EXHIBIT

SLATER 2

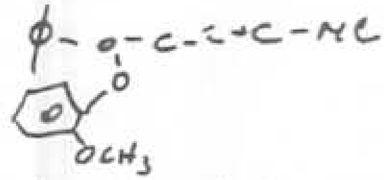
I00000

11-12-70. Extended meeting of CNS core committee Stark, Rathburn, Owen, Molloy, Slater + Fuller. Lots of talk esp. about interaction of drugs with apomorphine - Elavil + Aventyl enhance gnawing but DMI + Tofranil do not. Also gave us get urea analyzed. Stark felt that the discussion was useful. but Molloy was depressed.

The idea of setting patterns and then trying to select unique cpds for clinic seems pointless to me unless clinicians are more enthusiastic about blue sky experiments.

3-14-72

Molloy & Rathbun summarized current data on 94939



I do believe that we'll have an effective antidepressant with low level of side effects (at odds of 1/5) There have been ~~so~~ so many failures here.

9-16-72

Our first BP experiments with 9423 has shown a dose dependent increase in BP and a contraction of the NM after 0.3 & 1.0 mg/kg IV. Will try neurectomized cat today.

10/19/72 I presented a summary of data on 94939 to CNS committee on 10/07 + to Hess's staff today. Will recommend clinical trial. Remembering Gershon's many failures, I am betting 2:1 against but hope for the best. If the compound is an antidepressant it should have fewer side effects.

2/2/73 Left pen at home. Yesterday I began a campaign to get 82816, our aplysia 5HT uptake inhibitor, into the clinic soon. Nobody seemed ready to rush (ie Fuller, Wolfgang or Stark.) I think our present data are sufficient for a go-decision. No additional negative result will negate decision, but a large body of additional data will be collected.

000006

4-10-73

82816 (110143) reduced REM sleep in 5/6 cats
The 6th had almost none to start (dose 2.5+5 mg/kg).
Reserpine increases PLO spikes.

6-11-73 p-Cl amphetamine caused a long lasting (2-3 mos.) decrease in brain serotonin level. When 110,140 is administered ~~3 hr~~ 3, 6, 24 or 48 hours after pCA the 5HT decrease is reversed. But 110,140 at ~~24~~ > days did not alter the decrease when rats were killed on day 8. Could there be a lack of binding with and would 5HT still be down at day 9, 10 etc? Fuller may look into this. The major idea Lewis has, I merely suggested the 2 or 3 day wait.

6/12/73 Wesley + Fuller want to see whether we can develop a central 5-HT blocker using the drug indicated in 6 day old chicks by IV injection. I tried Epi in one chick & it is not very hard.

000008

6/25/73 · a second run using 5 mg/kg of 5HT did give something that looked like sleep & was different from control. 1 mg/kg + 110,140 gave sleep equal to 5 of 5HT; 53857 + [illegible] did [illegible] · [illegible] 10 mg/kg.
~~inadequate experiment~~

000009

10-11-73

Don Meyers reported abnormal EKG's in dogs treated with 9493 and one dog with a fulminating hepatitis. I think I am seeing some QT prolongation suggesting a delay in repolarization in cats. Worried.

12-14-73

In dogs treated with 94939, perifocal mononuclear + poly (?) infiltration associated with increase pigmentation was initially called "fulminating" hepatitis which is obvious nonsense. More recent reports call it a non-drug related finding.

1/18/74 Increasingly I am concerned about urinary retention with 110140. Dick Moore first noticed that our 24 hour cats often fail to urinate over night. Tues report that one new dog collected 215 ml in her bladder. Molley suggested that Tues check this in rats. The last 5 hour run does not suggest retention. We must do cysto exams: _____

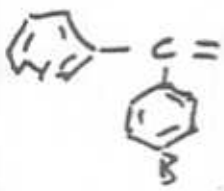
8-21- 21094 was thought to be a very active inhibitor of 5-HT uptake with less specificity than 110,140. It turns out that the original sample came from a mis-labelled bottle and was a Dupont cpd. with a fused-8 membered ring. Clinical trial by Iverson showed it to be inactive as an anti-depressant. It does have "amphetamine-like" activity. What does this mean in relation to 110,140?

foam cells again. A few weeks ago we learned that the rats on high doses of 110140 show foam cells in the lungs a finding we had with L-2,4 di Cl amphetamine. - Chlorphentermine which is still on the market in the US but may be off in Europe Murray Dubnick of Warner-Lambert warned Ray Fuller that we might see pulmonary lesions ~ 110140. How much should we worry?

9-25-74

110140 seems to cause foam cells in the lungs of rats like 32635 (2,4-dichlorodaphen.) and ?? also one see mitogen 2160. Is this a lipid related drug effect or does it relate to 5-HT. Should we inject 5-HT in rat?

502-75

Astra has initiated a clinical trial of  a specific 5-HT uptake inhibitor that also induces phospholipidosis. They feel that the foam cells in rats, which occurs after CPZ, Haloperidol + many other cpds, indicates a special but irrelevant stress. We are still trying to find whether 110,140 induces a reversible lesion.

10-13-75

[redacted] treated 5 patients with 94939. One pt. had a "spontaneous" lifting of depression at 40 mg dose level. This had occurred before in this pt. The others had at best modest improvement and each at 225-300 mg/day developed tremor Sx. One pt. w/ familial history of tremor began trembling at 25 mg/day.

1-16-76. 99638 is a Cl substituted cephalosporin with a spectrum and MIC's somewhat better than cephalexin. Chemically it is difficult + expensive. Marketing is interested in a low dose, less expensive Keflex substitute rather than a higher-priced Super-Keflex. An enormous effort is going into this project which I think is a mistake.

Talked with Bennett, Fuller, Molloy + Rathbun yesterday about J. Small's study of 10 pts on 94939. We were all puzzled by the high incidence of tremor and the question is whether some are extra-pyramidal reactions. Both Bennett + Lenhardt have lined-up possible investigators. It looks like about $2000/pt for 4 wks. On one patient, an obsessive-compulsive showed really remarkable improvement. But then all the patients were drug-naive.

6-16-76

Bennett went to Chicago to setup clinical trials on 94939 & 109514. Stark & I all somewhat distressed to learn that he has initiated at $56,000 study in our normal subjects with high level of anxiety in an operant challenge testing from 9 AM to 4 PM. etc etc. We said nothing negative to Bennett or Neal's but I did mention my concern to Johnson who is confident that we should wait & see. In the meantime Stark leaves on vacation on June 21 ... and will not be back until July 12. Then the Fall meeting in New Orleans (Aug. 16-19) then New school. I don't think very much good is going to come out of all this.

9-8-76

Talked with Marsden + Kiplinger about Bennett, 9 & 39 + report forms. The current delay results from preparation of form which is essential for starting. This I do not understand. Talked to Fuller to say that if Lemberger is not interested in acting as monitor for Iroquois then he, Molloy or I will have to take over.

2-14-77

At the moment our cats look not too hot. attempts to block HOIKO REM suppression with either methysergide or cyproheptadine did not work. M cats became sick + vomited. C cats very hyperactive. What does this mean.

4-13-77

Ivan Bennett visited [redacted] in Manhasset on Fuller's urging. Rie was qwl as pts. c̄ obsessive-compulsive for 94939.

5-13-77

Each time the telephone rings I wonder if Beedie is calling. I must be very interested. I have drawn a tentative list of when & in what order I would tell people. But now I'm going to finish the 11 o'clock hour.

10-10-78

Kay Fuller asked whether I would be willing to take over the clinical monitorship of fluoridine when Bob Shulman leaves. I said that I would not volunteer but if asked I would.

10-26-78

If 5-HT agonist effects contribute to LSD-induced hind flick, would fluoxetine enhance flicks or reduce dose?

000027

11-30-78

Our conversation about the needs for CV group was interrupted by a call from Shedden + Heer by an 8 AM appointment. I have a note saying that he'll be back in touch with me later the AM. I wonder

We returned to my office - not to discuss

CV situation, but to say that Shedden would like me to take over the monitorship of fluoxetine Called Shedden and agreed to do so.

Then called Nick + Johnson in San Diego so that they could talk to [redacted] about a clinical trial of fluoxetine for pain..

12/13/78 After a week in Naples we had a poor lot on Kingfish and Marie Hurst's house against Jim Berry's offer to look into Mead-Johnson. On looking at the mail delivered on Dec. 11, we found a letter from Hathaway of Michegan Homes about Sal Armogida's lot on Tarpon that we have now agreed to buy. I cancelled my trip to Evansville and am trying to send Ray in my place.

000029

12-21-78 As monitor, I have sent a protocol to [redacted], propranolol or analgesics for [redacted] and will start on Noble-

Dixon for Jim Harley came by to tell me he is happy that I'm going to Naples and stayed to say some embarassingly nice things...

12-22- Managed to get protocol proposals to both [redacted]wood [redacted]. Bendush thinks fluoxetine is part way down the tube and doesn't want to spend $4500 for me pt & narcolepsy.

1-29-79. Have just returned from a trip to West coast + Houston to set up trials of fluoxetine. [redacted] is willing to start obesity testing right away but that will have to wait until we have more outpatient data. [redacted] wants to run a inpatient study since he feels his [redacted] patients ≥ HAM-D > 20 are too sick to be alone - most do not have a supportive family situation. [redacted] will continue dystonia studies with less lab work and a modest budget. [redacted] wants to do 10 pilot pt. study for pain. I think we may get real data but I am not certain. Why did Ciba-Geigy turn off the EM/I study? Fabre will do an outpatient pilot. A strange but probably OK set up.

