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# Effects of Anticonvulsant Drugs Under Automaintenance and Negative Automaintenance Procedures[1]

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PICKER, M , E BLAKELY AND A POLING *Effects of anticonvulsant drugs under automaintenance and negative automaintenance procedures* PHARMACOL BIOCHEM BEHAV 24(3) 555–560, 1986 —The behavioral effects of phenytoin, phenobarbital, clonazepam, valproic acid, and ethosuximide were evaluated in food-deprived pigeons performing under automaintenance and negative automaintenance procedures Under the automaintenance procedure, brief periods of key illumination were followed by food delivery without regard to the subject's behavior In most instances, when drugs were not given this procedure engendered high rates of keypecking during almost all key illuminations (trials) Acute administrations of phenytoin (10–20 mg/kg), valproic acid (40–120 mg/kg), and ethosuximide (40–120 mg/kg) produced generally dose-dependent decreases in percent trials with a response and rate of responding Although phenobarbital (30–60 mg/kg) and clonazepam (2 5–7 5 mg/kg) produced little obvious effect on percent trials with a response, these drugs generally increased rate of responding Under the negative automaintenance procedure, food delivery followed only key illuminations during which keypecking did not occur Keypecking occurred at a low rate under this procedure, with no responses occurring during the majority of key illuminations Thus, this procedure appeared to involve responding elicited by respondent conditioning but suppressed by the response-dependent omission of food Across the same dose ranges evaluated under the automaintenance procedure, clonazepam and phenobarbital generally increased percent trials with a response and rate of responding in dose-dependent fashion Phenytoin similarly increased percent trials with a response but had little consistent effect on rate of responding Ethosuximide and valproic acid failed to affect responding under this procedure

Phenobarbital Clonazepam Phenytoin Valproic acid Ethosuximide Anticonvulsant drugs Respondent conditioning Pigeons Antipunishment effects Automaintenance Negative automaintenance

RECENT preclinical investigations [5, 12, 13, 17] have evaluated the behavioral effects of acute administrations of anticonvulsant drugs (e g , phenytoin, phenobarbital, clonazepam, valproic acid, ethosuximide) in pigeons performing under several operant conditioning procedures, including assays of learning (i e , repeated acquisition), short-term memory (i e , delayed-matching-to-sample) and performance (i e , schedules of reinforcement) The results of these studies indicate that there are quantitative as well as qualitative differences in the effects of these agents, and that whether a particular agent disrupts behavior at a given dose depends upon how the behavior in question is maintained For example, across a wide range of doses, valproic acid and ethosuximide similarly produce dose-dependent decreases in rate of responding under a multiple Fixed-Ratio Fixed-Interval schedule of food delivery [17], but produce quite different effects under delayed-matching-to-sample [13] and repeated acquisition procedures [12] Valproic acid produces substantial decreases in accuracy under both procedures, whereas ethosuximide has little effect on accuracy even at doses that substantially reduce rate of responding

The purpose of the present experiment was to further profile the behavioral actions of anticonvulsant drugs by examining their effects in pigeons performing under automaintenance and negative automaintenance procedures Procedurally resembling respondent conditioning, the automaintenance procedure specifies only the relation between a conditional stimulus (key illumination) and an unconditional stimulus (food delivery) In a typical automaintenance experiment, food-deprived pigeons are exposed to a series of trials in which the brief illumination of a response key precedes the delivery of food Under these conditions, birds eventually approach, orient towards, and peck the illuminated response key Despite the absence of a programmed dependency between keypecking and food delivery, pigeons will typically maintain a moderately high rate of pecking during key illumination Autoshaped responding has been demonstrated with numerous species (e g , rats, monkeys, humans), unconditional stimuli (e g , food, water, access to a sex partner), and procedural variations (see [8])

Although few studies have examined the effects of drugs under the automaintenance procedure, some have appeared

