Behavioral Interventions, Vol. 9, No. 2, 123–139 (1994)

CASE STUDY: THE COMBINED USE OF IMIPRAMINE AND BEHAVIOR MODIFICATION TO REDUCE AGGRESSION IN AN ADULT MALE DIAGNOSED AS HAVING AUTISTIC DISORDER

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The present study examined the behavior decelerative effects of combined imipramine (tofranil) and behavior modification in a severely retarded, depressed autistic man. A simple interrupted time-series design was conducted and the primary data analytic techniques consisted of modified trend analyses and dependent samples *t*-tests. Consistent with previous theory and scant empirical research, results indicated that combined imipramine and behavior modification significantly reduced daily episodes of self-directed and other-directed aggression. Specifically, controlling for the effects of time, the combined treatment regimen led to significant reductions in both level and slope across three topographies of aggressive behavior. Limitations of the present study and recommendations for future research were discussed. It was concluded that combined imipramine and behavior modification may be an effective strategy for reducing aggression in the developmentally disabled.

Aggression is a major concern among the developmentally disabled for a number of reasons. First and foremost, aggressive behavior poses a serious threat to oneself and to others (Campbell, Malone, & Kafantaris, 1990; Gardner & Cole, 1990; Harris & Handleman, 1990; Schroeder, Rojahn, Mulick, & Schroeder, 1990). Second, both clinical and direct care staff may find client-based aggression intimidating. Such staff intimidation, in turn, may result in fewer social interactions with clients and decreased treatment integrity (Harris & Handleman, 1990; Myers, Richards, & Huff, 1991). A third cause for concern is that client-based aggression tends to be incompatible with appropriate "on task" behavior (Gardner & Moffatt, 1990). Such incompatibility between aggres-

I gratefully acknowledge Theresa Cancilla and Steven Gargano for their invaluable assistance in completing this study. I am also grateful to David B. Allison for reviewing an earlier draft of the manuscript. Portions of this work were previously presented at the 1991 New York State Association for Behavior Analysis (NYSABA) poster seminar in Smithtown, New York.

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CCC 0084–5581/94/020123–17

sion and "on task" behavior, coupled with the general aversiveness of client-based aggression, typically results in less active treatment and fewer opportunities for learning (Lutzer, 1987; Van Houten, 1990). In combination, these three sequelae of aggressive behavior mitigate against treatment progress and in addition often impede client movement into less restrictive environments (Gardner & Moffatt, 1990; Hill & Bruininks, 1984; Rousey, Blacher, & Hanneman, 1990).

In most applied settings, aggression among the developmentally disabled is treated via a combination of behavior modification and pharmacotherapy (Dosen & Menolascino, 1990; Gualtieri, Golden, & Fahs, 1983; Matson & Gorman-Smith, 1986; Sokol & Campbell, 1988). Regarding behavior modification, it is recommended that operant-based behavioral programs be characterized by at least three criteria. First and foremost, behavior modification programs should be functionally-based (Carr, Robinson, & Palumbo, 1990; Foxx, 1982a, 1982b). Second, behavior modification programs should be perceived by specialists and nonspecialists alike as being socially valid and acceptable (Reimers, Wacker, & Koeppl, 1987; Wolf, 1978). Third, behavior modification programs should be characterized by high treatment integrity (Gresham, 1989).

Regarding pharmacotherapy, a number of agents and medications have been employed in treating aggressive behavior (Aman & Singh, 1988; Thompson, Hackenberg, & Schall, 1989). Examples of such aggression-reducing agents include naltrexone, fenfluramine, carbamazepine, clonidine, lithium, and propranolol (Chandler, Gualtieri, & Fahs, 1988; Fankhauser, Karumanchi, German, Yates, & Karumanchi, 1992; Panksepp, & Lensing, 1991; Sokol & Campbell, 1988; Sovner & Hurley, 1986; Stewart, Myers, Burket, & Lyles, 1990). Other medications that are frequently prescribed for aggression-reducing purposes include the neuroleptics and the benzodiazepines (Anderson *et al.*, 1984; Stewart *et al.*, 1990; Tu, 1979). Although a detailed discussion of these pharmacotherapeutic agents is beyond the scope of the present paper, the interested reader is referred to Aman and Singh (1988) and Breuning and Poling (1982) for excellent reviews.

