Prevalence and cost of diagnosed opioid abuse in a privately insured population in the United States

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INTRODUCTION

Pain is a prevalent and costly condition, with chronic pain impacting at least 100 million American adults and costing the nation up to $635 billion annually in medical treatment and lost productivity.1 To treat pain, physicians may turn to opioids, which are commonly prescribed for pain management; however, the use of opioids in chronic pain remains controversial because of concerns about potential misuse, abuse, and diversion.3

Sales of opioid pain relievers in the United States have increased ~4-fold from 1999 to 2008, with a parallel increase in the overdose death rates and substance abuse treatment admissions related to opioid pain relievers over this same time period.4 Over the period 2004 to 2008, the number of emergency department (ED) visits related to nonmedical use of opioid analgesics has more than doubled, from 144,600 in 2004 to 305,900 in 2008; unintentional opioid overdose deaths have increased fivefold from 1999 to 2009, rising from ~3,000 deaths in 1999 to 15,597 deaths in 2009.5,6 In the 2010 National Survey on Drug Use and Health (NSDUH), ~5.1 million people aged ≥12 years in the United States reported nonmedical use of a prescription pain medication within

ABSTRACT

Objective: To evaluate the prevalence, characteristics, associated healthcare resource utilization (HRU), and costs of diagnosed prescription opioid abusers (abusers) in a managed care population.

Methods: Patients aged ≥12 years with a claim for opioid abuse were identified in the Thomson MarketScan Commercial and Medicare Supplemental research databases between January 1, 2005 and September 30, 2010. HRU and costs (per patient per month) were calculated for all patients with an index date (date of opioid abuse diagnosis) from October 1, 2008 to September 30, 2009 and continuous eligibility through 6 months prior to (preindex) and 12 months after (postindex) date. Abusers were matched 1:3 on demographics to nonabusers.

Results: The overall prevalence of diagnosed opioid abuse was 0.195 percent during 2005-2010, with a twofold increase from 2005 to 2010. Diagnosed abuse was more prevalent in males (0.220 percent), those aged 18-25 years (0.271 percent), those from the Northeast region (0.231 percent), those with a comorbidity of pain (0.462 percent), and those with an opioid prescription (0.924 percent). A total of 15,398 abusers were matched to 46,194 nonabusers. Medical comorbidities were significantly higher (all p < 0.0001) in abusers versus nonabusers in the preindex and postindex periods. Each healthcare resource measured was significantly higher for abusers than nonabusers in the preindex and postindex periods (p < 0.0001). Total all-cause costs were higher for abusers than nonabusers in the preindex ($1,856 vs $372, respectively) and postindex ($2,138 vs $408) periods (p < 0.0001).

Conclusions: Opioid abuse increased over time and abusers were associated with significantly greater HRU and costs compared with nonabusers before and after the diagnosis of abuse.
the past month, and ~2.0 million people reported first
initiating nonmedical use of prescription pain med-
ication within the past year.\textsuperscript{7}

Prescription opioid abuse is associated with sub-
stantial costs, from both a societal and payer perspec-
tive. At the societal level, the cost of nonmedical use
of prescription opioids in the United States was esti-
imated at $53.4 billion annually, and prescription opi-
od abuse, dependence, and misuse was estimated at
$55.7 billion annually.\textsuperscript{8,9} It is estimated that the abuse
and illegal obtaining and resale of opioid pain reliev-
cost payers ~$72.5 billion annually.\textsuperscript{10} In a privately
insured population diagnosed opioid abuse patients
incurred $20,546 more in annual healthcare costs than
demographically similar controls, and Medicaid
(Florida) opioid abuse patients cost $15,183 in excess
of controls.\textsuperscript{11} Furthermore, the prevalence of diag-
osed opioid abuse in the privately insured population
increased fourfold from 1999 (0.05 percent) to
2007 (0.20 percent) and more than doubled in the
Florida Medicaid population from 1999 (0.18 percent)
to 2006 (0.50 percent).\textsuperscript{11} In a study of 37.5 million
Medicaid patients in the Medicaid Analytic eXtract
(MAX) files (2002-2003), the prevalence of opioid
abuse was found to be 0.87 percent, and annual costs
were nearly $6,000 higher annually for diagnosed opi-
od abusers compared with matched controls.\textsuperscript{12}

To date, the only noninterventional studies to
evaluate diagnosed prescription opioid abuse have
included a single private payer database (Ingenix
Employer Solutions [now OptumInsight\textsuperscript{[TM]} data], a
single state Medicaid database (Florida), or an older
national Medicaid database (MAX 2002-2003).\textsuperscript{11-13}
Furthermore, these previous studies provided lim-
ited information on the association of prescription
opioid use to that of diagnosed abuse.

The objectives of this retrospective cohort study
were to expand on previous research by evaluating
the prevalence of diagnosed opioid abuse over
time as well as to describe patient characteristics,
opioid treatment patterns, and associated resource
use and costs for those with diagnosed prescrip-
tion opioid abuse in a claims database of privately
insured patients for the most recent calendar year
available.

\section*{METHODS}

This retrospective cohort study used administra-
tive claims from the Thomson Reuters MarketScan\textsuperscript{®}
Commercial Claims and Encounters and Medicare
Supplemental research databases (70.5 million lives)
between January 2005 and September 2010.

\section*{Data source}

Data for the study were obtained from MarketScan
Commercial Claims and Encounters and Medicare
Supplemental databases (Thomson Reuters\textsuperscript{®}) for the
years 2005-2010. This database includes complete lon-
gitudinal records of inpatient services, outpatient serv-
ices, long-term care, and prescription drug claims cov-
ered under a variety of fee-for-service and capitated
health plans, including exclusive provider organiza-
tions, preferred provider organizations, point-of-serv-
Ice plans, indemnity plans, and health maintenance
organizations. The data are nationally representative,
quality controlled, and Health Insurance Portability
and Accountability Act of 1996 compliant.

Available information in this database includes
patient age, gender, census region, dates of eligibility
for health insurance, facility claims, provider claims,
pharmacy claims, and reimbursed and charged
amounts for all claims. All claims for any given patient
can be linked using unique encrypted identifiers.

\section*{Study population}

Patients were considered diagnosed prescription
opioid abusers (hereinafter also referred to as
abusers), based on \textit{International Classification of
Disease, Ninth Revision Clinical Modification (ICD-9-
CM)} codes, if they had a previous history of opioid
type dependence (304.0X), combinations of opioid
abuse with any other (304.7X), opioid abuse (305.5X),
or poisoning with opiates and related narcotics, not
heroin (965.00, 965.02, and 965.09). These ICD-9
codes have been used previously in similar studies
using claims databases to identify the population of
interest, that is, opioid abusers. Therefore, this group
included patients with claims for opioid abuse,
dependence, and poisoning. The control group
included patients who were not diagnosed with pre-
scription opioid abuse (hereinafter referred to as
nonabusers). To determine the prevalence of diag-
nosed opioid abuse by calendar year, patients aged
$\geq 12$ years as of January 1, 2005 were selected (age is
consistent with the NSDUH). For the remaining objec-
tives, patients had to be aged $\geq 12$ years as of October
1, 2008, had a diagnosis of opioid abuse during
October 1, 2008 to September 30, 2009, and had con-
tinuous eligibility in the 6-month preindex period.
(index being the date of opioid abuse diagnosis) through the 12-month postindex periods (Figure 1). Matching (1 abuser:3 nonabusers) was performed to ensure that the cohorts of abusers and nonabusers were closely balanced. Nonabusers were selected and matched to abusers by gender, age, and geographic region. The index date of a nonabuser was equal to the index date of its matched abuser from October 1, 2008 to September 30, 2009.

Assessments and analyses

Prevalence of diagnosed opioid abuse by calendar year. Prevalence of diagnosed opioid abuse was calculated as the number of unique individuals with a claim for opioid abuse divided by the total number of unique enrolled patients for the period of interest and was reported as a percentage. Prevalence was determined for all patients in the dataset by calendar year for each year from 2005 through 2010. The denominator included all patients aged ≥12 years in the dataset for each year of interest (eg, January 1, 2005 to December 31, 2005). The numerator included all cases identified with a diagnosis of opioid abuse during the same year of interest. Prevalence was calculated overall and by year of interest (2005, 2006, 2007, 2008, 2009, and 2010), by age (12-17, 18-25, 26-34, 35-54, 55-64, and 65+), gender, region (Northeast, North Central, South, and West), presence of pain-related conditions, and any opioid use.

Patient characteristics. Demographics (age, gender, region, health plans, and benefit plan types) and the presence of medical comorbidities in the 6-month preindex and 12-month postindex periods were evaluated for each patient. Select comorbidities were evaluated per ICD-9-CM codes as used in previous studies.11,12 Pain and nonpain-related medical conditions were tracked separately. Comorbidities were reported as a percentage of the population with specific comorbid conditions. A preindex Quan-Charlson14 comorbidity score was computed for each patient.

Healthcare resource utilization and costs. All-cause and opioid abuse-related healthcare resource utilization (HRU) and costs were evaluated in all patients in the dataset with index dates during October 1, 2008 to September 30, 2009 and with 6-month preindex through 12-month postindex continuous eligibility. All costs were charged costs (included copay and deductible) and were not adjusted. HRU (percentage, average per patient per month) and costs (average per patient per month) were determined for prescriptions filled, inpatient care, ED visits, and outpatient care in the 6-month preindex and 12-month postindex periods. All hospitalizations with same day admission and discharge dates were classified as ED visits. Opioid abuse-related healthcare utilization and costs included all inpatient stays and outpatient visits associated with ICD-9-CM codes of interest (304.0X, 304.7X, 305.5X, 965.00, 965.02, and 965.09).