000031

2-15-79

I made a progress report on fluoxetine to Heir's staff this AM. All went reasonably well except the analgesic part. Among other things, Lou Lemberger maintained that until we had our own preclinical data in animals confirming outside report we had no basis in science or morality for testing fluoxetine as an analgetic. I asked about naloxone and asthma. Should I call Lou + talk?

2-21-79 Herr said he was sorry that I have decided to retire Dec. He mentioned that Skip was impressed with my enthusiasm for fluoxetine. Came up in presentation at Exec. Committee meeting. Johnson says 40:60 chance on raise which may be about right. I have now told Herr that if asked, I would carry fluoxetine on a part time basis. That is an interesting possibility. At 20 hours / week / ie half time Smee wants full time Dec it would be very complicated.

2-26-79

The clinical trials of fluoxetine are moving slowly toward initiation. Fasola after ~~about~~ sitting on my rough draft for about a month decided to cancel his appearance before the Institutional Review Committee. I talked to Lemberger, who told Marsden who was initially cool but later seemed cooperative when told of the long delay. Will try to revise Clinical Brochure with Lemberger tomorrow.

000034

3-14-79. Deanna Knight has accepted our job.
Visited [redacted] yesterday. He is ready
to start as soon as we can supply forms
which should be March 28. If
his study progresses according to his
estimate projections he should have 10 hrs

on drug by the end of April. This should give him some idea of efficacy by the NCDEU meeting at the end of May. He says that if fluoxetine does not work in an open label study there is not too much reason to believe that a double blind study. He also wondered whether the transient improvements that we have had reported to us may represent inadequate dose. [redacted] mentioned in a recent telephone conversation that his not seeing as much change in platelet 5-HT uptake as Lemberger (which makes Lou angry!) and also that side effects in the patients receiving 60-40 regimen are not that different from 30-20 Eo —— I would guess that [redacted] will jiggle doses if he sees anything but he has promised to let me know so that we can file amendments with FDA prn. I think I should suggest to Bendush + Sheddan that I'll manage the Phase II fluoxetine trial and honestly turn it off if open label phase is completely discouraging, but mention the tryptophan, L-5HTP and joint study with nortriptyline should be considered. I'll tell them + Norton ...

3-8-79. All protocols for fluoxetine are now written. Will visit [redacted] next week. We should be able to get them start by April 1 and Zabre + [redacted] same time in April. We may get to the double blind phase by July. Will start on the protocol for that soon.

3-14-79

that I'll wind up my animal studies by Sept 15 and relieve both Jones and Moore for other studies. That if the clinical Phase II trial is still in progress I'll take interrupted vacation at least through Feb 15 to see it to an end or to Phase III. I would like to go to NCIDEV and would, if they wish, recruit another psycho pharmacologist.

4-12-79

The Japanese 55 year old physicist at Stanford is still not improved while taking fluoxetine. During first week dose was reduced from 60 to 5° because of lethargy + hypotension. At end of second week, I note in SCL 90 that he is nauseated. Once or twice more weeks and then ??. and this have gone by mind report was as of 3-27. Its hard to sit still. I do hope that he'll consent to a spinal tap.

4-26-79

[redacted] protocol approval and budget came in. He was for the 6 patient pilot study. I told him there is no way. Bendectin agreed to this.

5-15-79. Meeting ⊂ Shedden + Bendush went well as did presentation at Herr's Staff. As of today we have fragmentary evidence of efficacy and we had best be sure quickly. A slow deliberate approach will land us a year or two behind zimeldine fluvoxamine and paroxetine and thereby be worthless.

5-18-79 Off to NCDEU Why do fluoxetine patients start well and then fade? Do we need 1-5HTP? Molloy says it should work 2x L-DOPA and be almost as stable. I told Berndsh that we need more perceptive open label trials with diazepine, tricyclics etc.

5/30/79 While at the NCDEU meeting last week I was impressed with how difficult it would be to design and carry out a meaningful double blind study of fluoxetine. I had hoped to compare F with amitriptyline but [redacted] pointed out that there would be no double blind In addition I suspect that fluoxetine might not affect as many patients as amitriptyline. Finally it dawned on me that my old feeling that our best bet for a successful product will be a combination of an inhibitor of NE

with F. I discussed this with Fuller, Stark Morton, Raffey, Whole, Ostow and Shedden + the Medical Directors. Clearly, we must first show the F alone has some activity This & AM, I am inclined to run F against placebo for 3 weeks and if nothing happens go to amitriptyline Then compare rate of improvement of F v. placebo and F+A and P+A. The oriental physicist seemed to respond quickly to the amitriptyline after fluoxetine when in the past had had not done well on imipramine. Our cat data & REM sleep suggests some sort of additive effect. I talked with Dr [redacted] at [redacted]. He has had experience with fluvoxamine and would be willing to do studies with fluoxetine in [redacted] or [redacted] Would be, or his friend [redacted] in [redacted] be the kind of investigator to give us some positive results with F alone.

6-9-79 - [redacted] has good results with one pt. treated & 200 mg LSHTP + fluoxetine, better than before with 1200 mg. Now to deal & Kantrowitz, Christiansen + Barnett etc.

6-18-79 Trying to enlist more fluoxetine investigators. Not happy with Fabre - Wrote asking him to return pills, forms + 4/5 of grant.

6-29-79 Fabre has agreed to a double blind trial, but [redacted] wants a little more experience + wants to go to Univ. Pharmacie. Thinks [redacted] was to have sent us protocols but nothing came. Called to make an appt. in Kentucky [redacted] will be ready in Oct or Nov. Will also try [redacted] + [redacted] there.

7-13-79 Friday! [redacted], [redacted]'s associate at [redacted] called to tell me that a 26 year old female who has been on fluoxetine has a falling WBC 4.1, 4.4, 3.9, 3.3 with a normal differential, Hematocrit 4[redacted] ↓ to 33 ± 0.3%, Retic. Platelets 225,000. Hematologic consult this PM.

I had been planning to visit [redacted] + [redacted] and possibly [redacted] during the week of Aug. 6 but I guess I'll wait before I buy a ticket.

7-20- Visited [redacted] on 7-18. Pt's mother sometimes gives pt. Macrodantin. We couldn't be sure. Her marrow on 7-13 was "recovering" Count is rising slowly. Neither [redacted] nor Tobe seem concerned. We'll meet with Project Team on Monday 7-23. I am not entirely comfortable and I do suspect that this was fluoxetine related Tobe says he is hearing about increased pain during menstruation. I thought we had no young women but he says these are anovulatory or have tubal ligation etc.

8-9-79. Visited [redacted] and [redacted] in [redacted] They say that he can run a 20, 40, 60, 80 mg of fluoxetine study but 4 sets of patients started in Oct 1979 would take until July 1980 for completion. I expressed concern that 4 subjects at each dose might not be sufficient. He seemed confident that we would get answers. could be. We know that 20 rarely works

and that go causes lots of agitation so — I am going to recommend that we go ahead + support the project

[redacted] seemed like a sensible guy. His associate Mr. [redacted] seemed aware of which side is up. At [redacted] suggestion I called [redacted] and found that [redacted] had died. Dr. [redacted] called today and gave [redacted] good marks. [redacted] wanted to know whether Lilly would pay for hospitalization should a drug reaction occur. I called him to say that Benderoff will stand behind the physician Rx. He mentioned that Lilly has his CV. since he had applied for a job. Will check. Could be a good guy for the job.

8-17-79. The 4 above Double blind against placebo is ready to go if the grant is approved. Hes patient 103 has some corneal & conjunctival lesions as well as lobar infiltrates that Tobie says are probably viral in origin. We know more when he sees the patient again on Aug. 20.

8

8-21-79

[redacted] called yesterday to tell us that [redacted] had taken both of his patients off fluoxetine. One was a young man with suicidal risk and incipient thought disorder who probably should be classified as schizophrenic or schizoaffective. He was started on Mellaril. The other must be a simple failure.

I have not heard from [redacted] in several weeks and have had no case reports. Called yesterday while he was out. He did not return the call.

We did re-label and repackage the material for Fabry's study.

6-79

Today in R. Management Staff - approved project team status for the methyl analog of nisoxetine (? tolvoxetine) I have told both Fuller + Raffey that I do not believe that the company will ever recover research costs from profit for this one. I do think that the fluoxetine will be far enough ahead so that we can judge whether leukopenia is a characteristic of the class or just of the methoxy derivative

9-25-79

Told [redacted] in a letter that his failure to file case reports is what may prevent his patients from receiving fluoxetine.

10-1-79

Paul Stark will be taking over fluoxetine. We visited [redacted] + had a friendly meeting. Neil + I wanted to run a 2 week combination 1) Rebuild fluoxetine level. 2) 2 wks of 5 HTP + carbidopa + 3) Stop fluoxetine 4). maintain dose of 5 HTP - carbidopa. Stark was dubious, as was Fuller + Shudder said "bad"; another 8-12 months down the drain

000054

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INHIBITION OF REM SLEEP BY FLUOXETINE, A SPECIFIC INHIBITOR OF SEROTONIN UPTAKE*

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(*Accepted* 3 *October* 1977)

Summary—Fluoxetine, a specific inhibitor of serotonin uptake, suppressed REM sleep in cats. The onset of action was prompt and with doses of 2.5 mg/kg, (p.o.) the effect lasted a full 24 hr. After 2 or 3 weeks of daily dosing, the amount of REM sleep began to increase again. A small dose of fluoxetine added to a small dose of L-5-hydroxy-tryptophan caused a significant decrease in REM sleep whereas either treatment alone did not. Administered to *cerveau isolé* cats fluoxetine did not antagonize EEG desynchronization induced by the muscarinic stimulant arecoline, indicating the lack of a direct anticholinergic effect. These experiments indicate that REM sleep is suppressed when 5-HT accumulates at synapses as a consequence of fluoxetine administration. These data and a similar suppression of REM sleep that occurs when norepinephrine accumulates suggest that both NE and 5-HT can inhibit the cholinergic system that seems crucial for REM sleep. Non-REM sleep was usually increased in cats. In rats REM sleep was suppressed by fluoxetine but SWS did not increase.

