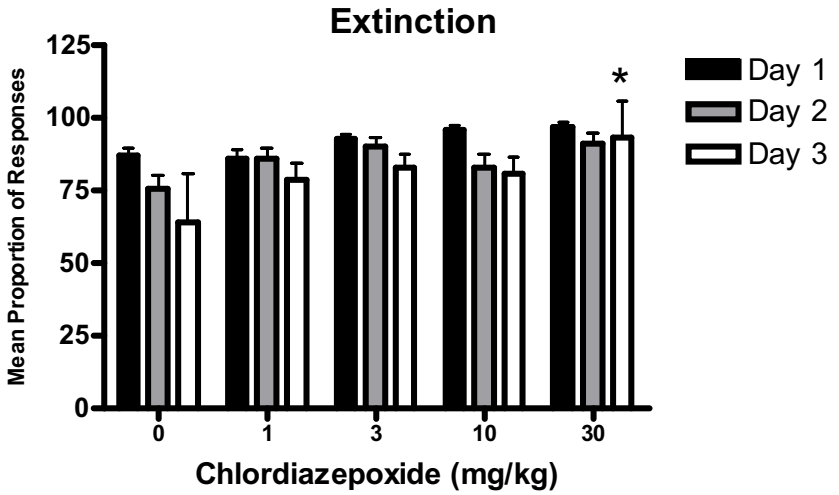

Figure 5. Effects of chlordiazepoxide on mean proportion of extinction responding. Effects of chlordiazepoxide (CDP) on responding on the right lever [R2] during 1 hr exposure to concurrent extinction schedules. Each bar represents the mean proportion of responding ± SEM of nine rats. Other details as in Figure 2.

followed by the 3 (M = 82.65), 10 (M = 80.65), 1 mg/kg (M = 78.66), and control (M = 63.96) groups. The effect of CDP on this measure was analyzed by two-factor ANOVA (dose and day as repeated factors). This showed a significant effect of dose [$F(4, 40) = 3.37$, $p < .05$] and day [$F(2, 40) = 4.22$, $p < .05$], but not a significant interaction of dose × day [$F(8, 40) = .46$, $p > .05$]. Bonferroni posttests revealed significant differences from vehicle control values during Day 3 in the 30 mg/kg group.

Because a between-subjects design was used, comparison of group means is appropriate, but it is also appropriate to examine within-group variability (Poling, Methot, & LeSage, 1995). Resurgence data for all subjects appear in Appendices B–F. With all measures and groups, most subjects exhibited similar levels of responding, but occasional outliers did appear (e.g., Appendix D).

DISCUSSION

As mentioned earlier, resurgence is the recurrence of a previously, but no longer reinforced behavior when a more recently reinforced behavior undergoes extinction. The extent to which resurgence (as well as other operant behavior) occurs can be understood only by appealing to an organism's learning history. It is important to note that resurgence is a robust outcome of sequential extinction and is potentially relevant to a number of clinical topics, including functional communication training, creativity, and relapse of undesirable behavior (Doughty & Oken, 2008).

The variables that influence resurgence are beginning to attract research interest (e.g., Bruzek et al., 2009; Da Silva et al., 2008; Lieving & Lattal, 2003; Podlesnik et al., 2006). The present study, the first of its kind, investigated the effects of the

benzodiazepine, CDP, on the resurgence of lever pressing responses emitted by male rats. An operant (left lever presses) was reinforced and subsequently extinguished. Then a second operant (right lever presses) was reinforced. Finally, 0, 1, 3, 10, 30 mg/kg doses of CDP were administered via intraperitoneal injections to groups of nine animals each during 3 consecutive days of 1-hr exposure to conditions in which all reinforcers for lever pressing were withheld.

The present research was predicated on the assumption that CDP might increase resurgence, because anti-punishment effects are often observed in studies that assess the behavioral effects of various GABA agonists (for a review, see Rasmussen, 2006). These include benzodiazepines, such as CDP, barbiturates, and ethanol (e.g., Barrett et al., 1985; Mansbach et al., 1988). That is, low to moderate doses of these drugs increase the rate of occurrence of operant responses suppressed by punishment without increasing similar, but unpunished, responses (Poling & Byrne, 2000). For example, in a study by Barrett et al. (1985), GABAergic compounds, including CDP (1-60 mg/kg), greatly increased rates of punished responding, but did not increase unpunished responding of the same topography.

