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Molindone: Effects in Pigeons Responding Under Conditional Discrimination Tasks

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PICKER, M. J., J. P. CLEARY, K. BERENS, A. H. OLIVETO AND L. A. DYKSTRA. *Molindone: Effects in pigeons responding under conditional discrimination tasks.* PHARMACOL BIOCHEM BEHAV 32(2) 439–445, 1989.—Pigeons were trained to respond under three conditional discrimination procedures; 1) a fixed-consecutive-number procedure with (FCN 8-SD) and without (FCN 8) an added external discriminative stimulus, 2) a delayed matching-to-sample (DMTS) procedure using 0-sec, 2-sec and 8-sec delay intervals, and 3) a repeated acquisition of behavioral chains (RA) procedure using a four-link response chain with three stimulus keys. The atypical neuroleptic agent molindone decreased accuracy under the FCN 8 at doses that had no effect on accuracy under the FCN 8-SD. Under the DMTS procedure, molindone-induced decreases in accuracy were directly related to the delay interval, with the largest relative decrements obtained at the 8-sec delay and the smallest at the 0-sec delay. Under the RA procedure, molindone decreased accuracy at doses that had little or no effect on the number of correct responses emitted. Relative to control values, molindone-induced decreases in accuracy were smallest under the DMTS and FCN 8-SD procedures and largest under the FCN 8 and RA procedures. The differential effects obtained with molindone under each of these procedures illustrate the need to employ a variety of assays when determining the behavioral actions of neuroleptics. In addition, this battery of behavioral tests may provide a useful tool for assessing the different neurochemical actions of neuroleptic compounds.

Pigeons Molindone Conditional discriminations Repeated acquisition Delayed matching-to-sample Fixed-consecutive-number Neuroleptics

MOLINDONE is a dihydroindoline compound with a chemical structure unrelated to the three prototypical neuroleptic classes (i.e., phenothiazines, butyrophenones, thioxanthenes). Unlike the prototypical neuroleptics, molindone does not elicit dopamine receptor supersensitivity (15), nor is it a strong antagonist of striatal dopamine-sensitive adenylate cyclase (11). Moreover, molindone does not effectively elicit spontaneous paw withdrawal in assays of extrapyramidal activity (8). Despite these unique properties, molindone is an effective antipsychotic agent (2,9).

In nonhumans responding under various schedules of reinforcement, molindone has effects similar to those of other neuroleptic agents. For example, like chlorpromazine and other phenothiazines, molindone decreases rates of responding under fixed-interval schedules at doses that have little effect on responding under fixed-ratio schedules (4, 14, 26, 34). Moreover, molindone inhibits conditioned avoidance responding (6) and decreases responding under shock-presentation schedules at doses that increase or have no effect on responding under shock-postponement schedules (3).

Although the effects of neuroleptic agents on schedule-controlled responding and conditioned avoidance responding have been examined extensively, there are few systematic comparisons of the effects of these compounds on tasks requiring conditional discriminations (19–21). Available investigations indicate, however, that there are substantial differences in the effects of neuroleptic agents when evaluated under these tasks [e.g., (13, 19–21)]. For example, certain phenothiazines (e.g., chlorpromazine) and thioxanthenes (e.g., chlorprothixene) interfere with performance under various conditional discrimination tasks (1, 16, 20–22, 24, 35), whereas the butyrophenones (i.e., haloperidol) and the benzamides (i.e., sulpiride) are devoid of this action (13, 17, 20, 21). Numerous factors could mediate the failure of the butyrophenones and benzamides to alter discrimination performance, including behavioral and pharmacological variables. Indeed, recent investigations indicate that the effects of neuroleptics are dependent upon the behavior being measured as well as the parameters employed in the discrimination task [e.g., (6, 20, 21, 29, 30)]. In addition, these

neuroleptics differ from the phenothiazines and other neuroleptics that decrease discrimination performance in that they have weak anticholinergic properties and weak antagonist activity on striatal dopamine-sensitive adenylate cyclase (11,12). In contrast to the neuroleptics noted above, molindone has both weak antagonist activity on striatal dopamine-sensitive adenylate cyclase and pronounced anticholinergic actions (11).

To determine the extent to which the dopamine-sensitive adenylate cyclase systems are involved in the discrimination-altering effects of neuroleptics and the role the discrimination task plays in modulating these actions, molindone was examined in pigeons responding under three conditional discrimination tasks; a DMTS procedure using delay intervals of 0, 2 and 8 sec, a fixed-consecutive-number (FCN) procedure with and without an added external discriminative stimulus and a repeated acquisition of behavioral chains (RA) procedure. Each of these procedures has been used extensively to characterize the effects of drugs on conditional discriminations [for reviews see (7, 10, 32)] and each is generally accepted as an assay of a different class of behaviors; that is, the DMTS an assay of short-term memory, the FCN an assay of the role of internal (response produced feedback) and external discriminative stimuli in modulating drug action, and the RA an assay of learning.

