Patient Scores at the End of Each Treatment*						
	BPRS		AIMS		WCST	
Patient	Placebo/ Haloperidol	SKF-38393/ Haloperidol	Placebo/ Haloperidol	SKF-38393/ Haloperidol	Placebo/ Haloperidol	SKF-38393/ Haloperidol
1†	46	36 ↓	7	3 ↓	17	13 ↓
2	62	50 ↓	7	3 ↓	Patient refused	
3	52	42 ↓	5	7	90	85 ↓
4†	37	34 ↓	3	1 ↓	20	32
5†	49	50	9	7 ↓	80	92
6	42	45	5	3 ↓	24	18 ↓
7†	56	57	5	3 ↓	42	78
8	43	42	2	1 ↓	22	42
9†	35	43	0	1	14	20
10	48	54	5	5	12	33
Mean	47	45.3	4.8	3.4	35.7	45.9

*BPRS indicates Brief Psychiatric Rating Scale; AIMS, Abnormal Involuntary Movement Scale; and WCST, Wisconsin Card Sorting Test perseverative errors; and an arrow, a decrease in score.
†Patient received SKF-38393 before placebo.

ing Test perseverative errors were reduced in three patients and increased in six others. Amelioration of schizophrenic symptom severity in only 3 of the 10 patients is not a very impressive result and could very well have happened by chance alone. On the other hand, this was a group of chronically unremitting patients in whom neuroleptics produced no therapeutic effects and in whom a 20% decrease in Brief Psychiatric Rating Scale scores constituted a clinically meaningful effect.

Probably the most discernible beneficial effect associated with SKF-38393 was the improvement of tardive dyskinesia as reflected by reductions in Abnormal Involuntary Movement Scale scores. Although in animals a DA/D-1 agonist may worsen oral dyskinesia,[5] a deficit in the dopaminergic transmission of the medial prefrontal cortex can lead to the development of abnormal movements in rodents, thus suggesting that reversing this deficit might abolish abnormal movements.[6]

Obviously, results based on a sample size of 10 patients cannot be generalized, nor can these results establish a therapeutic role for a novel pharmacological agent like SKF-38393 in combination with a DA/D-2 blocker. Rather, this trial should be viewed as an attempt to devise a pharmacological response to the latest elaborations of the DA hypothesis in schizophrenia, ie, increased and reduced dopaminergic activity can coexist in different areas of the schizophrenic brain and together contribute to generation of schizophrenic symptoms. This is an alernative formulation to the notion that dominated the field of drug development, that overall antidopaminergic activity is essential to the antipsychotic effect. By utilizing a DA/D-1 agonist and a DA/D-2 blocker, a strategy is devised that selectively affects discrete brain areas.

It should be noted that this study employs a single relatively low dose of SKF-38393. It is quite possible that higher doses might be more clinically effective than the present dose. If the beneficial effects of this two-drug combination are confirmed by other independent studies presently in course, attempts should be made to elucidate mechanisms of action. For example, studies of cerebral blood flow or SPECT during the Wisconsin Card Sorting Test could help establish if the therapeutic effects are mediated by the ability of SKF-38393 to effect cortical dopaminergic transmission. Other future studies should investigate the effects of SKF-38393 given without a neuroleptic, as well as attempt to establish the optimal therapeutic dose for this drug.

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Fluoxetine and Side Effects

To the Editor.—Bouchard and colleagues[1] recently reported an increased risk of extrapyramidal signs and symptoms during treatment with fluoxetine or other potent and selective inhibitors of neuronal uptake of serotonin. Others have noted such symptoms when this new antidepressant was combined with a neuroleptic agent,[2] leading to the question of whether a pharmacodynamic effect or a pharmacokinetic drug interaction was at work, as may occur with increased plasma concentrations of tricyclic antidepressants.[3] Bouchard et al suggested that such reactions with fluoxetine or similar agents *alone* might arise through the ability of serotonin uptake blockers to potentiate putative inhibitory effects of serotonin on the metabolic production or release of dopamine by neurons of the basal ganglia.

