CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ENDOCRINOLOGIC and METABOLIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 11/16/95

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SLIDES

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Dexfenfluramine for the Treatment of Obesity

Interneuron Pharmaceuticals, Inc.
Glenn L. Cooper, M.D.

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Issues Addressed on September 28, 1995

- Efficacy
- Primary pulmonary hypertension
- Risk/Benefit
- Serotonin depletion in animals

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Dexfenfluramine Pharmacology

- Increases serotoninergic neurotransmission and is not a sympathomimetic
  - Serotonin reuptake blocker
  - Releases serotonin
  - Serotonin receptor agonist
- Enhances satiety and reduces daily caloric intake
- No abuse potential

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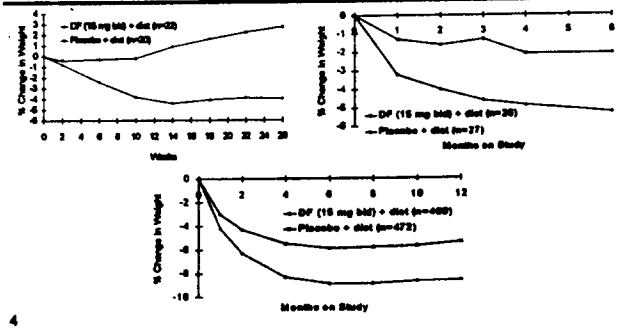
Effect of Dexfenfluramine vs. Placebo on Weight Loss in Long Term Studies



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Effect of Dexfenfluramine on % Weight Loss from Baseline Compared to Placebo

	Weight Loss at Endpoint (% of Patients)					
	≥ 5%			≥ 10%		
Study	DF	Placebo	p-value	DF	Placebo	p-value
INDEX	64	43	.0001	40	21	.0001
Noble	46	19	.027	21	7	.140
UK 18	36	6	.013	18	0	.045

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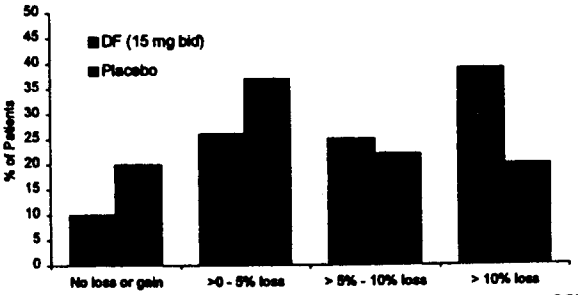
Effect of Dexfenfluramine on % Weight Loss from Baseline by Category Compared to Placebo - INDEX



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$p < 0.001$ difference between groups

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Efficacy

- Dexfenfluramine, as an adjunct to diet, was found to produce significantly more weight loss than placebo for up to one year
- Significantly larger proportions of patients lose clinically significant amounts of weight when compared to placebo

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Obesity and Excess Deaths

- From information currently available, one can estimate the number of deaths from certain diseases that could be attributed to obesity in the US in 1993.

Attributable to Obesity	
Cause-Specific deaths	Deaths from all causes
171,490 CHD deaths	
39,679 diabetes deaths	292,410
53,087 cancer deaths	
10,000 cerebrovascular deaths	

- An appreciable, but as yet unquantified, proportion of deaths arising from such conditions as non-CHD forms of heart disease and obstructive sleep apnea (examples) may be attributable to overweight

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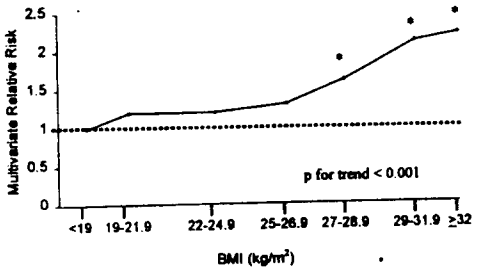
BMI and All Cause Mortality Risk, Women Never Smokers 1980-1992 with Prior Stable Weight



* $p < 0.05$

Manson et al., NEJM, Sept 1995

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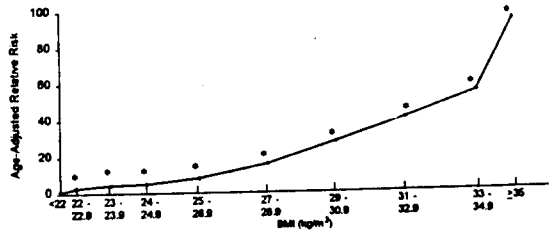
BMI and Risk of NIDDM



* $p < 0.05$

Colditz et al., Ann Int Med, 1995

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Intentional Weight Loss and Mortality Risk (Never-Smoking US White Women Aged 40-64 yrs)

- 28,388 obese women with no preexisting illness
- Intentional weight loss of ≥ 20 lb (9.1 kg) that occurred within the previous year was associated with a 25% reduction in all-cause, cardiovascular and cancer mortality

Williamson et al., Am J Epidemiol, 1995

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Intentional Weight Loss and Mortality Risk (Never-Smoking US White Women Aged 40-64 yrs)

- 15,069 women (BMI ≥ 27 kg/m²) with obesity and co-morbid conditions (CHD, hypertension, stroke, diabetes, cancer, or cirrhosis)
- Intentional weight loss of any amount was associated with:
  - 20% reduction in all-cause mortality
  - 30-40% reduction in diabetes-associated mortality
  - 40-50% reduction in mortality from obesity-related cancer

Williamson et al., Am J Epidemiol, 1995

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Dexfenfluramine Treatment Favorably Affects Obese Patients with Co-morbid Conditions

- Obese hypertensive patients
- Obese diabetic patients
- Obese dyslipidemic patients

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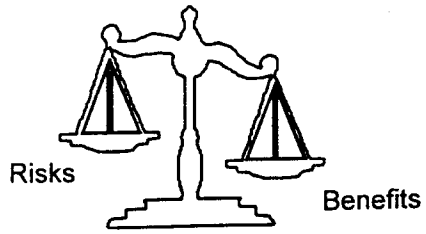
Dexfenfluramine has a Favorable Risk/Benefit Profile



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Dexfenfluramine Risk/Benefit Issues

- Primary pulmonary hypertension
- Responders analysis
- Indications and Usage
- Recent European regulatory decision

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Pulmonary Hypertension Post-Marketing Reports

Est'd exposure (1984-1994)	10,000,000
Total	101
Reported dyspnea before DF use	18
Number with underlying heart and/or lung disease (? secondary PH)	38
Exposure prior to dyspnea (? true cases of PH)	53

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International Primary Pulmonary Hypertension Study (IPPHS) - Conclusions

- "The exact role of the anorexigens in the risk of PPH cannot, however, be definitively established due to lack of knowledge of the pathogenic mechanisms, the lack of specificity of the effect within the class of anorexigens, the nonexclusion of all potential confounders and the low absolute risk."

IPPHS Investigators

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Response Predictors for Dexfenfluramine Treated Patients

Lost 4 lbs in 1st month of treatment		Lost ≥10% body weight by month 12: Response	Lost ≥10% body weight by month 12: Non-response
Non-response	22%	9%	91%
Response	78%	60%	40%

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Dosing and Administration

"Analysis of numerous variables revealed that patients who lose at least 4 lbs. in the first four weeks of treatment with dexfenfluramine have a statistically significant chance of losing at least 10% of their initial body weight by the end of one year of treatment."

"If a patient has not lost at least 4 lbs. in the first 4 weeks of treatment, the physician should consider discontinuation of dexfenfluramine."

Indication and Usage

- "Dexfenfluramine is indicated for the management of obesity in patients on a reduced calorie diet. Dexfenfluramine is recommended for obese patients with an initial body mass index 30, or 27 if there is risk or presence of other factors (e.g., hypertension, diabetes, hyperlipidemia)."

- "Below is a chart of Body Mass Index (BMI or kg/m^2) based on various heights and weights."

