DEPARTMENT OF VETERANS AFFAIRS
Pentoxifylline Summary

Pentoxifylline is one of the first drugs used to treat intermittent claudication. However, studies have conflicted on whether this drug is actually effective, with a recent trial of placebo, cilostazol and pentoxifylline demonstrating no benefit of pentoxifylline over placebo.[1]

In a meta analysis by Girolami[2], et al., thirteen trials involving pentoxifylline versus placebo were reviewed. Of these trials twelve were level one with only one being a level 2 trial. Pain-free walking distance was evaluated in 9 level 1 trials and in 1 level 2 trial. Three level 1 trials did not provide data in an appropriate format to be included in the final summary table. The pooled results of the other 6 studies documented a statistically significant effect of pentoxifylline on pain-free walking distance (common difference of the means, 21.0 m [95% CI, 0.7 to 41.3 m]), as compared with placebo. Total walking distance was evaluated in 8 Level 1 and in 1 Level 2 trials. One level 1 trial and the level 2 trial did not provide data in an appropriate format to be summarized. The pooled results of 7 level 1 studies yielded a statistically significantly beneficial effect of pentoxifylline over placebo (common difference of the means, 43.8 m [95% CI, 14.1 to 73.6 m]).

A meta analysis by Hood et al[3]., demonstrated the same findings. In a sensitivity analysis of the pain-free walking distance, significant treatment effects and no statistically significant heterogeneity were found when only trials were included that were "medically eligible" (involved patients with stage II disease and a pain-free walking distance of 50 to 200 m). In a similar sensitivity analysis of the absolute claudication distance, the two conditions resulting in a significant treatment effect and no significant heterogeneity were the inclusion of "medically eligible" trials and those with shorter treatment duration (13 weeks or less). The authors conclude that pentoxifylline may offer marginal benefit however larger and properly designed trials are required to demonstrate the actual benefit of the agent.

The recent Seventh ACCP congress[5] contains the following recommendation; “We recommend against the use of pentoxifylline (grade 1b)”. This is based on the evidence available that documents inconsistent trial outcomes with the agent in addition to a placebo benefit that was often significant.

For the first quarter of FY05 there are 15,868 unique patients receiving pentoxifylline, of these 12.7% are new starts (no Rx for the period 10/98 to 9/04). This reflects VA data only; patients may have received the agent from an outside provider.

1. Dawson DL, Cutler BS, Hiatt WR, et al. A comparison of cilostazol and pentoxifylline for treating intermittent claudication. *Am J Med*. 2000;109:523–530
2. Girolami B, Bernardi E, Prins MH, et al. Treatment of intermittent claudication with physical training, smoking cessation, pentoxifylline, or nafronyl: a meta-analysis. *Arch Intern Med*. 1999;159:337–345
3. Hood SC, Moher D, Barber GG. Management of intermittent claudication with pentoxifylline: meta-analysis of randomized controlled trials. *Can Med Assoc J*. 1996;155:1053–1059.
4. Lindgarde F, Labs KH, Rossner M. The pentoxifylline experience: exercise testing reconsidered. *Vasc Med*. 1996;1:145–154
5. Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3):609S-626S.

Source, y	Design	Sample†	Dosage‡	Duration	Run-in, wk	Washout, wk
Pentoxifylline						
Level 1						
Bollinger and Frei,[98] 1977	RDB	10/9	600	2 mo	NS	NA
Volker,[99] 1983	RDB	25/26	1200	1 mo	NS	NA
Tonak et al,[100] 1983	RDB	27/28	600	1 mo	NS	NA
Di Perri and Guerrini,[95] 1983	RDBC	12/12	1200	2 mo	12	2
Donaldson et al,[94] 1984	RDB	40/40	600	2 mo	NS	NA
Gallus et al,[97] 1985	RDBC	19/19	1200	2 mo	4	None
Gillings et al,[79] 1987	RDB	63/61	1200	6 mo	4-6	NA
Reilly et al,[96] 1987	RD and SB	15/10	400	3 mo	4	NA
Dettori et al,[91] 1989§	RDB	37/37	1200	12 mo	NS	NA
Lindgärde et al,[93] 1989	RDB	76/74	1200	6 mo	4-6	NA
Rudofsky et al,[101] 1989	RDB	75/79	600‖	2 wk	1	NA
Ernst et al,[92] 1992	RDB	20/20	600	3 mo	NS	NA
Level 2						
Sheffler et al,[102] 1994	RO	15/15	400‖	1 mo	2	NA
Nafronyl						
Level 1						
Clyne et al,[111] 1980	RDB	48/45	400	6 mo	NS	NA
Trübestein et al,[108] 1984	RDB	54/50	600	3 mo	4	NA
Adhoute et al,[107] 1986	RDB	64/54	600	6 mo	4	NA
Karnik et al,[106] 1988	RDBC	20/20	800	3 mo	2	None
Adhoute et al,[109] 1990	RDB	52/42	600	6 mo	4	NA
Moody et al,[110] 1994	RDB	85/95	600	6 mo	4	NA

