# Client Retention in the British Columbia Methadone Program, 1996-1999

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## ABSTRACT

**Background:** Methadone treatment for heroin addiction has been available for 40 years, but there is relatively little research on the effectiveness of Canadian programs. This paper describes one-year retention among the client cohorts entering the British Columbia Methadone Program during expansion between 1996 and 1999, and examines some factors previously shown to influence retention.

**Methods:** All methadone maintenance prescriptions dispensed to 1996-1999 program entrants were extracted from records of the BC Triplicate Prescription Program. Retention status and covariates were evaluated one year post-entry using logistic regression. Effects of retention status misclassification on time in the program were assessed with a Cox model for clients who received continuous daily dosing or short carries.

**Results:** Fifty-two percent of program entrants were still receiving methadone one year after entry; 24% had left the program at one year but later returned. Age at program entry and average daily dose of methadone were important predictors of continuation. In the logistic regression, only the 1999 year-of-entry cohort appeared to have a different retention trajectory. Year of entry is not a significant predictor of time in the program for those receiving daily or short carry doses only, and other results are consistent between models.

**Interpretation:** Retention rates in the BC Methadone Program are favourable and consistent with published rates. Program expansion does not reduce retention, once the effects of client age and dose are accounted for. Adequate daily dosing appears crucial to both initial retention and return to treatment.

#### La traduction du résumé se trouve à la fin de l'article.

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ethadone treatment for heroin addiction has been available for 40 years, but research on the effectiveness of Canadian programs is sparse.<sup>1-3</sup> The British Columbia (BC) Methadone Program is the largest in Canada. During 2001, more than 6,500 people were enrolled in the maintenance component of the program.<sup>4</sup>

In BC, methadone is prescribed almost exclusively by community physicians, and is dispensed by community pharmacists throughout the province. In 2001, 592 physicians were authorized to prescribe methadone, with approximately one half practicing in the Lower Mainland, one quarter on Vancouver Island and the remainder distributed throughout the rest of the province.<sup>4</sup> The College of Physicians and Surgeons of British Columbia (BCCPS) regulates methadone prescribers through a process of authorization, education, and supervision. In addition, the BCCPS works in collaboration with the British Columbia College of Pharmacists to authorize and supervise pharmacists who dispense methadone. Approximately 290 pharmacies currently dispense methadone throughout BC.

Although some methadone prescribers work in dedicated methadone treatment clinics, most prescribe methadone as part of a general medical practice. In 2001, 84% of methadone prescribers delivered methadone maintenance treatment (MMT) in a private practice, while 16% worked within a methadone clinic setting.<sup>4</sup> Most clinics provide ancillary psychosocial support services on-site. All methadoneprescribing physicians are encouraged to refer their methadone patients for additional support services through other medical and social service agencies. Methadone prescribers and dispensers are required to follow practice guidelines as specified by the BCCPS, and practice standards are monitored through routine audits.

The MMT program has expanded considerably over the past ten years by enlisting new physicians and pharmacists willing to prescribe and dispense methadone. Despite the expansion, however, no effectiveness studies had been completed.

Previous international studies have shown that participation in methadone maintenance treatment can lead to reductions in heroin use, criminal behaviour and HIV infections, and to improved health and

## TABLE I

Demographic and Treatment Characteristics of Entrants to the BC Methadone Maintenance Program, 1996-1999 by Response Group

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Image: space of the s				Counts					%	of group to	otal	
$\begin{array}{c c c c c c c c c c c c c c c c c c c $		treatment before 1 year, did	treatment before 1 year,	program at 1 year but	program at 1 year, not	Total		treatment before 1 year, did	treatment before 1 year,	program at 1 year but	program at 1 year, not	Total
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$		1,217	1,217	642	2,011	5,087		23.9	23.9	12.6	39.5	100.0
Female400430243696 $1,769$ (df $\stackrel{\circ}{=} 3, p = 0.19)$ 32.935.337.934.634.8Age at Entry10 - 19566127662104.65.04.23.34.120 - 294394632234811,60636.138.034.723.931.630 - 394434342507341,86136.435.738.936.536.640 - 492382251246091,19616.519.330.323.550 - 59313016114191LR $\chi^2 = 172.55$ 2.52.52.55.73.860 - 691042723(df = 15, p < 0.0001)		817	787	399	1.315	3.318	$IR \gamma^2 = 4.80$	67.1	64.7	62.1	65.4	65.2
Age at Entry10 - 19566127662104.65.04.23.34.120 - 294394632234811,60636.138.034.723.931.630 - 394434342507341,86136.435.738.936.536.640 - 492382251246091,19619.618.519.330.323.550 - 59313016114191LR $\chi^2$ = 172.552.52.52.55.73.860 - 691042723(df = 15, p < 0.0001)												
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Average Daily Dose< 40 mg												
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$			4	2	/	23	(df = 15, p < 0.0001)	0.8	0.3	0.3	0.3	0.5
$\begin{array}{cccccccccccccccccccccccccccccccccccc$	Average Daily I		101	60	100	FOO	$10^{2} = 127 = 2(df = 2) = 40,0001$	) 170	10.9	0.2	FO	0.0
$ \begin{array}{cccccccccccccccccccccccccccccccccccc$	< 40 mg						$LR \chi^2 = 127.53 (dl = 3, p < 0.0001)$	) 1/.2				
$\begin{array}{cccccccccccccccccccccccccccccccccccc$							$LR \chi^2 = 5.92 (df = 3. p < 0.0001)$	23.0				
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$							$LR \chi^2 = 104.56 (df = 3.5 \mu < 0.0001)$					
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$	100-119 mg						$IR \chi^2 = 73.41 (df = 3. p < 0.0001)$	5.4				
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$												
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$							$IR \gamma^2 = 8.69 (df = 3. p = 0.03)$					
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$							$IR \chi^2 = 0.43 (df = 3, p = 0.94)$					2.3
$\begin{array}{c ccccccccccccccccccccccccccccccccccc$												
Year of Entry199618327812237295515.022.819.018.518.819972553081484631,17421.025.323.123.023.119982973151745191,305LR $\chi^2 = 61.59$ 24.425.927.125.825.719994823161986571,653(df = 9, p < 0.0001)												
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$							$\kappa$					
$ \begin{array}{c ccccccccccccccccccccccccccccccccccc$	1996 <sup>′</sup>	183	278	122	372	955		15.0	22.8	19.0	18.5	18.8
1999 482 316 198 657 1,653 (df = 9, p < 0.0001)												
Average Daily Dose Mean 74.87 76.98 79.99 86.55 80.64 Kruskal-Wallis test = 295.98 SD 52.86 42.73 44.65 35.55 43.36 (df = 3, p < 0.0001)												
Mean 74.87 76.98 79.99 86.55 80.64 Kruskal-Wallis test = 295.98 SD 52.86 42.73 44.65 35.55 43.36 (df = 3, p < 0.0001)			316	198	657	1,653	(df = 9, p < 0.0001)	39.6	26.0	30.8	32.7	32.5
SD 52.86 42.73 44.65 35.55 43.36 (df = 3, p < 0.0001)	Average Daily I	Dose										
							(df = 3, p < 0.0001)					
Median 62.27 68.39 73.04 63.58 73.44			68.39	/3.04	63.58	/3.44						
Age at Program Entry		Entry	22.7	22.2	26.2	24.2	Knuelie Mallie test 162.20					
Mean $33.2$ $32.7$ $33.3$ $36.2$ $34.3$ Kruskal-Wallis test = 163.20												
SD 9.1 8.7 8.7 9.2 9.1 (df = 3, p < 0.0001) Median 32.4 31.7 33.3 36.6 34.0							(ui = 5, p < 0.0001)					
IVICUIAII J2.7 J1./ JJ.J JU.U J4.U	meulan	32.4	51.7	55.5	50.0	54.0						

social functioning.<sup>5</sup> Research evidence suggests a linear relationship between length of time in methadone treatment and improved outcomes.<sup>6</sup> The minimum treatment retention threshold for improved outcomes in methadone maintenance treatment is considered to be 12 months.<sup>3</sup> Factors shown to influence retention include take-home doses ("carries"),<sup>7</sup> methadone dose,<sup>8,9</sup> gender,<sup>10</sup> dispensing location,<sup>9</sup> client age,<sup>8</sup> and previous involvement with the criminal justice system.<sup>8</sup> Program expansion can also have a negative impact.<sup>11</sup>

The purpose of this paper is to briefly describe one-year retention among the client cohorts entering the BC MMT program between 1996 and 1999, a period of rapid expansion, and to examine the impact of some known contributors to retention.

#### METHODS

The study reported here was commissioned as part of a program evaluation by the BC Ministry of Health and the BCCPS, and access to anonymized program data was granted under the provisions of the BC *Freedom of Information and Protection of Privacy Act.*<sup>12</sup>

All methadone maintenance prescriptions dispensed to individuals registered in the program between 1990 and September 4, 2001 (anonymized to protect confidentiality) were extracted from records of the BC Triplicate Prescription Program. Data were initially included for analysis if the methadone recipient had a recorded gender and age between 10 and 69 years at program entry, and received a first maintenance prescription between January 1, 1996 and December 31, 1999\* (n = 5,124 clients). Yearly cohorts are based on the calendar year of the first dispensing date. Thirty-seven individuals were removed because their average daily methadone dose was more than 400 mg, as examination revealed probable errors in data entry at the pharmacy, aggregation of identifiers for confidentiality (e.g., for incarcerated clients), or abuse of the program. Removed cases did not differ on the other analysis factors, and discarding them did not change the results. Analyses are based on the remaining 5,087 clients.

Because some MMT clients in BC receive 'carries' of up to a month's supply of methadone at any one time, participants are considered to have left the program only when they have had no methadone for 30 days (i.e., they have a gap of 31 days or more between dispensing dates). They are, however, permitted to re-register to continue therapy at any time. We have used the 31-day rule to divide clients remaining in the program at one year into those whose treatment was uninterrupted (i.e., no gaps of 31 days or more) and interrupted/disrupted (at least one gap of 31 days or more) during their first year of program participation.

<sup>&#</sup>x27;First prescription' means there is no earlier methadone maintenance prescription recorded with the BC Triplicate Prescription Program. Some individuals may have received methadone outside the maintenance program (e.g., for withdrawal or pain), or outside BC.