Because both punishment and extinction are response-weakening operations, it is reasonable to hypothesize that drugs influence the behavioral effects of both operations similarly. The present results fail to confirm this hypothesis with respect to resurgence. Although the mean number of total resurgence responses in the 1 mg/kg group (M = 40.33) was higher than that of the control group (M = 34.44), this difference was not statistically significant and there was no compelling evidence that that chlordizepoxide at any dose facilitated resurgence in the present study. In fact, high doses reduced

resurgence responding relative to controls. Previous studies (e.g., Berntson, Sarter, Ruland, Hart, & Ronis, 1996; van Haaren & Anderson, 1997, 1998) have shown that similar doses also reduced punished responding, but low doses (e.g, 1, 3 mg/kg) produced anti-punishment effects.

Thus, the effects of chlordizepoxide across a range of doses appear to differ when resurgence responding and punished responding are compared. The reasons for this difference, and the conditions under which it appears, are presently unknown. It is certainly possible that low to moderate doses of CDP would increase resurgence under conditions different from those of the present study. Those conditions were, however, comparable to those used in most other studies of the phenomena (e.g., da Silva et al., 2008; Epstein, 1985; Lieving & Lattal, 2003) and it is not clear how conditions should be varied to alter the behavioral actions of CDP.

The present study examined the effects of CDP on a response currently undergoing extinction, as well as on resurgence responding. The effects of CDP on behavior exposed to extinction are well documented (for a review, see Leslie, Shaw, McCabe, Reynolds, & Dawson, 2004). Like other benzodiazepines, CDP often, but not inevitably, increases resistance to extinction. That is, operant behavior exposed to extinction is more persistent when the drug is given than under similar conditions where a placebo is given. This phenomenon is evident in a study by Buckland, Mellanby, and Gray (1986). They trained food-deprived rats to run in an alley under an FR 1 schedule of food delivery. Next, the rats were given CDP or saline injections prior to a series of extinction sessions. The results of the study indicated that the CDP group ran significantly faster, suggesting greater resistance to extinction.

It should be noted, however, that chlordizepoxide does not increase resistance to extinction across all preparations. This is evidenced by a study conducted by Williams, Gray, Sinden, Buckland, and Rawlins (1990), who found that lever pressing in rats under a discrete-trial FR 5 schedule of food reinforcement with only six reinforcers per day was less resistant to extinction in the presence of CDP. These results are similar to those of the present study, in which CDP decreased, not increased, resistance to extinction. That is, the mean number of responses currently undergoing extinction was significantly lower in groups that received higher doses of CDP than in the drug-free control group. It is noteworthy that CDP affected resurgence responding and responding currently undergoing extinction in the same fashion, with low doses having no effect and higher doses weakening responding. Resurgence and weakening of the just-reinforced operant occur in conjunction when extinction is arranged, so it is perhaps unsurprising that these related behavioral phenomena are similarly affected by the drug.

It is interesting that the mean proportion of overall resurgence responding for the control, 1, 3, and 10 mg/kg groups generally increased across days. However, the 30 mg/kg group showed no such trend. In fact, that group showed no visible trend whatsoever. In addition, the mean number of resurgence responses decreased in dose-dependent fashion during Days 2 and 3 across the control, 1, and 3 mg/kg doses before increasing in the 10 mg/kg group, and finally dropping off drastically in the 30 mg/kg group.

As described previously, the presence of resurgence was confirmed by examining performance of the control group (which received 0 mg/kg CDP). Although a statistical analysis via a paired *t* test revealed that the proportion of right-lever presses (no

associated history of food reinforcement) emitted during the first extinction session compared to the number of responses emitted on the left lever (the lever with an associated history of food reinforcement) during the first day of the resurgence condition was significantly higher, indicating that resurgence affected responding, the presence of a third manipulandum (R3) would have been beneficial. This would have allowed a comparison of resurgence responding between R2 (the previously, but no longer reinforced response) with R3 (an additional lever with no associated history of reinforcement).

Resurgence has been demonstrated to be repeatable only across two exposures to the resurgence procedure (Lieving & Lattal, 2003). Future studies could be conducted to see if the phenomenon is repeatable beyond two exposures. If this is so, then perhaps a reasonable baseline could be established and future within-subject pharmacological investigations could be carried out. The behavioral effects of a variety of drugs on resurgence could be assayed through more traditional, well-studied manipulations found in the discipline of behavioral pharmacology (e.g., schedules of reinforcement, reinforcer delay, and magnitude of reinforcement). Further, the investigation of the effects of drugs of abuse (e.g., cocaine, heroin) on resurgence may provide a possible mechanism of how and the extent to which individuals get pathologically involved with drugs.