Impairment of serotonergic mechanisms profoundly alters sleep patterns. Insomnia follows treatment with serotonin-depleting agents or destruction of serotonin-containing neurones in the median raphe (Jouvet, 1972). Depletion of monoamines by reserpine results in loss of slow wave sleep and bursts of ponto-geniculo-orbital (PGO) spikes (Brooks and Gershon, 1977). The decrease in brain levels of serotonin (5-HT) that follows administration of *p*-chlorophenylalanine coincides with a decrease in slow-wave sleep (SWS). Administration of the serotonin precursor, 5-hydroxy-tryptophan (5-HTP), reinstates sleep that lasts only for the few hours during which 5-HT levels are restored. Early in the recovery from insomnia induced by *p*-chlorophenylalanine, cats display showers of PGO spikes (Jalfré, Ruch-Monachon and Haefely, 1974). These spikes also appeared in cats treated with the monoamine-depleting benzoquinolizine, RO-1284. Administering 5-HTP to these cats decreases the number of spikes, indicating suppression by a serotonergic mechanism.

The consequences of decreased levels of 5-HT are clear and reproducible, but attempts to examine the effect of increased availability of 5-HT have been frustrated by lack of specific agents. The effects of tryptophan are modest (Hartmann, 1977). Though 5-HTP at high doses may increase sleep, the effects cannot be ascribed to increased activity of serotonin neurons since decarboxylation of 5-HTP can occur in other neurons as well. Monoamine oxidase inhibitors, which decrease SWS and paradoxical sleep (REM) elevate levels of catecholamines as well as 5-HT. Tricyclic antidepressants reduce REM sleep and usually increase SWS (Ritvo, Ornitz, LaFranchi and Walter, 1967) but these drugs generally inhibit re-uptake of both catecholamines and 5-HT. Although chlorimipramine itself selectively inhibits 5-HT uptake, its methylated metabolite inhibits norepinephrine (NE) uptake. Changes in sleep pattern after administration of this drug then become a consequence of an undetermined and mixed influence on both 5-HT and NE. Fluoxetine, (*dl-N*-methyl-3-phenyl-3-[α,α,α-trifluoro-*p*-tolyl)oxy] propylamine hydrochloride), and desmethyl fluoxetine are specific inhibitors of serotonin uptake that do not affect catecholamine uptake *in vivo* (Wong, Horng, Bymaster, Hauser and Molloy, 1974). In the present study fluoxetine was used to enhance serotonergic nerve function and was found to suppress REM and usually increase light or slow wave sleep.

METHODS

Sleep patterns were determined in male cats and rats carrying implanted electrodes. The animals were in sound-attenuated enclosures. One-minute segments of EEG were graded by the usual criteria (Slater, Jones and Moore, 1976) as awake, drowsy, light, light-to-deep slow-wave (SWS3), deep slow-wave (SWS4) and REM sleep in cats. Sleep patterns for each cat usually were reproducible from day to day over a period of a few weeks. The cats differed in age, time in the laboratory, temperament and, not surprisingly, in distribution of sleep stages. In rats, light sleep and both stages of slow-wave sleep were combined as SWS. Drugs were administered orally.

Cerveau isolé cats were prepared under ether anaesthesia. After making a coronal slot posterior to the

* A preliminary report of these data was presented at the Spring meeting of the FASEB (*Fedn Proc. Fedn Am. Socs exp. Biol.* 33: 564, 1974).

Key words: REM sleep, serotonin, fluoxetine, cholinergic.

EXHIBIT
SLATER - 1

bony tentorium and opening the dura, the brain stem was divided at the level of the junction of the inferior and superior colliculi with a modified nickel spatula inserted at a 46° or 50° angle. Stainless-steel 2 × 56 screws that reached, but did not penetrate, the dura served as surface leads. Bipolar insulated stainless-steel wire electrodes were placed in the lateral geniculate nucleus of the thalamus under stereotaxic control. The ether anaesthesia was stopped at least 1 hr before the experiment was begun. A dose of 0.1 mg/kg of atropine methiodide was injected to block peripheral cholinergic receptors.

When the pattern of slow-wave activity with intermittent "sleep spindles" was well established, 5 μg/kg of arecoline HCl, (i.v.) was injected. At 10-min intervals the dose was increased or decreased to determine how much arecoline was needed for induction of a desynchronized EEG. This threshold dose was determined again after intravenous injection of fluoxetine.

RESULTS

Cats—sleep pattern: 5-day trial

Three cats received fluoxetine on 5 consecutive days that were preceded or separated by days on which water was administered (Fig. 1). Since fluoxetine has a long duration of action (Parli and Hicks, 1974), EEG's were recorded for 22.5 hr. Each day the cats received drug or placebo at 8:45 a.m. Recording began at 9:00 a.m. and continued until 7:30 a.m. the next day, when the cats were exercised and observed outside the recording enclosure.

During the first 5-day course the three doses 1, 2.5 and 5 mg/kg all caused significant suppression of REM sleep; the two higher doses causing almost complete suppression (Fig. 1). While receiving 2.5 mg/kg of fluoxetine for 5 days, cat 82 had 8 min of REM sleep on one day, 4 min on two days and none on the two remaining days. During the period when cat 75 received 5 mg/kg, the percentage of time in REM sleep fell from 11.88 ± 0.88 to 0.18 ± 0.32. Both light sleep and SWS3 increased in this cat, while the awake periods remained virtually unchanged. This cat had less than 1% of SWS4 during both control and drug treatment. Most of the lost REM sleep time for the cats receiving 1 or 2.5 mg/kg (≠82 and 84) appeared as light sleep. While receiving only water, these two cats had 5.17 and 9.73% levels of SWS4 during the first 2½ hr of each day and a total of 1.13 and 4.22 for the 22.5 hr. During the first 3 days of fluoxetine treatment, SWS4 varied but was not detected in either cat at any time during the fourth and fifth day of drug treatment. Later in the week, SWS3 also decreased. The low level of REM sleep continued after cessation of drug administration returning to near control level in 9 days. Since the second 5 days of fluoxetine treatment was then begun, it was not known whether rebound would have occurred. In these and in subsequent experiments latency to SWS3 and REM sleep varied enormously between the cats during the control period. For any single cat, latency to SWS3 was usually about the same during control and drug periods, but the REM latency increased.

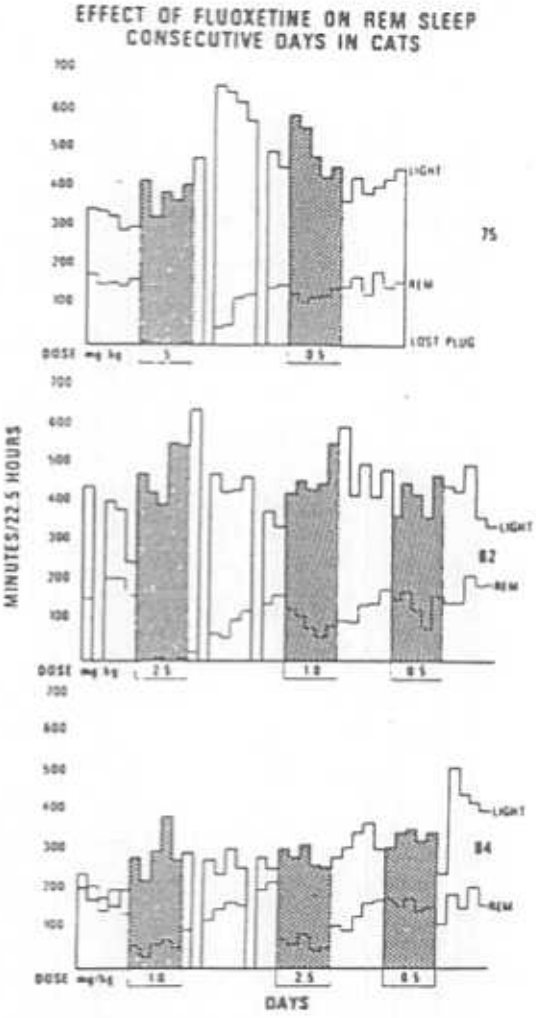

Fig. 1. Effect of fluoxetine on REM and light sleep in cats; EEG's were recorded for 22.5 hr each day. After a control period the cats received fluoxetine each morning for 5 days (cross-hatched interval). The clear areas indicate the days on which water was administered. Each bar equals one day. After the first drug period, there were 2 days of rest during which no recording was done. Slow-wave sleep and awake did not change. The dark line indicates minutes of light sleep and the thinner line, REM sleep. As indicated, cats 75 and 82 had days during the first drug period with no REM sleep at all.

The second course of fluoxetine depressed REM sleep less than the first (Fig. 1). Cat 84 had more REM sleep while receiving 2.5 mg/kg than it had the previous week on 1 mg/kg. In contrast, cat 82 during the first drug trial had almost no REM sleep on 2.5 mg/kg of fluoxetine. The level of light sleep remained high but did not seem to change with changes in drug administration.