Use of opioids was evaluated based on pharmacy claims for the 6-month preindex and 12-month postindex periods for each patient who had at least 6 months of eligibility before and 12 months after the index date. Use was reported as the percentage of patients with an opioid prescription, the number of unique opioids, and the average number of prescriptions filled per patient per month, overall, and by individual opioid or opioid drug category as follows: short-acting opioids (SAO; hydrocodone combinations, oxycodone combinations, oxycodone immediate release, oral transmucosal fentanyl, all other SAO) or long-acting opioids (LAO;
oxycodone extended release (ER), morphine ER, transdermal fentanyl, methadone, oxymorphone ER, all other LAO).

**Statistical analyses**

Demographic and baseline characteristics were compared between abusers and nonabusers using chi-square tests for categorical variables or dichotomous variables and two-sample t tests for continuous variables.

The preindex relative risk (RR) of comorbidities (abusers/nonabusers) and the percent change in RR was obtained from repeated measures models using Proc GENMOD in SAS® (SAS Institute, Inc., Cary, NC) with a binomial distribution and log link. Terms for age, gender, time, cohort, and time by cohort interaction were included in the model.

The response variable in each analysis of HRU and cost category is the change in the variable from preindex per month to postindex per month (difference in difference [DID]). DID was evaluated using a general linear model that included terms for cohort, Charlson comorbidity index, age, gender, any pain condition during the preindex period, health plan, and plan type. All analyses were performed using SAS® (version 9.2).

**RESULTS**

**Prevalence of diagnosed opioid abuse by calendar year**

The overall prevalence of diagnosed opioid abuse during 2005-2010 was 0.195 percent (Table 1). Diagnosed opioid abuse was more prevalent in males (0.220 percent), those aged 18-25 years (0.271 percent), those from the Northeast (0.231 percent), those with a comorbidity of pain (0.462 percent), and those with an opioid prescription (0.924 percent). The prevalence of diagnosed opioid abuse in 2010 was 0.145 percent, which was more than a twofold increase from 2005 (Table 2). The prevalence of

### Table 1. Overall prevalence of diagnosed abuse from 2005 to 2010

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Prevalence, percent</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.195</td>
<td>0.001</td>
</tr>
<tr>
<td>12-17</td>
<td>0.089</td>
<td>0.001</td>
</tr>
<tr>
<td>18-25</td>
<td>0.271</td>
<td>0.002</td>
</tr>
<tr>
<td>26-34</td>
<td>0.231</td>
<td>0.002</td>
</tr>
<tr>
<td>35-54</td>
<td>0.220</td>
<td>0.001</td>
</tr>
<tr>
<td>55-64</td>
<td>0.158</td>
<td>0.001</td>
</tr>
<tr>
<td>65+</td>
<td>0.102</td>
<td>0.001</td>
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<table>
<thead>
<tr>
<th>Gender</th>
<th>Prevalence, percent</th>
<th>SE</th>
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</thead>
<tbody>
<tr>
<td>Male</td>
<td>0.220</td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.172</td>
<td>0.001</td>
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<table>
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<tr>
<th>Region</th>
<th>Prevalence, percent</th>
<th>SE</th>
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<tr>
<td>Northeast</td>
<td>0.231</td>
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</tr>
<tr>
<td>North Central</td>
<td>0.188</td>
<td>0.001</td>
</tr>
<tr>
<td>South</td>
<td>0.192</td>
<td>0.001</td>
</tr>
<tr>
<td>West</td>
<td>0.192</td>
<td>0.001</td>
</tr>
<tr>
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<td>0.169</td>
<td>0.003</td>
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<thead>
<tr>
<th>Comorbidity of pain</th>
<th>Prevalence, percent</th>
<th>SE</th>
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<tbody>
<tr>
<td>No</td>
<td>0.087</td>
<td>0.000</td>
</tr>
<tr>
<td>Yes</td>
<td>0.462</td>
<td>0.002</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Prescription for opioids</th>
<th>Prevalence, percent</th>
<th>SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>0.086</td>
<td>0.000</td>
</tr>
<tr>
<td>Yes</td>
<td>0.924</td>
<td>0.003</td>
</tr>
</tbody>
</table>

SE, standard error of percent.
opioid abuse by geographical region increased consistently from 2005 to 2010 in each region; however, the prevalence in the Northeast increased the greatest (2.5-fold; 0.183 percent in 2010 vs 0.072 percent in 2005) compared with a 1.6- to 2.2-fold increase in the other regions (Figure 2). For each year evaluated, the prevalence of diagnosed opioid abuse was greater among males, patients aged 18 to 25 years, patients with a comorbidity of pain, and patients with an opioid prescription. For each year, the RR for diagnosed opioid abuse was greater for males than females (1.2-1.4), patients with a comorbidity of pain (3.9-5.4), and patients with a prescription for an opioid than those without (7.1-11.6; Table 2).

Healthcare resource utilization and costs

For the most recent calendar year available, a total of 15,398 abusers were matched (1:3) to 46,194 nonabusers. The demographic characteristics of abusers and matched nonabusers are presented in Table 3 and show that the two cohorts had similar proportions of each gender (46 percent were female), were similar in age (abusers, 41.90 ± 15.5 years; nonabusers, 42.56 ± 15.5 years), and were distributed similarly among the various geographic regions. Most abusers and matched nonabusers resided in the South (36.5 percent), followed by North Central (26.1 percent), West (25.3 percent), and the Northeast (11.8 percent) region (Table 3).

The percentage of all medical comorbidities examined was significantly higher (all p < 0.0001) in abusers compared with nonabusers in both the preindex and postindex periods (Table 4). The most prevalent comorbidities for both abusers and nonabusers were any pain condition followed by psychiatric disorders. During the preindex period, 60.8 percent of abusers and 24.2 percent of nonabusers (RR, 2.6) had any pain condition, and 44.4 percent of abusers and 6.8 percent of nonabusers (RR, 6.5) had a psychiatric disorder. In the postindex period, 69.7 percent of abusers and 35.9 percent of nonabusers (RR, 1.9) had any pain condition, and 65 percent of abusers and 10.9 percent of nonabusers (RR, 6) had a psychiatric disorder. The comorbidities with the largest RR in the preindex period included alcoholic hepatitis (RR, 76.6), other substance abuse (RR, 20.6), nonopioid poisoning (RR, 19.5), pancreatitis (RR, 14.6), other hepatitis (RR, 13.3), hepatitis A, B, or C (RR, 9.2), and psychiatric disorders (RR, 6.5; Table 4). Of the significant percent changes in RR in the postindex period from the preindex period, the greatest change was in the comorbidities of nonopioid poisoning (+145.0 percent; p < 0.0001), pancreatitis (−35.6 percent; p < 0.05), any pain condition (−31.9 percent; p < 0.0001), and psychiatric disorders (−9.4 percent; p < 0.0001; Table 4).

HRU and cost are presented in Table 5. HRU was significantly higher for abusers compared with nonabusers for each resource measured in both the preindex and postindex periods (p < 0.0001; Table 5). Abusers had more inpatient stays (10-fold), outpatient visits (threefold), office visits (threefold), ED
### Table 3. Baseline demographic and clinical characteristics of abusers and nonabusers

