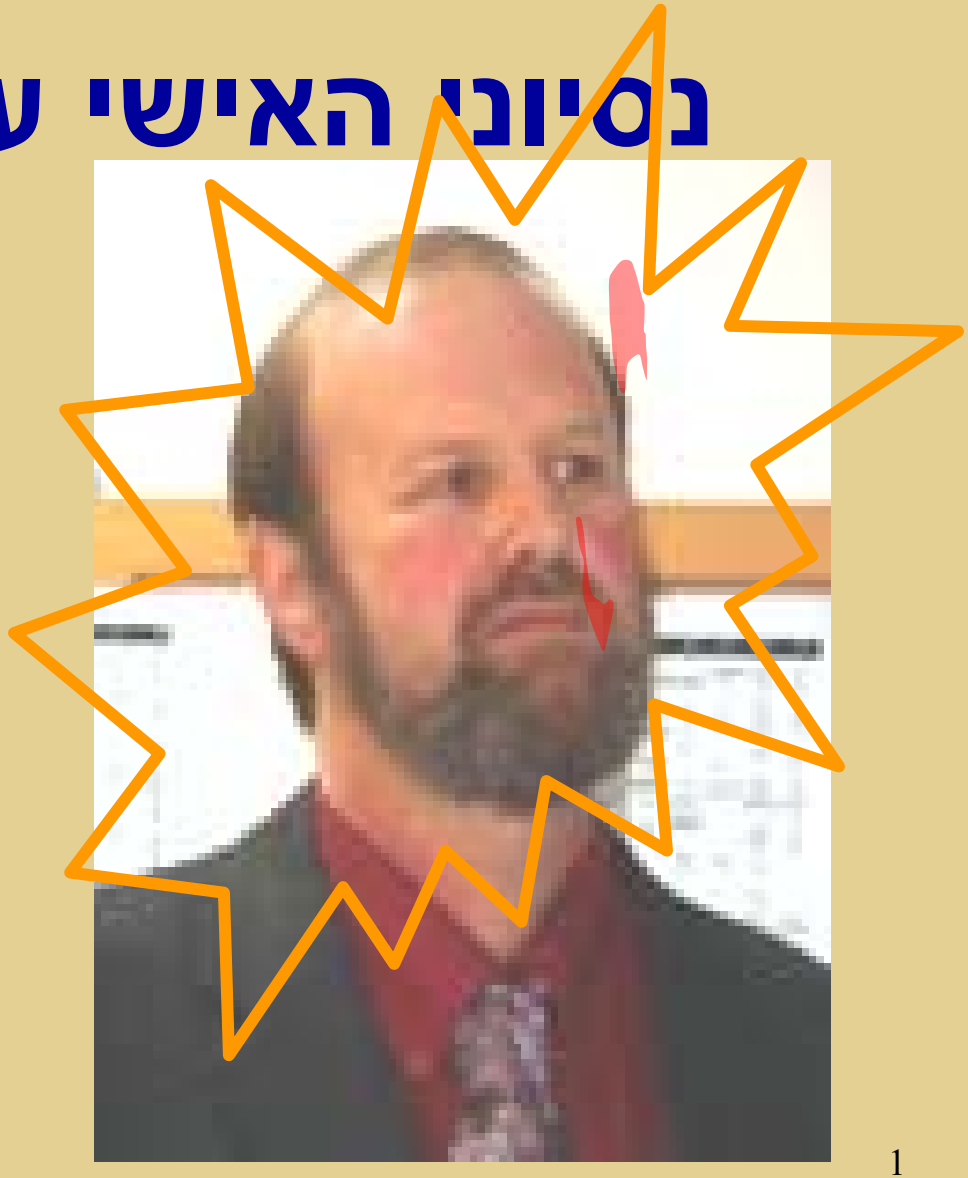
ההסתדרות הרפואית בישראל – החברה לחקר, מניעה וטיפול בטרשת עורקים
Israel Medical Association-Society for Research, Prevention and Treatment of Atherosclerosis

נסיוני האישי עם ניאצין



יעקב הנקין
המערך הקרדיולוגי
מרכז רפואי סורוקה

Niacin

>50 years experience
Good overall safety

- **Flushing**
- **GI effects**
  - **Exacerbation of ulcer**
- **Hepatotoxicity**
- ↑ uric acid
- ↑ glucose
- Atrial arrhythmias

Niacin Flushing

- **almost universal initially**
  many find it intolerable
  sometimes associated by pruritus and/or rash
- **tachyphylaxix usually develops later**
  within several weeks
- **prostaglandin induced**
  can be prevented by aspirin

- **Can be reduced by:**
  ***gradual increase in dose**
  ***taking drug with food (slows absorption)**
  ***avoiding concomitant hot drinks & alcohol**
  ***sustained-release preparations**

3

Nicotinic Acid

Drug Form	Brand	Classification	FDA approval
IR (crystalline)	**Various**	**Dietary Supplement**	**No**
	Niacor	**prescription**	
	Nicolar		**yes**
SR	**Slo-Niacin®**	**Dietary Supplement**	**No**

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JAMA®
The Journal of the American Medical Association

Rechallenge With Crystalline Niacin After Drug-Induced Hepatitis From Sustained-Release Niacin

Yaakov Henkin, MD; Karen C. Johnson, MD, MPH; Jere P. Segrest, MD, PhD

JAMA 1990;264:241-243

Lipoprotein Profiles and Liver Function Tests Before Niacin Therapy, During Therapy With Sustained-Release (SR) Niacin, and After Rechallenge With Crystalline (C) Niacin*

