

66 b. Saltzman, M.B. Safty of phenylpropanolamine. Ann. Emerg. Med. 12, 590/129-130/591 (1983).

This is a rebuttal of the article by Bernstein and Diskant (Ann. Emerg. Med. 11, 311-315, 1982, (Reference No. 43).

Category:  
Review.

67. Latimer, D. The peashooter perplex. High Times. Part I, August 1983, pp.60-65; Part II, September 1983, pp.40-45; Part III, October 1983, pp.45-97.

These are highly unscientific articles, not amenable to scientific critique.

Category:  
Review.

68. Rumpf, K.W. Horstkotte, H., and Bahlmann, J. Rhabdomyolysis after ingestion of an appetite suppressant. J. Amer. Med. Assoc. 250, 2112 (1983).

This report involves cathine, an isomer of phenylpropanolamine.

Category:

Phenylpropanolamine analog.

69. Clark, J.E., and Simon, W.A. Cardiac arrhythmias after phenylpropanolamine ingestion. Drug Intell. Clin. Pharm. 17, 737-738 (1983).

A 43-year-old female was admitted to the hospital with palpitations, shortness of breath, tinnitus, dizziness, diaphoresis, and inability to stand. Blood pressure was 180/120 mm Hg. After treatment with clonidine, the patient remained hypertensive (162/112 mm Hg) 24 hours later.

This patient had a history of hypertension. She admitted to taking an unspecified quantity of capsules (containing 75mg phenylpropanolamine and 200 mg caffeine per capsule) at a time not specified before symptomatology developed. ECG on admission revealed paroxysmal atrial tachycardia, which apparently resolved within 24 hours. Anxiety may have played a part in the patient's P.A.T. and initial elevated blood pressure. Use of other drugs was not addressed.

Category:

Overdoses, combinations of drugs, drug misuse.

70. Saltzman, M. B., Dolan, M.M., and Doyle, N. Comparison of effects of two dosage regimens of phenylpropanolamine on blood pressure and plasma levels in normal subjects under steady-state conditions. Drug Intell. Clin. Pharm. 17, 746-750 (1983).

Fourteen nonobese, normotensive male subjects participated in a random crossover study in which they were given either 25 mg phenylpropanolamine (nonsustained release tablets) 3 times per day or 75 mg phenylpropanolamine (sustained release capsule) once a day for a 4 day period. Supine and erect blood pressures were recorded at 0, 0.5, 1, and 2 hours after dosing on days 1, 2, and 3, and every hour for 12 hours on day 4. Blood was taken at various intervals during day 4; plasma concentrations of phenylpropanolamine were measured.

Mean values of systolic and diastolic blood pressures on day 4 in both regimens appeared to be the same; mean systolic pressures rose slightly during the 12 hours (from about 105 to about 117), but mean diastolic pressures did not seem to vary appreciably. Diastolic pressure rose above 90 in only one subject; he was on the 25 mg t.i.d. schedule, and this rise occurred 7 hours after the start of the study and 3 hours after the second 25 mg dose. Plasma concentrations of phenylpropanolamine did not seem to correlate well with blood pressures, but the concentrations indicated that both regimens (sustained and nonsustained release) had equal bioavailability.

One of the main problems with this study is lack of statistical analyses; thus, changes in blood pressures of each individual subject are not assessible. Although the authors commented on the peak diastolic pressure attained in one subject, they did not mention the peak systolic pressure measured, except in the boxes in Figure 1. Here, the maximum peak systolic pressure appears to be in Subject 1 (144 mm Hg on the sustained-release regimen at 11 hours), but the baseline pressure of the subject is not stated.

70 a. Johnson, D.A., Etter, H.S., and Reeves, D.M. Stroke and phenylpropanolamine use. Lancet 2, 970 (1983).

These cases appear to be overdoses. The first patient admitted a daily intake of 8-10 Dexatrim capsules (50 mg phenylpropanolamine and 200 mg caffeine per capsule) -- the author called them "pills" -- over a 3-month period. The second patient admitted to taking 3-9 Dietac preparations (37.5 mg phenylpropanolamine per "pill") over a 4-month period. It is likely that these patients took considerably more of these products than they admitted to.

Category:  
Overdoses, combinations of drugs, drug misuse.

71. Brody, J.E. Pills to aid the dieter: how safe are they?  
New York Times, November 9, 1983.

This newspaper article presents no new information of use in assessing the safety of products containing phenylpropanolamine.

Category:

Review.

71 a. Silverman, H.I. Letter to the Editor, New York Times,  
November 14, 1983.

This is a copy of a letter sent to the Editor, New York  
Times, refuting Jane Brody's column published in the November  
9, 1983 edition of that newspaper.

Category:

Review.

(cables)

ANALYSIS OF PUBLISHED ADVERSE REACTION REPORTS  
IN WHICH PPA WAS AN INGREDIENT

Reporting Period: 1965 through 1983

April 30, 1984

Prepared by:

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ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
CATEGORY: DRUG INTERACTION

INDEX <sup>1</sup> NO.	REPORTER	SUBJECT(S)	AGE(S)	SEX	MEDICAL HISTORY	PRODUCT <sup>2</sup> CATEGORY	PRODUCT/ DOSAGE	REPORTED <sup>3</sup> REACTION	ONSET = O DURATION = D TREATMENT = T <sub>x</sub>	OUTCOME	CONCLUSIONS
6	CUTHBERT <u>Brit Med J,</u> 1969, 1, 404-6	1 of 3 cases		M	Not available	T	50mg PPA MAO inhibitor, taken with tranlycypromine	Modest BP incr. at 50 mg, pro- nounced BP in- crease with MAO inhibitor	T <sub>x</sub> = phentolamine to reduce BP	No sequelae	Known drug interaction
	TONKS <u>Brit Med J,</u> 1965, 1	2 cases	45	F	Not available	C	Procol capsule 50 mg PPA 2.5mg isopropa- mide per cap. taken with MAO inhibitor	BP increase		No sequelae	Known drug interaction
			28	F	Not available	C	Procol capsule 50mg PPA 2.5mg isopropa- mide per cap. taken with MAO inhibitor	BP increase		No sequelae	Known drug interaction
49a	SMOOKLER <u>Annals of Emer Med,</u> 1982, 11:482- 484	1 case	28	M	Chronic depression	A	Anorectic 75 mg PPA with MAO in- hibitor (Nardil)	BP increase 180/120 Vomiting Headache	O = 1 hr. D = 24 hrs. T <sub>x</sub> = phentolamine to reduce BP	No sequelae	Overdose and drug inter- action, label warn- ing ignored
11	MCLAREN <u>Brit Med J,</u> 1976; 2; 283-284	1 case	31	M	Patient with glomerulo neph- ritis	C	250 mg Methyl- dopa (bid) 160 mg oxpre- nolol (tid) for prior hyper- tension  Triogesic (2 tabs, tid) 12.5 mg PPA 500 mg aceto- minophen per tab	BP: 200/150 Headaches Nausea	D = Discontinue Triogesic	BP returned to normal; continued on hypertensive medication	

<sup>1</sup>Index No.: Reference to Master Abstract number taken from "PPA Adverse Reaction Reports and Safety Studies."

<sup>2</sup>Product Category: T = Test drug; I = Illicit drug; A = Anorectic; C = CCABA type

<sup>3</sup>Reported Reaction: Blood pressure expressed in mm Hg

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
CATEGORY: DRUG INTERACTION

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15	CHOUINARD <u>Canadian Med</u> <u>Assoc J, 1978,</u> <u>119; 729-731</u>	1 case	27	F	Schizophrenia	C	1 Contac capsule 50 mg PPA 4mg chlorphenir- amine maleate 100 mg thiori- dazine	Ventricular arrhythmias Edema	O = 2 hrs	Fatal	Cardiac toxicity in- duced by thioridazine
	MASON <u>Brit Med J</u> <u>3/29/69;p.845</u>	1 case	38	F	Nardil (3 months)	C	Mucron tablet 32 mg PPA with MAO inhibitor	Frontal head- ache BP: 210/100	O = 15 min D = 10 hrs. T <sub>x</sub> = pethidine	No sequelae	Known drug interaction
	HUMBERSTONE <u>Brit Med J;</u> <u>3/29/69, vol. 1</u>	1 case	36	F	Berry aneurism	C	2 Mucron tablets phenactin 32 mg PPA 30mg phenylzine per tablet	Vomiting Photophobia Intercranial hemorrhage	O = 3 hrs	No sequelae	

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
 CATEGORY: NEUROLOGICAL DISTURBANCES

INDEX NO.	REPORTER	SUBJECT(S)	AGE(S)	SEX	MEDICAL HISTORY	PRODUCT CATEGORY	PRODUCT/ DOSAGE	REPORTED REACTION	OUTCOME = O DURATION = D TREATMENT = T <sub>x</sub>	OUTCOME	CONCLUSIONS
26	SCHAFFER <i>Am J Psychiat</i> 1980, 137:1256-1257	1 case	23	F		A	Permethene cap Dexatrim (6-10 per day) 150-300mg PPA 600-1200mg caffeine	Psychotic episode	O = 3 days D = 3 days T <sub>x</sub> = no drugs	No sequelae	Overdose
20	DEOCAMPO <i>J of the Med Soc of NJ</i> , 1979, 76, 591-92	1 case	44	F	Convulsive seizures at age 5 from cold medication	A	Diadex (anorectic) capsule 75mg PPA	Severe headache Blurred vision Sweating Grand mal seizure BP: 180/90	O = 1 hr D = 6 days T <sub>x</sub> = diazepam; dilatin	No sequelae	Prior history of neurological disorders
28	ACHOR <i>Am J Psychiat</i> , 1981, 138:3	3 cases	32	F	Postpartum dysphoric mood	A	Dexatrim capsule 75 mg PPA 200mg caffeine	Psychosis	O = 2 weeks	No sequelae	
			51	F	Mood irritability	A	Control capsule 75 mg PPA	Psychosis	O = 2 weeks	No sequelae	
			19	M	Family history of bipolar affective disorders	A	Dexatrim capsule 100 mg PPA 400mg caffeine	Psychosis	O = 3 months	No sequelae	Overdose

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
 CATEGORY: NEUROLOGICAL DISTURBANCES

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27	DIETZ JAMA, 1981; 245; 601-602	7 cases	20	F	Not available	A	75 mg PPA 1 capsule	Anxiety Agitation Dizziness *RR: 28 Pulse: 110bpm	O = 1-2 hrs D = 2-4 hrs	No sequelae	All 7 Dietz cases taken from Emergency Room records
27				F	Not available	A	75 mg PPA 200 mg caffeine 1 capsule	Anxiety Agitation Hallucinations Dizziness RR: 34 Pulse 120bpm	O = 1-2 hrs D = 2-4 hrs	No sequelae	
17				F	Not available	A	50 mg PPA 1 capsule	Agitation Dizziness RR: 26 Pulse 98bpm	O = 1-2 hrs D = 2-4 hrs	No sequelae	
22				F	Not available	A	75 mg PPA 1 capsule	Agitation Dizziness RR: 24 Pulse: 110bpm	O = 1-2 hrs D = 2-4 hrs	No sequelae	
45				F	Not available	A	50 mg PPA 200mg caffeine 1 capsule	Agitation Hallucinations RR: 20 Pulse: 95bpm	O = 1-2 hrs D = several days	Hospitalization for acute psychosis resolved over several days	
22				F	Not available	A	75 mg PPA 200mg caffeine 1 capsule	Anxiety Agitation RR: 26 Pulse: 108bpm	O = 1-2 hrs D = 2-4 hrs	No sequelae	
24				F	Experienced similar re- action to this one years earlier resulting in hos- pitalization and neurological examination	A	75 mg PPA 1 capsule	Anxiety Agitation Dizziness RR: 28 Pulse: 102bpm	O = 1-2 hrs D = 2-4 hrs	No sequelae	

\*RR = respiration rate  
in breaths per  
minute

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
 CATEGORY: NEUROLOGICAL DISTURBANCES

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23	NORVENIUS <u>Lancet, 1979, 11</u> 1376-1368	61 cases	Children up through 15 years (48 of the 61 cases)	M,F	Not available	C	Medications taken with PPA include antihistamines	Restlessness Irritability Aggressiveness Sleep disturbances Psychic disturbances		No reported sequelae	
		2 cases	3,8	M	Not available	C	Medications taken with PPA include antihistamines	Psychosis	O = 2 hrs D = 2 hrs	No sequelae	
		1 case	4	F	Not available	C	Medications taken with PPA include antihistamines	Psychosis Grand mal seizure		No sequelae	
		1 case	25	F	Not available	C	Medications taken with PPA include antihistamines	Psychosis	D = 1 day after stopping medication T <sub>x</sub> = cessation of drugs	No sequelae	
		1 case	17	M	Prior admissions to mental hospital	C	Medications taken with PPA include antihistamines	Psychosis Motor excitement Aggressive behavior		No sequelae	
7	CORNELIUS <u>Am J Psychiatry</u> 1984; 141, 120	1 case	28	F	Borderline personality disorder; history of suicide attempts and poly-substance abuse. 2 prior grand mal seizures in previous 6 mos following ingestion of large surreptitious amounts of Tramincol; symptoms suggestive of temporal lobe phenomena	C	Tramincol (12 oz "binge") Total drug content: 900 mg PPA HCl 450mg pheniramine maleate 450 mg pyrilamine maleate 1080mg dextromethorphan HBr 6.5g ammonium chloride	Paranoia Homicidal behavior Grand mal seizure	O = 24 hrs D = 5 days T <sub>x</sub> = 10mg i.v. with diazepam	Clinical temporal lobe seizure when rechallenged with 50mg PPA	Drug overdose mixed with alcohol

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
 CATEGORY: NEUROLOGICAL DISTURBANCES

