

# Patterns of drug use by participants in the Western Australian methadone program, 1984–1991

Greg Swensen, Kenneth F Ilett, Leon J Dusci, L Peter Hackett, Robert T T Ong, Allan J Quigley, Simon Lenton, Richard Saker and Jane Caporn

**Objectives:** To establish the extent to which participants in the WA methadone treatment program used opiates, cannabinoids, benzodiazepines, cocaine and amphetamines, and to define the pattern of such use over time. In addition, the relationships between methadone daily dose and the use of the various drug groups was examined.

**Design:** A retrospective analysis of data from 1678 samples from urinalysis screening over 13 separate surveys between 1984 and 1991. A mean of 35.9% of patients in the program was sampled on each occasion with each patient contributing only one sample in any one survey. Analytical techniques used included enzyme-multiplied immunoassay, thin-layer chromatography and gas chromatography–mass spectrometry.

**Results:** Methadone and/or its major metabolite were detected in most urine samples, indicating satisfactory compliance by patients. The detection of opiates increased from a mean of 27.1% of samples in 1984–1989 to a mean of 44.2% of samples in 1990–1991. Codeine or morphine were most frequently detected (94% of all opiate-positive samples) and were found together in 38.2% of opiate-positive samples. Detection of cannabinoids also increased from a mean of 45.2% of all samples during 1984–1987 to a mean of 56.4% of samples during 1990–1991. Benzodiazepines were found in a mean of 26.7% of samples but use was not time-related.

Detection of amphetamine-class drugs doubled from a mean of 8.3% of all samples (mid 1989 to mid 1990) to 16.8% of samples (mid 1990 to mid 1991). The major representatives of the latter group were methylamphetamine (47.3% of amphetamine-positive urines), amphetamine (15.7%) and ephedrine/pseudoephedrine (44.6%). Opiate use was significantly lower ( $P < 0.05$ ) in those patients taking more than 80 mg methadone/day. In addition, benzodiazepine use increased significantly ( $P < 0.05$ ) with increasing methadone daily dose. There was no relationship between methadone daily dose and use of cannabinoids or amphetamines.

**Conclusions:** The increase in the use of opiates, cannabinoids and amphetamines over the period 1984–1991 occurred about four years after the adoption of a harm minimisation treatment philosophy by the WA methadone program. The high prevalence of codeine and morphine in opiate-positive urine samples strongly suggested the use of "home-bake" heroin. In addition, the data showed that methylamphetamine and ephedrine/pseudoephedrine were the most frequently used psychostimulants. Suppression of opiate use in those clients receiving more than 80 mg methadone/day was consistent with earlier studies. However, the significant increase in use of benzodiazepines with increasing methadone daily dose requires further study.

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Methadone has been used as a treatment for heroin addiction in Western Australia since late 1973, and since mid 1978 the WA Alcohol and Drug Authority has been the only authorised provider of methadone in this State. Before the implementation of the National Campaign Against Drug Abuse, the WA methadone program emphasised abstinence as the major object of treatment, but since mid 1985 it has supported a policy consistent with the precepts of harm reduction.<sup>1-3</sup> Before a harm reduction policy was adopted, regular urinalysis testing was justified as a means of detecting methadone dose diversion and illicit drug use in the individual client. Although urinalysis testing has limitations,<sup>4</sup> is intrusive and a source of friction between program participants and treatment staff, its use has continued in some programs as it is perceived to be an instrument that "prevents" non-prescribed drug use during treatment. We have used urinalysis of a representative population sample to identify trends in drug use by the WA methadone treatment population over the seven-year period from 1984 to 1991.