EUROPEAN REGULATORY STATUS - October 27, 1995

- Amphetamine-like drugs restricted to short-term use in France
- Dexfenfluramine and fenfluramine may be used in responders for long-term (>1 yr) in France
- European Union decision likely to be similar to French action

Neurochemical Effects - Sept. 28, 1995 FDA Background Document

"The ^{19}F MRS technique used in this study is a research tool and its clinical applicability has not been validated. The results, however, offer support for the concept of non-accumulation of drug with duration of use and of concentrations well below those that produced neurotoxicity in experimental animals. Although the number of subjects was small, the small standard deviation offers a degree of comfort concerning the safety of this drug."

"PET is an experimental tool; in these studies, the data support the thesis of lack of effect of dexfenfluramine on serotoninergic receptors at doses used for production of weight loss."

FDA Background Package -
L. Lutwak, M.D., Ph.D. - Medical Review Officer
G. Troendle, M.D. - Deputy Director

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G. Troendle, M.D. - Deputy Director

Neurochemical Effects: Debate

- Neurotoxicity vs. neurochemical changes
- Serotoninergic class effect
- MDMA changes ≠ DF changes

Margin of Exposure is the Key Issue

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- 10 mg/kg/day DF (30 X recommended dose) = 900 mg/day in obese patients
- 30 X dose of common medications is often toxic
  - Acetaminophen - Liver failure, death
  - Imipramine - Seizures, cardiorespiratory collapse, death
  - Chlorpropamide- Hypoglycemic coma, death

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Margin of Exposure Calculations

Test	Dose (mg/kg)	Species	Outcome	Brain DF+dNF[a]	Margin
Argyrophilia	100	Mouse	No Effect	>100 μM	>25
Gliosis	12	Rat	No Effect	67 μM	>16
Reduction in Retrograde Transport	16	Rat	No Effect	107 μM	>25

[a]Concentrations estimated in separate pharmacokinetic experiments in the same species

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Margin of Exposure for Serotonin Depletion

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- Acute serotonin depletion is consistent with the pharmacology of this class of drugs
- High doses of DF produced prolonged, but reversible serotonin depletion
- A conservative no effect level provides a 10 to 20 fold margin of exposure in brain

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Effects of Dexfenfluramine on Brain Serotonin Content and Paroxetine Binding - Long -Term Mouse Study

Parameter	At End of 2 yrs of Treatment	Three Months After End of 2 yrs of Treatment
Serotonin Content[a]	109 ± 6 (n=10)	100 ± 8 (n=9)
Paroxetine Binding[a]	95 ± 8 (n=5)	130 ± 5 (n=5)
DF + dNF (μM) (brain)	51	0

[a]Expressed as percent control values

28 DF (27 mg/kg/day) in feed for 106 weeks

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Lack of Functional Impairment

- High dose administration in animals does not produce functional impairments
- Locomotor activity, cognition, aggression/social behavior

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Extensive Post-Marketing Experience

- Dexfenfluramine
  - First approval in 1985
  - Approved in 65 countries
  - Estimated > 10,000,000 patients treated worldwide
- Fenfluramine
  - Approved in US in 1973
  - Estimated > 30,000,000 patients treated worldwide with fenfluramine
- Fenfluramine 60 mg contains 30 mg dexfenfluramine

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Prozac® (Est'd 10,000,000 patients exposed) Post-Marketing Safety Reports (1988 - 1990)

Serious Events		Non-Serious Events	
CNS	589	CNS	5413
sleep disturbance	102	sleep disturbance	1063
dependence	7	dependency	27
amnesia	27	amnesia	151
Syncope	32	Pulmonary	432
Overdose	793	Galactorrhea	112
GI	60	GI	807
Cardiac	237	Cardiac	296
Withdrawal sx	21	Withdrawal sx	72
Hypertension	37	Hypertension	147
		Musculoskeletal	315

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Medicines Control Agency

- "We have now completed our assessment of the report prepared by Professor C. K. Atterwill, and have reviewed the spontaneous reports of neurological adverse drug reactions associated with dexfenfluramine and fenfluramine, received to date. We conclude that no action is required in relation to this aspect of the drugs' safety profile at present."

Dr. E. M. Cockburn, Ph.D., Senior Scientific Officer, Pharmacovigilance Assessment Group, Post Licensing Division, MCA

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Lack of Clinical Neuropsychological Effects of Dexfenfluramine in 17 Controlled Trials

- Neurocognition
- Depression
- Mood
- Sleep

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Clinical Impressions of Neuropsychiatric Assessments

"...dexfenfluramine does not appear to pose any risk of neuropsychiatric or neurocognitive adverse effects..."
Paul A. Spiers, Ph.D.
Clinical Psychologist/Neuropsychologist
Visiting Scientist, MIT

"In sum, I am impressed by the number of patients who have taken this substance without obvious adverse effects on the parameters that you list."
M. Marcel Mesulam, M.D.
Professor of Neurology and Psychiatry
Northwestern University Medical School

"I see no evidence for any adverse effects on brain function as monitored by neurologic, psychiatric, behavioral and cognitive examinations."
Malcolm Lader, D.Sc., Ph.D., M.D., F.R.C. Psych.
Professor of Clinical Psychopharmacology,
Institute of Psychiatry, University of London

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Clinical Impressions of Neuropsychiatric Assessments

"The data available for the assessment of the safety of fenfluramine with regard to neurotoxicity are considerable and the evidence available indicates that this drug is safe. Studies, using more sophisticated neuropsychological testing and functional brain imaging techniques, such as PET, can further establish the safety of the drug."
J. John Mann, M.D.
Professor of Psychiatry
College of Physicians & Surgeons
Columbia University

"...I could find no evidence of long-term neurotoxicity or neurofunctional impairment either on or off the drug in humans in therapeutic doses..."
A. John Rush, M.D.
Betty Jo Hay Distinguished Chair in Mental Health, Dept. of Psychiatry
Southwestern Medical Center

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Clinical Impressions of Neuropsychiatric Assessments

"In conclusion, I believe that dexfenfluramine, in the recommended doses, is safe for use in human subjects. There is no evidence of long-term neurotoxicity or impairment in behavioral or cognitive parameters in human subjects. Finally, given the world-wide exposure of dexfenfluramine, I believe that its safety profile is perhaps better established than most other psychoactive agents that are approved by the FDA for use in human subjects."
Emil F. Coccaro, M.D., Professor and Director
Clinical Neuroscience Research Unit
Department of Psychiatry
Medical College of Pennsylvania and Hahnemann University

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Clinical Impressions of Neuropsychiatric Assessments

"I have reviewed the enclosed clinical amendments and agree that there is no evidence of significant toxicity from dexfenfluramine. We have completed a study of DL-fenfluramine in children with similar findings."

Judith Rappaport, M.D.
FDA Consultant
National Institute of Mental Health

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Dexfenfluramine - Summary

- Long-term efficacy established
- Favorable effect on co-morbidities
- Well-tolerated
- Serious toxicities are very rare
- Neurochemical changes produced by high doses in animals have no clinical relevance
- Risk/benefit ratio is highly favorable

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Dexfenfluramine Agenda: November 16, 1995

I.	Introduction and Overview	Glenn L. Cooper, M.D.
II.	Co-morbidities	Arthur Rubenstein, M.D.
III.	Neurological Issues	
	A. Review of key preclinical data	John Blundell, B.Sc., Ph.D.
	B. Clinical neuropsych. studies	Richard Gammans, Ph.D.
IV.	Risk/Benefit	Gerald Faich, M.D., M.P.H.
V.	Phase IV	Marc Deitch, M.D.
VI.	Summary	Glenn L. Cooper, M.D.

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Arthur Rubenstein, M.D.