METHOD

Subjects

Sixteen White Carneaux pigeons maintained at 80% of their free-feeding weight served as subjects. Each pigeon was individually housed with free access to grit and water in a continuously illuminated room. All of the pigeons had previous drug histories, which consisted of exposure to various opioid compounds.

Apparatus

Six standard operant test chambers equipped with three-key pigeon work panels were used. An exhaust fan supplied ventilation and white noise was used to mask extraneous sound. Scheduling of experimental events and data collection were accomplished through the use of TRS 80 model IV and Apple II Plus microcomputers.

Delayed Matching-to-Sample

Four pigeons were exposed to a discrete trial DMTS procedure with an 8-sec intertrial interval (ITI). Each trial began with a 0.25-sec flash of the houselight, followed by the illumination of the center response key in red or green; center key illumination constituted presentation of the sample stimulus, and total responses on the sample stimulus divided by the time this stimulus was illuminated was used as a measure of response rate. Five responses (FR 5) on the center key turned off the sample stimulus and initiated a fixed duration delay interval of 0, 2, or 8 sec. During the delay period, the houselight remained illuminated, responses had no programmed consequences, and the keys were dark. Delays were selected at random with each delay programmed to appear equally often. Following the delay period, the two side keys were illuminated red or green in one of two possible configurations of color and position; illumination of the side keys constituted presentation of the comparison stimuli. A response to the comparison stimulus that matched the sample stimulus in color darkened both side keys, and every second correct response trial was followed by 3-sec access to grain. Correct response trials not followed by food delivery were followed by a 1-sec flash of the magazine light. Trials terminated by a nonmatching response (error) also darkened the keys and then initiated the ITI. Such trials were repeated until the pigeon responded to the appropriate comparison stimulus. Trials terminated if the response requirement on the sample stimulus was not completed within 35 sec of trial initiation or if the pigeon failed to respond to one of the side keys within 35 sec of the onset of the comparison stimuli. Such aborted trials were repeated after the ITI and were not recorded as errors. Sessions terminated after 140 trials or 50 min, whichever occurred first.

Fixed-Consecutive-Number

Four pigeons were exposed to a FCN schedule with and without an added external discriminative stimulus. Under the FCN schedule with the added external discriminative stimulus (FCN 8-SD), the two operative response keys were illuminated red and the eighth consecutive keypeck response on the right key (designated the work key) changed that stimulus to white; subsequent responses on the work key had no effect on the color of key illumination. After completing a minimum of eight consecutive responses on the work key, a single response on the left key (designated the reinforcement key) produced 3-sec access to grain and changed the work key color to red. Although recorded, multiple responses on the reinforcement key had no programmed consequences. Responding less than eight consecutive times on the work key and then responding on the reinforcement key reset the response requirement but had no effect on the color of key illumination. The contingencies under the FCN schedule without the added external discriminative stimulus (FCN 8) were identical to those arranged under the FCN 8-SD with the exception that when the FCN 8 was in effect the two response keys were illuminated green and no stimulus change (color of key illumination) was associated with the completion of the response requirement on the work key. Each component of the FCN schedule was in effect for 5 min or until eight reinforcers were earned. If eight reinforcers were earned before the end of the 5-min component, the keys and the houselight were darkened until the start of the next component. Each session started with the FCN 8-SD, followed by the FCN 8, and alternated thereafter until three components of each variant of the FCN schedule were completed.

Repeated Acquisition of Behavioral Chains

Eight pigeons were exposed to a three-key four-link chain RA schedule. Each of the four links in the chain was associated with a different key color; yellow with the first, red the second, green the third, and white the fourth and final link. At the start of each chain the three stimulus keys were illuminated yellow and a response on the correct key produced illumination of all three keys in the next color of the chain. Responses on the other two keys (incorrect responses) produced an 8-sec timeout during which all stimulus lights were darkened and responses had no programmed consequences. Incorrect responses did not reset the chain; that is, the stimuli presented after the timeout were identical to those arranged at the time of the error. Completion of five four-link chains resulted in 5-sec access to grain. The sequence of responses designated correct was repeated throughout a given session. In order to obtain a

steady-state measure of repeated acquisition the four-response sequence was changed on a daily basis. With the exception of various simple sequences (e.g., left, left, left, left) all possible four-response sequences were employed. Sessions terminated after 60 min or 10 reinforcers, whichever came first.