## Methods

This report describes the results from 13 periodic urine analysis surveys of the WA methadone treatment population between 1984 and 1991. The mean population sample size was 35.9% (range, 22.8%–75.0%). In the first four surveys (1984, 1986 and 1987), clients were accepted on a random basis as they presented at the clinic (during five to seven consecutive working weekdays) for their daily methadone dose, until a quota was satisfied. In the nine surveys from 1988 to 1991, a stratified random sample of clients (over a weekend) was selected from the methadone treatment population at the time of the survey. Stratification consisted of randomly selecting a quota for each of five strata, based on the length of stay in treatment (0–2.9, 3–5.9, 6–11.9, 12–35.9, and 36 months and over). Urine collections were supervised and each client contributed only one urine sample in any one survey. Thus, in this study, the unit of analysis is a urine sample.

Enzyme-multiplied immunoassay (EMIT, Syva Company, Palo Alto, Calif.) was used to test urine samples for amphetamines, barbiturates, benzodiazepines, and opiates and/or their metabolites on a Cobas Mira analyser. Urine samples found to be

WA Drug Data Collection Unit, Health Services Statistics and Epidemiology Branch

Health Department of WA, 189 Royal Street, East Perth, WA 6004.

Greg Swensen, BAppSc (SocWk), MA (Public Policy), Coordinator.

Combined Unit in Clinical Pharmacology and Toxicology

State Health Laboratory Services/University of WA, Nedlands, WA 6009.

Kenneth F Ilett BPharm PhD, Associate Professor in Pharmacology.

Leon J Dusci Assoc Chem, Chemist and Research Officer

L Peter Hackett LRSC Chemist and Research Officer

Robert T T Ong BSc Chemist and Research Officer.

WA Alcohol and Drug Authority, 7 Field Street, Mt Lawley, WA 6050.

Allan J Quigley, MB BS, Director Clinical Services.

WA Alcohol and Drug Authority, 354 William Street, Northbridge, WA 6004.

Simon Lenton, B Psych, M Psych (Clin) Manager, Non-Residential Services.

Richard Saker, MB BS, Senior Medical Officer, Non-Residential Services.

Jane Caporn, Registered Enrolled Nurse

No reprints will be available: Correspondence: Mr G Swensen.

positive for opiates by the EMIT polyclonal method were subjected to thin-layer chromatography (TLC) for detection of methadone, 2-ethylidene-1,5-dimethyl 1-3,3' diphenylpyrrolidine (EDDP, the major metabolite of methadone), and codeine and morphine. Urine samples which had tested positive for amphetamines by the EMIT polyclonal method were tested by gas chromatography-mass spectrometry (GC-MS) to identify amphetamine, methylamphetamine, methylenedioxymethylamphetamine, ephedrine/pseudoephedrine and related compounds.

Data relating the proportion of urine samples positive for methadone, EDDP, opiates, cannabinoids, benzodiazepines or amphetamines and the daily methadone dose were subjected to two-way analysis of variance. Differences between group means were examined using Fisher's least significant difference test at the  $P < 0.05$  level.

## Results

The size of the WA methadone program increased by more than 2.5 times (200 to 514 individuals) in the period from 1984 to 1991. In all surveys men outnumbered women (overall mean 1.39:1). During the period of the surveys, the mean age of participants increased from 29.6 years to 32.6 years and the mean duration of treatment increased from 17.1 to 24 months. Between 1984 and 1988, the mean daily methadone dose declined from 52.6 to 40.2 mg. From 1989 onwards, dose rates were higher with a mean of 52.3 mg/day.

Results for the detection of methadone, EDDP, opiates, cannabinoids, benzodiazepines and amphetamines in urine are shown in the Table. From 1984 to 1991 the percentage of participants whose urine samples tested positive for methadone generally decreased, from 87.0% to 53.5%, while the frequency of detection for EDDP was consistently in the range 74.1%–100%. Opiate-positive results were generally in the range 25%–30% up to 1989 and increased to 40%–50% in 1990–1991. In the last seven surveys conducted, opiate-positive urine samples (EMIT) were analysed for the presence of morphine and/or codeine. The data

show that codeine (alone) or morphine (alone) was detected in 6.5% and 38.2% of urine samples respectively, while codeine and morphine (together) were present in 49.2% of samples. Morphine and codeine accounted for 94% of opiate-positive results.

