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ANXIOLYTICS: IMPLICATIONS FOR THE TREATMENT OF AGRESSION IN
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*BREVE REVISIÓN DE LA INVESTIGACIÓN BÁSICA Y APLICADA
SOBRE LOS ANSIOLÍTICOS DE BENZODIAZEPINA:
IMPLICACIONES PARA EL TRATAMIENTO DE LA AGRESIÓN
EN LAS DISCAPACIDADES DE DESARROLLO*

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ABSTRACT

Recent research in both the basic behavioral pharmacology literature and applied developmental disabilities literature suggests a relationship between increased aggression and the use of benzodiazepines, specifically anxiolytics. The purpose of this review is to tie together the findings on benzodiazepine anxiolytics from basic pharmacology research and applied research in developmental disabilities. The similarities and differences in the research in both areas will be reviewed. Implications for the treatment of aggression in those with developmental disabilities are discussed.

Key Words: benzodiazepine, anxiolytic, punishment, extinction, aggression, developmental disabilities

RESUMEN

La investigación reciente en la literatura sobre farmacología conductual básica y la literatura aplicada sobre discapacidades de desarrollo sugiere una relación entre un incremento de la agresión y el uso de benzodiazepinas, específicamente ansiolíticos. El propósito de esta revisión es conectar los hallazgos sobre ansiolíticos de benzodiazepina en la investigación básica en farmacología y la investigación aplicada en discapacidades de desarrollo. Se revisarán las semejanzas y diferencias en la investigación en ambas áreas. Se discutirán las implicaciones para el tratamiento de a agresión en aquellos con discapacidades de desarrollo.

Palabras clave: benzodiazepina, ansiolítico, castigo, extinción, agresión, descapacidades de desarrollo

BRIEF REVIEW OF BASIC AND APPLIED RESEARCH ON BENZODIAZEPINE ANXIOLYTICS: IMPLICATIONS FOR THE TREATMENT OF AGGRESSION IN DEVELOPMENTAL DISABILITIES

The benzodiazepine drug class has four primary indicated uses – anxiolytic, sedative, hypnotic, and anticonvulsant. This paper focuses on benzodiazepine anxiolytics (there are other drugs with anxiolytic properties that are not members of the benzodiazepine class and are not included in this review). These anxiolytics are prescribed primarily for the treatment of anxiety disorders; however, there are additional indicated uses for these drugs such as in the treatment of alcohol withdrawal, epilepsy, tardive dyskinesia, and for preoperative sedation. Drugs include but are not limited to: alprazolam (Xanax), chlordiazepoxide (Librium), clonazepam (Klonopin), diazepam (Valium), lorazepam (Ativan), and oxazepam (Serax). These drugs exert their effects via the inhibitory gamma-aminobutyric acid (GABA) neurotransmitter system. Specifically, therapeutic effects are observed when both GABA and benzodiazepine respectively bind to GABA A and benzodiazepine receptors simultaneously (Stahl, 2000). Short-term use of these drugs is recommended as the potential for abuse, dependency, and withdrawal is high. Given these potential effects, their use in the general population has decreased. Nonetheless, they are prescribed for a substantial number of individuals with developmental disabilities to address behavior problems such as aggression (Kalachnik, Hanzel, Sevenich, & Harder, 2002). This trend in use is a concern because of the aforementioned side effects but also because of reported possible behavioral side effects (Kalachnik et al., 2002).

The purpose of this paper is twofold. First, we will provide a brief review of basic behavioral pharmacology research focusing primarily on the effects

of benzodiazepine anxiolytics (from here on referred to as anxiolytics) on responding in punishment and extinction procedures and a review of the available applied behavioral research on the effects of anxiolytics on aggression of individuals with developmental disabilities. Second, based on the findings in these literatures, we provide recommendations regarding the use of anxiolytics for the treatment of aggression in developmental disabilities.

A literature search was conducted via ERIC, Medline, PsychINFO, and PubMed using the terms "benzodiazepine", "anxiolytic", "punishment", "anticonflict", "extinction", "mental retardation", "developmental disability", and "aggression". Our search was limited to the English language. Additional articles were identified from the reference lists of previously identified articles. Only those studies that focused solely on benzodiazepine anxiolytics between the years of 1995 and 2005 were included in this review. Those studies focusing on methodology were excluded.

REVIEW OF BASIC RESEARCH

The most notable finding reported with anxiolytics is the anticonflict effect observed during punishment. The term "anticonflict" refers to the increase in behavior observed during punishment. That is to say when administered anxiolytics, responding suppressed by punishment actually increases while there are no increases seen for appetitive responding (Kleven & Koek, 1999). This is often referred to as a paradoxical reaction because instead of observing the anticipated change in behavior, an altogether different response is observed. Although some research has demonstrated that chronic administration of anxiolytics does not produce tolerance with respect to the anticonflict effect (e.g., Shumsky & Lucki, 1996) other research has suggested that tolerance at least for some anxiolytics does develop (e.g., diazepam) (Smith & Barrett, 1997). For persons with a history of punishment for antisocial behaviors, such as aggression, this could result in increased social problems.