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4	KANE <u>Am J Psychiat</u> 1966, 123, 484-487	3 cases	68	F	Acute rheumatoid arthritis Psychotic episode with prior medication	C	Ornade capsule 50 mg PPA 2.5 mg isopropamide 8mg chlorpheniramine per cap.	Psychosis	O = 3 weeks after medication	No sequelae	
			35	M	No history of emotional instability	C	Decongestant 50 mg PPA	Psychosis	O = 6 weeks after medication	No sequelae	
			36		Schizophrenia	C	Ornade capsules (bid)	Psychosis		No sequelae	
7	WHARTON <u>Brit J Psychiat</u> 1970, 117; 439-440	1 case	37	M	Consumed 30 tablets in 8 days	C	Super Anahist tablets Ascorbic acid Caffeine Aspirin 97.2mg phenacetin 12.5mg PPA 6.25mg thonzylamine HCl 6.25mg phenyltoloxamine per tablet	Psychosis	O = 8 weeks after medication	None reported	Overdose
27b	LEWITH <u>J Royal Coll of General Practitioners,</u> 1981, 31, 225	1 case	8	F	Bronchospasm	C	Dimotapp Elixir (combination product) 5 mg PPA 4 mg brompheniramine 5 mg phenylephrine HCl Haloperidol	Spasmodic torticollis (may have been present before) Oculogyric crisis	T <sub>x</sub> = stop medication	No sequelae	

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
CATEGORY: NEUROLOGICAL DISTURBANCES

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INDEX NO.	REPORTER	SUBJECT(S)	AGE(S)	SEX	MEDICAL HISTORY	PRODUCT CATEGORY	PRODUCT/ DOSAGE	REPORTED REACTION	ONSET = O DURATION = D TREATMENT = T <sub>x</sub>	OUTCOME	CONCLUSIONS
62a	MUELLER <u>Neurology, 1983</u> <u>33, 650-652</u>	11 cases	38	M	Not available	I	5-6 "pink pills" (PPA plus un- identified sub- stance in urine) Dose not given	Headache Tremors	0 = 1 hr	None reported	Illicit drug use
			37	M	Not available	I	"speed"	Headache Vomiting	0 = 1 hr	None reported	Illicit drug use
			22	M	Not available	I	3 "black beauties"	Severe Headache ECG abnormal	0 = 3 hrs	None reported	Illicit drug use Overdose
			21	M	Not available	I	2 "black beauties"	Headache Tremor Diaphoresis Nausea Vomiting Pupils were 8/8 and poorly reactive		None reported	Illicit drug use
			19	F	Not available	I	"pink ladies" "speckled pups"	Headache Diaphoresis Vomiting ECG abnormal	0 = ½ hr	None reported	Illicit drug use
			29	M	Not available	I	2 "black beauties" Marijuana	Bizarre behavior		None reported	Overdose Illicit drug use
			25	F	Not available	I	Overdose of "unknown white pill"	Acute psychosis Chronic undifferentiated schizophrenia		None reported	Overdose Illicit drug use
			13	M	Not available	?	None stated	Attempted suicide by hanging		None reported	
			17	F	Not available	I	Several "black beauties"	Alleged sexual assault		None reported	Overdose Illicit drug use
			17	F	Not available	I	50mg PPA 25mg pseudo-ephedrine 200mg caffeine	Seizures	0 = 20 min	None reported	Illicit drug use
			27	F	Not available	I	g caffeine 25mg ephedrine	Seizure	0 = 11 hrs	None reported	Illicit drug use

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
CATEGORY: NEUROLOGICAL DISTURBANCES

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INDEX NO.	REPORTER	SUBJECT(S)	AGE(S)	SEX	MEDICAL HISTORY	PRODUCT CATEGORY	PRODUCT/ DOSAGE	REPORTED REACTION	ONSET = O DURATION = D TREATMENT = T <sub>x</sub>	OUTCOME	CONCLUSIONS
43	BERNSTEIN <u>Annals of Emer Med, 1982, 11; 311-315</u>	1 case	18	F	None	C	2 Comtrex tab. (Combination product). 25mg PPA 1mg CPM 10mg DMHBR 325mg APAP per tablet	BP: 210/130 Pulse: 120bpm Grand mal seizure Severe headache Blurred vision Nausea Epigastric pain Shakiness	O = 2½ hrs T <sub>x</sub> = diazepam; hydroxyzine	No sequelae	
51	MUELLER <u>Ann Neurol, 1982 11, 322</u>	1 case	17	F	Not available	I	Illicit drug; PPA with pseudoephedrine caffeine and another drug 1 tablet	Seizure Headache	O = 20-30 mins D = days T <sub>x</sub> = phenobarbital 90mg/day	No sequelae	Illicit drug containing PPA with PSE and caffeine
70a	JOHNSON <u>Lancet, 1983, ii, 970</u>	2 cases	24	M	None	A	Anorectic 400-500mg PPA 1.6-2g caffeine for 3 mos	Right sided hemiparesis		No neurological deficit after 1 year	Overdose
			34	M	Anorectic use for 4 mos	A	Anorectic; 113-300mg PPA per day for 4 mos	Right sided hemiparesis		No neurological deficit after 10 months	Overdose
59	LAKE <u>J Clin Psychopharm April 1983, 3 97-100</u>	1 case	21	M	No prior manic episode 2 yrs earlier had depression and abused drugs Family has history (2 of 4 older siblings) of mania, both w/ major bipolar affective disorder	I	4 "black beauties" each contain: 100-200mg caff. 25mg ephedrine 50mg PPA	Psychosis Palpitations Diaphoresis Flushing Hyperactive	O = 30 min D = 3 weeks T <sub>x</sub> = thioridazine (300mg daily)	Subsequent psychological testing subject had major bipolar affective disorder and to be manic	Overdose Illicit drug use

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
 CATEGORY: RENAL FAILURE/ANALGESIC NEPHROPATHY

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INDEX NO.	REPORTER	SUBJECT(S)	AGE(S)	SEX	MEDICAL HISTORY	PRODUCT CATEGORY	PRODUCT/ DOSAGE	REPORTED REACTION	ONSET = O DURATION = D TREATMENT = T <sub>x</sub>	OUTCOME	CONCLUSIONS
17a	BENNETT <u>Lancet</u> , 1979, ii, 42-43	1 case	28	F	Not available	A	Fullstop; 25 mg PPA/tablet for 3 weeks; also 325 mg ASA .650mg APAP (tid)	Renal failure BP: 100/60 pulse: 102bpm Tenderness in abdominal wall	O = 3 weeks D = 3 months	Full re- covery after 3 months	Possible analgesic nephropathy
45a	KNAPP <u>Arch Intern Med</u> , 1982, 142; 1197- 1199	1 case	37	M	propoxyphene 8 caps/day; APAP (tid) used daily for several years	C	Sinutabs (com- bination pro- duct) acetaminophen phenacetin PPA phenyltoloxamine citrate propoxyphene over 6 mo period	Analgesic nephropathy		None reported	PPA use in- cidental to analgesics, the actual causative agents
49	SWENSON <u>JAMA</u> , 1982, 248(10)	1 case	21	M	"binge drinking"	A	30-50 Dexatrim capsules 50 mg PPA 200 mg caffeine per tablet with 9½ quarts malt beverage	Renal failure Weakness Gastrointes- tinal bleeding BP: 100/60 Serum creatinine: 11.3ng/dl		In 3 days serum crea- tinine con- centration was 2.7mg/dl	Overdose with excess alcoholic intake; potential rhabdomyoly- sis
30b	DUFFY <u>Southern Med J</u> 1981, 74 1548-1549	1 case	25	M	suicidal	A	34 diet "pills" providing total dose of 1.2 g PPA 5.0 g caffeine	BP: normal Anorexia Malaise/fatigue Acute renal failure	O = 12 hours D = 7 days	No sequelae	Overdose with sui- cidal intent

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
CATEGORY: CARDIOVASCULAR

INDEX NO.	REPORTER	SUBJECT(S)	AGE(S)	SEX	MEDICAL HISTORY	PRODUCT CATEGORY	PRODUCT/DOSAGE	REPORTED REACTION	ONSET = O DURATION = D TREATMENT = T <sub>x</sub>	OUTCOME	CONCLUSIONS
2	OSTERN <u>JAMA, 1965;</u> <u>194,240</u>	1 case	20	M	No hypertension or headaches	C	4 Ornade span- sules containing a total of: 200 mg PPA 10mg isopropa- mide iodide 32mg chlorphen- iramine HCl	Severe head- ache BP inc:220/120 Pulse: 110bpm Disoriented Photophobia Hyperactive reflex	O = 20 min D = 18 hrs	No sequelae	Overdose
3	LIVINGSTON <u>JAMA, 1966; 196,</u> <u>143</u>	2 cases		M		C	Contac, each capsule has 50mg PPA, dose not stated	BP inc: 180/110		No sequelae	
8	GIBSON <u>Lancet, 1972,</u> <u>ii, 492</u>	1 case	28	M	Not available	C	2 Mucron tabs containing 64 mg PPA; hard cheese	BP increase Chest tightness Headache		No sequelae	
26b	PATTERSON <u>J of Forensic Sci</u> <u>1980, 2512</u>	1 case	19	F	Suicidal	C	10-12 RuTuss tabs containing a total of: 600 mg PPA 300mg PSE 96mg CPM 3 mg BA	Acute respira- tory distress Endocarditis		Fatality from non- bacterial endocarditis	Overdose with sui- cidal intent
53	WEESNER <u>Clin Pediatrics,</u> <u>1982, 21:700-701</u>	1 case	14	F	Suicidal	I	Illicit drug use; 50 mg PPA 25 mg ephedrine 200mg caffeine 15-18 capsules	Arrhythmia Pulse: 180bpm Nervousness Tremors Blurred vision	O = 1-5 hrs T <sub>x</sub> = Ipecac, charcoal, lidocaine propranolol	No sequelae	Overdose with sui- cidal intent
	MISAGE <u>Brit Med J,</u> <u>11/7/70,</u> <u>vol. 4</u>	1 case	46	F	Hypertensive (4 years); bethanidine	C	3 Ornade capsules 50 mg PPA 8 mg chlorphen- iramine 2.5 mg isopropa- mide per capsule	Hypertension	D = 15 hrs	No sequelae	Overdose

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
CATEGORY: CARDIOVASCULAR

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9	PETERSON <u>JAMA, 1973;</u> <u>223</u>	1 case	15	F	Anorectic used for several weeks	A	25 mg PPA 25 mg caffeine (tid) for 5 weeks	Vomiting Occipital headache BP: 188/112 210/130 Paroxysms of ventricular and atrial tachycardia	T <sub>x</sub> = 0.8mg atropine sulfate 60mg lidocaine	No sequelae	
5	SHAPIRO <u>N Eng J Med, 1969; 280:1363</u>	1 case		F	Normotensive	A	25 mg PPA	BP increase		None reported	
55	HOWRIE <u>J of Pediatrics; 1983, 102</u>	1 case	13	F	Not available	A	75mg PPA 200mg caffeine (o.d. for 14 days, b.i.d. for 1 day)	BP: 210/100 Headache Seizure Nausea	O = 2 hrs D = several hrs T <sub>x</sub> = phenytoin	No sequelae	Overdose
69	CLARK <u>Drug Intelligence and Clinical Pharmacy, 1983; 17, 737-738</u>	1 case	43	F	Hypertension	A	75 mg PPA 200 mg caffeine (Dose unknown)	Palpitation Shortness of breath Tinnitus Dizziness Diaphoresis Tachycardia BP decrease from 180/120 to 140/110	D = 24 hrs T <sub>x</sub> = clonidine	No sequelae	Dose unknown
19	HOROWITZ <u>Med J Aust, 1979, 1, 175-176</u>	1 case	17	F	Not available	A	Trimolets 85 mg "PPA," immediate release; 6 capsules equivalent to 510mg PPA	Dizziness Headache Nausea (after 6 Trimolets) BP: 200/120 Rechallenge with 1 Trimolelet: no adverse effect on pulse, but BP increased	O = 3 hrs D = 48 hrs T <sub>x</sub> = bedrest	No sequelae	Same as above

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
CATEGORY: CARDIOVASCULAR

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16	FREWIN <u>Med J Aust;</u> 1978; <u>2</u> , 497-498	1 case	21	F	Not available	A	Trimolets 85 mg "PPA" 1 capsule	Severe head- ache Vomiting BP: 190/120	O = 1½ hr D = 5½ hrs	No sequelae	Foreign dosage form with excessively high dose
17	LEE <u>Lancet</u> , 1979, <u>1</u> , 1110-1111	1 case	27	F	Not available	A	Trimolets (od) 85mg "PPA" for some months Indomethacin cap- sule  With Trimolets alone: No blood pressure change With indomethacin: slight blood pressure increase	BP: 200/110 Headache	O = 15 min D = 1 day T <sub>x</sub> = morphine, phentolamine	No sequelae	Same as above
21	KING <u>Med J Aust</u> , 1979; <u>2</u> , 258	1 case	29	F	Not available	A	Trimolets, 85mg "PPA" 1 capsule	Chest tight- ness Dyspnea Palpitations Neck pain High BP Irregular HR	O = 30 min D = 1 day	No sequelae	Same as above
22	TEH <u>Med J Aust</u> , 1979, <u>2</u> , 425-426	1 case	23	M	Not available	C	2 Contac caps 50mg PPA 0.2mg bella- donna alka- loids/cap	Weakness Headache Pounding chest BP: 160/110	O = 4 hrs D = 1 day T <sub>x</sub> = bedrest	No sequelae	Same as above
24	HOROWITZ <u>Lancet</u> , 1980, <u>1</u> , 60-61	20 of 37 cases tested	21-28		Not available	C	Trimolets @ 85mg "PPA" immediate re- lease	Diastolic BP greater than 100 in 12 Ss	O = 1-3 hrs	No sequelae	Same as above
		4 of 34 cases tested	21-28		Not available	A	Contac @ 50mg PPA controlled re- lease	Diastolic BP greater than 100 in 4 Ss	O = 1-3 hrs	No sequelae	Same as above

