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## Health Care Utilization and Morbidity Associated With Methadone and Buprenorphine Treatment

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### *Summary*

**Background:** Methadone and buprenorphine treatment reduce the high mortality associated with heroin addiction, but even in-treatment, Standardised Mortality Rates are high. **Aim:** This study investigates the nature of morbidity associated with methadone and buprenorphine treatment, and investigates predictors of health care utilization among people in a variety of treatment settings. **Methods:** Collation of data from earlier studies, and from published reports. **Findings:** In a recent study of an entry cohort, the SMR was 5.52 [4.62, 5.65]; suicide and overdose accounted for 2/3 of the mortality, but allowing for this, mortality rates remain elevated. Cancer, heart disease and respiratory disease were the three major contributors to mortality. Taken in conjunction with a recent study of medical co-morbidity, this suggests that alcohol, tobacco and other drug use represent the major factors contributing to serious illness in treated opioid addicts. In addition, side-effects of treatment may themselves contribute to some morbidity. Lack of access to health care does not appear to be a contributing factor, as opioid users consult doctors (other than their methadone doctors) at rates far higher than the general population. Predictors of doctor attendance "outside" doctors were psychological distress, and benzodiazepine use. Adjusting for these factors, we found evidence that quality of methadone treatment was a significant predictor of doctor attendance, with better clinical care being associated with less outside doctor attendance. **Conclusion:** There is a paradox; heroin users have significant physical illness, but their attendance for health care tends to be driven by psychological distress, and can be improved by good care within treatment programs. The priority in addressing health problems of stabilised heroin users is dealing with alcohol and tobacco problems.

*Key Words:* Methadone, buprenorphine, morbidity, mortality

### 1. Introduction

Studies have repeatedly demonstrated high age-adjusted mortality associated with opioid dependence. The major factor contributing to mortality has consistently been overdose, and in some jurisdictions, HIV infection. In addition, a further significant contributor to mortality has been suicide [10, 14]. In some jurisdictions, mortality is significantly influenced by spread of HIV among injecting drug users, with very high mortality reported from some jurisdictions [6]. A meta-analysis of studies published prior to the late 1990s found that

the standardized mortality rate ratio was elevated 13.2 times in HIV negative heroin users [12].

The appropriate public health response has been to promote participation in treatment, which reduces the risk of overdose [12] and reduces the risk of HIV transmission. In addition, treatment allows attention to co-morbidity, and may help reduce the risk of suicide, through provision of counselling, support, and prescribing of psychotropic medication, which may potentially reduce the burden of self-harm in this population.

A key question for this paper is how to optimise the effectiveness of treatment in reducing risk and mortal-

ity. Although there is ample evidence that while people remain in treatment in the Opioid Treatment Program, their risk of death is diminished, there is evidence that many people cycle in and out of treatment [4], and the post-treatment period is one of increased risk of death [8]. In addition, during treatment many people drink excessively, smoke cannabis, and misuse other drugs. These behaviours probably contribute to long-term morbidity, and alcohol dependence to the risk of overdose and suicide.

The current study investigates evidence of the morbidity and health risks associated with heroin use, and at the optimal role of medical practitioners in reducing the burden of disease, and the burden of health care costs. It also focuses on the question of whether there is differential effectiveness between methadone and buprenorphine in reducing health care costs and burden of disease.

## 2. Morbidity associated with heroin addiction

This population has a substantial burden of coexisting disease. In a recent study on mortality associated with methadone and buprenorphine treatment, we identified that the age mortality rate for the cohort was 5.52 times higher (95%CI [4.62-6.55]) than the age standardised mortality rate for the Australian community. The major causes of death in the cohort were overdose and suicide, but the SMR was higher than could be accounted for by the excess of deaths due to overdose and suicide.