On the first day of the third week of drug treatment cat 75 lost its plug. Sleep patterns did not change

during this week in the other two cats (82 and 84) which were receiving 0.5 mg/kg of fluoxetine.

Long-term trial. Additional experiments were performed during which doses of fluoxetine were administered on a daily basis but EEG's recorded on only 2 days each week. This procedure was used to examine the effects of long-term administration of fluoxetine since several weeks of daily recording often loosened the plug on a cat's head. Cat 75, for example, was lost to further recording on the 30th day of the preceding study. In addition, allowing the cats to remain in their home cages enabled better observation of their appearance and behaviour to be made.

After the cats had been receiving drug treatment for a few days, it was noticed that their pupils were dilated, but still responsive to light. The degree of mydriasis seemed to be dose-related. By the fourth day of drug treatment the cats receiving the larger doses, which had been friendly for years, began to growl and hiss. They became distinctly unfriendly, but with careful handling it was possible to administer the drug in the usual way. The cats seemed to see clearly and did not seem to be hallucinating. They became less irritable toward the end of the second week of drug administration. After cessation of the drug treatment, the cats returned to their usual friendly behaviour in a week or two; those on the higher doses recovering more slowly. The severity of the behavioural change was dose-related being more severe and lasting longer in the cats receiving the highest dose. The cats treated with 0.5 mg/kg orally each day showed only modest irritability, which decreased and virtually disappeared even while they were still receiving the drug. During the first trial after 3 control sessions cats received fluoxetine (0.5, 1 or 2.5 mg/kg) on 8 consecutive days. Sleep patterns were recorded on day 1, 6, 8 and 10. As shown in Figure 2, a statistically significant (2-way analysis of variance) decrease occurred in REM sleep. Deep sleep (SWS4) also decreased but because of the variability and very low levels in some cats, this change was not significant at all dose levels nor was the change in SWS3. Light sleep time did increase, but the total sleep time stayed about the same.

In another experiment, drug administration continued for 19 or 31 days with 6 or 10 recording days during drug treatment and 4 or 8 recording days during the recovery phase. The changes in the EEG are illustrated graphically in Figure 3. Each point is the mean of the percentage of time that two cats receiving a given dose of fluoxetine spent in the various phases of sleep on one day of recording. Again, the decrease in REM sleep and the increase in light sleep can be seen. In the cats treated with 2.5 mg/kg this effect persisted without much change for 6 recording sessions, which covered 19 days of treatment. The question was raised as to how a serotonin receptor antagonist might affect the altered pattern of sleep. Two cats on the high dose (2.5 mg/kg) received 1 mg/kg of

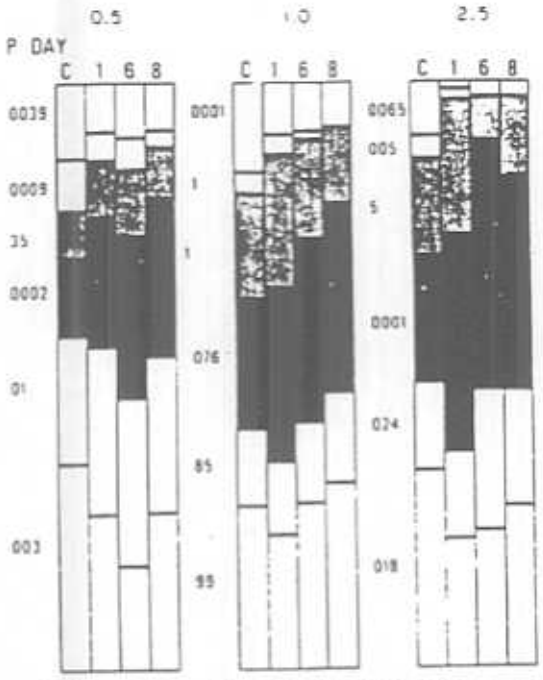

Fig. 2. Effect of fluoxetine on sleep pattern. Cats received fluoxetine on 8 consecutive days. Sleep patterns were recorded three times before drug administration and on day 1, 6 and 8 of drug treatment. Each bar graph represents the mean of results for 2 cats. The number at the top indicates dose in mg/kg. (p.o.). Column C is the mean for 3 control days. Columns labelled 1, 6 or 8 are from recordings of the corresponding day of drug treatment. The stages from the top down are REM, sleep, SWS4, SWS3, light, drowsy and awake. The length of each segment indicates the portion of time spent in that stage of sleep. Total sleep time, indicated by the solid segments and the segments above it, did not change in any consistent way; REM sleep (the top clear area) and SWS4, (the next lightly stippled area) decreased. The *P*-values beside the bar graph indicate that the changes in REM sleep were significant ($P < 0.01$ by analysis of variance) but that changes in SWS4 occurring after 1 mg/kg were not.

methysergide on the 19th day. Both became agitated; they slept much less than before and REM sleep was completely absent. The day after this trial each of the cats appeared ill and all drugs were stopped. These two cats recovered slowly; return to the pre-drug pattern of sleep and behaviour took about two weeks. It was quite clear that methysergide, an agent known to block the effects of 5-HT on peripheral tissue receptors, did not restore a sleep pattern resembling the control.

The cats receiving 0.5 or 1.0 mg/kg of fluoxetine continued for a total of 31 days. Suppression of REM sleep had decreased by the fourth week of recording, and light sleep remained high. When the drug treatment was stopped in these cats, recovery occurred over a shorter period of time than with the larger dose. The amount of REM sleep did not increase over baseline. This absence of a REM-rebound may be a consequence of the long half-life of fluoxetine and its biologically active metabolite, desmethylfluoxetine (Parli *et al.*, 1974).

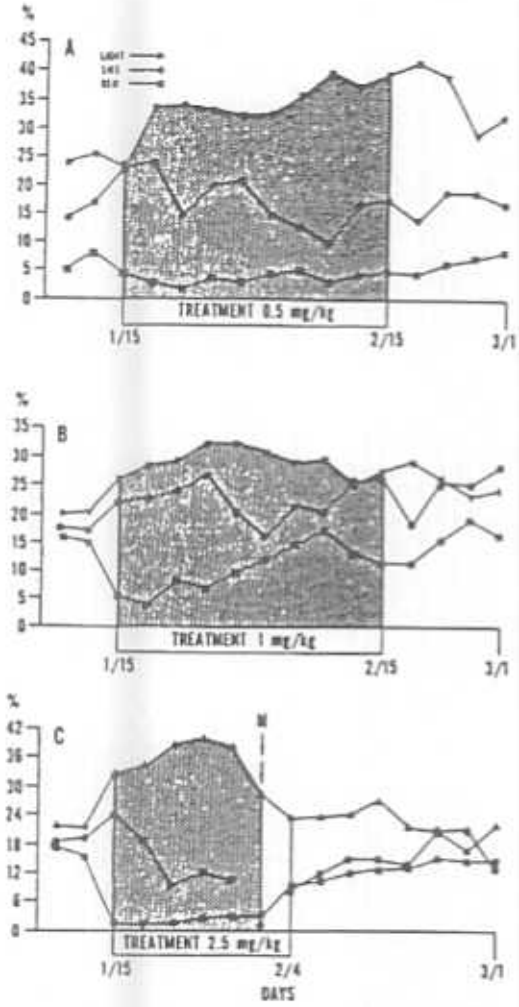

Fig. 3. Each vertical set of points indicates the mean percentage of sleep stage on one day; EEG's were recorded twice each week but drug was administered every day; MI indicates the administration of 1 mg/kg, (p.o.) of methysergide which blocked SWS and REM sleep.

In a 5-hr experiment, 9 cats received water one day and 1 mg/kg of fluoxetine on the next day. The percentage of SWS increased from 38.0 ± 3.85 (SE) to 59.52 ± 4.67, a difference significant at $P < 0.01$. Among the 9 cats, 69 periods of REM sleep with a median duration of 5.7 min occurred after control medication, and 35 periods with median duration of 6 min, after fluoxetine. Counting the number of PGO spikes, occurring during REM sleep periods that exceeded 3 min, did not reveal any obvious difference in density. Fluoxetine decreased the number of REM periods but did not affect the duration or the PGO density during REM sleep. The PGO spikes occurring in 3 cats during 3 min were counted, beginning 1 min after the onset of REM sleep periods of sufficient length. After control treatment, 125.9 ± 6.37 (SE) spikes occurred in 20 periods of REM sleep and, after 1 mg/kg of fluoxetine, 131.44 ± 4.55, during 9 periods.

Co-administration of fluoxetine and 5-HTP. One group of 6 cats previously used in these and other sleep experiments received a placebo oral dose of water at 8:30 a.m. on Tuesday and Wednesday on each of 3 weeks that were separated by 1 week without treatment. On Thursdays and Fridays, 2 cats received fluoxetine, 2 received 5-HTP and 2 received both medications according to a cross-over design. Recording sessions lasted 5 hr. On the first drug day, 10 mg/kg of 5-HTP was administered either alone or in combination with fluoxetine to 4 cats. All these cats vomited and the sleep data from that day were not included. It was then found that doses of 2.5 mg/kg or 5.0 mg/kg of 5-HTP caused vomiting but 1 mg/kg did not. For the remaining 5 treatment days, the dose of 5-HTP was 0.5 mg/kg orally. The dose of fluoxetine was 0.5 mg/kg orally.

