ORIGINAL ARTICLE

Comparing Drug-Related Hospital Morbidity Following Heroin Dependence Treatment With Methadone Maintenance or Naltrexone Implantation

Hanh T. T. Ngo, BSc(Hons); Robert J. Tait, PhD; Gary K. Hulse, PhD

Context: Most research on heroin dependence treatments assesses short-term changes in patients' self-reported drug use. To our knowledge, long-term sustainability of changes in patients' drug use and associated hospital morbidity posttreatment have not been studied.

Objectives: To evaluate drug-related hospital morbidity in heroin users at 6 months and 3½ years after receiving naltrexone implant treatment and to compare these results with outcomes from a similar cohort treated with methadone maintenance treatment.

Design: Retrospective longitudinal follow-up, using data prospectively collected via a state hospital (public and private) reporting system.

Setting: Perth, Western Australia. Methadone maintenance dosage was generally dispensed daily by registered community pharmacies. Naltrexone implant treatment was performed as a day procedure at a community clinic.

Participants: A total of 522 and 314 heroin-dependent persons (according to *DSM-IV*), first time treated with methadone maintenance or a naltrexone implant, respectively, between January 1, 2001, and December 30, 2002, were identified, using health record linkage.

Main Outcome Measures: Planned outcomes included crude hospital admission rates, adjusted changes in risks (odds ratio [OR]), and rates (rate ratio) of "overdose-related" and "non–overdose-related" hospital morbidity associated with opioid vs nonopioid drugs 6 months and 3½ years posttreatment.

Results: Following naltrexone implant treatment, opioid-related risk decreased for overdose (OR, 0.23; 95% confidence interval [CI], 0.11-0.48) and nonoverdose (OR, 0.64; 95% CI, 0.46-0.89) conditions at 3½ years. Such reductions were not observed after methadone treatment. Overdose on nonopioid drugs increased in older patients to 6 months: OR of 16.31 (95% CI, 3.07-86.53) for naltrexone and OR of 5.03 (95% CI, 1.18-21.54) for methadone. Nonoverdose (eg, dependence and withdrawal) associated with nonopioid drugs also increased for patients receiving the naltrexone implant: OR of 1.52 (95% CI, 1.04-2.23) at 3½ years. In addition, there were 6 drug-related deaths: 5 after methadone maintenance and 1 after naltrexone implantation.

Conclusions: Naltrexone implants, but not methadone maintenance, has long-term benefits in reducing opioid-related hospital morbidity. However, long-lasting and increased nonopioid drug–related morbidity following naltrexone implantation is particularly concerning. Similar studies are required to confirm these findings.

Arch Gen Psychiatry. 2008;65(4):457-465

Author Affiliations: School of Psychiatry and Clinical Neurosciences, University of Western Australia, Crawley, Western Australia, Australia.

HEROIN DEPENDENCE IMposes a large burden on society in addition to causing the individual user numerous harms.[1,2] Besides psychosocial interventions, several pharmacotherapies are available for heroin dependence. Thus far, methadone maintenance treatment (MMT) has been the most extensively researched and proved effective in terms of treatment retention, reduced heroin use and criminal activities, and improved general health and social outcomes.[2-4] Despite this, research on the sustainability of such changes, especially health related, is still somewhat limited.[5] Also, abuse of multiple drugs (including nonopioids) among patients undergoing MMT may be problematic but has not received adequate attention.[6,7] Further concerns with methadone, an opioid agonist, have been that it enables the co-use of illicit opioids, including heroin,[8,9] and it has potential for abuse through diversion.[9,10]

An alternative approach is provided by the use of the opioid antagonist naltrexone, which emphasizes abstinence. Despite its proved effectiveness in blocking the effect of heroin, oral naltrexone has not

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 04/26/2017

been successful in real-life treatment settings because of patients' noncompliance, leading to premature withdrawal from treatment and return to heroin use.[11] Evidence from case studies[12,13] suggests the possibility of reduced opioid tolerance, causing opioid overdoses (including fatal) and related morbidity following naltrexone treatment. Another concern is that naltrexone-treated heroin users may adopt new (nonopioid) drugs of choice while unable to experience the pleasurable effect of heroin.[14]

In an attempt to overcome the noncompliance issue associated with naltrexone treatment, several sustained-release naltrexone products have been manufactured and evaluated for the treatment of opioid dependence.[15-17] In Australia, naltrexone implants (Go Medical Industries Pty Ltd, Perth, Western Australia)[18] are available to heroin-dependent patients under the Therapeutic Goods Administration's Special Access Scheme. Initial assessment suggests that these naltrexone implants can provide therapeutic naltrexone coverage (blood concentration of at least 2 ng/mL) for approximately 6 months for a standardized 70-kg person,[18] although others report 1 ng/mL at 5 to 6.5 months.[19] In addition, a report[14] on a cohort of 361 heroin users treated for the first time with naltrexone implants between January 17, 2001, and December 4, 2002, showed no incidence of opioid overdose requiring hospitalization in the first 6 months of treatment. A follow-up of the same patient cohort, also via record linkage, for a mean of 1.78 years posttreatment found reduced hospitalizations because of substance- and non–substance-related mental illness following naltrexone implant treatment (NIT).[20]

This research is set out with 3 aims. First, it extends the research of Hulse et al,[14] which reported on opioid overdose outcomes at 6 and 12 months after NIT. The present study evaluates 6-month posttreatment outcomes concerning "overdose-related" (or poisoning) and "non–overdose-related" hospital admissions associated with opioid vs other (nonopioid) drugs in the same cohort of patients receiving NIT. Second, it assesses the sustainability of these morbidity changes by evaluating the previously described outcomes to 3½ years after treatment entry. Third, it assesses these changes in the NIT cohort with reference to those observed in another cohort of heroin users entering MMT for the first time, during the same period of 2001-2002.