In light of the potpourri of medications that have been utilized as aggression-reducing agents, it is surprising that so few studies have systematically examined the tricyclic antidepressants. Specifically, with the exception of a few recently published studies on clomipramine (Garber, McGonigle, Slomka, & Monteverde, 1992; Gordon, Rapoport, Hamburger, & Mannheim, 1991; Gordon, Rapoport, Hamburger, State, & Mannheim, 1992; McDougle *et al.*, 1992), the tricyclic antidepressants have received relatively little research attention as potential aggression-reducing agents (Gualtieri & Hawk, 1982).

One tricyclic antidepressant that may hold particular promise as an aggres-

sion-reducing agent is imipramine or tofranil (Chandler *et al.*, 1988; Field, Aman, White, & Vaithianathan, 1986). Pharmacologically, imipramine exerts its primary therapeutic effect by blocking norepinephrine reuptake (Julien, 1988). As a potential aggression-reducing agent, imipramine has several desirable properties. Specifically, imipramine does not impair information processing and it is one of the least sedating of the tricyclic antidepressants (Julien, 1988). In fact, several researchers (Chandler *et al.*, 1988; Field *et al.*, 1986) recommend imipramine as *the* agent of choice for tempering aggressive behavior in the developmentally disabled.

In light of previous research suggesting that imipramine is an effective aggression-reducing agent (Chandler *et al.*, 1988; Field *et al.*, 1986), especially when depressive features are evident (Dosen & Menolascino, 1990), the present study conducted an open trial of combined imipramine and behavior modification in an attempt to reduce the aggressive behavior of a severely retarded, depressed autistic man. It was hypothesized that relative to pretreatment or baseline levels of aggression, the frequencies of posttreatment self-directed and other-directed aggressive episodes would be significantly reduced.

METHOD

Subject

The subject (S) was a 25-year-old man diagnosed as having Autistic Disorder (DSM-III-R) and residing in an intermediate care facility (ICF). Intelligence testing with the Stanford-Binet (Form LM) yielded a full-scale IQ of 32. The Vineland Adaptive Behavior Scales yielded age equivalents ranging from 1-year, 8-months (Socialization) to 3-years, 7-months (Daily Living Skills). Since and prior to his placement, S exhibited numerous self-directed and other-directed aggressive behaviors both at the ICF and at his day-treatment program.

Previous attempt to reduce S's aggression

Allison, Basile and MacDonald (1991) attempted to reduce S's aggression via a combination of behavior modification, antecedent exercise, and lorazepam (a short-acting benzodiazepine). Their results indicated that exercise alone (i.e., jogging) significantly reduced other-directed physical aggression at the ICF. Lorazepam alone, however, was ineffective at reducing other-directed aggression. The combination of antecedent exercise plus lorazepam exerted an intermediate aggression-reducing effect. In other words, exercise plus lorazepam was more effective than lorazepam alone but less effective than exercise alone. Furthermore, regardless of treatment condition (i.e., exercise, lorazepam, or exercise

plus lorazepam), the number of other-directed aggressive episodes at S's day treatment center remained unchanged. Unfortunately, despite its apparent efficacy, the exercise program had to be terminated due to high staff turnover and other logistic problems.

Present attempt to reduce S's aggression

In the present study, an attempt was made to reduce S's aggression via combined functionally-based behavior modification and imipramine. Regarding the behavior modification program, which was already in place prior to beginning imipramine treatment,[1] the primary technique or strategy employed consisted of DRA-O or the differential reinforcement of alternative and other appropriate behaviors. Previous research suggests that relative to other behavior decelerative procedures, DRA-O is one of the least aversive and most widely accepted behavioral treatment modalities (Allison & Silverstein, 1991). Furthermore, DRA-O has been shown in previous research to be an effective and socially valid strategy for increasing appropriate behaviors (Bird, Hepburn, Rhodes, & Moniz, 1991; Saloviita, 1988; Tarnowski, Rasnake, Mulick, & Kelly, 1989; Vollmer, Iwata, Smith, & Rodgers, 1992).

In the present study, S was reinforced during waking hours at the ICF on an FI-30 schedule (i.e., every 30 min) provided he was engaged in structured activity, had not aggressed toward others, and had not engaged in property destruction. In addition, staff were instructed to ignore (i.e., extinguish) all verbal and nonverbal signs of agitation and to simply redirect S to task. Informal observations of direct care staff interactions with S, and daily examination of staff data recording sheets, suggested that S's behavioral program was monitored and administered with fairly good treatment integrity.