An analysis of variance revealed significant differences only in the amount of REM sleep (Table 1). The decreased REM sleep in cats treated with fluoxetine alone was not significant at the 95% level (Duncan Multiple Range Test). However, the cats that received both fluoxetine and 5-HTP had significantly less REM sleep than controls or cats treated with 5-HTP alone. This joint action suggests that the change in REM sleep was indeed a consequence of increased 5-HT at serotonergic synapses.

Cerveau isolé. Electroencephalograms recorded from surface leads in normal cats vary in pattern. For several hours after transection of the brain stem at the ponto-mesencephalic junction, a single characteristic record predominates. The basic form consists

Table 1. Effect of 5-hydroxytryptophan and fluoxetine on the sleep of cats

	n	AWK	SWS	REM
Control	18	29.42 ± 6.78	36.52 ± 6.48	14.70 ± 5.53[a]
5-HTP	6	28.32 ± 4.28	38.25 ± 5.10	15.20 ± 5.21[a]
Fluoxetine	6	25.41 ± 14.98	48.29 ± 15.36	8.74 ± 5.08[a,b]
5-HTP + Fluoxetine	6	28.09 ± 10.10	44.24 ± 14.51	5.70 ± 3.19[b]

[a] All 6 cats received water by gavage on 2 consecutive days. The next 2 days, they received 5-HTP 0.5 mg/kg, fluoxetine 0.5 mg/kg or both 5-HTP and fluoxetine in random order. A week without treatment separated each trial.

[b] In preparing the results for analysis, a mean was computed for control days and treatment days for each cat each week. Thus, the data in the table are the means of the 2-day means which were computed. The letter superscripts (a,b) indicate the results of a Duncan Multiple Range Test at 0.05 level of probability. Values with the same letter are not different from each.

of 4–6 Hz waves interrupted periodically by spindles of 10–12 Hz activity of higher voltage. When decerebrate cats are kept alive for several days or weeks other wave forms will emerge (Jouvet, 1972). During the first few hours, however, the pattern of slow activity interrupted by sleep spindles usually continues without change. After intravenous injection of muscarinic cholinergic stimulants such as phyostigmine or arecoline, the EEG changes to one of low voltage high frequency. The threshold dose for desynchronization by arecoline of the EEG in the *cerveau isolé* cat varies between 2.5–50 μg/kg. Doses of atropine as small as 0.1 mg/kg, (i.v.), will cause a substantial increase in this dose and may block the effect entirely (Rathbun and Slater, 1963). The response is, therefore, a sensitive test for central anticholinergic activity of the muscarinic type.

Three of 4 cats, in which the brain was divided at the ponto-mesencephalic junction, showed well-defined slow wave activity with intermittent spindling in the surface EEG. In these 3 cats, doses of arecoline of 10 or 20 μg/kg (i.v.) converted the synchronized EEG to a desynchronized pattern. When these cats were treated with 1 and then 3 mg/kg of fluoxetine, (i.v.), the threshold dose of arecoline did not change.

Rat–Sleep Pattern

Four rats received various doses of fluoxetine during a series of range finding experiments. On the first two consecutive days they received water and on the next two, either water, or 2.5, 5 or 10 mg/kg of fluoxetine; EEG's were recorded for 7.5 hr. The consistent observation from these trials was a decreased amount of REM sleep in rats treated with 5 or 10 mg/kg of fluoxetine (Table 2). Although one of the 2 rats treated with 10 mg.kg was awake for most of the first drug day and had a 38% reduction of SWS on the second day, the other rat had increased SWS (17 and 16%) on the same two days. Rats with 2.5 mg/kg did not show a change in sleep pattern. Fluoxetine treatment did not increase SWS in these rats.

Table 2. Effect of fluoxetine on sleep pattern of rats

Dose (mg/kg)	n	Percentage of sleep state (7.5 hr) AWK	SWS	REM
0	4	45.8	45.6	8.61
0		47.7	44.1	7.67
0	2	43.6	52.1	4.4
2.5		55.1*	40.9	4.0
0	2	46.4	42.5	11.1
2.5		45.1	44.3	10.6
0	4	42.2	46.9	10.9
5		47.0	48.0	5.0*
0	2 × 2†	39.9	48.3	11.7
5		45.3	48.2	6.5*
0	2	48.6	43.4	8.0
10		67.8	30.8	1.5

* Over a period of 3 months, 4 rats received various doses of fluoxetine on 2 consecutive days that followed 2 days on which they had received water by gavage. For statistical analysis, it was judged necessary to divide the data into compatible sets. The first number of each pair is the mean of the observations on Tuesday and Wednesday and the second number, the mean for Thursday and Friday. Differences marked with an asterisk were significant by an analysis of variance.

† The same 2 rats run for 2 weeks.

DISCUSSION

Fluoxetine selectively blocks uptake of serotonin by isolated synaptosomes (Wong *et al.*, 1974). In the brain, re-uptake is a major factor in terminating the action of serotonin. Interference with this process should increase the amount of serotonin at synaptic clefts. The reduction of serotonin turnover in fluoxetine-treated rats provides biochemical evidence that this has occurred. The decreased firing rate of raphe neurones confirms this neurophysiologically (Clemens, Sawyer and Cerimele, 1977). Potentiation of ACTH secretion induced by 5-HTP adds a neuroendocrine parameter to indicate again that fluoxetine, by inhibiting neuronal re-uptake of 5-HT, enhances serotonergic mechanisms (Fuller, Snoddy and Molloy, 1976).

Fluoxetine is completely specific for blocking 5-HT uptake *in vivo* without affecting norepinephrine uptake at well-tolerated doses. For example, fluoxetine in rats (Fuller, Perry and Molloy, 1974) and mice (Fuller, Perry, Snoddy and Molloy, 1974) prevents the depletion of 5-HT by *p*-chloroamphetamine but does not affect norepinephrine depletion by 6-hydroxydopamine. This specificity is also confirmed by a simple unpublished blood pressure experiment in which fluoxetine had little effect on the pressor response to tyramine or norepinephrine whereas nisoxetine, like the tricyclic antidepressants, blocked the effect of tyramine and increased the pressor effect of norepinephrine. The administration of fluoxetine can be used as a tool for studying the consequences of increased 5-HT at synaptic clefts.

Tricyclic antidepressants which suppress REM sleep and increase SWS, are relatively non-specific inhibitors of monoamine uptake usually inhibiting NE uptake more than 5-HT. Nisoxetine is a NE uptake inhibitor chemically related to fluoxetine but without activity on 5-HT uptake at concentrations achieved after reasonable doses. Experiments with fluoxetine and nisoxetine should help in the understanding of how NE and 5-HT affect sleep. Nisoxetine, like the tricyclic antedepressant, and fluoxetine clearly inhibited REM sleep (Slater *et al.*, 1976).

Cats showed an unequivocal loss of REM sleep after receiving fluoxetine. The effect of a marginally effective dose of fluoxetine (0.5 mg/kg orally) was made statistically significant by the co-administration of a small non-emetic dose of 5-HTP (0.5 mg/kg). This demonstrates a serotonergic suppression of REM sleep and of the PGO spikes characteristic of this stage of sleep. Jalfre *et al.* (1974) suppressed PGO spikes with doses of 5-HTP in cats pretreated with *p*CPA. During the 24 hr following large, emetic doses

of 5-HTP or tryptophan. Ursin (1976) did not find a decrease in the time cats spent in stage REM sleep but she did report an increase in latency to REM sleep after both amino acids. These studies are difficult to interpret because of the vomiting, but they do seem to confirm the suppression of REM sleep and PGO spikes by 5-HT.

In the present study when cats were treated for several weeks with fluoxetine, REM sleep began to return and PGO spikes were seen during both wakefulness and during other stages of sleep. This emergence of REM sleep and PGO spikes in the presence of fluoxetine suggests that 5-HT modulates rather than controls the electroencephalographic signs. Cholinergic mechanisms are probably the final common pathway through which REM-related phenomenon are expressed (Sitaram, Mendelson, Wyatt and Gillin, 1977). Hobson and McCarley (1976) have suggested that this cholinergic process can be inhibited by either serotonergic or noradrenergic neurones. Since tricylic antidepressants (which interfere with monoamine uptake), nisoxetine (a relatively specific inhibitor of norepinephrine uptake chemically similar to fluoxetine) and fluoxetine itself (a specific inhibitor of 5-HT uptake), all decrease the amount of REM sleep, dual monoamine mechanisms for suppression of REM sleep seems an attractive hypothesis.

In some of the present experiments, fluoxetine increased the amount of SWS on the first day but not on later days. Light sleep, which in this laboratory refers to an EEG pattern of mixed slow activity (4–6 Hz), occasional spindles (8–12 Hz) and some (less than one-third) fast activity, was usually increased in cats. This stage marks the border between wakefulness and asleep, between conscious and unconscious. In this sense, the present data fit with Jouvet's (1972) suggestion that increases in 5-HT are concerned with the initiation of sleep and the present experiments fit the monoamine theory of sleep, but the suppression of REM sleep has been more striking than any increase in SWS.

During the course of these experiments two unexpected findings were encountered. The present authors are at a loss to explain why cats receiving fluoxetine for several days began to hiss and growl or why this behaviour decreased with continued treatment. The subjects who received fluoxetine in a Phase I clinical trial (Lemberger, unpublished data) have not described any change in mood nor have observers noted any change in affect.