	Dose, g	Time, wk†	TC, mmol/L	LDL-C, mmol/L	IDL-C, mmol/L	HDL-C, mmol/L	VLDL-C, mmol/L	AST, U/L	ALT, U/L	AP, U/L	TB, μmol/L
					Patient 1						
Pretreatment	. . .	. . .	6.30	3.85	0.90	0.95	0.60	25	23	72	9
SR niacin	4.0	1	4.85	NA	NA	NA	NA	800	700	56	14
C niacin	4.0	20	4.00	2.05	0.30	1.50	0.15	32	28	70	7
					Patient 2						
Pretreatment	. . .	. . .	9.05	7.45	0.30	1.20	0.10	34	30	73	7
SR niacin	2.0	24	7.35	5.20	0.45	1.60	0.10	227	870	2325	121
C niacin	2.5	37	4.75	2.90	0.25	1.50	0.10	31	10	93	9
					Patient 3						
Pretreatment	. . .	. . .	5.55	2.80	1.10	0.85	0.80	34	26	65	7
SR niacin	2.0	6	3.40	1.55	NA	1.15	0.70	160	155	85	9
C niacin	>2.0	20	4.75	2.85	0.55	1.05	0.30	36	15	76	7

Gradual dose escalation
1 tab = 500 mg

week	breakfast	dinner
1	-	0.5
2	0.5	0.5
3	0.5	1
4	1	1
5	1	1.5
6	1.5	1.5
7	1.5	2.0
8	2.0	2.0

6

Gradual dose escalation
1 tab = 500 mg

תמיד לאחר אוכל
עם כוס מים קרים
להמנע משתיה חמה או אלכוהול
במידת הצורך, אספירין 250 מ"ג

we

4	1	
5	1	1.5
6	1.5	1.5
7	1.5	2.0
8	2.0	2.0

THE AMERICAN JOURNAL of MEDICINE.

Niacin Revisited: Clinical Observations on an Important but Underutilized Drug

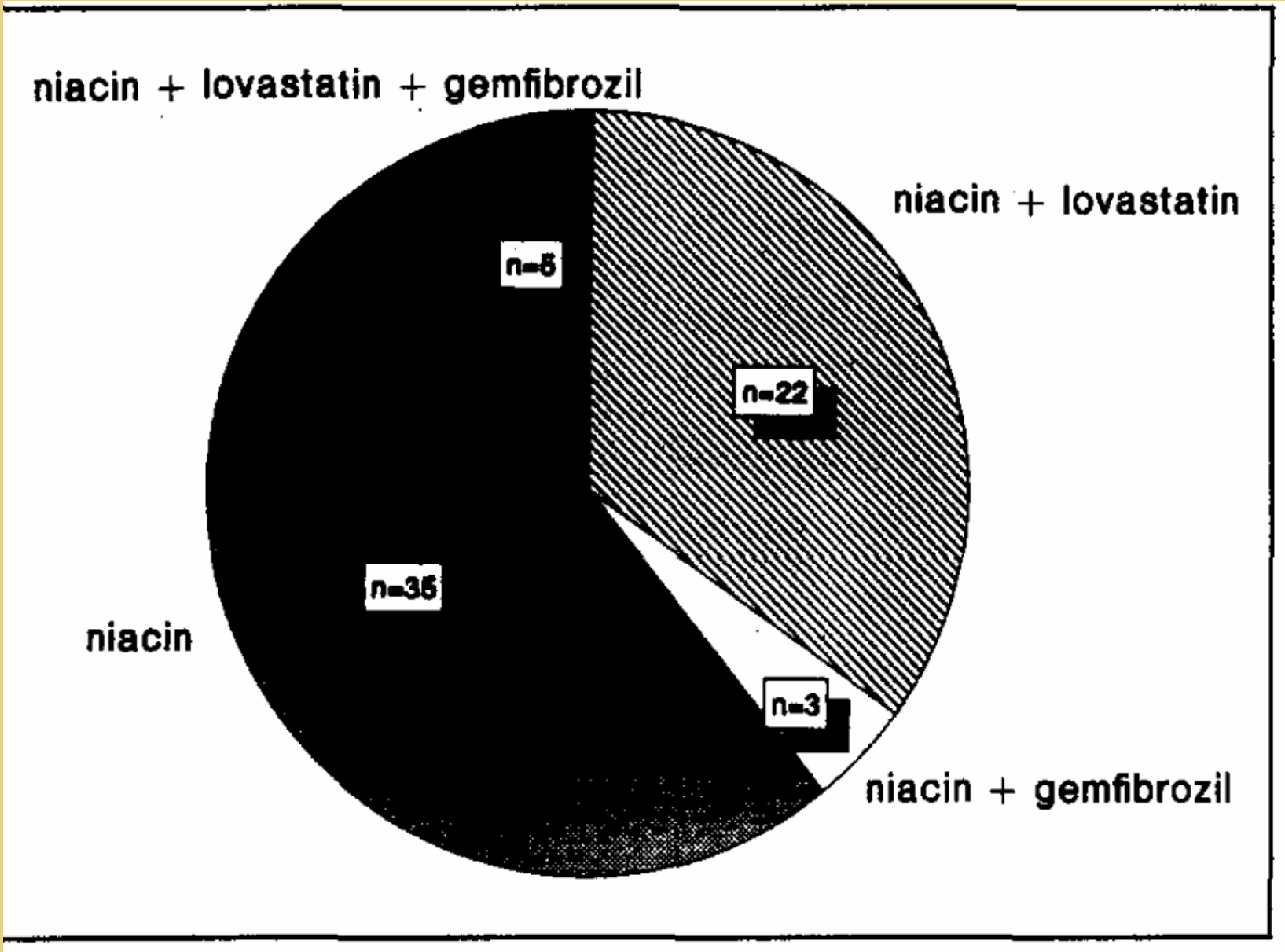
YAAKOV HENKIN, M.D., ALBERT OBERMAN, M.D., DAVID C. HURST, Ph.D., JERE P. SEGREST, M.D., Ph.D., *Birmingham, Alabama*

