Effects of Fluoxetine on Aggressive Behavior of Adult Inpatients with Mental Retardation and Epilepsy

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Nineteen mentally retarded inpatients with epilepsy and a history of current or recent aggressive behavior were treated with 20 mg of fluoxetine daily. All were concurrently taking other psychotropic medications, including carbamazepine and neuroleptics. A standardized rating scale (MOAS) was used to assess the effects of fluoxetine on aggressive behavior. There were wide individual differences in drug response. In nine patients, fluoxetine treatment was associated with increased aggression, while drug withdrawal led to a decrease to below pretreatment levels. Two hypotheses concerning the apparent association between fluoxetine and increased aggression are discussed: 1) adverse effects secondary to either drug interaction or fluoxetine overmedication; and 2) a specific serotonergically mediated effect on the regulation of aggression. This study suggests that the clinician who treats mentally retarded patients with impulsive aggressive behavior should remain aware that fluoxetine may have diverse effects on aggression that vary over time and interindividually.

Self-injurious behavior and interpersonal aggression are common in patients with severe mental retardation. These behavioral problems are often unresponsive to pharmacotherapy. However, recent studies have shown that serotonin uptake-inhibiting drugs ameliorate impulsive aggressive behavior in patients with severe personality disorder (*Coccaro* et al., 1990) in elderly patients with organic brain syndromes (*Pinner* and *Rich*, 1988), and in mentally retarded patients (*Markowitz*, 1992).

With these encouraging findings in mind, we made the decision to treat 19 mentally retarded adult inpatients with fluoxetine. These patients displayed frequent bouts of aggressive behavior that were unresponsive to pharmacotherapy. Unlike previous studies, the effects of fluoxetine on aggressive behavior were measured by means of a standardized rating scale and the sample was large enough to allow statistical analysis of data.

Method

The subjects were 19 adult patients with mental retardation and epilepsy who had been institutionalized for a long period in two mental retardation clinics. Patients, 14 of whom were male, ranged from 20 to 47 years. Due to the patients' legal situation, informed consent was obtained from family members or legally appointed guardians. The study employed an alternating control-treatment-control design. The pretreatment and posttreatment phases lasted between eight and 26 weeks (median = 20 weeks) and between six and 14 weeks (median = eight weeks) respectively. Ten patients were treated with fluoxetine for eight weeks. In the remaining patients the length of treatment varied between four and 14 weeks (median = eight weeks). During treatment, the patients were treated with 20 mg of fluoxetine daily in the morning. All the patients were taking other psychotropic medication. The type and the doses of this medication were maintained at a constant level during the study period (Table **1**).

Frequency of seizures was recorded daily, and plasma levels of antiepileptic drugs were measured weekly. Fluoxetine treatment did not modify either the frequency of seizures or the plasma levels of antiepileptic drugs. Aggressive behavior was measured by using the Modified Overt Aggression Scale (MOAS) (*Kay* et al., 1988 a). The MOAS is an inpatient rating scale that assesses verbal aggression, aggression against objects, self-aggression, and aggression against others. Based on the assumption that the index of frequency may be a poor approximation of the severity of aggressive acts (*Kay* et al., 1988 a, p. 540), the MOAS was not designed to provide actual counts of episodes of aggression. Instead, for each category of aggressive behavior, the rater checks the highest applicable rating point to describe the most serious act of aggression committed by the patient during the specified observation period. The MOAS provides a weighted score for each type of aggression and a weighted total score that reflects the overall seriousness of aggression. Cross-sectional and longitudinal observations of psychiatric inpatients have documented the discriminative validity of the MOAS and its internal, inter-rater, and retest reliability (*Kay* et al., 1988 b).