## TABLE II

#### Demographic and Treatment Characteristics of Clients Receiving Daily or Short-carry Doses Only by Response Group

01					0 / /	, ,	•	•	
	Counts			% of group total					
	before 1 year, did	Left treatment before 1 year, returned	at 1 year not	Total	Test	Left treatment before 1 year, did not return	Left treatment before 1 year,	In program at 1 year not	Total
Total (N) Sex	688	583	1,166	2,437		28.2	23.9	47.8	100.0
Male Female	471 217	389 194	765 401	1,625 812	LR $\chi^2 = 1.59$ (df = 2, p = 0.45)	68.5 31.5	66.7 33.3	65.6 34.4	66.7 33.3
Age at Entry 10 - 19 20 - 29 30 - 39 40 - 49 50 - 59 60 - 69	27 242 254 144 17 4	29 212 204 120 16 2	35 259 424 362 83 3	91 713 882 626 116 9	LR χ2 = 96.13 (df = 10, p < 0.0001)	3.9 35.2 36.9 20.9 2.5 0.6	5.0 36.4 35.0 20.6 2.7 0.3	3.0 22.2 36.4 31.0 7.1 0.3	3.7 29.3 36.2 25.7 4.8 0.4
Average Daily I < 40 mg 40 - 59 mg 60 - 79 mg 100-119 mg 120-139 mg 140-159 mg 160-199 mg 200-299 mg 300+ mg	Dose 122 223 166 92 37 18 6 8 11 5		47 183 336 360 148 52 18 15 7 0	236 578 650 570 222 86 33 31 22 9	LR $\chi^2 = 97.49$ (df = 2, p < 0.0001) LR $\chi^2 = 82.49$ (df = 2, p < 0.0001) LR $\chi^2 = 5.52$ (df = 2, p = 0.06) LR $\chi^2 = 81.11$ (df = 2, p < 0.0001) LR $\chi^2 = 35.64$ (df = 2, p < 0.0001) LR $\chi^2 = 5.73$ (df = 2, p = 0.0005) LR $\chi^2 = 1.82$ (df = 2, p = 0.40) LR $\chi^2 = 4.72$ (df = 2, p = 0.94) LR $\chi^2 = 11.76$ (df = 2, p = 0.003)	$17.7 \\ 32.4 \\ 24.1 \\ 13.4 \\ 5.4 \\ 2.6 \\ 0.9 \\ 1.2 \\ 1.6 \\ 0.7$	11.5 29.5 25.4 20.2 6.3 2.7 1.5 1.4 0.7 0.7	$\begin{array}{c} 4.0\\ 15.7\\ 28.8\\ 30.9\\ 12.7\\ 4.5\\ 1.5\\ 1.3\\ 0.6\\ 0.0\\ \end{array}$	$9.7 \\ 23.7 \\ 26.7 \\ 23.4 \\ 9.1 \\ 3.5 \\ 1.4 \\ 1.3 \\ 0.9 \\ 0.4$
Year of Entry 1996 1997 1998 1999	105 138 189 256	149 158 139 137	227 268 297 374	481 564 625 767	LR $\chi^2 = 61.59$ (df = 9, p < 0.0001)	15.3 20.1 27.5 37.2	25.6 27.1 23.8 23.5	19.5 23.0 25.5 32.1	19.7 23.1 25.6 31.5
Average Daily I Mean SD Median Age at Program	68.90 44.62 59.77	72.66 39.05 65.97	82.80 28.54 80.88	76.45 36.80 72.68	Kruskal-Wallis test = 216.36 (df = 2, p < 0.0001 )				
Mean SD Median	33.3 8.9 33.0	33.1 8.9 32.5	36.8 9.1 37.3	34.9 9.2 35.1	Kruskal-Wallis test = 92.81 (df = 2, p < 0.0001 )				

The distribution of covariates across response groups was evaluated using chisquare tests for categorical variables. The Kruskal-Wallis test was used to compare the means of continuous variables and chisquare tests for trend.

Model 1 used logistic regression to assess the likelihood that individuals would fall into one of four groups at one year postentry: group 'LN' comprised those who were not receiving methadone\* and who did not return to the program at any time before the end of the observation period (September 4, 2001); group 'LR' were not receiving methadone at one year but did return at some time in the observation period; group 'D' were receiving methadone at one year but their treatment had been interrupted; and group 'N' remained in the program at one year with uninterrupted treatment. Because there were four possible responses, we used the CATMOD procedure in SAS (Version 8.01, SAS Institute Inc., Cary, NC, 1999-2000) for this component.

There is a risk of misclassifying responses in this model. This may be due to the unequal length of observation possible following individuals' first year in the program. Early entrants in the 1996 cohort, for example, could return to the program and be classified as 'LR' for over four years, while those entering late in 1999 could do so for less than one year. It may also result from the fact that we are looking for a 'non-event' - the first date that no methadone is received. Individuals may be misclassified as remaining in the program because their last amount of methadone dispensed covers the one-year date, but if the assumed rate of consumption is too low (i.e., there has been a dose increase for the last prescription) then this will be incorrect.

To assess the impact of misclassification on our results, Model 2 included only the first year post-entry for clients who received no long carries and had no interruptions; that is, no interval between dispensing dates of more than 7 days. Using a Cox model (PROC PHREG in SAS), time in the program was measured as days between the first and last prescriptions in the year, using the other covariates from Model 1.

## RESULTS

Client demographic and treatment characteristics for the full cohort (n = 5,087) are shown in Table I. Fifty-two percent of the cohort remained in treatment at one year, and another 24% had left the program at one year but later returned. Only 24% of the cohort left treatment before one year and never returned.

While the response groups do not differ in their proportions of male to female clients, they have a significantly different age distribution at program entry. The

<sup>\*</sup> Individuals are classified as receiving methadone on a given date if either methadone was dispensed to them on that date, or the latest amount dispensed would have covered that date if consumed at the rate of the next most recent amount. If an individual is consuming 50 mg/day, for example, 250 mg is assumed to last 5 days.

## TABLE III

Results of Logistic Regression for Status at One Year After Entering Program, All Clients (N = 5,087)