TABLE I

Baseline Characteristics of the HTR and NTP Groups

Group	Number	Age (years)	Gender (M:F)	Weight Index	Diabetics	TC	LDL-C	HDL-C	VLDL-C
						mg/dL (mmol/L)			
HTR	17	49 ± 2	14:3	0.50 ± 0.17	8 (47%)	325 ± 20 (8.41 ± 0.5)	226 ± 17 (5.82 ± 0.4)	40 ± 3 (1.03 ± 0.1)	56 ± 14 (1.45 ± 0.4)
NTP	65	55 ± 2	45:20	0.43 ± 0.11	3 (5%)	259 ± 9 (6.07 ± 0.2)	178 ± 9 (4.60 ± 0.2)	39 ± 2 (1.01 ± 0.1)	43 ± 8 (1.11 ± 0.2)
p		NS	NS	<0.004	<0.01	<0.001	<0.01	NS	NS

HTR = heart transplant recipients; NTP = nontransplant patients; TC = total cholesterol; LDL-C = low-density lipoprotein cholesterol; HDL-C = high-density lipoprotein cholesterol; VLDL-C = very-low-density lipoprotein cholesterol.


niacin + lovastatin + gemfibrozil
niacin + lovastatin
n=5
n=22
n=35
niacin
n=3
niacin + gemfibrozil

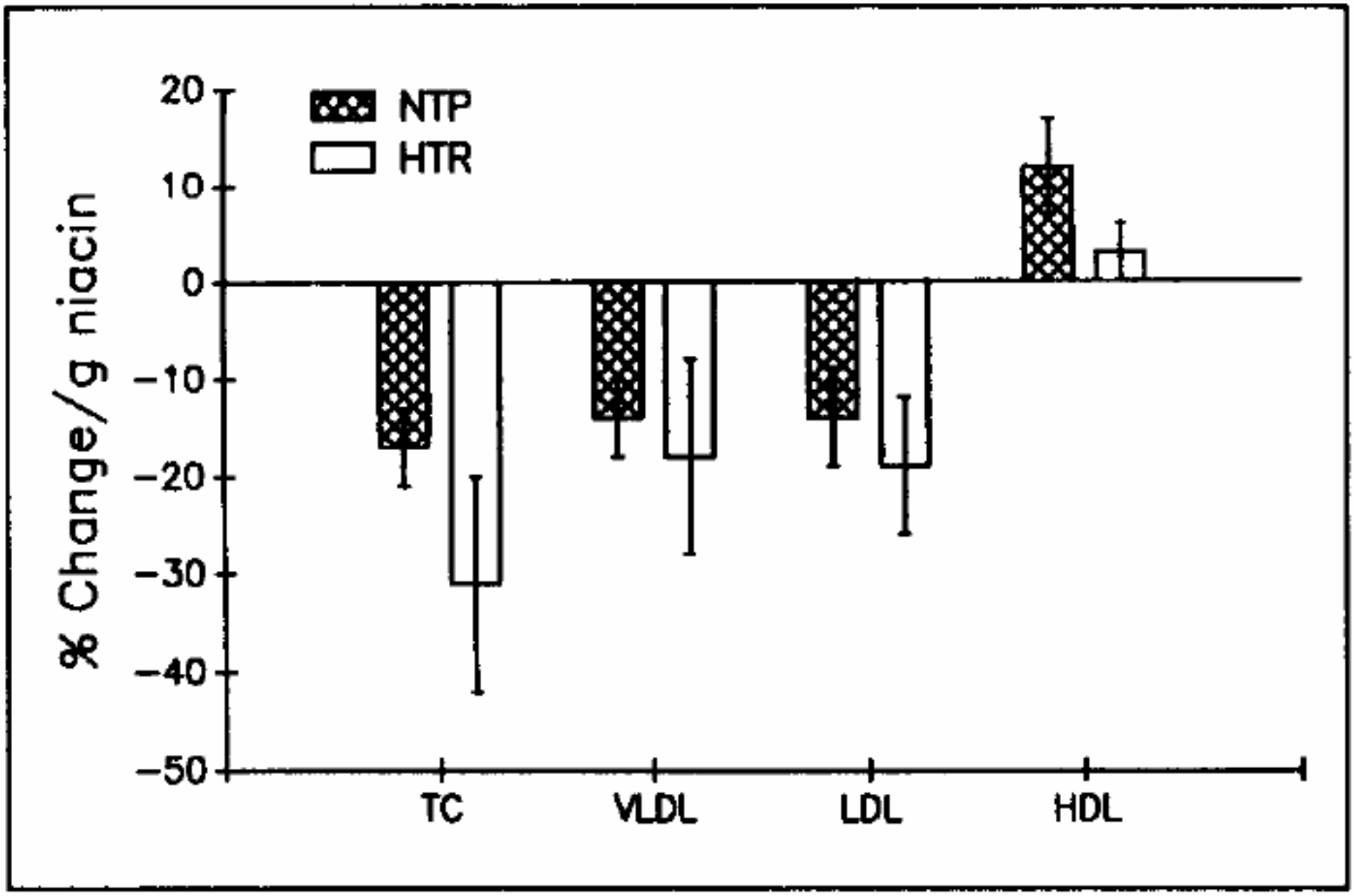

NTP
HTR
% Change/g niacin
20
10
0
−10
−20
−30
−40
−50
TC
VLDL
LDL
HDL

TABLE III

Effects of Baseline Lipoprotein Levels on Niacin Response

	Subgroups According to Baseline Lipoprotein Levels					
	HDL-C (mg/dL)		LDL-C (mg/dL)		VLDL-C (mg/dL)	
	<35 (n = 12)	>35 (n = 18)	<160 (n = 14)	>160 (n = 16)	<20 (n = 15)	>20 (n = 15)
Percent change HDL-C per g niacin	+14	+11	+10	+5	+15	+8
(baseline, mg/dL)	(28 ± 10)	(48 ± 6)	(37 ± 2)	(46 ± 2)	(45 ± 7)	(38 ± 1)
Percent change LDL-C per g niacin	−4	−19	−7	−18	−23*	−3*
(baseline, mg/dL)	(169 ± 5)	(193 ± 7)	(130 ± 3)	(221 ± 5)	(195 ± 8)	(167 ± 9)
Percent change VLDL-C per g niacin	−23	−10	−19	−12	−4†	−26†
(baseline, mg/dL)	(54 ± 8)	(11 ± 2)	(37 ± 7)	(24 ± 5)	(13 ± 2)	(55 ± 8)

Abbreviations as in Table I.
*$p < 0.05$ between high and low subgroups.
†$p < 0.01$ between high and low subgroups.