Professor and Chairman
Department of Medicine
University of Chicago

Patients with Co-morbid Conditions

- Obese hypertensive patients
- Obese diabetic patients
- Obese dyslipidemic patients

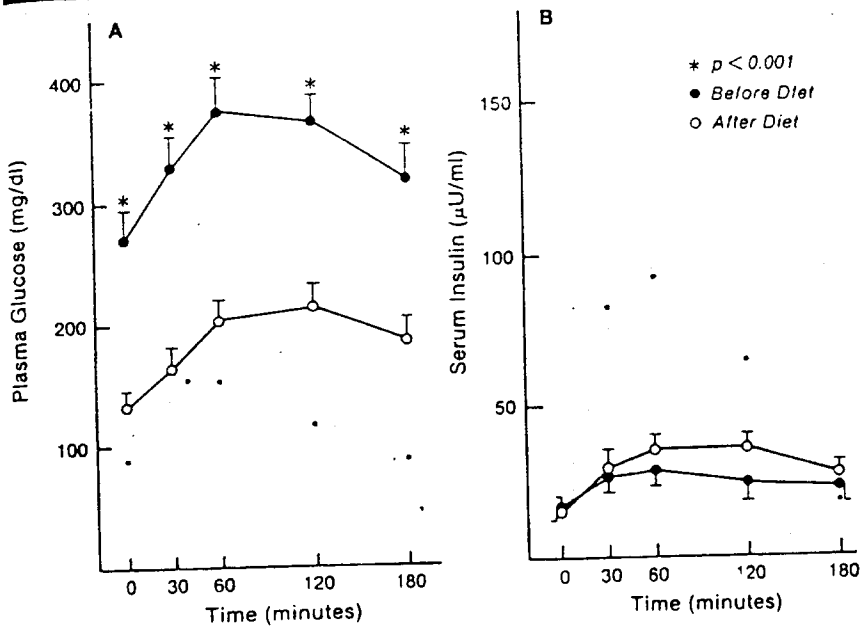
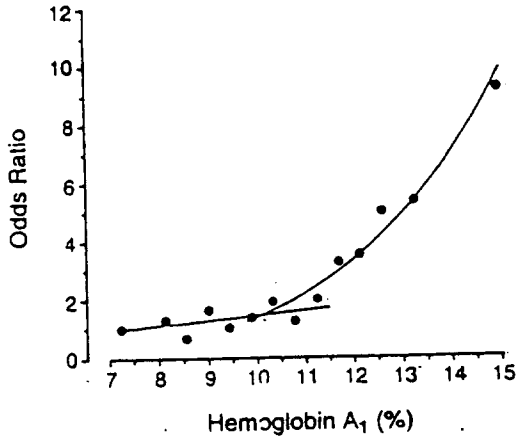


FIG. 1. Plasma glucose response (*A*) and serum insulin response (*B*) to 75-g oral glucose-tolerance test before (●) and after (○) diet therapy. Results are plotted as means ± SE. *Shaded area* indicates normal range (means ± SE).



Hemoglobin A_{1c} (%)	5.8	6.4	7.2	8.0	8.8	9.6	10.5	11.3	12.1
Blood glucose (mg/dl)	108	139	169	199	229	259	289	319	350

Figure 1. Relation between Mean Hemoglobin A_1 Values and the Risk of Microalbuminuria in Patients with IDDM.

Stewart, GO et al (1993). **Med. J. Australia** 158:167-169.

12 week randomized, double-blind study of dexfenfluramine vs placebo in obese, NIDDM patients.

During treatment, the dexfenfluramine group showed:

(i) greater weight loss than placebo (-3.3 vs + 0.3kg)
(ii) greater reduction in FBS (-1.0 mmol/L vs +0.6 mmol/L, p 0.01)
(iii) greater reduction in HbA_{1c} (-1.4% vs + 0.2%, p=0.002)
(iv) greater reduction in triglycerides (-0.3 mmol/L vs + 0.2% mmol/L, p 0.017)
(v) no change in cholesterol
(vi) no change in systolic or diastolic BP

Willey, KA et al (1992). **Diabetic Medicine** 9:341-343.

12 week randomized, placebo controlled, double blind study of dexfenfluramine in obese NIDDM treated with metformin with or without a sulfonylurea.

During treatment, the dexfenfluramine group showed:

(i) significant weight loss (98.7 to 94.9 kg, $p<0.01$)
(ii) significant decrease in fructosamine (313 to 274 µmol/L, $p<0.01$)
(iii) significant decrease in HbA_{1c} (7.5 to 6.3%, $p<0.001$)
(iv) significant decrease in diastolic BP (85 to 73 mmHg, $p<0.001$)
(v) significant decrease in systolic BP (137 to 128 mmHg, $p<0.05$)

At the end of the study period, the dexfenfluramine treated group had significantly lower HbA_{1c}, fructosamine, and diastolic BP compared to the placebo group.

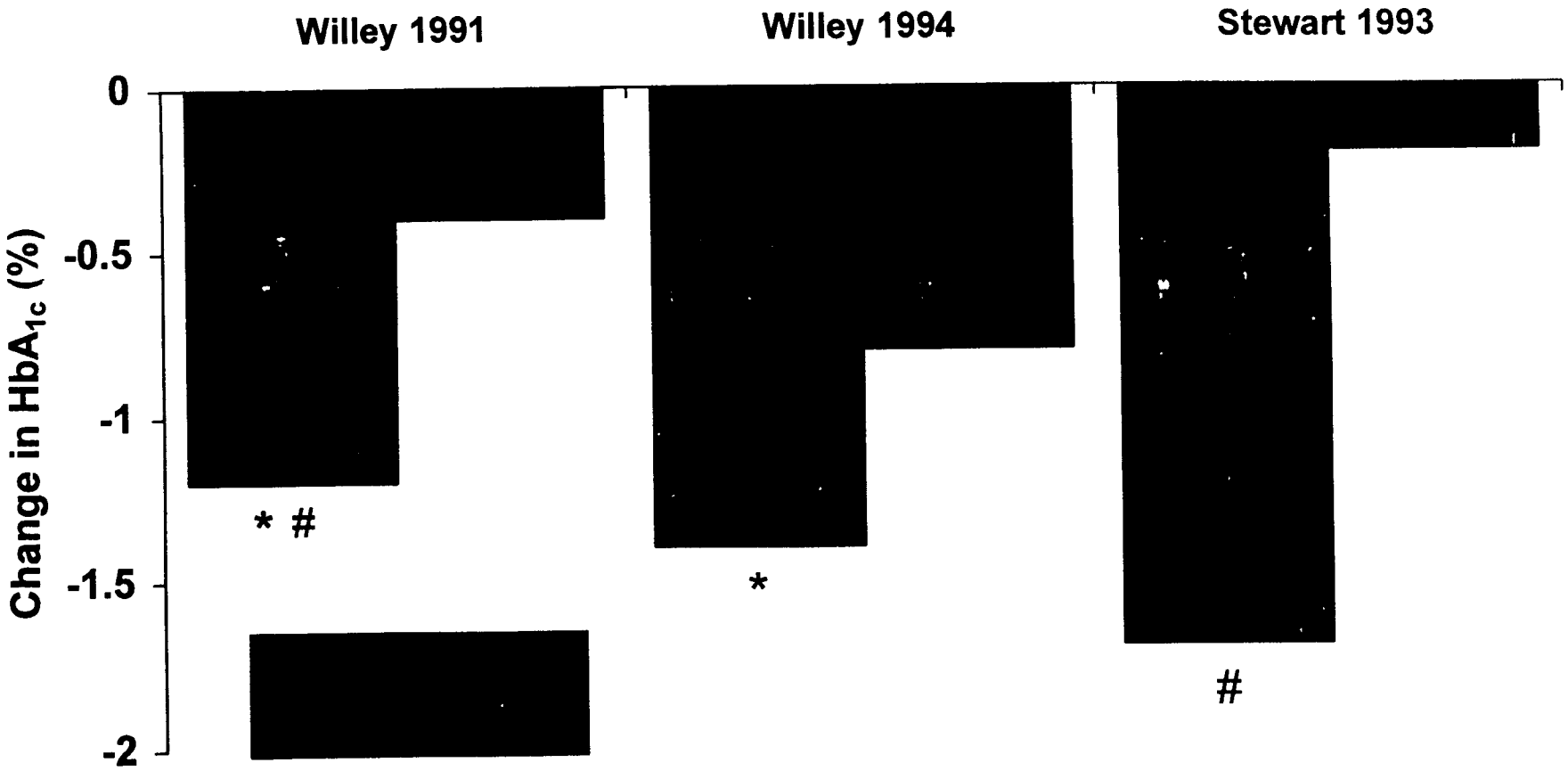
Willey, KA et al (1994). **Diabetic Medicine** 11:701-704.