Pharmacological Procedure

After response rates and accuracy levels stabilized under each of the conditional discriminations, a dose-effect curve was determined for molindone (a gift from Endo Laboratories, Garden City, NJ). Each dose of molindone was given on a single occasion, in an irregular order that varied across pigeons. Drugs were given no more than twice a week and vehicle control injections no more than once a week. Molindone and vehicle controls were administered IM, 30 min prior to the start of the session at an injection volume of 1.0 ml/kg. Molindone HCl was dissolved in isotonic saline and distilled water; doses are expressed as the salt.

RESULTS

Delayed Matching-to-Sample

During baseline and vehicle control sessions, the percent of correct responses under the DMTS procedure decreased with increases in the delay interval. The mean levels of percent correct responses across pigeons were 93% (range of 88% to 95%) at the 0-sec, 80% (range of 68% to 84%) at the 2-sec and 68% (range of 59% to 73%) at the 8-sec delay interval. Figure 1 shows the effects of molindone on percent correct responses at the three delay intervals and on response rates in the presence of the sample stimulus. Across the dose range evaluated, molindone decreased the percent of correct responses in a dose-dependent fashion. The relative magnitude of these decreases was directly related to the duration of the delay interval; that is, the smallest relative decrements in percent correct responses was obtained at the 0-sec delay and largest at the 8-sec delay interval. At the 10 mg/kg dose, molindone decreased percent correct responses to 85% at the 0-sec delay, 63% at the 2-sec delay, and 55% at the 8-sec delay. Only at this dose was percent correct responses at least 2 S.E.s below control values at each of the delay values. It should be noted, however, that this dose of molindone eliminated responding in two of the pigeons tested. Molindone decreased rates of responding to the sample stimulus in a dose-dependent fashion.

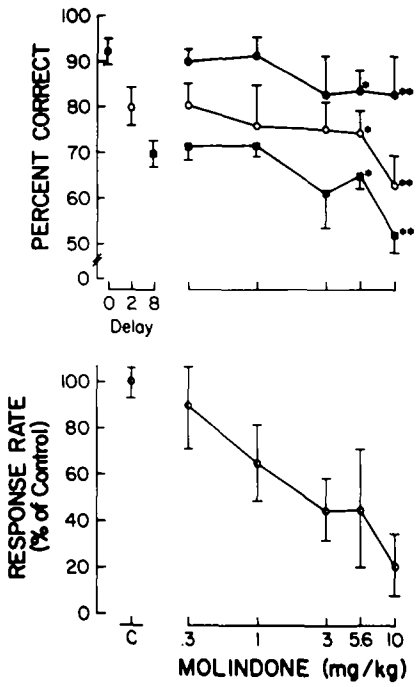

FIG. 1. Effects of molindone on the percent of correct responses and response rates for four pigeons responding under a delayed matching-to-sample procedure. Data in the top panels represent the percent correct responses at the 0-sec, 2-sec and 8-sec delay intervals averaged across the four pigeons. Data for percent correct responses were included only when an individual pigeon completed at least 30 trials during the sessions; asterisks (*) indicate the number of pigeons that failed to meet this criterion. The bottom panel shows rate of responding to the sample stimulus (i.e., on the center response key) expressed as the percent of response rates obtained during control sessions, which are indicated at "C." Vertical lines for all data points represent 1 S.E. During control sessions, mean response rate in the presence of the sample stimulus was 1.45 responses/sec.

Fixed-Consecutive-Number

Data obtained during baseline and vehicle control sessions under the FCN schedules indicated that the percent of reinforced response runs (i.e., responding eight or more consecutive times on the work key and then responding on the reinforcement key) was 88% (range of 81% to 98%) under the FCN 8-SD and 79% (range of 75% to 86%) under the FCN 8. In addition, a comparison of the conditional probability functions indicated that the two FCN schedules engendered distinct patterns of responding (see control data in Fig. 2). A typical pattern of responding under the FCN 8-SD consisted of making 8 to 10 responses on the work key and then switching to the reinforcement key, thus producing a relatively steep conditional probability function. Much flatter conditional probability functions were obtained under the FCN 8, where the conditional probabililty of switching to the reinforcement key increased as a function of the number of consecutive responses on the work key. Figure 2 shows the effects of molindone on the percent of reinforced runs, response rates and conditional probability functions under each of the FCN schedules. Molindone decreased the percent of reinforced runs under the FCN 8 at doses that had no effect under the FCN 8-SD. Under the FCN 8, the 1.0, 3.0 and 5.6 mg/kg doses of molindone decreased percent correct responses by at least 2 S.E.s below the control mean. The selective disruption of stimulus control was also reflected in the conditional probability functions. At the 3.0 and 5.6 mg/kg doses, molindone increased the conditional probability of switching to the reinforcement key after completing 11 or less consecutive responses on the work key under the FCN 8. Conditional probability functions were unaffected under the FCN 8-SD. In contrast to these differential effects, molindone produced comparable decreases in response rates under both variants of the FCN schedule.