METHODS

PARTICIPANTS

All participants met the criteria for opioid dependence.[21]

NIT Cohort

Between January 2001 and December 2002, 437 opioid users were treated for the first time with a naltrexone implant (Go Medical Industries Pty Ltd)[18] at a not-for-profit community-based clinic in Perth, Western Australia (WA). Of these subjects, 361 were eligible. Ineligible cases included non–WA residents (n=53), those who gave no consent (n=5), those with early implant removal (n=3), and those who were incarcerated (n=15).[14] One of the ineligible (incarcerated) cases was also a treatment crossover. Among 361 participants, 333 (92.2%) were identified through the WA Data Linkage System hospital morbidity database. Nineteen (eligible) treatment crossover cases were removed for separate analysis, resulting in 314 individuals retained for the main analyses. There were 129 females (41.1%) (mean age, 27.1 years; SD, 8.1 years). The mean age of males was 29.0 years (SD, 7.5 years).

MMT Cohort

Of the 660 people in the MMT cohort, 2 were excluded for receiving methadone for pain management. In addition, 1 duplicate case, 1 case with an invalid date of death, and 1 ineligible treatment crossover case (see the "NIT Cohort" subsection of the "Participants" section in the "Methods" section) were also excluded. Of the 655 eligible cases, 541 (82.6%) were identified in the hospital admission database. The 19 (eligible) treatment crossover cases were removed for separate analysis. Consequently, 522 eligible single-treatment cases were included in the main analyses. There were 324 males (62.1%) (mean age, 32.1 years; SD, 8.9 years). The mean age of females was 30.4 years (SD, 9.1 years).

TREATMENT PROCEDURE

In WA, methadone syrup is prescribed to opioid-dependent persons by medical practitioners and dispensed by pharmacists at drug treatment agencies or community pharmacies. Each patient is authorized by the State Department of Health before pharmacotherapy is initiated. Prescribers and pharmacists are registered with and report to the State Department of Health. Approximately one-third of prescribers are public; the remainder are private.[22] All prescribers follow a standardized treatment protocol[23] for assessment and induction procedures, starting and maintenance dosages, treatment review, and treatment termination. The recommended commencement dosage is between 20 and 25 mg. The daily maintenance dosage ranges between 60 and 100 mg. Separate guidelines are also developed for pharmacists. The usual practice is patients take their medication daily at a dispensing location, to avoid diversion to nonpatients. Occasionally, however, "take-home" doses can be given to trusted patients. Patients, particularly the unemployed, pay a nominal amount for treatment.

Naltrexone implant treatment is performed as a day procedure[18] at a not-for-profit community clinic. Like all MMT prescribers and pharmacists, the naltrexone clinic is also directly regulated by the WA Department of Health. There is a relatively significant cost for the implant; however, this can be waived by the clinic or repaid by the patient in periodic small installments.

STUDY PROCEDURE

The 2 cohorts were followed up retrospectively and longitudinally via record linkage, enabled by the well-established WA Data Linkage System.[24,25] The latest hospital record available for this study was July 26, 2006.

DATA ACQUISITION

All patients in the NIT group had given their consents in writing for their records to be accessed for research purposes. With the appropriate ethics approvals (see "Ethics Approvals" subsection in the "Methods" section), the research team applied to the WA Data Linkage System for hospital morbidity data on the patients.

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 04/26/2017

For the MMT cohort, following ethics approvals, the authors made a request to the Chemical Dependency Treatment Unit, Department of Health, for data on all patients who first registered with the state's MMT program between January 2001 and December 2002. Patients' data (name, sex, birth date, and address) were supplied directly to the WA Data Linkage System, bypassing the research team to ensure patients' confidentiality, for record linkage with hospital morbidity data.

DATA DEFINITIONS

Each hospital admission in WA is assigned at least 1 diagnosis (to indicate the reason for hospitalization) by the physician on duty. Diagnoses are then coded into codes available from the *International Classification of Diseases* by trained coders. In this article, drug-related hospital morbidity is categorized along 2 dimensions: (1) type of drugs (opioid vs nonopioid) and (2) nature of morbidity ("overdose" [poisoning] vs "other" [nonoverdose], such as withdrawal and drug-induced psychotic disorder). A hospital admission is considered opioid related if at least 1 of its diagnoses involves an opioid-based drug (eg, T40.1 [heroin overdose]). Nonopioid drug events (eg, T42.4 [benzodiazepine overdose]) do not involve any opioid-related diagnosis. However, the dichotomy of overdose vs other morbidity may not be defined uniquely for one same hospital admission. For example, an admission is defined as an overdose event and an other event if at least 1 of its diagnoses involves a poisoning code (eg, T40.1) and at least another diagnosis involves a nonpoisoning drug-related code (eg, F11.5 [psychotic disorder induced by heroin]). The eTable (available at http://www.archgenpsychiatry.com) shows the mapping of diagnostic codes to research categories from the *International Statistical Classification of Diseases, 10th Revision*[26] and the *International Classification of Diseases, Ninth Revision, Clinical Modification*,[27] which cover the study period from July 3, 1997, to June 30, 2006.

DATA ANALYSIS

First, we documented all the drug-related hospital morbidities recorded during the 6 months and 3½ years pretreatment and posttreatment, respectively, in the 2 cohorts. Drug-related deaths that occurred within the 3½ years posttreatment were also considered (a severe form of) drug-related morbidity. Morbidity statistics for noncrossover and crossover cases were presented separately. For the noncrossover cases (which constituted 97.7% of the total study sample), we also conducted the following statistical analyses.

