

CERTIFIED MAIL, RETURN RECEIPT REQUESTED

March 4, 2000

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Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
HFA-305, Room 1061
5630 Fishers Lane
Rockville, MD 20852

Re: Docket No. 99P-4053/CP 1
Citizen's Petition: Proposed Amendment to Classification and Product Labeling for the
Sympathomimetic amine Phentermine

Dear Sir or Madam:

We would like to respond to the comments by Medeva Pharmaceuticals, Inc. (Medeva) through its Vice President, Terrance C. Coyne, M.D., and its attorneys (Richards & O'Neil, LLP; David Cohen, Esq.) to our above-labeled Citizen's Petition.

We would also like to provide you with additional, recently obtained data that confirm the ability of a single low dose of phentermine (15 mg, p.o.) to inhibit platelet monoamine oxidase (MAO) activity, thereby raising platelet serotonin levels in people. Twenty-seven adult female subjects provided blood basally and then again two hours after taking a single oral dose (15 mg) of phentermine. As before, platelet serotonin exhibited highly significant increases in median ($p < 0.0005$) and mean ($p < 0.0007$) levels; the percentage increases were both significant at the $p < 0.001$ and $p < 0.0005$ levels, respectively. This is not an ambiguous finding. These data are being prepared for publication. With our previous publication the number of subjects tested is now forty-three.

Response to Medeva Comments:

In brief, our data do fully support the claims made in our petition. Our references to Dr. Rothman's retracted editorial are neither misleading nor irrelevant. Our petition in no way contradicts existing labeling regulations. Phentermine is not adequately labeled at present concerning all of the serotonin drugs with which it can react. Finally, there is an abundant chemical foundation supporting labeling as a MAO inhibitor (MAOI).

1. Measuring Human MAO Inhibition

We are aware of no examples of drugs inhibiting MAO in laboratory animals but not in humans. Can Dr. Coyne provide such evidence?

It is not possible to perform an ex vivo experiment on a reversible MAOI, like phentermine, in human platelets, because the inhibitor washes off the enzyme, and is highly diluted, in the course of the enzyme assay. Precisely for this reason, we have measured increases in platelet

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serotonin levels, the integral of MAO inhibition, instead of doing the *ex vivo* study that Dr. Coyne proposed. If one wanted to design an experiment that would most likely fail to demonstrate an MAO inhibitory effect with phentermine, then the type suggested by Dr. Coyne would be ideal.

2. Human platelets do metabolize serotonin

This finding has been well established for decades. The finding reflects the fact that, in human platelets, serotonin is a substrate for MAO-B (see Donnelly, CH, Murphy, DL Substrate- and inhibitor-related characteristics of human platelet monoamine oxidase. *BIOCHEM PHARMACOL* 26:853-858, 1977.

3. Potency of Phentermine

Phentermine clearly is not as potent as the typical MAOI's used clinically (e.g., tranylcypamine, phenelzine). However, it is nearly as potent as several drugs (e.g., iproniazid, moclobemide) that were designed to treat clinical depression by inhibiting MAO.

Medeva implies that reversible MAOI's like phentermine or moclobemide increase plasma serotonin and decrease levels of the deaminated metabolite 5-HIAA. Is Dr. Coyne aware of any evidence that moclobemide produces these effects? We are not.

4. Validity of Findings

It should be noted that our data and interpretation were reviewed and accepted by three objective, anonymous reviewers for the publication in the *Lancet*, and two objective, anonymous reviewers for the *Biochemical Pharmacology* publication. Their conclusions differ from those of Medeva's Vice President.

5. Dr. Rothman's Editorial

We are attaching a full set of documents relating to Dr. Rothman's retraction of his "Editorial". As you will note, both he and *Synapse's* editor published apologies for failing to inform their readers of Dr. Rothman's conflicts of interest and his defamatory statement. They also provided a cash settlement to the organization (The Center for Brain Science and Metabolism Charitable Trust) that supported our work. We believe that Dr. Rothman's failure to articulate his ownership of weight-loss clinics, many of which administer phentermine to their patients, renders his publications on phentermine suspect at best.

6. Labeling Regulations

The label for phentermine does not address its potentially dangerous use, as a MAOI, with numerous other drugs (e.g., L-Dopa, St. John's Wort, 5-hydroxytryptophan).

