

Fluoxetine and Methylphenidate in Combination for Treatment of Attention Deficit Disorder and Comorbid Depressive Disorder

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ABSTRACT

Children and adolescents with attention deficit disorders (usually with comorbid conditions), who had shown inadequate therapeutic responses to methylphenidate, were treated by the addition of fluoxetine to methylphenidate. After 8 weeks in open trial, all 32 patients showed positive therapeutic responses in attention, behavior, and affect. Thirty of the 32 children showed clinically significant responses and the other two had statistically but not clinically significant responses. After 12 weeks of treatment, one patient showed a deterioration in clinical status. The children had improved report card grades in major academic subjects ($p < 0.0001$), and showed significant improvements ($p < 0.0001$) on the Children's Global Assessment Scale (C-GAS), Conners Parents Rating Scales (CPRS), and Children's Depression Inventory (CDI). Children who initially appeared more impaired on the C-GAS, CDI, CPRS, and GPA showed more improvement on the combined regimen. No significant side effects were observed, using a gradual elevation of fluoxetine dosage. About 40% of the patients showed substantial clinical effects with doses of fluoxetine below 20 mg daily. These preliminary results suggest that fluoxetine and methylphenidate in combination may be safe and effective for some children with attention-deficit hyperactivity disorder (and with comorbid anxiety or depressive symptoms) who do not show adequate responses to methylphenidate or fluoxetine alone.

INTRODUCTION

ALTHOUGH BOTH psychostimulants and tricyclic antidepressants (TCAs) have been demonstrated effective for treating attention deficit disorders (ADD) (Green 1991, 1992; Greenhill 1992a, 1992b), these medications have important limitations.

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Psychostimulants are limited because of their (1) ineffectiveness in about 30% of ADD patients (Biederman and Jellinek 1984, Barkley 1990); (2) disruptive effects on appetite and sleep (Hunt et al. 1991a); (3) short half-life, which causes "roller coaster" swings of mood and self-control throughout the day (Hunt et al. 1991a); (4) inadequate control of irritability, oppositionality, anxiety, and/or depressive symptoms, which are often comorbid with ADD (Biederman et al. 1991, Livingston et al. 1992); and (5) tendency to induce irritability and dysphoria in some patients (Barkley 1990).

Tricyclic antidepressants, particularly desipramine, have been demonstrated useful for improving mood and decreasing hyperactivity in ADD (Biederman et al. 1989a), and they lack limitations 2, 3, and 4. However, most studies have found TCAs less effective than stimulants (for review, see Campbell et al. 1985). Limitations of TCAs include (1) failure to significantly improve concentration (Wender 1988) or performance on cognitive tasks (Donnelly et al. 1986); (2) induction of excessive sedation in some patients; (3) serious and potentially lethal cardiovascular side effects, e.g., slowed cardiac conduction, arrhythmias, and heart block, to which prepubertal children may be especially vulnerable (Baldessarini 1990); and (4) extreme toxicity in overdose. Reports of sudden death of several children aged 8–9 years who were taking desipramine at apparently therapeutic levels (Medical Letter 1990, Popper and Elliott 1990, Riddle et al. 1991) have caused many clinicians to be especially wary of using TCAs with prepubertal children. In addition, parents informed of the risks often withhold consent for use of TCAs with their children and adolescents.

Other medications have been tried alone when stimulants or TCAs are ineffective or not well-tolerated (Green 1992). With the exception of clonidine (Hunt et al. 1991a), little empirical data are available to demonstrate their efficacy.

Various medications have been tried in combination with methylphenidate (MPH) or TCAs to complement or enhance these mainstay agents, but each combination studied thus far has significant limitations. TCAs have been combined with MPH (Garfinkel et al. 1983), but this option has all the limitations of TCAs mentioned above and may elevate the serum levels of both medications. Hunt and associates (1991a) reported on combined use of MPH and clonidine, but noted that the effectiveness of this combination seems restricted to "hyperaroused" patients with attention-deficit hyperactivity disorder (ADHD).

In an effort to find another safe and effective alternative for ADD patients whose symptoms respond inadequately to stimulant medications, we have tested the combination of fluoxetine (Prozac) with methylphenidate. We selected fluoxetine (FLU) because our clinical experience had shown that this antidepressant may be effective for a variety of affective and behavioral symptoms of ADD, and carries less liability for serious side effects than do TCAs.