The mydriasis that occurred in cats treated with fluoxetine was also puzzling. There seems to be no neuroanatomical basis for mydriasis as a consequence of activation of serotonergic pathways. Pupillary dilation often is a sign of anticholinergic activity. This seemed an unlikely explanation since the EEG pattern of high-voltage slow-wave activity that occurs in cats treated with atropine or scopolamine was not seen. Fluoxetine did not affect the threshold dose of arecoline that induced EEG desynchronization in the *cerveau isolé* cat. Since small doses of atropine sulphate (0.1 mg/kg) either elevate the threshold dose or completely block arecoline-induced desynchronization, it was concluded that fluoxetine does not act as a central anticholinergic blocking drug. Unpublished data of Dr James Aiken on several isolated smooth muscle systems indicate that fluoxetine is not a cholinergic blocking agent peripherally. If fluoxetine suppresses REM sleep and PGO spikes through serotonergic inhibition of a cholinergic pathway, the mydriasis may also be a consequence of an analogous mechanism.

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C O N F I D E N T I A L

Minutes No. 79-1
Meeting of January 10, 1979
Clinical Research Plans Committee

Members Present - Dr. C. L. Bendush
Dr. G. E. Gutowski
Dr. I. S. Johnson
Dr. L. Lemberger
Dr. J. H. Marsden
Dr. F. B. Peck, Jr.
Dr. W. I. H. Shedden

Present For One
or More Items - Mrs. M. M. Arnett
Dr. C. R. Christensen
Mr. H. F. Daniels
Dr. P. V. Demarco
Mr. G. D. Draper
Mr. A. J. Ferrara
Dr. R. B. Kammer
Dr. W. H. Mikulaschek
Dr. C. E. Redman
Dr. P. Stark

Other Recipients - Dr. A. E. Amundson
Dr. H. A. Barnett
Dr. R. A. P. Burt
Mr. W. G. Davis, Jr.
Mr. J. W. Eastes
Dr. E. H. Flynn
Dr. R. H. Furman
Dr. W. W. Hargrove
Dr. E. B. Herr, Jr.
Dr. G. V. Kaiser
Dr. G. F. Kiplinger (Erl Wood)
Dr. L. R. Levine
Dr. D. M. Morton
Dr. H. Murao (Kobe)
Dr. C. W. Pettinga
Dr. A. Pohland
Mr. E. L. Step
Dr. J. G. Whitney
Dr. R. H. Williams

G. E. Gutowski
2061

gw

EXHIBIT
SLATER 6

Minutes No. 79-1
Meeting of January 10, 1979
Clinical Research Plans Committee

Fluoxetine

Dr. I. H. Slater summarized the current clinical experience with fluoxetine before outlining the Plan A proposal.

Phase I clinical studies have established that fluoxetine is tolerated at single doses up to 90 mg (the highest given). The desmethyl metabolite, which possesses a pharmacologic profile similar to that of fluoxetine, has a very long half-life and accounts for the long duration of action of fluoxetine.

Phase II clinical trials in mental depression are underway at four centers. So far, patients have been treated with 30 mg daily for 7 days followed by 20 mg daily for 3 weeks or more. Approximately 20 patients have been treated according to this regimen, and most have failed to show improvement. One patient experienced a dramatic recovery and was continued on fluoxetine for an additional period and then discharged from the hospital. A few other patients have shown lesser degrees of response. No consistent side effects other than nausea, to which tolerance seems to develop, have been seen at these doses. Single instances of frank paranoia, a convulsion, a palpable thyroid, and a case of corneal pigmentation (which later subsided) were also reported in those receiving fluoxetine. Some data on 5-hydroxyindolacetic acid levels in cerebrospinal fluid are available, and these data suggest that the dose may be too low to inhibit serotonin uptake in brain. Higher doses will be examined.

One study in dystonia musculorum deformans has started. Two patients were treated with doses as high as 70 mg daily. At the top dose in both patients, sleepiness and lethargy were observed. One patient treated at 60 mg of fluoxetine daily responded well and is being continued on treatment.

Clinical trial materials have been shipped for a study in postanoxic intention myoclonus, but this study has not yet started. A protocol has been received for a study in patients with narcolepsy/cataplexy. Another investigator has asked to study fluoxetine in patients with chronic pain, and this study will probably be done if a satisfactory protocol can be worked out.

If clinical data are accumulated as anticipated, an NDA decision (mental depression) could be reached by December, 1979.

Dr. J. H. Marsden felt that safety information was insufficient at this time to justify undertaking a study in obese patients (which may be mentally disturbed) at this time. CRPC agreed to postpone the proposed obesity study until more patient experience had been gained.

With this one exception, CRPC approved Plan A as proposed (estimated cost $1 million)

Dr. L. Lemberger provided a partial proposal for Plan C. This was not circulated with the agenda. CRPC accepted this partial proposal with the stipulation that this will be expanded as more information from Plan A develops.

CRPC also directed that the proposed package insert section be deleted from Plan A.

LILLY RESEARCH LABORATORIES

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June 14, 1979

4

Louis F. Fabre, Jr., M.D., Ph.D.
Medical Director
Research Testing Inc.
5503 Crawford Street
Houston, Texas 77004

Dear Lou:

When we talked in Florida a couple of weeks ago you indicated that the population of depressed patients available at The Houston Clinic was committed to other studies. We discussed the possibility of using people in Austin, and I asked that the normal laboratory values for that clinic be sent to me so that I could amend the protocol. I have not received this.

This study was to have been a prelude to a 40 patient double blind trial comparing fluoxetine with either placebo or some other agent. I know that you are involved in several clinical trials, and have been wondering if we are being realistic in our projections. We originally talked of completing the 5 patient pilot in time for the NCDEU meeting and starting the double blind shortly thereafter. It really seems to me that you are not going to be in a position to get on with the double blind phase of fluoxetine in the near future and probably are not justified in taking time to complete the 5 patient pilot study.

I am inclined to accept what seems inevitable and suggest that you abandon the fluoxetine trial now without further effort. You did complete one fifth of the agreement.

Would you be willing to return the medication, the forms and four fifths of the grant money. I make this suggestion without bitterness or hard feelings. My aim is to complete 3 or 4 double blind studies that will indicate whether fluoxetine is an active antidepressant. I should be collecting data toward the goal and need the help of investigators ready to go now. If you are willing to drop out, I hope I can find other investigators who are not as busy as you are now.

Sincerely,

I. H. Slater, M.D.
Research Advisor

IHS:dk

bcc: Dr. H. A. Barnett
Dr. C. N. Christensen

Dr. R. W. Fuller
Dr. L. Lemberger
Dr. I. H. Slater

July 23, 1979

Food and Drug Administration
Bureau of Drugs, HFD 120
Attention: Document Control Room 108-34
5600 Fishers Lane
Rockville, Maryland 20857

Gentlemen:

Re: IND 12274 - Compound LY110140 - Fluoxetine Hydrochloride (Psychotropic Agent)

IND Protocol No. 13, which was submitted August 7, 1978, outlined a study by [redacted] in patients with primary major depressive disorders. The dosage regimen was revised in accordance with our letter of December 11, 1978. It is again being revised, as indicated below.

During the first week of the study, each patient will be given one placebo capsule each morning. If at the end of the week the Hamilton score shows a decrease of 20% or falls below 20, placebo will be continued for another week. If the Hamilton score at the end of the second week again shows a 20% decrease or falls below 20, the patient will not continue in the study. This revision necessitates a change in Section 2.f.2. regarding severity of depression from "at least 18" to "at least 20."

The initial dose of fluoxetine will be one 20-mg capsule given in the morning of the first day. On days 2 and 3, a 20-mg capsule will be given both in the morning and at noon. On day 4, two 20-mg capsules will be given in the morning and one 20-mg capsule at noon. At the investigator's discretion, this dose may be continued for five weeks. It may be reduced if clinically indicated, and, in instances where the dose is reduced because of agitation, diazepam may be administered as needed.

The protocol was amended March 16, 1979, to include patients with severe or disabling compulsive or obsessive

EXHIBIT
SLATER 8

Pz 221 2274

symptoms. If such patients are enrolled in the future, the dosage regimen outlined above will be used.

The administration of chloral hydrate for sleep will not be restricted to only once a week as indicated in the protocol.

Very truly yours,

ELI LILLY AND COMPANY

H. A. Barnett, M.D.
Medical Advisor
Regulatory Affairs

HAB:bs

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August 3, 1979

Lawrence Gosenfeld, D.O.
Brentwood VA Hospital
Wilshire and Sawtelle Blvd.
Los Angeles, CA 90073

Dear Dr. Gosenfeld:

The enclosed protocol describes a double blind parallel study - fluoxetine against imipramine. By using bottles labeled Morning Doses and Bedtime Dose we avoid giving patients a bunch of envelopes. I am submitting this draft to our Protocol Review Committee with a reasonable hope that they will not ask for major changes. I am discussing with our management methods by which we could extend the study to cover a period of 3-6 months. Please let me have your comments and suggestions.

If you think it appropriate, you may want to forward the protocol for approval by your Institutional Review Committee.

Sincerely,

I. H. Slater, M.D.
Research Advisor

IHS:dk

Attachment

EXHIBIT
SLATER 12

Part of Slater Ex 12

IND 12274
IND PROTOCOL NUMBER 14

A CONTROLLED STUDY OF THE TREATMENT
OF MAJOR DEPRESSIVE DISORDERS WITH FLUOXETINE HCl (110140)

Objectives: To evaluate the anti-depressive efficacy and safety of fluoxetine in outpatients with major depressive disorders.

1. Investigator:

Lawrence Gosenfeld, D.O.
Brentwood Veterans Administration Hospital
Wilshire and Sawtelle Blvd.
Los Angeles, CA 90073

2. Study Design:

a. This is a randomized double blind parallel study. The study group will consist of 40 patients with a major depressive disorder being treated as inpatients at Brentwood Veterans Administration Hospital Medical Center.