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
CATEGORY: CARDIOVASCULAR

13

INDEX NO.	REPORTER	SUBJECT(S)	AGE(S)	SEX	MEDICAL HISTORY	PRODUCT CATEGORY	PRODUCT/ DOSAGE	REPORTED REACTION	ONSET = O DURATION = D TREATMENT = T <sub>x</sub>	OUTCOME	CONCLUSIONS
10	RUMACK <u>Clin Tox, 1974</u> 7:573-581	3 cases	23	F	Not available	C	15-30 Ornade capsules 50 mg PPA 8 mg chlorpheniramine 2.5mg isopropamide per capsule	Temp: 44.5°C RR: 60/min BP: 90/78 Pulse: 140bpm Hyperthermia Respiratory distress Agitation Thrombocytopenia	O = 14 hrs T <sub>x</sub> = 4 days	Fatality Hemodialysis Endotracheal intubation	Overdose
13				M	6 week history of systemic hypertension & tachycardia	C	Ornade capsule 50 mg PPA 8 mg chlorpheniramine 2.5mg isopropamide per cap; 50 mg imipramine	BP: 144/90 Pulse: 110bpm	O = 6 weeks T <sub>x</sub> = Discontinue drugs 3 weeks	No sequelae; High BP occurred without PPA use	Potential drug interaction
17				M	Not available	C	15-20 Ornade capsules 50 mg PPA 8mg chlorpheniramine 2.5mg isopropamide per cap	Vomiting BP: 280/140 Hallucinations Arrhythmias Pulse: 84bpm RR: 16	O = 3 hrs T <sub>x</sub> = 500cc D5W gastric lavage, physostigmine	No sequelae	Overdose
1	SALMON <u>Br Med J, 1965,</u> <u>1, 193</u>	1 case	16	M	"Drug ingestion"	C	8 Eskornade capsules; 50mg PPA 2.5 mg isopropamide 5mg diphenylpyraline per capsule	Vomiting Severe headache BP: 190/150 Restlessness Excitation Retinal veins congested Pupils dilated Talking incoherently	O = 1 hr	No sequelae	Overdose

ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE  
 CATEGORY: CARDIOVASCULAR

INDEX NO.	REPORTER	SUBJECT(S)	AGE(S)	SEX	MEDICAL HISTORY	PRODUCT CATEGORY	PRODUCT/DOSAGE	REPORTED REACTION	ONSET = O DURATION = D TREATMENT = T <sub>x</sub>	OUTCOME	CONCLUSIONS
38	PENTEL Br Heart J, 1982, 47, 51-54	3 cases	24	F	No heart disease No hypertension No ingestion of other drugs	C	One capsule 50 mg PPA 4 mg chlorphen- iramine 0.2 mg bella- donna alka- loids	Dyspnea Headache Blurred vision Nausea Confusion Chest pain BP: 204/148 Pulse: 112bpm Abnormal car- diac enzymes	O = 3 hrs D = 48 hrs	No sequelae	
			13	F	No hypertension No heart disease No ingestion of other drugs Suicidal intent	C	8 capsules 50 mg PPA chlorphen- iramine 2.5mg isopropa- mide per capsule	Headache BP: 190/110 Pulse: 120bpm Abnormal car- diac enzymes	O = 2 hrs D = 48 hrs	No sequelae	Overdose
			31	F	Schizophrenic urecholine trifluo- perazine Suicidal intent	A	40 tablets 50mg PPA 200mg caffeine per tablet	Vomiting BP: 180/120 Pulse: 90bpm Abnormal car- diac enzymes	O = 1 hr D = 36 hrs	No sequelae	Overdose
47	PENTEL Lancet, 1982 ii, 274	1 case	23	F	Alpha-adrenergic hypersensitivity	C	1 Contac capsule 50 mg PPA 4 mg chlorphen- iramine 0.2mg bella- donna alka- loid per capsule	Chest tight- ness Severe head- ache BP: 200/150 Pulse: 112bpm	O = 1 hr D = 5 hrs	No sequelae	
52a	DUVERNOY Med Intel, 4/17/69; 280 (16)	1 case	21	M	Sarcoidosis	C	3 Ornade capsules 50mg PPA 8 mg chlorphen- iramine 2.5mg isopropa- mide per capsule	Abdominal pain Headache BP: 240/120 Nausea		No sequelae	Overdose

## ADVERSE REACTION REPORTS ASSOCIATED WITH PHENYLPROPANOLAMINE

15

## CATEGORY: CEREBROVASCULAR EFFECTS

INDEX NO.	REPORTER	SUBJECT(S)	AGE(S)	SEX	MEDICAL HISTORY	PRODUCT CATEGORY	PRODUCT/DOSAGE	REPORTED REACTION	ONSET = O DURATION = D TREATMENT = T <sub>x</sub>	OUTCOME	CONCLUSIONS
21	KING Med J Aust, 1979; 2, 258	1 case	37	F	Not available	A	2 Trimoletscaps. 85 mg "PPA" per capsule	Headache Chest pain Fever Sweating Nausea Vomiting Slurred speech Weakness Cerebral hemor- rhage Mild dysphasia	O = 4 hr D = 2 weeks	Full re- covery after two weeks	Overdose Foreign dosage form
27a	ELLIOT Med J Aust, 1981 1, 13	1 case	54	F	Diabetes Normoten- sive	A	1 Dietgard cap 75 mg PPA	Confusion Headache Vomit Comatose BP: 160/100		Fatality due to occipital hemorrhage, No evidence of hyper- tension	
43	BERNSTEIN Annals of Emer Med, 1982, 11, 311-315	2 cases	26	M	History of drug ingestion	I	Illicit drug: 2 capsules 50 mg PPA 200mg caffeine 25mg ephedrine per capsule; & whiskey	Respiratory distress Hemorrhage Vomiting BP: 134/78 Pulse: 60bpm	O = 3-4 hrs D = 12 hrs	Fatality due to intra- cranial hemorrhage	Illicit drug use with prior his- tory of drug ingestion
			17	M	History of drug ingestion	I	Illicit drug 2 capsules 50 mg PPA 25 mg ephedrine 200mg caffeine per capsule	Comatose Intracere- bral hemor- rhage Grand mal seizure Psychosis BP: 120/60 Pulse: 60bpm	O = 6 hrs D = 4 days T <sub>x</sub> = supportive treatment	Fatality due to intra- cranial hemorrhage	Illicit drug use with prior his- tory of drug ingestion

(summaries)

## PHENYLPROPANOLAMINE ADVERSE REACTION

### REPORTS AND SAFETY STUDIES<sup>1</sup>

- (1) Salmon PR, hypertensive crisis with Eskornade. Br. Med. J., 1965; 1:193.

A 16 year old male was admitted within 2 hours after ingestion of an overdose of 8 Eskornade capsules containing 400 mg of PPA. He had apparently taken these because of nasal discharge but awoke an hour or two later with a severe headache and became restless and excitable, talking incoherently and vomiting frequently. On admission the patient was confused and very restless, had a tachycardia of 104 beats/minute and a B.P. of 190/150 mm Hg. The pupils were fixed and widely dilated and the retinal veins were congested, but there was no papilledema.

The patient recovered fully and became normotensive. Eskornade spansules contain phenylpropanolamine hydrochloride 50 mg, isopropamide iodide 2.5 mg and diphenylpyraline 5 mg. Eight capsules contain 400 mg of PPA (130 mg is released immediately and the rest over 10-12 hours). The recommended oral dose for the treatment of nasal decongestion is 50 mg T.I.D. The 130 mg of PPA which was released soon after ingestion of the Eskornade may be assumed to be sufficient to produce severe hypertensive crisis.

- (2) Ostern S, Dodson, WH. Hypertension following Ornade ingestion. JAMA, 1965; 194:240.

A 20 year old male was brought to the hospital complaining of severe bilateral occipital headache of 20 minutes duration. Twenty minutes prior to the onset of the headache the patient admitted ingesting an overdose of four Ornade Spansules for sleep. The 200 mg of phenylpropanolamine HCl, and isopropamide iodide 10 mg (total amount in 4 Ornade Spansules) induced the following toxic reactions: a B.P. of 220/120 mm Hg, pulse rate 110/beats/minute, marked photophobia, spasm of the paravertebral musculature and generalized increased muscle tone, and hyperactive but equal deep tendon reflexes plus a dry mouth.

- (3) Livingston, PH. Transient hypertension and phenylpropanolamine. JAMA, 1966: 196:143.

Anecdotal case of two young men who ingested Contac (a proprietary preparation containing 50 mg of phenylpropanolamine; belladonna alkaloids 0.2 mg; chlorpheniramine maleate 4 mg) for treatment of acute rhinitis at an unspecified time period prior to taking a physical examination. Blood pressures were found to be approximately 180/110 mm Hg. but returned to normal the following day after discontinuance of the medication.

- (4) Kane, FJ, Green, BQ. Psychotic episodes associated with the use of common proprietary decongestants. Am. J. Psychiat. 1966; 123: 484-487.

Three cases of a temporal relationship between the ingestion of a decongestant compound containing phenylpropanolamine (Ornade) and the occurrence of acute psychotic episodes are presented. Each capsule contains; PPA 50 mg, chlorpheniramine 8 mg and Isopropamide 2.5 mg.

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<sup>1</sup>For complete list of safety studies refer to reference no. 36 which provides studies in tabular form by dose; time of study; facility where done and conclusions.

- (4A) Mitchell, C.A., Possible cardiovascular effect of phenylpropanolamine and belladonna alkaloids, *Curr. Therap. Res.*, 10, 47-53, 1968.

Two groups of volunteers, 32 and 6 respectively, were given capsules containing (1) phenylpropanolamine 50 mg in sustained action (SA) form (2) PPA 50 mg as SA plus belladonna alkaloids 0.25 mg and (3) a placebo. Each test product was taken for a period of 1 week by the group of 32 volunteers who used one capsule twice daily. The group of 6 took 2 capsules for one single dose on two separate occasions. Blood pressure and pulse rate were studied with recordings made in the sitting position. No pressor effect was noted following any of the three study substances. In the study employing the PPA/BA combination a decrease in pulse rate was noted attributed by the authors to vagal effects of the BA.

- (5) Shapiro, SR. hypertension due to an anorectic agent. *N. Engl. J. Med.*, 1969; 280:1363.

Anecdotal case of transient hypertensive crisis in a previously normotensive middle-aged woman who ingested an anorectic preparation containing phenylpropanolamine 25 mg. No clinical data reported.

- (5a) Duvernoy, W.F.C., Positive phentolamine test in hypertension induced by a nasal decongestant. *Med Intelligence*, 280(16), 877, April 17, 1969.

This report describes a 21 year old male patient with PPA induced hypertension. The patient was in acute distress and complained of abdominal pain, headaches and nausea. Initial BP was 240/120, decreased to 170/120 after administration of phenobarbital and codeine. Later 5 mg of phentolamine was injected intravenously and his BP was 120/85 2 hours later and the headache subsided with the decrease in BP. After repeated questioning he admitted to having ingested 3 Ornade Spansules on the afternoon of admission.

- (6) Cuthbert, MF, Greenberg, MP and Morley, SW. cough and cold remedies: a danger to patients on monoamine oxidase inhibitors, *Brit. Med. J.* 1969, .1, 404-406. (see also tab. 41-8)

In 3 men 50 mg PPA induced modest rise in supine systolic BP with a more pronounced rise following 100 mg dose. No BP effects were noted with a 50 mg timed release product. Significant BP increase in 1 subject when 50 mg PPA given in combination with a MAO inhibitor.

- (7) Wharton, BK. nasal decongestants and paranoid psychosis, *Brit. J. Psychiat.*, 1970, 117, 439-440.

Paranoid psychosis in one patient following use of a proprietary preparation "Super Anahist." Ingredients include ascorbic acid, caffeine, aspirin, phenacetin, phenylpropanolamine hydrochloride 12.5 mg., phenyltoloxamine citrate 6.25 mg., and thonzylamine hydrochloride 6.25 mg.

- (8) Gibson, GJ and Warrell, DA. Hypertensive crises and phenylpropanolamine, *Lancet*, 1972, ii, 492.

Increase in BP, headache, chest tightness following 64 mg PPA dose (Mucron tablets) taken concurrently with hard cheese.

- (9) Peterson, RB, Vasquez, LA. Phenylpropanolamine induced arrhythmias, JAMA. 1973; 223: 324-325.

A 15 year old girl was brought to the hospital following the sudden severe onset of occipital headache. The patients BP on admission was 188/112 mm Hg. and rose to 210/130 mm Hg. during the next 20 minutes. An EKG demonstrated frequent premature ventricular and atrial contractions with paroxysms of ventricular and atrial tachycardia. The patient had been taking a proprietary antiobesity preparation containing 25 mg of phenylpropanolamine, 25 mg of caffeine, 25 mg methylcellulose and assorted vitamins, which was ingested 3 times per day for a period of 5 weeks.

- (10) Rumack, BH, Anderson, RS, Wolfe, R et al. Ornade and anticholinergic toxicity: hypertension, hallucinations, and arrhythmias. Clin. Toxicol. 1974; 7:573-581.

A 17 year old male ingested 15 to 20 Ornade spansules (each capsule contains phenylpropanolamine 50 mg, chlorpheniramine 8 mg and isopropamide 2.5 mg). Three and one-half hours later the patient began vomiting, became markedly excited, and began hallucinating. The patients BP was 200/100 to 230/130 with a pulse rate of 96. A peak BP of 280/140 was reached at which time the patient developed a ventricular ectopic arrhythmia. Several doses of physostigmine were given IV following which the patient recovered without sequelae.

A 23 year old female ingested 15-30 Ornade spansules. Multiple problems were encountered in the management of this patient i.e., hyperthermia, respiratory distress, agitation, hypotension, thrombocytopenia. On the 4th hospital day the patient died. Postmortem examination revealed diffuse small vessel thromboses, extensive infarcts of the heart, liver, brain, kidneys and intraalveolar hemorrhage of the lungs.

A 13 year old male medicated with imipramine and Ornade capsules for enuresis and allergic rhinitis was admitted with tachycardia and an elevated BP. Discontinuation of all medication resulted in no change in CDV hemodynamics at 6 days albeit a BP decrease at 30 days. Rechallenge using imipramine and the antihistaminic chlorpheniramine maleate induced a BP rise suggesting the anticholinergic effects of both drugs are synergistic.