While FLU alone appeared useful in our experience for alleviating behavioral and affective symptoms of ADD, it failed to facilitate sustained attention as effectively as the stimulants. This observation is consistent with the findings of Barrickman et al. (1991) that FLU produced global improvement of behavioral and affective symptoms in 19 ADHD children, whereas significant changes in measures of focused attention were not observed.

Thus, it was hypothesized that a combined drug treatment involving methylphenidate (for attentional symptoms) and fluoxetine (for behavioral and affective symptoms) might be more effective than either drug alone.

FLU is being used increasingly in children and adolescents for treatment of depression and anxiety symptoms (Boulos et al. 1992, Riddle et al. 1990, 1992). Accumulating experience has shown that higher doses of FLU can cause uncomfortable side effects, such as restlessness, hyperkinetic behavior, and insomnia (King et al. 1991, Riddle et al. 1990, 1991). However, FLU appears safe for children and adolescents, at least in short-term administration (Boulos et al. 1992, Riddle et al. 1990, 1991, 1992) and lacks the dangerous toxicity of TCAs in overdose (Riddle et al. 1989a).

Thus, the combination of MPH and FLU was expected to be safe and, because the therapeutic profiles of the two agents appear to complement each other, potentially effective.

Greenhill (1992a, 1992b) has recently cautioned, without empirical support, against combining methylphenidate with other medications, particularly antidepressants such as fluoxetine, because methylphenidate can elevate the concentration of antidepressants in the blood stream and may therefore increase the likelihood of adverse side effects. Although these interactions can occur, such problems can be avoided by slow titration, careful monitoring, and appropriate dose adjustment.

METHOD

Subjects

The children and adolescents studied were all outpatients in the private practices of the authors. Thirty-two consecutive patients, aged 9–17 years, clinically judged to have had an inadequate response to stimulant therapy were studied. All patients satisfied DSM-III-R criteria for ADHD. These and other Axis I diagnoses were confirmed by DISC-R patient interview (Shaffer et al., in press).

Approximately 30% were elementary school students, and the remainder were students in junior or senior high school. No patients with significant medical problems, mental retardation, psychosis, or substance abuse problems were included in this study. Table 1 shows the age distribution of patients, the expected preponderance of males, the relatively high socioeconomic status (Hollingshead Two-Factor Index), and above-average full-scale IQ scores (mean 119 on WISC-R/WAIS-R) in this sample group.

All patients had been treated with MPH for at least 2 months without satisfactory response. Despite appropriate MPH treatment, all had one or more of the following indicators of inadequate response: score >65 on at least two scales of Conners Parents Rating Scale; C-GAS scores >50; CDI scores >15. For each patient, these measures reflected continuation of serious problems related to ADD in home, school, or both, despite treatment with appropriate levels of MPH.

Comorbid diagnoses

Few of our patients presented with "pure" ADD; virtually all met criteria for at least one other Axis I diagnosis as well. This is consistent with the observation that a majority of patients diagnosed with ADD have at least one other comorbid psychiatric diagnosis (Halperin et al. 1991, Livingston et al. 1992).

Table 2 shows Axis I diagnoses comorbid with ADD in this sample. Twenty-five children and adolescents (78%) presented with symptoms of dysthymic disorder, including six with superimposed major depression.

Frequency of oppositional defiant disorder (ODD) and conduct disorder (CD) is also shown in Table 2. Nineteen patients (59%) met diagnostic criteria for ODD, and four (13%) met criteria for CD. In addition six patients met criteria for one or several of the anxiety disorders.