7. Phentermine as MAO Inhibitor

Reversible MAOI's like phentermine and moclobemide do not interact clinically with the tyramine in aged cheeses and other foods. This is one of their advantages over the more potent irreversible MAOI's used to treat depression.

Phentermine, an amine, most likely compartmentalizes in the body, concentrating within certain tissues, cells, and organelles. Therefore, plasma concentrations of phentermine would not be expected to provide a good indication of concentrations at its sites of action (MAO inhibition in nerve tissue; dopamine release from such tissue).

Response to comments from Richards & O'Neil, attorneys for Medeva

1. Interneuron

The companies that previously marketed the fenfluramines, Wyeth-Ayerst and Interneuron Pharmaceuticals, Inc. have stated repeatedly in corporate documents that they do not intend to ever market these compounds again. This is in part due to their short patent lives, and in part due to the continuing litigation concerning possible toxic effects.

Dr. Richard Wurtman has had no association whatsoever with Interneuron Pharmaceuticals since having resigned as a Director and Scientific Advisor on July 28, 1999.

2. The Center for Brain Sciences and Metabolism Charitable Trust

The Center for Brain Sciences and Metabolism Charitable Trust, founded in October 1997, has, in its articles of incorporation, a specific mandate to study issues related to nutrition and the brain. This mission includes, for example, research on drugs like phentermine, which acts on the brain to modify eating behaviors. Why then should it be unusual for the Center to support research on phentermine's exact effects on the brain? Dr. Maher, formerly a trustee for the Center, has been invited to serve as an expert with the MultiDistrict Litigation proceedings precisely because he is an expert in this field.

3. Correspondence and Meetings with the FDA

While Mr. Cohen describes our interactions with the FDA as "lobbying", we believe that most scientists and citizens would interpret it as providing an important regulatory agency with new information it needs in order to make informed public policy.

4. Dr. Mehendale's Study

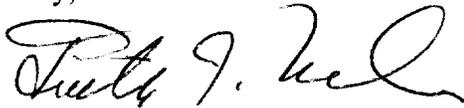
Dr. Mehendale's earlier publication underwent peer-review. We expect that the reviewers will continue to stand behind the publication, even with the passage of time.

5. Dr. Wurtman's Association with Phentermine

Finally, Dr. Wurtman has had no association with any lawsuit regarding phentermine or the fenfluramines. Dr. Wurtman's only connection with these drugs has been the recent notice from a law firm (Sheller, Ludwig & Badey, P.C.) representing a phentermine manufacturer that he may be deposed.

We appreciate this opportunity to respond to Medeva's comments to our Citizen's Petition. We believe that our respondent points are further evidence of scientific validation for this petition and for an affirmative decision by the FDA in this matter.

Sincerely,



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SETTLEMENT AND RELEASE AGREEMENT

Agreement dated as of the 2nd day of June, 1999, by and between Wiley-Liss, Inc., a subsidiary of John Wiley & Sons, Inc. ("Wiley"), Dr. Richard Rothman, Dr. John Johnson, Dr. Richard Wurtman, Dr. Ismael Ulus, and Dr. Timothy Maher, individuals.

WHEREAS Wiley is the publisher of, and owner of all rights in and to, a proprietary Journal named "Synapse"; and

WHEREAS Dr. Johnson is the Editor-in-Chief of Synapse; and

WHEREAS Synapse published a Letter to the Editor in its May 1999 issue written by Dr. Rothman (hereinafter the "Letter", copy attached as Exhibit A); and

WHEREAS Drs. Maher, Ulus, and Wurtman have raised certain allegations concerning the Letter; and

WHEREAS the Parties hereto wish to totally resolve, settle and compromise all claims that Drs. Maher, Ulus, and/or Wurtman (collectively the "Complaining Parties") may have against Wiley, Drs. Rothman, and/or Johnson (collectively, the "Publisher Parties") and any related claims that the Publisher Parties may have against the Complaining Parties;

NOW, THEREFORE, in consideration of the foregoing and of the mutual covenants that follow, it is agreed that upon execution of this Settlement and Release Agreement:

1. Wiley will publish in Synapse the attached "Retraction and Apology" from Dr. Rothman (Exhibit B), and the attached "Clarification and Apology" (Exhibit C) from Dr. Johnson on behalf of the Synapse, in paginated form at the end of the July 1999 issue of Synapse (Vol. 33, No.1). The titles of Exhibits B and C will be included on the document themselves, and will also be included in the Table of Contents for Volume 33, Issue Number 1, as well as the cumulative Table of Contents at the end of Volume 33. The documents will also be listed in the Author Index (under names Rothman and Johnson, respectively) and will be appropriately listed in the subject index.
2. Wiley will send a letter to Index Medicus, ISI, and each of the abstracting and indexing services that receives Synapse on a regular basis, to the following effect:

