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EFFECTS OF THIORIDAZINE (MELLARIL) ON
TITRATING DELAYED MATCHING TO SAMPLE
PERFORMANCE IN MENTALLY RETARDED ADULTS

by

Timothy Theodore Wysocki

A Dissertation
Submitted to the
Faculty of The Graduate College
in partial fulfillment of the
requirements for the
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Timothy Theodore Wysocki

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CHAPTER I

INTRODUCTION

The prevalence of psychotropic drug use in institutions for the mentally retarded has been surveyed several times in the past decade. Lipman (1970) surveyed 109 of these institutions in the United States and reported that 51% of the residents were receiving one or more psychotropic medications on a chronic basis. Of these, 58% were receiving either chlorpromazine (Thorazine) or thioridazine (Mellaril), two neuroleptic drugs of the phenothiazine family. Several more recent, although less comprehensive, surveys reported similar results, indicating that there has been no clearly decreasing trend in the use of these drugs with the mentally retarded in the past decade (Silva, 1979; Sprague, 1977; DiMascio, Note 1). Thus, it appears that psychotropic drugs continue to be widely used as an acceptable method of treatment for the behavior problems associated with mental retardation.

However, a court order emanating from the Wyatt vs. Stickney case (1972) stipulated that psychotropic drugs shall not be prescribed in amounts which impair the acquisition or display of habilitative responses (see Sprague and Baxley, 1978 for a review of the legal issues surrounding the use of psychotropic drugs with the mentally retarded). Despite this judicial pressure toward institutional reform, the prescribing physician currently has little available data upon which to base such precise medical judgements. Sprague and

Werry's (1971) review of 182 drug studies with the mentally retarded revealed only four which included any assessment of drug effects on learning or performance measures. Similarly, in a review of research on psychotropic drug effects on learning and related behavioral processes in children, Aman (1978) found only nine studies concerned with chlorpromazine and only one investigation of thioridazine's effects on learning.

While it is popularly assumed that psychotropic drugs will render an individual more amenable to treatment by other therapies, the few available studies do not support this assumption. Paul, Tobias and Holly (1972) studied a variety of psychotropic drugs and reported that none of them appeared to facilitate the effectiveness of either behavior modification or milieu therapy. McCahey, Thompson and Zimmerman (1977) reported data which indicated that chlorpromazine administration caused a retarded woman to earn fewer reinforcers in a token economy. Breuning, O'Neill and Ferguson (in press) compared the separate and combined effects of psychotropic drugs and a response cost procedure on a variety of inappropriate behaviors in mentally retarded adults. They found that the response cost procedure alone was more effective than either psychotropic drugs alone or the two approaches in combination with one another. They concluded that the drug administration may have actively impaired the effectiveness of the behavioral intervention. Marholin, Touchette and Stewart (1979) analyzed the effects of a brief withdrawal of chronic chlorpromazine administration on a variety of appropriate social and adaptive behaviors in five mentally retarded adults. While the effects of this

manipulation were highly individualized, several of the subjects revealed increases in some appropriate behaviors subsequent to the termination of the medication. These effects disappeared when the drug administration was reinstated.

While these few studies are suggestive, it is clear that a wide range of research remains to be done in order to determine the effects of interactions between specific drugs, adaptive behaviors and behavior modification procedures.

There is a particularly urgent need for research which establishes "dose-response" relationships for drug effects on learning and adaptive behaviors. Sprague, Barnes and Werry (1970) provided one such study in a comparison of the effects of methylphenidate and thioridazine on performance of a "delayed response" task by behaviorally disordered children. Methylphenidate increased accuracy while thioridazine decreased accuracy on the task. While the subjects received two dose levels of each drug, no dose-dependent effects were found. However, the authors suggested that this may have been a result of using a rather narrow dose range and that perhaps wider dosage differences may have been more sensitive to such effects.

The present study represents an attempt to elaborate upon the Sprague et al. (1970) findings by examining the effects of a wide range of doses of thioridazine upon performance of a similar discrimination task.