In deciding to initiate an imipramine trial in conjunction with the behavior modification program, two factors were given strong consideration. The first of these two factors concerned S's affect and behavior. Specifically, S frequently displayed sad affect and he often cried and engaged in vigorous hand-wringing just prior to becoming aggressive. Based on these behaviors and his apparent

[1] Due to the applied nature of the treatment setting and the necessity for continuous behavioral programing, it was not possible (nor ethical) to postpone initiation of the behavior modification program until S received medical clearance to begin the imipramine trial. Consequently, the DRA-O based behavioral program was initiated several months prior to the imipramine protocol. This design feature may be conceptualized as a strength of the present study in that S was allotted ample time to habituate to the novelty of the behavioral program before beginning imipramine treatment. To the extent that S habituated to the novelty of the behavioral program, thus relegating the program to a constant yet relatively unattended to aspect of the treatment environment, any pre- to post-imipramine behavioral changes can be more confidently attributed to the imipramine protocol. In other words, because of the allocated habituation period, the effects of imipramine treatment should be relatively unconfounded by the behavior modification program.

sad affect, it was hypothesized by the clinical staff that S was experiencing an agitated depression. According to Sovner and Hurley (1986), the experience of prolonged agitated depression may trigger episodic bouts of aggression in the developmentally disabled.

In addition to S's affect and behavior, a second factor guiding the present imipramine trial was the fact that S met three of the four selection criteria for tricyclic antidepressant (TCA) therapy as outlined by Chandler *et al.* (1988). Specifically, S evidenced symptoms of anxiety (e.g., pressured speech, wringing of hands, hypervigilance), his behavioral difficulties followed an episodic course, and he was caffeine sensitive. The fourth TCA selection criteria, that of having a family history of panic disorder, was not satisfied.

Dependent variables

Three behavioral outcomes served as dependent variables in the present study. The first of these three outcomes consisted of frequency of tantrumous outbursts at the ICF. For the purpose of the present study, tantrumous outbursts were defined as nonself-injurious aggressive episodes directed toward other persons and/or property. The second dependent variable consisted of frequency of self-injurious behaviors (SIBs) at the ICF. As operationalized in the present study, SIBs occurred each time S engaged in any of the following self-directed aggressive behaviors: biting, scratching, pinching, hitting, slapping, kicking, or hair pulling. The third dependent variable was labeled frequency of aggressive behaviors at S's day treatment program. These behavioral outcomes consisted of episodes of other-directed physical aggression toward persons and property, in addition to episodes of object throwing and table-flipping (i.e., literally turning tables, desks and chairs upside down).

Experimental procedures

Preintervention (baseline) data

Baseline frequency data were collected for 35 days on tantrumous outbursts at the ICF, for 14 days on self-injurious behaviors at the ICF, and for 35 days on aggressive behaviors at the day treatment center.

Imipramine administration

S began receiving 25-milligrams (mg) of imipramine daily on 7/5/90. The daily dosage was titrated upward as follows: (1) increased to 50 mg daily on

7/8/90, (2) increased to 75 mgs daily on 7/11/90, (3) increased to 100 mg daily on 7/26/90, and (4) increased to 150 mg daily on 10/6/90.

Postintervention data

Postintervention data were collected from 7/5/90 to 11/30/90 (approximately a 5-month period).

Design and data analyses

The present study utilized a quasi-experimental, simple-interrupted time-series design (Cook & Campbell, 1979). The primary data analytic technique consisted of modified trend analysis through multiple regression (Gorsuch, 1983; Simonton, 1977). Such a generalized least squares procedure is appropriate with time-series data when autocorrelated residuals are evident, as was the case in the present study.[2] In addition to modified trend analyses, dependent samples *t*-tests were conducted to compare the baseline and treatment means of each dependent variable.

RESULTS

Pre- and postintervention means and standard deviations for the three dependent variables are presented in Table 1. As the values in Table 1 indicate, the means for all three behavioral indices were greater at pre- vs. postintervention, suggesting that S was more physically aggressive prior to initiating the imipra-

TABLE 1. Descriptive data for the dependent variables.