<table>
<thead>
<tr>
<th>Demographic characteristic</th>
<th>Abusers (N = 15,398)</th>
<th>Nonabusers (N = 46,194)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (percent)</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Female</td>
<td>7,135 (46.34)</td>
<td>21,405 (46.34)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>8,263 (53.66)</td>
<td>24,789 (53.66)</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>Overall mean age (SD)</td>
<td>41.90 (15.48)</td>
<td>42.56 (15.50)</td>
<td></td>
</tr>
<tr>
<td>Male mean age (SD)</td>
<td>40.41 (15.34)</td>
<td>41.05 (15.37)</td>
<td></td>
</tr>
<tr>
<td>Female mean age (SD)</td>
<td>43.63 (15.45)</td>
<td>44.30 (15.48)</td>
<td></td>
</tr>
<tr>
<td>Age group, y, n (percent)</td>
<td></td>
<td></td>
<td>&lt;0.0001†</td>
</tr>
<tr>
<td>12-17</td>
<td>574 (3.73)</td>
<td>1,203 (2.60)</td>
<td></td>
</tr>
<tr>
<td>18-34</td>
<td>4,670 (30.33)</td>
<td>13,956 (30.21)</td>
<td></td>
</tr>
<tr>
<td>35-44</td>
<td>2,865 (18.61)</td>
<td>8,586 (18.59)</td>
<td></td>
</tr>
<tr>
<td>45-54</td>
<td>3,964 (25.74)</td>
<td>11,706 (25.34)</td>
<td></td>
</tr>
<tr>
<td>55-64</td>
<td>2,472 (16.05)</td>
<td>7,935 (17.18)</td>
<td></td>
</tr>
<tr>
<td>65+</td>
<td>853 (5.54)</td>
<td>2,808 (6.08)</td>
<td></td>
</tr>
<tr>
<td>Geographic region</td>
<td></td>
<td></td>
<td>1.000</td>
</tr>
<tr>
<td>Northeast</td>
<td>1,821 (11.83)</td>
<td>5,463 (11.83)</td>
<td></td>
</tr>
<tr>
<td>North Central</td>
<td>4,016 (26.08)</td>
<td>12,048 (26.08)</td>
<td></td>
</tr>
<tr>
<td>South</td>
<td>5,627 (36.54)</td>
<td>16,881 (36.54)</td>
<td></td>
</tr>
<tr>
<td>West</td>
<td>3,893 (25.28)</td>
<td>11,679 (25.28)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>41 (0.27)</td>
<td>123 (0.27)</td>
<td></td>
</tr>
<tr>
<td>Health plan indicator</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Employer</td>
<td>12,426 (80.70)</td>
<td>38,188 (82.67)</td>
<td></td>
</tr>
<tr>
<td>Health plan</td>
<td>2,972 (19.30)</td>
<td>8,006 (17.33)</td>
<td></td>
</tr>
<tr>
<td>Type of benefit plan</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Missing/unknown</td>
<td>569 (3.70)</td>
<td>2,873 (6.22)</td>
<td></td>
</tr>
<tr>
<td>Comprehensive</td>
<td>909 (5.90)</td>
<td>2,205 (4.77)</td>
<td></td>
</tr>
<tr>
<td>EPO</td>
<td>131 (0.85)</td>
<td>449 (0.97)</td>
<td></td>
</tr>
</tbody>
</table>
visits (ninefold), surgical procedures (twofold), and laboratory tests (threefold) compared with nonabusers in the preindex and postindex period (Table 5). The average inpatient length of stay per hospitalization for abusers was 11-fold longer than for nonabusers in the preindex period (1.28 vs 0.12, respectively) and 13-fold longer in the postindex period (3.06 vs 0.23; Table 5). The DIDs for HRU were small though significant (Table 5).

Total all-cause healthcare costs (per patient per month) were five times higher for abusers than nonabusers in both the preindex ($1,856 vs $372, respectively) and postindex ($2,138 vs $408) periods; abusers had excess costs of $1,484 in the preindex period and $1,730 in the postindex period compared with matched controls (Figure 3; Table 5). The largest cost drivers were total outpatient and inpatient costs. Total outpatient costs were four times higher for abusers compared with nonabusers in the preindex ($777 vs $205) and postindex ($860 vs $221) periods. Total inpatient costs were eight times higher for abusers compared with nonabusers in the preindex ($712 vs $85) and postindex ($881 vs $101) periods. The cost for ED visits was nine times higher for abusers compared with nonabusers in both the preindex ($126 vs $13) and postindex ($129 vs $15) periods (Table 5). Abuse-related inpatient stays and abuse-related outpatient visits were higher in the postindex period ($301 and $116) than the preindex period ($89 and $26), respectively. The DID for total cost was $245 more for abusers (Table 5). The DID indicated inpatient utilization was the biggest cost driver. Abuse-related inpatient stays were 34 percent of the total inpatient costs.

The mean number of prescriptions filled per patient per month (including opioids and nonopioids) was greater for abusers than nonabusers in the preindex (3.4 vs 0.9, respectively) and postindex (3.4 vs 1.0) periods (p < 0.0001, Table 5). More abusers than nonabusers received an opioid prescription in both the preindex (68 percent vs 14 percent, respectively) and postindex (75 percent vs 22 percent) periods (p < 0.0001; Table 6). The mean number of opioid prescriptions per patient per month was greater for abusers (0.94 and 0.86) compared with nonabusers (0.06 and 0.06) in the preindex and postindex periods, respectively. Of the opioid prescriptions, SAO prescriptions were filled by more abusers and nonabusers than LAO prescriptions. Hydrocodone combinations were the most common SAO prescription filled (Table 6). The mean costs for all opioid prescriptions per patient per month were significantly higher for abusers compared with nonabusers in the preindex ($146 vs $3) and postindex ($161 vs $3) periods (p < 0.0001). The LAO prescriptions had a higher mean cost than the SAO prescriptions (Table 6). The DIDs in number of opioid prescriptions and cost were small and bidirectional (Table 6).

**DISCUSSION**

The results from this study affirm those of other studies that used similar methodology but different...
<table>
<thead>
<tr>
<th>Comorbidity condition</th>
<th>Preindex†</th>
<th>Postindex‡</th>
<th>Percent change in RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Other substance abuse</td>
<td>3,374 (21.91)</td>
<td>489 (1.06)</td>
<td>20.6</td>
</tr>
<tr>
<td>Nonopioid poisoning</td>
<td>659 (4.28)</td>
<td>102 (0.22)</td>
<td>19.5</td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td>6,842 (44.43)</td>
<td>3,149 (6.82)</td>
<td>6.5</td>
</tr>
<tr>
<td>HIV-AIDS</td>
<td>46 (0.30)</td>
<td>63 (0.14)</td>
<td>2.2</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>25 (0.16)</td>
<td>11 (0.02)</td>
<td>7.0</td>
</tr>
<tr>
<td>Skin infections/abscesses</td>
<td>949 (6.16)</td>
<td>929 (2.01)</td>
<td>3.1</td>
</tr>
<tr>
<td>Gastrointestinal bleed</td>
<td>1,115 (7.24)</td>
<td>1,226 (2.65)</td>
<td>2.8</td>
</tr>
<tr>
<td>Cirrhosis/chronic acute liver disease</td>
<td>356 (2.31)</td>
<td>276 (0.60)</td>
<td>3.9</td>
</tr>
<tr>
<td>Hepatitis A, B, or C</td>
<td>268 (1.74)</td>
<td>89 (0.19)</td>
<td>9.2</td>
</tr>
<tr>
<td>Alcoholic hepatitis</td>
<td>25 (0.16)</td>
<td>1 (0.00)</td>
<td>76.6</td>
</tr>
<tr>
<td>Other hepatitis</td>
<td>22 (0.14)</td>
<td>5 (0.01)</td>
<td>13.3</td>
</tr>
<tr>
<td>Pancreatitis</td>
<td>182 (1.18)</td>
<td>38 (0.08)</td>
<td>14.6</td>
</tr>
<tr>
<td>Sexually transmitted disease</td>
<td>527 (3.42)</td>
<td>986 (2.13)</td>
<td>1.6</td>
</tr>
<tr>
<td>Any pain condition</td>
<td>9,361 (60.79)</td>
<td>11,168 (24.18)</td>
<td>2.6</td>
</tr>
<tr>
<td>Herpes simplex</td>
<td>95 (0.62)</td>
<td>149 (0.32)</td>
<td>1.9</td>
</tr>
<tr>
<td>Burns</td>
<td>65 (0.42)</td>
<td>50 (0.11)</td>
<td>3.9</td>
</tr>
<tr>
<td>Trauma</td>
<td>3,707 (24.07)</td>
<td>4,118 (8.91)</td>
<td>2.7</td>
</tr>
<tr>
<td>Cancer</td>
<td>448 (2.91)</td>
<td>856 (1.85)</td>
<td>1.6</td>
</tr>
<tr>
<td>Low back pain</td>
<td>5,043 (32.75)</td>
<td>2,961 (6.41)</td>
<td>5.2</td>
</tr>
<tr>
<td>Other back/neck disorders</td>
<td>4,853 (31.52)</td>
<td>3,361 (7.28)</td>
<td>4.4</td>
</tr>
<tr>
<td>Arthritis</td>
<td>5,557 (36.09)</td>
<td>6,157 (13.33)</td>
<td>2.7</td>
</tr>
<tr>
<td>Neuropathic pain</td>
<td>1,272 (8.26)</td>
<td>1,059 (2.29)</td>
<td>3.7</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>1,082 (7.03)</td>
<td>437 (0.95)</td>
<td>7.5</td>
</tr>
<tr>
<td>Migraine/headache</td>
<td>1,779 (11.55)</td>
<td>1,307 (2.83)</td>
<td>4.1</td>
</tr>
</tbody>
</table>

HIV, human immunodeficiency virus; RR, relative risk.
*Data source: MarketScan Commercial Claims and Encounters and Medicare Supplemental databases (Thomson Reuters, 2008-2009).
†p < 0.0001 for all comparisons of abusers and nonabusers.
‡p < 0.0001 for percent change in RR.
§p < 0.05 for percent change in RR.
### Table 5. Healthcare resource utilization and cost among abusers and nonabusers in the preindex and postindex periods