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Poling and associates [11, 14, 15, 18], for example, found that morphine, atropine, LSD, and quipazine produced generally dose-dependent decreases in the number of trials with a response and rate of responding Even drugs with known rate-dependent effects, such as *d*-amphetamine and pentobarbital, reduced the percentage of key illuminations with a response and rate of responding The effects of anticonvulsants other than pentobarbital on automaintained responding have not been determined

A variant of the automaintenance procedure, termed negative automaintenance, has also been effectively employed to study the effects of anticonvulsants and other drugs This procedure resembles the automaintenance procedure, with the exception that responding during the period of key illumination prevents the scheduled food delivery, food delivery follows only trials in which no responses occur Responding does occur under these conditions, although compared to the automaintenance procedure, percent trials with a response and rate of responding are much reduced Thus, the negative automaintenance procedure appears to involve responding elicited by respondent conditioning and simultaneously suppressed by an operant dependency, i e , response-dependent omission of food [1,8] To date, the only drugs that have been reported to increase responding under this procedure are those with known antipunishment or anxiolytic effects, such as the anticonvulsant diazepam and the barbiturate pentobarbital [14,15] How phenytoin, valproic acid, and other anticonvulsant drugs affect responding under the negative automaintenance procedure is unclear

## METHOD

### *Subjects*

Eight experimentally naive White Carneaux pigeons, maintained at approximately 80% of their free-feeding weights (390–480 g), served as subjects Each bird was individually housed with unlimited access to grit and water in a constantly illuminated room

### *Apparatus*

Three test chambers measuring 38 cm high, 30 cm wide, and 40 cm long were employed A 5 cm by 5 cm opening, horizontally centered in the work panel 8 cm above the floor of the chamber, allowed access to a magazine filled with mixed grain when the magazine was raised The magazine, when raised, was illuminated by a 7-W white bulb Two response keys, 2 5 cm in diameter, were symmetrically located on the work panel, 12 cm from the adjacent wall and 24 cm above the chamber floor Only the right response key was operative during the experimental session Ambient chamber illumination was provided by two clear 7-W bulbs centered in the transparent ceiling of the chamber Continuous white noise masked extraneous sounds

Scheduling of experimental events and data collection were accomplished through the use of a Digital Equipment Corporation PDP8/A minicomputer using interfacing and software (SUPERSKED) provided by State Systems Inc (Kalamazoo, MI)

### *Behavioral Procedure*

Prior to the start of the experiment proper, all pigeons were trained to approach and eat from the raised food magazine After each subject consistently ate from the raised