Changes to individuals' risk for hospital drug-related diagnoses following treatment were assessed for the 2 treatment cohorts using logistic regression (PROC LOGISTIC) in SAS, version 9.1.2.[28] Risks were modeled according to treatment type (NIT vs MMT), time relative to treatment (after vs before), and, most important, their interaction. Confounding variables (age and sex) and their modifying effects (or interactions) with treatment type and time relative to treatment were also examined. Odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated for comparisons of interest. Models were fitted separately for the 4 research categories of hospital diagnoses and for the 2 periods of follow-up (6 months and 3½ years).

At the population level, posttreatment changes to overall hospital admission rates were assessed within each cohort, using Poisson regression (PROC GENMOD). A similar approach to model fitting as described in the previous risk analysis was taken. Rate ratios (RRs) and associated 95% CIs were computed.

Periods of posttreatment follow-up shorter than 6 months or 3½ years (depending on the analysis in question) contributed by patients who died before these time points were taken into account in the model-fitting procedure, using the SAS statistical software's "offset" function.

ETHICS APPROVALS

This study received ethics approvals from the Human Research Ethics Committee (University of WA) and the Confidentiality of Health Information Committee (WA Department of Health) to access deidentified data on the NIT cohort, who provided written consent, and nonidentifiable data on the MMT cohort.

RESULTS

MORTALITY

Within 3½ years of treatment, there were 18 deaths, with 6 being drug related: 5 after MMT and 1 after NIT. Two MMT deaths were within the first 2 weeks of treatment: a combined drug overdose (day 1) and a nonopioid drug overdose (day 11). Causes of death also showed the other 3 MMT deaths resulted from overdoses: 2 were opioid related and 1 involved nonopioid drugs. The fatality occurring after NIT was from the crossover group (treated with MMT, then NIT), which was opioid related. Of these 6 drug-related deaths, only 2 patients were hospitalized for drug-related problems posttreatment. Although this study focuses on drug-related morbidity that was serious enough to necessitate hospitalization, mortalities that occurred as a result of drug misuse that were not already represented in the hospital morbidity data system were also counted as incidences of serious drug morbidity. As such, the remaining 4 fatalities were also included accordingly in **Table 1** and all subsequent analyses.

CRUDE RATES

Table 1 shows the number of hospital admissions related to the 4 research categories and the number of cases involved. At 6 months and 3½ years, hospitalization rates increased for the MMT cohort in all categories of diagnoses except opioid overdoses at 3½ years. For the NIT cohort, however, admission rates in opioid-related categories improved at 6 months and 3½ years but deteriorated markedly in the nonopioid drug categories. These findings were further explored in **Table 2** and **Table 3**.

ANALYSIS OF RISKS

Opioid Overdoses

Table 2 shows no statistically significant change in opioid-related overdose risk for the first 6-month period following either treatment. Also, no significant change was observed for patients receiving MMT at 3½ years posttreatment. Among patients in the NIT group, the odds for opioid overdose decreased by more than 4-fold at 3½ years posttreatment. The crude OR for patients in the NIT group was the same at 6 months and 3½ years, but only

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 04/26/2017

Table 1. Distribution of Observed Hospital Morbidities and Cases (Crossover Cases Excluded)

Diagnosis Category	Methadone Maintenance Group (N=522)				Naltrexone Implant Group (N=314)			
	Events	Cases Involved	Total Follow-up, Person-Years	Crude Rate[a]	Events	Cases Involved	Total Follow-up, Person-Years	Crude Rate[a]
6-mo Data								
Opioid related								
Overdose								
Before treatment	5	4	261	1.9	5	4	157	3.2
After treatment	10[b,c]	9[c]	260	3.8	1	1	157	0.6
Other								
Before treatment	70	52	261	26.8	59	43	157	37.6
After treatment	82	60	260	31.5	41	34	157	26.1
Nonopioid related								
Overdose								
Before treatment	5	5	261	1.9	2	2	157	1.3
After treatment	10[c]	8[c]	260	3.8	9[d]	8	157	5.7
Other								
Before treatment	29	22	261	11.1	12	10	157	7.6
After treatment	46	24	260	17.7	31	24	157	19.7
3½-y Data								
Opioid related								
Overdose								
Before treatment	33	24	1827	1.8	41	35	1099	3.7
After treatment	31[e]	28[e]	1805	1.7	12	9	1094	1.1
Other								
Before treatment	223	132	1827	12.2	332	141	1099	30.2
After treatment	298	157	1805	16.5	181	108	1094	16.5
Nonopioid related								
Overdose								
Before treatment	25	20	1827	1.4	31	18	1099	2.8
After treatment	38[c]	30[c]	1805	2.1	32	25	1094	2.9
Other								
Before treatment	150	77	1827	8.2	105	58	1099	9.6
After treatment	171	78	1805	9.5	138	80	1094	12.6

[a] Rates are per 100 person-years.
[b] Two of these events were incurred by 2 patients in the first 14 days of treatment.
[c] Inclusive of 1 fatality, in which there were no associated hospital admissions.
[d] Two of these events were classified as "sedative poisoning," incurred by 2 patients in the first 14 days of treatment.
[e] Inclusive of 3 fatalities, in which there were no associated hospital admissions.

the latter was statistically significant. In addition, at 3½ years, there was significant evidence for decreased risk with increasing age in the NIT cohort (OR, 0.31 [95% CI, 0.15-0.68] for a 35-year-old patient vs a 25-year-old match), although this was not so evident in the MMT cohort (OR, 0.72; 95% CI, 0.51-1.03).

Opioid Other (Nonoverdose)

Similarly, Table 2 shows marked reductions in risk for other opioid hospitalization at 3½ years after NIT. No significant changes were observed for patients in the MMT group. For both periods, females generally were at greater risk than males (eg, at 6 months, the OR was 1.62 [95% CI, 1.21-2.18]). Also, the treatment × age interaction was significant. For instance, at 3½ years, between 2 patients in the MMT group, aged 35 and 25 years, the OR was 0.77 (95% CI, 0.65-0.91), while a similar risk-reducing effect of increasing age was not observed in patients in the NIT group.