- (11) McLaren EH. Severe hypertension produced by interaction of phenylpropanolamine with methyldopa and oxyprenolol. Br. Med. J. 1976; 2: 283-284.

The blood pressure of a 31 year old male was controlled on methyldopa 250 mg twice daily and oxyprenolol 160 mg three times a day. Triogesic tablets (phenylpropanolamine 12.5 mg and acetaminophen 500 mg) were prescribed in a dose of 2 tablets 3 times a day for symptomatic treatment of a cold. The patient became hypertensive (BP 200/150 mm Hg.) but when the Triogesic was stopped and the patient continued to take the methyldopa and oxyprenolol, his blood pressure was brought back under control. Notable in this case is that patient was hypertensive prior to using Triogesic and had pre-existent glomerulonephritis.

- (12) Griffiths, RR, Brady, JV, and Snell, JD. Relationship between anorectic and reinforcing properties of appetite suppressant drugs: Implications for assessment of abuse liability. *Biological Psychiatry*, 1978 apr; 13(2): 283-290.

A quantitative ratio measure was developed which permitted comparisons between the reinforcing and anorectic potency of eight phenylethylamine anorectics and cocaine in laboratory baboons. The order of these compounds based upon this ratio bears a reasonable correspondence to clinical drug evaluations. The measure may provide information for preclinical evaluation of relative abuse potential of anorectic drugs. Of the eight anorectics, both fenfluramine and phenylpropranolamine failed to maintain self-infusion rates above saline control at any dose tested providing the preclinical assessment conclusion that both drugs lack the potential of abuse liability. (Cross reference no.'s 31: 36-8 Acute Section).

- (13) Food and Drug Administration(USA) 1976 review of reports to the Bureau of Drugs pertaining to adverse reactions of all phenylpropranolamine containing products by brand name. A total of 31 toxic overdoses were reported. Patients ranged in age from 14 months to 30 years. Doses reported to induce an adverse effect range from 12.5 mg (14 mo. old patient) to 1750 mg (18 year old patient). Overall symptoms reported include; lethargy, hypertension, nausea, vomiting, dizziness, tachycardia, convulsions (200 mg dose). Products reported on are multicomponent containing ingredients in addition to PPA alone.

- (14) Anon. September, 1976 Establishment of a Monograph for OTC Cold, Cough, Allergy, Bronchodilator and Antiasthmatic Drug Products;  
Food and Drug Administration (USA), DHEW, Federal Register, Sept. 9, 1976; Docket No. 76N-0052.

Clinical experience has confirmed that phenylpropranolamine and its salts (oral) are safe in the dosage ranges used (25-50 mg) as nasal decongestants. Individuals with normal blood pressure receiving PPA alone either as a 50 mg plain capsule 4 times daily or as a 50 mg sustained release capsule 2 times daily had no significant effect on BP or pulse rate. No adverse effect on CDV system was noted after 5 to 42 days of treatment. Intravenous administration induced dose-related systolic BP increase in humans. A 16-28 mm Hg. increase following 20-25 mg and a 44-82 mm Hg. following 50 mg were observed. No EKG disturbances were observed.

(Cross reference numbers 36a; 37; 48a)

- (15) Chouinard, G., Ghadirian, AM, Jones, BD. death attributed to ventricular arrhythmia induced by thioridazine in combination. *Canadian Med. Assc. J.*, 119, 729-731, 1978.

A 27 year old woman died after taking her usual dose of thioridazine, 100 mg/day, in combination with a single capsule of Contac C (phenylpropranolamine HCl 50 mg and 4 mg of chlorpheniramine maleate). Thioridazine is known to have induced fatal ventricular arrhythmias in the past. The authors suggest that phenylpropranolamine, an ephedrine like substance may have favored the initiation of the ventricular arrhythmia that was considered to be the likely cause of death.

- (16) Frewin, DB, Leonell, PP, Frewin, ME. Hypertension after ingestion of Trimolets. Med. J. Aust. 1978; 2 497-498.

A 21 year old nurse presented with severe headache after ingesting one phenylpropanolamine (Trimolet) tablet. No specific therapy was provided and her BP normalized within a few hours of admission. Trimolets contain 85mg of d-phenylpropanolamine in immediate release form.

- (17) Lee, KY, Vandongen, R., Beilin, L.J. Severe hypertension after ingestion of an appetite suppressant with indomethacin. Lancet, 1979; 1:1110-1111. SEE ALSO REFERENCE NO. 26c PUBLISHED IN 1980 WHICH IS AN APPARENT ABSTRACT OF THIS ORIGINAL 1979 ARTICLE. NOTE THE INITIAL RECORDED BP OF 200/110 IN THE 1980 ABSTRACT WHILE THIS 1979 PUBLICATION INDICATES DIASTOLIC BP AS UNRECORDABLE.

A 27 year old woman had been taking one capsule of Trimolets (active ingredient 85 mg of phenylpropanolamine) for some months as an appetite suppressant. No side effects were noted until she took 25 mg of indomethacin for the treatment of tendonitis. Within 15 minutes the patient developed a bifrontal headache which became throbbing and severe. Thirty minutes later her systolic BP was 210 (diastolic pressure was unrecordable). One hour after ingestion of the indomethacin her BP was 150/80 with a pulse rate of 72 per minute. Under controlled conditions indomethacin and Trimolets were given independently and in combination. When Trimolets were given alone no change in BP was observed; indomethacin administration was followed by only a small rise in diastolic pressure. When 25 mg indomethacin was given 40 minutes after a Trimolet capsule, the patient developed a severe throbbing headache and systolic and diastolic BP rose to a maximum of 200 and 150 mm Hg, respectively.

(Cross reference number 26c)

- (17a) Bennett, William M., Hazards of the appetite suppressant phenylpropanolamine, Lancet, July 7, 1979, 8132;42.

A 28 year old female was admitted to hospital with progressive renal failure and persistent muscle tenderness. She was placed on a low protein diet and renal function and her symptoms improved. A biopsy revealed acute interstitial nephritis. The patient had been taking phenylpropanolamine ("Fullstop") for 3 weeks prior to the onset of her symptoms. Over the same period she had taken 2-3 325 mg aspirin and 650 mg acetaminophen. Three months after her illness she was completely well. (Cross reference number 49).

The letter writer suggests that PPA be withdrawn from pharmaceutical preparations considering the possible adverse effects.

- (18) Anon. Adverse interactions of drugs. Med. Letter Drug Ther. 1979; 21: 5-12.

Hypertensive crisis can occur with concurrent use of phenylpropanolamine and monamine oxidase inhibitors. Review article.

- (19) Horowitz, JD, McNeil, JJ, Sweet, B. et al. Hypertension and postural hypotension induced by phenylpropanolamine. Med. J. Aust., 1979; 1:175-176.

A 17 year old woman had taken Trimolets capsules (phenylpropanolamine 85 mg, ferrous gluconate 15 mg and various vitamin additives) twice daily in an attempt to lose weight. On the morning admitted she had ingested 6 Trimolets developing headache/nausea. A supine BP of 200/130 mm Hg. was recorded. She was treated with bed rest and during the next 48 hours her BP returned to 130/70. Rechallenge with one Trimolet capsule 3 weeks later resulted in no change in pulse rate but a prolonged rise in BP (supine, 175/120 mm Hg) 90 minutes after ingestion of the drug. A double blind crossover trial of 1 Trimolets capsule versus placebo in 6 normotensives resulted in a rise in supine BP to a mean of 151/100 mm Hg following Trimolets. The PPA in Trimolets is in immediate release form.

- (20) Deocampo, P.D., Convulsive seizures due to phenylpropanolamine, J. of the Med. Soc. of NJ, 1979, 76, 591-592.

Single case report of 44 year old woman with history of convulsive seizures following use of "cold medications" who experienced a grand mal convulsion and hypertension shortly after ingesting a 75 mg sustained action preparation of phenylpropanolamine. Patient recovered with no sequelae.

- (21) King, J. Hypertension and cerebral hemorrhage after trimolets ingestion. Med. J. Aust. 1979; 2:258.

A 29 year old woman ingested one Trimolets tablet and 30 minutes later complained of tightness in the chest, dyspnoea, palpitations and neck pain. The physician reports the patient had high blood pressure and irregular heart rate, however, no details were provided. The next day the patients BP was 130/90 mm Hg. Each tablet contains 85 mg PPA immediate release.

A 37 year old woman took 2 Trimolets tablets (170 mg phenylpropanolamine HCl) before going to bed and awoke with a mild occipital headache, chest pain, fever, and sweating. The headache became more severe and she felt nauseated and vomited. Thirty minutes later she developed weakness of the right arm and leg associated with facial weakness and slurring of speech. A physical and CT scan revealed a small cerebral hemorrhage. After two weeks, the patients symptoms had virtually resolved and her BP remained at normal levels.

- (22) Teh, AYF. Phenylpropanolamine and hypertension. Med. J. Aust., 1979 2: 425-426.

Approximately 3 hours after ingestion of 2 Contac 500 capsules (phenylpropanolamine 50 mg and belladonna alkaloids 0.2 mg) a 23 year old male experienced generalized weakness, frontal headache, and a pounding sensation in the chest. About 4 hours after the onset of symptoms, the BP (supine) was 160/110 and the pulse was 54 beats/minute. The symptoms subsided over the next few hours and his BP was 130/80 three hours after admission.

- (23) Norvenius, G; Widerlov, E. and Lonnerholm, G. Phenylpropanolamine and mental disturbances, Lancet, 1979, ii, 1367-1368.

Psychotic episodes and psychic disturbances reported via the 1979 Swedish Adverse Reaction Committee Compilation. Sixty-one cases of which 48 were children whose dominant symptoms included: restlessness, irritability, aggressiveness, and sleep disturbances. Other drugs taken concurrently included the antihistamines.

- (24) Horowitz, JD, Howes, LG, Christophides, N. et al. Hypertensive responses induced by phenylpropanolamine in anorectic and decongestant preparations. *Lancet*, 1980; 1:60-61.

Horowitz administered one capsule of Trimolets (85 mg phenylpropanolamine per capsule) to 37 healthy subjects; 35 subjects took a matching placebo. The mean diastolic BP before capsule ingestion was  $70 \pm 1.4$  mm Hg. in the active treatment subjects and  $74 \pm 1.4$  for placebo medication subjects. Blood pressure reached a peak between 1.5 - 3.0 hrs. after capsule ingestion. Mean peak supine diastolic BP was  $94 \pm 2.6$  (active medication) and  $77 \pm 1.6$  mm Hg. for control subjects. Peak supine diastolic BP's of 100 mg Hg. or greater were recorded in 12/37 subjects receiving active medication and 1/35 receiving the placebo. Symptoms reported by subjects receiving Trimolets were: tingling feelings in the head (6); dizziness (non-postural) (5); dizziness (postural) (4); palpitations (5); headache (2); chest tightness (3); rash (3); tremor (2); nausea (2), tinnitus (1). Seventeen subjects on Trimolets did not report any side effects. The PPA in Trimolets is in immediate release form.

Contac 500 (50 mg phenylpropanolamine per capsule) was taken by 34 subjects and 35 subjects took the matching placebo. Ingestion of the active medication was associated with a small mean rise in maximum supine blood pressure 1.5 to 3.0 hours after ingestion.

	<u>Initial Supine Diastolic BP</u>	<u>Mean Peak Supine Diastolic BP at 1.5 - 3 hrs.</u>
Placebo	$77 \pm 2.2$	$77 \pm 1.4$
Contac 500	$78 \pm 1.9$	$83 \pm 1.5$

Supine diastolic BP of 100 mg Hg. or more developed in 4 subjects on Contac 500 but none of the placebo subjects. No subjects reported symptoms on either active or placebo medication. Contac is SA dosage form.

- (25) Silverman, HI, Kreger, BE, Lewis, GP, Karabelas, A., Paone, R., Foley, M. Lack of side effects from orally administered phenylpropanolamine and phenylpropanolamine with caffeine: a controlled three-phase study. *Curr. Therap. Res.*, 28 185-194. 1980(August).

A three-phase multisite site study was designed to determine the cardiovascular effects of orally administered 25 mg phenylpropanolamine hydrochloride alone and in combination with 100 mg of caffeine. Thirty-seven subjects divided into three separate groups received either phenylpropanolamine alone, phenylpropanolamine plus caffeine, or a placebo. Supine blood pressures and pulse rates were measured immediately prior to drug administration and at 30 - or 60-minute intervals over a four-hour period after administration. There was no statistical difference at the 95% confidence level in either systolic or diastolic blood pressures with respect to either test preparation based on baseline values throughout the study.

- (26) Schaffer, CB and Ali, MW. Psychotic reaction caused by proprietary oral diet agents. Am. J. Psychiatry, 1980, 137:10, 1256-1257.

Single case report of 26 year old female who experienced a psychotic event following use of "copious amounts" of PPA dosage forms for the purpose of losing weight. Patient suspected of ingesting 6 to 10 capsules; a significant overdose daily. There were no adverse sequelae following medication discontinuance.

- (26a) Mashford, M.L., Coventry, D., Raftos, J., Roeser, P., Zacest, R. Adverse Drug Reactions Advisory Committee: Report for 1979. Med. J. Australia, 1980, 2/10, 569-571.

Under the section of this report, on OTC drugs, the Adverse Drug Reactions Advisory Committee (ADRAC) noted that in 1979 ADRAC provided comments and data on PPA in support of a restriction on the use of PPA. A review of the scheduling of PPA containing products was requested in 1978. Reports of hypertension associated with PPA were especially noted. No new data reported in this article.

- (26b) Patterson, F.K. Delayed fatal outcome after possible Ru-Tuss overdose. J. Forensic Sci., 1980, 25/2 349-352.

Death resulted from the delayed onset of the acute respiratory distress syndrome and disseminated intravascular coagulation with left ventricular mural thrombus formation and nonbacterial thrombotic endocarditis approximately five days after an alleged attempted suicide by the ingestion of ten to twelve prolonged-action Ru-Tuss tablets. Although these lesions are thought to be similar in pathogenesis, this combination has not been previously reported in association with a drug overdose. The delay in onset is also of interest because of its clinical implications.