	Preintervention			Postintervention		
Variables	*M*	*SD*	*n*	*M*	*SD*	*n*
1. Tantrumous outbursts	1.2	.88	34	.30	.69	149
2. Self-injurious behaviors	3.4	3.9	12	.64	1.8	149
3. Day treatment aggression	9.4	11.4	23	.96	4.1	93

n = Number of data points in series.

[2] In order to ascertain whether or not the residuals were autocorrelated, a two-step procedure was followed. First, using autoregressive integrated moving average (ARIMA) modeling, a best-fitting model was calculated for each time-series. Second, the residual terms resulting from each best-fitting model (which for all three dependent variables was a first-order autoregressive (AR-1) model) were then autocorrelated. In all three cases (i.e., frequency of tantrums, self-injurious behaviors, and day treatment aggression), significant lag-1 coefficients were obtained thus indicating the presence of autocorrelated residuals.

mine treatment. In addition, visual inspection of the standard deviations in Table 1 reveals greater variability at preintervention for two of the three dependent variables (i.e., frequency of self-injurious behaviors at the ICF and frequency of aggressive behaviors at day treatment). Specifically, for frequency of self-injurious behaviors, the standard deviations at pre- and postintervention were 3.9 and 1.8 respectively ($F(11,148) = 4.86$, $p < .0001$). For frequency of day treatment aggressive behaviors, the pre- and postintervention standard deviations were 11.4 and 4.1 respectively ($F(22,92) = 7.70$, $p < .0001$). These data suggest that imipramine had a stabilizing effect on frequency of self-injurious behaviors at the ICF and frequency of day treatment aggression.

Dependent samples *t*-tests comparing the pre- and postintervention means for each dependent variable are presented in Table 2. Consistent with the pattern

TABLE 2. Dependent samples *t*-tests comparing pre- and postintervention means.

Variables	*t*	*d.f.*	*p*
1. Tantrumous outbursts	6.56	181	<.0001
2. Self-injurious behaviors	2.48[1]	11.4	.0299
3. Day treatment aggression	3.50[1]	23.4	.0019

The means for all three dependent variables were significantly greater at preintervention.
[1]Corrected for unequal variances.

of means reported in Table 1, the *t*-tests in Table 2 indicate significantly greater preintervention means for all three dependent variables (all p's $< .03$). These data suggest that combined imipramine and behavior modification significantly reduced the frequencies of tantrumous outbursts, self-injurious behaviors, and day treatment aggressive behaviors. However, despite the information they provide, pre- to postintervention mean differences are of limited utility for at least two reasons.

The first reason concerns the fact that mean differences, in and of themselves, are incapable of providing information regarding fluctuations or trends in time-series data. The second reason concerns the fact that mean differences are uninformative regarding the extent to which behavior change is the result of active treatment vs. the mere passage of time. In response to these two limitations regarding mean differences, and considering the residual autocorrelation obtained for all three dependent variables, modified trend analyses through multiple regression (Gorsuch, 1983; Simonton, 1977) were conducted on each dependent variable.

The first dependent variable examined through modified trend analysis was frequency of tantrumous outbursts at the ICF. The hierarchical multiple regres-

TABLE 3. Hierarchical multiple regression results for frequency of tantrumous outbursts.

Steps	*R*	R^2	$AdjR^2$	*F*	*p*	*d*
1. Time	.38	.15	.14	31.0	<.0001	.83
2. Treatment	.45	.21	.20	23.4	<.0001	.19
3. Time by Treatment	.50	.25	.23	19.5	<.0001	.12

d = Cohen's effect size estimate as calculated per Friedman (1982).

sion results for tantrumous outbursts are presented in Table 3. As was the case for all three dependent variables, the first predictor entered into the regression model was time (coded sequentially from 1 through x, where x represents the last posttreatment data point collected). As indicated via the values in Table 3, time was a statistically significant predictor, accounting for 15% of the variance in frequency of tantrumous outbursts ($F(1,181) = 31.0, p < .0001$, effect size estimate $d = .83$[3]).