TABLE IV

Patients Who Discontinued Niacin

Category	Total Number of Patients	Average Niacin Dose (g)	Number Discontinuing Therapy (%)	Reasons for Discontinuation (Number of Patients)					
				Diabetes	Skin	Gastrointestinal	Palpitations	Hypotension	Hepatitis
Hepatitis									
HTR	66	2.5 ± 0.4	9 (14)	1	2	2	1	1	3
NTP (total)	17	1.3 ± 0.1	11 (65)	10	—	—	—	—	—
Diabetics	8	—	8 (100)	7	—	—	—	1	—
Nondiabetics	9	—	3 (33)	3	—	—	—	—	—

HTR = heart transplant recipients; NTP = nontransplant patients.

TABLE V

Niacin-Induced Hepatitis

Patient*	Age (years)	Gender	Niacin		Maximal Liver Function Tests				Additional Drugs	Brand†
			Type	Dose (g)	SGOT (U/L)	SGPT (U/L)	Alkaline Phosphatase (U/L)	Bilirubin (μmol/L)		
1	50	F	SR	2.0	227	240	2,325	7.1 (121)	Verapamil, HCTZ	Nicobid
2	62	M	SR	4.0	800	700	56	0.8 (14)	—	Major pharmaceutical
3	47	M	SR	2.0	160	155	85	0.5 (7)	Dipyridamole, diltiazem	Slo-Niacin
4	24	F	SR	2.0	212	145	222	1.7 (29)	‡	Nicobid
5	66	M	SR	3.0	208	N/A	126	0.8 (14)	—	Various types
6	66	M	SR	3.0	193	150	117	0.8 (14)	Lovastatin	K-Mart
7	66	F	SR	1.0	135	81	173	0.8 (14)	—	?
8	50	F	?§	1.5	1,670	970	143	0.5 (7)	Lovastatin	?

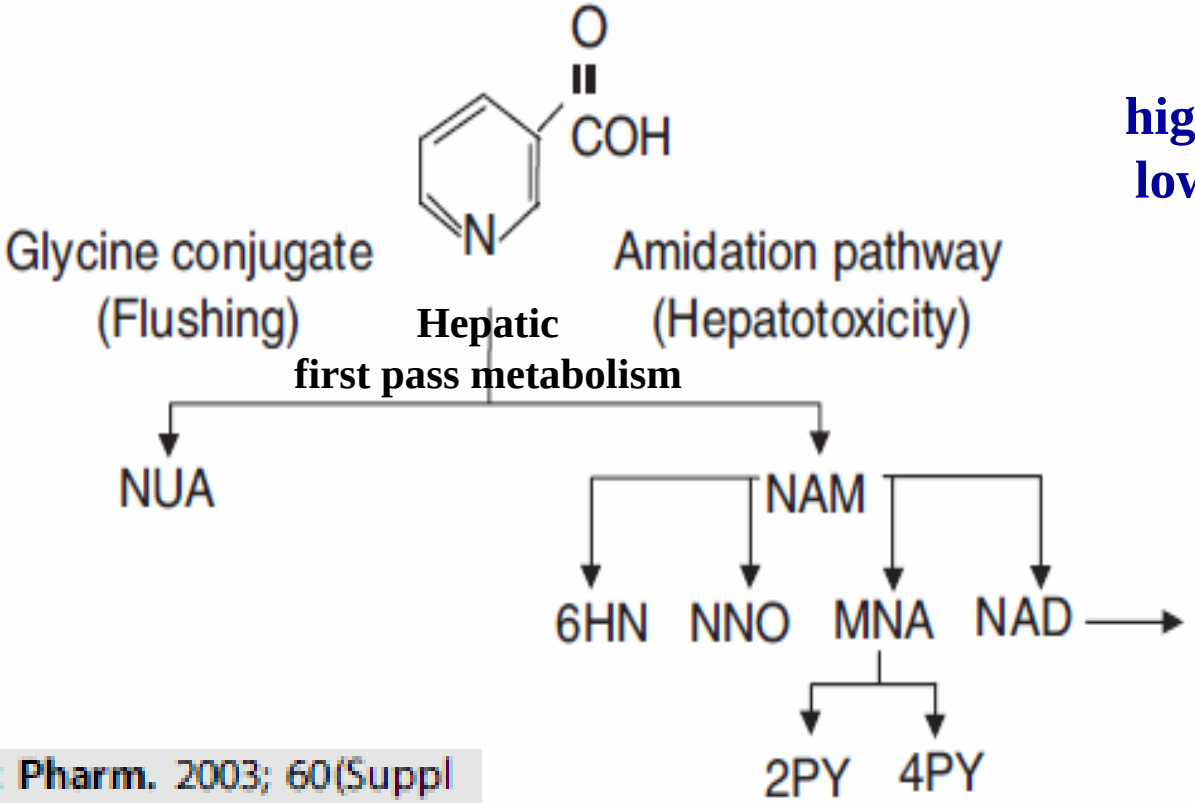
Overview of niacin formulations: Differences in pharmacokinetics, efficacy, and safety

JOHN A. PIEPER

Figure 1. Pathways for niacin metabolism. Reprinted with permission. NUA = nicotinuric acid, NAM = nicotinamide, 6HN = 6-hydroxynicotinamide, MNA = *N*-methylnicotinamide, NNO = nicotinamide-*N*-oxide, NAD = nicotinamide adenine dinucleotide, 2PY and 4PY = pyridone metabolites.