12 week randomized, placebo controlled, double blind study of dexfenfluramine in obese NIDDM treated on insulin and metformin.

During treatment, the dexfenfluramine group showed:

(i) reduction in mean HbA_{1c} from 8.5 to 7.1%, p 0.02
(ii) no significant changes in weight, BMI, BP, cholesterol or fructosamine.

Double-blind, Placebo-Controlled Studies of Dexfenfluramine In Obese Diabetic Patients



* p< 0.05 from baseline
# p< 0.05 from placebo

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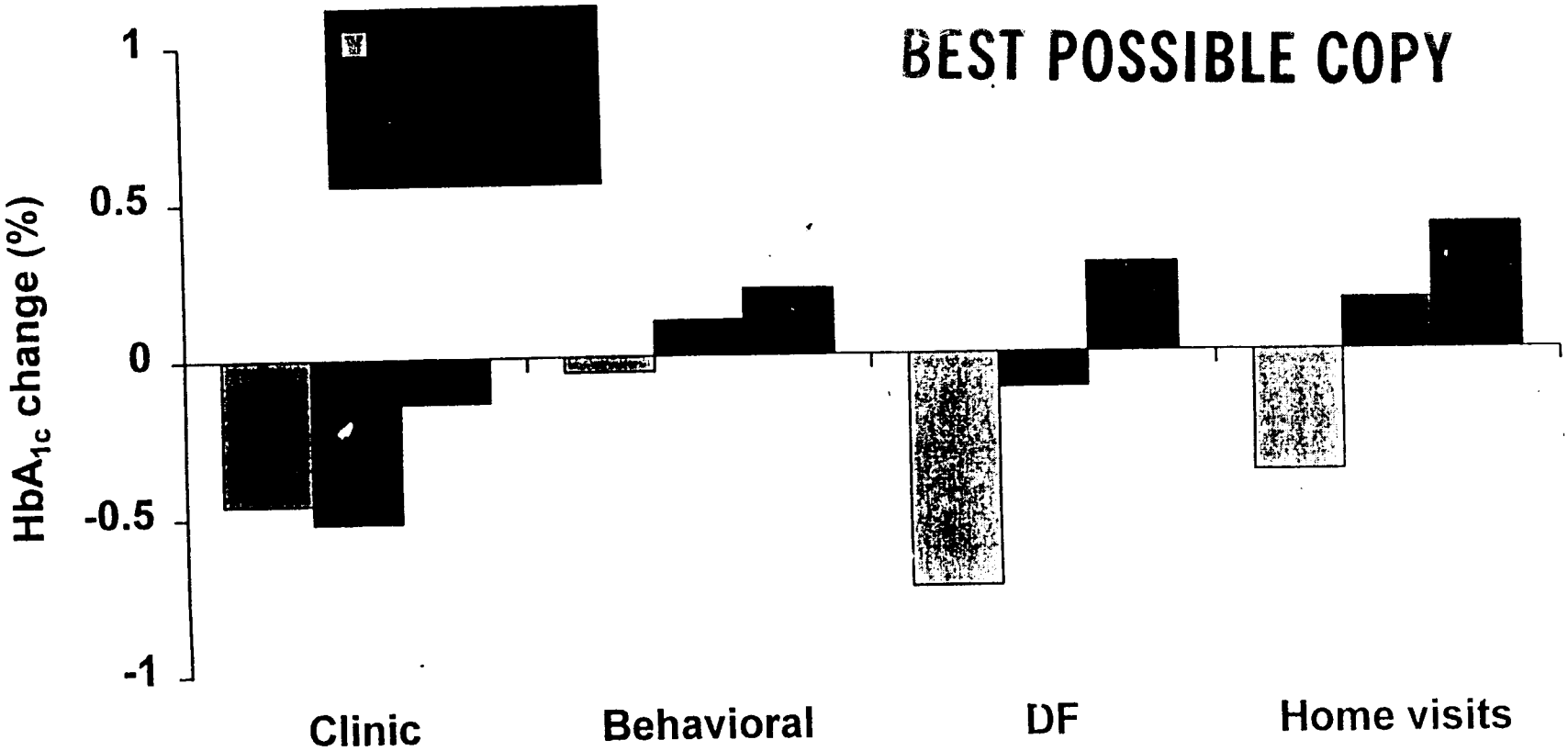
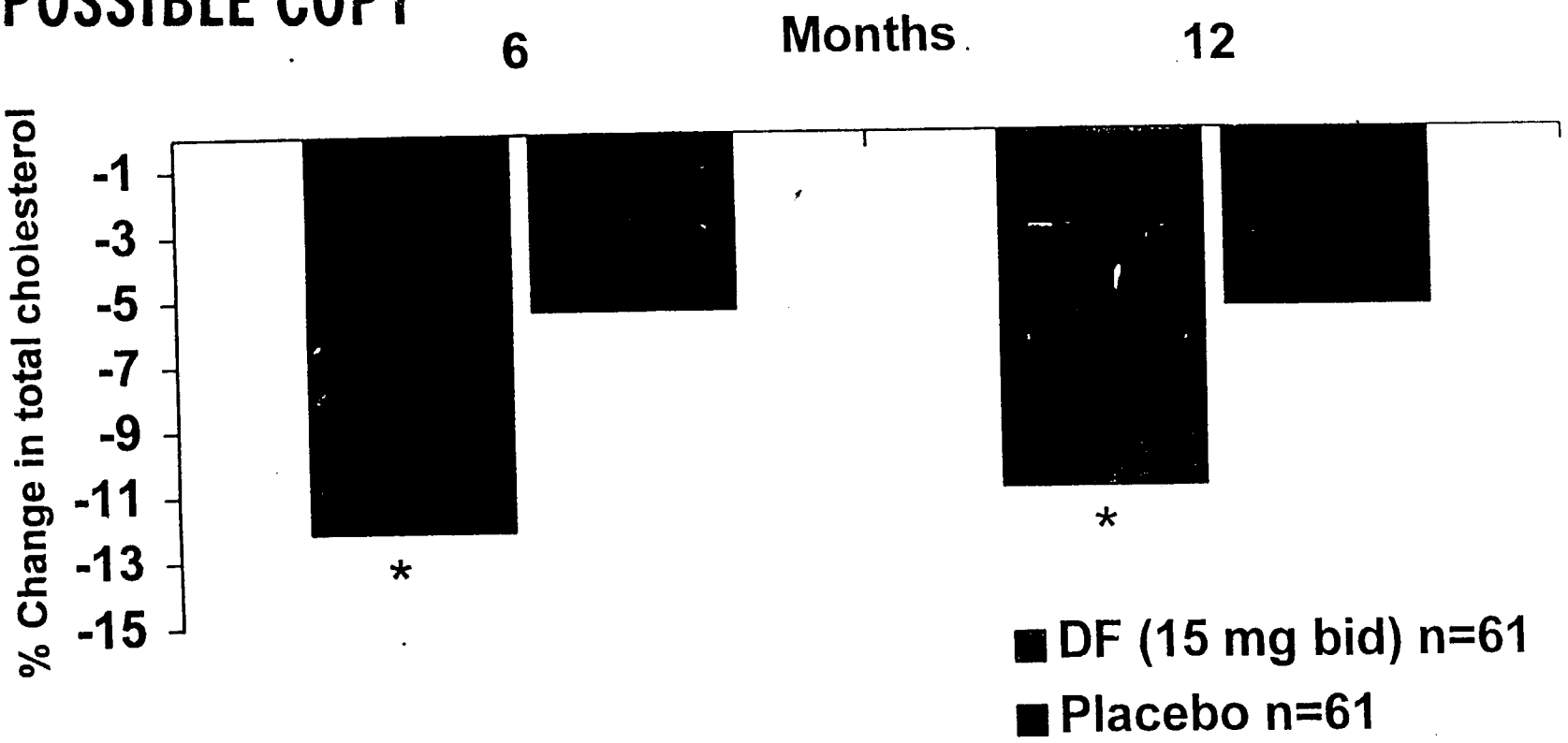
Comparison of Weight Loss Strategies in Obese Diabetic Patients