The second predictor entered into the regression model (for all three dependent variables) was treatment, dummy coded "1" for preintervention and "2" for postintervention. Treatment accounted for an additional 6% unique variance in frequency of tantrumous outbursts ($F(2,180) = 23.4, p < .0001, d = .19$) above and beyond the effects of time alone. The third predictor variable entered into each regression model consisted of a time by treatment interaction term. For frequency of tantrumous outbursts, the interaction term accounted for an additional 4% unique variance ($F(3,179) = 19.5, p < .0001, d = .12$) above and beyond the effects of time and treatment, suggesting that the slope or rate of change of tantrumous outbursts declined over time. In combination, the three predictor variables entered into the regression equation (i.e., time, treatment, and time by treatment) accounted for 25% of the variance in S's tantrumous outbursts at the ICF. As a complement to the multiple regression results, the time-series for tantrumous outbursts is depicted graphically in Figure 1.

The second dependent variable examined through modified trend analysis was frequency of self-injurious behaviors at the ICF. The hierarchical multiple

[3] The effect size estimate d, originally developed by Cohen (1988) for use in group research, represents the relative magnitude of effect of a treatment (vs. control) condition on a specified dependent variable. In the present single-case analysis, the effect size estimates were calculated by converting the *F*-statistics for each trend component to corresponding *d*-statistics using the following formulae outlined by Friedman (1982), where *dfn* equals degrees of freedom for the numerator and *dfd* degrees of freedom for the denominator: (1) For $dfn = 1, d = 2[(F/dfd)^{.5}]$; and (2) For $dfn > 1, d = 2[(dfn(F)/(dfd))^{.5}]$.

In interpreting these effect size estimates, the reader should be aware of an important caveat. Specifically, because of the presence of residual autocorrelation, the effect size estimates for time alone may evidence significant positive bias. However, in contrast, the *d*-statistics for both treatment and time by treatment, controlling for the effects of time, should represent relatively unbiased estimators (see Gorsuch, 1983, for a discussion of autocorrelation and effect size estimates within the context of modified trend analysis).

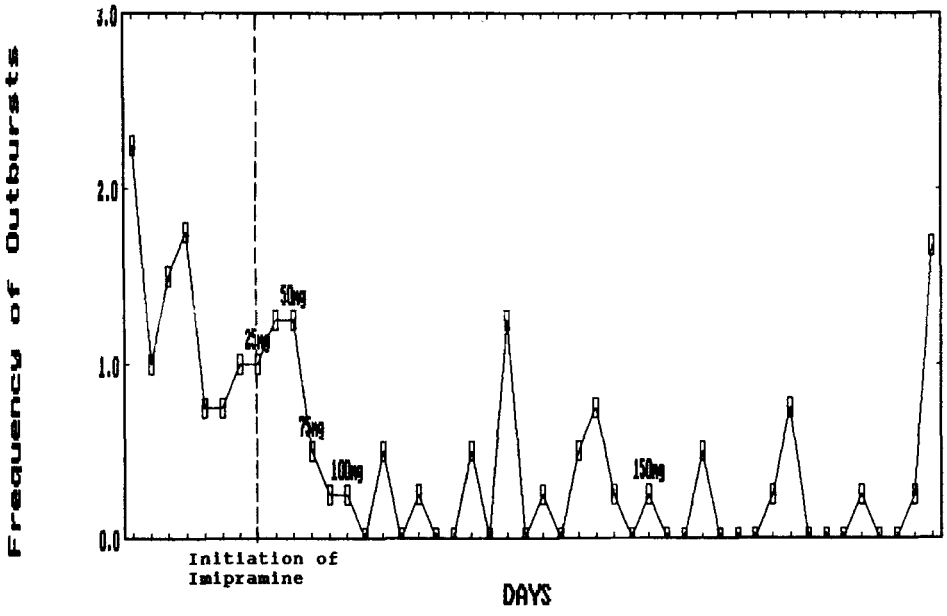

Figure 1. Frequency of tantrumous outbursts.