Over the period 1984 to 1991, cannabinoids were detected in 33%–60% of the treatment population. With the exception of the June 1984 survey, the percentage of cannabinoid-positive urine samples increased from around 30%–40% in 1985–1987 to 50%–60% in 1989–1991. Benzodiazepines were detected in a mean of 26.8% (range 18%–35%) of urine samples, but there was no consistent time-related pattern in these data.

Testing for amphetamines began in 1989. A mean of 16.8% of urine samples tested positive for amphetamine-class drugs in the four surveys between June 1990 and June 1991, compared with 8.3% positive samples in the four surveys between March 1989 and April 1990. Methylenedioxymethylamphetamine (MDMA) was detected only in the June 1990 survey while methylamphetamine (mean, 47.3%) and its metabolite amphetamine (mean, 15.7%) were found (usually together) in most surveys. Amphetamine alone was found in only three surveys (mean, 9%). Ephedrine/pseudoephedrine was found in all surveys (mean, 44.6%).

For the eight surveys between 1989 and 1991, it was possible to categorise the percentages of urine samples positive for opiates, methadone, EDDP, amphetamines, cannabinoids and benzodiazepines according to the daily methadone dose (0–20, 21–40, 41–60, 61–80 and >80 mg; Figure) received by the clients.

The presence of both methadone and EDDP increased with increasing methadone dose. For methadone, the mean percentage of positive specimens in the 41–60 mg and 61–80 mg dose groups were similar, while the percentage of positive specimens in both

these groups was significantly different ( $P < 0.05$ ) from the percentages in the other dose groups. For EDDP, the percentage of positive specimens in the 0–20 mg dose group was significantly lower ( $P < 0.05$ ) than for all other dose groups. The mean percentage of opiate-positive samples varied significantly ( $P < 0.05$ ) between surveys (24.8%–50.0%), and between methadone dose groups (26.1%–44.9%).

The percentage of opiate-positive specimens in the >80 mg dose group was significantly ( $P < 0.05$ ) lower than in all other dose groups. Cannabinoid-positive samples varied from 45.9% to 59.8% (mean data) between surveys, and from 45.4% to 58.3% between dose groups, but these differences were not significant. The mean percentage of benzodiazepine-positive specimens varied from 20.2% to 34.4% between surveys (not significant), and from 16.8% to 44.3% between dose groups ( $P < 0.05$ ). In the >80 mg dose group, the mean percentage of specimens positive for benzodiazepine was significantly greater ( $P < 0.05$ ) than in all other dose groups, while mean data for the 0–20 mg and 21–40 mg dose groups were significantly lower ( $P < 0.05$ ) than for the 61–80 mg group. The percentage of amphetamine-positive specimens varied from 5.6% to 19.9% (mean data) between surveys ( $P < 0.05$ ), and from 10.3% to 14.8% between dose groups (not significant).

## Discussion

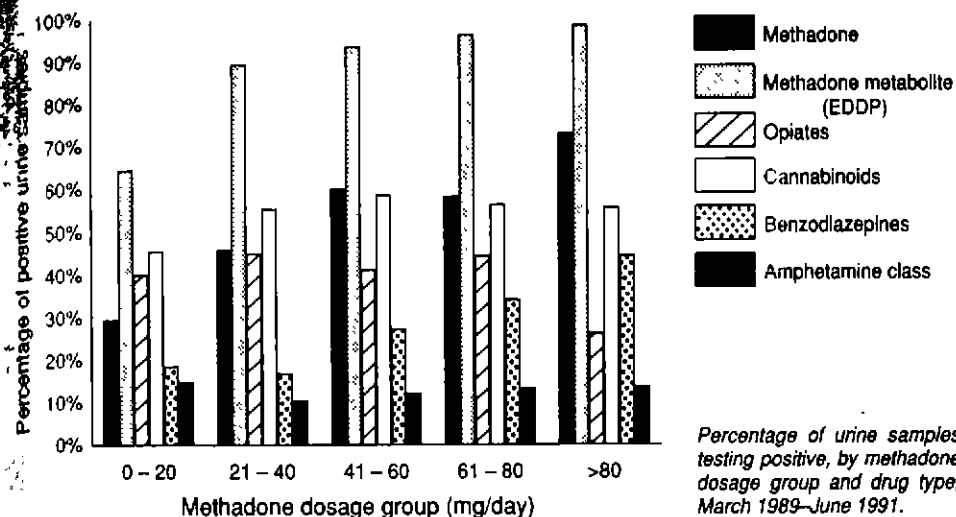
In this study, the unit of analysis was a urine sample, with a selection of individual patients providing one sample per survey. The frequency of drug appearance was expressed as the percentage of urine samples testing positive for that drug. The distribution of positive results between individuals was not considered separately.