Patient was a 19 year old white female who allegedly ingested 10-12 Ru-Tuss tablets, which each contain 50 mg PPA HCl, phenylephrine HCl 25 mg, chlorpheniramine maleate 8 mg, hyoscyamine 0.1936 mg, atropine sulfate 0.0362 mg and scopolamine hydrobromide 0.0121 mg. Due to excessive ingredient content Ru-Tuss is no longer marketed. (Cross reference 41-19)

- (26c) Lee, K.Y., Bellin, L.J., and Vandongen, R. Severe hypertension following ingestion of an appetite suppressant PPA with indomethacin. Aust. and New Zealand J. Med. 1980, 10(1), 122. (THIS ARTICLE IS ONLY AN ABSTRACT OF ORIGINAL ARTICLE WHICH WAS FIRST PUBLISHED IN 1979 - SEE REFERENCE NO. 17) HOWEVER THE DATA REPORTED IN THIS 1980 PUBLICATION IS NOT IDENTICAL - NOTE IN THE 1980 ARTICLE INITIAL BP IS STATED AS 200/110 WHILE THE 1979 ARTICLE INDICATES DIASTOLIC BP AS UNRECORDABLE.

This brief report apparently originally published in 1979, describes an interaction between phenylpropanolamine (85 mg taken daily for some months by a 27 year old woman) and indomethacin (25 mg). About 15 minutes after taking the indomethacin she developed a severe headache and was admitted to a hospital. Severe hypertension (200/110) was observed. She was readmitted later to determine if her hypertension was drug induced. Neither phenylpropanolamine alone or with placebo produced hypertension. Indomethacin alone caused a small rise in BP. Administration of indomethacin and PPA again resulted in severe headache and hypertension. The report recommends restrictions on the use of PPA, given its "propensity to cause hypertension when given alone or with other commonly used drugs".  
(Cross reference number 17)

- (27) Dietz, AJ, Amphetamine-like reactions to phenylpropranolamine, JAMA, 245, 601-602, 1981.

Phenylpropranolamine hydrochloride is an "amphetamine-like" substance that is found in 64 different over-the-counter preparations for colds and appetite suppression. It is also found in numerous prescription drugs. Recently, it has been reported to cause symptoms of sympathomimetic-like effects, such as severe hypertension, hypertensive crisis, and possible renal failure. Also, several cases of psychotic episodes while taking phenylpropranolamine have been reported. This is a report of seven patients who have experienced acute CNS effects. These effects range from stimulation of the medullary respiratory center to tremor, restlessness, increased motor activity, agitation, and hallucinations. Cases were taken from emergency room records and do not represent direct observations by author.

- (27a) Elliott, C.F. & Whyte, J.C. PPA & hypertension. Med. J. Australia, 1981, 1/13, 715.

This letter is a response to an earlier report of intracerebral hemorrhage following ingestion of PPA and reports a second case.

A 54 year old woman (with mature onset diabetes, but previously normotensive) was admitted to hospital with headache, vomiting and confusion and quickly became comatose. Her BP was 160/100 on admission (110/70 3 days previously). She died the day after admission and autopsy revealed a left occipital hemorrhage and showed no evidence of hypertensive changes in cerebral vessels, heart or lungs.

The patient had bought Dietgard capsules (75 mg PPA) the day prior to her hospital admission. She took one capsule on that day and another the day of admission. The dosage form was immediate release.

The authors state that this report does not prove any association between PPA and cerebral hemorrhage, but suggest a possible link.

- (27b) Lewith, G.T. & Davidson, F. Dystonic reactions to Dimotapp elixir. J. Royal College of General Practitioners, 1981, 31/225, 241.

An 8 year old girl was prescribed Dimotapp elixir (brompheniramine maleate 4 mg, phenylephrine hydrochloride 5 mg and PPA hydrochloride 5 mg per 5 ml) for a cough. When a 5 ml nocte dose was only partly effective, it was increased to 10 ml nocte. As soon as the Dimotapp was increased she had increasingly severe episodes of spasmodic torticollis eventually culminating in an oculogyric crisis. She received a 1.5 mg dose of haloperidol the day before the oculogyric crisis. After stopping the Dimotapp elixir and haloperidol she had no further dystonic reaction.

The authors speculate that the haloperidol precipitated a more severe dystonic reaction, but spasmodic torticollis had been present for 2 months before and disappeared when the elixir was stopped.

- (28) Achor, MB, and Stein, I. Diet aids, mania, and affective illness. *Am. J. Psychiatry*, 138:3, 1981.

Three single case history reports of patients who developed psychotic reactions following use of OTC diet aids. All three patients had a familial history of psychosis.

- (29) Blum, A., Phenylpropanolamine: an over-the-counter amphetamine?, 1981, *JAMA*, 245, 13: 1346-1347.

Critical editorial in review of OTC diet aids. No new data presented. Technical errors in data presented are present in article.  
(Cross reference number 34)

- (29a) O'Connor, T.W. Losing weight: The pharmacist's role in counseling obese people, *NARD J.*, 103, 49-52, March 1981.

The pharmacist's role in counseling obese people to lose weight by dieting, exercise and the use of diet aid products was discussed. Phenylpropanolamine, alone or in combination with caffeine and benzocaine, were described as diet aid products. The potential sympathomimetic side effects of phenylpropanolamine were also discussed. Guidelines for use of PPA include using it in conjunction with a balanced, caloric-restricted diet, over short periods of time (up to 12 weeks). No original data in this review article.

- (30) Personal communication; March 2; March 25, 1981: H.I. Silverman and R.S. Frank, U.S. Department of Justice, DEA; personal communication on "Look-Alike" Drugs.

Letter makes note of the fact that information published in article by Dietz (ref. no. 27 in this compilation) is the only information that has reached the DEA in which adverse neurological reactions following ingestion of PPA is described.

- (30a) Seppala, T., E. Nuotto and K. Korttila, Single and repeated dose comparison of three antihistamines and phenylpropanolamine: psychomotor performance and subjective appraisal of sleep. *Br. J. Clin. Pharm.* 1981, 12:179-188.

A double-blind cross-over study, with nine healthy male students compared placebo, antihistamines and PPA. In contrast to antihistamines, PPA made subjects more alert and quick witted. PPA improved reaction speed, reaction accuracy and enhanced flicker recognition throughout the study. Unlike other medication PPA was not found to produce mood elevation. The authors conclude PPA is harmless to psychomotor performance and driving skills.

- (30b) Duffy, W.B. et.al. Acute renal failure due to phenylpropanolamine. *Southern Medical Journal*, Dec. 1981, (12):1548-1549.

A 25 year old healthy male ingested 34 diet pills (each containing 35 mg of PPA and 140 mg of caffeine) as a suicide gesture. Total amount PPA 1190 mg and caffeine 4760 mg. A renal biopsy performed 5 days after ingestion of these drugs revealed acute tubular necrosis. Neither acute interstitial nephritis or severe hypertension, which have been reported in other patients, were present in this case. As far as the authors could determine acute renal failure with tubular necrosis has not been previously reported as a consequence of PPA overdose.

- (31) Griffiths, R.R., Brady, J.V., Bigelow, G.E., Predicting the dependence liability of stimulant drugs, In Thompson, T and Johnson, C.E. Eds., "Behavioral Pharmacology of Human Drug Dependence" (NDA Research Monograph No.37, pp. 182-196, DHHS Publ. No. (ADM) 81-1137, Govt. Printing Office, Washington D.C. 1981.

Phenylpropanolamine in spite of its wide availability as a non prescription appetite suppressant is neither associated with nor reported to be misused by humans on the basis of self administration studies and clinical reports. PPA has no dependence liability.

- (31a) Wellman, P.J., Malpas, P.B. and Wikler, K.C. Conditioned taste aversion and unconditioned suppression of water intake induced by phenylpropanolamine in rats. *Physiological Psychology*, 9(2), 203-207, 1981.

The putative aversive properties of phenylpropanolamine (PPA), an analog of amphetamine, were delineated in two behavioral tests. In a conditioned taste aversion paradigm, PPA (10, 20, or 40mg/kg) was found to induce dose-dependent taste aversion, whereas identical dosages of PPA were found to produce dose-dependent unconditioned suppression of water intake in 23.5-h water-deprived rats. Comparison of the dose-response curves for the aversion and hypodipsia induced by PPA indicates that a single process, presumably malaise or toxicosis, may mediate these effects. These findings question the notion that PPA induces anorexia via activation of a CNS satiety mechanism and lend credence to the suggestion advanced herein that nonspecific malaise may mediate the moderate anorectic activity of PPA observed in rodents and humans.

- (32) Anon., The New Diet Pills, *Consumer Reports* 1982, January 14-16.

Biased non-scientific article written in non technical language. Article contains significant errors in data reported; omits specific safety data and provides over emphasis on speculation and opinion rather than scientific fact.

- (32a) Dougherty, R.J.. Pseudo-speed: Look-alikes or pea-shooters. *New York State Journal of Medicine*, January 1982: 74-75.

After alcohol and marijuana, pseudo-speed is reported to be the 3rd most abused drug in Central New York. Pseudo-speed contains PPA, caffeine and other uncontrolled drugs. The rush produced by pseudo-speed is reportedly not quite as good as cocaine, but producing an adequate buzz when combined with alcohol. Many people in the 20's were found to be using pseudospeed to enable them to work 60-80 hour work weeks. Three case studies of people using from 3-20 capsules per day, usually in conjunction with alcohol.

- (33) Gruson, L., A controversy over widely sold diet pills, *N.Y. Times*, Feb. 13, 1982.

Biased non-scientific article reporting on a cerebrovascular (CVA) incident in a person who allegedly used a diet preparation containing PPA.

- (34) Silverman, H.L., Lewis, G.P. Phenylpropanolamine, JAMA, 1982, 247, 460 (Jan 22/29).

Provides factual data and references to scientific articles which substantiate PPA's lack of any potential for abuse liability and verification of both safety and effectiveness when used in the clinically recommended dosage. (Cross reference number 29)

- (35) Griboff, S.I. and Silverman, H.I. A double blind clinical evaluation of a phenylpropanolamine-caffeine-vitamin combination and a placebo in the treatment of exogenous obesity. Curr. Therapeutic Research, 17(6), 535-543, June, 1975; Altschuler, S., Conte, A., Sebok, M., Marlin, R., Winick, C. Three controlled trials of weight loss with phenylpropanolamine. Int. J. of Obesity 6, 549-556, 1982.

Compilation of systolic and diastolic blood pressures and pulse rates from four separate clinical studies conducted in evaluation of PPA's clinical effectiveness as an anorexiant. No significant BP effects or clinically adverse findings noted in these studies which extended over 4 (1 study); 6 (2 studies) and 8 (1 study) week periods.

- (36) Compilation of safety studies employing a total of over 1500 volunteers using phenylpropanolamine. Thirty separate studies are tabulated where patients were studied for periods ranging from one day to a total of 6 months. Daily (24 hours) doses of PPA ranged from 25 mg to 200 mg given orally. All investigators concluded in each of their separate studies which extends over a 15 year period that PPA did not induce a clinically adverse effect on either blood pressure or pulse rate. Compilation follows this narrative bibliography.

- (36a) Anon., May, 1982, Establishment of a Monograph for Oral Health Care Drug Products for Over-the-Counter Human Use; Food and Drug Administration (USA) DHHS, Federal Register, May 25, 1982; Docket No. 81N-0033.

The Expert Review Panel concludes PPA is safe.  
(Cross reference numbers 14; 37; 48a)

- (37) Anon., February, 1982, Establishment of a Monograph for Weight Control Products for Over-the-Counter Human Use; Food and Drug Administration (USA) DHHS, Federal Register, February 26, 1982; Docket No. 81N-0022, pp. 8466-8484.

The Expert Review Panel evaluating weight reducing aids concluded phenylpropanolamine as both safe and effective for use as an anorexiant in a weight reducing program. The Panel also concluded PPA to have no stimulant effects. (Cross reference numbers 14; 36a; 48a)

- (37a) Gardner, E.R., Hall, R.C.W. Psychiatric symptoms produced by over-the-counter drugs, Psychosomatics, 32/2, 186-190, February, 1982.

Many OTC drugs can produce psychiatric symptoms and patients may deny or conceal use of these drugs, or do not consider them to be "drugs". PPA, present in many diet preparations, analgesics and decongestants, deserves particular attention. A number of psychiatric and physical symptoms are listed. Interactions of PPA with caffeine, MAO inhibitors and other drugs are also noted.

- (38) Pentel, P. et.al. Myocardial injury after PPA injection. *Heart J.*, 1982; 47; 51-54.

Three case histories are presented. Two patients ingested gross overdoses 400 mg and 2000 mg of PPA respectively. All 3 patients were asymptomatic and normotensive in follow up. Myocardial injury after acute ingestion of PPA is reported. Preparations taken were not PPA exclusively e.g., Case I used PPA 50 mg, CPM 4 mg, BA 0.2 mg; Case II PPA 400 mg, CPM 48 mg, Isopropamide 20 mg; Case III PPA 2 g, caffeine 8 g. Ventricular arrhythmias, ECG and serum enzyme abnormalities are provided as evidence of cardiomyopathy.

- (39) Escobar, J.I., Karno, M. Chronic hallucinosis from nasal drops. *JAMA*, 247, 1982; 1859-1860, Editorial (p. 1867).

Note: SE described is for nasal decongestants other than PPA. The article is included in this compilation via relationship to sympathomimetic nasal decongestants generally. Twenty year case history of chronic hallucinogenic responses associated with the use of EPHEDRINE; PSEUDOEPHEDRINE; DESOXYEPHEDRINE; PHENYLEPHRINE OXYMETAZOLINE; nose drops and oral nasal decongestants used in combination with antihistamines. References provided to reports of mania (PSEUDOEPHEDRINE) and use of EPHEDRINE to alleviate depression. Other references are made to psychotic case history reports where PPA has been used Wharton (1970) and Schaffer (1980) see references 7; 26.

- (40) MacPhail, RC, Comparison of the effects of phenylpropanolamine and caffeine on schedule-controlled performance. *Federation Proceedings* 1982 41(4) Abstract 4696.