<table>
<thead>
<tr>
<th>HRU and cost per patient per month</th>
<th>Preindex period†</th>
<th>Postindex period†</th>
<th>DID‡§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abusers (N = 15,398)</td>
<td>Nonabusers (N = 46,194)</td>
<td>Abusers (N = 15,398)</td>
</tr>
<tr>
<td><strong>Total cost (IP + OP + prescriptions), n (percent)</strong></td>
<td>14,855 (96.47)</td>
<td>35,369 (76.57)</td>
<td>15,391 (99.95)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>1,856 (4,446.1)</td>
<td>372 (1,406.3)</td>
<td>2,138 (4,577.3)</td>
</tr>
<tr>
<td><strong>IP total,§ n (percent)</strong></td>
<td>2,996 (19.46)</td>
<td>1,234 (2.67)</td>
<td>6,817 (44.27)</td>
</tr>
<tr>
<td><strong>Mean HRU (SD)</strong></td>
<td>0.05 (0.13)</td>
<td>0.01 (0.03)</td>
<td>0.07 (0.12)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>712 (3,552.7)</td>
<td>85 (1,007.6)</td>
<td>881 (3,831.0)</td>
</tr>
<tr>
<td><strong>OP total,</strong> n (percent)</td>
<td>14,424 (93.67)</td>
<td>32,139 (69.57)</td>
<td>15,352 (99.70)</td>
</tr>
<tr>
<td><strong>Mean HRU (SD)</strong></td>
<td>2.23 (2.33)</td>
<td>0.70 (1.11)</td>
<td>2.57 (2.34)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>777 (1,548.9)</td>
<td>205 (715.4)</td>
<td>860 (1,447.2)</td>
</tr>
<tr>
<td><strong>Prescriptions filled,</strong> n (percent)</td>
<td>13,195 (85.69)</td>
<td>28,383 (61.44)</td>
<td>13,974 (90.75)</td>
</tr>
<tr>
<td><strong>Mean HRU (SD)</strong></td>
<td>3.40 (3.31)</td>
<td>0.90 (1.44)</td>
<td>3.42 (3.10)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>367 (764.9)</td>
<td>82 (289.6)</td>
<td>398 (736.5)</td>
</tr>
<tr>
<td><strong>Other HRU and costs of interest</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Abuse-related IP stays,</strong> n (percent)</td>
<td>674 (4.38)</td>
<td>4,986 (32.38)</td>
<td>674 (4.38)</td>
</tr>
<tr>
<td><strong>Mean HRU (SD)</strong></td>
<td>0.01 (0.04)</td>
<td>0.04 (0.06)</td>
<td>0.01 (0.04)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>89 (1,027.7)</td>
<td>301 (955.4)</td>
<td>89 (1,027.7)</td>
</tr>
<tr>
<td><strong>Abuse-related OP visits,</strong> n (percent)</td>
<td>2,568 (16.68)</td>
<td>12,901 (83.78)</td>
<td>2,568 (16.68)</td>
</tr>
<tr>
<td><strong>Mean HRU (SD)</strong></td>
<td>0.17 (0.74)</td>
<td>0.52 (1.08)</td>
<td>0.17 (0.74)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>26 (180.5)</td>
<td>116 (262.7)</td>
<td>26 (180.5)</td>
</tr>
<tr>
<td><strong>Average IP length of stays per hospitalization, n (percent)</strong></td>
<td>2,996 (19.46)</td>
<td>1,234 (2.67)</td>
<td>6,817 (44.27)</td>
</tr>
<tr>
<td><strong>Mean (SD), days</strong></td>
<td>1.28 (3.81)</td>
<td>0.12 (1.00)</td>
<td>3.06 (5.45)</td>
</tr>
<tr>
<td><strong>Office visits, n (percent)</strong></td>
<td>13,036 (84.66)</td>
<td>28,552 (61.81)</td>
<td>14,325 (93.03)</td>
</tr>
<tr>
<td><strong>Mean HRU (SD)</strong></td>
<td>0.85 (0.87)</td>
<td>0.30 (0.40)</td>
<td>0.86 (0.78)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>80 (123.2)</td>
<td>27 (60.2)</td>
<td>85 (115.3)</td>
</tr>
</tbody>
</table>

*DID = DID of cost = Abusers - Nonabusers,†§§ Preindex period| Abusers (N = 15,398) | Nonabusers (N = 46,194) | Postindex period| Abusers (N = 15,398) | Nonabusers (N = 46,194) | DID†‡ |
Table 5. Healthcare resource utilization and cost among abusers and nonabusers in the preindex and postindex periods* (continued)

<table>
<thead>
<tr>
<th></th>
<th>Preindex period†</th>
<th>Postindex period‡</th>
<th>DID‡§</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Abusers (N = 15,398)</td>
<td>Nonabusers (N = 46,194)</td>
<td>Abusers (N = 15,398)</td>
</tr>
<tr>
<td>ED (IP or OP) visits, n (percent)</td>
<td>5,959 (38.70)</td>
<td>3,839 (8.31)</td>
<td>8,770 (56.96)</td>
</tr>
<tr>
<td>Mean HRU (SD)</td>
<td>0.18 (0.43)</td>
<td>0.02 (0.08)</td>
<td>0.18 (0.39)</td>
</tr>
<tr>
<td>Mean cost (SD), $</td>
<td>126 (416.3)</td>
<td>13 (98.3)</td>
<td>129 (396.3)</td>
</tr>
<tr>
<td>Surgical procedures (IP or OP), n (percent)</td>
<td>8,424 (54.71)</td>
<td>16,108 (34.87)</td>
<td>10,814 (70.23)</td>
</tr>
<tr>
<td>Mean HRU (SD)</td>
<td>0.30 (0.53)</td>
<td>0.13 (0.27)</td>
<td>0.29 (0.45)</td>
</tr>
<tr>
<td>Mean cost (SD), $</td>
<td>143 (613.4)</td>
<td>44 (255.4)</td>
<td>127 (401.0)</td>
</tr>
<tr>
<td>Laboratory tests, n (percent)</td>
<td>10,221 (66.38)</td>
<td>20,146 (43.61)</td>
<td>13,526 (87.84)</td>
</tr>
<tr>
<td>Mean HRU (SD)</td>
<td>0.39 (0.63)</td>
<td>0.16 (0.29)</td>
<td>0.47 (0.61)</td>
</tr>
<tr>
<td>Mean cost (SD), $</td>
<td>79 (238.1)</td>
<td>20 (122.5)</td>
<td>105 (254.8)</td>
</tr>
</tbody>
</table>

DID, difference in difference; ED, emergency department; HRU, healthcare resource utilization; IP, inpatient; OP, outpatient; SD, standard deviation.
*Data source: MarketScan Commercial Claims and Encounters and Medicare Supplemental databases (Thomson Reuters; 2008-2009).
†p < 0.0001 for all comparisons of abusers and nonabusers.
‡DID equals (abusers postindex − preindex) − (nonabusers postindex − preindex).
§p < 0.0001 for DID comparisons unless otherwise noted.
¶Includes all IP HRU and costs (ie, IP ED visits, IP laboratory tests, IP surgical procedures, abuse-related IP stays).
**Includes all OP HRU and costs (ie, OP ED visits, OP laboratory tests, OP surgical procedures, abuse-related OP visits).
††Includes all prescriptions filled (opioids and nonopioids).
‡‡Includes all IP stays associated with ICD-9-CM codes of interest (304.0X, 304.7X, 305.5X, 965.00, 965.02, and 965.09).
§§Includes all OP visits associated with ICD-9-CM codes of interest (304.0X, 304.7X, 305.5X, 965.00, 965.02, and 965.09).
¶¶Not significant.

Figure 3. Per patient per month costs for abusers and nonabusers for the preindex and postindex periods.
*p < 0.0001 compared with nonusers.
Table 6. No. of opioid prescriptions and cost among abusers and nonabusers in the preindex and postindex periods

<table>
<thead>
<tr>
<th>No. of opioid prescriptions and cost per patient per month</th>
<th>Preindex‡</th>
<th>Postindex‡</th>
<th>DID‡</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioid prescriptions, n (percent)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Opioid abusers (N = 15,398)</td>
<td>10,471 (68.00)</td>
<td>6,247 (31.52)</td>
<td>11,472 (74.50)</td>
</tr>
<tr>
<td>Nonabusers (N = 46,194)</td>
<td>6,247 (0.23)</td>
<td>0.86 (0.22)</td>
<td>0.06 (0.22)</td>
</tr>
<tr>
<td><strong>Mean prescriptions (SD)</strong></td>
<td>0.94 (1.12)</td>
<td>0.06 (0.23)</td>
<td>0.86 (0.92)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>146 (613.0)</td>
<td>3 (57.8)</td>
<td>161 (570.3)</td>
</tr>
<tr>
<td><strong>SAO prescriptions, n (percent)</strong></td>
<td>8,349 (54.22)</td>
<td>6,111 (31.23)</td>
<td>8,520 (55.33)</td>
</tr>
<tr>
<td><strong>Mean prescriptions (SD)</strong></td>
<td>0.60 (0.92)</td>
<td>0.05 (0.20)</td>
<td>0.43 (0.68)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>42 (465.3)</td>
<td>1 (42.7)</td>
<td>31 (429.8)</td>
</tr>
<tr>
<td><strong>Hydrocodone combinations, n (percent)</strong></td>
<td>5,980 (38.84)</td>
<td>3,943 (58.54)</td>
<td>6,000 (38.97)</td>
</tr>
<tr>
<td><strong>Mean prescriptions (SD)</strong></td>
<td>0.32 (0.62)</td>
<td>0.03 (0.15)</td>
<td>0.21 (0.44)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>7 (20.3)</td>
<td>0 (4.0)</td>
<td>4 (14.7)</td>
</tr>
<tr>
<td><strong>Oxycodone combinations, n (percent)</strong></td>
<td>2,739 (17.79)</td>
<td>1,097 (2.37)</td>
<td>3,081 (20.01)</td>
</tr>
<tr>
<td><strong>Mean prescriptions (SD)</strong></td>
<td>0.11 (0.34)</td>
<td>0.01 (0.06)</td>
<td>0.08 (0.25)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>6 (32.8)</td>
<td>0 (6.2)</td>
<td>5 (28.4)</td>
</tr>
<tr>
<td><strong>Oxycodone IR, n (percent)</strong></td>
<td>1,074 (6.97)</td>
<td>130 (0.28)</td>
<td>1,233 (8.01)</td>
</tr>
<tr>
<td><strong>Mean prescriptions (SD)</strong></td>
<td>0.05 (0.24)</td>
<td>0.00 (0.03)</td>
<td>0.04 (0.21)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>4 (35.4)</td>
<td>0 (1.4)</td>
<td>3 (26.6)</td>
</tr>
<tr>
<td><strong>Tramadol</strong></td>
<td>1,410 (9.16)</td>
<td>630 (1.36)</td>
<td>1,947 (12.64)</td>
</tr>
<tr>
<td><strong>Mean prescriptions (SD)</strong></td>
<td>0.04 (0.21)</td>
<td>0.01 (0.05)</td>
<td>0.04 (0.17)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>1 (6.4)</td>
<td>0 (1.9)</td>
<td>1 (4.6)</td>
</tr>
<tr>
<td><strong>All other SAO, n (percent)</strong></td>
<td>2,076 (13.48)</td>
<td>1,416 (3.07)</td>
<td>2,487 (16.15)</td>
</tr>
<tr>
<td><strong>Mean prescriptions (SD)</strong></td>
<td>0.07 (0.29)</td>
<td>0.01 (0.06)</td>
<td>0.06 (0.23)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>25 (461.5)</td>
<td>0 (41.9)</td>
<td>18 (427.2)</td>
</tr>
<tr>
<td><strong>LAO prescriptions, n (percent)</strong></td>
<td>5,921 (38.45)</td>
<td>351 (0.76)</td>
<td>7,778 (50.51)</td>
</tr>
<tr>
<td><strong>Mean prescriptions (SD)</strong></td>
<td>0.36 (0.60)</td>
<td>0.01 (0.08)</td>
<td>0.45 (0.64)</td>
</tr>
<tr>
<td><strong>Mean cost (SD), $</strong></td>
<td>102 (333.0)</td>
<td>2 (35.7)</td>
<td>130 (319.3)</td>
</tr>
</tbody>
</table>