Repeated Acquisition of Behavioral Chains

During baseline and vehicle control sessions under the RA procedure, all pigeons completed the maximum number of 50 chains per session, while making an average of 27% (range of 20% to 34%) errors. Figure 3 shows the effects of

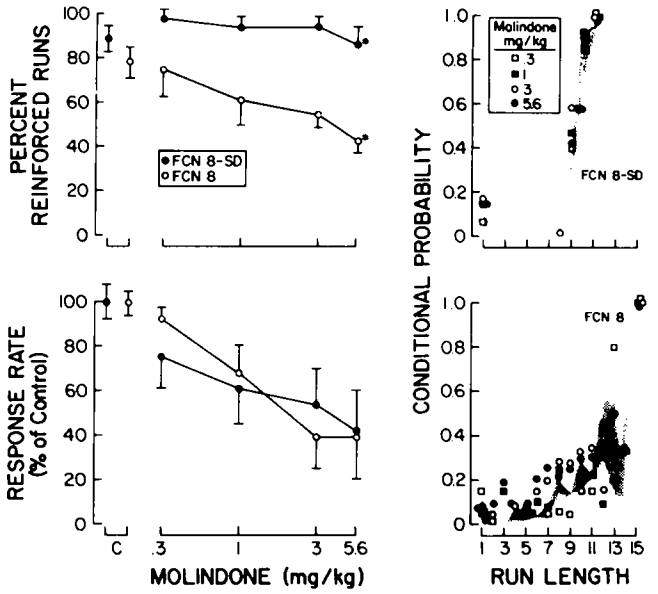

FIG. 2. Effects of molindone on the percent of reinforced runs, response rates, and conditional probability functions for four pigeons responding under a fixed-consecutive-number schedule with (FCN 8-SD) and without (FCN 8) an external discriminative stimulus. Under each FCN schedule, drug data for percent of reinforced runs (top left panels) were included only when an individual pigeon earned at least eight reinforcers during the session; asterisks (*) indicate the number of pigeons that failed to meet this criterion. Drug data for response rates represent mean group performance expressed as the percent of individual control performances which are indicated on the left of these panels at "C." Vertical lines for all data points represent 1 S.E. During vehicle control sessions, mean response rates were 1.44 responses/sec under the FCN 8-SD and 1.78 responses/sec under the FCN 8. Panels on the right indicate the effects of molindone on the conditional probability functions for one pigeon under the FCN 8-SD and FCN 8 schedules. The ordinate gives the probability that the pigeon will stop responding after a number of consecutive responses on the work key, indicated on the abscissa, and then respond on the reinforcement key. The shaded areas represent the range over control sessions. For simplicity, drug data were excluded from the figure when the conditional probability of switching to the reinforcement key was zero.

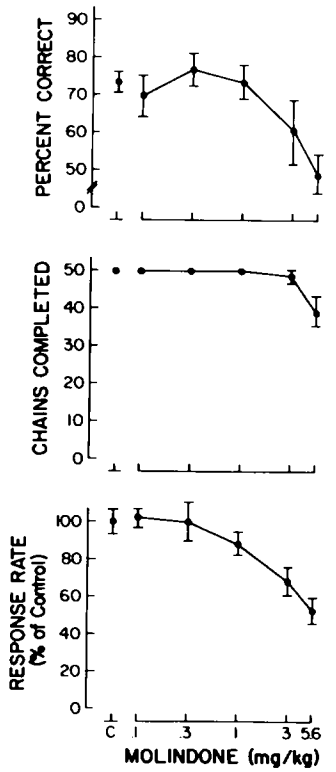

FIG. 3. Effects of molindone on overall percent correct, chains completed and response rate in eight pigeons responding under a repeated acquisition of behavioral chains procedure. Data in the panels illustrating percent correct, chains completed and response rate represent mean group performance. For these panels, vertical lines represent 1 S.E.; those S.E.s that fell within the data point are not illustrated. Control performances in these panels are indicated at "C." Drug data for response rates represent mean group performance expressed as the percent of individual control performances. During control sessions, mean response rate was 0.23 responses/sec.