$ \begin{array}{c cccpt} &    R v {\rm s} {\rm IN} & 0.313 & 0.115 & 7.43 & 0.006^{\circ} & 1.37^{\ast\ast} & (1.09, 1.71) \\ &    V {\rm s} {\rm IN} & 0.036 & 0.133 & 10.7 & 0.001 & 0.65 & 0.030 & 0.84 \\ &    R v {\rm s} {\rm IN} & 0.036 & 0.033 & 10.7 & 0.001 & 0.65 & 0.030 & 0.84 \\ &    R v {\rm s} {\rm IN} & 0.045 & 0.079 & 1.44 & 0.229 & 1.16 & 0.079 & 1.17 \\ &    V {\rm ear} \ of entry 1997 &    R v {\rm s} {\rm IN} & 0.048 & 0.108 & 0.45 & 0.501 & 1.64 & 0.071 & 1.12 \\ &    V {\rm ear} \ of entry 1998 &    R v {\rm s} {\rm IN} & 0.087 & 0.148 & 0.35 & 0.557 & 1.09 & 0.682 & 1.46 \\ &    V {\rm ear} \ of entry 1998 &    R v {\rm s} {\rm IN} & 0.270 & 0.148 & 0.35 & 0.074 & 1.22 & 0.098 & 1.51 \\ &    (reference 1996) &    V {\rm s} {\rm IN} & 0.277 & 0.146 & 3.13 & 0.074 & 1.22 & 0.098 & 1.51 \\ &    (reference 1996) &    V {\rm s} {\rm IN} & 0.277 & 0.146 & 3.13 & 0.074 & 1.22 & 0.098 & 1.51 \\ &    (reference 1996) &    V {\rm s} {\rm IN} & 0.476 & 0.129 & 1.37 & 0.0001 & 1.69^{***} & (1.12, 1.29) \\ &    (reference 1996) &    V {\rm s} {\rm IN} & 0.476 & 0.129 & 1.37 & 0.0001 & 0.49^{***} & 0.35 & 0.66 \\ & (reference 60.79  {\rm mg}) &    V {\rm s} {\rm IN} & 0.218 & 0.144 & 1.4 & 0.236 & 1.44 & 0.035 & 0.14 & 0.78 \\ &    (reference 60.79  {\rm mg}) &    V {\rm s} {\rm IN} & 0.218 & 0.168 & 2.533 & 0.0010 & 0.79^{***} & 0.066 & 0.71 \\ & (reference 60.79  {\rm mg}) &    V {\rm s} {\rm IN} & 0.218 & 0.108 & 2.533 & 0.0071 & 0.78^{**} & 0.046 & 0.71 \\ &    (reference 60.79  {\rm mg}) &    V {\rm s} {\rm IN} & 0.218 & 0.108 & 2.533 & 0.0071 & 0.78^{**} & 0.046 & 0.71 \\ & (reference 60.79  {\rm mg}) &    V {\rm s} {\rm IN} & 0.248 & 0.108 & 2.533 & 0.0071 & 0.78^{**} & 0.046 & 0.71 \\ &    (reference 60.79  {\rm mg}) &    V {\rm s} {\rm IN} & 0.248 & 0.108 & 2.533 & 0.0071 & 0.78^{**} & 0.166 & 0.060 \\ &    (reference 60.79  {\rm mg}) &    V {\rm s} {\rm IN} & 0.248 & 0.108 & 2.533 & 0.0071 & 0.78^{**} & 0.166 & 0.061 \\ &    (reference 60.79  {\rm mg}) &    V {\rm s} {\rm IN} & 0.224 & 0.277 & 0.22 & 0.653 & 0.38 & 0.051 \\ &    (reference 60.79  {\rm mg}) &    V {\rm s} {\rm IN} & 0.024 & 0.277 & 0.22 & 0.033 & 1.510 \\ &    (re$	Variable	Parameter	Estimate	SE	Chi-Sq	Pr Chi-Sq	Odds Ratio	95% CI
D vs IN   -0.683   0.151   20.42   <0.0001	Intercept	LR vs LN	0.313	0.115		0.006		(1.09, 1.71)
$ \begin{array}{c} \text{Sex} (\text{reference} = \text{male}) & \text{IV} \text{ sl} \text{ N} \text{ sl} \text{ IN} & -0.436 & 0.133 & 10.7 & 0.001 & 0.65 & (0.50, 0.84) \\ \text{ Vear of entry 1997} & \text{IV} \text{ sl} \text{ N} & 0.145 & 0.103 & 1.97 & 0.160 & 1.16 & (0.94, 1.49) \\ \text{ Vear of entry 1997} & \text{IV} \text{ sl} \text{ N} & 0.064 & 0.111 & 0.57 & 0.449 & 1.09 & (0.67, 1.13) \\ \text{ (reference 1996)} & \text{UV} \text{ sl} \text{ N} & 0.027 & 0.129 & 0.43 & 0.037 & 1.029 & (0.46, 1.16) \\ \text{ (reference 1996)} & \text{UV} \text{ sl} \text{ N} & 0.197 & 0.129 & 0.43 & 0.074 & 1.22 & (0.98, 1.51) \\ \text{ (reference 1996)} & \text{UV} \text{ sl} \text{ N} & 0.277 & 0.129 & 0.43 & 0.074 & 1.22 & (0.98, 1.51) \\ \text{ (reference 1996)} & \text{UV} \text{ sl} \text{ N} & 0.471 & 0.127 & 1.33 & 0.077 & 1.29 & (0.37, 1.22) \\ \text{ (reference 1996)} & \text{UV} \text{ sl} \text{ N} & 0.471 & 0.127 & 13.7 & 0.000 & 1.60^{***} & (1.12, 2.01) \\ \text{ (reference 1996)} & \text{UV} \text{ sl} \text{ N} & 0.398 & 0.144 & 7.7 & 0.000 & 1.60^{***} & (1.12, 0.09) \\ \text{ (reference 1996)} & \text{UV} \text{ sl} \text{ N} & 0.398 & 0.144 & 7.7 & 0.0001 & 1.23^{***} & (1.99, 3.22) \\ \text{Average daily dose <40 mg } & \text{IV} \text{ sl} \text{ N} & 0.555 & 0.108 & 26.33 & -0.0001 & 1.57^{***} & (0.46, 0.71) \\ \text{Average daily dose 80-59 mg } & \text{IV} \text{ sl} \text{ N} & 0.555 & 0.108 & 26.33 & 0.0001 & 0.57^{***} & (0.46, 0.71) \\ \text{Average daily dose 80-59 mg } & \text{IV} \text{ sl} \text{ N} & 0.122 & 0.113 & 3.33 & 0.060 & 1.24 & (0.99, 1.54) \\ \text{Average daily dose 80-59 mg } & \text{IV} \text{ sl} \text{ N} \text{ sl} \text{ N} & 0.212 & 0.113 & 3.33 & 0.021 & 1.28 & (1.04, 1.58) \\ \text{(reference 60-79 mg)} & \text{UV} \text{ sl} \text{ N} & 0.122 & 0.173 & 2.38 & 0.100 & 1.77^{**} & (0.46, 0.72) \\ \text{Average daily dose 10-119 mg } & \text{IV} \text{ sl} \text{ N} & 0.122 & 0.173 & 2.38 & 0.100 & 1.77^{**} & (0.46, 0.71) \\ \text{Average daily dose 10-119 mg } & \text{IV} \text{ sl} \text{ N} & 0.277 & 0.277 & 0.2 & 0.659 & 0.88 & (0.51, 1.52) \\ \text{Average daily dose 10-19 mg } & \text{IV} \text{ sl} \text{ N} & 0.277 & 0.277 & 0.2 & 0.659 & 0.88 & (0.51, 1.52) \\ \text{Average daily dose 10-19 mg } & \text{IV} \text{ sl} \text{ N} & 0.277 & 0.277 & 0.24 & 0.990 & 0.223 & 0.138 & 0.277 & 0.234 & 0.991 \\ $								
Sex (reference = male)   LR vs LN   0.095   0.079   1.44   0.229   1.10   (0.94, 1.29)     Vear of entry 1997   LR vs LN   0.064   0.113   0.457   0.501   0.94   (0.77, 1.13)     Vear of entry 1997   LR vs LN   0.064   0.114   0.357   1.09   (0.82, 1.43)     Vear of entry 1998   N st LN   0.027   0.120   4.43   0.033   1.31   (1.02, 1.69)     Vear of entry 1996   N st LN   0.277   0.146   3.13   0.007   1.29   (0.07, 1.27)     Vear of entry 1999   LR vs LN   0.447   0.127   7   0.000   1.63***   (1.31, 2.01)     Vear of entry 1999   LR vs LN   0.446   0.109   1.9.5   0.0001   1.63***   (1.31, 2.01)     Vereference 60-79 mg)   LV s LN   0.398   0.122   57.81   <0.0001								
	Sox (reference - male)							
vear of entry 1997   Rv s IN   -0.059   0.088   0.411   0.57   0.449   1.09   (0.87, 1.35)     (reference 1996)   D vs LN   0.087   0.148   0.35   0.557   1.09   (0.82, 1.46)     (reference 1996)   D vs LN   0.127   0.110   3.19   0.024   1.22   (0.98, 1.51)     (reference 1996)   D vs LN   0.447   1.31   0.074   1.22   (0.98, 1.51)     (reference 1996)   D vs LN   0.446   0.147   0.006   1.43***   (1.31, 2.01)     (reference 6196)   D vs LN   0.398   0.144   7.7   0.006   1.43***   (1.21, 97)     Average daily dose < 40 mg	Sex (reference – male)							
Year of entry 1997   I.R. vs.LN   0.084   0.111   0.57   0.449   1.09   (0.87, 1.35)     Year of entry 1996   Nv s.LN   0.271   0.129   4.43   0.035   1.31*   (1.02, 1.69)     Year of entry 1998   R.v s.LN   0.277   0.120   4.43   0.035   1.31*   (1.02, 1.69)     Year of entry 1999   LV s.LN   0.471   0.127   7.7   0.000   1.66***   (1.32, 2.03)     Year of entry 1999   LV s.LN   0.4471   0.127   7.7   0.000   1.63***   (1.31, 2.01)     (reference 1996)   N vs.LN   0.471   0.127   7.81   e0.0001   2.3***   (1.91, 2.20)     (reference 60-79 mg)   D vs.LN   0.218   0.184   1.4   0.236   (1.44   0.036, 0.60)     (reference 60-79 mg)   D vs.LN   0.212   0.113   3.53   0.060   1.24*   (0.94), 1.54)     (reference 60-79 mg)   D vs.LN   0.212   0.113   3.53   0.060   1.24*   (0.99), 1.54)								
Ireference 1996)   D vs LN   0.087   0.148   0.35   0.557   1.09   (0.82, 1.46)     Year of entry 1996   Rv s LN   0.1271   0.129   4.43   0.035   1.31*   (1.22)   (0.35, 1.31*   (1.22)   (0.35, 1.31*   (1.22)   (0.35, 1.31*   (1.22)   (0.35, 1.31*   (1.22)   (0.35, 1.31*   (1.22, 1.69)   (1.22, 1.69)   (1.22, 1.69)   (1.22, 1.69)   (1.22, 1.69)   (1.22, 1.29)   (1.22, 1.29)   (1.21, 1.21)   (1.21, 1.21)   (1.21, 1.29)   (1.21,	Varia ( anti- 1007							(0.79, 1.12)