TABLE 4. Hierarchical multiple regression results for frequency of self-injurious behaviors

Steps	*R*	R^2	$AdjR^2$	*F*	*p*	*d*
1. Time	.18	.03	.03	5.6	.0194	.37
2. Treatment	.35	.12	.11	11.1	<.0001	.38
3. Time by Treatment	.37	.14	.12	8.2	<.0001	.04

d = Cohen's effect size estimate as calculated per Friedman (1982).

regression results are presented in Table 4. The first predictor variable entered into the regression model, time, accounted for 3% of the variance in frequency of self-injurious behaviors ($F(1,159) = 5.6$, $p < .02$, $d = .37$). The second predictor variable entered, treatment, accounted for an additional 9% unique variance in frequency of self-injurious behaviors ($F(2,158) = 11.1$, $p < .0001$, $d = .38$). The third predictor variable, the time by treatment interaction term, explained an additional 2% unique variance in frequency of self-injurious behaviors ($F(3,157) = 8.2$, $p < .0001$, $d = .04$). In combination, the three predictor variables accounted for 14% of the variance in S's frequency of self-injurious behaviors at the ICF. In addition to the multiple regression results presented

in Table 4, the time-series for self-injurious behaviors is depicted graphically in Figure 2.

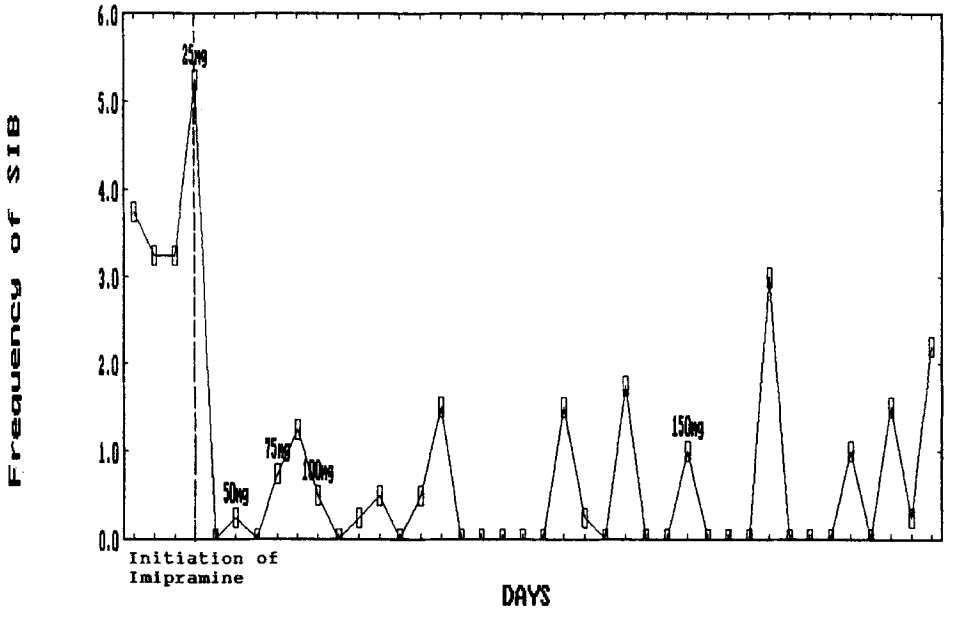

Figure 2. Frequency of self-injurious behaviors.

The third and final modified trend analysis examined S's frequency of day treatment aggressive behavior as the dependent variable of interest. The hierarchical multiple regression results are presented in Table 5. As the values in

TABLE 5. Hierarchical multiple regression results for frequency of day treatment aggression

Steps	*R*	R^2	$AdjR^2$	*F*	*p*	*d*
1. Time	.41	.17	.16	22.9	<.0001	.90
2. Treatment	.49	.24	.23	17.8	<.0001	.22
3. Time by Treatment	.60	.35	.34	20.5	<.0001	.36

d = Cohen's effect size estimate as calculated per Friedman (1982).

Table 5 indicate, the first predictor variable, time, accounted for 17% of the variance in frequency of day treatment aggressive behaviors ($F(1,114) = 22.9$, $p < .0001$, $d = .90$). The second predictor variable entered into the regression model, treatment, accounted for an additional 7% unique variance in frequency of day treatment aggression ($F(2,113) = 17.8$, $p < .0001$, $d = .22$). The third

predictor variable, the time by treatment interaction term, explained an additional 11% unique variance in frequency of day treatment aggressive behaviors ($F(3,112) = 20.5, p < .0001, d = .36$). In combination, the three predictor variables accounted for 35% of the variance in S's frequency of day treatment aggression. As a complement to the multiple regression results presented in Table 5, the time-series for day treatment aggression is depicted graphically in Figure 3. As a final comment on the modified trend analyses, none of the