molindone on overall percent correct responses, chains completed and response rates under the RA procedure. Molindone produced large decreases in the overall percent of correct responses and small decreases in the total number of chains completed. Thus, as the dose of molindone increased, the number of errors per session increased while the number of correct responses remained approximately the same. These decreases in percent correct responses were at least 2 S.E.s below the control mean at the 3.0 and 5.6 mg/kg doses. Molindone decreased response rates in a dose-dependent fashion but did not eliminate responding in any of the pigeons tested. The effects of molindone on the within-session cumulative number of errors and the distribution of errors across the session are shown in Fig. 4. A within-session analysis of the distribution of errors during control sessions indicated that the number of errors per chain completed decreased as the number of chains completed increased. In addition, approximately 45% of the total number of errors emitted during the session occurred prior to earning the first reinforcer and an additional 16% prior to the second. The number of errors per reinforcer gradually declined, and then remained stable at 3–4% per reinforcer between the fifth and tenth reinforcer earned. In terms of the total number of errors, molindone produced large increases in the number of errors during the acquisition phase of the session (i.e., prior to earning the first few reinforcers); number of errors per reinforcer earned decreased dramatically during the performance phase (i.e., after earning the first few reinforcers), although they still remained above control values. In terms of the distribution of errors across the session, molindone's effects were comparable to those obtained during control sessions; that is, the proportion of the total errors emitted during the acquisition and performance phases were similar to those obtained during control sessions.

Comparisons Across Discrimination Procedures

The effects of molindone on accuracy and response rates under the DMTS, FCN 8 and RA procedures are compared in Fig. 5. Under the DMTS procedure, the relative magnitude of molindone's accuracy-decreasing effects were largest at the 8-sec delay interval, thus, accuracy at the other

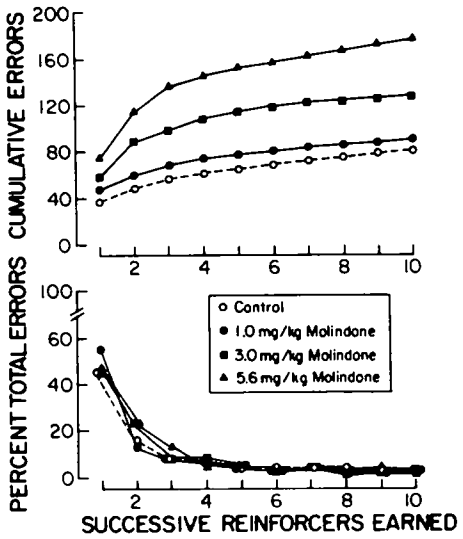

FIG. 4. Effects of selected doses of molindone on the cumulative number of errors and the percent of the total number of errors at each reinforcer earned under the repeated acquisition of behavioral chains procedure. All data reflect the mean group performance for eight pigeons.

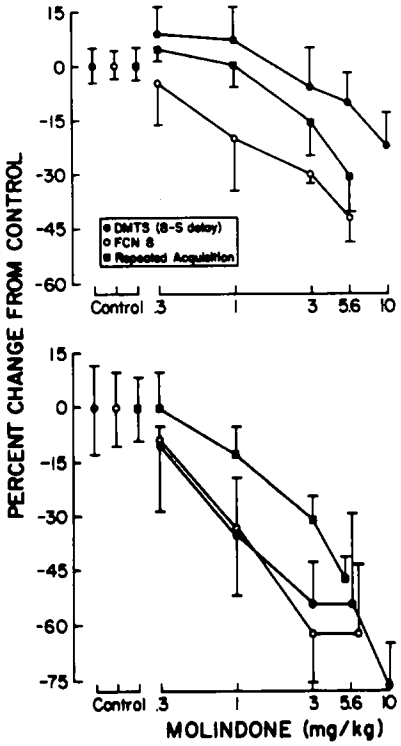

FIG. 5. Effects of molindone on accuracy levels (top panel) and response rates (bottom panel) for pigeons responding under the delayed matching-to-sample (DMTS), fixed-consecutive-number without the external discriminative stimulus (FCN 8) and repeated acquisition of behavioral chains (RA) procedures. Accuracy levels reflect the percent of correct responses obtained under the DMTS and RA procedures, and percent of reinforced runs under the FCN 8 procedure. Drug data represent the mean of each group's performance expressed as the percent change from control sessions. Control data for each procedure are indicated at "C." For all data points, vertical lines represent 1 S.E.

delay intervals are not shown. Accuracy values during control sessions for each of these procedures was slightly different, with the DMTS (8-sec delay) engendering accuracy levels of 68%, the RA 74% and the FCN 8 79%. Thus, for ease of comparison, these data are expressed as the percent of change from control values. Under the DMTS procedure, the maximum relative decrease in accuracy at the 8-sec delay interval was 9% at the 5.6 mg/kg dose and 22% at the 10 mg/kg dose. Assuming 50% percent correct responses represents chance performance, the maximum relative decrease in accuracy at this delay value would not be expected to exceed 26%. Relative to control values, the 5.6 mg/kg dose of molindone decreased the percent of reinforced runs by 43% under the FCN 8, whereas this dose had no effect under the FCN 8-SD (data not depicted). The 5.6 mg/kg dose of molindone decreased the percent of correct responses by 34% under the RA procedure.