In the present study, the ratings were made by a clinical psychiatrist in cooperation with members of primary care staff who were blind to the medication change and research objectives. Using daily records of patients' behavior, the raters as-

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Patient	Sex	Age (years)	Diagnosis	Medication (daily dose)
1	M	31	Severe mental retardation Partial seizures	Carbamazepine 600 mg Phenobarbital 100 mg Thioridazine 300 mg Lorazepam 2.5 mg
2	M	29	Severe mental retardation Grand mal	Carbamazepine 1400 mg Phenobarbital 200 mg Phenytoin 100 mg Phenobarbital 200 mg
3	M	47	Severe mental retardation Grand mal	Phenobarbital 150 mg
4	M	33	Severe mental retardation Absence and clonic seizures	Tiapride 600 mg Phenobarbital 150 mg
5	M	31	Severe mental retardation Grand mal	Carbamazepine 1000 mg Phenobarbital 150 mg Lorazepam 2.5 mg
6	M	32	Severe mental retardation Grand mal	Clotiapine 40 mg Orphenadrine 50 mg Carbamazepine 1000 mg Phenytoin 150 mg Phenobarbital 300 mg Clonazepam 0.5 mg Nitrazepam 5 mg
7	M	28	Severe mental retardation Absence seizures	Phenytoin 100 mg Phenobarbital 100 mg Phenobarbital 100 mg Clotiapine 20 mg
8	M	28	Severe mental retardation Grand mal and absence seizures	Phenobarbital 125 mg Valproic acid 1500 mg Lorazepam 1.25 mg
9	M	31	Severe mental retardation Simple partial seizures	Clonazepam 1 mg Desmethyldiazepam 4 mg
10	F	22	Moderate mental retardation Grand mal	Carbamazepine 600 mg Valproic acid 1200 mg Phenobarbital 75 mg
11	F	41	Unspecified mental retardation Grand mal and atonic seizures	Carbamazepine 1200 mg Phenobarbital 100 mg Valpromide 1500 mg Phenobarbital 100 mg
12	F	32	Unspecified mental retardation Grand mal	Phenytoin 150 mg Phenobarbital 300 mg Carbamazepine 1200 mg Clonazepam 1.5 mg
13	M	21	Severe mental retardation Grand mal	Carbamazepine 1500 mg Phenobarbital 200 mg
14	F	22	Unspecified mental retardation Grand mal and absence seizures	Valproic acid 1000 mg Carbamazepine 600 mg Clonazepam 1.5 mg
15	M	20	Moderate mental retardation Absence seizures	Valproic acid 1250 mg Phenobarbital 200 mg
16	F	24	Severe mental retardation Grand mal	Carbamazepine 1200 mg Phenobarbital 150 mg Clonazepam 3 mg Thioridazine 30 mg
17	M	20	Severe mental retardation Grand mal and absence seizures	Carbamazepine 1200 mg Valproic acid 1900 mg Phenobarbital 50 mg
18	M	26	Severe mental retardation Grand mal	Carbamazepine 1200 mg Barbexaclone 200 mg Desmethyldiazepam 2 mg
19	M	29	Unspecified mental retardation Grand mal	Phenytoin 300 mg Barbexaclone 300 mg Clonazepam 4 mg

Tab. 1 Diagnoses and concurrent medication of 19 mentally retarded patients with a history of aggressive behavior who received fluoxetine 20 mg/day.

Tab. 2 Mean monthly scores on the Modified Overt Aggression Scale (MOAS) of 19 mentally retarded patients with a history of aggressive behavior who received fluoxetine 20 mg / day.

Patient	Weeks of Treatment	Pre-treatment	Treatment	Post-treatment
1	12	20.83	33.20	16.50
2	14	0.00	0.00	0.00
3	10	2.00	3.20	3.20
4	14	2.80	5.43	0.00
5	12	6.91	25.20	6.40
6	10	6.18	3.20	9.60
7	8	10.00	10.67	4.00
8	14	2.00	0.00	0.80
9	14	43.60	44.86	0.80
10	8	0.00	0.00	0.00
11	8	12.33	14.00	14.00
12	8	9.00	12.00	11.00
13	8	28.00	38.50	10.33
14	8	0.00	0.00	0.00
15	8	0.00	0.00	0.00
16	8	2.00	2.00	2.00
17	4	0.00	0.00	0.00
18	8	1.33	3.00	1.67
19	8	0.00	12.00	0.00

sessed the severity of aggression during the preceding week (clinic A, patients 1–9, rater: E.V.) or the preceding month (clinic B, patients 10–19, rater: F.N.). For all patients, the data used for statistical analysis were the mean monthly scores.