"We wish to call your attention to the fact that the Letter to the Editor by Richard B. Rothman entitled "Is Phentermine...etc." in Synapse, Volume 32, No. 2, p. 141 (May 1999) has been retracted by the author, and that the Editor of Synapse has published a clarification. The retraction and the clarification are to be indexed as follows:

Richard B. Rothman, "Retraction and Apology." Synapse, Vol. 33, No. 1,
p.__(July 1999)

John E. Johnson, Jr., "Clarification and Apology." Synapse, Vol. 33, No. 1,
p.__(July 1999)

We would appreciate your ensuring that any abstracts of and citations to the Letter to the Editor be accompanied by appropriate references to the retraction and the clarification."

3. Wiley will pay \$8,500 in full settlement for the benefit of the Center for Brain Science and Charitable Trust. The check for the payment shall be made payable to the Palmer and Dodge Fiduciary Account, where it shall be held in escrow pending full execution of this Agreement by all parties hereto.
4. The Complaining Parties hereby individually and collectively release the Publisher Parties, their subsidiaries, affiliates, successors, heirs and assigns from all actions, causes of action, suits, debts, dues, sums of money, accounts, reckoning, bonds, bills, specialties, covenants, contracts, controversies, agreements, promises, variances, trespasses, damages, judgments, extents, executions, claims, and demands whatsoever, in law or equity, against the Publisher Parties, their subsidiaries, affiliates, executors, administrators, successors, heirs and assigns, which the Complaining Parties, their executors, administrators, heirs, successors and assigns ever had, now have or hereafter can, shall or may, have for, upon, or by reason of any matter, cause or thing arising out of, relating to, or concerning publication of the Letter whatsoever, from the beginning of the world to the date of this Agreement.
5. The Publisher Parties hereby individually and collectively release the Complaining Parties, their executors, administrators, successors, heirs and assigns from all actions, causes of action, suits, debts, dues, sums of money, accounts, reckoning, bonds, bills, specialties, covenants, contracts, controversies, agreements, promises, variances, trespasses, damages, judgments, extents, executions, claims, and demands whatsoever, in law or equity, against the Complaining Parties, their executors, administrators, successors, heirs and assigns, which the Publisher Parties, their subsidiaries, affiliates, executors, administrators, heirs, successors and assigns ever had, now have or hereafter can, shall or may, have for, upon, or by reason of any matter, cause or thing arising out of, relating to, or concerning publication of the Letter whatsoever, from the beginning of the world to the date of this Agreement.
6. This Agreement constitutes the entire agreement between the parties. Except for the Exhibits referred to herein, there are no other terms, conditions or provisions, express or implied, and any amendment or waiver of the terms, conditions or provisions of this Agreement shall be made only in writing signed by the parties.
7. This Agreement may be signed in two or more counterparts, each of which shall be deemed an original but all of which together shall constitute one and the same agreement.
8. Neither of the parties concedes any liability, nor the validity of any of the claims referenced herein.
9. This Agreement shall be construed and interpreted pursuant to the laws of the State of New York applicable to contracts wholly entered into and performed in the State of New York.

IN WITNESS WHEREOF, the parties have executed this Agreement as of the day and year first written above.

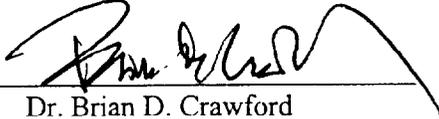
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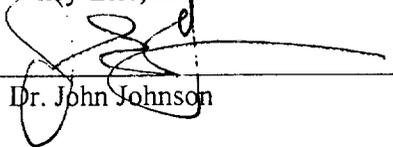
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Dr. Richard Wurtman

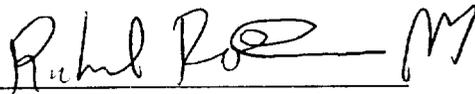
By: _____
Dr. Timothy Maher

By: _____
Dr. Ismael Ulus

FOR THE PUBLISHER PARTIES

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Dr. Brian D. Crawford
Vice President and General Manager
Life and Medical Sciences
Wiley-Liss, Inc.