During control sessions, rates of responding differed substantially across the procedures, with the FCN 8 and DMTS procedures producing relatively high rates of responding (1.78 and 1.44 responses/sec, respectively), and the RA relatively low rates (0.23 responses/sec). Across the dose range evaluated, however, molidone produced comparable decreases in the mean overall rates of responding under each of these procedures.

DISCUSSION

The present investigation evaluated the effects of the atypical neuroleptic molindone under three conditional discrimination procedures. The finding that molindone produced a dose-related disruption of accuracy (discrimination performance) under each of these procedures is similar to those obtained in previous investigations of the effects of certain phenothiazines, dibenzodiazepines, tricyclic dibenzoxazepines and thioxanthenes in pigeons responding under discrimination tasks (13, 20, 21, 31, 35). These findings are, however, in contrast to those reported with the butyrophenones (i.e., haloperidol) and benzamides (i.e., sulpiride), each of which has been reported to have no effect on discrimination performance (13, 17, 20, 21). Thus, the present findings support a growing body of literature which indicates that there are qualitative differences in the effects of neuroleptic agents when evaluated in nonhumans responding under procedures requiring conditional discriminations.

Evaluations of the effects of neuroleptics under conditional discrimination tasks generally indicate that neuroleptics with moderate to pronounced anticholinergic actions (5, 18, 23, 25, 27) decrease discrimination performance, whereas neuroleptics with only weak anticholinergic actions (5, 18, 23, 25, 27) have little or no effect on discrimination performance. Those neuroleptics with weak anticholinergic actions, namely the benzamides and butyrophenones, also differ from the neuroleptics (e.g., phenothiazines, dibenzodiazepines, tricyclic dibenzoxazepines, thioxanthenes) that decrease discrimination performance in that they are weak antagonists of striatal dopamine-sensitive adenylate cyclase, an effect shared by molindone (11,12). That molindone, but not the benzamides and butyrophenones, disrupted discrimination performance suggests that this behavioral effect is not necessarily mediated by antagonism of striatal dopamine-sensitive

adenylate cyclase. The anticholinergic actions of neuroleptics cannot, however, account for the complete spectrum of neuroleptic-induced behavioral actions under discrimination tasks. For example, the potency ranking for neuroleptics (including molindone) in terms of their response rate-suppressing effects [(3, 4, 19, 20), present investigation] are highly correlated with the potency ranking for these drugs in terms of their ability to antagonize dopamine receptors [see (18,25)]. Moreover, pimozide, a diphenylbutylamine with minimal anticholinergic actions (5), has been reported to disrupt discrimination performance under some discrimination tasks (28) and not others (29,30).

The procedure under which molindone produced the largest decrease in accuracy was the FCN schedule. This accuracy-decreasing effect was selective in that molindone decreased accuracy under the FCN 8 at doses that had no effect on accuracy under the FCN 8-SD. This finding is in agreement with previous investigations which indicate that the addition of an external discriminative stimulus can modulate the disruptive behavioral effects of the neuroleptics pimozide and clozapine (13, 19, 28). Although similar effects have been reported with the phenothiazines' chlorpromazine and promazine, the extent to which the external discriminative stimulus attenuated the disruptive effects of these drugs was considerably smaller (13).

Under RA procedures, chlorpromazine has been reported to produce a dose-dependent disruption of accuracy (31,33). Based on the cumulative errors, chlorpromazine's accuracy-decreasing effect appeared to be most evident during the acquisition phase (i.e., error rates prior to obtaining the first few reinforcers) of the session. Similar findings were obtained in the present investigation following the administration of molindone. However, an analysis of the distribution of molindone-induced errors revealed that molindone increased the total number of errors without altering the distribution of errors across the session. That the distribution of errors across the session was not appreciably altered indicates that molindone had similar effects on error rates across the acquisition and performance (i.e., error rates after obtaining the first few reinforcers) phases of the session.