Cumming and Berryman (1965) described several variants of the matching to sample discrimination. In a typical delayed matching to sample procedure, a sample stimulus is presented to the subject.

After the occurrence of a response which is designed to insure that the subject actually observed the sample stimulus, the sample disappears. After a delay interval elapses, two or more comparison stimuli are presented. The subject's task is to choose the comparison stimulus which is identical to the previously presented sample stimulus.

Cumming and Berryman (1965) introduced a variation of this procedure which is termed titrating delayed matching to sample. In this procedure, the delay between termination of the sample stimulus and presentation of the comparison stimuli depends upon the accuracy of the subject's performance on previous trials. Accurate performance results in increasing the delay for the subsequent trial, while inaccurate performance results in decreasing the delay interval. Using this procedure, Scheckel (Note 2) established the limit of delay reached by monkeys under a variety of drug conditions. With chlorpromazine, he found that the limit of delay decreased linearly with increasing doses of the drug.

Dews (1955), Laties and Weiss (1966), Laties (1972), and Thompson (1975; 1978) have observed that behavior under weak stimulus control will be more sensitive to drug manipulations than will behavior under stronger stimulus control. Thus, performance at the longer delays in titrating delayed matching to sample should readily reveal the behavioral effects of drugs. The present study, then, was designed to assess the effects of thioridazine on performance of a titrating delayed matching to sample discrimination by mentally retarded adults.

CHAPTER II

METHOD

Subjects

Four adult residents of a state institution for the developmentally disabled, each of whom had received a particular daily dose of thioridazine for at least 150 days prior to the experiment, served as subjects. An interdisciplinary team of professionals, including a physician and a psychologist, had identified each of them as a candidate for gradual withdrawal from the medication. Criteria for their selection were either low frequency or low severity of inappropriate behaviors and/or independent evidence which indicated specific environmental variables which controlled the occurrence of existing inappropriate behaviors. The subjects were receiving no other psychotropic or anticonvulsant medications. Table I provides a summary of other pertinent subject characteristics.

Each subject's guardian and the institution's research committee approved the subject's participation in the study after receiving a description of the procedures. All subjects were free to withdraw from the study at any time, subsequent to their own, or their guardian's, request.

Setting and apparatus

Testing sessions occurred in a room which was 3.0 m wide by 7.1 m

Table I. Summary of pertinent subject characteristics.

TABLE I

SUMMARY OF PERTINENT SUBJECT CHARACTERISTICS

Subject	Sex	Age (Yrs.)	Body Weight (kg)	Baseline Daily Dose (mg)	IQ (Test)	Months on Baseline Dose
S	F	24	54.3	800	62 (WAIS)	7
T	M	27	75.8	400	78 (WAIS)	5
C	M	22	78.0	400	51 (Leiter)	33
J	F	20	65.0	400	51 (Leiter)	24

long. The room contained a table and a chair with an intelligence panel mounted on top of the table. The intelligence panel consisted of a horizontal array of three 15.2 cm square plexiglas response panels. A projection device provided the capability of illuminating a 5.0 cm square in the center of each response panel with any of three colors: red (about 640 nm.), green (about 530 nm.), or blue (about 480 nm.). All subjects could accurately name each of these colors prior to the experiment. A 15.2 cm square reinforcement dispenser was mounted 10.1 cm below the center response panel. Reinforcers consisted of "Reese's Pieces" candies for Subject C and stainless steel ball bearings, exchangeable for a variety of backup reinforcers, for the remaining subjects. These backup reinforcers were cupcakes or cookies for Subject T, chewing gum for Subject J and assistance in writing letters home for Subject S. Once the experimenter had selected a reinforcer for a given subject, the same reinforcer was used in all subsequent sessions.

Stimulus presentations and delivery of consequences were controlled automatically by relay circuitry located in an adjacent room. A printing counter and run time meter recorded trial-by-trial performance automatically. The accuracy of the circuitry was insured prior to each session by simulation of several trials.

Procedure

The subjects received thioridazine orally in its suspension form in order to insure its ingestion. The ward nurses administered

the drug in two equal doses daily. Baseline doses were 800 mg daily for Subject S and 400 mg daily for the other subjects. Ward attendants were not informed of medication changes for any of the subjects. The assigned physicians ordered and monitored all medication changes.