By: 
Dr. John Johnson

By: 
Dr. Richard Rothman

*Letter to the Editor***Is Phentermine an Inhibitor of Monoamine Oxidase? A Critical Appraisal**

At the International Congress on Obesity (8/29/98 to 9/3/98) Dr. Richard Wurtman presented an abstract entitled: "Phentermine, an unrecognized MAO inhibitor, probably increases free plasma serotonin when given with serotonin uptake blockers." Similar information was just published in a recent issue of *Lancet* (Maher et al., 1999). The authors assert that phentermine, an amphetamine analog and FDA-approved anorectic agent, inhibits MAO at therapeutic doses. Co-administration of MAO inhibitors (MAOIs) and antidepressants is contraindicated. The authors concluded, 1) that it is unwise to combine phentermine with antidepressants such as fluoxetine and, 2) "if a subject were to be treated with a drug or other drugs, (like "Fen/Phen") that inhibit both 5-HT uptake and MAO activity, plasma 5-HT could thus rise to unacceptable levels [which] . . . could lead to pulmonary hypertension . . . and cardiac valve lesions." This abstract was widely publicized without the benefit of peer review, critical commentary and sometimes without mention of important conflicts of interest. Thus, the purpose of this letter is to provide a critical review of the phentermine/MAO hypothesis.

BACKGROUND

Monoamine oxidase, generally abbreviated as MAO, is an enzyme that metabolizes neurotransmitters dopamine (DA), serotonin (5-HT) and norepinephrine (NE). This enzyme plays an important role in modulating the levels of these neurotransmitters (Copper et al., 1991). MAO exists in two forms: MAO-A and MAO-B. The two enzymes differ in their distribution in bodily tissues, their sensitivity to different inhibitors and their substrate specificity (Schoepp and Azzaro, 1981; Copper et al., 1991; Strolin Benedetti and Dostert, 1987; Saura et al., 1992). MAO-A preferentially metabolizes 5-HT: the K_m value of 5-HT for MAO-A is about 200 μM (Robinson, 1985; Gerlach et al., 1992) and is about 2 mM for MAO-B (Gerlach et al., 1992). Either form of MAO (Schoepp and Azzaro, 1981) metabolizes NE and DA. Thus, inhibition of MAO-A increases synaptic levels of 5-HT, DA and NE and decreases the concentration of their metabolites. Treatment of humans with MAO-A inhibitors increases plasma 5-HT (Celada et al., 1992b). MAO-B preferentially metabolizes phenethylamine. The tissue distribution of the two forms of MAO varies

among species. For example, in rats MAO-A metabolizes brain DA (Brannan et al., 1998; Kumagai et al., 1991) whereas in humans and monkeys this is mainly done by MAO-B (Knoll, 1986; Heinonen and Lammintausta, 1991; Garrick and Murphy, 1980). Human platelets contain only MAO-B which does not metabolize 5-HT (Youdim, 1988).

Concurrent administration of medications that block 5-HT uptake (SSRIs) or promote its release (fenfluramine) with MAO inhibitors is contraindicated. This is reflected in the FDA-approved labeling of these medications. It has long been recognized that this can lead to very high 5-HT levels in the brain producing what is called the "serotonin syndrome" (Sternbach, 1991; Hilton et al., 1997; Sporer, 1995). Patients with this syndrome present with fever, muscular rigidity, nausea and alterations in level of consciousness (Sternbach, 1991). It is a serious side effect, which occurs acutely, rather than insidiously. Combining an MAO inhibitor with a medication such as fenfluramine would predictably lead to the occurrence of acute adverse side effects. Combining an MAO inhibitor with other types of antidepressants, such as those which inhibit NE uptake, could lead to dangerous increases in blood pressure - the so called "hypertensive crisis."

Amphetamine-like drugs are known to inhibit MAO (Scorza et al., 1997). Structure-activity studies show that amphetamine and its analogs are weak inhibitors of MAO-A and generally ineffective at MAO-B (Scorza et al., 1997; Mantle et al., 1976). Amphetamine was reported by Scorza et al. (1997) to inhibit MAO-A with an IC_{50} of 11 μM and to be without effect on MAO-B at a dose of 100 μM . Mantle et al. (1976) determined the K_i values of dextroamphetamine at MAO-A and MAO-B. The reported values were 20 μM for MAO-A and 770 μM at MAO-B. Phentermine in general is about 10 times less potent than amphetamine in various animal assay systems. Thus, one might expect that the K_i of phentermine for MAO-A would be in the range of 100 μM . This is similar to the 75 μM value reported by Wurtman (see below). A consensus opinion appears to be that amphetamine, which is quite similar to phentermine, inhibits MAO-A only at very high doses.