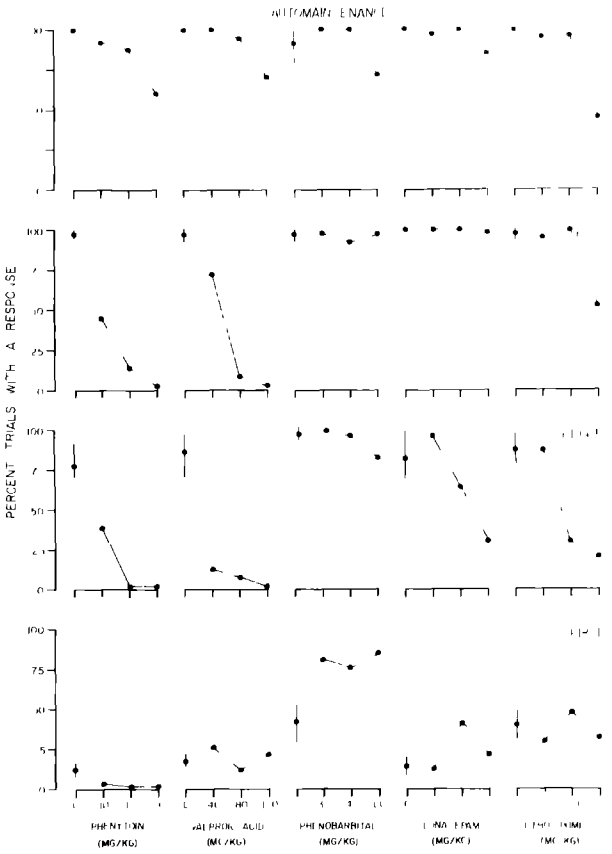


FIG 1 Effects of phenytoin, valproic acid, phenobarbital clonazepam, and ethosuximide on percentage of key illuminations (trials) with a response for individual pigeons exposed to an automaintenance procedure Drug data represent the mean percent trials with a response for two determinations at each dose Control data, indicated by C, represent the mean percent trials with a response during the six vehicle control sessions preceding drug administration during individual dose-effect determinations, vertical lines indicate the range across these sessions

magazine, it was exposed to two consecutive sessions in which 40 4-sec food presentations were programmed under a Random-Time 1-min (RT 1-min) schedule Under this schedule, on the average of once every minute the food magazine was raised for 4 sec

At the start of the experiment proper, four subjects were exposed to a standard forward pairing automaintenance procedure [1] and four subjects to a negative automaintenance procedure (similar to that described by [23]) For the automaintenance subjects, each trial consisted of a 6-sec illumination of the right response key in green At the offset of the key light the food magazine was raised for 4 sec regardless of the pigeon's behavior Each session consisted of 40 key illuminations programmed under an RT 1-min schedule Responses were without programmed consequences and the response key was darkened during the intertrial interval Sessions were typically conducted 7 days per week at about the same time each day

For the negative automaintenance subjects, keypeck responses during the period of key illumination prevented the scheduled food delivery, responses had no effect on the duration of key illumination Otherwise, all experimental con-

TABLE 1

MEAN RESPONSES PER MINUTE DURING TRIALS WITH A RESPONSE FOR PIGEONS RESPONDING UNDER AUTOMAINTENANCE AND NEGATIVE AUTOMAINTENANCE PROCEDURES DURING VEHICLE AND DRUG SESSIONS

| Automaintenance | | | | | Negative Automaintenance | | | | |
|---|---|---|---|---|---|---|---|---|---|
| **Phenytoin (mg/kg)** | | | | | | | | | |
| Pigeon | Saline* | 10† | 15 | 20 | Pigeon | Saline | 10 | 15 | 20 |
| P821 | 86 (60–120) | 115 | 120 | 45 | P6215 | 10 (10–10) | — | — | — |
| P38 | 87 (80–90) | 60 | 40 | 10 | P5333 | 13 (10–20) | 20 | 15 | 15 |
| P1048 | 23 (20–30) | 25 | — | — | P5847 | 10 (10–10) | 10 | 20 | 10 |
| P1831 | 22 (20–30) | 10 | — | — | P402 | 15 (10–20) | 10 | 15 | 10 |
| **Valproic Acid (mg/kg)** | | | | | | | | | |
| Pigeon | Saline | 40 | 80 | 120 | Pigeon | Saline | 40 | 80 | 120 |
| P821 | 157 (130–190) | 215 | 225 | 205 | P6215 | 10 (10–10) | 10 | 10 | 15 |
| P38 | 68 (50–90) | 75 | 50 | 20 | P5333 | 12 (10–20) | 10 | 15 | 15 |
| P1048 | 26 (23–30) | 20 | 20 | — | P5847 | 25 (20–40) | 30 | 25 | 20 |
| P1831 | 22 (10–30) | 20 | 10 | 10 | P402 | 13 (10–20) | 10 | 15 | 10 |
| **Phenobarbital (mg/kg)** | | | | | | | | | |
| Pigeon | Saline | 30 | 45 | 60 | Pigeon | Saline | 30 | 45 | 60 |
| P821 | 53 (20–90) | 105 | 160 | 180 | P6215 | 10 (10–10) | 10 | 10 | 15 |
| P38 | 66 (50–80) | 83 | 75 | 110 | P5333 | 13 (10–20) | 15 | 20 | 20 |
| P1048 | 88 (70–100) | 110 | 95 | 60 | P5847 | 10 (10–10) | 10 | 10 | 15 |
| P1831 | 18 (10–20) | 15 | 20 | 30 | P402 | 0 (0–0) | 10 | 10 | 15 |
| **Clonazepam (mg/kg)** | | | | | | | | | |
| Pigeon | Saline | 0 25 | 0 50 | 0 75 | Pigeon | Saline | 0 25 | 0 50 | 0 75 |
| P821 | 192 (130–240) | 215 | 250 | 205 | P6215 | 0 (0–0) | 30 | 40 | 45 |
| P38 | 68 (50–80) | 105 | 90 | 95 | P5333 | 10 (10–10) | 10 | 10 | 15 |
| P1048 | 35 (30–50) | 55 | 25 | 20 | P5847 | 13 (10–20) | 20 | 30 | 20 |
| P1831 | 20 (10–30) | 45 | 20 | 15 | P402 | 12 (10–20) | 15 | 15 | 20 |
| **Ethosuximide (mg/kg)** | | | | | | | | | |
| Pigeon | Saline | 40 | 80 | 120 | Pigeon | Saline | 40 | 80 | 120 |
| P821 | 120 (50–200) | 100 | 125 | 15 | P6215 | 10 (10–10) | 10 | 10 | 10 |
| P38 | 63 (40–80) | 60 | 60 | 40 | P5333 | 20 (20–20) | 15 | 10 | 20 |
| P1048 | 28 (20–40) | 20 | 15 | 10 | P5847 | 13 (10–20) | 10 | 10 | 10 |
| P1831 | 13 (10–20) | 10 | 10 | 15 | P402 | 11 (10–20) | 20 | 20 | 10 |