During a pre-experimental phase, the subjects received training in zero delay matching to sample (Cumming and Berryman, 1965). The sessions always occurred at the same hour of the day for a given subject. Subjects remained alone in the experimental room throughout each session. Discriminative stimuli were either red, blue, or green squares projected onto the response panels. At the start of each trial, the center response panel was illuminated with one of the three colors as a sample stimulus. Depression of the center response panel terminated its illumination and simultaneously resulted in the illumination of both side response panels with comparison stimuli. One of the comparison stimuli was identical to the sample, while the other was a non-matching color. Position of the non-matching comparison stimulus varied randomly. Each of the three colors appeared equally often as the sample, matching comparison and non-matching comparison stimulus. Depression of the "matching" response panel terminated its illumination and resulted in the delivery of one reinforcer, as well as the presentation of a 0.5 sec, 1000 Hz tone. Depression of the "non-matching" response panel terminated the illumination of all response panels for a 10 sec timeout period. A failure to depress either side response panel within 30 sec of the appearance of the comparison stimuli also yielded a 10 sec timeout. Such trials were considered to be equivalent to errors. At the conclusion of the timeout

period, or 5 sec after the delivery of a reinforcer, the center response panel was again illuminated, providing the subject with the opportunity to initiate the next trial. Every trial on which an incorrect choice response was made was repeated until the subject completed it correctly.

Sessions consisted of 30 minutes of training in this discrimination. Pre-experimental training continued until a subject maintained 90% accuracy over two consecutive sessions. Subjects remained at the baseline dose of thioridazine throughout the pre-experimental training.

Once all subjects had mastered the basic discrimination, thioridazine doses were reduced systematically in a multiple-baseline-across-subjects design (Baer, Wolf and Risley, 1968). Concurrent with these drug reductions, the subjects participated in bi-weekly assessments of their performance of a titrating delayed matching to sample discrimination. Stimulus presentations and programmed consequences occurred as during pretraining sessions, except that a delay occurred between depression of the illuminated center response panel and the presentation of comparison stimuli on the side response panels. The length of the delay interval varied according to a titration schedule. Sessions began at a delay of 0 sec. Once the subject emitted four consecutive correct responses at that delay, the delay interval was increased to 1 sec for the subsequent trial. Thereafter, following four consecutive correct responses at a given delay, the delay value was increased for the next trial through the progression: 0,1,2,3, 4,5,6,7,8,10,12,15,18,21,24,27,30,35,40,45,50,55,60,65,70,75,90, and

105 sec. Each incorrect response resulted in decreasing the delay interval for the next trial to the previous step in this progression. Sessions ended after the first error following 30 minutes of task performance. If, during a given session, a subject progressed through a delay value of 10 sec without an error, a slight alteration in the titration procedure was followed in the next session. For those sessions, the delay value was increased following each two consecutive correct responses until the first error was made. Thereafter, the standard titration schedule was in effect for the remainder of the session. This aspect of the procedure was included in an attempt to minimize the influence of within-session satiation upon accuracy of performance.

The primary dependent variable was the limit of delay, defined as the longest delay value at which the subject emitted four consecutive correct responses within a given session. Other performance measures which were recorded were the sample latency (time in seconds to press the center response panel once the sample stimulus appeared) and the choice latency (time in seconds to press a side response panel once the comparison stimuli appeared).

CHAPTER III

RESULTS

Fulfillment of the criterion for discontinuation of pre-experimental training required four sessions for Subject C, three for Subject T and two for Subjects S and J. Subjects T and J were placed in the community after Days 110 and 121, respectively. Neither participated in the study after those dates.

Figure 1 presents the limit of delay reached during each session by each subject. Again, the limit of delay was defined as the longest delay value at which the subject emitted four consecutive correct responses during each session. The performance of all subjects was characterized by increases in the limit of delay after, and only after, dose reductions had occurred. The sole exception to this relationship was the decline in Subject C's performance when the thioridazine dose was reduced from 200 mg to 100 mg daily. A dosage reversal for Subject J revealed increases and decreases in the limit of delay as the dose was alternately decreased and increased.