Measures

Baseline assessments included Children's Global Assessment Scale (C-GAS) (Shaffer et al. 1983), Conners Parent Rating Scale (CPRS-48) (Conners 1990), and Children's Depression Inventory (CDI)

TABLE 1. DESCRIPTIVE DATA

	<i>n</i>	<i>Mean</i>	<i>SD</i>	<i>Percent</i>
Age (years)				
9–11	9	10.44	0.73	28
12–14	9	13.56	0.73	28
15–17	14	16.07	0.83	44
Gender				
Male	30	—	—	94
Female	2	—	—	6
IQ (WISC-R Full Scale)	32	119	14	—
Socioeconomic status				
I	5	—	—	15.6
II	13	—	—	40.6
III	13	—	—	40.6
IV	1	—	—	3.1

TABLE 2. COMORBIDITY WITHIN ADD SAMPLE

	<i>Number</i>	<i>Percent</i>
Conduct disorder	4	13
Oppositional defiant disorder	19	59
Dysthymia	25	78
Major depressive disorder	6	18
Anxiety disorders	6	18

(Kovacs 1985). After 8 weeks of unblinded treatment, these measures were repeated. In addition, patients' report card grades for the primary academic subjects (not electives) were recorded at the outset of this combined treatment and at the end of the first full marking period (usually 10 weeks) after initiation of combined treatment.

Data analysis

Data analysis was conducted with nonparametric statistics (Wilcoxon signed-rank test) to allow for nonnormal sample distribution. Some analyses employed rank-transformed data to reduce the effects of nonparametric sample distribution. Regression analysis of rank-transformed data was conducted to determine magnitude of change in the measures.

Treatment

Before addition of FLU, all patients were taking methylphenidate hydrochloride (MPH) 17–60 mg daily, administered in divided doses two to four times, depending upon the needs and responses of the patient. Schedules optimized patient response by the "absolute dose" method with careful "fine tuning" of dose and timing (Greenhill 1992a). Each patient was started on a minimal dose of MPH, usually 5 mg once daily in the early morning. The dose was then gradually increased in 2.5–5 mg increments until a significant clinical response was obtained, side effects became problematic, or the maximum of 20 mg per single dose was reached. Once an apparently effective single dose had been determined, two or three additional doses were introduced, titrated, and monitored. (We have found this method to be more effective than commonly recommended mg/kg formulae that do not adequately consider the wide variability of individual response thresholds for MPH. Our experience indicates that the mg/kg formulae for MPH tend to overmedicate some patients and undermedicate others.)

For the patients in this study, careful efforts to find an effective dosing schedule with MPH were only partially successful. Clinical evaluations of reports from parents, teachers, and patients themselves indicated that MPH was of some benefit, but significant problems remained despite adjustments of dose and timing.

The most common complaints during MPH-only treatment were severe impulsivity and hyperactivity in late afternoon and throughout each evening. Many parents also reported difficulties in getting their children up and organized in the morning. Depressed or anxious mood and chronic irritability throughout most days were also common before and during treatment with MPH alone.

In view of these limitations in the treatment with MPH alone, informed consent was obtained to add FLU to the MPH regimen. Patients and families were informed of alternative medication options, including the use of other stimulants, TCAs, and clonidine. Primarily because of the partial effectiveness of MPH, the families decided to proceed with the addition of FLU.

To augment the only partially successful treatment with MPH, FLU was begun at 2.5 mg/day (age <12 years) or at 5 mg/day (age ≥12 years). Over several weeks, the dose of FLU was raised or lowered in increments of 2.5 mg or 5 mg/day at intervals of 3–4 days, according to patient response. The maximum dose was 20 mg/day; 19 patients (59%) were taken to this level and the others were stabilized at doses ranging from 2.5 to 15 mg/day. Table 3 gives the number of patients at each specific daily dose.

TABLE 3. TOTAL DAILY DOSES OF FLUOXETINE (MG)

	<i>n</i>	<i>Percent</i>
20	19	59
10-15	6	18
5-7.5	4	12
2.5	3	9

Fractional doses (<20 mg) were prepared by dissolving the contents of a 20-mg pulvule in 8 oz (one cup) of water. Pharmaceutical company research has shown the aqueous solution to remain stable for more than 5 days (Atul Pande, M.D., Eli Lilly Co. personal communication). Increments as little as 2.5 mg (1 oz) were easily accommodated in this way. Commercially available fluoxetine elixir (20 mg/5 ml) was judged too difficult to measure and too expensive to warrant use in this study.