*Control data represent the mean rate of responding during trials in which at least one response occurred during the six vehicle control sessions preceding drug administrations, numbers in parentheses indicate the range across these sessions

†Drug data represent the mean rate of responding during trials in which at least one response occurred during two determinations at each dose A — indicates that no responses were recorded during either of the two determinations at a given dose

ditions were identical to those described under the automaintenance conditions For both groups, these experimental conditions remained in effect throughout the duration of the experiment

*Pharmacological Procedure*

After the percent trials with a response and rate of responding showed no obvious upward or downward trend (20–26 sessions), the following drugs were tested phenytoin, valproic acid, phenobarbital, clonazepam, and ethosuximide Phenytoin was injected as a commercially prepared solution (Parke-Davis, Morris Plains, NJ) diluted with isotonic saline solution Valproic acid (Saber Laboratories, Morton Grove, IL) and phenobarbital (Sigma Chemical Co , St Louis, MO) were dissolved in distilled water with sufficient sodium hydroxide to neutralize the drug to the sodium salt Doses for these drugs are expressed as the salt Clonazepam (Hoffman-La Roche, Nutley, NJ) was dissolved in a solution consisting of 98% propylene glycol and 2% ethyl alcohol Isotonic saline solution alone served as the vehicle for ethosuximide (Warner-Lambert, Ann Arbor, MI) Doses for these drugs are expressed as the base Isotonic saline solution was used as the control vehicle for all drugs