**R indicates randomized; DB, double-blind; NS, not specified; NA, not applicable; C, crossover; SB, single-blind; and O, open.*

†Total number of patients (active treatment/placebo).

‡Unless otherwise stated, the dosage is expressed as milligrams per day, orally.

§Factorial design, 3 groups: pentoxifylline, acenocoumarol, and placebo (see the "Pentoxifylline" subsection of the "Results" section of the text).

‖Intravenously.

Source, y	Pentoxifylline		Placebo		Difference	95% CI
	No.	Mean ± SD	No.	Mean ± SD		
Pain-Free Walking Distance, m						
Di Perri and Guerrini,[95] 1983	24	351 ± 185	24	291 ± 122	60	−31 to 151
Donaldson et al,[94] 1984	40	119 ± 74	40	129 ± 109	−10	−51 to 31
Gillings et al,[79] 1987	67	140 ± 111	61	128 ± 90	12	−24 to 48
Lindgärde et al,[93] 1989	76	139 ± 148	74	126 ± 120	13	−30 to 56
Rudofsky et al,[101] 1989	75	217 ± 142	79	162 ± 79	55	19 to 91
Ernst et al,[92] 1992	20	364 ± 236	20	384 ± 228	−20	−169 to 129
Common difference of the means	. . .	. . .	. . .	. . .	21.0	0.7 to 41.3
Total Walking Distance, m						
Bollinger and Frei,[98] 1977	10	697 ± 396	9	270 ± 605	427	−63 to 917
Volker,[99] 1983	25	465 ± 118	26	290 ± 86	175	117 to 233
Reilly et al,[96] 1987	15	175 ± 137	10	191 ± 159	−16	−139 to 107
Gillings et al,[79] 1987	67	195 ± 124	61	193 ± 105	2	−38 to 42
Rudofsky et al,[101] 1989	75	360 ± 250	79	287 ± 215	73	−1 to 147
Lindgärde et al,[93] 1989	76	198 ± 157	74	200 ± 138	−2	−50 to 46
Ernst et al,[92] 1992	20	504 ± 257	20	420 ± 229	84	−72 to 240
Common difference of the means	. . .	. . .	. . .	. . .	43.8	14.1 to 73.6
Ankle-Brachial Index at Rest						
Gallus et al,[97] 1985	19	0.61 ± 0.16	19	0.59 ± 0.16	0.02	−0.08 to 0.12
Donaldson et al,[94] 1984	40	0.52 ± 0.26	40	0.57 ± 0.24	−0.05	−0.20 to 0.06
Rudofsky et al,[101] 1989	75	0.66 ± 0.12	79	0.64 ± 0.12	0.02	−0.02 to 0.06
Dettori et al,[91] 1989	37	0.71 ± 0.17	37	0.65 ± 0.13	0.06	−0.01 to 0.10
Common difference of the means	. . .	. . .	. . .	. . .	0.01	−0.02 to 0.05
Ankle-Brachial Index After Exercise						
Donaldson et al,[94] 1984	40	0.27 ± 0.25	40	0.34 ± 0.30	−0.07	−0.19 to 0.05
Dettori et al,[91] 1989	37	0.62 ± 0.21	37	0.52 ± 0.19	0.10	0.007 to 0.19
Common difference of the means	. . .	. . .	. . .	. . .	0.008	−0.07 to 0.08

**Mean represents mean effect of the treatment by the end of the study period; CI, confidence interval; and ellipses, data not applicable.*