Utilizing this protocol over 12 weeks in these 32 children, we did not find any side effects severe enough to warrant discontinuation of either medication. We monitored weekly for the following side effects: headache, nervousness, sleep problems, drowsiness, restlessness, tremor, dizziness, fatigue, nausea, diarrhea, dry mouth, anorexia, and problems with vision. Many patients reported slight indications of one or another of these symptoms ("a funny kind of headache once in a while," feeling "a little restless," or "waking up for just a few minutes once or twice during the night") over the first few weeks of augmentation with FLU. When these minor complaints were reported, dose was not increased until the problem stopped; if the complaint persisted, dose was reduced.

Earlier studies using FLU with children and adolescents reported significant problems with side effects such as agitation and gastric distress (King et al. 1991, Riddle et al. 1991), but those adverse effects may have been dose related (Boulos et al. 1992; Riddle 1992). Most of the earlier studies used a fixed starting dose of 20 mg without gradual titration. It now appears clear that for many children and adolescents, 20 mg is an excessive dose of FLU. Even for those who may eventually benefit from a dose of 20 mg/day or more, side effects are likely to be minimized if a lower starting dose and slow titration strategy are employed.

Although we encountered no significant side effects in the 8-12 weeks of the study, we did find that one of our patients later developed episodic feelings of restlessness and agitation. Starting after 3 months of the combined treatment, this episodic restlessness and agitation persisted for several weeks, even after reduction of the FLU dose. This side effect led us to discontinue the FLU while continuing the MPH. The episodes of agitation and restlessness ceased within 2 weeks after the FLU was discontinued. The long half-life of fluoxetine and its desmethyl metabolite may account for such late-onset side effects (Renshaw et al. 1992).

Concurrently with the pharmacologic interventions, a variety of psychosocial interventions were employed. In weekly meetings with patients and their parents, psychoeducation, social skills training, cognitive-behavioral, individual and conjoint family therapy interventions were undertaken in varying combinations depending on needs of the patient. These interventions probably augmented the effects of the pharmacotherapy in ways difficult to assess; such concurrent interventions are necessary and cannot be controlled for in private practice.

RESULTS

All 32 patients showed a positive therapeutic response to the addition of FLU to MPH. Thirty of 32 (94%) children showed clinically significant responses and the other two had statistically but not clinically significant responses. Only one patient showed a deterioration in clinical status, which appeared after the study period of 12 weeks.

Comparisons of clinical assessments of children on MPH alone and 8 weeks after implementation of the combined MPH-FLU regimen are shown in Table 4, along with academic grade-point averages before and 12 weeks after introduction of FLU.

TABLE 4. MEASURES PRE- AND POSTFLUOXETINE

Measure	Prefluoxetine		Postfluoxetine ^a		
	Mean	SD	Mean	SD	<i>p</i>
CGAS	44	6	60	6	<0.0001
CDI	22	9	8	4	<0.0001
CPRS-48					
Conduct	79	16	58	12	<0.0001
Learning	84	10	64	10	<0.0001
Psychosomatic	61	18	54	13	<0.1071
Impulsive	70	15	53	14	<0.0001
Anxiety	63	12	54	11	<0.0010
Hyperactivity index	81	11	59	10	<0.0001
Grade-point averages	1.6	0.65	2.6	0.5	<0.0001

^a At 8 weeks after initiating fluoxetine.

Global functioning (CGAS) improved dramatically ($p < 0.0001$). Mean functioning before introduction of FLU was in the range of moderately severe impairment ("moderate degree of interference in functioning in most social areas or severe impairment of functioning in one area"); it improved on the combined regimen to the mild to moderate range ("variable functioning with sporadic difficulties/symptoms").

The patients described these changes in remarkably similar ways ("Things that used to bother me a whole lot don't seem to bother me that much anymore," "I don't get so uptight or crabby so much all the time"). Many parents reported much fewer frequent conflicts and emotional outbursts between the patient and family members in the early morning and late afternoons.

Mean CDI scores for the group declined from 22 to 8 over the trial. This is a reduction from the clinical range for depressive symptoms into the nonclinical range. Improvement in depressive symptoms was especially noticeable in children for whom hyperactivity was minimal; they tended to appear more lethargic and depressed initially and to respond particularly well to the addition of FLU. Most patients reported feeling "in a better mood more of the time" on the combined medications, and "not so much up and down every day" as on the MPH alone.