Nonopioid Overdoses

In Table 2, age effect modification of time relative to treatment (ie, after vs before treatment) was significant ($P < .001$) for the 6-month period. It shows that, for the shorter time frame, nonopioid drug overdose risk stayed unchanged in younger patients (those aged 25 years). However, the risk significantly increased in older patients (those aged 35 years) receiving either treatment (OR of 5.03 [95% CI, 1.18-21.54] for those receiving MMT and OR of 16.31 [95% CI, 3.07-86.53] for those receiving NIT; $\alpha = .05$ for both). No posttreatment change was significant at 3½ years. The main effect of age was significant ($P < .001$), indicating a decrement of 5% in odds (95% CI, 0.92-0.98) for every 1-year increment in age.

Nonopioid Other

In Table 2, for both periods, the risk remained relatively constant after MMT, but increased significantly for pa-

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 04/26/2017

Table 2. Change in Hospital Morbidity Risk Over 6 Months and 3½ Years of Treatment Entry (Crossover Cases Excluded)

Length of Follow-up	Treatment Group	After vs Before Treatment Data: Crude OR	After vs Before Treatment Data: Model Estimate OR (95% CI)
	Opioid Overdose Data		
6 mo	MMT	2.30	2.28 (0.70-7.45)
	NIT	0.25	0.25 (0.03-2.23)
3½ y	MMT	1.18	1.19 (0.68-2.08)
	NIT	0.25	0.23 (0.11-0.48)[a]
	Opioid Other Data		
6 mo	MMT	1.20	1.08 (0.74-1.57)
	NIT	0.73	0.76 (0.47-1.24)
3½ y	MMT	1.22	1.30 (0.98-1.71)
	NIT	0.74	0.64 (0.46-0.89)[a]
	Nonopioid Overdose Data		
6 mo (age 25 y)	MMT	1.63	1.28 (0.39-4.18)
	NIT	4.16	4.14 (0.87-19.77)
6 mo (age 35 y)	MMT	1.63	5.03 (1.18-21.54)[a]
	NIT	4.16	16.31 (.07-86.53)[a]
3½ y	MMT	1.53	1.55 (0.87-2.77)
	NIT	1.40	1.43 (0.76-2.68)
	Nonopioid Other Data		
6 mo	MMT	1.10	0.91 (0.52-1.57)
	NIT	2.65	2.54 (1.19-5.43)[a]
3½ y	MMT	1.03	1.03 (0.73-1.45)
	NIT	1.42	1.52 (1.04-2.23)[a]

Abbreviations: CI, confidence interval; MMT, methadone maintenance treatment; NIT, naltrexone implant treatment; OR, odds ratio.
[a] Significant at $\alpha = .05$.

Table 3. Change in Hospital Admission Rates Over 3½ Years of Treatment Entry (Crossover Cases Excluded)

Diagnosis Category	Incidence Rate Ratio (95% Confidence Interval): After vs Before MMT	Incidence Rate Ratio (95% Confidence Interval): After vs Before NIT
Opioid		
Overdose	0.90 (0.54-1.48)	0.29 (0.15-0.55)[a]
Other	1.35 (1.14-1.61)[a]	0.55 (0.46-0.65)[a]
Nonopioid		
Overdose	1.54 (0.93-2.55)	1.03 (0.63-1.69)
Other	1.11 (0.88-1.38)	1.33 (1.01-1.73)[a]

Abbreviations: See Table 2.
[a] Significant at $\alpha = .05$.

tients in the NIT group. Again, patients treated at an older age had a reduced risk for other nonopioid hospitalizations (eg, at 3½ years, the OR was 0.96 [95% CI, 0.94-0.98] for each 1-year age increment).

ANALYSIS OF RATES

As seen in Table 3, opioid overdose hospital admissions decreased to less than one-third after NIT but remained the same after MMT. Opioid overdose hospitalizations decreased posttreatment among female patients (RR, 0.34; 95% CI, 0.19-0.63). Furthermore, within the female patient group, patients 30 years and older incurred fewer hospital admissions than their younger counterparts (RR, 0.32; 95% CI, 0.16-0.65).

Hospitalization because of other opioid conditions increased after MMT but decreased after NIT. Female users treated at an age older than 30 years incurred a lower morbidity level than their younger peers (RR, 0.74; 95% CI, 0.62-0.90), while this age effect was not observed in males.

Other nonopioid drug morbidity increased significantly following NIT but remained essentially unchanged after MMT. A significant 3-way interaction effect between treatment cohort, time relative to treatment, and treatment age ($P = .048$) indicated that hospital morbidity increased after MMT among patients treated at an age younger than 30 years (RR, 1.54; 95% CI, 1.15-2.08). Similar pretreatment-posttreatment changes were not observed among older patients in the MMT group, nor in patients receiving NIT in either age group.

CROSSOVER CASES

Patients who were first treated with MMT then moved to NIT generally had a poorer health profile, incurring more hospital admissions, than those who had NIT followed by MMT, before first treatment entry and after second treatment (**Table 4**). For both subgroups, however, between the 2 treatments, drug-related hospital morbidity was concerned with psychiatric diagnoses and not overdose. Also, drug-related hospitalization was higher after NIT than after MMT in general.

COMMENT

Overall, the study findings indicate that NIT was associated with a substantial decrease in opioid-related hospital morbidity but an increase in nonopioid drug-related hospital morbidity. The MMT cohort experienced no significant changes in drug-related hospitalization, except for an elevated risk for nonopioid drug overdose in older patients during the initial 6 months after treatment entry and an overall increased admission rate associated with "nonoverdose" opioid conditions at 3½ years.