Completers

Manning et al, 1995

Effect of Dexfenfluramine on Total Cholesterol in Hypercholesterolemic Patients - INDEX



* $p \leq 0.002$

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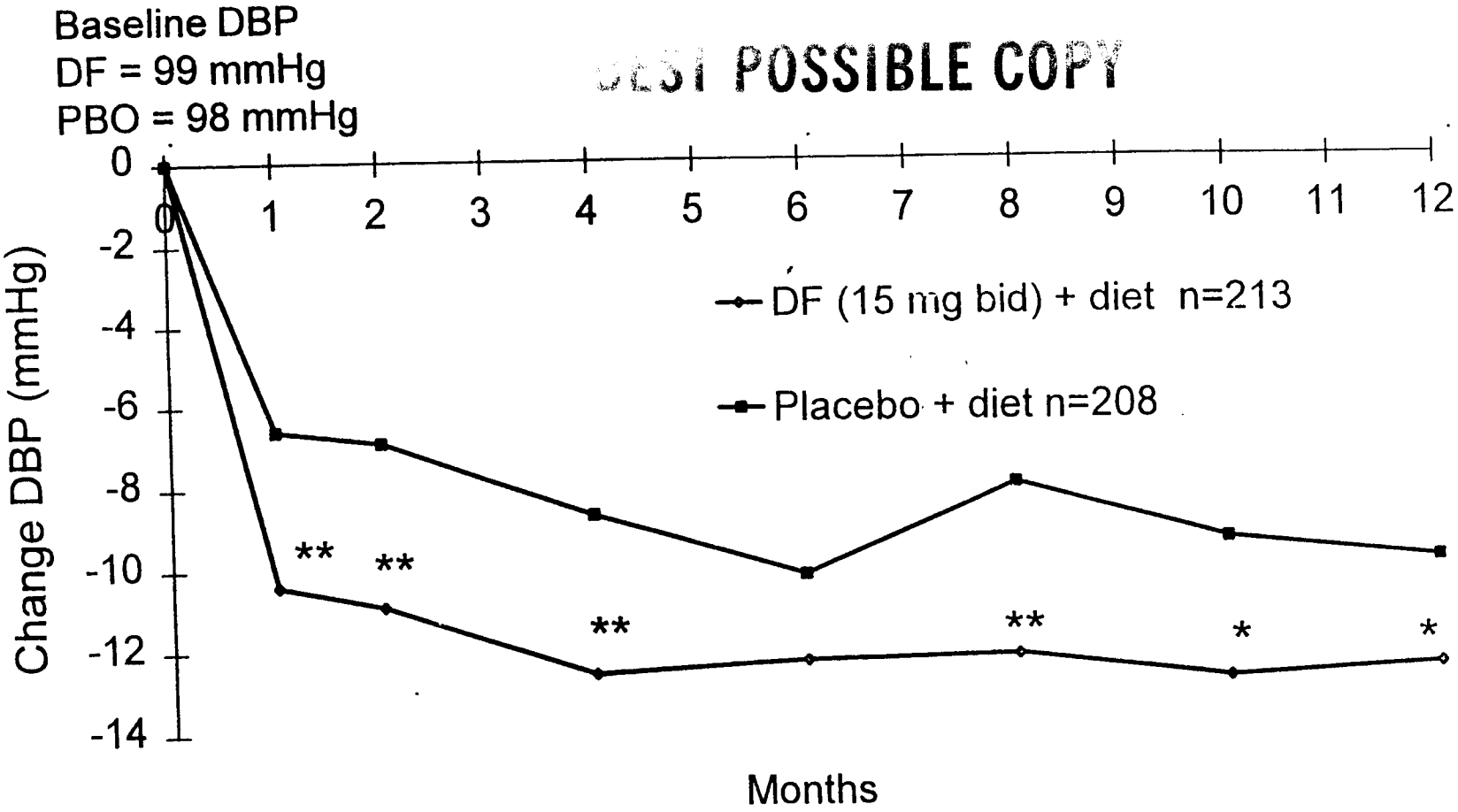
Change in Diastolic Blood Pressure in Hypertensive Patients - INDEX



*p ≤ 0.042
**p ≤ 0.001

LOCF

Kolanowski, J et al (1992). **Eur. J. Clin. Pharm.** 42:599-606.

12 week randomized, double-blind study of dexfenfluramine vs placebo in obese hypertensive subjects.

During treatment, the dexfenfluramine group showed:

(i) greater weight loss than placebo (-6.0 vs +1.4kg)
(ii) a significant drop in supine systolic (155 to 144, p 0.01) and diastolic (103 to 99 mmHg, p 0.003) BP
(iii) a significant drop in resting venous and urinary NE

These changes were present at one month and then the values gradually returned towards the baseline.

Summary

- No evidence that dexfenfluramine treatment adversely affects diabetic control, lipid concentrations or blood pressure
- Data are suggestive of favorable effects on diabetic control, lipid concentrations and blood pressure
- Dexfenfluramine is an effective weight loss agent in obese patients with comorbid conditions

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John Blundell B.Sc., Ph.D.
Chair & Professor of Psychobiology
University of Leeds, UK

1

Dexfenfluramine is Different From PCA, MDA and MDMA

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- *"We have not studied this with fenfluramine but we think that it is likely to be very similar"*
- *"While we have not done exhaustive studies ... on fenfluramine ... the effects of fenfluramine are essentially identical to those of parachloroamphetamine (PCA)"*
- *"We have observed with PCA and MDA an almost complete loss of retrograde axonal transport in the raphe neurons and ... we have not studied it with fenfluramine"*

(Transcript, September 28,1995)

2

Generally-Accepted Indices Specific for Neurotoxicity

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Measures	5,7-DHT	PCA	MDMA	MDA	DF
Silver Staining (cell degeneration)	+	+	+	+	-
↑GFAP (degeneration)	+	+	+	+	-
↓Retrograde transport (function)	+	+		+	-
Dopaminergic involvement	+	+	+	+	-

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Effects of Pair Feeding on Cortical 5-HT in the Rat (1→10mg/kg)

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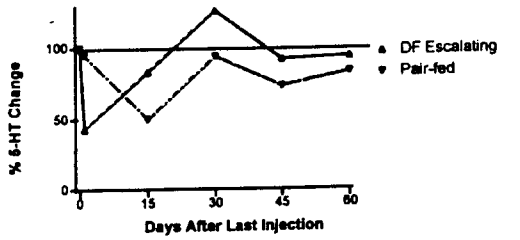

(Rose and Jenner 1994)

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Food Deprivation Alone Leads to Changes in Cortical 5-HT and Transporter Levels

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- Food deprivation in rats increases 5-HT release and lowers 5-HT levels
  (Curzon et al 1975)
- Lean mice have significantly lower (42%) brain cortex 5-HT levels than obese animals fed a high fat diet
  (Rowland 1994)
- Food deprivation in rats reduces (32%) paroxetine binding after two weeks
  (Huether et al 1995)
- Dieting lowers plasma tryptophan and upregulates 5-HT_{2c} receptors in man
  (Cowen et al 1995)

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Specific Studies Undertaken to Respond to FDA Questions

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(1) Retrograde transport

(2) Long-term study to demonstrate no adverse effects

(3) Brain concentration in humans

(4) Calculation of exposure margins

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Richard E. Gammans, Ph.D.