$\begin{array}{c c} \mbox{vs LN} & 0.271 & 0.129 & 4.43 & 0.035 & 1.31* & (1.02, 1.69) \\ \mbox{vs LN} & 0.197 & 0.110 & 3.19 & 0.074 & 1.22 & (0.98, 1.51) \\ \mbox{vs LN} & 0.257 & 0.146 & 3.13 & 0.077 & 1.29 & (0.97, 1.72) \\ verage daily dose < 40 mg & LR vs LN & 0.486 & 0.109 & 19.95 & <0.0001 & 1.63*** & (1.31, 2.01) \\ \mbox{verage daily dose < 40 mg & LR vs LN & 0.398 & 0.144 & 7.7 & 0.006 & 1.43*** & (1.32, 1.31) \\ \mbox{verage daily dose < 40 mg & LR vs LN & 0.720 & 0.154 & 22 & <0.0001 & 2.53*** & (1.99, 3.22) \\ \mbox{verage daily dose < 40 mg & LR vs LN & 0.720 & 0.154 & 22 & <0.0001 & 0.54*** & (1.36, 2.37) \\ \mbox{verage daily dose 40-59 mg & LR vs LN & 0.218 & 0.184 & 1.4 & 0.236 & 1.24 & 0.087, 1.78) \\ \mbox{verage daily dose 40-59 mg & LR vs LN & 0.555 & 0.108 & 26.33 & <0.0001 & 0.57*** & 0.46, 0.71) \\ \mbox{verage daily dose 40-59 mg & LR vs LN & 0.212 & 0.113 & 3.53 & 0.066 & 1.24 & 0.09, 1.54) \\ \mbox{verage daily dose 40-99 mg & LV vs LN & 0.212 & 0.113 & 3.53 & 0.066 & 1.24 & 0.09, 1.54) \\ \mbox{verage daily dose 40-99 mg & LV vs LN & 0.212 & 0.113 & 5.3 & 0.061 & 1.24 & 0.09, 1.54) \\ \mbox{verage daily dose 100-119 mg & RV vs LN & 0.612 & 0.133 & 7.37 & 0.007 & 0.7** & 0.54, 0.90) \\ \mbox{vs LN & 0.092 & 0.192 & 0.123 & 0.630 & 1.10 & 0.751, 160) \\ \mbox{verage daily dose 120-139 mg & LV vs LN & 0.295 & 0.197 & 2.24 & 0.135 & 1.34 & (0.91, 1.98) \\ \mbox{verage daily dose 120-139 mg & RV vs LN & 0.292 & 0.172 & 0.459 & 0.33 & 0.57 & 0.27, 1.19) \\ \mbox{verage daily dose 120-139 mg & LR vs LN & 0.295 & 0.197 & 2.24 & 0.135 & 1.34 & (0.91, 1.98) \\ \mbox{verage daily dose 120-139 mg & LR vs LN & 0.295 & 0.197 & 2.24 & 0.135 & 1.34 & (0.91, 1.98) \\ \mbox{verage daily dose 120-139 mg & LR vs LN & 0.029 & 0.192 & 0.233 & 0.660 & 0.12, 1.26 & 2.21) \\ \mbox{verage daily dose 120-139 mg & LR vs LN & 0.020 & 0.253 & 0.06 & 0.88 & 0.51, 1.52) \\ \mbox{verage daily dose 120-139 mg & LR vs LN & 0.270 & 0.379 & 2.25 & 0.133 & 0.57 & 0.27, 1.19 \\ \mbox{verage daily dose 100-19 mg & RV vs LN & 0.270 & 0.379 & 2.25 $								
$\begin{array}{l l l l l l l l l l l l l l l l l l l $	(reference 1996)							
$\begin{array}{c c} \mbox{Ver} of entry 1999 & IR vs LN 0.471 0.127 13.7 0.000 1.60*** (1.25, 2.05) (1.4$								
$\begin{array}{l creference 1990} & LR vs LN 0.486 0.109 19.95 0.0001 1.63*** (1.31, 2.01) \\ (reference 1996) & Vs LN 0.398 0.144 7.7 0.006 1.49*** (1.12, 1.97) \\ Nv s LN 0.930 0.122 57.81 0.0001 2.53*** (1.99, 3.22) \\ (reference 60-79 mg) & Vs LN 0.218 0.184 1.4 0.236 1.24* (0.87, 1.78) \\ Vv s LN 0.218 0.184 1.7.1 0.0001 1.79*** (1.36, 2.37) \\ (reference 60-79 mg) & Vs LN 0.255 0.108 26.33 0.0001 0.57*** (0.46, 0.71) \\ (reference 60-79 mg) & Vs LN 0.212 0.113 3.53 0.006 1.24* (0.99, 1.54) \\ (reference 60-79 mg) & Vs LN 0.212 0.113 3.53 0.0060 1.24* (0.99, 1.54) \\ (reference 60-79 mg) & Vs LN 0.212 0.113 3.53 0.0060 1.24* (0.99, 1.54) \\ (reference 60-79 mg) & Vs LN 0.212 0.113 0.145 0.6 0.439 0.89 (0.67, 1.19) \\ Nv s LN 0.515 0.143 12.99 0.0000 1.67*** (1.26, 2.21) \\ (reference 60-79 mg) & Vs LN 0.012 0.133 7.37 0.007 0.7** (0.54, 0.90) \\ Nv s LN 0.355 0.143 12.99 0.0000 1.67*** (1.26, 2.21) \\ Nv s LN 0.022 0.123 0.630 1.10 (0.75, 1.60) \\ Nv s LN 0.022 0.123 0.630 1.10 (0.75, 1.60) \\ Nv s LN 0.022 0.127 0.2 0.659 0.88 (0.51, 1.52) \\ (reference 60-79 mg) & Vs LN 0.012 0.277 0.2 0.659 0.88 (0.51, 1.52) \\ Nv S LN 0.024 0.247 0.98 0.323 0.76 (0.48, 1.27) \\ Nv s LN 0.024 0.247 0.98 0.323 0.76 (0.48, 1.27) \\ Nv s LN 0.024 0.247 0.98 0.323 0.76 (0.48, 1.27) \\ Average daily dose 140-159 mg \\ LR vs LN 0.051 0.319 2.55 0.133 0.57 (0.27, 1.19) \\ Nv S LN 0.051 0.319 2.58 0.108 0.60 (0.32, 1.12) \\ Nv S LN 0.051 0.379 2.55 0.133 0.57 (0.27, 1.19) \\ Nv S LN 0.051 0.379 2.55 0.133 0.57 (0.27, 1.19) \\ Nv S LN 0.040 0.235 0.46 (0.806 0.994 (0.57, 1.54) \\ (reference 60-79 mg) & Vs LN 0.051 0.379 2.55 0.133 0.57 (0.27, 1.19) \\ Nv S LN 0.040 0.235 0.47 0.492 0.79 (0.39, 1.56) \\ (reference 60-79 mg) & Vs LN 0.046 0.327 1.54 0.47 0.492 0.79 (0.39, 1.56) \\ Nv S LN 0.040 0.235 0.47 0.492 0.79 (0.39, 1.55) \\ (reference 60-79 mg) & Vs LN 0.040 0.235 0.42 (0.65) 0.48 (0.57, 1.54) \\ (reference 60-79 mg) & Vs LN 0.040 0.235 0.42 (0.65) 0.48 (0.57, 1.54) \\ (reference 60-79 mg) & Vs LN 0.040 0.235 0.42 (0.65) 0.48 (0.57, 1.54) \\ (referen$	(reference 1996)							
		N vs LN	0.471	0.127	13.7	0.000	1.60***	(1.25, 2.05)
	Year of entry 1999	LR vs LN	0.486	0.109	19.95	< 0.0001	1.63***	(1.31, 2.01)
$\begin{array}{c c} \mbox{Nvs} \ln & 0.930 & 0.122 & 57.81 & <0.0001 & 2.53^{***} & (1.99, 3.22) \\ \mbox{Nvs} \ln & 0.218 & 0.184 & 1.4 & 0.236 & 1.24 & (0.87, 1.78) \\ \mbox{Nvs} \ln & 0.585 & 0.141 & 17.13 & <0.0001 & 1.79^{***} & (1.36, 2.37) \\ \mbox{Nvs} \ln & 0.555 & 0.108 & 26.33 & <0.0001 & 0.57^{***} & (0.46, 0.71) \\ \mbox{Ireference} 60-79 mg & Lv s \ln & 0.224 & 0.113 & 3.53 & 0.060 & 1.24 & (0.99, 1.54) \\ \mbox{Nvs} \ln & 0.212 & 0.113 & 3.53 & 0.060 & 1.28 & (1.04, 1.58) \\ \mbox{Ireference} 60-79 mg & Lv s \ln & 0.212 & 0.113 & 0.145 & 0.6 & 0.439 & 0.89 & (0.67, 1.19) \\ \mbox{Nvs} \ln & 0.212 & 0.113 & 0.145 & 0.6 & 0.439 & 0.89 & (0.67, 1.19) \\ \mbox{Nvs} \ln & 0.013 & 0.145 & 0.6 & 0.439 & 0.89 & (0.67, 1.54) \\ \mbox{Nvs} \ln & 0.029 & 0.122 & 0.23 & 0.630 & 1.10 & (0.75, 1.60) \\ \mbox{Average} daily dose 100-119 mg & Lv s \ln & 0.515 & 0.143 & 12.99 & 0.000 & 1.67^{***} & (0.54, 0.90) \\ \mbox{Average} daily dose 120-139 mg & Lv s \ln & 0.294 & 0.133 & 2.58 & 0.108 & 0.75 & (0.52, 1.07) \\ \mbox{Average} daily dose 120-139 mg & Lv s \ln & 0.294 & 0.277 & 0.2 & 0.659 & 0.88 & (0.51, 1.52) \\ \mbox{Average} daily dose 140-159 mg & Lv s \ln & 0.022 & 0.277 & 0.2 & 0.659 & 0.88 & (0.51, 1.52) \\ \mbox{Average} daily dose 140-159 mg & Lv s \ln & 0.026 & 0.233 & 0.06 & 0.304 & (0.57, 1.60) \\ \mbox{Average} daily dose 140-159 mg & Lv s \ln & 0.008 & 0.244 & 0 & 0.974 & 0.99 & (0.62, 1.60) \\ \mbox{Average} daily dose 120-199 mg & Lv s \ln & 0.012 & 0.319 & 2.58 & 0.108 & 0.60 & (0.32, 1.12) \\ \mbox{Average} daily dose 100-199 mg & Lv s \ln & 0.024 & 0.233 & 0.06 & 0.806 & 0.94 & (0.57, 1.54) \\ \mbox{Average} daily dose 100-199 mg & Lv s \ln & 0.026 & 0.323 & 0.16 & 0.806 & 0.934 & (0.57, 1.54) \\ \mbox{Average} daily dose 100-199 mg & Lv s \ln & 0.026 & 0.323 & 0.16 & 0.806 & 0.94 & (0.57, 1.54) \\ \mbox{Average} daily dose 200-299 mg & Lv s \ln & 0.026 & 0.327 & 1.54 & 0.215 & 0.67 & (0.32, 1.26) \\ \mbox{Average} daily dose 200-299 mg & Lv s \ln & 0.028 & 0.396 & 0.31 & 0.79 & 0.27 & (0.48, 0.95) \\ \mbox \ln & 0.228 & 0.327 & 0.14 & 0.709 & 1.25 & (0.39, 4.35) \\ \m$	(reference 1'996)	D vs LN	0.398	0.144	7.7	0.006	1.49***	(1.12, 1.97)
$ \begin{array}{l c c c c c c c c c c c c c c c c c c c$		N vs LN		0.122	57.81	< 0.0001		
	Average daily dose < 40 mg						0.49***	