Results

As a group, the patients showed marked changes in aggressive behavior over the three phases of the trial (Table **2** and Figure **1**). Fluoxetine treatment was associated with significant changes in the MOAS ratings of total aggression (Friedman test, chi-square = 7.88, df = 2, $p < 0.02$), verbal aggression (Friedman test, chi-square = 7.00, df = 2, $p = 0.03$), and selfaggression (Friedman test, chi-square = 7.24, df = 2, $p < 0.03$). The ratings for all the categories of aggression increased during drug treatment and decreased after drug withdrawal. In the postdrug period, the ratings for assault directed against others decreased below baseline levels and those of selfaggression dropped to zero for all the patients. In view of the fact that six patients, in spite of their recent history of aggressive behavior, had zero scores at baseline, we repeated the statistical analysis by limiting the sample to those patients (N = 13) who displayed bouts of aggression during the pretreatment phase. The changes in the MOAS ratings of total aggression remained significant (Friedman test, chi-square = 6.43, df = 2, $p < 0.04$).

Data analysis based on total group means concealed wide interindividual differences. We observed three different patterns of response to fluoxetine. Nine patients (Group 1, patients 1, 3–5, 11–13, 18, 19) showed an increase in aggression (Friedman test, chi-square = 11.70, df = 2, $p < 0.003$), eight patients (Group 2, patients 2, 7, 9, 10, 14–17) showed no appreciable change (Friedman test, chi-square = 4.00, df = 2, n.s.), and two patients (Group 3, patients 6 and 8) showed a diminution of aggressive behavior (no statistics due to the exiguity of the sample). After drug withdrawal, the MOAS ratings of the patients in Groups 1 and 2 decreased sharply and dropped to

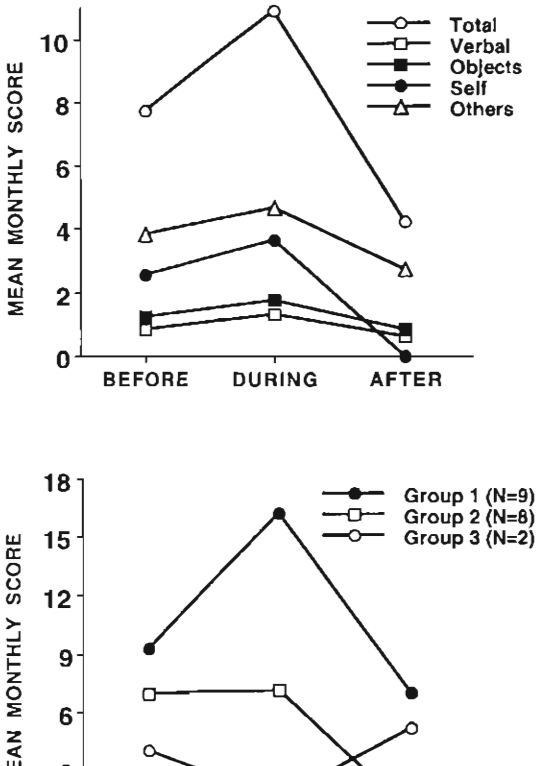

Fig. 1 Patients' Modified Overt Aggression Scale (MOAS) ratings before, during, and after fluoxetine treatment. Top: total group means for different categories of aggression. Bottom: patterns of drug response in subgroups of patients.

below the pretreatment levels. In contrast, aggressive behavior on the part of the two patients in Group 3 increased again to above the pretreatment levels.

We were not able to identify any demographic and / or clinical variable that might explain this individual variation in response to fluoxetine. Even though the mean MOAS total score at baseline was higher in Group 1 (worse with fluoxetine) than in Group 2 (unchanged) and 3 (better with fluoxetine), such a difference was not statistically significant (Kruskal-Wallis test, H = 2.81, df = 2, n.s.) (Figure **1**).