Three doses of each drug and vehicle control were in-

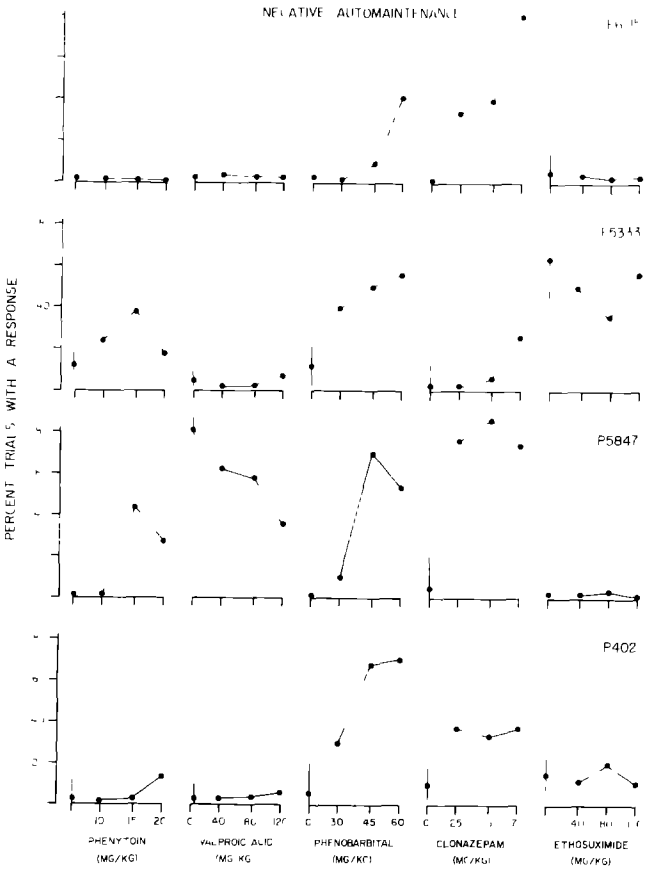


FIG 2 Effects of phenytoin, valproic acid, phenobarbital, clonazepam, and ethosuximide on percentage of key illuminations (trials) with a response for individual pigeons exposed to a negative automaintenance procedure Drug data represent the mean percent trials with a response for the two determinations at each dose Control data, indicated by C, represent the mean percent trials with a response during the six vehicle control sessions preceding drug administration during individual dose-effect determinations, vertical lines indicate the range across these sessions

jected intramuscularly 30 min before the experimental session, at an injection volume of 1 ml/kg Drug doses and the presession injection interval were selected on the basis of previous studies conducted in our laboratory [12, 13, 17] Each bird received all doses of each drug on two occasions Drugs and doses were administered in an irregular order that varied across subjects Drugs were administered in a BBCDBBCD design, where B represents baseline sessions, C vehicle control sessions, and D drug sessions

## RESULTS

During baseline and vehicle control sessions, the automaintenance procedure engendered high rates of responding on almost 90% of the trials for 3 of the 4 subjects, 1 subject evidenced relatively low rates of responding and made one or more responses on fewer than 40% of all key illuminations Reading from left to right, Fig 1 shows the percentage of key illuminations during which at least one response occurred when phenytoin, valproic acid, phenobarbital, clonazepam, and ethosuximide were given to individual subjects exposed to the automaintenance procedure In this figure, drug data represent the mean for the two determinations at each dose, control data represent the mean precent trials with a response during the six vehicle control sessions preceding drug administrations Drugs were considered to produce an effect only when the mean of the two determinations at each dose fell outside of the control range, which is indicated in this figure by vertical lines For all subjects, there were no apparent differences between the first and second determination for any of the drugs tested, or in the direction or magnitude of the drug effect as a function of the sequence of drug administrations

Phenytoin produced large dose-dependent decreases in the percent trials with a response for all subjects Rate of responding during those key illuminations (trials) in which responding occurred, indicated in Table 1, were similarly affected For valproic acid and ethosuximide, three subjects showed dose-dependent decreases in percent trials with a response For these subjects, valproic acid and ethosuximide generally reduced rate of responding, although in most instances this effect was not directly dose-dependent or consistent across subjects Subject P1831, who responded on few trials during control sessions, was little affected across the dose range studied Phenobarbital and clonazepam produced quite different effects For three subjects, only the highest dose of phenobarbital decreased percent trials with a response The magnitude of this phenobarbital-induced decrease in responding was relatively small (always less than 30%) During trials in which at least one response occurred, phenobarbital typically increased rate of responding When phenobarbital was administered, both percent trials with a response and rate of responding were increased for subject P1831, who responded on less than 55% of all key illuminations during control sessions Clonazepam had no consistent effect on percent trials with a response However, drug-induced increases in rate of responding were evident for all subjects at the low dose of clonazepam, moderate and high doses produced little consistent effect