$\begin{array}{c c} & {\rm NvsIN} & 0.585 & 0.141 & 17.13 & <0.0001 & 1.79^{***} & (1.36, 2.37) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & -0.246 & 0.136 & 3.27 & 0.071 & 0.78 & 0.064, 0.102) \\ {\rm (neference 60-79mg)} & {\rm DvsIN} & 0.212 & 0.113 & 3.53 & 0.060 & 1.24 & (0.99, 1.54) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & 0.248 & 0.108 & 5.33 & 0.021 & 1.28^* & (1.04, 1.58) \\ {\rm (neference 60-79mg)} & {\rm DvsIN} & -0.362 & 0.133 & 7.37 & 0.007 & 0.7^{***} & (0.54, 0.90) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & 0.052 & 0.133 & 7.37 & 0.007 & 0.7^{***} & (0.54, 0.90) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & 0.092 & 0.192 & 0.23 & 0.630 & 1.10 & (0.75, 1.60) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & 0.092 & 0.192 & 0.23 & 0.630 & 1.10 & (0.75, 1.60) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & 0.0244 & 0.247 & 0.98 & 0.323 & 0.78 & (0.48, 1.27) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & -0.244 & 0.247 & 0.98 & 0.323 & 0.78 & (0.48, 1.27) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & -0.244 & 0.247 & 0.98 & 0.323 & 0.78 & (0.48, 1.27) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & -0.570 & 0.379 & 2.25 & 0.133 & 0.57 & (0.27, 1.19) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & -0.062 & 0.235 & 0.06 & 0.806 & 0.94 & (0.32, 1.12) \\ {\rm Average daily dose 160-199mg} & {\rm IRvsIN} & -0.062 & 0.253 & 0.06 & 0.806 & 0.94 & (0.32, 1.12) \\ {\rm Average daily dose 10-199mg} & {\rm IRvsIN} & -0.062 & 0.255 & 0.20 & 0.888 & 1.04 & (0.57, 1.54) \\ {\rm (reference 60-79mg)} & {\rm DvsIN} & -0.062 & 0.255 & 0.02 & 0.886 & 1.04 & (0.57, 1.54) \\ {\rm Average daily dose 10-199mg} & {\rm IRvsIN} & -0.062 & 0.255 & 0.20 & 0.886 & 1.04 & (0.57, 1.54) \\ {\rm Average daily dose 10-199mg} & {\rm IRvsIN} & -0.062 & 0.255 & 0.20 & 0.886 & 1.04 & (0.57, 1.54) \\ {\rm Average daily dose 300-399mg} & {\rm IRvsIN} & -0.078 & 0.377 & 0.371 & 0.105 & (0.36, 1.26) \\ (reference 60-79mg) & {\rm DvsIN} & -0.024 & 0.351 & 0.29 & 0.0001 & 0.66^{+**} & (0.24, 0.39) \\ {\rm Average daily dose 300-399mg} & {\rm IRvsIN} & -0.322 & 0.366 & 4.18 & 0.041 & $					1 4			
$ \begin{array}{l lllllllllllllllllllllllllllllllllll$	(reference oo / 5 mg)							
	Average daily dose 40-59 mg							
$\begin{array}{c c c c c c c c c c c c c c c c c c c $								
$ \begin{array}{l c c c c c c c c c c c c c c c c c c c$	(Telefence 00-7 9 mg)							
(reference 60-79 mg)   D vs LN   -0.113   0.145   0.6   0.439   0.89   (0.67, 1.19)     Average daily dose 100-119 mg   LR vs LN   0.515   0.143   7.37   0.007   0.7**   (0.54, 0.90)     Average daily dose 100-119 mg   LR vs LN   0.515   0.143   12.99   0.000   1.67***   (1.26, 2.21)     Average daily dose 120-139 mg   LR vs LN   0.295   0.197   2.24   0.135   1.34   (0.91, 1.98)     (reference 60-79 mg)   D vs LN   -0.122   0.277   0.2   0.659   0.88   (0.51, 1.52)     Average daily dose 140-159 mg   LR vs LN   -0.008   0.244   0   0.974   0.99   (0.62, 1.60)     (reference 60-79 mg)   D vs LN   -0.570   0.379   2.25   0.133   0.57   (0.27, 1.19)     Average daily dose 160-199 mg   LR vs LN   -0.062   0.253   0.06   0.806   0.94   (0.57, 1.54)     (reference 60-79 mg)   D vs LN   0.241   0.351   0.47   0.492   0.79	Average deily deep 80.00 mg							
Average daily dose 100-119 mg (reference 60-79 mg)   N vs LN   -0.362   0.133   7.37   0.007   0.7**   (0.54, 0.90)     Average daily dose 100-119 mg (reference 60-79 mg)   D vs LN   0.092   0.192   0.23   0.630   1.10   (0.75, 1.60)     Average daily dose 120-139 mg (reference 60-79 mg)   D vs LN   0.295   0.197   2.24   0.133   0.78   (0.48, 1.27)     Average daily dose 140-159 mg (reference 60-79 mg)   D vs LN   -0.244   0.247   0.98   0.323   0.78   (0.48, 1.27)     Average daily dose 140-159 mg (reference 60-79 mg)   D vs LN   -0.008   0.244   0   0.974   0.99   (0.62, 1.60)     Average daily dose 140-159 mg (reference 60-79 mg)   D vs LN   -0.512   0.319   2.58   0.108   0.60   0.322, 1.19)     Average daily dose 100-199 mg   LR vs LN   -0.062   0.233   0.66   0.806   0.94   (0.57, 1.54)     (reference 60-79 mg)   D vs LN   0.241   0.351   0.47   0.492   0.79   0.39, 1.56     (reference 60-79 mg)	(reference (0, 70 mm))							
$\begin{array}{l c c c c c c c c c c c c c c c c c c c$	(reference 60-79 mg)							
					/.3/		0./**	
Average daily dose 120-139 mg (reference 60-79 mg)Lv s LN D vs LN -0.122-0.295 0.2770.183 0.2442.58 0.1080.108 0.6590.75 0.135(0.52, 1.07) 1.34Average daily dose 140-159 mg (reference 60-79 mg)Lv s LN D vs LN D vs LN -0.5120.247 0.2440.98 0.2470.323 0.980.78 0.974(0.48, 1.27) 0.994Average daily dose 160-199 mg 					12.99			
$\begin{array}{llllllllllllllllllllllllllllllllllll$	(reference 60-79 mg)							
$\begin{array}{c} (reference 60-79 \text{ mg}) & D \text{ vs LN} & -0.122 & 0.277 & 0.2 & 0.659 & 0.88 & (0.51, 1.52) \\ \text{Average daily dose 140-159 \text{ mg}} & L \text{ vs LN} & -0.244 & 0.247 & 0.98 & 0.323 & 0.78 & (0.48, 1.27) \\ \text{Average daily dose 140-159 \text{ mg}} & L \text{ vs LN} & -0.008 & 0.244 & 0 & 0.974 & 0.99 & (0.62, 1.60) \\ \text{(reference 60-79 \text{ mg})} & D \text{ vs LN} & -0.570 & 0.379 & 2.25 & 0.133 & 0.57 & (0.27, 1.19) \\ \text{N vs LN} & -0.571 & 0.379 & 2.25 & 0.108 & 0.60 & (0.32, 1.12) \\ \text{Average daily dose 160-199 \text{ mg}} & L \text{ vs LN} & -0.062 & 0.253 & 0.06 & 0.806 & 0.94 & (0.57, 1.54) \\ \text{(reference 60-79 \text{ mg})} & D \text{ vs LN} & -0.241 & 0.351 & 0.47 & 0.492 & 0.79 & (0.39, 1.56) \\ \text{N vs LN} & -0.241 & 0.351 & 0.47 & 0.492 & 0.79 & (0.39, 1.56) \\ \text{Average daily dose 200-299 \text{ mg}} & L \text{ vs LN} & -0.406 & 0.327 & 1.54 & 0.215 & 0.67 & (0.35, 1.26) \\ \text{(reference 60-79 \text{ mg})} & D \text{ vs LN} & 0.785 & 0.304 & 6.69 & 0.010 & 2.19^{**} & (1.21, 3.97) \\ \text{Average daily dose 300-399 \text{ mg}} & L \text{ vs LN} & -1.299 & 0.636 & 4.18 & 0.041 & 0.27^{*} & (0.08, 0.95) \\ \text{(reference 60-79 \text{ mg})} & D \text{ vs LN} & 0.788 & 0.478 & 2.73 & 0.099 & 2.20 & (0.86, 5.61) \\ \text{Age at entry 10-19} & L \text{ vs LN} & -0.327 & 0.251 & 1.69 & 0.193 & 0.72 & (0.44, 1.18) \\ \text{(reference 30-39)} & D \text{ vs LN} & -0.327 & 0.251 & 1.69 & 0.193 & 0.72 & (0.44, 1.18) \\ \text{Age at entry 20-29} & L \text{ vs LN} & -0.474 & 0.092 & 20.29 & <0.0001 & 0.66^{***} & (0.25, 0.79) \\ \text{(reference 30-39)} & D \text{ vs LN} & -0.201 & 0.117 & 2.96 & 0.085 & 0.82 & (0.65, 1.03) \\ \text{(reference 30-39)} & D \text{ vs LN} & -0.201 & 0.117 & 0.18 & 0.672 & 1.05 & (0.84, 1.32) \\ \text{Age at entry 40-49} & L \text{ vs LN} & 0.823 & 0.271 & 14.36 & 0.0001 & 1.56^{***} & (1.28, 1.89) \\ \text{(reference 30-39)} & D \text{ vs LN} & -0.039 & 0.138 & 0.080 & 0.781 & 0.96 & (0.73, 1.26) \\ \text{(reference 30-39)} & D \text{ vs LN} & -0.078 & 0.327 & 0.241 & 0.750 & 0.92 & (0.44, 1.18) \\ \text{(reference 30-39)} & D \text{ vs LN} & -0.036 & 0.270 & 0.138 & 0.667 & 1.32 & (0.65, 1.03) \\ \text{(reference 30-39)} & D \text{ vs LN} & -0$								(0.52, 1.07)
Average daily dose 140-159 mg (reference 60-79 mg)   N vs LN   -0.244   0.247   0.98   0.323   0.78   (0.48, 1.27)     Average daily dose 140-159 mg (reference 60-79 mg)   LR vs LN   -0.070   0.379   2.25   0.133   0.57   (0.27, 1.19)     Average daily dose 160-199 mg (reference 60-79 mg)   LR vs LN   -0.512   0.319   2.58   0.108   0.60   (0.32, 1.12)     Average daily dose 160-199 mg (reference 60-79 mg)   D vs LN   -0.241   0.351   0.47   0.492   0.79   (0.39, 1.56)     Average daily dose 200-299 mg   LR vs LN   -0.040   0.285   0.02   0.888   1.04   (0.60, 1.82)     Average daily dose 300-399 mg   LR vs LN   0.139   0.386   0.13   0.718   1.15   (0.57, 1.54)     Average daily dose 300-399 mg   LR vs LN   0.129   0.636   4.18   0.041   0.27*   (0.08, 5.61)     Age at entry 10-19   LR vs LN   -0.327   0.251   1.69   0.193   0.72   (0.44, 1.18)     (reference 30-39)   D vs LN   -0.32								