The decreases in accuracy obtained under the FCN 8 and RA procedures were considerably larger than those obtained under the DMTS procedure. Although molindone-induced decrements in accuracy under the DMTS were small, their relative magnitude varied across delay intervals with the smallest decreases obtained at the shortest delay interval (0-sec) and largest at the longest delay interval (8-sec). These findings are similar to those reported with the phenothiazines, thioxanthenes and dibenzodiazepines when evaluated under the DMTS procedure (20, 21, 24).

By using the three different conditional discrimination tasks, the present investigation was able to demonstrate that the relative magnitude of molindone's accuracy-decreasing effects varied across tasks and was determined in part by the parameters employed in each task. For example, the 5.6 mg/kg dose of molindone had little effect on accuracy under the FCN 8-SD and DMTS procedures. At this dose, accuracy levels were decreased considerably under the RA and the FCN 8 procedures. Thus, it would appear that the RA and FCN 8 procedures are more sensitive to molindone's accuracy-decreasing effect than the DMTS and FCN 8-SD procedures. Although these findings suggest that some conditional discriminations are more sensitive to the disruptive effects of molindone, it is possible that these differential effects reflect the different types of behavior emitted in each task (see Introduction). In addition, altering procedural parameters under any of these tasks (e.g., increasing the response requirement in the FCN) could alter the relative magnitude of drug-induced decreases in accuracy. Moreover, the procedures used in the present investigation differed in terms of the relative magnitude of the potential drug-induced decreases in accuracy. For example, accuracy levels of 50% would be indicative of chance performance under the DMTS procedure where only two response options are available on each trial. Such limitations on decreases in accuracy were not potential problems under the FCN and RA procedures. Nevertheless, the battery of tests used in the present investigation may provide a useful tool for studying the behavioral effects of neuroleptic drugs as well as provide a behavioral baseline for assessing the different neurochemical actions of these drugs. Moreover, the differential behavioral effects obtained in the present investigation illustrate further the need to employ a variety of assays when evaluating the behavioral actions of drugs.

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REFERENCES

1. Altman, J. L.; Appel, J. B.; McGowan, W. T., III. Drugs and the discrimination of duration. Psychopharmacology (Berlin) 60:183–188; 1979.
2. Ayd, F. J., Jr. A critical evaluation of molindone (Moban): A new indole derivative neuroleptic. Dis. Nerv. Syst. 35:447–452; 1974.
3. Barrett, J. E. Antipsychotic drug effects on the behavior of squirrel monkeys differentially controlled by noxious stimuli. Psychopharmacology (Berlin) 77:1–6; 1982.
4. Barrett, J. E. Comparison of the effects of antipsychotic drugs on schedule-controlled behavior in squirrel monkeys and pigeons. Neuropharmacology 22:519–524; 1983.
5. Christensen, A. V.; Arnt, J.; Hyttel, J.; Larsen, J.-J.; Svendsen, O. Pharmacological effects of a specific dopamine D-1 antagonist Sch 23390 in comparison with neuroleptics. Life Sci. 34:1529–1540; 1984.
6. Davidson, A. B.; Weidley, E. Differential effects of neuroleptics and other psychotropic agents on acquisition of avoidance in rats. Life Sci. 18:1279–1284; 1976.
7. Dykstra, L. A.; Genovese, R. F. Measurement of drug effects on stimulus control. In: Greenshaw, A. J.; Dourish, C. T., eds. Experimental psychopharmacology. Clifton, NJ: Humana Press; 1987.
8. Ellenbroek, B. A.; Peeters, B. W.; Honig, W. M.; Cools, A. R. The paw test: a behavioral paradigm for differentiating between classical and atypical neuroleptic drugs. Psychopharmacology (Berlin) 93:343–348; 1987.
9. Gallant, D.; Bishop, M. P. Molindone: A controlled evaluation in chronic schizophrenic patients. Curr. Ther. Res. 10:441–445; 1968.