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DATA PRESENTED TO SUPPORT THE PHENTERMINE/MAO HYPOTHESIS

The major assertion of the Wurtman group is that phentermine acts as an MAO inhibitor. Several pieces of data are said support this hypothesis. A key observation is that phentermine inhibits MAO activity, as measured using 5-HT as the substrate, and rat lung, liver and brain as the enzyme source, with a K_i of about $75\mu\text{M}$. Another observation is that administration of phentermine to human volunteers increased platelet 5-HT and decreased plasma 5-HT. The magnitude of these effects is not stated. These effects, which occurred following a single acute dose of 15 mg phentermine and after 5 days of daily administration of 30 mg phentermine, is ascribed to inhibition of platelet MAO. Although no direct evidence that phentermine inhibits platelet MAO is provided, the authors conclude that phentermine inhibits MAO at typical therapeutic doses in humans.

CRITIQUE OF THE PHENTERMINE/MAO HYPOTHESIS

As noted above, the fact that phentermine inhibits MAO-A is not unexpected, since amphetamine is known to have a K_i of about $10\mu\text{M}$ at MAO-A and to be ineffective at MAO-B (Scorza et al., 1997). Many investigators use 5-HT as the substrate when they wish to measure MAO-A activity (Schoepp and Azzaro, 1981). Thus, the K_i value of phentermine for MAO reported by Wurtman is for MAO-A, not MAO-B. Importantly, human platelets contain just MAO-B (Youdim, 1988), which does not metabolize 5-HT. Phentermine, like amphetamine, is likely to be an even weaker inhibitor of MAO-B. Assuming this to be the case, then it is highly unlikely that phentermine could inhibit platelet MAO-B. Even if phentermine were to inhibit platelet MAO-B, the enzyme does not metabolize 5-HT. Indeed, Youdim stated in a paper on the subject (Youdim, 1988) "5-HT oxidation is hardly affected by the platelet enzyme and MAO inhibitors have no net effect on its accumulation." Some speculate that the purpose served by platelet MAO-B is not to metabolize 5-HT, but to protect platelet 5-HT from other substances that might release it. For example, tyramine, which can release platelet 5-HT, is metabolized by platelet MAO-B (Schoepp and Azzaro, 1981). In summary, the hypothesis that phentermine increases platelet 5-HT via inhibition of platelet MAO is not supported by the literature. In the absence of direct evidence that such a mechanism operates, the hypothesis must be rejected and some explanation other than MAO inhibition must be sought to explain how oral phentermine increases platelet 5-HT.

Neurochemical Studies

Neurochemical experiments show that MAO-A inhibition increases brain 5-HT and decreases its metabolite, 5-HIAA (Kato et al., 1986; Kumagai et al., 1991; Matos

et al., 1990; Carboni and Di Chiara, 1989). For example, Celeda and Artigas (1993) showed that systemically administered MAO-A inhibitors, both irreversible and reversible ones, increased extracellular 5-HT and decreased 5-HIAA in the frontal cortex and raphe nuclei of rats. If phentermine blocks MAO-A, then it too should increase extracellular 5-HT. However, in vivo microdialysis studies conducted in rat show that phentermine preferentially releases DA and has little effect on neuronal 5-HT (Shoaib et al., 1997; Balcioglu and Wurtman, 1998a; Balcioglu and Wurtman, 1998b). Similar findings occur with amphetamine, which increases extracellular 5-HT only at higher doses (Kankaanpaa et al., 1998).

A recent study by Halladay et al. (1998) which measured tissue levels of DA and 5-HT and their metabolites also demonstrate that phentermine does not exert MAO blocking activity in the rat. These researchers showed that administration of 12 mg/kg phentermine, which is a large dose, decreased the tissue levels of the DA metabolites, DOPAC and HVA, consistent with its DA releasing action, but that it did not decrease tissue levels of 5-HIAA, which would happen if phentermine blocked MAO (see above).

In summary, both reversible and irreversible inhibitors of MAO-A increase extracellular levels of 5-HT and decrease extracellular levels of 5-HIAA. Similar neurochemical changes occur with tissue levels of 5-HT and 5-HIAA. Phentermine has little if any effect on brain 5-HT and 5-HIAA, and thus can not be blocking MAO-A.