PPA HCL was given to rats in dosage ranging from 3.125 - 25 mg/kg body weight. PPA produces dosage related decreases in overall responding but did not disrupt the temporal pattern of responding except at 25 mg/kg, which almost completely suppressed responding.

- (41) Phenylpropanolamine over the counter (editorial). *Lancet* April 10, 1982, 8276:839.

This editorial mentions a number of reports of adverse effects following PPA ingestion, including myocardial injury severe hypertension and psychotic reactions. There are few reports of death from PPA overdose. There is now an attempt to market PPA as an anorexiant in the U.K. The editorial suggests that the potential for abuse should be considered by the regulatory authorities.(22 refs.)

- (42) Saltzman, M.B., Phenylpropanolamine over the counter (letter). *Lancet*, May 29, 1982, 8283:1242.

This letter is in response to the April 10th *Lancet* editorial. The letter notes that references in the editorial refer to a limited number of patients, taking PPA at well above recommended levels. The letter mentions 3 studies not cited in the editorial and states that PPA used alone is devoid of abuse potential and CNS effects, and notes Menley & James Labs clinical studies of over 400 obese patients which indicate that PPA is safe. (Data has been submitted to the FDA and will be published later in 1982.)

- (43) Bernstein, E., and B.M. Diskant, Phenylpropanolamine: A potentially hazardous drug. *Annals of Emergency Medicine*, June 1982, 11(6): 311-315 or 43-47.

Three cases of toxic reaction following relatively small doses of PPA are presented.

(1) An 18 year old obese woman developed a hypertensive crisis and grand mal seizures after ingesting 2 Comtrex tablets. (each tablet contains: PPA 12.5 mg, CPM 1 mg, DMHBR 10 mg, APAP 325 mg.)

(2) A 26 year old man ingested 3-6 ounces of whiskey and 2 black capsules later identified as containing PPA 50 mg, caffeine 200 mg and 25 mg ephedrine each. Upon admission the man was in obvious-respiratory distress. The patient died 11 hours after admission. A consulting neurosurgeon thought the patient had suffered an intracranial hemorrhage.

(3) A 17 year old man ingested 2 black capsules (200 mg caffeine, 25 mg ephedrine, 50 mg PPA). He was admitted about 17 hours after ingestion and was somnolent and disoriented. About 15 hours after admission he became deeply comatose. The patient died on the 4th hospital day and autopsy revealed a massive intracerebral hemorrhage.

A discussion of the pharmacology of PPA and the previously reported side effects and drug interaction follows the case studies.  
(cross reference no. 56A).

- (44) Rumack, Barry H., Phenylpropanolamine: A potentially hazardous drug (editorial), *Annals of Emergency Medicine*, June 1981, 11(6):332.

This editorial addresses the problem "illicit abuse of illicit-looking drugs" such as combinations of PPA, ephedrine and caffeine. These drugs may be safe for use separately. They are not safe for use in combination or when used in abuse amounts. Their use in prescribed amounts as OTC products appears to be safe, but the writer questions their effectiveness.  
(cross reference no. 56A).

- (45) Noble, R.E., Phenylpropanolamine and blood pressure (letter). *Lancet*, June 19, 1982, 8296:1419.

This letter is in response to the April 10th *Lancet* editorial on PPA. The author has studied over 400 obese patients (results to be published elsewhere). None of the dosages in the study (50 mg PPA, 50 mg PPA and 200 mg caffeine in sustained release form) caused a significant increase in blood pressure. As the study progressed there was a reduction in blood pressure.

- (45a) Knapp, M., Avioli, L.V. Analgesic nephropathy, *Arch. Intern. Med.*, 142:6, 1197-1199, June, 1982.

A case study of a 37 year old man is presented. He had been ingesting up to 8 capsules daily of propoxyphene HCl (Darvon) for many years. He also took a combination of acetaminophen, phenacetin, phenylpropanolamine HCl and phenyltoloxamine citrate (Sinutabs) 3 times a day for at least 12 years. Analgesic nephropathy seems a likely diagnosis. Renal acidosis in excess of that expected for the degree of renal failure and sodium ion are useful diagnostic clues.

- (46) Cohen, B.I. Safety of phenylpropanolamine (letter). Lancet, July 10, 1982, 8289:96.

This is a letter in response to the May 29 Saltzman letter on the safety of PPA which refers to normal daily doses of 75 mg/day. Cohen cites the PDR as a reference for recommended doses of 150 mg/day and states that "safety requirements should govern both uses and the clinical evidence justifying use should be consistent".

- (47) Pentel, P. and Mikell, F. Reaction to phenylpropanolamine/chlorpheniramine/belladonna compound in a woman with unrecognized autonomic dysfunction (letter). Lancet, July 31, 1982, 8292:274.

A 23 year old woman had chest tightness, severe headaches and hypertension after taking a single decongestant tablet containing 50 mg PPA ( Contac ) 4 mg chlorpheniramine and 0.2 mg belladonna alkaloids. Later observation showed that the patient's increase in systolic BP after 25 mg PPA was equal to that of normal subjects after 100 mg. The letter writers suggest that alpha-adrenergic hypersensitivity due to anatomic insufficiency was the cause of the patient's increased sensitivity.

The hypertension produced by PPA alone was less than experienced when taking Contac containing an anticholinergic and an antihistamine. This potentially clinically important drug interaction is discussed.

- (48a) New drug status of OTC combination drug products containing caffeine, phenylpropanolamine and ephedrine. Federal Register Frid. August 13, 1982; Docket No. 82N-0266, pp. 35344-35346.

FDA advises triple combination of PPA, caffeine, ephedrine is neither safe nor effective for legitimate use. Considers so-called "look-alikes" to be "new drugs". FDA voted to eliminate surreptitious use of triple combinations as counterfeit stimulants of prescription remedies. (cross-reference no.'s 14; 36a; 37; 56).

- (48) Tornatore, F.L. and Gilderman, A.M. Substance-induced organic mental disorders. American Pharmacy, Sept. 1982, N522(a):43-46.

Hypothetical case report provided: A 24 year old obese college student was hospitalized with a diagnosis of schizophrenia. Later discussion with a clinical pharmacist revealed no family or personal history of mental illness. In the past year she has used an amphetamine for weight reduction and taken additional PPA hoping she would lose weight faster. Her diagnosis was changed to drug-induced organic mental disorder. An 8 month followup showed no symptoms or further psychiatric intervention. A discussion of substance-induced organic mental disorders accompanies the case report.

X (49) Swenson, R.D., Golper, T.A. and Bennett, W.M. Acute renal failure and rhabdomyolysis after ingestion of phenylpropanolamine-containing diet pills. JAMA, Sept. 10, 1982, 248(10):1216.

(Rhamdomyolysis - disintegration or dissolution of muscle associated with excretion of myoglobin in the urine.)

Two case studies are presented 1) A 28 year old woman developed acute renal failure after ingesting PPA (Fullstop) for 3 weeks. She showed symptoms, signs and lab evidence of rhabdomyolysis. 2) A 21 year old man was admitted 5 days after ingesting 9½ quarts of malted beverage and 30-50 tablets of Dexatrim (each with 50 mg of PPA HCl and 200 mg of caffeine). He complained of weakness and muscle tenderness.

Both patients had acute renal failure and rhabdomyolysis. In neither case could a direct cause and effect relationship between PPA and rhabdomyolysis be established, but the writer suggests that it is likely and suggests several causal mechanisms. Note: Only patient 2 is reported for the first time. Patient 1 was reported by Bennet in a letter to Lancet 3 years earlier (Lancet, 1979, 2, 42-43) see reference 17a.

Pat. 1 28 yr Female Full Stop 25 mg tab+ ASA+ APAP Doses not specified and only via persistent question by MD was information obtained.

Pat. 2 21 yr Male Alcohol 9.5 qts. = 19 pts = 9000ml  
5% C<sub>2</sub>H<sub>5</sub>OH = 450 ml C<sub>2</sub>H<sub>5</sub>OH  
30 X 50 mg PPA = 1500 mg  
50 X 50 mg PPA = 2500 mg  
30 X 200 mg Caff = 6000 mg  
50 X 200 mg Caff = 10000 mg

(cross reference no. 63)

- (49a) Smookler, S., Bermudez, A.J. Hypertensive crisis resulting from an MAO inhibitor and an over-the-counter appetite suppressant, *Annals of Emergency Medicine*, 11:9, 482-484, September, 1982.

A 28 year old man being treated with Nardil for chronic depression who developed a hypertensive crisis and a severe occipital headache one hour after ingesting two capsules of Control (75 mg PPA) an OTC appetite suppressant. The adverse reactions between MAO inhibitors and phenylpropanolamine are discussed as are the dangers of using Demerol to treat the headache and Aldomet to treat the hypertension.

- (50) Friedman, R.B., P. Kindy, and J.A. Reinke. What to tell patients about weight loss methods 2. *Drugs. Postgraduate Medicine*, October 1982; 74(4): 85-88.

The use of amphetamine as diet aids has largely been replaced by other related drugs which seem to be effective but have troublesome CNS or sympathomimetic side effects. PPA has been found to have a greater anorectic effect than previously thought. However once drugs are stopped the weight is usually regained.

- (50a) Marshall, T.J., Stoudemire, A. Phenylpropanolamine effects, *Psychosomatics*, 23: 10, 1055, October, 1982

An exchange of letters claiming catatonia as an adverse effect of PPA and a rebuttal denying this adds little to the existing literature on this drug.

- (51) Mueller, S.M. and Solow, E.B. "Seizures associated with a new combination pick me up pill". *Ann. Neurol.*, March 1982, 11(3): 322

"Pick me ups" also known as "look-alikes" (combination of caffeine, PPA and sometimes another drug) has been associated with seizures in a 17 year old woman, two weeks postpartum. She took a single pill which she believed to be an amphetamine. Two seizures occurred within an hour of taking the tablet. No further seizures occurred, even when a regimen of phenobarbital was discontinued six months later. Neurologists are reminded that seizures as well as fatal cerebral hemorrhages can be associated with "pick-me-ups"!

- (52) Altschuler, S., Conte, A., Sebok, M., Marlin, R., Winick, C. Three controlled trials of weight loss with phenylpropanolamine. *Int. J. of Obesity*, 6, 549-556, 1982.

A multisite double-blind study was designed to determine the effectiveness of a phenylpropanolamine-caffeine combination in achieving weight loss. Two-hundred and one obese adult patients were divided into three separate groups in which phenylpropanolamine/caffeine was compared with either placebo (6 weeks), mazindol (6 weeks), or diethylpropion (8 weeks). In these clinical trials, phenylpropanolamine/caffeine proved to be as effective as mazindol and diethylpropion and significantly more effective than placebo in achieving weight loss. Overall, phenylpropanolamine/caffeine had fewer side effects than mazindol and diethylpropion. Its use as an effective anorectic agent in the treatment of obesity is reviewed.

(Cross reference number 35)

- (53) Weesner, K.M., Denison, M., Roberts, R.J. Cardiac arrhythmias in an adolescent following ingestion of an over-the-counter stimulant, *Clinical Pediatrics*, 21:11, 700-701, November, 1982.

Due to the ready availability of OTC stimulants containing phenylpropanolamine HCl, ephedrine and caffeine these preparations have become abuse items for adolescents. This makes it increasingly likely that patients will be observed to have arrhythmias and hypertension as a result of overdose.

A case report of a 14 year old white female who ingested 15-18 capsules of RJ8 (ephedrine 25mg, caffeine 200mg, phenylpropanolamine 50mg). About 1.5 hours later she complained of blurred vision, nervousness, tremors and inability to walk. She was given ipecac and activated charcoal at a local hospital. On admission her blood pressure was 104/62mm Hg, with a heart rate of 180 beats/min. and frequent aberrant beats.

Lidocaine therapy was initiated and when it did not affect the arrhythmias IV propranolol (1mg over 3 minutes) was administered. Recovery was uneventful. Propranolol appears to be the treatment of choice in these cases. (Cross reference number 48a)

- (54) Greenblatt, David J., Shader, Richard I. Phenylpropanolamine and the Completion of Volume 2 Editorial, *J of Clinical Psychopharmacology*, 2 (6), 369-370, 1982.

PPA is a stimulant and is marketed as such and also as a decongestant and anorectic. Numerous products contain PPA including Dietac, Dexatrim, Orande and Novahistine. PPA is structurally similar to metaraminol, ephedrine and amphetamine. Although it was pointed out as long ago as 1969 that PPA is a potentially dangerous drug it is frequently ignored. The clinical psychopharmacological community should take a stronger education stand with health care policy makers and regulators to control more strongly the use of over-the-counter preparations and to require greater education of the public as to their potential for harm.

- (54a) Finton, C.K., Barton, M., Chernow, B. Possible adverse effects of phenylpropanolamine (diet pills) on sympathetic nervous system function - caveat emptor! *Military Medicine*, 147, 1072, December, 1982.

PPA is a sympathomimetic drug structurally similar to amphetamine and ephedrine. It is found in 64 over-the-counter preparations sold for symptomatic relief of colds, as well as for appetite suppression. The amount of PPA in each preparation varies from 3.125 mg in children's cold tablets to as much as 85 mg in adult's diet pills. The sympathomimetic effects include restlessness, tremor, palpitations, anxiety, agitation, insomnia and confusion. There are numerous, adverse, idiosyncratic effects reported in the literature. The most noted of these is hypertension and hypertensive crisis. In spite of the reports of adverse reactions, PPA remains an over-the-counter preparation; in fact, the advisory panel to the FDA has recommended an increase in the amount that could be put in the proprietary drugs. Until further studies define the safety and efficacy of PPA, we urge limited, judicious use and close patient follow-up.

- (54b) Silverstone, T. Psychopharmacology of hunger and food intake in humans. *Pharmac. Ther.*, 19, 417-434, 1983.

The anorectic possibilities of a number of drugs is discussed. PPA administered to 48 subjects led to a significant reduction in intake compared to placebo. Two other studies (one involving a PPA-caffeine combination) of several weeks showed PPA causing a greater weight loss than placebo. Drugs which increase hunger are also described.