Overdose	44	Suicide	20		
Cancer	8	IHD	5		
MVA	5	Other accident	2	Shot	2
HIV	1	Liver failure	1	DVT	1
Found dead	4	other	2		

## 3. Burden of medical disease

We have recently conducted a study on mortality in a cohort of people entering OTP, and found an elevated mortality rate. In particular, overdose and deliberate self-harm (suicide) accounted for 2/3 of the deaths. However, even allowing for these factors, there remained an excess mortality, adjusted for age. The causes of mortality are shown in Table 1.

In summary, in this entry cohort liver disease was a rare cause of death, as was HIV. Overwhelmingly, overdose and suicide were the leading cause of mortality within 5 years of entry to treatment, accounting for 2/3 of deaths.

Despite this, the existence of deaths due to cancer and ischaemic heart disease seems high in a population

		Buprenorphine (n=3513)	Methadone (n=2646)	Total (n=6159)
Sex	F	1056	912	1968
	M	2457	1734	4191
Age at entry	10-14	3	1	4
	15-19	289	191	480
	20-24	1058	649	1707
	25-29	860	622	1482
	30-34	562	498	1060
	35-39	324	299	623
	40-44	209	219	428
	45-49	119	105	224
	50-54	61	46	107
	55-59	19	12	31
	60-64	5	3	8
65-69	4	0	4	
70-74	0	1	1	
Mean age		29.1	30.2*	29.6

\*t=-4.8991, p<0.001

this age. The age distribution of the cohort is shown in Table 2. Buprenorphine patients were on average 13 months younger, a statistically significant difference, but one of little importance in considering mortality.

Further data on medical morbidity was presented by Darke [9], in an investigation of 841 cases of fatal opioid overdose. This study documented incidental autopsy findings, and presented data on coexisting disease. In the group, as in most Australian samples of injecting drug users, HIV was positive in a low proportion (3.2%). Cardiac disease was noted at autopsy in several patients. LV hypertrophy was present in 5.9%, and severe coronary artery disease in 5.7%. Lung disease was identified at autopsy in 13.2% of cases, and liver pathology in somewhat more. The findings are shown in Tables 3 and 4.

The findings indicate a steep increase with age in

	15-24	25-34	35-44	>44
Bronchopneumonia	15.9	16.4	8.6	9.9
Bronchitis	4.9	2.6	3.7	2.7
Fibrosis	3.5	4.6	8.4	17.3
Emphysema	1.4	1.1	3.7	13.3

	15-24	25-34	35-44	>44
HCV +	56	63	87	75
Steatosis	18.2	32.6	49.5	52.0
Fibrosis	7.7	9.1	13.6	12.0
Cirrhosis	2.1	4.3	9.2	25.3

the percentages with serious pathology - pulmonary fibrosis, emphysema, and cirrhosis. While chronic HCV infection is undoubtedly a contributor to hepatic fibrosis and cirrhosis, the very high prevalence of fatty liver is probably largely attributable to alcohol, and presumably in this group cirrhosis is most commonly the result of combined HCV and alcoholic liver disease. Similarly, the rising incidence of lung disease with age is presumably a result of smoking.

Further evidence that the most effective response to the morbidity associated with injecting drug use lies in optimising treatment of drug dependence comes from a recent report on mortality in people diagnosed with HCV and HBV infections [1]. The commonest cause of death was drug overdose.

#### 4. Summary - medical comorbidity and heroin use

These two Australian studies confirm that there is a rising rate of medical comorbidity with age, and that much of this comorbidity is related to drug dependence. Smoking (tobacco and cannabis) is presumably the most significant factor contributing to lung disease (and possibly to coronary artery disease), and alcohol is a significant contributor to liver disease.

This is an issue which is likely to become increasingly relevant in jurisdictions with long-established methadone programs, where there is an ageing cohort of people in treatment, among whom medical comorbidity is likely to become more frequent. This is illustrated in a US study of people dying during methadone maintenance. The authors reported a very different pattern of mortality to what was observed in our study of an entry cohort. Older patients, who had been on long-term treatment, tended to die of chronic diseases; 20% of patients who died in treatment died of liver disease, 18% of cardiovascular disease, and only 14% of drug overdose [16].