Vice President
Clinical Research
Interneuron Pharmaceuticals, Inc.

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Medical and Safety Review Of Clinical Behavioral and Cognitive Data on Dexfenfluramine

- Extensive clinical data available
- No important adverse clinical neurobehavioral effects

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Neuropsychological Testing of Dexfenfluramine

- Extensive data from 16 of 17 controlled trials contained in original NDA submission (May 1993)
- New data from recently completed long-term trial (Noble Long-Term Study)
- Prospectively-defined safety and efficacy endpoints
- Comprehensive dossier prepared post-September 28th meeting
- Expert panel reviewed dossier

3

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Expert Reviewers

John Rush, MD	Betty Jo Hay Chair in Mental Health UT Southwestern Medical Center Chair, DSM-IV Mood Disorders Grp.
J. John Mann, MD	Head, Department of Neuroscience NY State Psychiatric Institute Professor of Psychiatry,Columbia University
M.-Marsel Mesulam, MD	Professor of Neurology and Psychiatry Dir of Center for Behavioral & Cognitive Northwestern University Medical School
Kenneth Heilman, MD	Professor of Neurology University of Florida
Paul A. Spiers, PhD	Clinical Neuropsychologist MIT Clinical Research Center

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Expert Reviewers

Donald Robinson, MD	Professor of Psychiatry Univ of Connecticut
Ira Shoulson, MD	Lasagna Professor of Experimental Therapeutics, Univ of Rochester
Emil Coccaro, MD	Professor of Psychiatry Director of Clinical Neuroscience Medical College of Pennsylvania
Malcolm Lader, MD, PhD	Head, Clinical Psychopharmacology Professor of Psychiatry Institute of Psychiatry, London

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Symptom Complexes Reviewed for Safety

Behaviors <u>Regulated</u> by Serotonin

- Appetite (i.e., Hyperphagia)
- Mood or Emotion (Depression, Anxiety)
- Suicide & Impulsivity (Anger, Hostility, Aggression)

Behaviors <u>Affected</u> by Serotoninergic Drugs

- Sleep
- Cognitive Function
  (Attention, Concentration, Executive Function, Memory)
- Peripheral Nervous System (Paresthesia)

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Scope of Review

- Clinical Trials
  - 17 Controlled studies (14 placebo-controlled)
    - »1333 DF and 1073 placebo-treated patients
    - »10 studies ≥ 12 weeks (3 studies 6-12 months)
  - Integrated Safety Summary Database
- Post-Marketing Safety Database
- 55 publications with clinical psychological testing

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Controlled Clinical Studies with Neuropsychological Data

Study	Patients	Outcome Measures
IP92-003	n=329	Neurological Exam, HAM-D
IP92-005	n=327	Neurological Exam, HAM-D
MIT124	n=80	HAM-D
MIT296	n=87	POMS, SSS
VanItallie	n=86	BDI
INDEX	n=1047	Sleep
C010	n=74	Sleep, Activity, Mood
C003	n=39	Sleep
UK18	n=45	POMS, VAMS
Noble LT	n=71	MMS, SSS, CES-D, POMS

8

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Number of Patients Evaluated In Clinical Trials

Behaviors	Patients Evaluated	
	DF	Placebo
Appetite	458	289
Mood	662	464
Suicidal Thoughts	395	241
Impulsivity	103	101
Sleep	1117	942
Cognitive Function	80	78
Neurologic Exam	478	270

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Neurobehavioral Rating Instruments

- Mood
  - Hamilton Depression Rating Scale (HAM-D)
  - Beck Depression Inventory (BDI)
  - Center for Epidemiologic Studies (NIMH) - Depression Scale (CES-D)
  - Profile of Mood States (POMS)
- Sleep
  - Stanford Sleepiness Scale (SSS)
  - Sleep Questionnaires (SQ)

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Neurobehavioral Rating Instruments

- Cognition
  - Mini-Mental State Examination (MMS)
  - Digit Symbol Substitution Test (DSST)
  - Letter Cancelation Test (LC)
  - Digit Elimination Test (DE)
  - Simple Auditory Reaction Time (RT)
  - Continuous Performance Test (CPT)
  - Pursuit Rotor Test (PRT)
  - Critical Flicker Fusion (CFF)

11

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Effect of Dexfenfluramine on Appetite Post-Treatment

- No difference between placebo and DF-treated patients in change from baseline preference for any food type 4 to 52 weeks after DF discontinuation
  - »IP92-003 (3 mo tx, 1 mo follow-up)
  - »IP92-005 (3 mo tx, 1 mo follow-up)
  - »Noble Long-Term Study (6 mo tx, single-blind 12 mo placebo tx)

12

Effect of Dexfenfluramine on Depression During Treatment and Post-Treatment

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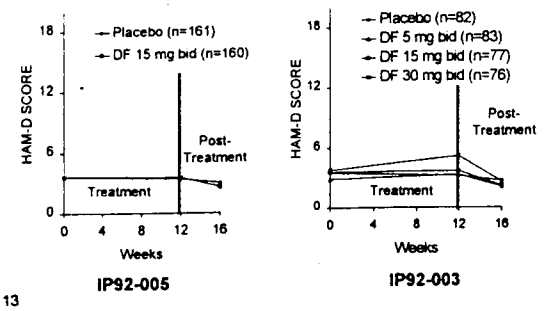

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Effect of Dexfenfluramine on Depression - Van Itallie Study

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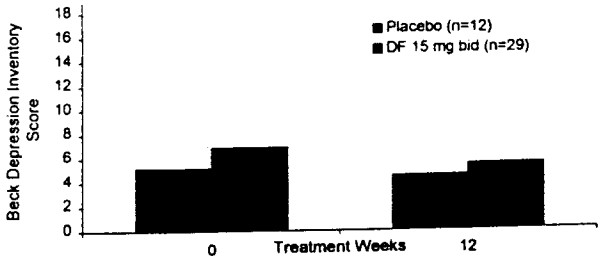

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Effect of Dexfenfluramine on Mood - UK 1

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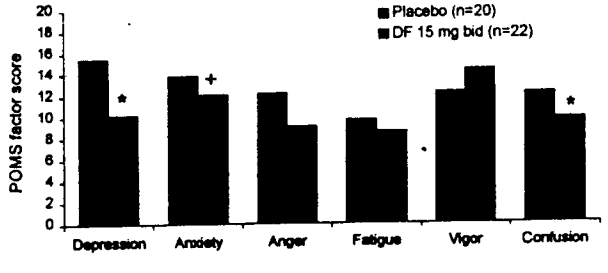

*p≤0.05, + p=0.059

LOCF

15

Effects of Dexfenfluramine on Suicidal Behavior

11/16/95

- Suicidal ideation (HAM-D item 3) is not increased on DF treatment or after abrupt discontinuation
- No change in serotonin-2 receptor number in humans (Two Clinical PET Studies)
- Low rate of suicide and suicide attempts post-marketing

	Rate/100,000/yr	
	Suicides	Suicide Attempts
Dexfenfluramine	0.003	0.06
Nurses Health Study	6	NA

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Effect of Dexfenfluramine on Impulsivity

11/16/95

- POMS Anger/Hostility
  - No difference between DF and placebo during treatment or post-treatment follow-up
- Impulsivity Indices (DSST, CPT, LC)
  - No differences between DF and placebo on DSST, CPT
  - Significantly less impulsivity on LC among DF-treated patients

17

Effect of Dexfenfluramine on Sleep Parameters

11/16/95

- Sleep Scales
  - Sleep assessments in 10 controlled studies showed mild sleepiness in DF-treated patients
    - »Early in treatment
    - »Resolved with continued treatment
  - No difference between DF and placebo following discontinuation for up to 12 months