- (55) Howrie, Denise L., Wolfson, Jerome H. Phenylpropanolamine-induced hypertensive seizures, *J of Pediatrics*, 102, 143-145, January, 1983.

A healthy adolescent 13 year old experienced hypertension, severe headache and two seizures after taking sustained release diet pills containing 75 mg of PPA and 200 mg caffeine once daily for 2 weeks and 2 pills on the morning of the seizures. These drugs must now be considered in the differential diagnosis of hypertension and seizures.

- (55a) Soloway, R.A. Poisonings in the otolaryngologist's office. *Ear, Nose and Throat Journal*, 62(2), 112-115, February 1983.

Potentially toxic substances found in the offices of 6 ENT practices are described. Emergency treatment of PPA ingestion is advised since intractable hypertension has been associated with relatively small doses. Pediatric ingestion in excess of 50 mg should be removed from the stomach by induced emesis or lavage.

- (56) Smith, David E. Look-alike drugs and drugs of deception - epidemiological, toxicological and clinical considerations, *International Drug Report*, 24 (3), 3-7, March, 1983.

Review of look-alike drugs and drugs of deception using clinical and research experience coupled with a review of the literature. This includes PPA. (Cross reference number 48a).

- (56a) Bernstein, E., Diskant, B., Troutman, W., Spalding, C. Letter to the editor (R. Krome) *Annals of Emergency Medicine* dated March 8, 1983.

Letter (unpublished) provides further comment on earlier article and published letter of Saltzman (*Lancet* May 29, 1982 - tab 42) in regard to phenylpropanolamine. This letter questions anorectic effectiveness as regards risk/benefits ratio and long term weight loss. Letter also suggests that diet preparations containing PPA with caffeine appear to have replaced the illegal triple combination look alikes. (cross reference no.'s 43 & 44).

- (57) Mueller, Shirley M. Phenylpropanolamine, a nonprescription drug with potentially fatal side effects, *New England J of Medicine*, 308 (11), 653, March 17, 1983.

Psychic disturbances, headache, seizures, stroke and death have been reported as complications resulting from the ingestion of PPA. The writer of this letter attributes this situation to the increase of PPA containing products marketed since 1980, when amphetamines were more difficult to obtain because of tightening federal restrictions. An FDA advisory review panel concluded in January 1979 that PPA was generally safe and effective for weight control for up to 12 weeks in a daily dosage of up to 150 mg in divided doses. (FDA advised maximum allowable dose of PPA as diet aid is 75 mg; F.R. February 26, 1982 - Cross reference number 37).

Physicians should be aware that their patients may have used PPA and should be asked specifically about OTC medications since they may not think of these as "drugs". Drug screening of urine or gastric contents may be necessary since patients are reluctant to admit to ingestion of pills they believe to be amphetamines.

- (58) Nicholi, A.M. The nontherapeutic use of psychoactive drugs; a modern epidemic. *NEJM*, 308, 925-933, April 21, 1983.

A review article which includes comments on the use of selected psychoactive drugs. The article states that "because of the increase during the past two years of over-the-counter stimulants and mail order pseudoamphetamines that look and sound like real amphetamines. These readily available pills contain caffeine or the mild stimulant phenylpropanolamine. Many of the people who take them may think they are taking real amphetamines and report them as such in a survey". The author neglects to mention the Food and Drug Administration has made the sale of OTC stimulants illegal and requiring the filing of NDA's since they are now considered to be new drugs. The FDA by this action effectively eliminates the surreptitious use of triple combinations containing ephedrine, PPA and caffeine sold as counterfeit stimulants of prescription remedies. Furthermore only caffeine is a recognized OTC stimulant. PPA is not a stimulant as effectively proven by the studies of Griffiths, et al (1978 and 1981 respectively) reference number entries 12 and 31 and the human safety studies completed at the Behavioral Pharmacology Unit of the Johns Hopkins University; Report dated December 6, 1982 reference number 36-8 (Acute Section) of compilation of safety studies. (Cross reference 48a).

- (59) Lake, C.R., Tenglin, R., Chernow, B., Holloway, H.C. Psychomotor stimulation-induced mania in a genetically predisposed patient: a review of the literature and report of a case. *J of Clinical Psychopharmacology*, 3 (2), 97-100, April, 1983.

A 21 year old single male was admitted to a psychiatric inpatient ward four days after ingesting four "black beauty" capsules. Upon admission he was fully oriented with memory intact and had normal neurological and physical examinations with no evidence of organicity. A urine drug screen was negative. He denied symptoms of schizophrenia. Speech was continuous and pressured, demonstrating marked flight of ideas, distractability and lack of insight and judgement. The patient's past history revealed that 2 years previous to admission the patient had become socially withdrawn, sad and hopeless and had suicidal ideations. His family history was relevant in that two of his four brothers had been hospitalized with mania on several occasions both with major bipolar affective disorder. The father, the patient and two older brothers abuse alcohol. The manic symptoms persisted for 3 weeks after admission. The continued presence of drug was apparently not necessary for continuing manic behavior. Psychological testing was performed 3 weeks after admission which showed a markedly manic individual bordering on psychosis.

The case does not appear to meet the criteria for secondary mania because of the prior depressive episode and the strong family history of bipolar disease. Only long term follow-up will determine whether this manic episode represents "speed" - induced activation of a primary major bipolar affective disorder or "secondary mania" - a one-time episode caused by the "speed".

- (60a) Lund, M.E. Over-the-counter overdose. *Emergency Medicine*, 15(8), 175-188, April 30, 1983.

The physiological effects of PPA are described. Several cases of severe hypertension resulting from single or repeated 85 mg doses are mentioned, as are various cardiovascular side effects. Generally 100 mg of PPA is considered an adult toxic dose. Toxic doses in children are more difficult to define. Patients at risk from sympathomimetics are those who already have hypertension, those with autonomic dysfunction and those taking MAO inhibitors.

- (60) Ekins, B.R., Spoerke, D.G. An estimation of the toxicity of non-prescription diet aids from seventy exposure cases. *Vet. Hum. Toxicol.* 25 (2), 81-85, April, 1983.

This paper provides a review of seventy patients who had taken an overdose of either PPA or PPA in combination with caffeine using for this purpose one of several name brands appetite suppressant products. Twenty-four patients were males; 46 patients were females with ages ranging from 9 months to 12 years of age for the males and 1½ to 54 years of age for the females. Overdoses were on account of either accidental childhood ingestion (ages ranging from 9 months to 12 years) or self destructive or substance abuse (ages ranging from 11 to 54 years). Age and sex ratios of these groups provided no striking differences or findings. Dexatrim and Extra Strength Dexatrim accounted for the great preponderance of overdose exposures; 29 patients had taken Dexatrim and 21 patients had taken E.S. Dexatrim. Many of the patients had none to mild symptoms only following the overdose. Of the patients over 14 years of age who ingested PPA only mild symptoms developed including nausea, vomiting, abdominal cramps, headache, hot flashes, sweating, labored breathing, irritability and tachycardia (140 beats/minute). Onset of symptoms usually occurred from 30 minutes to 1 hour with a duration approximating 15 hours. The estimated dose of symptomatic patients was 17.5 mg/kg (approximately 50 times the recommended 25 mg dose). The 17.5 mg/kg dose is probably predictive of symptoms of excessive dosing with PPA. When combinations of PPA and caffeine were used the toxic dose is estimated to drop to approximately 10 mg/kg. The authors conclude that as a result of this study the majority of overdoses involving OTC diet aids is not serious and may only require decontamination of the digestive tract and supportive care. In children following an 8-10 mg/kg dose emesis is recommended and this dose is expected to produce only mild symptoms if at all. Further the authors indicate that the lack of serious side effects in either the cases with only PPA or combination of PPA with caffeine raises questions about the serious reactions noted in earlier published reports.

- (61) Greenwood, J. The case against PPA, *The Pharmaceutical J*, May 21, 1983, 585-586.

This UK article is a summary of the adverse effects including cases of deliberate overdose, and drug interactions reported for PPA over the last 15 years. The author speculates that since all the reported cases required immediate hospitalization that use of PPA should be carefully considered. No new data are presented in the review.

- (62) Krenzelok, E.P. Street Speed. The Pennsylvania Pharmacist, 149-150, May, 1983.

Adverse effects from "fake speed" and even the popular appetite suppressants can occur following the ingestion of even "therapeutic" amounts. The primary ingredients in street speed are phenylpropanolamine (up to 50 mg), ephedrine (up to 25 mg), and caffeine (up to 250 mg). The common variety of appetite suppressants sold in pharmacies may contain as much as 75 mg of phenylpropanolamine per dosage form. Although not ubiquitous in the literature, there are several reports describing adverse health effects associated with use of prescription and proprietary drugs containing phenylpropanolamine. The most notable detrimental effect manifested by excessive phenylpropanolamine intake is hypertension. A recent retrospective review of street speed patients evaluated in an emergency room, revealed that 63% had at least mild hypertension following documented ingestion of the fake speed. A variety of other effects are common in these individuals and less life-threatening than hypertension such as headache, palpitations restlessness and insomnia. Additional objective findings commonly seen with street speed use include episodes of nausea and vomiting which may occur even with caffeine and PPA alone. Confusion and psychotic behavior are also commonly encountered.

- (62a) Mueller, S.M. Neurologic complications of phenylpropanolamine use. Neurology, 33(5), 650-652, May 1983.

Eleven patients (six male, five female) had neurologic symptoms after ingesting "look-alike" pills containing PPA. Two of these patients had also ingested caffeine and two patients had ingested unidentified substances in addition to PPA. Five patients had a headache with elevated blood pressure, three of these patients vomited, two were diaphoretic and two were tremulous. One patient had dilated pupils, Four patients had cardiac irregularities. Four patients had psychiatric symptoms (acute psychosis, attempted suicide and reported bizzare behavior and paranoia). Two patients had seizures.

- (63) Blewitt, G.A. and Siegel, E.G. Renal Failure, Rhabdomyolysis and Phenylpropanolamine. JAMA, June 10, 1983, 249(22): 3017-3018.

Provides rebuttal to reference number 49, Swenson, R.D. et al. Acute renal failure and rhabdomyolosis after ingeston of phenylpropanolamine-containing diet pills. JAMA, Sept. 10, 1982, 248(10): 1216.

Blewitt and Siegel indicate the 2 cases reported by Swenson, R.D. et al do not support their speculation of PPA causing renal failure or rhabdomyolysis and that there is no literature support to their theory. Swenson, R.D. et al in reply to the Blewitt, G.A. and Siegel, E.G. letter indicating that liver disease and interstitial nephritis induced by the use of ampicillin trihydrate complicate their claim of PPA induced renal failure in patient 1 and that alcohol was a contributory factor to rhabdomyolysis and kidney failure in patient 2. They go on to state "for most people we have no doubt that this drug (phenylpropanolamine) can be used safely". (Cross reference number 49)

- (63a) Cohen, S. The rise and fall of the look-alikes. Drug Abuse and Alcoholism Newsletter, 12(4), June 1983.

The evolution and decline of the "look-alike" drug matter is described. Many look-alikes consist of a combination of PPA, ephedrine and caffeine. Look-alikes usually contain 25-50 mg of PPA. People with hypertension or coronary artery disease should not use PPA. Larger than average doses have been associated with dizziness, tremulousness, anxiety, palpitations and nausea. There have been published reports of sudden marked rises in blood pressure resulting in cerebral hemorrhages and PPA induced psychosis (not footnoted).

- (64) Caperton, E. Raynaud's phenomenon - role of diet pills and cold remedies. Postgraduate Medicine, 73 (6), 290-291, June, 1983

This article reports 3 women with significant complication of Raynaud's phenomenon. Symptoms stopped for 2 of the women when they discontinued use of PPA containing diet pills or cold remedies. In 2 of the 3 patients severe Raynaud's phenomenon had affected all 4 extremities and hemorrhagic vasculitic lesions were seen on the toes. The third, a 37 year old 106 lb woman continued taking diet pills and had a stroke. A test for antinuclear antibody was positive thus lupus may underlie her vascular sensitivity.

- (64a) Saltzman, M.B. Phenylpropanolamine (letter). Am. Fam. Physician, 27(6), 23, 26, 28, June 1983.

A letter in response to an article on nonprescription anorexiant states that PPA lacks abuse potential and that psychiatric and CNS disturbances are largely due to inappropriate doses, or PPA ingested in combination with other drugs. The author of the article responded that OTC drugs are not always taken in appropriate ways and that there are other published reports of problems associated with PPA use.

- (65) George, E. Lawsuit Claims Dexatrim Pill Caused Stroke. Arlington Journal (newspaper) July 15, 1983 (friday).

News article describing lawsuit by a Jeffrey W. Young; attorney Thomas P. Mains, Jr. claiming CVA following the use of Extra Strength Dexatrim. Plaintiff stated he used Extra Strength Dexatrim for its supposed stimulant effect to keep awake and not for its anorectic effect. States he took "one pill about 10 PM and perhaps another about two hours later". An adverse effect occurred while driving "a short time later". Young felt a "tingling sensation like all the hair on my neck was standing up on end. Then came the headache". Edward Nida, FDA spokesman who apparently was contacted by the Arlington Journal reporter stated "there's no lack of information and cautions on the label. It's getting people to read it that's the problem".

- (65a) McEwen, J. Phenylpropanolamine-associated hypertension after the use of "over-the-counter" appetite suppressant products. *The Medical Journal of Australia*, 2: 71-73, July 23, 1983.

Eight apparently normotensive Australian women patients developed hypertension after taking appetite-suppressant preparations which contained high doses of phenylpropanolamine. The margin between the maximum dose permitted to be sold in some States of Australia without prescription, and the doses documented as causing hypertension is small. Three patients took twice the recommended dose - a pattern of behavior which has been described previously. Changes to the regulations governing the availability of phenylpropanolamine may have reduced the risk of this adverse effect, but the use and misuse of preparations still available over-the-counter may not be without danger.

- (66) Krupka, L.R., Vener, A.M. Over-the-counter appetite suppressants containing phenylpropanolamine hydrochloride (PPA) and the young adult: usage and perceived effectiveness. *J. Drug Education*, 13 (2), 141-152, 1983.