There was some variability in the sampling procedures used in our study. Random sampling was used in the first four surveys (pre-1988), while a stratified random sampling was used in the nine post-1987 surveys. In addition, the percentage of the population studied in the 13 surveys varied from 22.8% to 75.0% (mean  $\pm$  standard error of mean [SEM], 35.9%  $\pm$  3.9%). Although these factors suggest that our data should be interpreted with caution, it should be noted that the major analysis of changes in the pattern of drug use has been restricted to the eight surveys that occurred between 1989 and 1991, when the sampling procedure was the same and the percentage of the population samples was relatively constant (30.6%  $\pm$  2.2%).

Table 1: Percentage of urine sample testing positive for higher frequency drugs

Survey	Methadone	EDDP*	Opiates	Cannabinoids	Benzodiazepines	Amphetamine class
June 1984	87.0%	97.0%	23.0%	60.0%	35.0%	—
June 1986	76.0%	85.0%	24.0%	33.0%	20.0%	—
February 1987	88.0%	100.0%	32.0%	36.0%	18.0%	—
November 1987	77.0%	97.0%	28.0%	41.0%	21.0%	—
April 1988	75.0%	92.0%	29.0%	48.0%	30.0%	8.6%
March 1989	73.4%	90.1%	25.7%	47.0%	18.5%	11.7%
November 1989	46.9%	90.3%	28.3%	51.7%	26.2%	6.0%
February 1990	57.6%	86.9%	36.4%	50.3%	33.8%	6.8%
April 1990	65.5%	94.5%	39.6%	60.5%	22.6%	14.7%
June 1990	44.1%	83.3%	49.0%	59.8%	26.5%	21.7%
November 1990	43.4%	75.5%	50.0%	46.2%	33.0%	14.0%
March 1991	40.6%	84.6%	42.0%	61.5%	32.9%	14.0%
June 1991	53.5%	89.9%	48.0%	60.1%	31.1%	16.9%

\*The major metabolite of methadone.



Percentage of urine samples testing positive, by methadone dosage group and drug type, March 1989-June 1991.

TLC screening confirmed that patients were compliant, with 74.1% to 100% showing positive results for the presence of EDDP, the major metabolite of methadone. On the other hand, the presence of methadone itself in urine decreased by about 40% between 1984 and 1991. The reason for this decrease could not be identified specifically, but induction of hepatic drug metabolism by one of the other drugs taken concomitantly seems likely. We speculate that cannabis use may be causative, firstly because its use showed a general increase of some 30% over the study period and secondly because chronic smoking of cannabis is known to increase the systemic clearance of drugs such as theophylline and antipyrine,<sup>5,6</sup> most probably by way of induction of hepatic cytochrome P-450.<sup>7</sup>

The use of opiates showed a marked increase of some 20% over the study period. It is possible that this was partly due to the harm reduction policy introduced in 1985 which, compared with the previous policy, most favoured the admission of injecting drug users regarded as the least likely to maintain a low risk (e.g., non-injecting drug use) lifestyle without methadone treatment. There is some indirect support for this proposition as the size of the total annual treatment population increased by 83.5%, from 387 patients in 1984 to 710 patients in 1990, with much of the growth in the numbers treated being due to increases in the number of readmitted patients.<sup>8</sup> Nevertheless, the harm minimisation policy by itself seems unlikely to have had a significant influence since the increased frequency of opiate-positive results did not occur until 1990. The increased frequency of opiate-positive results could also have been influenced by an increase in the availability of illicit heroin, although we have no evidence to support or deny this hypothesis.