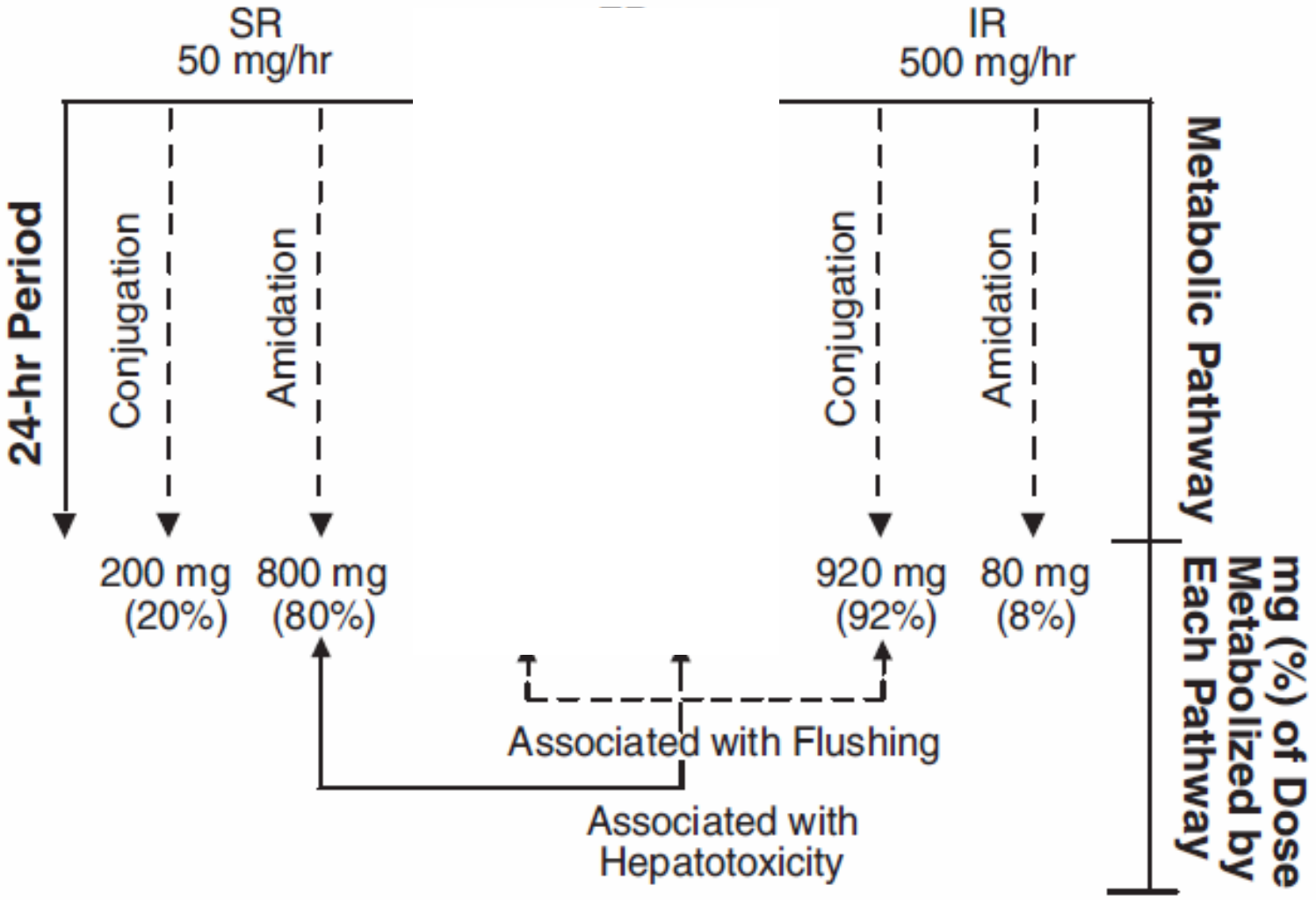
low-affinity, high-capacity

high-affinity, low-capacity



Am J Health-Syst Pharm. 2003; 60(Suppl 2):S9-14

Figure 2. Simulation of niacin metabolism using a 1000-mg dose. SR = sustained release, ER = extended release, IR = immediate release.



Nicotinic Acid

Drug Form	Brand	Classification	FDA approval
IR (crystalline)	**Various**	**Dietary Supplement**	**No**
SR	**Slo-Niacin®**	**Dietary Supplement**	**No**
ER	**Niaspan (Abbott)**	**Rx**	**Yes**