18

Incidence of Memory Loss, Confusion and Loss of Concentration in Clinical Studies

11/16/95

	% Reporting (minus Placebo)		
	Confusion	Amnesia	Think Abn
Dexfenfluramine (n=1159)	0.1	0.8	0.9
Fluoxetine (n=1178)	NA	0.4	0.5
Paroxetine (n=2963)	1.1	0.3	1.1
Nefazodone (n=3496)	2.0	1.5	1.6
Sertraline (n=1199)	NA	< 1	0.6

19

Effect of Dexfenfluramine on POMS Confusion Factor at End of Treatment

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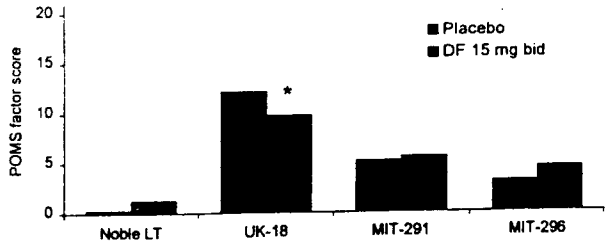

20 * $p < 0.05$ LOCF

Effect of Dexfenfluramine on Cognitive Indices

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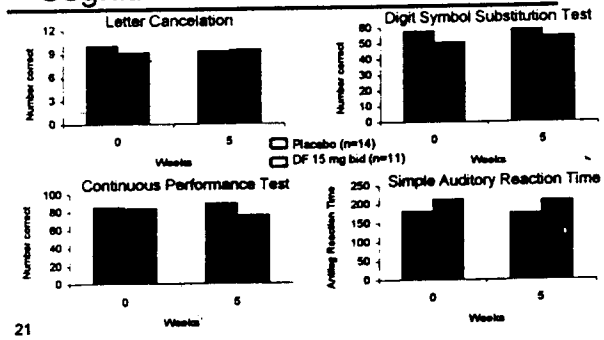

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Effects of Dexfenfluramine on Cognition

- No effect of Dexfenfluramine on:
  - Digit Symbol Substitution
  - Letter Cancelation
  - Digit Elimination
  - Simple Auditory Reaction Time
  - Continuous Performance Test
  - Pursuit Rotor
  - Critical Flicker Fusion
- No evidence of adverse effect on POMS Confusion Factor in four studies

22

Effects of Dexfenfluramine on Neurological Function

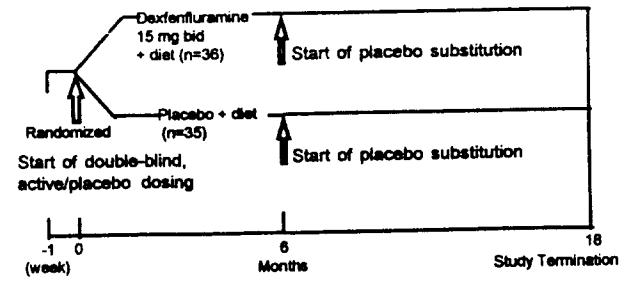
11/16/95

- A systematic neurological evaluation was included in 3 studies involving 470 DF and 254 placebo-treated patients
  - » Motor examination: muscle bulk, tone, muscle strength, deep tendon reflexes, coordination, balance
  - » Sensory examination: joint vibration, vibration, light touch, pin sensation
  - – No differences were found between DF and placebo-treated patients
- There is no difference in the incidence of paresthesia between DF (1.1%) and placebo-treated (1.1%) in the Integrated Safety Database

23

Effects of Dexfenfluramine on Cognitive Function in Obese Patients

11/16/95



24 Noble Long-Term Study

Effects of Dexfenfluramine on Cognitive Function in Obese Patients

11/16/95

	Baseline	Active Treatment 3m	Active Treatment 6m	Placebo Substitution 9m	Placebo Substitution 13m	Placebo Substitution 18m
Mood (POMS)	x	x	x	x	x	x
Cognition (MMS)	x	x	x	x	x	x
Depression (CES-D)	x	x	x	x	x	x
Sleep (SSS)	x	x	x	x	x	x

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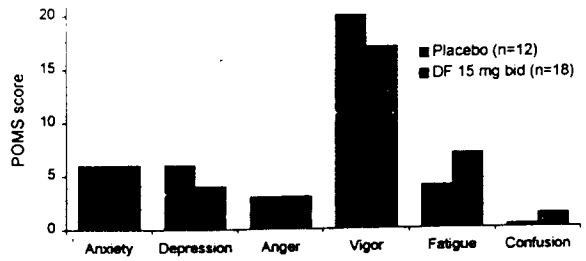
Noble Long-Term Study

Effect of Dexfenfluramine on Mood 12 Months after Double-Blind Phase

11/16/95



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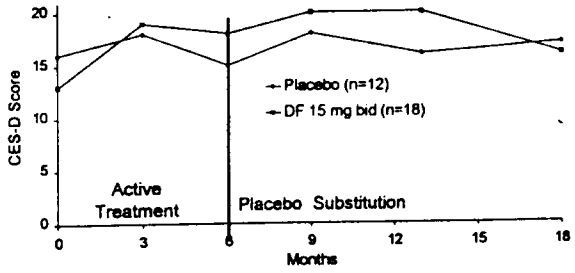
Noble Long-Term Study

Effect of Dexfenfluramine on Depression Symptom Rating

11/16/95

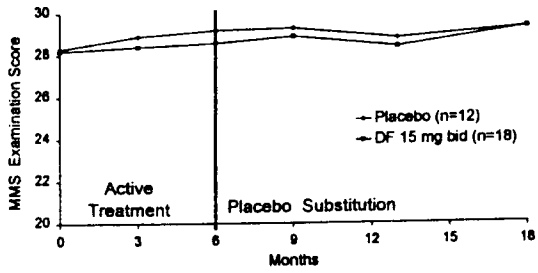


27

Noble Long-Term Study

Effects of Dexfenfluramine on Cognition

11/16/95



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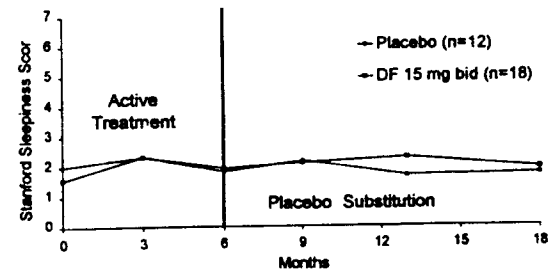
Noble Long-Term Study

Effects of Dexfenfluramine on Sleep

11/16/95



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Noble Long-Term Study

Noble Long-Term Study - Summary

11/16/95

- DF 15 mg bid did not produce any changes in mood, depressive symptoms, or cognition during 6 months of treatment compared to placebo
- No changes in mood, depressive symptoms, sleep or cognition were observed in DF-treated patients in the 12 month follow-up period when compared to placebo-treated patients

30

Effect of Dexfenfluramine on Symptom Complexes Reviewed for Safety

11/16/95

Behaviors Regulated by Serotonin

- Reduces Appetite during tx, no effect post-treatment (i.e., Hyperphagia)
- No effect on Mood or Emotion (Depression, Anxiety)
- No effect on Suicide & Impulsivity (Anger, Hostility, Aggression)

Behaviors Affected by Serotoninergic Drugs

- Mild, transient drowsiness during tx, no effect post-treatment
- No effect on Cognitive Function (Attention, Concentration, Executive Function, Memory)
- No effect on the Peripheral Nervous System (Paresthesia)

31

Conclusions

11/16/95

Following an extensive review of multiple, sensitive neuropsychological parameters in a large database of obese patients treated with dexfenfluramine, we find no evidence for neurotoxicity

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Risk and Benefit of Dexfenfluramine Treatment

11/16/95

Gerald A. Faich, M.D., M.P.H.

President
Pharmaceutical Safety Assessments, Inc.