*†‡§**
Table 6. No. of opioid prescriptions and cost among abusers and nonabusers in the preindex and postindex periods* (continued)

<table>
<thead>
<tr>
<th>No. of opioid prescriptions and cost per patient per month</th>
<th>Preindex‡</th>
<th>Postindex‡</th>
<th>DID‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Opioid abusers (N = 15,398)</td>
<td>Nonabusers (N = 46,194)</td>
<td>Abusers (N = 15,398)</td>
</tr>
<tr>
<td>Oxycodone ER, n (percent)</td>
<td>1,303 (8.46)</td>
<td>121 (0.26)</td>
<td>1,268 (8.23)</td>
</tr>
<tr>
<td>Mean prescriptions (SD)</td>
<td>0.07 (0.29)</td>
<td>0.00 (0.05)</td>
<td>0.05 (0.24)</td>
</tr>
<tr>
<td>Mean cost (SD), $</td>
<td>39 (296.6)</td>
<td>1 (30.8)</td>
<td>33 (265.0)</td>
</tr>
<tr>
<td>Morphine ER, n (percent)</td>
<td>976 (6.34)</td>
<td>87 (0.19)</td>
<td>1,049 (6.81)</td>
</tr>
<tr>
<td>Mean prescriptions (SD)</td>
<td>0.05 (0.24)</td>
<td>0.00 (0.04)</td>
<td>0.04 (0.21)</td>
</tr>
<tr>
<td>Mean cost (SD), $</td>
<td>8 (65.0)</td>
<td>0 (11.2)</td>
<td>7 (67.7)</td>
</tr>
<tr>
<td>Transdermal fentanyl, n (percent)</td>
<td>847 (5.50)</td>
<td>73 (0.16)</td>
<td>871 (5.66)</td>
</tr>
<tr>
<td>Mean prescriptions (SD)</td>
<td>0.04 (0.20)</td>
<td>0.00 (0.03)</td>
<td>0.03 (0.178)</td>
</tr>
<tr>
<td>Mean cost (SD), $</td>
<td>11 (77.5)</td>
<td>0 (9.1)</td>
<td>9 (63.9)</td>
</tr>
<tr>
<td>Buprenorphine</td>
<td>2,824 (18.34)</td>
<td>19 (0.04)</td>
<td>5,139 (33.37)</td>
</tr>
<tr>
<td>Mean prescriptions (SD)</td>
<td>0.15 (0.41)</td>
<td>0.00 (0.02)</td>
<td>0.28 (0.54)</td>
</tr>
<tr>
<td>Mean cost (SD), $</td>
<td>38 (109.5)</td>
<td>0 (5.4)</td>
<td>76 (151.4)</td>
</tr>
<tr>
<td>Methadone, n (percent)</td>
<td>649 (4.21)</td>
<td>38 (0.08)</td>
<td>750 (4.87)</td>
</tr>
<tr>
<td>Mean prescriptions (SD)</td>
<td>0.03 (0.167)</td>
<td>0.00 (0.024)</td>
<td>0.03 (0.159)</td>
</tr>
<tr>
<td>Mean cost (SD), $</td>
<td>1 (4.40)</td>
<td>0 (0.60)</td>
<td>1 (4.30)</td>
</tr>
<tr>
<td>All other LAO,** n (percent)</td>
<td>799 (5.19)</td>
<td>83 (0.18)</td>
<td>942 (6.12)</td>
</tr>
<tr>
<td>Mean prescriptions (SD)</td>
<td>0.03 (0.18)</td>
<td>0.00 (0.03)</td>
<td>0.03 (0.16)</td>
</tr>
<tr>
<td>Mean cost (SD), $</td>
<td>1 (11.8)</td>
<td>0 (3.1)</td>
<td>1 (10.9)</td>
</tr>
</tbody>
</table>

DID, difference in difference; ER, extended release; HCl, hydrochloride; IR, immediate release; LAO, long-acting opioid; SAO, short-acting opioid; SD, standard deviation.

*Data source: MarketScan Commercial Claims and Encounters and Medicare Supplemental databases (Thomson Reuters; 2008-2009).

†p < 0.0001 for all comparisons of abusers and nonabusers.

‡DID equals (abusers postindex – preindex) – (nonabusers postindex – preindex).

§p < 0.001.

¶All other SAO include oral transmucosal fentanyl, hydromorphone HCl, acetaminophen/butalbital/caffeine/codeine phosphate, acetaminophen/coffine/dihydromorphone bitartrate, acetaminophen/codeine phosphate, acetaminophen/pentazocine HCl, acetaminophen/proxyphene HCl, acetaminophen/proxyphene napsylate, aspirin/butalbital/coffine/codeine phosphate, aspirin/codeine phosphate, butorphanol tartrate, codeine sulfate, fentanyl citrate, meperidine HCl/promethazine HCl, meperidine HCl, methadone HCl, naloxone HCl/pentazocine HCl, opium, proxyphene HCl, proxyphene napsylate, tapentadol HCl.

**All other LAO include tramadol ER, oxymorphone ER, hydromorphone HCl and levorphanol tartrate.
databases, demonstrating that the annual prevalence of diagnosed opioid abuse has increased over time, diagnosed abusers are associated with significantly greater HRU and costs compared with nonabusers, and diagnosed abusers are associated with a greater RR for comorbidities and use of prescription opioids compared with nonabusers. This study expanded on previous studies by evaluating prevalence over time by geographic region and RR over time by gender, presence of comorbidities, and presence of prescription opioids. In addition, for the most recent calendar year in the database, this study also compared comorbidities, HRU, costs, and specific prescription opioid use during both the preindex (ie, before the date of diagnosed abuse) and postindex periods.

There was a 116 percent increase in the annual prevalence of diagnosed opioid abuse from 2005 to 2010 in this population. White et al. reported an increase of 336 percent from 1999 to 2007 in a privately insured database and an 183 percent increase from 1999 to 2006 in the Florida Medicaid population. Comparing similar years (2005-2007), the prevalence of diagnosed abuse was about 50 percent lower in the population studied here. This may be due, in part, to the inclusion of Medicare patients in the current study. Indeed, the prevalence of diagnosed opioid abuse in patients aged ≥65 years was lower compared with the other age groups.

Consistent with the increase in diagnosed abuse from 2005 to 2010, the prevalence increased in each geographical region over this period of time with the Northeast having the greatest increase. This is similar to the study that examined the Medicaid population in 2002-2003 in which the Eastern region had the highest prevalence of 1.9 percent compared with the other regions (0.5-0.6 percent). The 2010 NSDUH survey results reported the rates of past year substance dependence or abuse of illicit drugs or alcohol were highest in the West (10.0 percent), followed by the Northeast (8.9 percent), Midwest (8.8 percent), and the South (7.8 percent). This is of interest as much of the media attention given to the abuse of prescription opioids often describes the problem as being more common in the South (Appalachia and Florida). Although the data from the current study suggest increased prevalence of opioid abuse in the Northeast, possible explanations for this high prevalence may include regional differences in practice or diagnosis, or population density.