A detailed analysis of opiate-positive urine

samples showed that 38.2% contained morphine alone, while 6.5% contained codeine alone. By contrast, 49.2% of samples tested positive for both morphine and codeine, suggesting the use of codeine-containing preparations and/or "home bake" heroin synthesised from codeine.<sup>9</sup> Endogenous metabolic formation of morphine from codeine by hepatic cytochrome P-450 2D6 in "extensive metaboliser" individuals is now well recognised,<sup>10</sup> and the 6.5% of patients with opiate-positive samples who had only codeine in their urine samples are most likely "poor metaboliser" individuals who lack this isozyme of cytochrome P-450. In recent years, the use of both prescription and non-prescription compound analgesics containing codeine has been common.<sup>11</sup> Purchase of codeine-containing compound analgesics for "home bake" heroin synthesis has been so prevalent that pharmacists in WA have restricted product sales. Thus, it seems that much of the increase in opiate-positive urine samples is due to the use of "home bake" heroin.

Amphetamine use approximately doubled between 1989 and 1991. Detailed analysis showed that methylamphetamine and ephedrine/pseudoephedrine were most prevalent. The low frequency of detection of amphetamine alone in urine samples indicates that most of the amphetamine detected was derived metabolically from methylamphetamine. The assay used in these studies did not permit differentiation of the optical isomers ephedrine and pseudoephedrine.

While benzodiazepine use was common (26.8% of all samples), there was no time-related pattern. Our testing did not enable identification of the individual substances used, but direct patient enquiry revealed that the most common drugs were oxazepam, diazepam and flunitrazepam, obtained from a general practitioner. The reasons for the high

level of anxiolytic use are not clear. However, their intoxicating effect with resultant dose escalation and the development of tolerance has been well documented.<sup>12</sup>

As would be expected, the percentage of samples positive for methadone and EDDP increased significantly with increasing methadone dose. Failure to detect methadone and/or EDDP, particularly in those patients receiving a daily dose of 20 mg or less could be due to the sensitivity of our TLC detection method, but is most likely a product of the range of half-lives for the drug (15-55 h)<sup>13</sup> and/or time between last dose and collection of the urine sample.

For opiate-positive urine samples, the most interesting finding was that the percentage of positive samples was significantly lower among those patients receiving more than 80 mg methadone/day. In this regard, our findings are consistent with the proposition that higher methadone doses will suppress opiate use,<sup>14</sup> and with the finding that maintenance of an adequate plasma concentration of methadone is necessary for optimal treatment response.<sup>15-17</sup> However, it is not possible to infer causality from our data. The strong positive correlation between the percentage of urine samples positive for benzodiazepines and the daily dose of methadone was unexpected. However, it is known that participants of methadone programs who use benzodiazepines have higher levels of anxiety,<sup>12</sup> and recent studies have found an association between benzodiazepine use and increased HIV risk behaviour.<sup>18,19</sup> It may be that clients taking high doses of methadone who are unresponsive to further intoxication from illicit opioid use, use benzodiazepines to gain intoxication through a different receptor mechanism. Further studies are needed in this area.

We speculate that regular urinalysis surveys in methadone programs may identify subgroups with specific patterns of high-risk drug use. This information could assist in targeting harm reduction measures such as counselling and education. Specific studies are needed to address this question.