Figure 2 presents the percentage of correct responses at each of the delay values separately for each dosage condition. Again, the data indicate increased accuracy at lower doses. In general, the lower the dose, the more accurate was performance at each delay. This effect was more pronounced at intermediate and long delays for each subject. The decrement in Subject C's performance during the 100 mg condition was the only clear exception to this relationship. Figure

Figure 1. Limit of delay reached each session by each subject as a function of daily thioridazine dose.

FIGURE 1

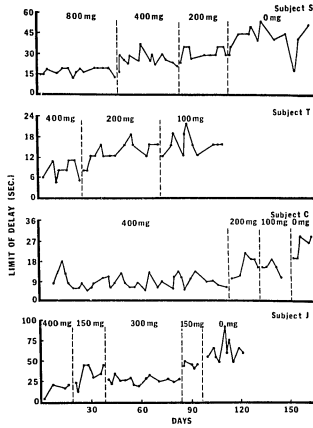
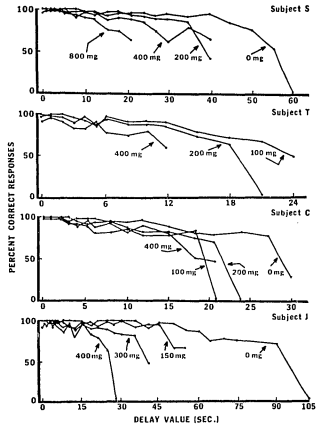


Figure 2. The percentage of correct responses at each of the delay values separately for each dosage condition. (Data from both of the 150 mg conditions for Subject J are combined for clarity of presentation.)

FIGURE 2



2 also indicates that, for the three subjects who were taken completely off of the drug, the largest performance increments occurred following the reduction to 0 mg from the previous dose.

The effects of thioridazine on mean sample latency (the time between availability of the sample stimulus and the first depression of the center panel) appear in Figure 3. Subjects S and T showed consistent increases in this measure after each dose reduction. The results for Subjects C and J were highly variable. However, these latter two subjects also appeared to show increases in mean sample latency during the 0 mg condition.

The drug's effects on mean choice latency (the time between availability of the comparison stimuli and the first depression of a side response panel) appear in Figure 4. In general, this measure was less sensitive to dosage reductions. It typically remained stable, although some increases occurred following reductions to 0 mg.

Standard institutional data collection procedures indicated no systematic changes in the frequency of inappropriate behaviors for any of the subjects. None of the subjects was placed back on thioridazine or any other psychotropic drug within 90 days of the completion of the experiment.

Figure 3. Mean sample latency for each subject for each session.

FIGURE 3

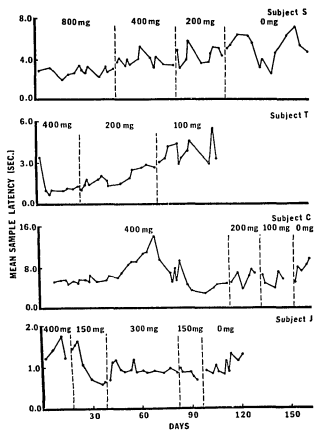
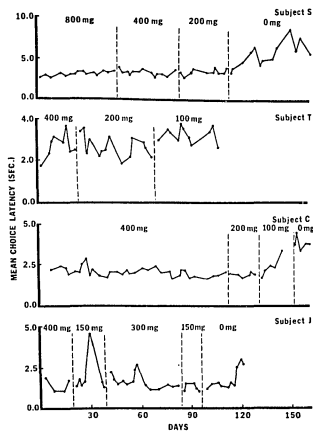


Figure 4. Mean choice latency for each subject for each session.

FIGURE 4



CHAPTER IV

DISCUSSION

From the data presented in Figures 1 and 2, it appears that the withdrawal of chronically administered thioridazine resulted in increased accuracy of delayed matching to sample performance. The limit of delay increased after, and only after, dose reductions had occurred. This conclusion is bolstered by the finding that Subject J's performance varied systematically with the drug dose through a reversal of the dose level. These findings suggest very strongly that thioridazine impairs delayed matching to sample performance in the mentally retarded.