A survey of 944 young adults regarding their usage and perceived effectiveness of over-the-counter (OTC) diet pills containing PPA showed that 30.1% of the women had consumed these preparations during the year prior to the interview. Women who either perceived themselves as being very overweight and/or desired to lose the most poundage tended to consume more diet pills. About 25% of the women who had ingested appetite suppressants reported various side effects. The vast majority of women (86%) believed that the pills were useful only on a very short-term basis, or that they acted as placebos, with little or no anorectic action and/or they were completely ineffective. Only 3.7% of the men had used an OTC diet preparation. In a second survey of 425 young adults the potentiality for overdose was demonstrated by the 47% of the women who had used two or more OTC preparations (diet pills and/or decongestants) containing PPA in a 24 hour period and the 10% who had consumed three or more.

- (66a) Committee on Drugs. "Look-alikes". *Pediatrics*, 72(2), 256-257, August, 1983.

This article alerts pediatricians to the existence of look-alike-drugs which resemble amphetamines in the appearance of the tablets or capsules but which are actually OTC products such as PPA. Identification of these substances can be difficult and conventional toxicological screening does not detect PPA. PPA in doses of 50-85 mg has increased blood pressure to hypertensive levels. Combinations of PPA and other OTC drugs have produced amphetamine like reactions. Regular dosage forms are more likely to be toxic than timed release preparations.

- (66b) Saltzman, M.B. Safety of phenylpropanolamine. *Annals of Emergency Medicine*, 12(9), 590-592, September, 1983.

With reply by Edward Bernstein, Barry Diskant, William Troutman and Charles Spalding Dr. Saltzman, Medical Director of Menley & James Laboratories argues for the safety of PPA, saying that reports mentioned in an earlier article involve an idiosyncratic reaction, ingestion of PPA with other substances or unusually large doses. Dr. Saltzman also says that reports of hypertension induced by PPA are not consistent with data obtained in Menley & James studies. Drs. Bernstein, Diskant, Troutman and Spalding call for more data to be collected on the utilization of OTC diet preparations. They point out that there are between 23-60 million hypertensive people in the U.S. one third of which are undetected. They also note that there is growing evidence that certain people exhibit "rather variable responses to sympathomimetic agents" (either universally strong or weak). Both letters cite an absence of data in the studies cited by the other side.

- (67) Latimer, D. The peashooter perplex. Part I, *High Times*, August 1983, 60-65; Part II, *High Times*, September, 1983, 40-45; Part III, *High Times*, October, 1983, 45-97.

Layperson type article reviewing so-called "look-alike" triple combination products of ephedrine, caffeine and phenylpropanolamine. Review includes mention of DAWN; PPA adverse reaction reports; OTC product names; NIDA; FDA; DEA and several companies manufacturing both prescription and OTC preparations. Article also reviews history of PPA/OTC anorectics beginning with their initial introduction (1937) and concludes with the recommendation for Category I anorectic status by an FDA panel in 1979.

- (68) Rumpf, K.W., et al. Rhabdomyolysis after ingestion of an appetite suppressant. *JAMA* 250(16), 2112, Oct. 28, 1983.

A letter from Germany reports a patient who had taken an overdose of the appetite suppressant cathine HCl (formerly d-norpseudoephedrine). The patient took 20 pills each day containing 15 mg cathine HCl, 8mg of the analeptic nikethamide, 10 mg caffeine and salicylate sodium and 19 other low-dose herbal ingredients. The patient developed severe rhabdomyolysis. Serum creatinine and serum myoglobin values returned to normal within the next 3 weeks and no underlying muscular disease or residual impairment of renal function was later evident. (cross reference 49 & 63).

- (69) Clark, J.E., Simon, W.A. Cardiac arrhythmias after phenylpropanolamine ingestion. *Drug Intelligence and Clinical Pharmacy*, 17, 737-738, Oct., 1983.

Physicians and pharmacists should be alerted to the potential adverse effects of phenylpropanolamine-containing products, which may include exaggerated hypertensive effects, arrhythmias (premature ventricular and atrial contractions together with paroxysmal ventricular or atrial tachycardia), psychotic reactions, and neurologic effects (grand mal seizures and intracerebral hemorrhage). A case of paroxysmal atrial tachycardia in a woman, after ingestion of diet pills containing phenylpropanolamine and caffeine is reported.

- (70) Saltzman, M.B., Dolan, M.M., Doyne, N. Comparison of effects of two dosage regimens of phenylpropanolamine on blood pressure and plasma levels in normal subjects under steady-state conditions. Drug Intelligence and Clinical Pharmacy, 17, 746-750, Oct., 1983.

Plasma levels and blood pressure responses to two dosage regimens of phenylpropanolamine (PPA) - 25 mg, immediate-release tablets three times per day and a 75 mg controlled-release capsule once per day - were compared in 14 normal subjects. To obtain steady-state conditions, subjects were given the test materials for four-day periods, and blood pressure and plasma PPA levels were measured on day 4. The dosage forms were equally bioavailable, based on a 95-percent confidence coefficient, and neither produced hypertensive effects. The highest diastolic pressure was 96 mm Hg three hours after a 25 mg dose. Mean PPA plasma levels showed no correlation with mean blood pressure readings at any point during a 12 hour test period. These data show that, in these subjects, a daily dosage of PPA 75 mg, either in divided doses of 25 mg each or in a dependable controlled-release formula, produces no indication of pressor effects.

- (70a) Johnson, D.A., Etter, H.S. and Reeves, D.M. Stroke and phenylpropanolamine use. Lancet, 8356, 970, October 22, 1983.

Two cases of stroke following use of diet pills containing PPA are reported in this letter. One male, age 24, had been taking 8-10 diet pills (Dexatrim with 50 mg PPA per tablet) daily for 3 months. The other male, age 34, had been taking 3-8 pills (Dietac with 37.5 mg PPA per tablet) daily for 4 months. Both patients had right-sided hemiparesis. Hypertension does not seem to have been a factor in either of these patients. The first patient at one year was reported to have had no neurological relapses. The second patient after 10 months had no neurological residual deficits.

- (71) Brody, J. New York Times, Wednesday November 9, 1983.

Science writer J. Brody provides a terse critical article on the use of PPA as an anorectic agent. Citing several critical articles including Dietz (1981), Horowitz (1980), Swedish adverse reaction statistics (1979) and Lancet editorial (April, 1982). Ms. Brody questions both the safety and usefulness of the drug. She infers that the 1979 Panel report (published in the Federal Register in February, 1982) on the use of weight reducing agents made its conclusions and recommendations on the basis of inconclusive, incomplete and scanty data. A relationship to amphetamine and potential problems as a drug of abuse is inferred. Nowhere in the one-sided article does Ms. Brody provide citations which speak to PPA's safety, effectiveness and lack of abuse potential.

- (72) Mason, W.D., Mason, J.S. Improved high pressure liquid chromatographic method for phenylpropanolamine in human plasma. Analytical Letters, 16(B9), 693-699, 1983.

A high-pressure liquid chromatographic analysis of phenylpropanolamine in plasma following extraction, back extraction and pre-column derivitization with O-phthalaldehyde is presented. The method is improved by the use of phenylethanolamine as internal standard. Using fluorescence detection, the method is sufficiently sensitive to quantitate 5 ng/ml in 0.5 ml plasma with a standard error of estimate of 2.7 ng/ml when calibrated over the 0 to 240 ng/ml range. Analysis of over 2000 clinical samples have shown the method to be highly specific and-reliable.

- (73) Anon., November, 1983, Enforcement Action Under New Drug Provisions of the Federal Food, Drug, and Cosmetic Act; Certain OTC Drug Products; Advisory Opinion: Food and Drug Administration (USA) DHHS, Federal Register, November 18, 1983; Docket No. 83A-0339, pp. 52513-52514.

FDA advises that combinations of (a) caffeine in combination with ephedrine or pseudoephedrine; (b) PPA in combination with ephedrine or pseudoephedrine and (c) PPA in combination with caffeine are considered to be new drugs. The only legal OTC preparation that may be sold as a stimulant is caffeine as the single active ingredient. The stimulant label may not be applied to any other OTC drug other than caffeine and not to the drugs indicated in a, b or c. The intent of this action by FDA is to eliminate misuse and abuse of the aforementioned products.

(cross reference no.'s 14; 36a; 37; 48a)

- (74) Appelt, G.D. The safety of phenylpropanolamine (letter). J. Clin. Psychopharmacology, 3(5), 333, October, 1983.

This letter responds to an editorial and abstract published in the Journal of Clinical Psychopharmacology, December 1982, on the safety of phenylpropanolamine. The author comments that the cases cited actually referred to the no longer marketed and FDA unapproved combinations of PPA, ephedrine and caffeine. Reports of adverse reactions to PPA should be examined for evidence of hypersusceptibility, dosage and dosage form ingested, concurrent pathology, and the presence of other drugs. PPA toxicity should not be evaluated on the basis of reports of adverse reactions from combination products.

- (75) Saltzman, M.B. Phenylpropanolamine (letter). New England J. of Medicine, 310(6), 395, 1983.

This letter from Saltzman of Menley and James Laboratories is in response to a March 17, 1983 NEJM issue letter from S.M. Mueller. Saltzman points out that the reports cited by Mueller involve high unspecified doses, "look-alike" drugs or unusual histories and notes that "properly manufactured and marketed nonprescription PPA products taken as directed have had an excellent safety record".

- (76) Waggoner, W.C. Phenylpropanolamine overdose (letter). Lancet, Vol. II, 1503-1504, December 24, 1983.

This letter responds to an October 22, 1983 Lancet issue letter from D.A. Johnson regarding two case reports of PPA chronic overdose. Waggoner states that since PPA is a sympathomimetic amine it is not surprising that overdose causes vascular effects. He also notes that in normal therapeutic doses PPA has had an exceptional safety record. There is no solution to this problem, (overdose), it is more likely to be found by addressing the subjects at risk rather than the host of substances they misuse.

- (77) Cornelius, J.R., Soloff, P.H., Reynolds, C.F. Paranoia, homicidal behavior, and seizures associated with phenylpropanolamine. *Am. J. Psychiatry*, 141(1), January, 1984.

Anecdotal case history of a 28 year old woman with a borderline personality disorder and history of multiple suicidal attempts and polysubstance abuse who attempted a homicidal maneuver on a family member following the ingestion of large amounts of cough syrup. In the 24 hours preceding the attempted homicide the patient had ingested approximately 12 ounces of cough syrup containing a total of:

Phenylpropanolamine HCl	900	mg
Pyrilamine Maleate	450	mg
Pheniramine Maleate	450	mg
Dextromethorphan HBr	1.08	g
Ammonium Chloride	6.48	g

The authors attribute the psychotic episode to phenylpropanolamine while discounting the effect of the other active ingredients which were taken in large overdose. A 50 mg PPA HCl challenge dose was given which is alleged to have induced a clinically observed seizure. No challenge using the other active ingredients alone or in combination was provided. In view of the patients clinical and drug history, the lack of challenge with active ingredients other than PPA HCl, the magnitude of overdoses taken by this patient and whether the patient had abstained from the use of medication prior to the administration of a "challenge" dose of PPA HCl it is difficult to ascribe the abnormal behavior to PPA HCl alone. In the 24 hours prior to the homicidal gesture the overdoses taken of each of the active medications in the cough syrup were:

	12 ounces contain	Single Recommended Adult Dose	Maximum 24 hour Adult Dose	Overdose
Phenylpropanolamine HCl	900 mg	25 mg	150 mg	6 times
Pheniramine Maleate	450 mg	12.5 mg	150 mg	3 times
Pyrilamine Maleate	450 mg	12.5 mg	150 mg	3 times
Dextromethorphan HBr	1080 mg	20 mg	120 mg	9 times

Intoxication, abuse, abnormal behavior, convulsions and psychotic events have been reported for antihistamines and for dextromethorphan and are well documented in the literature.

- (78) Assessment of Phenylpropanolamine (PPA) Abuse Risk in Weight Control Patients. George E. Bigelow, Ira A. Liebson, Roland R. Griffiths, Rosalind Trieber and Pat Nowowieski. Johns Hopkins University School of Medicine and Baltimore City Hospital, Baltimore, MD 21224. FASEB, April, 1984.

#### Method of Study

1. **Subjects:** Women at least 20% overweight were enrolled in a once weekly counseling program emphasizing behavioral change of eating and exercise habits. Subjects volunteered for concurrent pharmacological research participation.
2. **Design:** Subjects received for one week either PPA or placebo followed by one week of no medication followed by a medication (PPA) or placebo cross over week followed by a 4th week using therapy selected by patient. Two 4 week cycles were used for the 8 subjects participating in the double blind cross over study.
3. **Dosage Form:** 75 mg controlled release phenylpropanolamine given once daily.
4. **Summary of completed study** as submitted for presentation at the 1984 FASEB meeting.

PPA, marketed as a nonprescription anorectic, is a phenylethylamine structurally related to amphetamine. Its effects upon mood and drug preference were tested in a placebo-controlled double-blind cross over study which included a behavioral preference component. Participants were 8 women volunteers, 21 - 96% overweight, enrolled in a weight control clinic. Medications were prepared in color-coded capsules (75 mg PPA sustained release versus placebo) and 1 week supplies were dispensed on alternate weeks. Following exposure to each compound, patients selected, in a choice-exposure, the color-coded medication they would next receive this sequence repeated within subjects for 1-5 cycles. Color-codes and exposure orders were randomized. Results revealed mild mood-elevating effects of PPA without evidence of behavioral preference. Following one week of drug use patients reported, via the Profile of Mood States, significantly increased "Vigor" and significantly decreased "Fatigue" with PPA relative to placebo ( $p < 0.05$  in both cases). In drug preference trials PPA was chosen on 14 of 26 occasions (53.8%), indicating no significant difference from placebo. These data, indicating detectable PPA mood-altering effects without increases in drug preference or self-administration suggest low abuse liability.

CROSS FILE SHEET

FILE NO: 76N-052N/RPT

SEE FILE NO: 81N-0022/RPT003