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## Placebo-controlled trial of enteric coated aspirin in coronary bypass graft patients

### Effect on graft patency

Bernard E F Hockings, Mark A Ireland, Kim F Gotch-Martin and Roger R Taylor

**Objective:** To determine whether slow-release enteric coated aspirin (100 mg daily), commenced before operation, improves the patency of saphenous vein (SV) coronary artery bypass grafts at six months.

**Design and setting:** Double-blind, randomised, placebo-controlled study at a teaching hospital.

**Results:** One hundred and forty patients were randomly allocated to receive enteric coated aspirin or matching placebo. Similar groups of 50 (aspirin) and 52 (placebo) subjects completed the six months follow-up and had an angiogram to assess patency. Five patients treated with aspirin and nine who received placebo had at least one occluded SV graft; the distal ends of 6 of 128 SV grafts in aspirin-treated patients (4.7%) and 13 of 145 SV grafts in patients in the placebo group (9.0%) were occluded — the difference was not significant. An arterial graft was occluded in one other patient in each group (3% of arterial grafts). There was more postoperative blood loss, on average, in patients treated with aspirin, but the difference was not significant. Only one patient was withdrawn from long-term therapy because of possible gastrointestinal symptoms; most with-

drawals from the trial were necessitated by commencement of aspirin or non-steroidal anti-inflammatory therapy for musculoskeletal disorders.

**Conclusions:** The coronary bypass graft occlusion rate six months after surgery was low, and was lower on average in aspirin treated subjects but not significantly so. Long-term treatment with low-dose aspirin is recommended unless contraindicated.

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Saphenous vein (SV) coronary artery bypass grafts frequently become occluded within the first few weeks of placement. The occlusions are mainly thrombotic and related in part to endothelial denudation, surgical trauma and mechanical factors. Subsequently, intimal proliferation and later atherosclerotic changes appear, so that there is a progressive decrease in graft patency with time. By six months to a year 15%–30% of SV grafts are occluded and by 10 years half or more are occluded.

There is now good evidence that taking an aspirin-containing antiplatelet agent can reduce the early and medium term occlusion rate,<sup>1-4</sup> at least for grafts to small arteries

which have high occlusion rates.<sup>5-7</sup> The most suitable regimens have not been defined; the long-term addition of dipyridamole, as in one of the early major positive trials,<sup>6,7</sup> appears unnecessary,<sup>1,3-5,8</sup> although this drug may have a role before operation.

Generally, in the management of vascular disease, low-dose aspirin has become popular because of its adequate and probably relatively selective effect on platelet thromboxane A<sub>2</sub> production,<sup>9</sup> its low incidence of side effects and emerging evidence from clinical trials of its efficacy;<sup>4</sup> however, benefit from low-dose aspirin on SV graft patency has not been established.

At the time of planning our study, the benefits of aspirin (100 mg) on four-month occlusion rates had been reported by Lorenz et al., but in their study only 46 patients had had an angiographic study and the occlusion rate in the placebo group was unacceptably high.<sup>10</sup> The benefits of long-term high-dose aspirin and dipyridamole had also been demonstrated<sup>6,7</sup> but the results of other trials had been negative.<sup>1</sup>

Our placebo-controlled randomised trial of an enteric coated preparation of 100 mg of aspirin (Cartia, prepared with matching placebo by Smith Kline and French Laboratories (Australia) Ltd)<sup>9</sup> on graft patency at six months was commenced in December 1986. After 100 patients had completed follow-up and had an angiogram, the average occlusion rate at six months was lower in the actively treated group, but it was low in both groups and recruitment was suspended.

Department of Cardiology, Royal Perth Hospital, Wellington Street, Perth, WA 6001.

Bernard E F Hockings, MD, FRACP, Consultant Cardiologist.

Mark A Ireland, MB BS, FRACP, Consultant Cardiologist.

Kim F Gotch-Martin, RN, Research Nurse.

Roger R Taylor, MB BS, FRACP, Consultant Cardiologist; and Professor of Cardiology, University of Western Australia.

Reprints: Dr Bernard E F Hockings.