We tested this prediction in a laboratory model by measuring the accumulation of dopa after pretreating with a centrally active inhibitor of its decarboxylation (NSD-1015, 150 mg/kg intraperitoneally, 45 minutes before killing) as an index of catecholamine synthesis in forebrain regions of adult (250 g) Sprague-Dawley rats pretreated with fluoxetine at 10 mg/kg intraperitoneally, acutely at 4 hours before killing, or repeatedly daily for 2 weeks (5 d/wk) plus a final dose for the acute treatment, with all treatments balanced with saline-placebo control injections. Brain tissue was removed, dissected on ice into corpus striatum, nucleus accumbens septi, frontal and occipital cerebral cortex, hippocampus, and cerebellum, and frozen at −70°C until it was assayed for dopa concentrations by high-performance liquid chromatography with electrochemical detection by methods described elsewhere.[4] There

Effect of Acute and Repeated Treatment With Fluoxetine on Catecholamine Synthesis in Regions of Rat Brain*

Brain Area	Percent of Control (Dopa) ± SEM: Acute Fluoxetine	Repeated Fluoxetine
Striatum	77.8 ± 6.8†	70.5 ± 2.6†
Accumbens	70.6 ± 9.9†	85.0 ± 5.7
Hippocampus	88.1 ± 7.0	74.8 ± 6.0†
Frontal cortex	61.0 ± 5.1†	78.6 ± 1.7†

*Control values (saline-placebo pretreated, and then treated with NSD-1015) averaged 2.02 ± 0.10, 2.35 ± 0.12, 0.082 ± 0.011, and 0.194 ± 0.015 ng of dopa per milligram of wet brain tissue for striatum, accumbens, hippocampus, and frontal cortex, respectively.

†There was a significant difference from matched controls by t test at $P<.05$ or less (n = 10 rats per condition).

were no significant effects in occipital cerebral cortex or cerebellum, but results with other brain tissues showed significance (Table).

The results indicate that a relatively large dose of fluoxetine moderately but significantly inhibited the synthesis of catecholamines acutely in several dopamine-rich areas of the mammalian forebrain and that, while this short-term effect may diminish with repeated treatment elsewhere, it appeared to persist or even to increase in the hippocampus and the extrapyramidal region (striatum). The findings support the hypothesis of Bouchard et al[1] and are consistent with other evidence that serotonin may exert a significant inhibitory action on dopamine neurons of the midbrain and brain stem projecting to forebrain.[5] The present observations add further to the possibility that fluoxetine may exert indirect pharmacodynamic actions on nonserotonin systems of the brain as well as exert potentially clinically important pharmacokinetic interactions with other agents.

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More on Ethics of Drug Discontinuation Studies in Schizophrenia

To the Editor.—Chandler[1] raises an objection to the research method of Lieberman et al,[2] in which stable schizophrenics were withdrawn from antipsychotic medications and monitored for signs of relapse. He suggests that drug discontinuation studies are unethical. Lieberman et al countered, correctly, that neuroleptics have unacceptable side effects, are ineffective in approximately 30% of patients, and that some patients can remain drug-free for many years without relapse.[3]

As a group that is involved in similar relapse prediction studies, we are very sensitive to the objection raised by Dr Chandler. It is our experience that this discomfort, articulated in the name of ethics, is unfortunately shared by many health care professionals treating schizophrenic patients. Although we agree with Lieberman et al, we feel that an additional response is indicated.

We believe that this so-called ethical objection is misguided. It reflects an underlying paternalism, which ignores the fact that these patients were clinically stable, were aware of the risks involved, and gave their informed consent with the knowledge that they could discontinue the study at any time and receive treatment. We doubt that anyone would question the ethics of a carefully monitored anticonvulsant drug withdrawal study in consenting seizure patients who were clinically stable.

Drug-withdrawal studies are essential to further our understanding of the pathophysiologic relapse process. Neuroleptics have protean effects on neurochemistry, and render uninterpretable most, if not all, biological measures. Metabolites of antipsychotics can be found months after drug withdrawal.[4] A single dose of a neuroleptic can have antidopaminergic effects for up to 40 days.[5] Further studies using longer drug-free intervals are needed to help sort out what is attributable to the underlying pathophysiologic process and what represents sustained medication effects.

Why not raise the question of the ethics of performing bad science? We have not progressed significantly in improving the care of schizophrenic patients since antipsychotic drugs were introduced in the mid-1950s. We still do not have answers to the most basic questions: when, how much, and how long should these medications be used? Neuroleptics have been helpful in removing from our sight the more disturbing signs of psychosis, eg, catatonia and psychomotor agitation; however, the adverse effects are disliked by patients, who often choose to discontinue medications on their own.[6] Insisting that patients continue to take neuroleptics during research studies condemns them to the state of the art of the 1950s. We believe that there is an ethical imperative to conduct science in a manner that yields meaningful information.

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