Group means on all six scales of the Conners Parents Rating Scale showed improvement. Most striking were substantial reductions on conduct problems, learning problems, and the hyperactivity index score; all of these scales showed improvements of >20 percentile points, which brought them below the usual clinical cut-off of 65. The impulsivity scale showed a similar decline.

These scores reflect the parents' perception that their son or daughter with ADD was generally more cooperative, less argumentative, less belligerent, not so easily frustrated, and more likely to attend to schoolwork and other necessary tasks. This is not to say that all emotional and behavioral problems of the patients disappeared. It merely reflects a reduction from rather extreme problem levels to something more closely approximating the normal range of variation.

The anxiety and psychosomatic scales on the Conners scale showed less striking reductions. Notable improvement was seen in anxiety symptoms for several patients who had demonstrated some obsessional and perseverative tendencies or had a history of excessive fearfulness. The decline in psychosomatic symptoms may have been masked to some degree by mild drug side effects.

Most impressive among the improvements shown on these various measures was the dramatic jump in students' grade-point average (GPA), from the mid-D range to the mid-C range within one marking period. Buried in this group average are grades from some individuals who raised "C"s to "A"s or "D"s to "B"s.

Since these children had all been tried on psychostimulant medication and had shown no significant improvement until that medication was augmented with FLU, the improved GPA was especially striking. This was the measure whose improvement usually had the biggest impact upon the morale of the patient and family.

Regression analyses on our findings indicated that improvements in these measures were most striking for those whose problems were rated most severe in initial assessment, i.e., the worse a patient's initial scores on

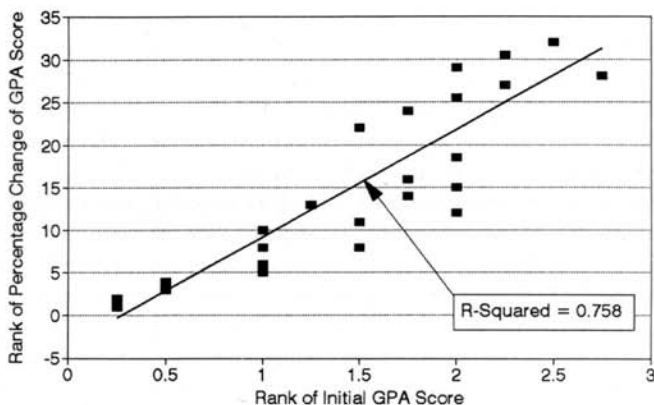


FIG. 1. Grade-point averages: relationship between initial measure and change.

each measure, the greater the magnitude of improvement after introduction of FLU. Figure 1 shows this result for GPA, and Table 5 reports the significant *F* values associated with these analyses for the other measures.

DISCUSSION

Taken together, these results offer evidence that FLU augmentation can substantially improve symptoms in some MPH-resistant children with ADD: (1) it produces a variety of improvements in some patients who are nonresponders or partial responders to MPH alone; (2) its longer duration of action avoids “roller-coaster” swings of mood and self-control; and (3) it helps to alleviate irritability, oppositionality, anxiety, and depressive symptoms and syndromes that often appear comorbidly with ADD.

Many children with ADHD present with additional comorbid diagnoses, including conduct, depressive, anxiety, and other disorders (Biederman et al. 1991). Given these high rates of comorbid diagnoses, treatment of ADD generally needs to address a cluster of symptoms much broader than those defined in the current criteria for ADD. In our sample, 78% presented with dysthymic disorder and 18% presented with major depression. This finding is consistent with the review of Hudson and Pope (1990), who identified ADHD as one of a family of eight discrete psychiatric disorders included in “affective spectrum disorder,” all of which generally respond to antidepressant medication and share common patterns of comorbidity in phenomenologic and family studies. In such cases, the combined use of MPH and FLU may be particularly advantageous.

The dramatic increase in GPA was noteworthy. Such improvements are not uncommon when students with ADD are started on psychostimulants and, perhaps for the first time ever, are able to sustain attention consistently on their classwork and homework assignments.