NALTREXONE IMPLANT TREATMENT

Although individual patients' risk of opioid-related hospitalization did not change significantly (statistically) within the first 6 months after NIT, it decreased significantly during the subsequent 3-year period for overdose and nonoverdose morbidity. These data indicate that extended patient follow-up may be required to allow positive changes in opioid drug use to emerge in patients receiving NIT. They also challenge the hypothesis that postulates reduced heroin tolerance, leading to increased risk for accidental opioid overdose, on naltrexone treatment cessation.[13]

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 04/26/2017

Table 4. Observed Hospital Morbidity in Treatment Crossover Cases

Treatment Order	Period	Person-Years	Opioid Overdose			Opioid Other			Nonopioid Overdose			Nonopioid Other		
			Events	Cases	Crude Rate[a]	Events	Cases	Crude Rate[a]	Events	Cases	Crude Rate[a]	Events	Cases	Crude Rate[a]
MMT to NIT (n=13)	3½ y (before first tx)	45.50	3	3	6.59	23	8	50.55	1	1	2.20	7	4	15.38
	Between 2 txs	6.75	0	0	0	3	2	44.44	0	0	0	1	1	14.81
	3½ y (after second tx)	44.46[b]	4	3	9.00	18	8	40.49	2	2	4.50	8	4	17.99
NIT to MMT (n=6)	3½ y (before first tx)	21.00	0	0	0	2	2	9.52	0	0	0	1	1	4.76
	Between 2 txs	4.92	0	0	0	3	3	60.98	0	0	0	0	0	0
	3½ y (after second tx)	21.00	0	0	0	6	3	28.57	0	0	0	0	0	0

Abbreviations: MMT, methadone maintenance treatment; NIT, naltrexone implant treatment; tx, treatment.
[a] Rates are per 100 person-years.
[b] Follow-up duration after the second treatment was of equal time length to before first treatment follow-back (ie, 3½ years per person), unless patients died before this designated period.

In contrast with posttreatment changes in opioid-related hospital morbidity, hospitalizations because of nonopioid drug abuse increased considerably following NIT. The changes were particularly robust, prevalent, and long lasting in the nonoverdose category, in which posttreatment hospitalization was consistently high across all ages and sexes, short- and long-term. This is not surprising given that polydrug use among heroin users is prevalent,[5-7,29] offering a likelihood of nonopioid drug substitution associated with reduced heroin (and other opioid) use.[30] Overdoses because of nonopioid drugs, however, were only worsened in the short-term for the older patient group.

METHADONE MAINTENANCE TREATMENT

Unlike NIT, drug-related hospital morbidity remained relatively constant posttreatment for patients in the MMT group, except for a short-term elevated risk for nonopioid drug overdoses among older patients and an increase in the frequency of nonoverdose opioid hospitalizations. For the optimist, these outcomes may be considered similar to many existing research findings,[5,29,31-33] which showed substantially reduced use of illicit opioids among methadone-treated heroin users. However, the lack of improvement in opioid-related morbidity after MMT in our study seems to portray a less encouraging picture of MMT than that of previous studies. Some major methodological differences can help explain this discrepancy. First, this study focuses on the adverse health consequences (namely, hospitalizations and deaths) of drug abuse following opioid dependence treatment. It is based on objective official health data collected prospectively and continually as incidences of interest occurred. Drug overdoses that lead to hospitalizations or deaths reflect the severe nature of drug abuse, especially in terms of its high-risk quantity and frequency. In contrast, most previous research focused predominantly on patients' drug use per se (and other psychosocial outcomes). Such research used self-reported data,[5,31,33] although some also used urine or hair analysis.[29,32,34] Retrospective self-report of drug use may have (recall) memory bias. The using patient may also underreport his or her illicit drug consumption.[35] Furthermore, urine and hair samples can show use at discrete time points but inferences on quantity or frequency of use cannot be drawn. Second, treatment retention and stability play a crucial role in effecting changes for a patient in the MMT group.[33,36] A statewide annual report estimates a retention rate of 66% for inpatient MMT programs and 64% to 68% for outpatient programs run by not-for-profit treatment agencies during the 2001 to 2003 period.[37] Patients are generally encouraged to stabilize while receiving methadone for at least 12 months.[23] One may, therefore, assume that approximately 66% of the patients in the MMT group were retained in treatment for at least 12 months. Such a retention rate is indicative of a high-threshold MMT program.[34,38] Nevertheless, without treatment data on individuals undergoing MMT, we cannot statistically assess the association between treatment retention and adverse health outcomes.

Another important feature of the MMT cohort was the 2 fatal overdoses occurring in the first 2 weeks of treatment. This suggests that patients undergoing MMT were at particularly high risk of drug overdoses in the initial stage of treatment, which concurs with earlier findings.[39-41]

SIMILARITIES BETWEEN THE NIT AND MMT COHORTS

For most categories of morbidity (ie, except for nonopioid drug overdoses), hospitalization risk decreased with increasing age at treatment, consistent with a previous study[20] on NIT. One may attribute this age effect to younger users' lack of experience and knowledge in harm reduction strategies in using drugs.[42] Also, similarly to this previous study,[20] we also observed an elevated risk for nonoverdose opioid morbidity in female users, compared with male counterparts. Background issues, such as childhood abuse and other types of violence experienced in adulthood (including sexual exploitation and domestic violence), in female drug users[43] may help explain this sex difference.

Both MMT and NIT were associated with an inflated risk for nonopioid drug overdoses within 6 months following treatment entry, mostly in older patients. This stands in stark contrast to the generally observed risk-

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 04/26/2017

reducing effect of increasing age in other categories of morbidity discussed in the study. This age-based difference in risk was no longer detected at 3½ years post-treatment, implying that patients built up tolerance to, and/or experience in using, their new (nonopioid) drugs of choice.