Among an ageing cohort of people in long term treatment, chronic diseases will become an increasing problem. While there may be a low yield from efforts to prevent the development of such problems by addressing alcohol and tobacco use, efforts to do so should clearly be part of treatment. A greater challenge is reducing the high rates of overdose and suicide, probably by retaining people better in treatment - and, again, by trying to emphasize the risks of alcohol, cigarette, cannabis and stimulant use among patients in treatment.

#### 5. Health Care utilisation

In relation to health care seeking, studies from Australia and USA have reported that opioid-dependent people are very heavy users of health care.

From the USA, a study from a managed care organisation investigated health care utilisation in 740 people identified as being opioid abusers [20]. Opioid abusers, compared with non-abusers, had significantly higher prevalence rates for a number of specific comorbidities, including non-opioid poisoning (78 X more common than among non-abusers), viral hepatitis (36 X), psychiatric illnesses (9 X), and pancreatitis (21 X). Prevalence rates for hospital inpatient visits for opioid abusers were more than 12 times higher compared with non-abusers, and mean annual direct health care costs for opioid abusers were more than 8 times higher than for non-abusers. The average health care costs of opioid abusers were 1.8 times higher than the average health care costs of depressed patients.

This data reinforces the findings from studies of morbidity and mortality - the pattern of health care utilization reflects drug-related and alcohol-related health problems, including drug overdose (either intentional or accidental).

An unpublished Australian study [18] found that patients on methadone were in the top 5% of health care utilization; over a two-year observation period, they saw doctors at a rate (and a cost) 3-3.5 times the state average. While in treatment, they generated an average of 69 Medicare services per annum; while out of treatment, 21.8 services per annum (compared to a state average of 11.7 services per annum).

One Australian study conducted many years ago investigated the relationship between health care utilization and outcomes of treatment [3]. The study interviewed 300 patients attending 3 methadone clinics. It was planned that each patient would be interviewed on 3 occasions over 12 months, and more than 80% of subjects were successfully followed up and completed the interviews.

There were considerable differences in the style of treatment delivered in the three clinics. In clinics 1 and 3, patients had weekly consultations of less than 5 minutes duration, on average, with their prescribing doctor. In clinic 2, patients were seen less often, for longer consultations (average 14 minutes). As part of the research project, an audit of clinic files was conducted, and the quality of documentation in the medical files was rated by a research assistant. This analysis revealed significant differences in documentation, with Clinic 2 files usually recording issues such as use of alcohol and cannabis, health concerns, and mental health issues, while documentation in the remaining clinics was patchy. Table 5 shows the ratings on 3 of the relevant scales against which files were assessed. From each clinic, 20 files were randomly selected, and a score of 0 or 1 given for each file if it documented relevant issues.

The difference between the records in the 3 clinics reflects the differing degrees to which a "treatment" ethos exists. In Clinic 1 (where the prescriber reported spending most of his time on "paperwork"), files were least informative and useful. In the other two clinics,

both prescribers reported spending more of their time in either counselling or medical attention, and the files reflect this more "clinical" orientation.

In general, patients reported high levels of satisfaction with their methadone doctors - although patients rating of their treatment were lowest in Clinic 1. Despite professing satisfaction with treatment, patients also reported a high level of attendance at other doctors; 184 subjects (61%) reported having sought medical care outside their clinics, for a total of 602 consultations, in the month prior to being interviewed. In part, the high level of attendance at outside doctors was due to patients seeking benzodiazepines; 68 subjects reported having seen an outside doctor for the purpose of obtaining a prescription. However, most patients who saw outside doctors were presenting with concerns over health or symptoms.