$\begin{array}{c c} \mbox{Average daily dose 140-159 mg} & LR vs LN & -0.008 & 0.244 & 0 & 0.974 & 0.99 & (0.62, 1.60) \\ \mbox{(reference 60-79 mg)} & D vs LN & -0.570 & 0.379 & 2.25 & 0.133 & 0.57 & (0.27, 1.19) \\ N vs LN & -0.571 & 0.319 & 2.58 & 0.108 & 0.60 & (0.32, 1.12) \\ \mbox{(reference 60-79 mg)} & LR vs LN & -0.062 & 0.253 & 0.06 & 0.806 & 0.94 & (0.57, 1.54) \\ \mbox{(reference 60-79 mg)} & D vs LN & -0.241 & 0.351 & 0.47 & 0.492 & 0.79 & (0.39, 1.56) \\ \mbox{(reference 60-79 mg)} & N vs LN & 0.040 & 0.285 & 0.02 & 0.888 & 1.04 & (0.60, 1.82) \\ \mbox{(reference 60-79 mg)} & D vs LN & 0.139 & 0.386 & 0.13 & 0.718 & 1.15 & (0.55, 1.26) \\ \mbox{(reference 60-79 mg)} & D vs LN & 0.785 & 0.304 & 6.69 & 0.010 & 2.19** & (1.21, 3.97) \\ \mbox{(reference 60-79 mg)} & D vs LN & 0.785 & 0.304 & 6.69 & 0.010 & 2.19** & (1.21, 3.97) \\ \mbox{(reference 60-79 mg)} & D vs LN & 0.223 & 0.597 & 0.14 & 0.709 & 1.25 & (0.39, 4.03) \\ \mbox{(reference 60-79 mg)} & D vs LN & 0.788 & 0.478 & 2.73 & 0.099 & 2.20 & (0.86, 5.61) \\ \mbox{(reference 60-79 mg)} & D vs LN & 0.302 & 0.196 & 2.39 & 0.122 & 0.74 & (0.50, 1.08) \\ \mbox{(reference 30-39)} & D vs LN & -0.302 & 0.196 & 2.39 & 0.122 & 0.74 & (0.50, 1.08) \\ \mbox{(reference 30-39)} & D vs LN & -0.414 & 0.092 & 20.29 & <0.0001 & 0.66*** & (0.42, 0.93) \\ \mbox{(reference 30-39)} & D vs LN & -0.247 & 0.098 & 6.27 & 0.012 & 0.78* & (0.64, 0.95) \\ \mbox{(reference 30-39)} & D vs LN & -0.247 & 0.098 & 6.27 & 0.012 & 0.78* & (0.64, 0.95) \\ \mbox{(reference 30-39)} & D vs LN & -0.247 & 0.098 & 6.27 & 0.012 & 0.78* & (0.64, 0.95) \\ \mbox{(reference 30-39)} & D vs LN & 0.050 & 0.117 & 0.18 & 0.672 & 1.05 & (0.84, 1.32) \\ \mbox{(reference 30-39)} & D vs LN & -0.247 & 0.098 & 6.27 & 0.012 & 0.78* & (0.64, 0.95) \\ \mbox{(reference 30-39)} & D vs LN & 0.050 & 0.117 & 0.18 & 0.672 & 1.05 & (0.84, 1.32) \\ \mbox{(reference 30-39)} & D vs LN & 0.027 & 0.098 & 6.27 & 0.012 & 0.78* & (0.64, 0.95) \\ \mbox{(reference 30-39)} & D vs LN & 0.0270 & 0.321 & 0.06 & 0.807 & 0.92 & (0.44, 1.73) \\ (reference$	(reference 60-79 mg)		-0.122	0.277				(0.51, 1.52)
$\begin{array}{l c c c c c c c c c c c c c c c c c c c$	0	N vs LN	-0.244	0.247	0.98	0.323	0.78	(0.48, 1.27)
(reference 60-79 mg)   D vs LN   -0.570   0.379   2.25   0.133   0.57   (0.27, 1.19)     Average daily dose 160-199 mg   LR vs LN   -0.062   0.253   0.06   0.806   0.94   (0.57, 1.54)     (reference 60-79 mg)   D vs LN   -0.241   0.351   0.47   0.492   0.79   (0.39, 1.56)     Average daily dose 200-299 mg   LR vs LN   -0.406   0.327   1.54   0.215   0.67   (0.35, 1.26)     Average daily dose 200-299 mg   LR vs LN   -0.406   0.327   1.54   0.215   0.67   (0.35, 1.26)     (reference 60-79 mg)   D vs LN   0.139   0.386   0.13   0.718   1.15   (0.54, 2.45)     N vs LN   0.785   0.304   6.69   0.010   2.19**   (0.08, 0.95)     (reference 60-79 mg)   D vs LN   0.223   0.597   0.14   0.709   1.25   (0.39, 4.03)     (reference 30-39)   D vs LN   -0.322   0.251   1.69   0.193   0.72   (0.41, 1.8)     (r	Average daily dose 140-159 mg	LR vs LN	-0.008	0.244	0	0.974	0.99	(0.62, 1.60)
N vs LN   -0.512   0.319   2.58   0.108   0.60   (0.32, 1.12)     Average daily dose 160-199 mg (reference 60-79 mg)   Us LN   -0.0241   0.351   0.47   0.492   0.79   (0.39, 1.56)     Average daily dose 200-299 mg   LR vs LN   -0.406   0.327   1.54   0.215   0.67   (0.35, 1.26)     Average daily dose 200-299 mg   LR vs LN   -0.406   0.327   1.54   0.215   0.67   (0.35, 1.26)     (reference 60-79 mg)   D vs LN   0.139   0.386   0.13   0.718   1.15   (0.54, 2.45)     Average daily dose 300-399 mg   LR vs LN   -1.299   0.636   4.18   0.041   0.27*   (0.08, 0.95)     (reference 60-79 mg)   D vs LN   0.723   0.597   0.14   0.709   1.25   (0.39, 4.03)     Age at entry 10-19   LR vs LN   -0.327   0.251   1.69   0.193   0.72   (0.44, 1.18)     M vs LN   -0.475   0.205   5.35   0.021   0.66***   (0.42, 0.93)     Age a	(reference 60-79 mg)	D vs LN	-0.570	0.379	2.25	0.133		
Average daily dose 160-199 mg (reference 60-79 mg)   LR vs LN   -0.062   0.253   0.06   0.806   0.94   (0.57, 1.54)     N vs LN   -0.241   0.351   0.47   0.492   0.79   (0.39, 1.56)     Average daily dose 200-299 mg (reference 60-79 mg)   LR vs LN   -0.406   0.327   1.54   0.215   0.67   (0.35, 1.26)     Average daily dose 200-299 mg   LR vs LN   -0.406   0.327   1.54   0.215   0.67   (0.35, 1.26)     (reference 60-79 mg)   D vs LN   0.785   0.304   6.69   0.010   2.19**   (1.21, 3.57)     Average daily dose 300-399 mg   LR vs LN   -1.299   0.636   4.18   0.041   0.27*   (0.08, 0.95)     (reference 60-79 mg)   D vs LN   0.788   0.478   2.73   0.099   2.20   (0.86, 5.61)     Age at entry 10-19   LR vs LN   -0.327   0.251   1.69   0.193   0.72   (0.44, 1.18)     (reference 30-39)   D vs LN   -0.475   0.205   5.35   0.021   0.66***	8							
(reference 60-79 mg)   D vs LN   -0.241   0.351   0.47   0.492   0.79   (0.39, 1.56)     Average daily dose 200-299 mg   LR vs LN   0.040   0.285   0.02   0.888   1.04   (0.60, 1.82)     (reference 60-79 mg)   D vs LN   0.139   0.386   0.13   0.718   1.15   (0.54, 2.45)     Average daily dose 300-399 mg   LR vs LN   0.785   0.304   6.69   0.010   2.19**   (1.21, 3.97)     Average daily dose 300-399 mg   LR vs LN   0.223   0.597   0.14   0.709   1.25   (0.39, 4.03)     (reference 60-79 mg)   D vs LN   0.223   0.597   0.14   0.709   1.25   (0.39, 4.03)     Age at entry 10-19   LR vs LN   -0.302   0.196   2.39   0.122   0.74   (0.50, 1.08)     (reference 30-39)   D vs LN   -0.327   0.251   1.69   0.193   0.72   (0.44, 1.18)     Age at entry 20-29   LR vs LN   -0.474   0.098   6.27   0.012   0.68***   (0.55, 1.03)<	Average daily dose 160-199 mg							(0.57, 1.54)
N vs LN   0.040   0.285   0.02   0.888   1.04   (0.60, 1.82)     Average daily dose 200-299 mg (reference 60-79 mg)   LR vs LN   -0.406   0.327   1.54   0.215   0.67   (0.35, 1.26)     Average daily dose 200-299 mg   LR vs LN   0.139   0.386   0.13   0.718   1.15   (0.54, 2.45)     Average daily dose 300-399 mg   LR vs LN   -1.299   0.636   4.18   0.041   0.27*   (0.08, 0.95)     (reference 60-79 mg)   D vs LN   0.223   0.597   0.14   0.709   1.25   (0.39, 4.03)     N vs LN   0.788   0.478   2.73   0.099   2.20   (0.86, 5.61)     Age at entry 10-19   LR vs LN   -0.302   0.196   2.39   0.122   0.74   (0.50, 1.08)     (reference 30-39)   D vs LN   -0.475   0.205   5.35   0.021   0.66***   (0.55, 0.79)     (reference 30-39)   D vs LN   -0.211   0.117   2.96   0.085   0.82   (0.65, 1.03)     (reference 30-39) <td>(reference 60-79 mg)</td> <td></td> <td></td> <td></td> <td>0.47</td> <td></td> <td></td> <td></td>	(reference 60-79 mg)				0.47			
Average daily dose 200-299 mg (reference 60-79 mg)   LR vs LN   -0.406   0.327   1.54   0.215   0.67   (0.35, 1.26)     Average daily dose 300-399 mg (reference 60-79 mg)   D vs LN   0.139   0.386   0.13   0.718   1.15   (0.54, 2.45)     Average daily dose 300-399 mg (reference 60-79 mg)   LR vs LN   -1.299   0.636   4.18   0.041   0.27*   (0.08, 0.95)     Age at entry 10-19   LR vs LN   0.788   0.478   2.73   0.099   2.20   (0.86, 5.61)     Age at entry 10-19   LR vs LN   -0.302   0.196   2.39   0.122   0.74   (0.50, 1.08)     (reference 30-39)   D vs LN   -0.327   0.205   5.35   0.021   0.66***   (0.42, 0.93)     Age at entry 20-29   LR vs LN   -0.414   0.092   20.29   <0.0001	(							
(reference 60-79 mg)   D vs LN   0.139   0.386   0.13   0.718   1.15   (0.54, 2.45)     Average daily dose 300-399 mg   LR vs LN   0.785   0.304   6.69   0.010   2.19**   (1.21, 3.97)     (reference 60-79 mg)   D vs LN   0.223   0.597   0.14   0.709   1.25   (0.39, 4.03)     N vs LN   0.788   0.478   2.73   0.099   2.20   (0.86, 5.61)     Age at entry 10-19   LR vs LN   -0.302   0.196   2.39   0.122   0.74   (0.51, 0.8)     (reference 30-39)   D vs LN   -0.327   0.251   1.69   0.193   0.72   (0.44, 1.18)     Age at entry 20-29   LR vs LN   -0.414   0.092   20.29   <0.0001	Average daily dose 200-299 mg							