10. Heise, G. A.; Milar, K. S. Drugs and stimulus control. In: Iversen, L. L.; Iversen, S. D.; Snyder, S. H., eds. Handbook of psychopharmacology, vol. 18. New York: Plenum Press; 1984.
11. Hyttel, J. Effects of neuroleptics on [3H]cis(Z)-flupenthixol binding and on adenylate cyclase activity in vitro. Life Sci. 23:551–556; 1978.
12. Jenner, P.; Marsden, C. D. The substituted benzamides—A novel class of dopamine antagonists. Life Sci. 25:479–486; 1979.
13. Laties, V. G. The modification of drug effects on behavior by external discriminative stimuli. J. Pharmacol. Exp. Ther. 183:1–13; 1972.
14. Leander, J. D.; McMillan, D. E. Rate-dependent effects of drugs. I. Comparison of d-amphetamine, pentobarbital and chlorpromazine on multiple and mixed schedules. J. Pharmacol. Exp. Ther. 188:728–739; 1974.
15. Meller, E. Chronic molindone treatment: Relative inability to elicit dopamine receptor supersensitivity in rats. Psychopharmacology (Berlin) 76:222–227; 1982.
16. Newland, M. C.; Marr, M. J. The effects of chlorpromazine and imipramine on rate and stimulus control of matching to sample. J. Exp. Anal. Behav. 44:49–68; 1985.
17. Nielsen, E. B.; Appel, J. B. The effects of drugs on the discrimination of color following a variable delay period: A signal detection analysis. Psychopharmacology (Berlin) 80:24–28; 1983.
18. Peroutka, S. J.; Snyder, S. H. Relationship of neuroleptic drug effects at brain dopamine, serotonin, alpha-adrenergic and histaminic receptors and clinical potency. Am. J. Psychiatry 137:1518–1527; 1980.
19. Picker, M. J. Effects of clozapine on fixed-consecutive-number responding in rats: A comparison to other neuroleptic drugs. Pharmacol. Biochem. Behav. 30:603–612; 1988.
20. Picker, M. J.; Massie, C. Differential effects of neuroleptic drugs on the delayed matching-to-sample performance of pigeons. Pharmacol. Biochem. Behav. 31:953–957; 1988.
21. Poling, A.; Picker, M. J.; Thomas, J. Effects of chlorprothixene, haloperidol, and trifluoperazine on the delayed matching-to-sample performance of pigeons. Pharmacol. Biochem. Behav. 21:721–726; 1984.
22. Pragay, E. B.; Mirsky, A. F.; Abplanalp, J. M. The effects of chlorpromazine and secobarbital on matching to sample and discrimination tasks in monkeys. Psychopharmacologia 15:128–138; 1969.
23. Richelson, E.; Divinetz-Romero, S. Blockade of psychotropic drugs of the muscarinic acetylcholine receptor in cultured nerve cells. Biol. Psychiatry 12:771–785; 1977.
24. Roberts, M. H. T.; Bradley, P. B. Studies on the effects of drugs on performance of a delayed discrimination. Physiol. Behav. 2:389–397; 1967.
25. Seeman, P. Brain dopamine receptors. Pharmacol. Rev. 32: 229–313; 1980.
26. Spealman, R. D.; Kelleher, R. T.; Goldberg, S. R.; DeWeese, J.; Goldberg, D. M. Behavioral effects of clozapine: Comparison with thioridazine, chlorpromazine, haloperidol and chlordiazepoxide in squirrel monkeys. J. Pharmacol. Exp. Ther. 224:127–134; 1983.
27. Snyder, S.; Greenberg, D.; Yamamura, H. I. Antischizophrenic drugs and brain cholinergic receptors. Arch. Gen. Psychiatry 31:58–61; 1974.
28. Szostak, C.; Tombaugh, T. N. Use of a fixed consecutive number schedule of reinforcement to investigate the effects of pimozide on behavior controlled by internal and external stimuli. Pharmacol. Biochem. Behav. 15:609–617; 1981.
29. Tombaugh, T. N. Effects of pimozide on nondiscriminated and discriminated performance in the pigeon. Psychopharmacology (Berlin) 73:137–141; 1981.
30. Tombaugh, T. N.; Ritch, M. A.; Shepherd, D. T. Effects of pimozide on accuracy of performance and distribution of correct responding on a simultaneous discrimination task in the rat. Pharmacol. Biochem. Behav. 13:859–862; 1980.
31. Thompson, D. M. Repeated acquisition as a behavioral baseline for studying drug effects. J. Pharmacol. Exp. Ther. 184:506–514; 1973.
32. Thompson, D. M. Stimulus control and drug effects. In: Blackman, D. E.; Sanger, D. J., eds. Contemporary research in behavioral pharmacology. Englewood Cliffs, NJ: Plenum Press; 1978.
33. Thompson, D. M. Selective antagonism of the rate-decreasing effect of *d*-amphetamine by chlorpromazine in a repeated acquisition task. J. Exp. Anal. Behav. 34:87–92; 1980.
34. Wenger, G. R. Effects of clozapine, chlorpromazine and haloperidol on schedule-controlled behavior. Pharmacol. Biochem. Behav. 11:661–668; 1979.
35. West, K. B.; Hernandez, L. L.; Appel, J. B. Drugs and visual perception: Effects of LSD, morphine and chlorpromazine on accuracy, bias and speed. Psychopharmacology (Berlin) 76:320–324; 1982.