3. Control Agents

Imipramine HCl

4. Drug Names and Codes

CT - 4468	Fluoxetine Capsules, 20 mg
CT - 4469	Placebo Capsules
CT -	Imipramine capsules, 25 mg
	Imipramine capsules, 50 mg

5. Selection of Treatment Groups:

a. Criteria for Inclusion

1. Outpatients
2. Either Sex - See 5.b.1.
3. 21 - 65 years of age
4. Participation will be voluntary. The nature of the study will be fully explained to the patient and all questions regarding the study answered fully. Upon approval, the informed consent form will be signed and retained by the investigator. A blank copy of the consent form to be used will be provided to the sponsor. Patients should be warned that excessive depression may occur from concurrent use of alcohol, barbiturates or other depressant drugs, about possible sedation and cautioned about driving an automobile.

5. Hamilton Psychiatric Rating Scale for Depression (HAMD) score of at least 20.
6. Raskin Depression Scale score to exceed Covi Anxiety Scale score.
7. Each subject will have an educational level and degree of understanding so that he can communicate with doctor and nurse intelligently, read, understand and complete the symptom check lists (Zung SDS and Patient's Global Impressions).
8. Expected to attend OPD reliably at weekly intervals.

b. Criteria for Exclusion (include all accepted contraindications to the use of imipramine since half of the patients will receive that drug)

1. Women of childbearing potential
2. Serious suicidal risk
3. Glaucoma
4. History of urinary retention
5. Cardiovascular disease especially patients with conduction defects and hypertensive patients being treated with guanethidine, clonidine or methyldopa
6. Significant other medical illnesses including hepatic, renal, respiratory, or hematological disease
7. Organic brain disease or history of seizures
8. Schizophrenia and other psychotic states likely to be aggravated by imipramine
9. Hyperthyroidism
10. History of severe allergies or multiple adverse drug reactions
11. History of drug abuse including alcohol
12. Inability to understand and complete self-rating scales
13. Concurrent administration of other psychoactive drugs including lithium
14. Use of monoamine oxidase inhibitors immediately before study
15. Improvement during washout period, e.g., Hamilton Depression score of more than 20% or below 20
16. Family History of "Failure to Thrive" or phospholipidoses

6. Study Procedures

a. Diagnostic Criteria

1. Research Diagnostic Criteria will be used (Appendix A). All patients will satisfy criteria for major depressive disorder and will be further classified if possible, as:
   a. Primary Major Depressive Disorder
   b. Recurrent Unipolar Major Depressive Disorder

c. Psychotic Major Depressive Disorder
d. Incapacitating Major Depressive Disorder
e. Endogenous Major Depressive Disorder
f. Agitated Major Depressive Disorder
g. Retarded Major Depressive Disorder

2. Severity

All patients will be at least moderately depressed with Hamilton Depression score ratings of at least 20 at the time of starting active medication and will have had no more than 20% decrease in Hamilton Depression score during the placebo week.

b. Clinical Examinations

1. Pre-therapy

a. Psychiatric evaluations will be performed at the time of admission to the study. This will include completion of the following:
   1. Modified Adult Personal Data Inventory
   2. Prior medication record
   3. Record of pre-treatment symptoms
   4. Hamilton Psychiatric Rating Scale for Depression
   5. Clinical Global Impression Scale
   6. Zung SDS Scale
   7. Raskin - Covi Scale

b. Physical examination and medical history

c. Ophthalmologic Examination

2. During therapy

a. At least weekly during the study, the patient will be rated by the following:
   1. Hamilton Psychiatric Rating Scale for Depression
   2. Raskin - Covi Scale
   3. Symptoms, Signs and Illness Form
   4. Clinical Global Impression scale
   5. Zung SDS Scale - at approximately the same time of day.
   6. Patient Global Impressions
   7. Other rating scales may be used in addition to these, but will not be submitted to the sponsor.

b. Pulse and blood pressure will be obtained in sitting positions, during each visit.

c. Weight will be recorded weekly.

If significant improvement occurs, e.g., Hamilton Depression Score decrease 20% or falls below 20, the patient will receive placebo capsules during the second week. A bottle labeled 1b (for blank) containing placebo will be supplied with each set. At the end of a week during which a patient receives medication 1b (placebo) an unnumbered form should be used and labeled 2b. The bottle labeled 2a (for active) will be given to patients to be entered into the fluoxetine-imipramine study. If a patient improved while taking medication from bottle 1b, e.g., Hamilton score decreases 20% or falls below 20, that patient will not be entered into the fluoxetine-placebo comparison study. Extra sets of bottles labeled 1a and 1b and sets of report forms will be supplied so that these patients can be replaced. A patient number will be assigned only to patients who will receive study drug, i.e., the non-responders to placebo.

3) Study Period 2.

a) Patients included in the study will receive 2 bottles of medication, one labeled Morning Doses, the other Bedtime Dose. The patient will be given written instruction on how to take medication. Schedule of number of capsules to be taken by patient:

	Time of Day		
	AM	Noon	H.S.
Day 1	1		1
Day 2, 3	1	1	1
Day 4-7	2	1	1
Day 8-11	2	0, 1 or 2	1
Day 12-14	2	0, 1 or 2	2
Week 3	2	0, 1 or 2	2-4

b) The capsules for AM and noon dose will be in bottle labeled Morning Doses. The other bottle will be labeled Bedtime Dose.

c) Fluoxetine--Morning Doses will contain capsules fluoxetine 20 mg and Bedtime Dose will contain capsules placebo.

d) Imipramine--Morning Doses will contain capsules imipramine 25 mg and Bedtime Dose will contain capsules imipramine 50 mg.

e) This schedule of capsule taking will result in the following doses:

	Fluoxetine	Imipramine
Day 1	20	75
Day 2, 3	40	100
Day 4-7	60	125
Day 8-11	40-80	100-150
Day 12-14	40-80	150-200
Week 3	40-80	150-300

f) At the investigator's discretion dose can be adjusted by manipulating the noon dose first, then the morning dose or bedtime dose.

4) a) If in the investigator's opinion, it is necessary, chloral hydrate 0.5 g or 1.0 g may be given for sleep. Administration of chloral hydrate will be recorded in the case report form.

b) If a patient complains of agitation, the dose of study drug should be reduced and the patient may receive diazepam at the investigator's discretion. This should be entered in the case report form.

7. Evaluability Criteria

Determination of clinical effectiveness will be based on the overall evaluation of changes in the scores of observer and self-rating scales (see section 6b for specific scales to be used). When possible, all ratings for a patient will be done by the same individual who will be experienced in the use of the scales being used. If ratings for the same patient are done by different persons, evidence of inter-rater reliability will be furnished to the sponsor.

8. Monitoring Adverse Drug Reaction

a. All data from SMA 12/60 and hematological examinations will be reported on the form supplied. Values outside the normal range for the laboratory will be circled. When clinically significant changes that the investigator does not regard as serious and requiring immediate notification of the sponsor occur, the test or tests will be repeated at the patient's next visit.

b. Serious reactions are to be reported to the sponsor immediately by telephone with follow-up written report.

c. A Symptoms, Signs and Illness Form wil be completed at end of each week to elicit behavioral and subjective side effects.

d. Range of normal laboratory values are to be furnished to the sponsor.

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9. Criteria for Discontinuing Drug

   a. Any patient who develops a serious adverse effect.

   b. Patients may be removed from the study upon their own request.

   c. Upon termination the investigator may, at his discretion, cautiously institute other forms of treatment, excluding for at least 2 weeks MAOI.

   d. Drug may be discontinued if serious risk of suicide develops.

10. Estimated Duration of Study

    6 months

11. Report Forms

    Every patient admitted to the study who receives study medication must have a Lilly case report submitted. A packet of report forms for the initial examination, weekly progress examinations and the final report will be supplied for each patient.

    Patients in an outpatient study may want to visit with their physician, the investigator, at times other than the prearranged weekly visit. Extra unnumbered report forms will be supplied. The portion of the form relevant to the patient's visit should be completed but the data will not be included in the overall statistical evaluation unless medication is stopped immediately as a consequence of this visit, in which case the final report form should be filed.

12. Statistical Analysis Plans

    The various rating scales will serve as the data base for evaluation of results. Data will be analyzed by appropriate statistical methods by Eli Lilly and Company.

13. Reports of Sponsor to Investigator

    a. Sponsor will notify each investigator whenever a serious adverse reaction report is received.

    b. Update of the clinical brochure will be supplied periodically.

    c. The investigator will be provided any results of statistical analysis of his data made by Eli Lilly. In addition, the investigator will be kept informed of results received from him whether they are favorable or unfavorable.

FLOW SHEET FOR FLUOXETINE STUDY

DEFINITIONS: Study drug means fluoxetine or the medication with which it is being compared.

Significant Improvement (SI) - HAMD decreases 25% or falls below 20 -- in contrast to -
No Change (NC) - HAMD is at least 20 and has not decreased 25%

WEEK 1	WEEK 2	WEEK 3	WEEK 4

All patients receive placebo
 	
Use Visit 2 forms at end of this week
	If (NC) - Study Drug (2a) use Visit 3 forms at end of week
	
	If (SI) - Placebo (1b) use extra forms and number week (2b)
		Continue Study Drug for total period of 5 weeks
		
		If (NC) - Study Drug (2a) use Visit 3 forms at end of week
		
		If (SI) - Drop from study and replace with new patient. Do not submit forms to sponsor.
			Continue study drug for total period of 5 weeks

08/03/79

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY • INDIANAPOLIS, INDIANA 46206 • TELEPHONE 317 261-2000

August 15, 1979

[redacted]

Dear [redacted]

As you know, we have two investigators who have been treating depressed outpatients with fluoxetine using 60 mg/day during the first week and usually 40 mg/day for four additional weeks. A third investigator using the same schedule of doses is treating recently admitted inpatients. All three of these investigators have reported lifting of the depression during the first week in some of their patients. Some patients have become agitated while a few complain of excessive sleepiness.