N vs LN   0.785   0.304   6.69   0.010   2.19**   (1.21, 3.97)     Average daily dose 300-399 mg (reference 60-79 mg)   LR vs LN   -1.299   0.636   4.18   0.041   0.27*   (0.08, 0.95)     (reference 60-79 mg)   D vs LN   0.223   0.597   0.14   0.709   1.25   (0.39, 4.03)     Age at entry 10-19   LR vs LN   -0.302   0.196   2.39   0.122   0.74   (0.50, 1.08)     (reference 30-39)   D vs LN   -0.327   0.251   1.69   0.193   0.72   (0.44, 1.18)     N vs LN   -0.475   0.205   5.35   0.021   0.66**   (0.55, 0.79)     (reference 30-39)   D vs LN   -0.201   0.117   2.96   0.085   0.82   (0.66, 1.03)     Age at entry 40-49   LR vs LN   -0.247   0.098   6.27   0.012   0.78*   (0.64, 0.95)     Age at entry 40-49   LR vs LN   0.442   0.101   19.33   <0.0001	(reference 60-79 mg)							
Average daily dose 300-399 mg (reference 60-79 mg)   LR vs LN   -1.299   0.636   4.18   0.041   0.27*   (0.06, 0.95)     (reference 60-79 mg)   D vs LN   0.223   0.597   0.14   0.709   1.25   (0.39, 4.03)     Age at entry 10-19   LR vs LN   0.788   0.478   2.73   0.099   2.20   (0.86, 5.61)     Age at entry 10-19   LR vs LN   -0.302   0.196   2.39   0.122   0.74   (0.50, 1.08)     (reference 30-39)   D vs LN   -0.327   0.251   1.69   0.193   0.722   (0.44, 1.18)     N vs LN   -0.475   0.205   5.35   0.021   0.62*   (0.42, 0.93)     Age at entry 20-29   LR vs LN   -0.414   0.092   20.29   <0.0001	(reference oo 75 mg)							
(reference 60-79 mg)   D vs LN   0.223   0.597   0.14   0.709   1.25   (0.39, 4.03)     Age at entry 10-19   LR vs LN   0.788   0.478   2.73   0.099   2.20   (0.86, 5.61)     Age at entry 10-19   LR vs LN   -0.302   0.196   2.39   0.122   0.74   (0.50, 1.08)     (reference 30-39)   D vs LN   -0.327   0.251   1.69   0.193   0.72   (0.44, 1.18)     N vs LN   -0.475   0.205   5.35   0.021   0.62*   (0.42, 0.93)     Age at entry 20-29   LR vs LN   -0.414   0.092   20.29   <0.0001	Average daily does 200,200 mg						2.19	
N vs LN0.7880.4782.730.0992.20(0.86, 5.61)Age at entry 10-19LR vs LN-0.3020.1962.390.1220.74(0.50, 1.08)(reference 30-39)D vs LN-0.3270.2511.690.1930.72(0.44, 1.18)N vs LN-0.4750.2055.350.0210.62*(0.42, 0.93)Age at entry 20-29LR vs LN-0.4140.09220.29<0.0001								
Age at entry 10-19   LR vs LN   -0.302   0.196   2.39   0.122   0.74   (0.50, 1.08)     (reference 30-39)   D vs LN   -0.327   0.251   1.69   0.193   0.72   (0.44, 1.18)     N vs LN   -0.475   0.205   5.35   0.021   0.66**   (0.42, 0.93)     Age at entry 20-29   LR vs LN   -0.414   0.092   20.29   <0.0001	(reference oo-7 9 mg)							
(reference 30-39)   D vs LN   -0.327   0.251   1.69   0.193   0.72   (0.44, 1.18)     N vs LN   -0.475   0.205   5.35   0.021   0.62*   (0.42, 0.93)     Age at entry 20-29   LR vs LN   -0.414   0.092   20.29   <0.0001	A							
N vs LN   -0.475   0.205   5.35   0.021   0.62*   (0.42, 0.93)     Age at entry 20-29 (reference 30-39)   LR vs LN   -0.414   0.092   20.29   <0.0001								
(reference 30-39)   D vs LN   -0.201   0.117   2.96   0.085   0.82   (0.65, 1.03)     N vs LN   -0.247   0.098   6.27   0.012   0.78*   (0.64, 0.95)     Age at entry 40-49   LR vs LN   0.442   0.101   19.33   <0.0001	(reference 30-39)							(0.44, 1.18)
(reference 30-39)   D vs LN   -0.201   0.117   2.96   0.085   0.82   (0.65, 1.03)     N vs LN   -0.247   0.098   6.27   0.012   0.78*   (0.64, 0.95)     Age at entry 40-49   LR vs LN   0.442   0.101   19.33   <0.0001							0.62*	(0.42, 0.93)
N vs LN   -0.247   0.098   6.27   0.012   0.78*   (0.64, 0.95)     Age at entry 40-49   LR vs LN   0.442   0.101   19.33   <0.0001							0.66***	(0.55, 0.79)
Age at entry 40-49   LR vs LN   0.442   0.101   19.33   <0.0001   1.56***   (1.28, 1.89)     (reference 30-39)   D vs LN   -0.039   0.138   0.08   0.781   0.96   (0.73, 1.26)     N vs LN   0.050   0.117   0.18   0.672   1.05   (0.84, 1.32)     Age at entry 50-59   LR vs LN   0.823   0.271   14.36   0.000   2.28***   (1.34, 3.88)     (reference 30-39)   D vs LN   -0.078   0.321   0.06   0.807   0.92   (0.49, 1.73)     N vs LN   -0.078   0.268   0.1   0.750   0.92   (0.54, 1.55)     Age at entry 60-69   LR vs LN   0.277   0.642   0.19   0.667   1.32   (0.37, 4.64)     (reference 30-39)   D vs LN   -0.078   0.875   0.01   0.929   0.93   (0.17, 5.14)	(reterence 30-39)							
(reference 30-39)   D vs LN   -0.039   0.138   0.08   0.781   0.96   (0.73, 1.26)     N vs LN   0.050   0.117   0.18   0.672   1.05   (0.84, 1.32)     Age at entry 50-59   LR vs LN   0.823   0.271   14.36   0.000   2.28***   (1.34, 3.88)     (reference 30-39)   D vs LN   -0.078   0.321   0.06   0.807   0.92   (0.49, 1.73)     N vs LN   -0.086   0.268   0.1   0.750   0.92   (0.54, 1.55)     Age at entry 60-69   LR vs LN   0.277   0.642   0.19   0.667   1.32   (0.37, 4.64)     (reference 30-39)   D vs LN   -0.078   0.875   0.01   0.929   0.93   (0.17, 5.14)			-0.247	0.098			0.78*	(0.64, 0.95)
(reference 30-39)   D vs LN   -0.039   0.138   0.08   0.781   0.96   (0.73, 1.26)     N vs LN   0.050   0.117   0.18   0.672   1.05   (0.84, 1.32)     Age at entry 50-59   LR vs LN   0.823   0.271   14.36   0.000   2.28***   (1.34, 3.88)     (reference 30-39)   D vs LN   -0.078   0.321   0.06   0.807   0.92   (0.49, 1.73)     N vs LN   -0.086   0.268   0.1   0.750   0.92   (0.54, 1.55)     Age at entry 60-69   LR vs LN   0.277   0.642   0.19   0.667   1.32   (0.37, 4.64)     (reference 30-39)   D vs LN   -0.078   0.875   0.01   0.929   0.93   (0.17, 5.14)	Age at entry 40-49	LR vs LN	0.442	0.101	19.33	< 0.0001	1.56***	(1.28, 1.89)
N vs LN   0.050   0.117   0.18   0.672   1.05   (0.84, 1.32)     Age at entry 50-59   LR vs LN   0.823   0.271   14.36   0.000   2.28***   (1.34, 3.88)     (reference 30-39)   D vs LN   -0.078   0.321   0.06   0.807   0.92   (0.49, 1.73)     N vs LN   -0.086   0.268   0.1   0.750   0.92   (0.54, 1.55)     Age at entry 60-69   LR vs LN   0.277   0.642   0.19   0.667   1.32   (0.37, 4.64)     (reference 30-39)   D vs LN   -0.078   0.875   0.01   0.929   0.93   (0.17, 5.14)	(reference 30-39)	D vs LN	-0.039	0.138	0.08	0.781	0.96	(0.73, 1.26)
Age at entry 50-59   LR vs LN   0.823   0.271   14.36   0.000   2.28***   (1.34, 3.88)     (reference 30-39)   D vs LN   -0.078   0.321   0.06   0.807   0.92   (0.49, 1.73)     N vs LN   -0.086   0.268   0.1   0.750   0.92   (0.54, 1.55)     Age at entry 60-69   LR vs LN   0.277   0.642   0.19   0.667   1.32   (0.37, 4.64)     (reference 30-39)   D vs LN   -0.078   0.875   0.01   0.929   0.93   (0.17, 5.14)					0.18		1.05	
(reference 30-39)   D vs LN   -0.078   0.321   0.06   0.807   0.92   (0.49, 1.73)     N vs LN   -0.086   0.268   0.1   0.750   0.92   (0.54, 1.55)     Age at entry 60-69   LR vs LN   0.277   0.642   0.19   0.667   1.32   (0.37, 4.64)     (reference 30-39)   D vs LN   -0.078   0.875   0.01   0.929   0.93   (0.17, 5.14)	Age at entry 50-59						2.28***	
N vs LN-0.0860.2680.10.7500.92(0.54, 1.55)Age at entry 60-69LR vs LN0.2770.6420.190.6671.32(0.37, 4.64)(reference 30-39)D vs LN-0.0780.8750.010.9290.93(0.17, 5.14)	(reference 30-39)						0.92	
Age at entry 60-69LR vs LN0.2770.6420.190.6671.32(0.37, 4.64)(reference 30-39)D vs LN-0.0780.8750.010.9290.93(0.17, 5.14)	(							
(reference 30-39) D vs LN -0.078 0.875 0.01 0.929 0.93 (0.17, 5.14)	Age at entry $60-69$							
					0.19			(0.37, 4.04) (0.17, 5.14)
IN V5 LIN 0.010 0.00/ 1.01 0.1/9 2.20 (0.09, /.43)	(ICICICICE JU-J9)							
		IN VS LIN	0.010	0.007	1.01	0.179	2.20	(0.09, 7.43)