Kleven and Koek (1999) tested several anxiolytics to determine their anticonflict effects on responding in pigeons. Diazepam, alprazolam, chlordiazepoxide, and lorazepam in addition to other benzodiazepines, produced dose-related increases in suppressed responding on a multiple FR30 (food) FR30 (food+shock). Diazepam produced an anticonflict effect at four doses (0.1, 1, 10, 100mg/kg), alprazolam at two doses (1, 10mg/kg), and chlordiazepoxide and lorazepam at one dose (1mg/kg).

In an attempt to determine what conditions contribute to the increase in suppressed responding, Witkin (2002) compared baseline responding of rats on a multiple FR30 (food) FR10 (food), multiple FR30 (food) FR10 (food+shock) (responding maintained at 10% of nonpunished responding),

and multiple FR30 (food) FR10 (shock) schedules to responding on a multiple FR30 (food) FR10 (food+shock) schedule when on chlordiazepoxide. Administration of chlordiazepoxide (1-17 mg/kg) resulted in a dose-dependent increase in punished responding without any effect on non-punished responding when compared to the first two baseline conditions. When responding was evaluated under a multiple FR30 (food) FR10 (shock) schedule, chlordiazepoxide still increased suppressed responding although, not as high rates of responding as the multiple FR30 (food) FR10 (food+shock). However, when rats were initially trained under a multiple FR30 (food) FR10 (shock) schedule and then tested on an FR10 (shock) schedule, chlordiazepoxide did not affect suppressed responding and actually decreased it at higher doses. This may indicate an additive effect of reinforcement and chlordiazepoxide on suppressed responding. That is, when an organism has a history of reinforcement for appropriate responding, punishment for responses may be more successful.

Flores & Pellón (2000) evaluated the effect of diazepam (0.3, 1, 3, and 10mg/kg) on punished licking in rats. The researchers paired rats based on their licking rates. Within the pair, one rat was designated as a master rat and the other yoked. Half of the master rats were maintained between 5% and 30% of their unpunished licking rates with low amplitude shock (0.05 and 0.07mA) (low suppression) and the other half were maintained between 50% and 75% of unpunished licking rates with higher amplitude shock (0.10 and 0.12mA) (high suppression). Yoked rats received the same number and intensity of shock not contingent on licking behavior. Diazepam did not affect the punished or unpunished responding of the master rats in the low suppression condition and decreased licking rates of the yoked rats in the low suppression condition in a dose-dependent manner. For the high suppression rats, there were increases in punished responding for the master rats at two doses of diazepam (0.3 and 1mg/kg) and dose dependent decreases in licking for the yoked rats. This might indicate the need for more aversive punishment procedures when diazepam is prescribed in humans.

Other studies (e.g., Leslie et al., 2005; Leslie, Shaw, McCabe, Reynolds, & Dawson, 2004; McCabe et al., 2004) have found that those anxiolytics that affect GABA systems (e.g., benzodiazepines) can make behavior more or less resistant to extinction contingent on when the drug is administered. For example, in mice, if the drug is administered solely during the extinction phase the behavior is resistant to extinction. However, if the drug is administered during a partial reinforcement schedule, which is then followed by extinction, extinction seems to occur more quickly, suggesting that the drug may make organisms more sensitive to reinforcement, thereby increasing the discrimination between reinforcement and extinction.

It was also found that diazepam affects choice. In one study, rats were given a choice between two schedules. On one lever, immediate responding resulted in the delivery of a small reinforcer. On the second lever, delayed responding resulted in the delivery of a larger reinforcer. Researchers found that administering the benzodiazepine diazepam increased responding on the delayed scheduled for larger reinforcers (Evenden & Ryan, 1996).

Finally, research has evaluated the effects of benzodiazepines on aggression. Pietras and colleagues (2005) evaluated the effects of lorazepam on aggressive responding of humans and found that for a majority of their participants, lorazepam decreased aggressive responding (this paradigm involved the use of monetary-reinforced responses, escape responses, and an aggressive response). For one participant, however, a significant increase in aggressive responding was observed to occur.

The effects of diazepam on high and low aggressors have also been examined using female pigeons. At baseline pigeons were characterized as either high or low aggressors based on behavior demonstrated during interactions with novel intruders. After eight days of subchronic diazepam administration, a food competition was conducted. Those pigeons who had engaged in high baseline levels of aggression experienced significant decreases in aggressive behavior; however, those pigeons who had engaged in low-levels of aggression during baseline experienced significantly higher levels of aggression.