This study demonstrated the RR for diagnosed abuse was consistently greater in males each year (20-40 percent greater), which is similar to a previous study in which 33 percent more abusers were male. The 2010 NSDUH survey results reported the past year nonmedical use of pain relievers to be 40 percent greater among males; however, other studies have reported more abusers to be female. White et al. reported 9 percent and 66 percent more abusers were female in both the privately insured and Florida Medicaid database, respectively. Similarly, McAdam-Marx et al. reported that 4 percent more abusers were female than male in the US Medicaid population. The differences noted in the proportion of male and female abusers in the different studies may be caused by the differences in the populations studied.

The two most prevalent comorbidities among abusers, beside any pain condition, were other substance abuse and psychiatric disorders, similar to the findings described in previous studies. Other substance abuse and psychiatric disorders occurred at higher percentages in abusers compared with nonabusers in both the preindex and postindex periods. It is not surprising that these two comorbidities are higher among abusers and identified as a key characteristic associated with abuse as Rice et al. demonstrated.

The greater RR for pain comorbidities each year from 2005 to 2010 (RR, 3.9-5.4) and of having a prescription for an opioid (7.1-11.6) among abusers compared with nonabusers in this study is similar to other studies. However, two of these studies reported the RR much lower for both any painful comorbidity (1.3 and 2.8) and having a prescription for an opioid (1.5 and 3.0). Another study had a similar RR for any painful comorbidity and presence of a prescription for an opioid in both the privately insured and Florida Medicaid population as in this study.

Comparing excess healthcare cost of diagnosed abusers in this study with two previous studies that used an employer insurance database demonstrates similar results when adjusting for the consumer price index (CPI; www.bl.gov/cpi/). In this study, when excess costs postindex are annualized, the excess cost of diagnosed abusers is $20,752 in 2011. The excess cost of the 2005 and 2011 White et al. studies when adjusted for CPI is $18,622 and $21,881, respectively. The majority of costs were inpatient or outpatient related, and prescription costs accounted for about one-fifth of total costs.
This study was unique in that it evaluated comorbidities, HRU/costs, and prescription opioid use in the 6 months before the diagnosis of abuse. Of interest is that all endpoints evaluated in the 6-month period before a diagnosis of opioid abuse were also significantly greater for abusers compared with nonabusers. This may be caused by ongoing abuse, albeit undiagnosed, occurring within the abuser cohort before a diagnosis is made. One study indicated that among those admitted to a substance treatment center, prescription opioid abuse progressed from recreational abuse (eg, undiagnosed) to substance abuse treatment admission in an average time of ~19 months. This highlights the importance of identifying risks for abuse early.

Differences were observed in the RR for several comorbidities between the preindex and postindex periods. The significant increase in RR for postindex nonopioid poisoning compared with the preindex may be due to the recognition of abuse or the increased severity of the disease. The significant decrease in RR for psychiatric disorders, pancreatitis, and any pain condition is of interest; however, it is unclear that the diagnosis of abuse would explain this decrease.

Like previous studies that reported greater prescription opioid use among abusers, we found that 75 percent of abusers had an opioid prescription compared with 22 percent of nonabusers in the postindex period. White et al. reported 66 percent of diagnosed opioid abuse patients had a prescription for an opioid compared with 20 percent of matched controls in the privately insured database, and 74 percent of diagnosed opioid abuse patients had a prescription for an opioid compared with 30 percent of matched controls in the Florida Medicaid database. The authors also found that SAO were used by more patients than LAO for both of the diagnosed abuse and matched control populations evaluated. In Medicaid population study (MAX files), 53 percent of abusers and 35 percent of matched controls had at least one prescription claim for an opioid. In this study, we also found that significantly more abusers had a preindex prescription opioid than nonabusers. Similar to White et al., we found that SAO were used by more patients than LAO. The predominant SAO used in the preindex and postindex periods was hydrocodone, the most prescribed opioid. Buprenorphine was the predominant LAO used in both the preindex and postindex periods; this may be due to the use of buprenorphine to treat opioid dependence.

Results of the present study must be viewed against the limitations of the study. First, a potential exists for misclassification of diagnosed abuse based on standard ICD-9-CM codes in healthcare claims data. Secondly, ICD-9-CM codes do not allow for differentiation between abuse of prescription opioids and abuse of nonprescription (illicit) drugs. Third, the ICD-9-CM codes rely on clinician recognition and training in opioid abuse and addiction; the extent of this recognition and training is not known. Fourth, it is possible that undiagnosed abusers were included in the nonabusers group. Fifth, the cost and comorbidity profile described in this study is only for diagnosed abuse patients and may underreport the total nonmedical use of prescription opioids.

**CONCLUSIONS**

In the population studied, the overall prevalence of diagnosed abuse more than doubled from 2005 to 2010 with the Northeast region experiencing the greatest increase. Diagnosed abuse was more prevalent in males, those aged 18 to 25 years, those with a comorbidity of pain, and those with an opioid prescription for each year evaluated. In the most recent year evaluated, diagnosed abusers were associated with significantly greater HRU and costs compared with nonabusers before and after the index date of diagnosed abuse (ie, the preindex and postindex periods). The results from this study affirm those of other studies that used similar methodology but different databases.11-13

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REFERENCES


Increased opioid prescribing for the management of chronic noncancer pain has been accompanied by an increase in opioid abuse. A 2007 US government survey found that 14 percent of adults engaged in nonmedical use of pain relievers during their lifetime, including nearly 2 percent who reported inappropriate use of oxycodone. These data reflect abuse rates among individuals who were prescribed analgesic medications legitimately and those who obtained them illegitimately. Given widespread abuse, it is not surprising that many primary care physicians are concerned about the risk of opioid abuse and lack confidence in how to minimize that risk. For example, it has been shown that implementation of a urine drug monitoring protocol may decrease the rate of substance abuse in opioid-treated patients by 50 percent, yet the majority of physicians who prescribe opioids do not routinely conduct urine drug monitoring, and most prescribers have difficulty interpreting urine drug monitoring results accurately.

For prescribers, potential strategies to reduce prescription opioid abuse include implementation of the recommendations of clinical guidelines on the use of opioids; appropriate use of formulations...
designed with impediments to abuse; and compliance with legislative and regulatory measures addressing prescription drug abuse, such as the US Food and Drug Administration (FDA) long-acting opioid Risk Evaluation and Mitigation Strategies (ERLA opioid REMS), Washington State Guidelines on Opioid Dosing, and the Florida State Law on Controlled Substance Prescribing. We compiled a list of nine distinct strategies for minimizing abuse and responding to aberrant drug-related behaviors:

1. conducting a thorough patient assessment (history and physical);
2. assessment of the risk for substance abuse;
3. use of controlled-substance agreements;
4. selection of an appropriate opioid and careful dose titration;
5. observance of an opioid dose ceiling for most patients;
6. use of formulations designed with impediments to tampering;
7. compliance monitoring (eg, pill counts and urine screening);
8. adherence to practice guidelines; and
9. compliance with regulatory and legal measures.

Given the prevalence of opioid prescribing and opioid abuse, it is important to determine whether the effectiveness of these recommended strategies is substantiated by clinical outcomes research. We performed a systematic review to identify and grade the level of evidence of data in support of potential strategies for minimizing abuse potential and responding to aberrant drug-related behaviors in opioid-treated patients.

**SEARCH METHODS**

**Strategy**

Searches of PubMed under nine general headings (detailed below) related to minimizing opioid abuse risk and addressing aberrant drug-related behavior were performed on January 18, 2013, for English language clinical trials and practice guidelines published in the past 5 years. Results obtained were reviewed to identify citations relevant to assessing the effectiveness of strategies for minimizing abuse risk and addressing aberrant drug-related behavior. We consulted current pain society guidelines from the United States and Canada on opioid therapy for chronic noncancer pain, which summarizes thorough literature reviews on these topics, and we also reviewed the literature to identify articles published more than 5 years ago.

**Individual searches**

Search 1, regarding patient assessment, used the search terms, “initial examination OR initial screening OR baseline screening OR initial medical assessment OR medical history AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 74 citations, of which eight were found to be relevant.

Search 2, regarding risk assessment, used the search terms, “current opioid misuse measure OR opioid risk tool OR screener and opioid assessment for patients with pain revised OR SOAPP-R OR risk assessment tools OR risk of abuse AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 122 citations, of which eight were found to be relevant.

Search 3, regarding controlled-substance agreements, used the search terms, “contract OR agreement AND (controlled substance OR opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 31 citations, of which three were found to be relevant.

Search 4, regarding dose titration, used the search terms, “dose escalation OR dose titration OR increasing dose AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 34 citations, of which one was found to be relevant.
Search 5, regarding dose ceiling, used the search terms, “opioid AND high dose AND abuse” and identified 42 citations, of which five were found to be relevant upon manual review.

Search 6, regarding formulations designed with impediments to abuse, used the search terms, “abuse deterrent OR abuse resistant OR crush resistant OR tamper resistant OR opioid antagonist OR naloxone OR naltrexone OR aversive OR aversion OR niacin OR prodrug AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxycodone OR oxymorphone OR Acurolx OR Embeda OR Remoxy OR Oxecta OR Egalet OR Suboxone OR TQ-1015 OR COL-003) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 604 citations, of which six were found to be relevant upon manual review.

Search 7, regarding compliance monitoring, used the search terms, “urine testing OR urine screening OR urine toxicology OR urine analysis OR urinalysis AND (opioid) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 115 references, of which 12 were found to be relevant.