To estimate the effects of treatment on health care seeking, logistic regression was used, with the dependent variable being whether subjects had seen an "outside" doctor in the month prior to interview. Two significant predictors of seeing outside doctors were benzodiazepine misuse, and psychological distress (as measured by the General Health Questionnaire (GHQ)). Patients who reported having used benzodiazepines were more likely to report having seen an outside doctor (OR 2.2, 95%CI [1.05,2.9],  $p=0.008$ ); for each point on the GHQ score, patients were more likely to have seen a doctor (OR 1.1, 95%CI[1.05,1.13],  $p=0.0001$ ). Treatment delivered in the different methadone clinics also appeared to be a strong predictor; adjusting for benzodiazepine use and distress, relative to Clinic 2, subjects from Clinic 1 were more likely to have seen a doctor (OR 2.4, 95%CI[1.8,3.4],  $p=0.006$ ). Clinic 3 was intermediate, and did not differ significantly from the other two clinics.

Clearly, such correlation observations represent only modest evidence, but it is plausible that in a setting in which people receive less perfunctory treatment, they are less likely to consult other doctors. An important objective of treatment is to contain distress. Less frequent and longer appointments provides the opportunity to listen to the patients, a simple process, but crucial in containing distress. The data cited above suggest that

Table 5: Rating of medical record keeping in three clinics

	1	2	3
SUBTOTAL – Assessment	19	77	76
SUBTOTAL – co-morbidity	22	68	34
SUBTOTAL – periodic review	6	75	24
Total rating	57	220	134

this has the important benefit of reducing minimizing health care utilization.

## 6. Summary - Morbidity and health care seeking

Heroin users in OTP have significant medical and psychiatric co-morbidity, and elevated mortality rates, but at least within Australia, the high mortality rates do not appear to be the result of being unable to access health care. Rather, lifestyle issues - predominantly, misuse of legal, illicit and prescribed drugs, along with erratic participation in treatment, appear to be the major factors contributing to morbidity and mortality.

There is limited evidence that treatment with methadone or buprenorphine can reduce use of non-opioid drugs. The TOPS study [11] did find a fall in non-opioid drug use (except alcohol) in patients remaining in methadone maintenance. However, in John Ball's study of 6 American methadone clinics, he reported that there was no reduction in use of most non-opioid drugs with longer treatment [2].

Rather than being the result of medical problems, much doctor attendance appears to be driven by either drug-seeking, or by psychological distress. There is some evidence that one consequence of prolonged opioid exposure is an increase in somatic focusing [15], and there is some evidence that practitioners in OTP clinics can reduce or contain distress by good clinical care.

## 7. A footnote - are there differences in morbidity associated with methadone and buprenorphine?

Recent research has identified 3 medical problems in which medications used for management of opioid dependence may contribute to morbidity and mortality. Methadone, but not buprenorphine, causes prolongation of the QT interval [19], and this has been associated with case reports of ventricular tachycardia, and some evidence that it contributes to mortality [7]. Sleep studies have revealed central sleep apnea and respiratory dysfunction in up to 30% of people in stable methadone treatment [17]; it is unknown whether this problem also occurs with buprenorphine. Methadone treatment is also associated with hormonal changes (sexual function and hormonal changes in patients exhibiting as menstrual changes in women, and opioid induced androgen deficiency in men; and a risk of osteoporosis) [13]. The effect of buprenorphine upon sexual function and hormone levels is less clear, with one report that there is less hormonal suppression with buprenorphine [5].

At this stage, it is not possible to say whether these reports of differences in adverse effects of medications

have implications for reducing morbidity associated with the Opioid Treatment Program. This is a topic for ongoing research.

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## Contributors

Dr. Bell drafted the paper. Ms Butler performed analysis.

## Conflict of Interest

Dr Bell has received funding support from Reckitt Benckiser, manufacturers of buprenorphine. Ms Butler: none declared.