DIFFERENCES BETWEEN NIT AND MMT

Use of nonopioid drugs by patients receiving NIT resulted in a marked and consistent (short- and long-term) increase in nonoverdose hospitalization, such as dependence and withdrawal, while similar outcomes did not apply to the MMT cohort. This may reflect the inherent difference between the 2 approaches—MMT as opioid maintenance, in which some level of additional illicit opioid (and other nonopioid drug) use is possible; and NIT, in which the antagonism of heroin and related opioid effect[18,44] may lead to the patient ceasing opioid use and adopting nonopioid drugs.

Another difference between the 2 cohorts concerned their opioid-related risk profiles by age. Specifically, older patients who received NIT were at less risk of opioid overdose, but no such age effect existed for opioid nonoverdose morbidity (eg, dependency or withdrawal). This is understandable, if one accepts the previous hypotheses that (1) length of use positively correlates with age[8] and (2) tolerance for the abused drugs is built up over time. In contrast, the risk of opioid overdose in patients receiving MMT was comparable across age groups, with older patients less likely to incur opioid-related hospitalizations that were not overdoses, such as dependency and withdrawal, compared with younger counterparts. The first part of this finding (regarding opioid overdoses) is slightly incongruent with existing literature, in which overdoses were more likely in older users,[8] for which we have no plausible explanation to offer. For the latter part (opioid nonoverdose), we hypothesize that older users' (1) improved knowledge and experience in (safer) opioid drug use, (2) increased involvement with nonopioid drugs, and/or (3) decreased involvement with opioid drugs may account for these findings.

STRENGTHS AND LIMITATIONS

The key strength of this research lies in its novelty, scope, and methods. To our knowledge, this is the first study that investigates long-term drug-related health problems of a sizeable cohort of heroin users treated with naltrexone implants, an unregistered pharmacotherapy for opioid dependence. To our knowledge, it is also the first to assess, on an intention-to-treat basis, NIT–related health outcomes with reference to those associated with MMT. It does so by using objective, systematic, and validated administrative health data.

Despite these strengths, certain limitations need to be acknowledged. First, the MMT cohort is only included as a reference group to help facilitate the evaluation and discussion of the outcomes associated with NIT. Therefore, while within-group comparisons can be viewed with confidence, any between-group comparisons must be interpreted with great caution. Clearly, the lack of controlled randomized sampling prevents us from imputing causative inferences on the results. Specifically, the study does not control for several important factors inherently differentiating the 2 cohorts, such as motivation level, situational influences, socioeconomic background, and preexisting illness. Another related issue is the unavailability of medication dosage and treatment retention data on individual patients receiving MMT, which prevents a complete assessment of the drug-related health outcomes of these patients. Second, the lower tracking rate of the MMT cohort (82.6%; vs 92.2% in the NIT cohort) could result in favorable bias in MMT outcomes: there is evidence[45] that difficult–to–follow-up individuals have higher incidences of adverse outcomes than others. Conversely, our exclusion of 3 cases with implant removal in the first week might have favorably biased the interpretation for NIT data.

Third, concerns have been raised in regard to administrative health data, such as hospital diagnoses based on *International Classification of Diseases* codes. (1) These data, although objective, may lack the level of details that other types of data (eg, medical file notes and interviews) can afford.[25] Thus, they may not fully reflect all incidences of problematic drug use. (2) Transition from *International Classification of Diseases, Ninth Revision, Clinical Modification* to *International Statistical Classification of Diseases, 10th Revision* codes may not always be consistent; we provide the mapping table (eTable) to assist reader comprehension. (3) Knowledge of the patient's addiction (through the patient's disclosure) may potentially bias the physician's diagnosis (eg, by misassigning a diagnosis of substance abuse to the patient's admission cause, although the admission may be drug unrelated). Fortunately, such bias clearly is not possible with our overdose morbidity category. As for the nonoverdose morbidity category, we expect such misdiagnoses to be rare and/or to have insignificant effect on the actual outcomes, because this study investigated principal and additional (or related) diagnoses available for each admission. In WA, substance abuse treatment is provided by services external to the hospitals. Consequently, hospital physicians are not readily aware of patients' drug issues without their symptoms or disclosures.

Finally, given the high prevalence of polydrug abuse among heroin users,[29,30] it may be of interest to evaluate how this pattern of multiple drug use changed following MMT or NIT. For example, Darke and colleagues[29] reported that, among a sample of 615 treated heroin users, reduced opioid use was parallel to reduced use of cocaine, amphetamines, and benzodiazepines, but not alcohol and cannabis. Because of the elaborateness of such analyses under our study's framework, these issues could form the basis for subsequent research inquiry.

In light of this study, it may be appropriate to advise prospective patients of the need to balance differential risks before entering NIT (improved opioid-related morbidity but worsened nonopioid drug–related morbidity) or MMT (no significant change in drug-related morbidity, but with nonnegligible mortality risk during treatment induction). The study also poses some challenges to those working in the field of illicit opioid dependence. First, for persons entering MMT, continued

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 04/26/2017

illicit opioid abuse indicated by ongoing hospital admissions is a significant concern. That this persists in some patients for several years suggests that alternative pharmacotherapies should be offered and their risks fully explained to these patients. Second, it seems that for some patients an imminent price for reduced heroin use following treatment is an increase in nonopioid drug abuse and associated morbidity. This is evident in MMT only with respect to nonopioid drug overdoses among older patients in the short-term posttreatment but is prevalent across overdose and nonoverdose conditions for NIT, presenting a major concern for the latter. Therefore, health professionals should attend closely to the prevalence of polydrug use in heroin users, as a coexisting dependence problem and an almost inevitable consequence of reduction or cessation of heroin use. Interventions need to genuinely and effectively incorporate multiple facets of their rehabilitation: clinical, personal, familial, social, and legal. Third, although each study is unique and stands on its own merits, certain discrepancies in our findings and others call for the need for a standardized approach to measuring treatment outcomes. In doing so, relevant research findings can be compared with confidence, which in turn will meaningfully inform clinical intervention practice.[46]