I am anxious to continue to collect data on the use of fluoxetine as a treatment for major depressive disorders. It has been some time since we received a case report from your unit. Is there any hope that you can continue the studies you started some time ago?

Sincerely,

I. H. Slater, M.D.
Research Advisor

IHS:dk

LILLY RESEARCH LABORATORIES

DIVISION OF ELI LILLY AND COMPANY · INDIANAPOLIS, INDIANA 46206 · TELEPHONE (317) 636-2211

September 6, 1979

[redacted]

Dear [redacted]

The toxicology experiment with fluoxetine, L-5HTP and carbidopa has started. Final results, including pathology, should be available by year end, and we can then file an addendum to the protocol. Have you done anything with the revised protocol that I sent on August 16?

It has been some time since I have had any word about your fluoxetine studies. I do not know whether [redacted] relapsed while on placebo, whether [redacted] improved, whether you have added new patients or even how the marrow culture experiment [redacted] turned out.

The pharmaceutical industry and clinical research are both regulated industries. The FDA is charged with the responsibility of overseeing both activities and we, both you and I, must make a reasonable effort to comply with regulations. You and Dr. Sherman filed with the FDA a Research Protocol that described an experiment to test whether fluoxetine would benefit patients with intention myoclonus. That protocol specified a mechanism for you to supply data to us. Failure to comply with the procedures described in the protocol places us both in jeopardy. There is nothing I need less at this stage of my life than an investigation by the FDA; I will be retiring as of December 31, this year.

For some time I have been under pressure from Regulatory Affairs in the company to do something about your study. My colleagues there have urged me to terminate your trial since they believe that your failure to supply us with data is not helping with the clinical evaluation of fluoxetine and may sooner or later get Lilly into trouble with the FDA. Can you make some effort to comply with the protocol so that the study can continue?

I have supported your attempt to help patients with intention myoclonus, but I will not be here next year and I would guess that if you send no data, Lilly will send no drug.

Sincerely,

I. H. Slater, M.D.
Research Advisor

IHS:dk

cc: Dr. H. A. Barnett
Regulatory Affairs

EXHIBIT
SLATER 4

Pz 520 603

[redacted]

September 19, 1979

I.H. Slater, M.D.
Research Advisor
Lilly Research Laboratories
Division of Eli Lilly and Company
Indianapolis, Ind. 46206

Dear Dr. Slater:

The protocol which you sent me on August 16 looks all right with the exception that you had mentioned that the ophthamalogical exam could be carried out by myself or [redacted] in the office and include just the external exam and funduscopic.

As you probably have realized, the money that was initially given to me by Lilly for this study is not adequate and in fact recently the study has been carried out with the funds I have been able to raise. I know this is standard procedure with orphan diseases as I have encountered the same problems with other drug companies and myoclonus, since it is an unprofitable disorder and of lesser interest to the pharmaceutical industry. Unfortunately, this affects the number of lab tests, clinic visits and other procedures which should be carried out in a well controlled clinical study. I had mentioned this to you a number of months ago and you thought you could be of some assistance in obtaining a similar degree of funding as for a fluoxetine study in mental depression.

I believe the threats in your last letter that fluoxetine may not be made available to my patients with myoclonus is unfair since they should be entitled to the same therapeutic advantage of modern medical science as patients with more profitable diseases. Therefore, if Lilly is unable to finance the continuation of this study, I will attempt to raise the money myself, as best I can, in order that we may continue to study the therapeutic use of fluoxetine in patients with myoclonus.

In response to your letter of September 6, 1979, I am sorry that you thought that I have been purposely unresponsive to your letters. As you know, I was away on vacation during much of August and did

EXHIBIT
SLATER 5

I.H. Slater, M.D.

not arrive back to work until after Labor Day. There is little to report as no patient of mine has taken any fluoxetine during the last 2 months. The last white cell count on the patient with leukopenia was 3900 and weekly white counts since hospitalization have been around this level. The bone marrow culture from [redacted] revealed a low normal growth with one colony and 2 clusters. There was inadequate growth to evaluate the effect of adding fluoxetine and furadantin in vitro.

Thank you for the information from chemical abstracts and the update on your animal toxicology with 5HTP. I will be most interested in further progress reports on this.

Congratulations on your pending retirement.

Sincerely,

[redacted]

November 21, 1989

Mr. Dan G. Russell
cc: Dr. I. H. Slater

Re: [redacted]

I recently visited with [redacted], [redacted] outpatient research nurse, concerning their fluoxetine study in outpatients. It was learned that they had enrolled four patients, however two of these patients never returned after the first visit. One other patient completed seven visits but had only minimal improvement and experienced excessive stimulation as a side effect. Another patient discontinued the study at visit three because of lack of efficacy. The doctor had also indicated that extreme agitation was a side effect in this patient.

It was my impression from reviewing the case reports that they were very sloppily filled out and very incomplete.

Based on the slowness with which this study has progressed, this would appear to be a last minute effort to enroll an additional five patients in order to obtain full payment. It is my impression that this study will never be completed satisfactorily.

Mr. T. H. Bratten, Jr.
Clinical Research Coordinator

THB;djr

#4

CONFIDENTIAL

Minutes No. 79-8
Meeting of November 28, 1979
CLINICAL RESEARCH PLANS COMMITTEE

Members Present

Dr. C. L. Bendush
Dr. G. E. Gutowski
Dr. L. Lemberger
Dr. J. H. Marsden
Dr. F. B. Peck, Jr.
Dr. W.I.H. Shedden

Present for One or More Items

Mrs. M. M. Arnett
Dr. C. N. Christensen
Mr. H. P. Daniels
Mr. A. J. Ferrara
Dr. K. W. Fuller
Dr. D. P. Henry
Dr. K. S. Ishael
Dr. R. J. Kraay
Dr. C. E. Redman
Dr. T. R. Slater
Dr. P. Stark

Other Recipients

Dr. M. E. Amundsen
Dr. R. A. P. Burt
Mr. W. S. Davis, Jr.
Mr. J. W. Eastes
Dr. E. H. Flynn
Dr. R. H. Furman
Dr. W. R. Hargrove
Dr. E. B. Kerr, Jr.
Dr. I. S. Johnson
Dr. G. F. Kipfinger (Erl Wood)
Dr. O. M. Morton
Dr. H. Marao (Kobe)
Dr. C. W. Pettinga
Dr. A. Pohland
Dr. E. L. Step
Dr. J. G. Whitney
Dr. R. H. Williams

Committee discussion of this meeting has been summarized on the attached sheets.

Also attached are the following plans approved during this meeting:

[redacted]

Fluoxetine [LY110140] - Revised Plan A

[redacted]

Generally, only members of CRPC receive copies of proposed and approved plans. If you wish to review copies of approved plans, please contact me.

EXHIBIT
SLATER 7

G. E. Gutowski
2061

hw

Attachments

Minutes No. 79-8
Meeting of November 28, 1979
CLINICAL RESEARCH PLANS COMMITTEE

Fluoxetine [LY110140] - Revised Plan A

Dr. I. H. Slater reviewed the status of fluoxetine clinical trials as a background to proposed revisions in the original (approved) Plan A. The primary thrust of clinical studies continues to be directed to the treatment of depression. Trials in essential hypertension, pain, obesity, and narcolepsy will continue their deferred status.

Open-label studies in the treatment of depression continue, with somewhat improved responses when dose levels have been increased. Pilot experiments for double-blind trials are in progress. Comparator drugs are imipramine and amitriptyline. A question was raised as to the need for two positive control drugs. While the FDA likely would require comparative data only against one control, the other was added for the sake of in-house comfort.

Dr. Slater indicated that he had hoped to have sufficient antidepressant data to reach a NDA decision within six months. Responding to a point which questioned the necessity of additional dose-ranging studies (Dr. Ban), CRPC decided not to alter plans at this time, but retained the option of rejecting the grant request when finally submitted.

Dr. W.L.H. Shedden summarized CRPC's position on fluoxetine studies as follows:

1. An effective dose appears to have been established through double-blind studies.

2. The goal now is to consolidate fluoxetine's position first in depression, proceeding as rapidly as possible. This will necessitate maintaining close contacts with investigators.

CRPC approved the modifications proposed for fluoxetine's Plan A, subject to the provisions noted above.

#4

CORRECTED COPY

December 24, 1979

I. H. Slater, M.D.
Lilly Research Laboratories
Division of Eli Lilly and Company
Indianapolis, Indiana 46206

Dear Dr. Slater:

Enclosed find the data on the last patient treated on the fluoxetine study. As the records indicate, this patient experienced psychotic worsening on active drug which improved somewhat after it was discontinued.

In review of the eleven patients treated with fluoxetine we were not impressed with the antidepressant activity of the drug. There were two patients that entered remission on the study but in both cases we question whether this was drug related. In the others there was either no change or clinical worsening. Side effects were minimal on any of the doseage regimens.

I have received the final payment in support of the study. It has been a pleasure collaborating with you.

Sincerely,

Professor of Psychiatry

[redacted]

Enclosure/

EXHIBIT
SLATER 11