TABLE 5. REGRESSION AND CORRELATION ANALYSES: SEVERITY OF INITIAL MEASURE VS. CHANGE

<i>Measure</i>	<i>R</i> ²	<i>F</i> statistic	<i>p</i> value
CDI	0.15	5.49	0.026
CPRS-48			
Conduct	0.19	7.18	0.012
Learning	0.13	4.52	0.042
Psychosomatic	^a	—	—
Impulsive	0.37	17.85	0.0002
Anxiety	0.25	10.22	0.0033
Hyperactivity index	0.23	8.73	0.0060
Grade-point average	0.76	94.15	0.0001

^a Insufficient variance to perform analysis.

The finding that 30 of 32 children with ADHD showed clinically significant improvement upon the addition of FLU to methylphenidate is also interesting in that the effect of FLU was often seen at relatively low doses. In using FLU in combination with MPH, 41% of our patients showed optimal clinical responses at doses of FLU below 20 mg daily. The use of a slow upward titration of FLU may have helped minimize the final doses. Further, the gradual elevation of FLU dosage appeared to minimize side effects, at least in relation to most currently available reports in the child and adolescent literature.

The mechanism by which the combination of FLU and MPH helped to produce these improvements, which neither medication seemed able to produce alone, is unclear. One possible explanation is that FLU may modify the pharmacokinetics of MPH, perhaps by intensifying or prolonging MPH action. This may be particularly helpful to some ADD patients who are unresponsive to MPH used conventionally.

Alternatively, FLU may alter the brain's responsiveness to dopamine. The possible mechanisms of serotonin interactions with dopamine are receiving increasing attention, including recent animal studies which suggest that serotonin may play a role in regulation of the responsiveness of several dopamine systems (Beasley et al. 1992, Benloucif and Galloway 1991, Chen et al. 1991, Kelland et al. 1990, Serra et al. 1990). Additional animal studies have explored the possible role of fluoxetine in metabolism of dopamine (Baldessarini et al. 1992) and on the monamine content of the brain (Caccia et al. 1992).

Beyond possibly affecting dopamine levels in various brain regions, FLU may directly impact upon other ADD and comorbid symptoms. Low levels of serotonin have been linked to increased impulsivity, aggression, and suicidality (Linnoila and Virkkunen 1992), whereas high serotonin levels are associated with excessive inhibition and risk avoidance (Cloninger 1987). In some children, FLU may directly alleviate some ADD symptoms (Barrickman et al. 1991), such as impulsivity, in ways which indirectly facilitate improvement of other symptoms, such as concentration.

Further, FLU may indirectly modify the interactions among multiple neurotransmitter systems involved in ADD. As Hunt and colleagues (1991b) have noted, multiple neurotransmitter systems are likely to be involved in complex interactive ways to shape the broad range of cognitive and behavioral symptoms associated with various subtypes of ADD. For example, it seems likely that the beneficial effects of MPH on sustained attention may result not from a global increase of dopamine in the cortex, but from an alteration of the ratio of dopamine to norepinephrine in certain subsystems. FLU may affect this complex interaction in ways which are beneficial for some patients whose symptoms do not respond adequately to other treatments.

Finally, since fluoxetine has been found to have some value in treating ADHD symptoms (Barrickman et al. 1991), the combination of MPH and FLU may be effective because each drug has a slightly different spectrum of action on ADHD symptoms. MPH may be more effective with attentional symptoms, and FLU may be more effective with behavioral and affective symptoms (Barrickman et al. 1991) associated with ADHD. This approximates the clinical reasoning often used in combining a stimulant with a TCA or with clonidine for treating stimulant-resistant children with ADHD. In view of the favorable side effect profile and the high efficacy found in this preliminary study, clinicians might instead consider combining a psychostimulant with FLU rather than combining a stimulant with a TCA.

Our study was limited by its small sample, unblinded design, and lack of cross-over or placebo control. Yet despite these limitations, the findings suggest that FLU may be a safe and valuable adjunct to MPH for treatment of ADD and some comorbid disorders in some children and adolescents. However, clinicians should use caution in the application of these findings, being alert to the possibility of untoward results from this combination of medications with other patients, especially over longer periods of treatment.

This study extends the evidence supporting the notion that, when conventional single medication treatments are ineffective, the cautious use of combined medications may provide alleviation of otherwise disabling symptoms.

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