Clinical Studies

As clinically available medications, MAO inhibitors have been widely studied. Thus, there exist measurable biochemical effects of MAO inhibitors that can be used to test the phentermine/MAO hypothesis. Since there are no studies this writer is aware of which report the biochemical effects of phentermine in humans, amphetamine studies will be used instead.

Zametkin et al. (1985) measured urinary monoamines and metabolites and plasma NE and its metabolite (MHPG) in 14 boys at baseline and after 4 weeks treatment with either dextroamphetamine or MAO inhibitors. This study showed the expected effect of an MAO inhibitor on NE metabolism (increased normetanephrine and decreased levels of the metabolites VMA and MHPG) and DA metabolism (decreased HVA). A NE "metabolism index" used by the authors showed a huge increase from 0.041 to 0.846. In contrast, dextroamphetamine had the opposite effect on normetanephrine and no change in the metabolism index (0.043 at baseline and 0.048 after treatment). The authors state, based on these results, "even a minor degree of monoamine oxidase A inhibition [by dextroamphetamine] would be likely to shift the ratio more dramatically since even two weeks after stopping MAOIs the ratio is 0.093." Also of importance is the fact that the MAOIs decreased

DA metabolites (HVA and DOPAC) as expected and that dextroamphetamine had no effect on these measures. Of importance, dextroamphetamine Scorza et al. (1997) is a more potent inhibitor of MAO-A than phentermine. Donnelly et al. (1989) reported similar results after 3 weeks treatment with dextroamphetamine. Contrary to the data reported by Wurtman for phentermine, Donnelly et al. (1989) reported that dextroamphetamine did not increase platelet 5-HT.

Celada et al. (1992b) examined the effect of chronic administration MAO-A inhibitors on plasma 5-HT, platelet 5-HT and plasma 5-HIAA. Similar results were obtained phenelzine, an irreversible inhibitor of MAO-A and MAO-B, and the reversible inhibitor of MAO-A, brofaromine. Both medications increased plasma 5-HT by about 200%. These investigators also observed an increase in platelet 5-HT content, an effect that can be attributed to the increased levels of plasma 5-HT. Plasma 5-HIAA decreased. These findings do not occur with dextroamphetamine, which does not decrease plasma 5-HIAA (Zametkin et al., 1985) and which does not increase platelet 5-HT (Donnelly et al., 1989). Moreover, in contrast to the findings with the MAO inhibitors (Celada et al., 1992b), Wurtman reports that phentermine decreased plasma 5-HT slightly.

In summary, the biochemical effects of amphetamine in humans is much different than that of MAO inhibitors. Inhibition of MAO leads to a predictable set of changes in monoamine metabolites, which is not seen, with daily administration of amphetamine (Zametkin et al., 1985). The changes in platelet 5-HT reported by Wurtman for phentermine is not seen with amphetamine (Donnelly et al., 1989) indicating the need to replicate the Wurtman findings. In any case, since amphetamine is a more potent inhibitor of MAO than phentermine, this suggests that any change in platelet 5-HT induced by phentermine is not likely due to inhibition of MAO.

Assuming that phentermine inhibits MAO-A with a K_i of about 75 μ M, do therapeutic doses of phentermine achieve high enough concentrations to block MAO-A? A study conducted by Douglas (1983) showed that daily administration of phentermine at a mean daily dose of about 37 mg produced plasma levels of about 0.7 μ M. This concentration is in the range where phentermine interacts with its therapeutic sites of action, the DA and NE transporters, but is well below its K_i value for MAO-A.

PHENTERMINE/FLUOXETINE, CARDIAC VALVULOPATHY AND PRIMARY PULMONARY HYPERTENSION

A major conclusion reached by Wurtman is that: "if a subject were to be treated with a drug or other drugs, (like "Fen/Phen") that inhibit both 5-HT uptake and MAO activity, plasma 5-HT could thus rise to unacceptable levels [which] . . . could lead to pulmonary hyperten-