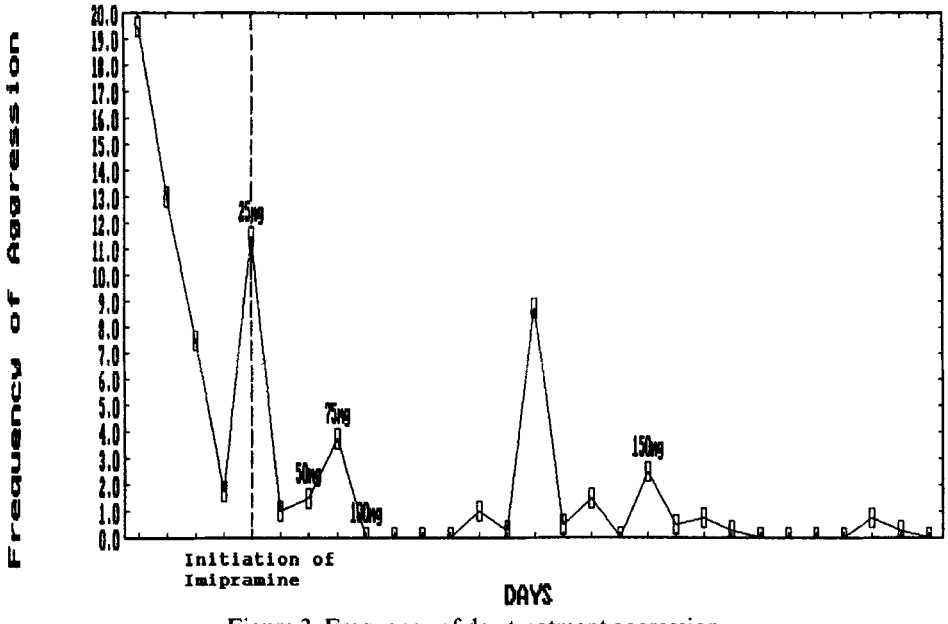

Figure 3. Frequency of day treatment aggression.

residual terms from the hierarchical multiple regressions were autocorrelated. In other words, as discussed by Gorsuch (1983) and Simonton (1977), it appeared that the linear trend due to time was the process responsible for the residual autocorrelation observed among the dependent variables of interest. Once the effects of time were partialled-out via hierarchical multiple regression, the residual autocorrelation disappeared.

DISCUSSION

It was predicted that, relative to pretreatment levels of aggression, imipramine and behavior modification would significantly reduce posttreatment levels of self-directed and other-directed aggressive behavior. Results of the present simple-interrupted time-series were encouraging. Specifically, combined imipramine and behavior modification significantly reduced S's frequencies of tantrumous outbursts and self-injurious behaviors at the ICF. In addition, imipramine and behavior modification significantly reduced S's frequency of day treatment aggressive behavior, a finding that failed to emerge during the previously conducted exercise plus lorazepam trial (Allison *et al.*, 1991). These data, which support the efficacy of imipramine as an aggression-reducing agent, are consistent with previous theory and research suggesting that dysregulation of the noradrenergic system is a probable cause of aggression in the developmentally disabled (e.g., Young, Kavanagh, Anderson, Shaywitz, & Cohen, 1982).

In addition to the decelerative effects of imipramine and behavior modification, informal observations suggested that S was less depressed and less anxious at post- vs. pretreatment. Specifically, S's affect steadily improved throughout the duration of treatment and fewer episodes of crying and hand-wringing were noted. Regarding treatment acceptability, both clinical and direct care staff perceived the combined imipramine and behavior modification protocol to be an acceptable and humane form of treatment. In addition, the targetted treatment outcomes appeared to be socially valid. Specifically, at post- vs. pretreatment, the ICF and day program staff as well as S's parents agreed that S was less disruptive, less intimidating, more approachable, and more amenable to participating in structured programing.

In order to fully appreciate the relative magnitudes of the treatment effects obtained across the three dependent variables, a few comments are in order regarding the modified trend analyses and the obtained effect size estimates. With regard to the trend analyses, significant effects were found for *time*, *treatment*, and *time by treatment* across all three outcome measures. The significant effects for time suggested that independent of treatment, S's self-directed and other-directed aggressive behaviors decreased over time. The effects for treatment suggested that above and beyond the effects of time, significant reductions were obtained in S's *level* or frequency of aggressive behavior. The effects of time by treatment indicated that above and beyond the effects of time and treatment alone, significant reductions were obtained in the *slope* or rate of change of S's aggressive behavior. These statistically significant time by treatment interaction effects indicate that, relative to pretreatment, S's aggression was less variable and more stable during posttreatment.