Since the treatment phase ranged from four to 14 weeks, it was possible for the effect of fluoxetine to vary with the length of treatment. To exclude such a possibility, we performed three different types of statistical analysis. First, we limited our analysis to the subsample of patients with the same length of treatment (8 weeks, N = 10). The changes in the MOAS ratings of total aggression remained significant (Friedman test, chi-square = 8.45, df = 2, $p < 0.02$). Second, we calculated the correlation between length of treatment and percent-change scores (i.e., percent change from baseline MOAS total score). The two variables were not correlated (Spearman rho = 0.05, N = 19, n.s.). Third, categorical comparison of the patients in Group 1 (worse with fluoxetine, N = 9) and those in Groups 2 and 3 (unchanged or better with fluoxetine, N = 10) showed that the

length of treatment did not differ in the two groups (Mann-Whitney test, U=43.5, n.s.).

Discussion

Nine of the 19 (47%) patients in this study showed an increase in aggressive behavior during fluoxetine treatment. Several considerations suggest that such an increase was not coincidentally related to fluoxetine. First, the duration of the pretreatment period was long enough to ensure a reliable estimate of each patient's baseline level of aggression. Second, the stability of the environment in which the patients lived allows us to exclude the occurrence of significant psychosocial stress factors that might elicit aggressive reactions unrelated to medication. Third, in this subgroup of patients, the ratings of aggressive behavior decreased consistently after drug withdrawal. For these reasons, it is likely that both the intensification of aggressive behavior during the treatment period and its decrease below baseline levels in the postdrug period were induced by fluoxetine.

These results should be interpreted in the context of two potential methodological limitations. First, this study did not have a double-blind, placebo-controlled design. However, it is unlikely that open treatment biased the assessment of patients' aggressive behavior. The MOAS puts a strong emphasis on overt aggressive behavior and leaves little room for the rater's subjective interpretations. In addition, the ratings of patients' aggressive behavior were conducted in cooperation with members of primary care staff who were blind to the medication change and research objectives. Finally, to the extent that bias did occur, we would expect this bias to result in an underestimation rather than an overestimation of patients' aggressive behavior, since the study hypothesis was that fluoxetine might exert antiaggressive effects.

Second, the interpretation of our results is complicated by the fact that patients were taking a variety of other drugs, including carbamazepine and neuroleptics. In combination with fluoxetine, carbamazepine may produce a 5-HT toxicity syndrome (*Power* and *Cowen*, 1992), while neuroleptics may amplify the ability of fluoxetine to cause extrapyramidal symptoms (*Chouinard*, 1991). As a consequence of fluoxetine overmedication, some patients may have experienced adverse psychological symptoms (e.g., anxiety and / or dysphoria) that, because of compromised verbal expression, manifested themselves *via* behavioral exacerbation. However, the fact that, during the study period, none of the patients developed akathisia, restlessness, agitation, or other behavioral signs typical of the serotonin syndrome (*Sternbach*, 1991) contradicts the hypothesis that the increase in aggressive behavior was secondary to a toxic hyperserotonergic state. Nevertheless, it cannot be ruled out that drug interaction may have had a negative effect on behavior control.

An alternative possibility is that fluoxetine induced the behavioral changes *via* a specific effect on the serotonergically mediated regulation of aggression. There is a large body of evidence from both animal and human studies to suggest that a reduced central serotonergic function leads to aggressive and destructive behavior (*Eichelman*, 1992). As a potent 5-HT reuptake blocker, fluoxetine should lead to an enhanced 5-HT neurotransmission. However, data from receptor binding, neurophysiological, and behavioral studies disagree as to whether the ultimate effects of uptake inhibition are an increase or decrease in serotonergic transmission (*Winslow* and *Insel*, 1990; *Lesch* et al., 1991).

Clearly, the clinical data presented here are not suitable for testing biochemical pathogenetic hypotheses. However, our results are relevant to the current debate about the emergence of aggression during fluoxetine treatment (*Mann* and *Kapur*, 1991; *Power* and *Cowen*, 1992). We believe that the clinician treating mentally retarded patients with impulsive aggressive behavior should be aware that fluoxetine may have diverse effects on aggression that vary over time and interindividually. Additional clinical and neurobiological research is needed to characterize those patients who experience adverse responses to fluoxetine.

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