sion . . . and cardiac valve lesions." The underlying assumption here is that elevated plasma 5-HT is the cause of fenfluramine-associated primary pulmonary hypertension (PPH) (Abenheim et al., 1996) and cardiac valvulopathy (Connolly et al., 1997). However, the role of 5-HT in the pathogenesis of both of these serious adverse effects is not established. For example, some investigators have hypothesized that fenfluramine-like medications elevate blood 5-HT thereby producing PPH in susceptible individuals (Abenheim et al., 1996). This proposal, however, is not consistent with the finding from many laboratories that fenfluramine actually lowers blood 5-HT and does not increase plasma 5-HT (Raleigh et al., 1986; Martin and Artigas, 1992; Celada et al., 1994; Stubbs et al., 1986; Kolakowska et al., 1987; Redmon et al., 1997; Donnelly et al., 1989), an effect which follows its mechanism of action: blockade of 5-HT uptake by platelets. SSRI antidepressants have the same effect on blood and plasma 5-HT as fenfluramine (Celada et al., 1992a; Hyttel et al., 1984; Menys et al., 1996; Salazar et al., 1994). Since both phentermine and SSRIs actually lower plasma 5-HT (Celada et al., 1992a), it is difficult to see how combining these medications will increase plasma 5-HT.

Moreover, it is noteworthy that neither phentermine (Anonymous, 1997), fluoxetine, nor the combination (Griffen and Anchors, 1998) are implicated as a cause of cardiac valvulopathy. Regarding PPH, rigorous epidemiological data contributed by Abenheim et al. (1996) show that fenfluramine and d-fenfluramine increase the risk of PPH. There exists to-date very few cases, and no controlled studies, linking PPH to the use of phentermine (Backmann et al., 1972; Schnabel et al., 1976).

CLINICAL EXPERIENCE WITH PHENTERMINE, PHENTERMINE/FLUOXETINE AND PHENTERMINE/FENFLURAMINE

The combined use of phentermine and fluoxetine in obese patients is reported to be safe and without significant adverse effects. Anchors (1997) reported on the use of Phentermine/Fluoxetine in several hundred patients as has Padla and Spoke (1977). Dhurandhar and Atkinson (1996) reported a controlled study with Phentermine/Fluoxetine. The treatment experience shows that the combination is safe, effective and well-tolerated. If phentermine were inhibiting MAO-A at clinically relevant doses then there should have been a higher incidence of the serotonin syndrome than was observed. Similarly, the combination of a phentermine with fenfluramine should have produced a significant number of patients with the serotonin syndrome if indeed phentermine blocked MAO-A. However, despite millions of people being treated with phentermine/fenfluramine, the serotonin syndrome did not emerge as a frequent adverse effect. Routine medical practice

dictates that patients receiving MAO-A inhibitors must be on a special "low tyramine" diet. This is to decrease the probability of a hypertensive crisis. Despite decades of use, the need for a special low tyramine diet during treatment with phentermine has not emerged as being necessary. The most likely reason for this is that phentermine does not inhibit MAO-A.

SUMMARY

Phentermine produces a spectrum of concentration-dependent biochemical effects. It interacts with NE transporters at 0.1 μ M, DA transporters at about 1 μ M, 5-HT transporters at 15 μ M and MAO-A at about 100 μ M. When administered at typical anorectic doses, phentermine primarily interacts with DA and NE transporters and does not produce biochemical or neurochemical effects which would occur if it were inhibiting MAO-A. Some other explanation other than MAO inhibition must be sought to explain how oral phentermine increases platelet 5-HT, since platelet MAO-B does not metabolize platelet 5-HT, and since amphetamine-type drugs are even weaker inhibitors of MAO-B than MAO-A. Clinical studies in humans have shown that amphetamine, which is a more potent inhibitor of MAO-A than phentermine, does not inhibit MAO-A at therapeutic doses. Neither phentermine alone, fluoxetine alone or their combined use have been associated with cardiac valvulopathy, and clinical experience has shown their combined use to be free of significant adverse effects. Viewed collectively, there appears to be no data to support the hypothesis that phentermine inhibits MAO at typical therapeutic doses.

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REFERENCES

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Exhibit B

Retraction and Apology:

Dear Dr. Johnson:

My *Letter to the Editor* in the May 1999 issue of SYNAPSE (32:141-145, 1999) raised questions as to the scientific basis for claims that phentermine acts as an inhibitor of monoamine oxidase at therapeutic doses, and was intended to provide a critical review of the phentermine/MAO hypothesis. In my introductory remarks, I asserted that an abstract co-authored by Richard Wurtman and his colleagues (**citation here**) " was widely publicized without the benefit of peer review, critical commentary, and sometimes without mention of important conflicts of interest." To the extent that statement may have misled any readers, I now retract it in its entirety, and offer my sincere apologies to Dr. Wurtman and to his colleagues, Dr. Timothy Maher and Dr. Ismail Ulus.