Under the negative automaintenance procedure, two subjects (P5333, P5847) responded on more than 70% of key illuminations during the initial dose-effect determination Between the first and second dose-effect determinations for these birds, percent trials with a response decreased to approximately 15–20% Subjects P402 and P6215 consistently responded on fewer than 25% of key illuminations (a mean of 4 4% with a range from 0–23%) There were no apparent differences between the results of the first and second determination for any of the drugs tested, or in the direction or magnitude of drug effects as a function of the sequence of drug administrations

Figure 2 shows the effects of phenytoin, valproic acid, phenobarbital, clonazepam, and ethosuximide on the percent trials with a response for individual pigeons exposed to a negative automaintenance procedure Phenytoin increased the percent trials with a response for three subjects without affecting rate of responding during trials in which at least one response occurred (see Table 1) Subject P6215 did not respond during any session in which phenytoin was administered With one exception (30 mg/kg of phenobarbital for subject P6215) all doses of phenobarbital and clonazepam produced large increases in percent trials with a response, and generally increased rate of responding The magnitude of these drug-induced increases in rate of responding were typically small At the high dose of these drugs, most pigeons responded on at least 50% of the key illuminations (a range

from 43–83%), thus losing more than half of the possible food deliveries In contrast to phenobarbital and clonazepam, valproic acid and ethosuximide had little effect on percent trials with a response or rate of responding for three subjects For subject P5847, where responding occurred during approximately 70% of the trials during control sessions preceding administrations of valproic acid, the drug generally decreased percent trials with a response without substantially reducing rate of responding Ethosuximide reduced percent trials with a response only at the moderate dose for subject P5333, who responded on more than 45% of key illuminations during control sessions Rate of responding for this subject was also reduced at this dose

## DISCUSSION

The finding that key pecking was reliably maintained under the automaintenance procedure is consistent with previous findings [3], which indicate that, despite the absence of a programmed dependency between keypecking and food delivery, the temporal pairing of key illuminations with food delivery is a sufficient condition to establish and maintain responding That pigeons typically responded during relatively few of the key illuminations when exposed to the negative automaintenance procedure is also in agreement with the results of previous investigations [15,23] Earlier findings similarly indicate that, although the negative automaintenance procedure does engender responding, both percent trials with a response and rate of responding under this procedure are considerably lower than under conventional automaintenance procedures Not surprisingly, the imposition of a negative response-food dependency, which is essentially a punishment operation, is a sufficient condition to suppress behavior

Under the automaintenance procedure, phenytoin, valproic acid, and ethosuximide generally decreased the percent trials with a response and rate of responding in dose-dependent fashion These drug-induced decreases in responding parallel those reported when these drugs are administered to pigeons responding under other discrete-trial (e g , delayed-matching-to-sample, repeated acquisition) and free-operant (e g , Fixed-Ratio and Fixed-Interval schedules of reinforcement) procedures [12, 13, 17] Across the dose range examined, phenobarbital and clonazepam had little effect on percent trials with a response for most subjects However, since responding occurred on almost all key illuminations during control sessions under this procedure, drug-induced increases would not be readily apparent This ceiling effect may account for the failure of other drugs with reported rate-dependent effects (e g , pentobarbital, amphetamine) to increase percent trials with a response under this procedure [14,18] No such ceiling effect was evident with one subject in the present experiment this bird typically responded on less than 55% of the key illuminations during control sessions For this subject, phenobarbital and clonazepam substantially increased the number of trials in which at least one response occurred