However, despite the statistical significance of all three trend components (i.e., time, treatment, and time by treatment), it is important to recognize that

the effect size estimates obtained were not equivalent across trend components. In fact, for two of the three dependent variables (i.e., frequency of tantrumous outbursts at the ICF and frequency of day treatment aggression), the largest behavior decelerative effects resulted from the mere passage of time, with effect size estimates *d* of .83 and .90 respectively. Although these time estimates may be somewhat artifactually inflated due to residual autocorrelation, their relative magnitudes are such that even in the absence of residual autocorrelation they would still represent the largest effects. Regarding the third dependent variable, frequency of self-injurious behaviors at the ICF, the effect size estimates for time and treatment were approximately equivalent (.37 and .38 respectively).

The effect size estimates for the second trend component (i.e., treatment) were small-moderate to moderate, with *d*-statistics ranging in magnitude from .19 (tantrumous outbursts) to .38 (self-injurious behaviors). Regarding the third trend component (i.e., time by treatment), the effect size estimates for frequency of tantrumous outbursts and frequency of self-injurious behaviors were small, with obtained *d*-values of .12 and .04 respectively. However, in contrast, the time by treatment effect size estimate for frequency of day treatment aggression was moderate in magnitude with an obtained *d*-value of .36.

In summary, the effect size estimates for the three trend components in the present study were variable, ranging from moderate to large for *time*, small-moderate to moderate for *treatment*, and small to moderate for *time by treatment*. From an interpretive standpoint, these data suggest that above and beyond the effects of time alone, combined imipramine and behavior modification led to significant reductions in the levels (i.e., frequencies) and slopes (i.e., rates of change) of a variety of self-directed and other-directed aggressive behaviors in a severely retarded, depressed autistic man.

Limitations of the present study

There were several limitations of the present study. First, in addition to receiving imipramine, S also received lorazepam (6 mg daily) throughout the duration of the combined imipramine and behavior modification trial. Although it is possible that lorazepam may have interacted with imipramine to reduce S's aggression, the probability of this occurring seems rather remote for at least two reasons. First and foremost, previous attempts at reducing S's aggression (Allison *et al.*, 1991) failed to support lorazepam as an effective behavior reductive agent. Second, S began receiving lorazepam (6 mg daily) several months prior to initiating the imipramine protocol. The fact that reductions in aggression did not occur until *after* the initiation of imipramine suggests that lorazepam exerted little if any confounding influence.

A second limitation of the present study concerns the fact that reliabilities of the dependent variables were not assessed. A third limitation concerns the applied nature of the treatment setting. Specifically, because of the need to apprise all clinical personnel of medication changes and potential medication side-effects, it was not possible to keep staff "blind" to the treatment protocol. Consequently, expectancy effects may have operated in the present study to influence data collection. A fourth limitation of the present study concerns the fact that a simple interrupted time-series design was employed. Specifically, because such a design is purely quasi-experimental (Cook & Campbell, 1979), plausible rival alternative hypotheses such as maturation cannot be entirely discounted.

Recommendations for future research

In light of the present data and considering the limitations noted above, there appear to be at least two distinct yet equally profitable directions for future research. The first recommendation is that future research employ stronger quasi-experimental designs, such as reversal designs or multiple baseline designs, in an effort to minimize the potential for plausible rival alternative hypotheses. For example, several multiple baseline designs across subjects, each consisting of three staggered simple interrupted time-series (e.g., baseline-behavior modification; baseline-imipramine; baseline-combined behavior modification and imipramine), would allow for significantly greater explication of the incremental effectiveness of imipramine over and above the effects of behavior modification alone.

The second recommendation for future research is that studies evaluate the relative effectiveness of imipramine and other aggression-reducing agents in the context of double-blind, placebo-controlled crossover designs with random patient assignment and assessment of dose-response relationships. Of particular interest would be crossover designs comparing imipramine, which exerts primarily noradrenergic effects, against other pharmacotherapeutic agents such as fenfluramine and clomipramine whose mechanisms of action are primarily serotonergic.

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