Submitted for Publication: July 10, 2007; final revision received October 8, 2007; accepted October 23, 2007.
Correspondence: Hanh T. T. Ngo, BSc(Hons), School of Psychiatry and Clinical Neurosciences, University of Western Australia (Mail Code M521), 35 Stirling Hwy, Crawley, Western Australia 6000, Australia (hanh.ngo@uwa.edu.au).
Author Contributions: Ms Ngo takes full responsibility for the integrity of the data as supplied and the accuracy of the data analysis. All authors certify to have full access to all the study data.
Financial Disclosure: None reported.
Funding/Support: This study is part of ongoing research supported by the National Health and Medical Research Council (grant 353545) and the Office of Mental Health, Western Australia Department of Health. Since this study, the authors have initiated further studies on the naltrexone implants, which are contracted to the University of Western Australia by Go Medical Industries Pty Ltd under a Commonwealth Government Australian Industries grant.
Additional Information: The eTable is available at http://www.archgenpsychiatry.com. Hospital morbidity and mortality data were extracted by the Data Linkage Unit at the Western Australia Department of Health.

REFERENCES

1. Hulse GK, English DR, Milne E, Holman CDJ. The quantification of mortality resulting from the regular use of illicit opiates. *Addiction*. 1999;94(2):221-229.
2. Ward J, Hall W, Mattick RP. Role of maintenance treatment in opioid dependence. *Lancet*. 1999;353(9148):221-226.
3. Barnett PG, Hui SS. The cost-effectiveness of methadone maintenance. *Mt Sinai J Med*. 2000;67(5-6):365-374.
4. Harris KA, Arnsten J, Joseph H, Hecht J, Marion I, Juliana P, Gourevitch M. A 5-year evaluation of a methadone medical maintenance program. *J Subst Abuse Treat*. 2006;31(4):433-438.
5. Gossop M, Marsden J, Stewart D, Treacy S. Change and stability of change after treatment of drug misuse: two-year outcomes from the National Treatment Outcome Research Study. *Addict Behav*. 2002;27(2):155-166.
6. Amato L, Davoli M, Perucci CA, Ferri M, Faggiano F, Mattick RP. An overview of systematic reviews of the effectiveness of opiate maintenance therapies: available evidence to inform clinical practice and research. *J Subst Abuse Treat*. 2005;28(4):321-329.
7. Stewart D, Gossop M, Marsden J. Reductions in non-fatal overdose after drug misuse treatment: results from the National Treatment Outcome Research Study (NTORS). *J Subst Abuse Treat*. 2002;22(1):1-9.
8. Darke S, Ross J, Hall W. Overdose among heroin users in Sydney, Australia, I: prevalence and correlates of non-fatal overdose. *Addiction*. 1996;91(3):405-411.
9. Neale J. Methadone, methadone treatment and non-fatal overdose. *Drug Alcohol Depend*. 2000;58(1-2):117-124.
10. Gibson A, Degenhardt L. *Mortality Related to Naltrexone in the Treatment of Opioid Dependence: A Comparative Analysis: Technical Report*. Sydney, Australia: National Drug and Alcohol Research Centre; 2005:229.
11. Sullivan MA, Vosburg SK, Comer SD. Depot naltrexone: antagonism of the reinforcing, subjective, and physiological effects of heroin. *Psychopharmacology (Berl)*. 2006;189(1):37-46.
12. Gibson AE, Degenhardt LJ, Hall WD. Opioid overdose deaths can occur in patients with naltrexone implants. *Med J Aust*. 2007;186(3):152-153.
13. Miotto K, McCann MJ, Rawson RA, Frosch D, Ling W. Overdose, suicide attempts and death among a cohort of naltrexone-treated opioid addicts. *Drug Alcohol Depend*. 1997;45(1-2):131-134.
14. Hulse GK, Tait RJ, Comer SD, Sullivan MA, Jacobs IG, Arnold-Reed DE. Reducing hospital presentations for opioid overdose in patients treated with sustained release naltrexone implants. *Drug Alcohol Depend*. 2005;79(3):351-357.
15. Brewer C. Naltrexone implants for opiate addiction: new life for a middle-aged drug [comment]. *Pharm J*. 2001;267(7162):260.
16. Comer SD, Collins ED, Kleber HD, Nuwayser ES, Kerrigan JH, Fischman MW. Depot naltrexone: long-lasting antagonism of the effects of heroin in humans. *Psychopharmacology (Berl)*. 2002;159(4):351-360.
17. Hulse GK, Arnold-Reed DE, Ngo H, Reece S. Naltrexone implants in the treatment of heroin addiction. In: McKenna CR, ed. *Trends in Substance Abuse Research*. New York, NY: Nova Science Publishers Inc; 2007:71-88.
18. Hulse GK, Arnold-Reed DE, O'Neil G, Chan CT, Hansson R, O'Neil P. Blood naltrexone and 6-β-naltrexol levels following naltrexone implant: comparing two naltrexone implants. *Addict Biol*. 2004;9(1):59-65.
19. Waal H, Frogopsahl G, Olsen L, Christophersen AS, Mørland J. Naltrexone implants: duration, tolerability and clinical usefulness. *Eur Addict Res*. 2006;12(3):138-144.
20. Ngo HT, Tait RJ, Arnold-Reed DE, Hulse GK. Mental health outcomes following naltrexone implant treatment for heroin dependence. *Prog Neuropsychopharmacol Biol Psychiatry*. 2007;31(3):605-612.
21. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. ed 4. Washington, DC: American Psychiatric Association; 1994.
22. Australian Institute of Health and Welfare. *Alcohol and Other Drug Treatment Services in Australia 2001-02: Report on the National Minimum Data Set* . Canberra: Australian Institute of Health and Welfare; 2003. Drug Treatment Series, No. 2; AIHW category HSE 28.
23. Drug and Alcohol Office. *Western Australia Clinical Policies and Procedures for the Use of Methadone and Buprenorphine in the Treatment of Opioid Dependence*. Perth: Drug and Alcohol Office, Government of Western Australia (WAADA); 2006:1-105.
24. Brameld KJ, Thomas MAB, Holman CDJ, Bass AJ, Rouse IL. Validation of linked administrative data on end-stage renal failure: application of record linkage to a "clinical base population." *Aust N Z J Public Health*. 1999;23(5):464-467.
25. Holman CDJ, Bass AJ, Rouse IL, Hobbs MST. Population-based linkage of health records in Western Australia: development of a health services research linked database. *Aust N Z J Public Health*. 1999;23(5):453-459.
26. World Health Organization. *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*. Geneva, Switzerland: World Health Organization; 1992. Reprinted with corrections, 1996.
27. World Health Organization. *International Statistical Classification of Diseases, Ninth Revision, Clinical Modification: ICD-9-CM*. Geneva, Switzerland: World Health Organization; 1986.
28. *SAS* [computer program]. Version 9.1.2. Cary, NC: SAS Institute Inc; 2002-2003.
29. Darke S, Williamson A, Ross J, Teesson M. Reductions in heroin use are not associated with increases in other drug use: 2-year findings from the Australian Treatment Outcome Study. *Drug Alcohol Depend*. 2006;84(2):201-205.
30. Best D, Harris J, Gossop M, Farrell M, Finch E, Noble A, Strang J. Use of nonprescribed methadone and other illicit drugs during methadone maintenance treatment. *Drug Alcohol Rev*. 2000;19(1):9-16.