Taken together, research on the effects of benzodiazepines on aggressive responding supports previous findings that benzodiazepines can decrease aggressive responding for most; but for some, an idiosyncratic increase in aggression can be observed. It is still unclear, however, what factors might be responsible for observed increases in aggression associated with benzodiazepine use.

REVIEW OF APPLIED RESEARCH

Well-controlled applied research on the use of anxiolytics in developmental disabilities is not as extensive as with animals and provides mixed results regarding the effectiveness for treating aggression (see Kalachnik et al., 2002). Nonetheless, these drugs are often prescribed to address psychiatric issues and behavior problems (e.g., aggression) in people with developmental disabilities. While aggression is not always a common side-effect of anxiolytics in typically developing humans (Cherek, Steinberg, Kelly, Robinson, & Spiga, 1990) it may be more common in those with developmental disabilities (Kalachnik et al., 2002). Persons with mental retardation often respond differently to medication than those in the typical population. This may make them more

vulnerable to negative behavioral side effects of medication. For persons with mental retardation, instead of suppressing aggression, anxiolytics may further exacerbate it (Antochi, Stavrakaki, & Emery, 2003). This effect has also been referred to as a "paradoxical effect" in the literature. For example, Kalachnik, Hanzel, Sevenich, and Harder (2003), described the case of an individual with mental retardation who displayed tantrum behavior during a higher percentage of intervals while taking clonazepam than after it was discontinued. Additionally, the participant showed a rate-decreasing effect during the withdrawal of the drug.

However, other study results have suggested that anxiolytics might decrease aggression. In one study evaluating the effect of multiple treatments (behavioral and medical) on aggression and anxiety in a boy with Blood-Injury-Injection Phobia, Hagopian and colleagues (2001) found that the use of behavioral interventions in combination with alprozalam resulted in higher compliance with more invasive medical techniques. Still other studies report that anxiolytics have no effect on aggression (neither decrease nor increase frequency nor intensity) (e.g., Luiselli, Blew, Keane, Thibadeau, & Holzman, 2000).

There are no studies that have demonstrated specific mechanisms responsible for the disparity in responding to these medications, particularly in humans with impaired cognitive ability. Based on current information, however, one might hypothesize that differences might be related to general response to behavioral contingencies. For example, in the Hagopian et al. (2001) study, reinforcement for appropriate responding was available. Perhaps, while aggressive responding is typically punished in society, persons with mental retardation may have a less well-established history of reinforcement for appropriate responding. Additionally, while there may be this lack of reinforcement for appropriate responding, the anxiolytic medication may act as an abolishing operation for their history of punishment for aggressive responding.

CONCLUSION

In this review, we found similarities in the basic and applied literatures. For example, paradoxical reactions to benzodiazepines are reported in the basic behavioral pharmacological literature and there are references to similar phenomena in the applied literature. Taking into consideration the findings from both basic and applied research, there are clear clinical implications when using anxiolytics to treat problem behavior such as aggression.

First, with regards to the use of punishment, given that some anxiolytics are known to cause increases in behavior under punishment conditions, we

suggest that anxiolytics and punishment procedures not be used together. However, if punishment procedures are to be used to treat problem behavior in conjunction with anxiolytic use, procedures must be implemented consistently and not with poor fidelity as basic research demonstrates that anxiolytics may make behavior resistant to low intensity punishment (Flores & Pellón, 2000). Punishment procedures should also be introduced prior to anxiolytic use (Witkin, 2002). Second, the demonstration that benzodiazepines increase responding on delayed schedules of reinforcement for larger reinforcers has implications for applied work in terms of fading reinforcement. We suggest starting benzodiazepines before attempting to decrease the frequency of reinforcement delivered and then simultaneously increasing the amount of reinforcer delivered while decreasing the reinforcement ratio. Additionally, it might be beneficial to ensure that the person has a well-established history of reinforcement for socially appropriate behaviors that may interfere with the potential paradoxical effect of anxiolytics. Finally, if extinction procedures are to be implemented, anxiolytics may not be the best drug to use since it is associated with resistance to extinction (Leslie et al., 2004; Leslie et al., 2005; McCabe et al., 2004). If anxiolytics and extinction are both used, however, the anxiolytic should be implemented prior to the implementation of extinction. Also, the potential "disinhibition effect" associated with benzodiazepine may contraindicate their use altogether.

Poling and LeSage (1995) noted limited data on the social validity of the use of psychotropic medication with individuals with developmental disabilities. By comparing the findings from basic research with applied studies we believe we may be able to begin to ascertain which drugs and behavioral interventions may best address problem behaviors in developmental disabilities. That is, by identifying those drugs with specific effects on operant behavior in the laboratory, clinicians may be better able to identify treatments that are most efficacious for those with developmental disabilities in applied settings.

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