Response groups:

LN = not in program at one year, did not return during observation period

LR = not in program at one year, returned during observation period

D = in program at one year, at least one interruption longer than 30 days during first year

N = in program at one year, no interruptions longer than 30 days during first year p < 0.05 \*\* p < 0.01 \*\*\* p < 0.001

mean and median ages of the group remaining in undisrupted treatment for one year are both higher than those in the group who left treatment and did not return, while the left-and-returned group is youngest. With the exception of a small number of categories, the four response groups appear to have quite different patterns of dosing.

A significant trend (p<0.0001) toward younger average client age and lower average daily dose from 1996 to 1999 appears in analysis of year-of-entry cohorts (not shown).

Table II describes the characteristics of the client sub-group (n = 2,437) used for Model 2. By definition, members of response group D are excluded. Though the comparison with those not in the subgroup is not shown, sub-group members tend to be older (67% vs 61% over age 30 at entry, p<0.0001) and are more likely to

be male (67% vs 64%, p<0.04). There are also fewer clients receiving an average daily dose of 120 mg/day or more than in those not included (14% vs 7%, p<0.0001).

The results of the logistic regression appear in Table III. The reference group for the response analysis is LN, those who had left the program at one year and did not return. The impact of year of entry is in relation to 1996, and of average daily dose is in relation to 60-79 mg/day, the

## TABLE IV

Cox Model of One-Year Retention, Program Clients Receiving Daily or Short-carry Doses Only (N = 2,487)

Variable	Parameter Estimate	SE	Hazard Ratio	95% CI for Hazard Ratio
Age at entry 10-19	0.029	0.147	1.03	(0.77, 1.37)
Age at entry 20-29	0.192	0.068	1.21**	(1.06, 1.38)
Age at entry 40-49	-0.273	0.078	0.76**	(0.65, 0.89)
Age at entry 50-59	-0.765	0.182	0.47***	(0.33, 0.66)
Age at entry 60-69	0.213	0.412	1.24	(0.55, 2.77)
Sex $(0 = male)$	-0.106	0.061	0.89	(0.80, 1.01)
Year of entry 1997	0.057	0.086	1.06	(0.89, 1.25)
Year of entry 1998	-0.026	0.084	0.98	(0.83, 1.15)
Year of entry 1999	-0.049	0.082	0.95	(0.81, 1.12)
Average daily dose < 40 mg	0.939	0.095	2.56***	(2.12, 3.08)
Average daily dose 40-59 mg	0.563	0.076	1.76***	(1.51, 2.04)
Average daily dose 80-99 mg	-0.323	0.090	0.72***	(0.61, 0.86)
Average daily dose 100-119 m	ng -0.412	0.130	0.66**	(0.51, 0.85)
Average daily dose 120-139 m		0.181	0.84	(0.59, 1.20)
Average daily dose 140-159 m		0.265	1.03	(0.61, 1.72)
Average daily dose 160-199 m	ng 0.297	0.257	1.35	(0.81, 2.23)
Average daily dose 200-299 m	ng 1.092	0.267	2.98***	(1.77, 5.03)
Average dailý dose 300-400 m	ng 3.748	0.347	42.01***	(21.31, 83.16)
Reference categories:	* p < 0	.05		
Age at entry = 30-39	** p < 0	0.01		
Year of entry = 1996	***' p <	0.001		
Average daily dose 60-79 mg				

average range. Age at entry refers to the 30-39 age group, which contains the largest number of individuals.

Client gender appears to have no notable effect. Year of entry has a marginal impact until 1999, when it appears to improve retention. Average daily dose appears predictive of return to the program, but not of continuous treatment, up to 120 mg/day, though confidence intervals are wide and the results should be interpreted cautiously. Older age at entry is associated with greater likelihood of return to the program, and younger age with interrupted treatment.

The results of the Cox model are found in Table IV. Increased age is associated with improved one-year retention, as are average doses up to 120 mg/day. Year of entry is no longer statistically significant.

Figure 1 shows one-year retention in the program from Model 2, stratified by average daily dose categories.

#### DISCUSSION

Retention rates in the BC Methadone Program are favourable and consistent with rates reported for other programs.<sup>13</sup> While we cannot determine causality in an observational study, our models show consistent associations between one-year retention and our limited set of factors. Any misclassification in Model 1 does not appear to be influencing these results.

As in other studies, older clients remain in the BC program longer (other than the very oldest cohort, which is very small). This study suggests that younger clients may also have a more disrupted course of treatment.

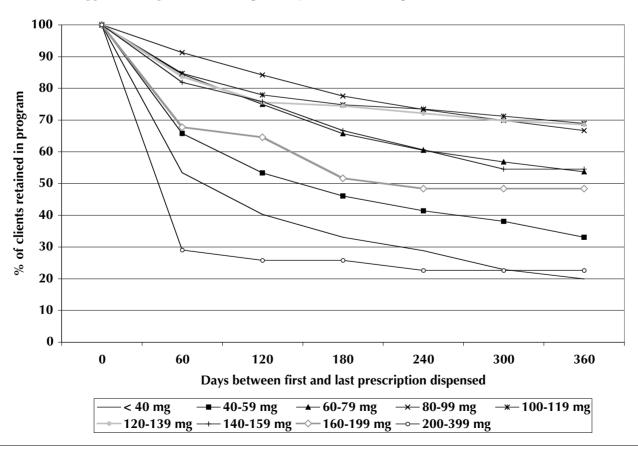


Figure 1. One-year retention in MMT program clients receiving daily or short-carry doses only by average daily methadone dose

Average daily dose is both a predictor of retention and potentially modifiable. The minimum dose recommended by expert consensus is 60 mg per day.<sup>5</sup> It is possible that the clients in our study receiving low doses (32% of participants) could be helped to remain in treatment longer if their daily doses were increased. Our data suggest that increasing doses to the provincial average range would have the strongest impact, and doses up to 120 mg/day would also be helpful. The margin of uncertainty in both models, however, suggests that this effect may be confounded by variables we were unable to measure, such as illicit drug use and clustering by physician.

Unlike a previous study of a smaller Australian methadone program's expansion,<sup>11</sup> retention rates in the BC Methadone Maintenance Program were largely unaffected through a period of rapid expansion. Later year-of-entry cohorts were no more likely to leave the program before one year, but Model 1 suggests the course of treatment may have changed in more recent years.

Study limitations are mostly related to restrictions imposed by the administrative databases from which our data are drawn. Data fields are limited to basic demographic information, drug dose, duration and frequency of dispensing. Other variables of interest, such as high- versus low-threshold methadone maintenance, concomitant use of illicit drugs, and use of additional psychosocial and primary care services, are not fully recorded. We are also unable to identify why clients had interruptions or left the program, or to adjust for the effects of patient clustering by clinic or physician.

The structure of the BC program also imposes an inherent limitation independent of the data sources. In order to account for the availability of extended 'carries', participants are considered to have left treatment only when they have had no methadone dispensed to them for 31 days or more. Some individuals identified as receiving a prolonged 'carry' may actually have left treatment for a short time and then returned, so the size of the disrupted-treatment group may be underestimated.

Our study suggests that many clients who leave before one year of methadone maintenance return to treatment, and that those who received a daily dose of methadone in the higher therapeutic range are more likely to return. These findings emphasize the importance of 'keeping the door open' for program dropouts to return to treatment, as well as that of adequate dosing – not only to enhance initial retention, but also to improve return-totreatment rates.

## REFERENCES

- 1. Lehman F, Lauzon P, Amsel R. Methadone maintenance: Predictors of outcome in a Canadian milieu. J Subst Abuse Treat 1993;10(1):85-89.
- Fischer B, Gliksman L, Rehm J, Daniel N, Medved W. Comparing opiate users in methadone treatment with untreated opiate users: Results of a follow-up study with a Toronto opiate user cohort. *Can J Public Health* 1999;90(5):299-303.
- 3. Brands B, Blake J, Marsh D. Changing patient characteristics with increased methadone availability. *Drug Alcohol Depend* 2002;66:11-20.
- The Council of the College of Physicians and Surgeons of British Columbia. 2001 Annual Report. Vancouver, 2001.

- 5. National Consensus Development Panel. Effective medical treatment of opiate addiction. *JAMA* 1998;280(22):1936-43.
- 6. Ward J, Mattick RP, Hall W (Eds.). Methadone Maintenance Treatment and Other Opioid Replacement Therapies. Amsterdam: Harwood Academic, 1998.
- Rhoades HM, Creson D, Elk R, Schmitz J, Grabowski J. Retention, HIV risk, and illicit drug use during treatment: Methadone dose and visit frequency. *Am J Public Health* 1998;88(1):34-39.
- Magura S, Nwakeze PC, Demsky SY. Pre- and in-treatment predictors of retention in methadone treatment using survival analysis. *Addiction* 1998;93(1):51-60.
- 9. Gaughwin M, Solomon P, Ali R. Correlates of retention on the South Australian Methadone Program 1981-91. *Austr N Z J Public Health* 1998;22(7):771-76.
- Thiede H, Hagan H, Murrill CS. Methadone treatment and HIV and Hepatitis B and C risk reduction among injectors in the Seattle area. *J Urban Health* 2000;77(3):331-45.
- Bammer G, Battison L, Ward J, Wilson S. The impact on retention of expansion of an Australian public methadone program. *Drug Alcohol Depend* 2000;58:173-80.
- Freedom of Information and Protection of Privacy Act (RSBC 1996, Chapter 165). Victoria: Queen's Printer, 2003.
- Farre M, Mas A, Torrens M, Moreno V, Cami J. Retention rate and illicit opioid use during methadone maintenance interventions: A metaanalysis. *Drug Alcohol Depend* 2002;65:283-90.

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## RÉSUMÉ

**Contexte :** Le traitement à la méthadone des héroïnomanes est disponible depuis 40 ans, mais on a relativement peu étudié l'efficacité des programmes canadiens. Notre étude décrit la persévérance sur un an des cohortes de clients qui se sont inscrits au programme de méthadone de la Colombie-Britannique durant sa phase de développement, entre 1996 et 1999. Nous avons aussi examiné quelques-uns des facteurs ayant une influence connue sur la persévérance.

**Méthode :** Toutes les ordonnances de méthadone délivrées aux personnes inscrites au programme entre 1996 et 1999 ont été extraites des dossiers du Triplicate Prescription Program de la C.-B. L'état de persévérance et ses covariables ont été évalués un an après l'inscription à l'aide d'une analyse de régression logistique. Les effets des erreurs de classement de l'état de persévérance sur la durée de participation au programme ont été évalués à l'aide du modèle Cox pour les clients bénéficiant d'une dose quotidienne continue ou de doses de dépannage.

**Résultats :** Cinquante-deux p. cent des personnes inscrites au programme recevaient encore de la méthadone un an après leur inscription; 24 % avaient quitté le programme avant un an, mais y étaient revenues par la suite. L'âge lors de l'inscription et la dose quotidienne moyenne de méthadone étaient d'importants prédicteurs de la persévérance. L'analyse de régression logistique a indiqué que seule la cohorte inscrite en 1999 semblait plus susceptible d'abandonner le traitement en moins d'une année sans le reprendre par la suite. Une analyse plus poussée a montré que cet effet pouvait résulter d'une erreur de classement, car l'année d'inscription n'est pas un prédicteur significatif de la durée d'inscription au programme pour les personnes qui ne reçoivent que des doses quotidiennes ou de dépannage.

**Interprétation :** Les taux de persévérance du programme de méthadone de la C.-B. sont favorables et conformes aux taux publiés. Le développement du programme n'a pas réduit la persévérance, compte tenu de l'âge des clients et des doses administrées. Une dose quotidienne suffisante semble être un élément crucial, à la fois pour la persévérance initiale et pour la reprise du traitement.