Specifically, I have learned that the abstract in question was in fact selected by the organizers of the International Congress on Obesity (8/29-9/3/98) as one of a small number of "hot topic" submissions worthy of special attention at the meeting, where open commentary on the research was invited, including a poster presentation by the three co-authors. The attention given their work at that venue, of which I was unaware, would indicate that their preliminary report received greater scientific scrutiny than is given to the typical meeting abstract in the biomedical sciences. Moreover, although my *Letter to the Editor* cited also a study by Maher, Ulus, and Wurtman published subsequently in the LANCET (**citation here**) the casual reader may not have inferred from my citation alone the distinction conferred on the latter report by virtue of its publication in the LANCET, an international journal that is known for its peer-reviewed content.

I now wish to clarify that with regard to my statement concerning "important conflicts of interest", my statement was not meant to imply that these authors personally had failed to disclose such information where it existed. Rather, my remark was meant as a comment on the reporting practices of news media that disseminated their findings from this area of scientific inquiry-- some of which deemed it important to include mention of factual information regarding the various professional interests and affiliations of authors--and others of which did not. I am advised that Dr. Maher and his colleagues disclosed any possible conflicts of interest when their work was submitted for publication, and that as a matter of routine, such information was also included in press publicity material issued by the Massachusetts Institute of Technology and the Massachusetts College of Pharmacy and Health Sciences (<http://web.mit.edu/newsoffice/nr/1998/fenphen.html>; <http://www.mcp.edu/news/1-4-99.htm>). In some subsequent news reports, this information was published and in others not.

It is a matter of public record that I am Board Certified Psychiatrist and Medical Director of BE-LITE, a chain of for-profit weight-loss centers (www.belite.com), and that I use phentermine and a variety of other FDA-approved medications in the treatment of obesity and psychiatric disorders. The fact that I am Medical Director of BE-LITE was made known to SYNAPSE but was not disclosed to readers of the Journal because it was not deemed to be relevant. I do not have any financial interests in any pharmaceutical companies, including ones which manufacture or sell phentermine.

Finally, to the extent that my comments noted in the first paragraph of this letter, or the omission of my affiliation misled any of the readers of SYNAPSE, I offer my sincere apologies.

Sincerely,
Richard B. Rothman, M.D., Ph.D.

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I thank Drs. Maher, Ulus, and Wurtman for bringing these concerns to my attention, and I apologize to them for my decision to publish Dr. Rothman's Letter to the Editor to SYNAPSE as submitted.

Respectfully,
John E. Johnson, Jr., Editor-in-Chief

SYNAPSE

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Respectfully,
John E. Johnson, Jr., *Editor-in-Chief*

COOPER
FPI

RICHARD WURTMAN

July 28, 1999

Glenn L. Cooper, M.D.
President and Chief Executive Officer
Interneuron Pharmaceuticals, Inc.
99 Hayden Avenue
Lexington, MA

Dear Glenn:

Thanks for your letter of July 26. I fully understand your position.

In light of your decision I have decided to resign my membership on Interneuron's Board of Directors, effective immediately. I do this not because of any loss of interest in, or enthusiasm for, the company; rather, I'll need to terminate this fiduciary responsibility if I am to undertake a successful relationship with another company. And since Interneuron apparently does not intend to continue 50% of my salary - as described in section 6(a) of my consulting contract, I will very likely be working closely with one or more companies after November 1. I have no present intention to work on any drugs for stroke that might compete with Citicoline: I believe that Citicoline is an excellent drug, and want to do whatever I can to ensure that it is a major success (including working with Interneuron, if it asks me to do so).

If Interneuron decides that my withdrawal from the company requires some sort of announcement, I'd like to have the opportunity to develop that announcement with you.

Please instruct your transfer agent to remove any restrictive legends from the back of my stock certificates (including any certificates held by my blind trust), and inform the transfer agent that I am no longer an affiliate of the company.

I wish you and the other Interneuron people the best of luck.

Sincerely yours,


Richard J. Wurtman, M.D.

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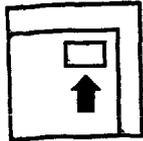
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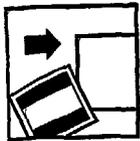
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