The possibility that the results represent a practice effect can be discounted for several reasons. First, the performance of Subjects S and C did not improve despite 15 and 34 baseline sessions, respectively. Second, the limit of delay stabilized within each of the longer dosage conditions. Finally, the reversal effect obtained with Subject J indicates that the limit of delay was functionally related to thioridazine dose despite the continuation of practice with the task and the passage of time.

Several characteristics of the drug's effects on the limit of delay should be mentioned. Despite the fact that thioridazine is excreted from the system very slowly, the behavioral effects of dosage reductions typically began to appear within several days of the drug change. Peak performance was usually reached within two to three

weeks. A similar effect was reported by Marholin, Touchette and Stewart (1979). They found that withdrawal of chronic chlorpromazine either resulted in behavioral changes within 48 hours or no such changes would be observed.

A second noteworthy characteristic of these data is that, for those subjects who were taken completely off of the drug, the largest increments in the limit of delay occurred following the reduction to 0 mg. This finding suggests that even quite low doses of the drug produce significant interference with performance of this conditional discrimination.

The finding that thioridazine impairs performance of a delayed matching to sample discrimination confirms and extends the results reported by Sprague, Barnes and Werry (1970). The present study extended their findings to a different task and demonstrated that dose-dependent decrements in task performance are evident when a broad range of doses is evaluated.

The present results also confirm those from Scheckel's (Note 2) investigation of chlorpromazine's effects on monkeys' performance of a titrating delayed matching to sample discrimination. Although Scheckel reported more substantial dose-dependent effects than were obtained in the present study, the two studies report similar findings despite the use of different drugs, different species and chronic versus acute drug administration.

The apparent increase in mean sample latency and mean choice latency at lower doses is a somewhat paradoxical finding. Most of the basic research with the phenothiazines indicates that these drugs

reduce the frequency of behavior maintained by positive reinforcement (Iversen and Iversen, 1975). Thus, withdrawal of the drug might be expected to decrease, rather than increase, the two latency measures. Only further research could identify which of the many possible variables is responsible for this effect. In any event, it is clear that neither latency measure declined systematically as the dosage of thioridazine was reduced. This observation indicates that the obtained increases in the limit of delay did not occur because subjects worked more rapidly under lower doses of thioridazine.

Finally, the apparent absence of increases in inappropriate behaviors as drug treatment was withdrawn should be interpreted cautiously. The subjects selected for this study cannot be considered representative of all mentally retarded adults receiving thioridazine. Each of the subjects had been identified by an interdisciplinary team of professionals as an ideal candidate for the drug reduction. Thus, the absence of increases in inappropriate behaviors probably illustrates the accuracy of the interdisciplinary team's predictions about the effects of drug withdrawal on these particular individuals. These data should not be interpreted as indicating that all mentally retarded adults can be taken off of thioridazine without undesirable behavioral effects.

The extent to which the performance decrements revealed in the present study are indicative of an effect which bears practical significance must be addressed by future research. These data suggest that performance in situations requiring that stimulus control persist

across a delay might be disrupted by the drug. Examples of such situations might include instructional procedures which require a specific response to occur some time after an instruction, model or prompt is presented (e.g., Garcia, 1976; O'Brien and Azrin, 1972; Streifel, Bryan and Aikins, 1974; Touchette, 1968; 1971).

Perhaps our primary obligation to the mentally retarded is to maximize their acquisition and maintenance of adaptive behaviors. While the present study does not directly indicate that thioridazine disrupts adaptive behavior, it does demonstrate that the drug impairs a behavioral process which probably forms the basis for much adaptive behavior. Any indication that a widespread practice might be exerting undesirable behavioral effects on the mentally retarded should be taken seriously. Until further research shows that the effects revealed in the present study are without practical significance, the indiscriminate use of thioridazine with the mentally retarded simply cannot be justified.

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