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 04/26/2017

31. Gossop M, Marsden J, Stewart D, Edwards C, Lehmann P, Wilson A, Segar G. The National Treatment Outcome Research Study in the United Kingdom: six-month follow-up outcomes. *Psychol Addict Behav*. 1997;11(4):324-337.
32. Gossop M, Marsden J, Stewart D, Lehmann P, Strang J. Methadone treatment practices and outcome for opiate addicts treated in drug clinics and in general practice: results from the National Treatment Outcome Research Study. *Br J Gen Pract*. 1999;49(438):31-34.
33. Teesson M, Ross J, Darke S, Lynskey M, Ali R, Ritter A, Cooke R. One year outcomes for heroin dependence: findings from the Australian Treatment Outcome Study (ATOS). *Drug Alcohol Depend*. 2006;83(2):174-180.
34. Waal H. Merits and problems in high-threshold methadone maintenance treatment. *Eur Addict Res*. 2007;13(2):66-73.
35. Pedersen W. Reliability of drug use responses in a longitudinal study. *Scand J Psychol*. 1990;31(1):28-33.
36. Darke S, Williamson A, Ross J, Teesson M. Non-fatal heroin overdose, treatment exposure and client characteristics: findings from the Australian Treatment Outcome Study (ATOS). *Drug Alcohol Rev*. 2005;24(5):425-432.
37. Drug and Alcohol Office, Government of Western Australia. DAO 2006 Annual Report (Section B). http://www.dao.health.wa.gov.au/Publications/tabid/99/DMXModule/427/Default.aspx?EntryId=620. Accessed January 18, 2008.
38. Grönbladh L, Gunne L. Methadone-assisted rehabilitation of Swedish heroin addicts. *Drug Alcohol Depend*. 1989;24(1):31-37.
39. Buster MC, van Brussel GH, van den Brink W. An increase in overdose mortality during the first 2 weeks after entering or re-entering methadone treatment in Amsterdam. *Addiction*. 2002;97(8):993-1001.
40. Caplehorn JRM, Drummer OH. Mortality associated with New South Wales methadone programs in 1994: lives lost and saved. *Med J Aust*. 1999;170(3):104-109.
41. Zador D, Sunjic S. Deaths in methadone maintenance treatment in New South Wales, Australia 1990-1995. *Addiction*. 2000;95(1):77-84.
42. Neira-León M, Barrio G, Brugal MT, De la Fuente L, Ballesta R, Bravo MJ, Silva TC, Rodriguez-Martos A; Project Itinere Group. Do young heroin users in Madrid, Barcelona and Seville have sufficient knowledge of the risk factors for unintentional opioid overdose? *J Urban Health*. 2006;83(3):477-496.
43. DiNitto DM, Webb DK, Rubin A. Gender differences in dually-diagnosed clients receiving chemical dependency treatment. *J Psychoactive Drugs*. 2002;34(1):105-117.
44. Ngo HT, Arnold-Reed DE, Hansson RC, Tait RJ, Hulse GK. Blood naltrexone levels over time following naltrexone implants (published online ahead of print June 19, 2007). *Prog Neuropsychopharmacol Biol Psychiatry*. doi.10.1016/j.pnpbp.2007.06.007.
45. Sims AC. Importance of a high tracing-rate in long-term medical follow-up studies. *Lancet*. 1973;2(7826):433-435.
46. West R, Hajek P, Stead L, Stapleton J. Outcome criteria in smoking cessation trials: proposal for a common standard. *Addiction*. 2005;100(3):299-303.

©2008 American Medical Association. All rights reserved.
Downloaded From: http://archpsyc.jamanetwork.com/ on 04/26/2017