Search 8, regarding compliance with clinical guidelines, used the search terms, “treatment guidelines OR practice guidelines OR guideline adherence OR protocol adherence OR guideline AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 44 references, of which two were found to be relevant.

Search 9, regarding legal and regulatory measures, used the search terms, “legislation OR law OR regulation OR regulatory OR prosecution OR penalty OR risk evaluation and mitigation’ OR ERLA opioid REMS AND (opioid OR buprenorphine OR codeine OR fentanyl OR hydrocodone OR hydromorphone OR morphine OR oxymorphone) AND (abuse OR addict OR misuse OR dependence OR overdose OR death OR fatal).” This search identified 111 references, of which five were found to be relevant.

Levels of evidence

The articles identified using this search strategy were graded on a scale adapted from the Oxford Centre for Evidence-Based Medicine (CEBM) Levels of Evidence (Table 1). Articles with level 1 (strong) evidence include systematic reviews of randomized, controlled clinical trials (RCTs) and individual RCTs with a narrow confidence interval; level 2 (moderate to strong) evidence includes systematic reviews of cohort studies, individual cohort studies, and low-quality RCTs. Level 3 (weak to moderate) evidence includes systematic reviews of case-control studies and individual case control studies, and level 4 (weak; incorporating CEBM levels 4 and 5) evidence includes case series and expert opinion without an explicit critical appraisal, or statements based on physiology, bench research, or first principles.

ABERRANT DRUG-RELATED BEHAVIOR DEFINED

Aberrant drug-related behaviors include any behavior that suggests nonmedical use of a drug and/or addiction. Common opioid-related aberrant drug-related behaviors typically fall within several categories, as summarized in Table 2. These categories include efforts to obtain opioids for misuse from sources other than the patient’s doctor. Research has shown that many patients steal or are given opioids by family members or friends with legitimate prescriptions and that opioids are also

<table>
<thead>
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<th>Table 1. Levels of evidence†</th>
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<td>Level of evidence</td>
<td>Type of evidence</td>
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<tr>
<td>1</td>
<td>SR of RCTS</td>
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<tr>
<td>1</td>
<td>RCT with narrow CI</td>
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<td>2</td>
<td>SR of cohort studies</td>
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<td>Cohort study</td>
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<td>2</td>
<td>Low-quality RCT</td>
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<td>SR of case control studies</td>
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<td>4</td>
<td>Case series</td>
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<td>4</td>
<td>Bench research</td>
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<td>Expert opinion</td>
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*Level 4 included Oxford Center for Evidence-Based Medicine levels 4 and 5. CI, confidence interval; RCT, randomized controlled trial; and SR, systematic review.
often diverted or stolen from pharmacies, medical practices, drugmakers, and addiction treatment centers.\textsuperscript{20} Patients may also attempt to obtain opioids by asking for frequent dosage increases or complaining of lost prescriptions. Evidence that a patient is not taking his prescribed opioid is also an aberrant drug-related behavior, potentially indicating that the patient is diverting the opioid.\textsuperscript{14}

**STRATEGIES TO PREVENT AND IDENTIFY ABERRANT DRUG-RELATED BEHAVIORS**

Our review of the literature evaluated nine basic strategies for preventing and identifying aberrant drug-related behaviors (Table 3). Levels of evidence for these strategies are presented below.

**Patient assessment**

Guidelines published in the United States\textsuperscript{7,9} and Canada\textsuperscript{6} recommend a thorough medical history and physical examination to establish the pain diagnosis, assess general medical condition and psychiatric status, and prior history of abuse. These recommendations are based on weak to moderate evidence that the strongest risk factors for current abuse are a history of abuse and psychiatric conditions.

As noted in US guidelines, a well-established and documented diagnosis of pain is essential before initiating opioid therapy. Factors to consider include the cause and severity of pain, its effects on function and quality of life, and prior treatment with opioids or nonopioid analgesics. These considerations are part of the risk versus benefit assessment regarding therapeutic choices which may indicate that, on balance, opioid therapy may not be appropriate for a given patient.\textsuperscript{7}

Level 2 evidence suggests that patients with a history of substance abuse have a higher risk of current abuse\textsuperscript{21-25} and that the majority of opioid abusers also have a history of abusing nonopioid substances, such as alcohol, nicotine, and other legal and illegal drugs.\textsuperscript{26-28} Level 2 evidence suggests that it is important to identify psychiatric conditions known to be frequently comorbid with substance abuse, such as depression, anxiety, bipolar disorder, and posttraumatic stress disorder.\textsuperscript{21,22,26-30} Several personality disorders (PDs) have also been associated with risk of substance abuse, including conduct disorder in adolescence, schizotypal PD, passive-aggressive PD, and borderline PD.\textsuperscript{30} Level 2 evidence also suggests that a history of physical or sexual abuse is associated with an increased risk of substance abuse,\textsuperscript{31} and that individuals who have contemplated or attempted suicide are also at increased risk.\textsuperscript{28}

In a study of 1,408 patients treated for opioid

<table>
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<th>Table 2. Common aberrant behaviors\textsuperscript{16-18}</th>
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<tr>
<td>Altering route of delivery</td>
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<tr>
<td>Crushing tablet to facilitate rapid release from tablet</td>
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<tr>
<td>Extraction in fluid for injection</td>
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<tr>
<td>Obtaining opioids from other sources</td>
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<tr>
<td>Diverted medicine</td>
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<tr>
<td>Doctor shopping</td>
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<tr>
<td>Stealing from another patient’s prescription</td>
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<tr>
<td>Borrowing drugs from another patient</td>
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<tr>
<td>Obtaining from nonmedical sources (eg, dealers)</td>
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<tr>
<td>Unsanctioned use</td>
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<tr>
<td>Taking more or less than the prescribed dose</td>
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<tr>
<td>Unauthorized dose escalations</td>
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<tr>
<td>Bingeing</td>
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<tr>
<td>Removing all or part of a supervised dose from the dosing site</td>
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<tr>
<td>Stockpiling</td>
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<tr>
<td>Drug seeking</td>
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<tr>
<td>Patient requests for higher doses</td>
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<tr>
<td>Recurrent prescription losses</td>
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<tr>
<td>Repeated requests for faxed prescriptions or fit-in appointments</td>
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<tr>
<td>Claims that nothing else works</td>
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<tr>
<td>Requests for specific drugs or brands</td>
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<tr>
<td>Prescription forgery</td>
</tr>
<tr>
<td>Patient statements</td>
</tr>
<tr>
<td>Acknowledgment of addiction</td>
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<tr>
<td>Admission of mood-elevating opioid effects</td>
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<tr>
<td>Acknowledgment of withdrawal symptoms</td>
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<tr>
<td>Resistance to changing therapy despite evidence of physical or psychological problem</td>
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<tr>
<td>Other behaviors</td>
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<tr>
<td>Concurrent use of other legal and/or illicit drugs</td>
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<tr>
<td>Selling or diversion</td>
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<tr>
<td>Missed prescriber appointments</td>
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<tr>
<td>Evidence of functional deterioration</td>
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</table>

In a study of 1,408 patients treated for opioid
abuse, two thirds of women and a little more than half of men had been treated for a psychiatric disorder (eg, depression, anxiety, and bipolar disorder) within the prior 12 months. Depression, anxiety disorders, and bipolar disorder are among the psychiatric diagnoses that may be neglected in the primary care setting, which means that abuse risk in the subset of these patients for whom opioids may be indicated may be underestimated.

**Reassessment of risk during treatment.** Guidelines for safe, effective opioid use recommend that regular reassessments should be conducted to identify evidence of behavioral or physical changes that may result from therapy, but again, this recommendation is supported by weak evidence. Aberrant drug-related behaviors such as those outlined in Table 2 may emerge with continued treatment, and persistent use and/or withdrawal symptoms may mean that the patient has become dependent on their opioid. Level 4 evidence suggests that clinicians should also regularly reassess the painful condition and document findings. Requests for increased opioid doses may reflect drug seeking, but it may also signal an increase in pain due to progression of the painful condition. Inadequate pain relief can precipitate behaviors described earlier: requests for more medication, attempts to obtain medication from other sources, taking doses higher than those prescribed and then running out. As stated earlier, level 4 evidence suggests that abuse risk changes over time, making repeat assessments an appropriate precaution, although the value of reassessment for preventing aberrant drug-related behaviors has not been demonstrated.

**Risk assessment**

**Assessment at initiation of opioid therapy.** There are currently several validated screening tools for assessment of pretreatment opioid abuse risk, including the Current Opioid Misuse Measure (COMM), Opioid Risk Tool (ORT), Screener and Opioid Assessment for Patients with Pain–Revised (SOAPP-R), and Prescription Drug Use Questionnaire. However, as stated in US and Canadian guidelines, only weak evidence supports the utility of these instruments for identifying patients at risk of opioid abuse.