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Appendix A

Western Michigan University Institutional Animal Care and Use Committee Approval

WESTERN MICHIGAN UNIVERSITY
Institutional Animal Care and Use Committee

Centennial
1903-2003 Celebration

Date: November 12, 2009

To: Alan Poling, Principal Investigator

From: Robert Eversole, Chair

Re: IACUC Protocol No. 09-08-02

Your protocol titled "Drug Effects on Resurgence" has received approval from the Institutional Animal Care and Use Committee. The conditions and duration of this approval are specified in the Policies of Western Michigan University. You may now begin to implement the research as described in the application.

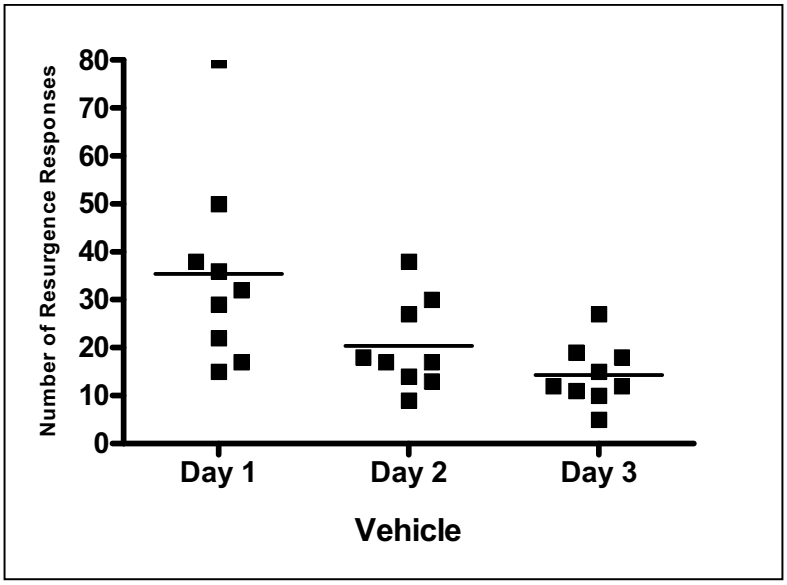
The Board wishes you success in the pursuit of your research goals.

Approval Termination: November 12, 2010

Walwood Hall, Kalamazoo, MI 49008-5456
PHONE: (269) 387-8293 FAX: (269) 387-8276

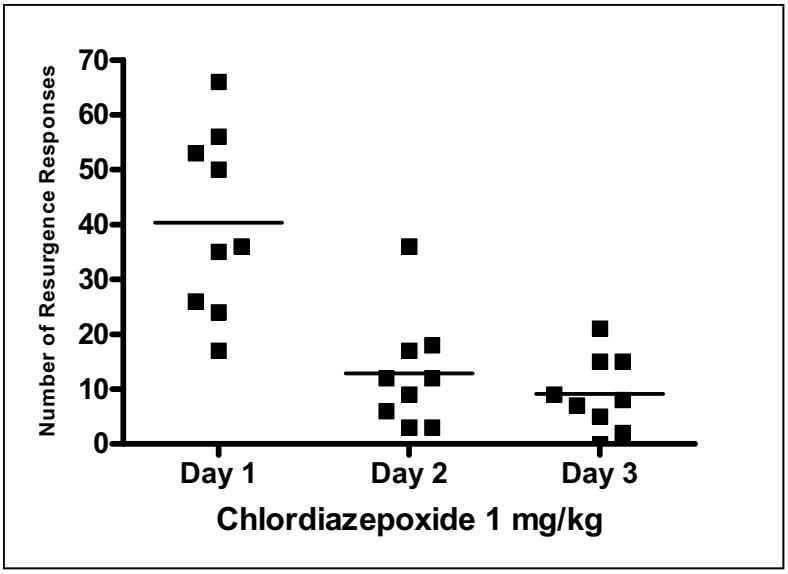
Appendix B

Vehicle Group Resurgence Responding in Raw Form


Number of Resurgence Responses
80
70
60
50
40
30
20
10
0
Day 1
Day 2
Day 3
Vehicle