## References

1. AMIN J., LAW M.G., BARTLETT M., KALDOR J.M., DORE G.J. (2006): Causes of death after diagnosis of hepatitis B or hepatitis C infection: a large community-based linkage study. *Lancet* 368(9539): 938-945.
2. BALL J.C., ROSS A (1991): The Effectiveness of Methadone Maintenance Treatment. Springer-Verlag, New York.
3. BELL J., WARD J., MATTICK R.P., HAYA., CHAN J., HALL W. (1995): An evaluation of private methadone clinics. National Drug Strategy Research Report No 4, Australian Government Publishing Service, Canberra
4. BELL J., BURRELL T., INDIG D., GILMOUR S. (2006): Cycling in and out of treatment; participation in methadone treatment in NSW, 1990-2002 *Drug Alcohol Depend* 81; 55-61.
5. BLIESENER N., ALBRECHT S., SCHWAGER A., WECKBECKER K., LICHTERMANN D., KLINGMULLER D. (2005): Plasma Testosterone and Sexual Function in Men Receiving Buprenorphine Maintenance for Opioid Dependence. *J Clin Endocrinol Metab* 90(1): 203-206.
6. BRUGAL M., DOMINGO-SALVANY A., PUIG R., BARRIO G., GARCÍA DE OLALLA P., DE LA FUENTE L. (2005): Evaluating the impact of methadone maintenance programmes on mortality due to overdose and aids in a cohort of heroin users in Spain. *Addiction* 100; 981-89.
7. CHUGH S.S., SOCOTEANU C., REINIER K., WALTZ J., JUI J., GUNSON K. (2008): A Community-Based Evaluation of Sudden Death Associated with Therapeutic Levels of Methadone, *Am J Med* 121(1): 66-71.
8. CLAUSEN T., ANCHERSEN K., WAAL H. (2008): Mortality prior to, during and after opioid maintenance treatment (OMT); a national, prospective cross-registry study. *Drug Alcohol Depend* 94; 151-57

9. DARKE S., KAYE S., DUFLOU J. (2006): Systemic disease among cases of fatal opioid toxicity. *Addiction*, 101(9), 1299-1305.
10. DARKE S., ROSS J. (2002): Suicide among heroin users: rates, risk factors and methods *Addiction* 97; 1383-1394.
11. FAIRBANK J.A., DUNTEMAN G.H., CONDELLI W.S (1993): Do methadone patients substitute other drugs for heroin? Predicting substance use at 1-year follow-up. *Am J Drug Alcohol Abuse*. 19(4):465-74.
12. HULSE G., ENGLISH D.R., MILNE E., HOLMAN C.D.J. (1999): The quantification of mortality resulting from the regular use of illicit opioids. *Addiction* 94(2); 221-9.
13. KIM T.W., ALFORD D.P., MALABANANA., HOLICK M. F., SAMET J.H. (2006): Low bone density in patients receiving methadone maintenance treatment. *Drug Alcohol Depend*, 85(3), 258-262.
14. MALONEY E., DEGENHARDT L., DARKE S., MATTICK R.P., NELSON E. (2007): Suicidal behaviour and associated risk factors among opioid-dependent individuals: a case-control study. *Addiction* 102; 1933-41.
15. MARTIN W.R., JASINSKI J.R., HAERTZEN C.A, KAY D.C., JONES B.E., MANSKY P.A., CARPENTER. R.W. (1973): Methadone - a reevaluation. *Arch Gen Psychiatry*, 28(2): 286-95.
16. MAXWELL J. C., PULLUM T.W., TANNERT K. (2005): Deaths of clients in methadone treatment in Texas, 1994-2002 *Drug Alcohol Depend* 78; 73-81
17. TEICHTAHL H., WANG D., CUNNINGTON D., KRONBORG I., GOODMAN C., PRODROMITIS A., DRUMMER O. (2004): Cardiorespiratory function in stable methadone maintenance treatment (MMTP) patients. *Addict Biol* 9 (3-4): 247-253.
18. WARD, P (2005): NDARC Technical Report, National Drug and Alcohol research Centre, Sydney.
19. WEDAM E.F., BIGELOW G.E., JOHNSON R.E., NUZZO P.A., HAIGNEY M.C.P. (2007): QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Arch Int Med* 177; 2469-75.
20. WHITE AG., BIRNBAUM H.G., MAREVA M.N., DAHER M., VALLOW S., SCHEIN J., KATZ N. (2005): Direct Costs of Opioid Abuse in an Insured Population in the United States. *J Manag Care Pharm* 11(6) 469-79.

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