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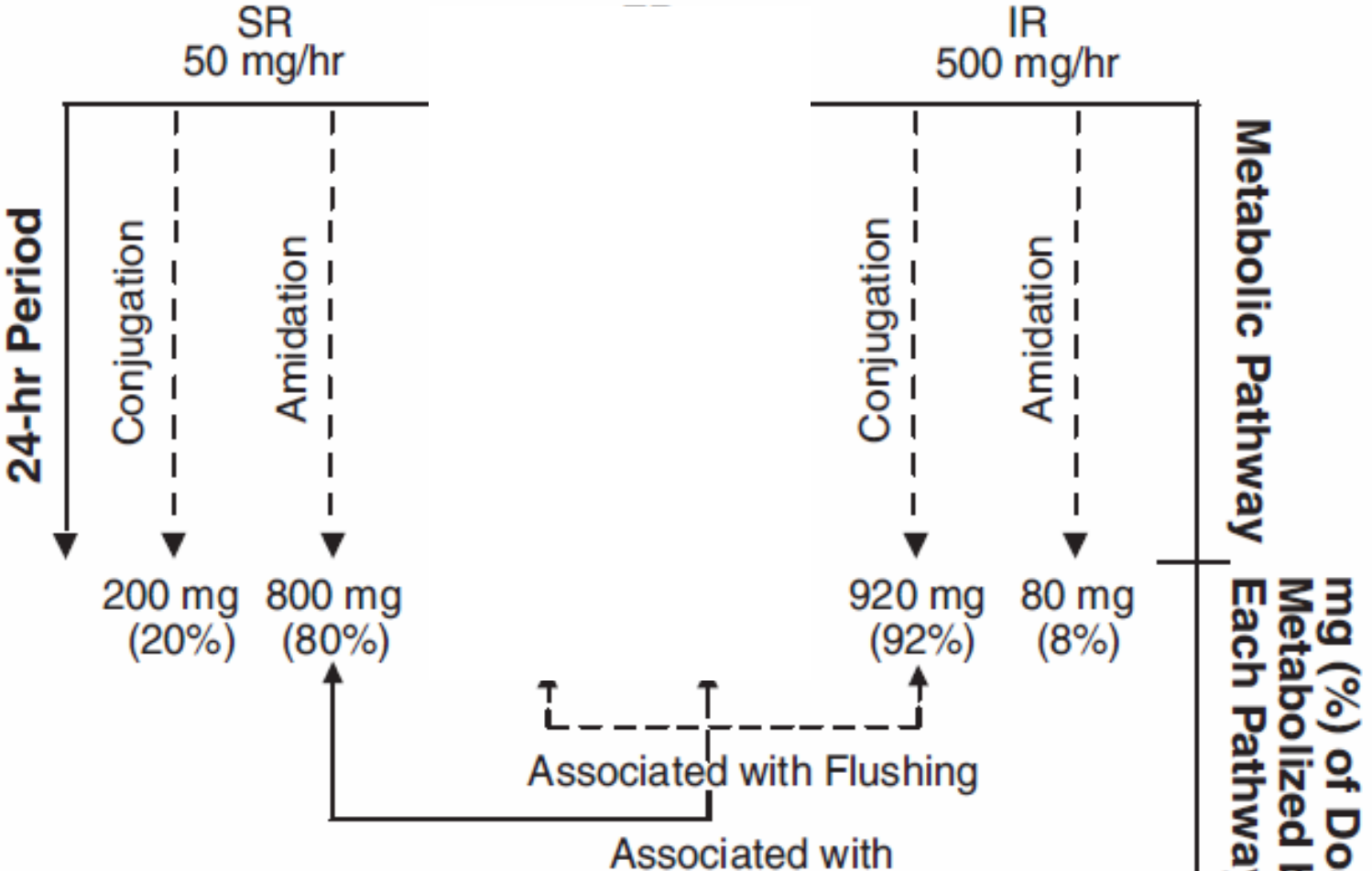
Niaspan

Figure 2. Simulation of niacin metabolism using a 1000-mg dose. SR = sustained release, ER = extended release, IR = immediate release.



Niaspan, the prolonged release preparation of nicotinic acid (niacin), the broad-spectrum lipid drug

L.A. CARLSON
King Gustaf V Research Institute, Karolinska Hospital, Stockholm, Sweden