1

11/16/95

RISKS	BENEFITS
PPH	Obesity-related Mortality Change
(IPPHS)	(Nurses Health Study, INDEX Morbidity must be considered)

2

International Primary Pulmonary Hypertension Study (IPPHS) - Origins

11/16/95

- Epidemic of PPH in Switzerland in 1960's due to amphetamine-like anorectic agent.
- Cluster of 10 to 15 dexfenfluramine associated PPH cases in early 1990's in France.

3

International Primary Pulmonary Hypertension Study (IPPHS)

11/16/95

- 95 cases - 21% exposed to anorexigens
- 355 controls - 6.5% exposed to anorexigens
- Anorexigen, obesity and systemic hypertension are independent risk factors for PPH with OR's of:

– Hypertension	=	2.5
– BMI >30	=	2.4
– DF and F	=	3.8
– All anorexigens >3 mo	=	10.6

4

Anorectic Agents and Primary Pulmonary Hypertension (PPH)

11/16/95

The international case control study (IPPHS) showed:

1. Obesity itself doubles the risk (OR 2.4)
2. DF and F exposure for less than 3 months little or no risk (lower bound near one)
3. Anorectic agents used for more than 3 months result in increased, but very rare risk (OR 10.6 and 1.9 excess cases per 100,000)

5

IPPHS Risk Estimates and Limitations

11/16/95

- 1.9 excess PPH cases per 100,000 DF treated patients is a "worst case" risk estimate since several factors may have operated to inflate this estimate.

1. Referral and diagnostic bias related to publicity
2. Recall bias
3. Obesity itself (confounding by indication)
4. Small numbers make further subset analyses precarious (fewer than 7 cases were obese and had more than 3 months of exposure)

6

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Effect of Referral and Recall Bias--IPPHS--Example

- For all anorexigens exposure for more than 3 months had a crude odds ratio of 7.5
- If 40% of cases (n=38) were not diagnosed and had the rate of exposure found for controls for a 3 month exposure (<1%), then their inclusion would drop the OR to 5.2
- Moreover, if only 2 controls had not recalled exposure of 3 months the OR would further drop to 3.7

THE POINT IS RELATIVELY SMALL CHANGES DUE TO BIASES HAVE CONSIDERABLE IMPACT

7

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IPPHS Limitations

- Case control and all observational studies measure association not cause
- Weight loss and fluctuation were not measured (serial weights were not collected--only maximum lifetime weight)
- Weight loss may be the real risk and account for most of the anorexigen association

8

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IPPHS - Origins

- Aminorex epidemic in early 60's
  - 400 to 1000 PPH cases in Switzerland, Austria, Germany
  - Rapid onset 6 months after marketing
  - Rate probably over 2000 per million (OR>1000)

9

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Nurses' Health Study

- 16 year follow-up of 115,000 nurses
- BMI and cause of death
- Age and smoking adjusted
- As BMI goes from 26 to 32:
  - All cause mortality increases 90% (968 excess lives lost per million per year)
  - CHD mortality increases 150% (575 excess lives lost per million per year)

10

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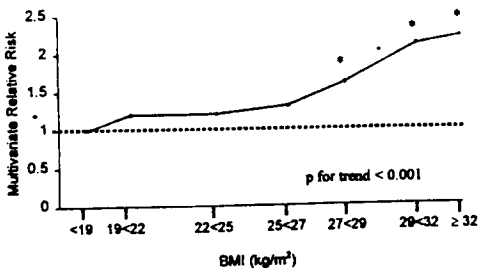
BMI and All Cause Mortality Risk, Women

Never Smokers 1980-1992 (1168 deaths)



* $p < 0.05$

Manson et al., NEJM, Sept 1995

11

11/16/95

Excess Deaths Per 100,000 Patient-Years Due to Obesity[1]

BMI[2] Change	Increased Risk[3] (Delta)	Excess[4] (Delta x 1076)
27 to 32	0.80	86
29 to 32	0.40	43
30 to 32	0.10	11

[1]NHS-Manson-Never smokers with stable weights, adjusted for age, physical activity, hormones, alcohol, dietary fat.
[2]Assuming final mean weight 191 lbs, 5'5" or 87 Kg (BMI 32)
[3]Difference between risk at 2 BMI's
[4]Using 1076 deaths for BMI 19 as referent

12

Effect of Dexfenfluramine on % Weight Loss at 12 Months from Baseline

11/16/95

Weight Loss	% Distribution INDEX (n=490)	EFIM (n=1400)
>15%	29	52
10-14.9%	23	
5-9.9%	20	24

13

Risk Benefit Assessment for Responders

11/16/95

- Start treatment of 100,000 women with a mean BMI of 32*
- Use INDEX to estimate change in BMI
- Use Nurse's Health Data to estimate benefit in terms of lives saved
- Use IPPHS to estimate risk

*range 30 to 34, average is woman 87 Kg and 1.65 m

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Benefit Model

11/16/95

Treat 100,000 women with mean BMI of 32[a] with DF for 1 year
Achieving the following results persisting for a year

No. (%)[b]	Loss Kg (% Body Wt)	Resultant BMI	Deaths Avoided[c]
20,000 (20%)	13.0 (15%)	27	17.2
20,000 (20%)	8.7 (10%)	29	8.6
20,000 (20%)	4.3 (5%)	30	2.2
Total Lives Saved Per 100,000 Treated Per Year			28.0

[a]range 28-36, mean wt. 191 lb 5'5" or 87 Kg and 1.65 m
[b]Conservative based on INDEX values (34% dropped BMI ≥6 units, 25% dropped 3 units, 30% dropped one unit)
15 [c]no. X data from Manson tables

Best Estimate of Benefit and Risk 100,000 Treated

11/16/95

1. Because of discontinuations in nonresponders, exposure and risk will be halved (from 1.9 to 1).
2. Adjusting for bias in the risk estimate probably halves the risk for the remaining patients.
3. Thus risk is likely to be less than 1/2 PPH case.
4. Benefit includes 28 lives saved and 44 myocardial infarcts and strokes prevented (total 72).
5. Thus, the benefit-to-risk ratio is about 144.

16

Can Weight Loss Reduce Mortality?

11/16/95

Weight Loss Results In:

1. Prompt improvements in glycemia, lipids, hypertension and quality of life.
2. 20% Reduction in all-cause mortality particularly for those with comorbidity.[1]
3. 50% Reduction in NIDDM with loss of 5 kg.[2]
4. 69% "cured" of NIDDM and 43% "cured" of hypertension after GI surgery.[3]

[1]ACS data AJE 1988
[2]Colditz et al. Ann Int Med 1995;481
17 [3]Swedish Obesity Study, 1995

Benefit / Risk Issues

11/16/95

1) Placebo Effect

Half of benefit due to diet, exercise and placebo. While true, the structure provided by trials is absent in most practice settings.

2) Risk is higher (not 1.9 but 2.7 per 100,000)

IPPHS data thin (fewer than 7 obese cases treated for 3 months)

Benefit to risk is still very large (considering serious morbidity and limited exposure because of discontinuations 72 ÷ 2.7 x ½ = 53)

18

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Conclusions

1. IPPHS results may have been affected by publicity and referral patterns and recall bias.
2. Obesity is an independent risk for PPH.
3. Absolute risk of dexfenfluramine-associated PPH is very small.
4. Dexfenfluramine is effective and will prevent excess obesity-related deaths.
5. The benefit to risk ratio is very large.

19

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11/16/95

Marc W. Deitch, M.D.

Vice President, Medical Affairs
Medical Director
Wyeth-Ayerst Laboratories

1

11/16/95

Phase IV Considerations

- Interneuron and its marketing partner Wyeth-Ayerst are committed to carrying out any required Phase IV investigations in a timely and expeditious manner

2

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Phase IV Considerations

- Wyeth-Ayerst and Interneuron have met with the Division on two separate occasions to discuss Phase IV considerations and clinical trial design

3

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