The phenobarbital- and clonazepam-induced increases in rate of responding during trials in which a response occurred are in agreement with findings indicating that other barbiturates and benzodiazepines may increase rates of responding under certain schedules of reinforcement [9,20] Such drug-induced increases in responding under the automaintenance procedure are surprising given the findings of previous investigations suggesting that a wide range of drugs, including benzodiazepines and barbiturates, generally decrease responding under the automaintenance procedure [11, 14, 18] Poling and Appel [14,15], for example, reported that other drugs with known rate-dependent effects, such as diazepam and pentobarbital, failed to increase the responding of pigeons under this procedure Poling and Thompson [18] also reported that *d*-amphetamine, a CNS stimulant with known rate-dependent effects, failed to increase the low rate responding of pigeons performing under a partial pairing automaintenance procedure This procedure was similar to that employed in the present study, with the exception that only 2 5% of key illuminations were followed by food, thereby eliciting rates of responding considerably lower than those generally obtained under full pairing automaintenance procedures

Under the negative automaintenance procedure, clonazepam and phenobarbital produced large increases in percent trials with a response At the high dose of these drugs most pigeons responded on more than 50% of all key illuminations, thus losing more than half of all available food deliveries These results extend pervious findings indicating that other barbiturates and benzodiazepines possess antipunishment effects [2,20] For these classes of drugs, antipunishment effects have previously been demonstrated under negative automaintenance procedures and under operant procedures in which responding is simultaneously maintained by response-dependent food delivery and suppressed by response-dependent electric shock [14, 15, 20] The finding that these drugs typically increased rate of responding is also consistent with those reported for other barbiturates and benzodiazepines under simple schedules of food reinforcement, although in some investigations these drugs nonselectively decrease high- and low-rate responding of pigeons and rats [9]

The finding that phenytoin increased percent trials with a response in 3 of 4 subjects in the present study without affecting rate of responding is in contrast to those reported when this drug is administered under other response suppression procedures Goldberg and Ciofalo [4], for example, found that low and moderate doses of phenytoin did not enhance the rate of responding of rats performing under a procedure in which responses were concommitantly maintained by a Variable-Interval schedule of food delivery and suppressed by response-dependent presentations of electric shock High doses nonselectively suppressed responding under this schedule and one in which responding was maintained only by food reinforcement Under a similar procedure employing a Fixed-Ratio 1 schedule of food delivery and shock presentations, valproic acid produced dose-dependent increases in responding at doses that had no effect on responding maintained under a Variable-Interval schedule of food presentation without shock [6,7] However, in the present study valproic acid failed to affect the percent trials with a response or the low rate of responding engendered by the negative automaintenance procedure Ethosuximide, like valproic acid, failed to affect either percent trials with a response or rate of responding Currently, there are no other reports describing ethosuximides' effect on punished responding

The present findings suggest that some anticonvulsant drugs which characteristically increase responding suppressed by response-dependent electric shock, such as the barbiturates and benzodiazepines, produce similar effects under the negative automaintenance procedure Although similar

outcomes across response suppression procedures were not evident with valproic acid and phenytoin, the effects of drugs on punished responding are known to be complex, determined by multiple and interactive variables [10] Given this, and the fact that few data concerning the effects of anticonvulsant drugs on punished responding are available, strong conclusions concerning similarities and differences in the effects of such drugs under negative punishment (i e , negative automaintenance) and positive punishment (i e , response-dependent shock delivery) procedures are not presently warranted It is clear, however, that the negative automaintenance procedure is a sensitive assay of drug effects, and that anticonvulsant drugs differ remarkably in their actions under this procedure

The findings of clinical investigations are generally consistent with preclinical findings which indicate that anticonvulsant medications can interfere with learning, memory and performance (see [16, 21 22, 25]) Although no clinical studies have directly assessed the effects of anticonvulsant drugs on behaviors suppressed by punishment procedures (positive or negative), the present findings suggest that some, but not all, anticonvulsant drugs may possess antipunishment effects Whether these preclinical findings can be generalized to humans, however, is unknown

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