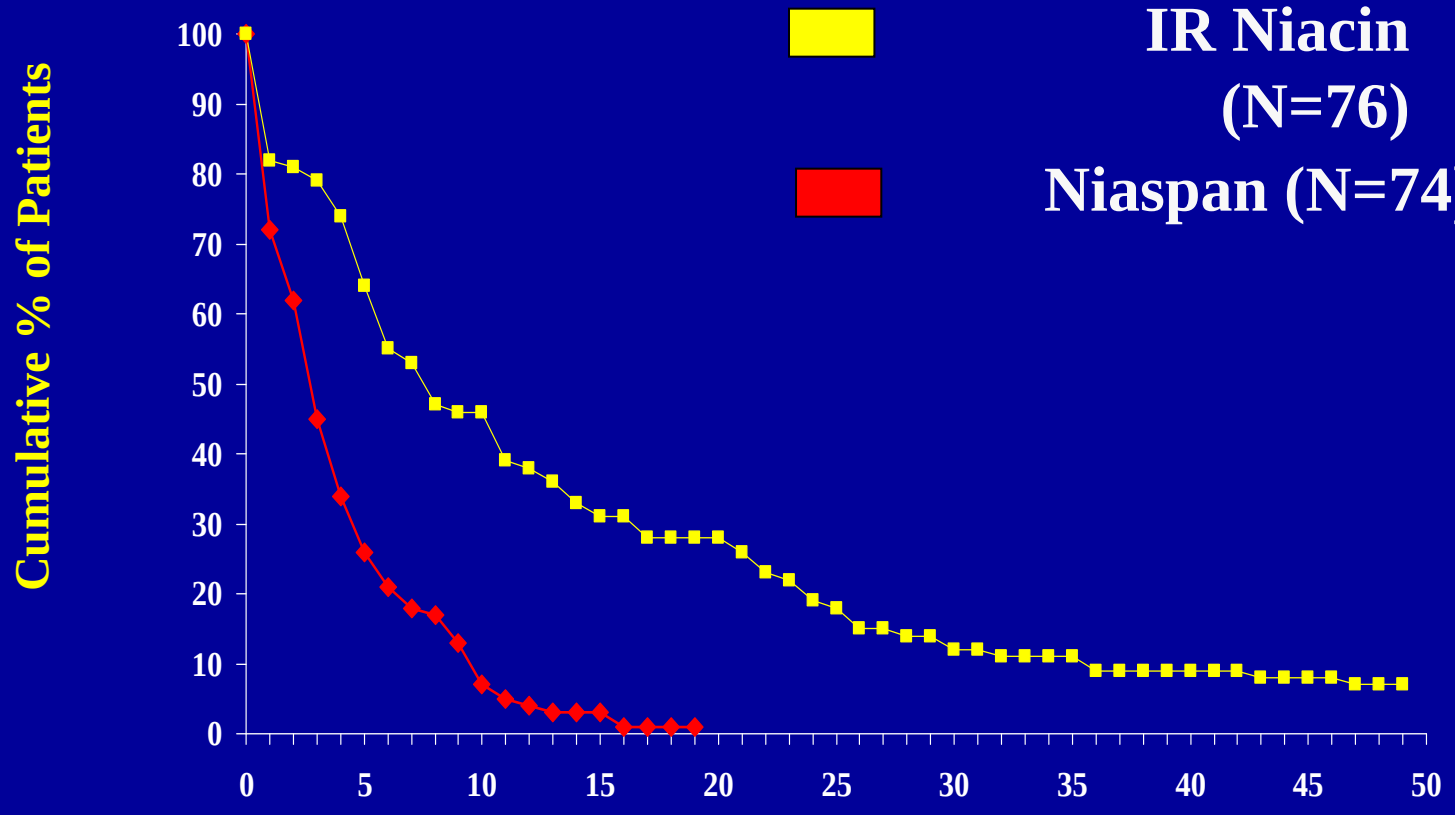
SUMMARY

Niacin (nicotinic acid) is the broad-spectrum lipid drug, which lowers the concentration of all atherogenic plasma lipids/lipoproteins and at the same time raises the levels of the protective HDL (high-density lipoprotein). Niaspan™ is a prolonged release (PR) formulation of niacin, which has considerable advantages over both immediate release (IR) and slow release (SR) formulations of this drug. The major early side effect of IR niacin, the flush, is reduced with Niaspan™. The hepatotoxic effects with SR niacin are not present with Niaspan™. It is suitable for once daily prescription at bedtime. Niaspan™ is effective as monotherapy and in combination with other lipid-lowering drugs such as statins and fibrates. It is particularly useful for treatment of the dyslipidaemia of type 2 diabetes, where IR but not PR niacin may deteriorate the diabetic condition. Overall, niacin, now available as the well-tolerable drug formulation Niaspan™, is the unique broad-spectrum lipid drug for the prevention and treatment of clinical atherosclerosis.

Keywords: Nicotinic acid; Niaspan; cholesterol; triglycerides; free fatty acids; treatment

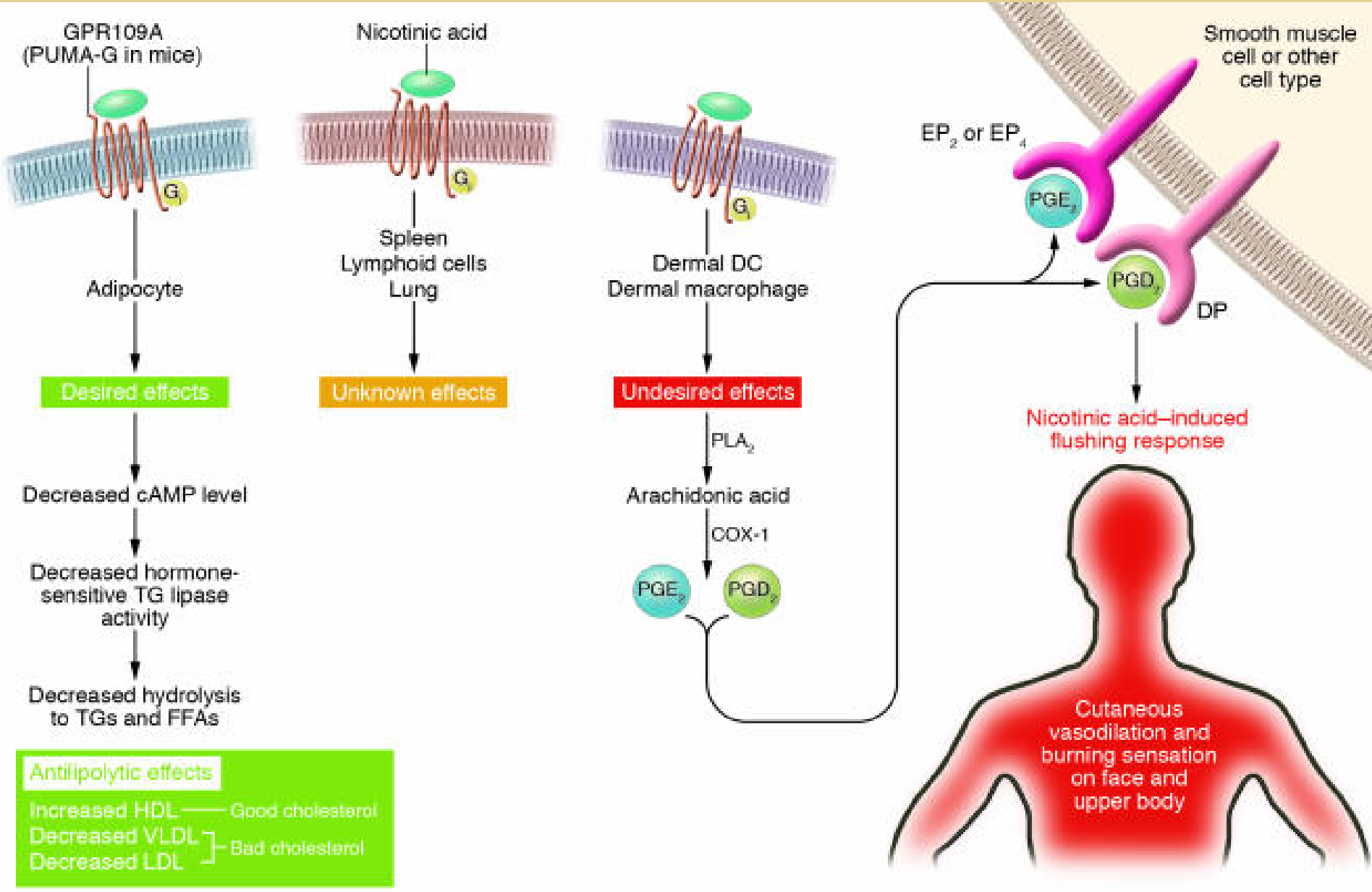
Flushing Episodes Per Patient

IR Niacin vs Niaspan: Double-Blind 16 Week Study*



*Data through Week 8 on comparable doses of both drugs (1500 mg)