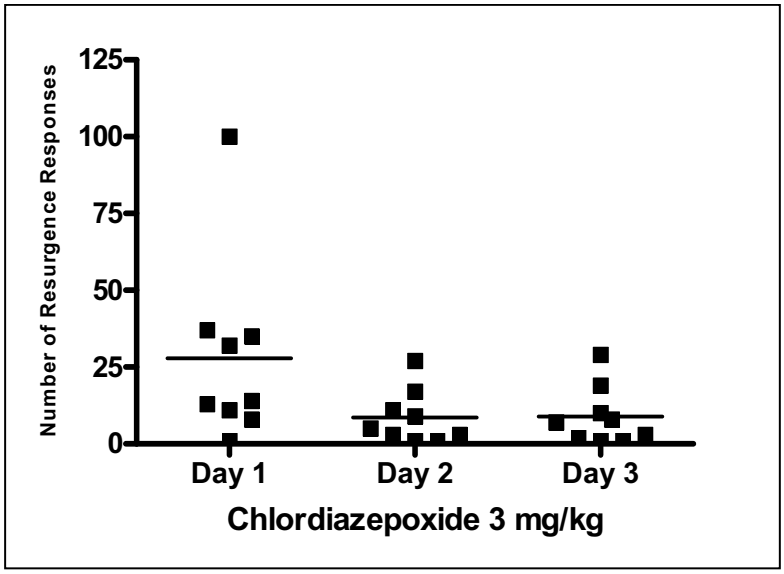
Appendix C

1 mg/kg Group Resurgence Responding in Raw Form


Number of Resurgence Responses
70
60
50
40
30
20
10
0
Day 1
Day 2
Day 3
Chlordiazepoxide 1 mg/kg

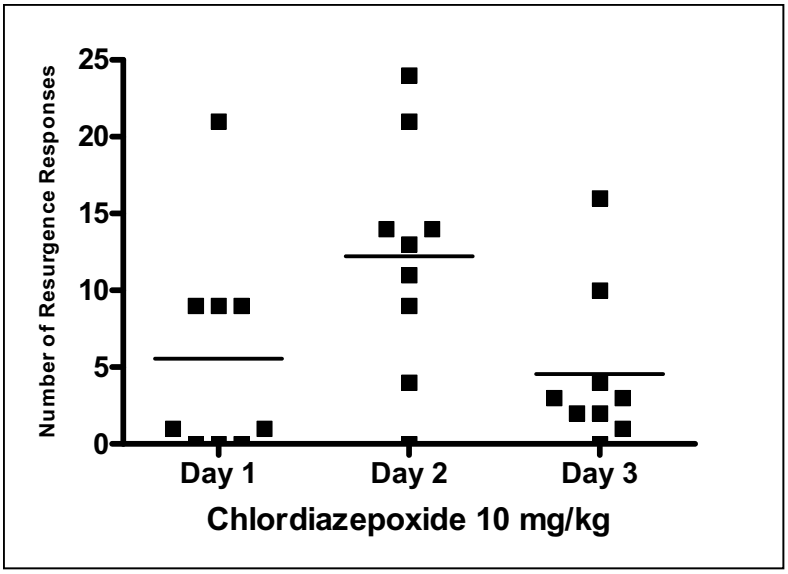
Appendix D

3 mg/kg Group Resurgence Responding in Raw Form


Number of Resurgence Responses
125
100
75
50
25
0
Day 1
Day 2
Day 3
Chlordiazepoxide 3 mg/kg

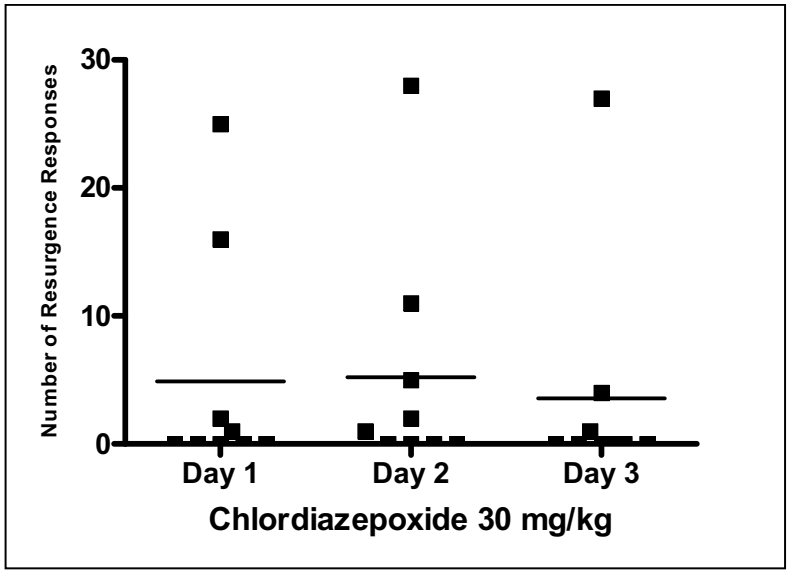
Appendix E

10 mg/kg Group Resurgence Responding in Raw Form


Number of Resurgence Responses
25
20
15
10
5
0
Day 1
Day 2
Day 3
Chlordiazepoxide 10 mg/kg

Appendix F

30 mg/kg Group Resurgence Responding in Raw Form


Number of Resurgence Responses
30
20
10
0
Day 1
Day 2
Day 3
Chlordiazepoxide 30 mg/kg