Tredaptive


GPR109A
(PUMA-G in mice)
Adipocyte
Desired effects
Decreased cAMP level
Decreased hormone-sensitive TG lipase activity
Decreased hydrolysis to TGs and FFAs
Antilipolytic effects
Increased HDL — Good cholesterol
Decreased VLDL
Decreased LDL — Bad cholesterol
Nicotinic acid
Spleen
Lymphoid cells
Lung
Unknown effects
Dermal DC
Dermal macrophage
Undesired effects
PLA2
Arachidonic acid
COX-1
PGE2
PGD2
Smooth muscle cell or other cell type
EP2 or EP4
PGE2
PGD2
DP
Nicotinic acid–induced flushing response
Cutaneous vasodilation and burning sensation on face and upper body

יתרונות וחסרונות לעומת ניאצין רגיל

- **יתרונות**
  - מאפשר טיטרציה מהירה יותר למינון של 2 גרם
  - פעם ביום
  - פחות flushing
  - פחות עליה בגלוקוז
  - פחות הפרעה בתפקודי הכבד
- **חסרונות**
  - פחות גמישות במינונים
  - אין evidence לגבי תוצאים קלינים
  - יותר יקר

נסיון אישי

	n	Dose g	age	BMI	DM	CHD	CVD	AE	D/C
Niaspan	**25**	**1.2**	**59.8**	**30.9**	**28 %**	**85 %**	**8 %**	**48 %**	**44%**
Tredaptive	**25**	**1.3**	**58.1**	**28.2**	**30 %**	**68 %**	**24 %**	**30%**	**30 %**

- **Flushing / Pruritus** **13**
- **Rash / Urticaria** **3**
- **Hyperglycemia** **4**
- **Hepatitis** **3**
- **Others** **2**

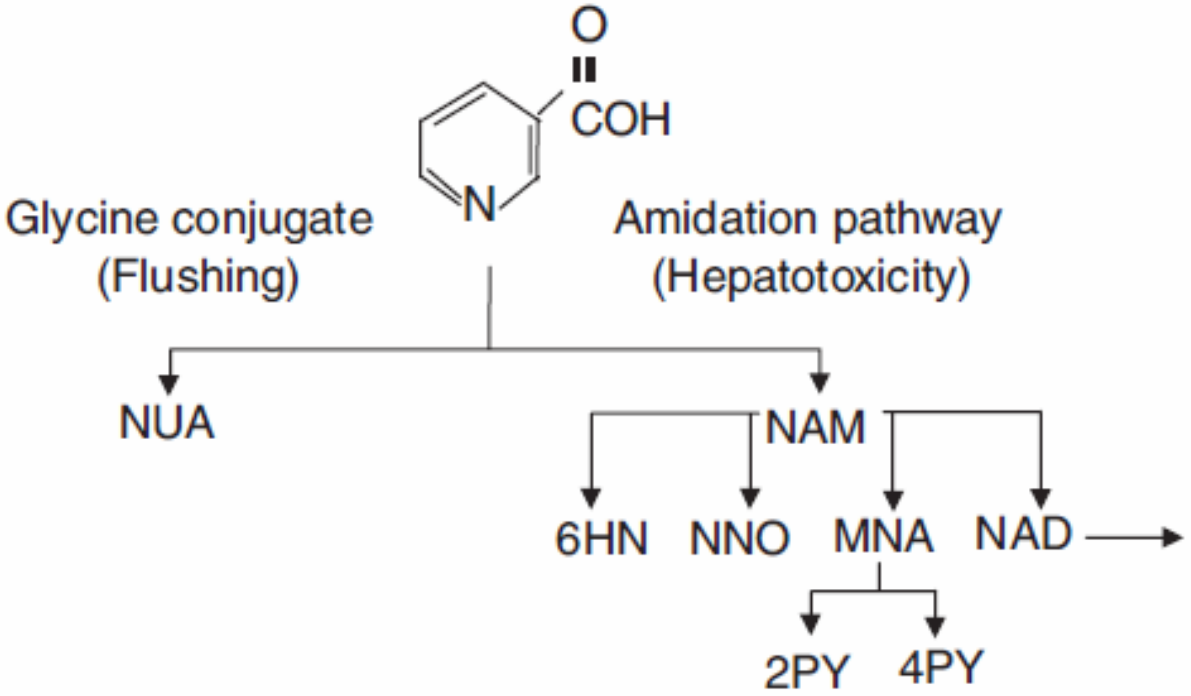
	Dose g	n	baseline				%Δ		
			TC	HDLc	Trig	Non HDLc	HDLc	Trig	Non HDLc
Niaspan									
	1.0	14	160±31	36±6	174 ±99	122 ±33	+14	-13	-40
	2.0	6	171±22	33±2	219 ±60	138 ±20	+15	-27	-36

Niaspan hepatotoxicity

Age	CHD	IR Niacin	Niaspan dose	GOT	GPT	AP	LDLc	HDLc	Re-challange
56	+	2.0	2.0	125	118	=	28	36	+
68	+	3.0	2.0	108	112	=	32	46	+
78	+	2.0	2.0	86	104	↑	34	42	

Mechanism(s) ?

Figure 1. Pathways for niacin metabolism. Reprinted with permission. NUA = nicotinuric acid, NAM = nicotinamide, 6HN = 6-hydroxynicotinamide, MNA = *N*-methylnicotinamide, NNO = nicotinamide-*N*-oxide, NAD = nicotinamide adenine dinucleotide, 2PY and 4PY = pyridone metabolites.



Factors that determine patient adherence

- Degree of adverse effects
- Patient expectations and preparedness
- Patient tolerance to adverse effects
- Physician's belief in drug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