Level 2 evidence suggests that risk factors included in screening tools vary between populations in ways that the screening tools do not pick up. For example, in a survey of older patients (n = 163) with chronic pain (level 2 evidence), risk factors for abuse included higher pain severity, lower

| Table 3. Identifying and preventing aberrant drug-related behaviors |
|----------------------|-----------------|
| Risk-reduction strategy | Level of evidence |
| Patient assessment | |
| Medical history and examination to determine legitimate analgesic needs prior to treatment | 2 |
| Assessment for psychiatric comorbidity | 2 |
| Reassessment of analgesic needs and psychiatric comorbidities during treatment | 4 |
| Assessment of abuse risk | |
| Validated screening tools (COMM, SOAPP-R, and ORT) to identify current or past drug abuse or heightened risk of abuse | 4 |
| Treatment agreement/contract | |
| Define appropriate opioid use | Lack of evidence |
| Establish compliance monitoring protocols | Lack of evidence |
| Agree on steps to be taken in response to signs of opioid misuse | Lack of evidence |
| Opioid selection and titration | |
| Start with low-potency opioids | 2-3 |
| Use long-acting formulations | 4 |
| Start with a low dose and titrate slowly | 4 |
| Observe a dose ceiling for most patients | 1-2 |
| Use tamper-resistant opioid formulations | 1-4 |
| Compliance monitoring, including | |
| Urine drug screening | 2-4 |
| Pill and patch counts | 2-4 |
| Feedback from pharmacies or caregivers | 2-4 |
| Continuous physician-patient communication | 2-4 |
| Adherence with treatment guidelines | Lack of evidence |
| Compliance with regulatory and legal measures | Lack of evidence |

COMM, Current Opioid Misuse Measure; ORT, Opioid Risk Tool; and SOAPP-R, Screener and Opioid Assessment for Patients with Pain–Revised.
disability scores, and depression. Problems with alcohol were not associated with increased risk. Risk factors such as alcohol are included in screening tools such as the SOAPP-R and ORT, but variability of risk according to age is not addressed in these assessments.6

Level 2 evidence suggests that there are also sex-specific factors that modify the importance of specific risk factors addressed in available screening tools. In an analysis of 29,906 patient assessments at 220 addiction treatment centers (level 2 evidence), men were more likely than women to abuse opioids at age ≥54 years; be manual laborers; have a history of incarceration; drink to intoxication >3 times weekly; or use marijuana, heroin, hallucinogens, or more than one substance. Women were more likely than men to live with children; be professionals or in management; use benzodiazepines or amphetamines; have medical or psychiatric problems; or have a history of suicide attempts, depression, anxiety, or emotional, physical, or sexual abuse.22 As with age, assessment tools such as the COMM or SOAPP-R do not capture sex-related differences for specific risk factors.

Level 4 evidence suggests that additional risk factors such as legal problems, a history of victimization, mental and physical health status, and geographic location are risk factors that are not captured in standard screeners and may be subject to change over time.35 Level 4 evidence also suggests that a majority of clinicians will comply with implementation of a uniform protocol for assessing abuse risk at the beginning of treatment, provided that the assessment tools are concise, are clinically relevant, and suit the time constraints of practice.42

Controlled-substance agreements

United States guidelines7,9,40 fall short of recommending a controlled-substance agreement. However, they do cite level 4 evidence (expert opinion) that a controlled-substance agreement may help clarify the treatment plan with the patient, patient’s family, and other clinicians involved in the patient’s care. Level 4 evidence also suggests that controlled-substance agreements may contain stipulations that patients may only get opioids from one pharmacy and fill prescriptions at one pharmacy, more frequent prescribing of smaller amounts of opioids, compliance monitoring protocols, and a list of aberrant drug-related behaviors that may prompt discontinuation of therapy. Canadian6 guidelines recommend that physicians and patients should enter into a controlled-substance agreement, citing weak evidence from several small trials but no randomized controlled trials. Level 1 evidence suggests that clinicians instructed in the use of controlled-substance agreements will use them15 and that identification of aberrant drug-related behaviors may lead to discontinuation of the agreement.39,43 However, evidence is lacking that these agreements reduce the frequency of aberrant drug-related behavior.

Level 2 evidence from a survey of 84 physician/patient pairs found that most clinicians entered into controlled-substance agreements with only a minority of their patients who were prescribed opioids, and that physicians were more likely to do so if the patient was considered to be at high risk of substance abuse. Approximately 40 percent of patients whose physicians reported they had a controlled-substance agreement in place reported that they were unaware of it; roughly one third of patients reported uncertainty about having a controlled-substance agreement in place regardless of whether their physician reported that one was in place.44 Hence, the value of these agreements may be limited by a lack of communication and consistency in their use.

Initial opioid selection and dose titration

First-line opioids. Canadian guidelines suggest that opioid therapy should start with a lower potency opioid, such as codeine or tramadol, which have been shown in some studies to have lower attractiveness for abuse and lower rates of abuse relative to the frequency with which they are prescribed compared with oxycodone, hydromorphone, and hydrocodone (level 2-3 evidence).6 United States guidelines say little about individual selection of opioids.7,9 In the United States, hydrocodone is both the most commonly prescribed first-line opioid and the most commonly abused opioid; however, it should be noted that although the total quantity of hydrocodone abused is large compared with other opioids, the proportion of all hydrocodone prescriptions that are diverted to abuse is low (level 2 evidence).45

High potency opioids. When low potency opioids prove ineffective, Canadian guidelines recommend a trial of a high-potency opioid, such as morphine, hydromorphone, oxycodone, or oxymorphone.6 The Canadian guidelines cite level 2 evidence that oxycodone, hydromorphone, and
perhaps hydrocodone have greater abuse liability compared with morphine, based on data from a large US population health surveillance database. They also cite level 1 evidence that oxycodone has more positive subjective effects compared with equianalgesic doses of morphine and level 2 evidence that oxycodone, hydromorphone, and hydrocodone have similar abuse liability.6

United States guidelines state that there is insufficient evidence to prefer the use of a long-acting formulation over a short-acting formulation for chronic pain on the basis of efficacy or safety considerations.7,9 However, Canadian guidelines recommend that older patients be prescribed long-acting opioids for reasons of treatment compliance and because these have more stable pharmacokinetics and pharmacodynamics, citing only level 4 evidence (expert opinion).6 With respect to mitigating the risk of opioid abuse, it must be remembered that extended-release (ER) formulations contain larger amounts of opioid compared with immediate-release (IR) formulations, potentially making them attractive for abusers who tamper with tablets by crushing them to accelerate oral release or facilitate intranasal use, or by dissolving them in a liquid to create a solution for intravenous abuse.46

**Dose titration.** Guidelines recommend that opioid treatment should begin as a time-limited trial with a small initial dose that is titrated slowly. Canadian guidelines recommend initial dosages equivalent to 5-10 mg of morphine four times daily, with incremental increases of 5-10 mg/wk. The preferred dose will result in a ≥2-point reduction in subjective pain rating on a 10-point scale and/or a similar improvement in function.

Level 4 evidence suggests that this method of slow, gradual titration might prevent administration of unnecessarily high opioid doses.6 During titration, opioids should be prescribed in small amounts (eg, weekly rather than monthly) to allow the clinicians to gauge response with each increase and watch for signs of aberrant drug-related behavior.47

Although this is intuitive, a single 135-patient study of veterans prescribed opioids for chronic pain found no difference in the occurrence of aberrant drug-related behaviors between patients held on a stable dose and those using a more liberal dose-escalation strategy (level 1 evidence).48 The present literature search found no published data supporting the value of slow, gradual titration as a means of preventing misuse.

**Dose ceiling**

Both 2009 US7 and 2011 Canadian6 guidelines state that doses above a morphine-equivalent (MED) 200 mg/d are considered high, with the Canadian guidelines surpassing the US guidelines by stating that the 200-mg MED should be the ceiling dose for most patients. Subsequent guidelines published in 2012 by the American Society of Interventional Pain Physicians (ASIPP) state that daily MED doses >90 mg are to be considered high.49 MED conversions for available opioids can be calculated using several online resources, including the Practical Pain Management Opioid Calculator,50 the GlobalRPh calculator,51 and the Johns Hopkins Opioid Conversion Program calculator.52

A systematic review (level 2 evidence) of 62 trials of high-potency opioids presented in the most recent Canadian guidelines found that for most patients, the preferred dose was well below 200-mg/d MED.6 Doses above 200 mg/d are considered high-dose therapy in both US7 and Canadian6 guidelines for the use of opioids. The Canadian guidelines recommend careful reassessment of patients approaching this “watchful dose.”47 As stated, the most recent US guidelines set the threshold for high-dose therapy much lower, at >90 mg/d MED.49

This is consistent with level 1 evidence that higher doses have been associated with an increased risk of overdose and mortality.53-56 In response to this increase, the state of Washington imposed a 120-mg/d MED ceiling on opioid prescriptions.11 Level 2 evidence demonstrated that imposition of this ceiling was accompanied by a 50 percent reduction opioid-related mortality in the state.57

**Formulations designed with impediments to abuse**

Patients who abuse ER opioids may manipulate them to accelerate opioid release from ingestion (eg, by chewing) or to alter the route of delivery to increase the rate of release from the tablet, which typically involves crushing of the tablet for insufflation or dissolving it in a solvent for intravenous use (level 3 evidence).46 Rapid onset of effect is an important factor increasing the attractiveness of an opioid for abuse (level 3 evidence).58 Increasingly, ER opioids are being reformulated to incorporate physical or chemical impediments to these types of
tampering (Table 4). Oxycodone CR, oxymorphone ER, and tapentadol ER are each formulated with hardened matrices designed to resist crushing and to turn into a viscous gel when immersed in fluids, making it difficult to either snort or inject the product. A formulation of oxycodone IR with potentially aversive ingredients is designed to cause mucosal irritation if the product is insufflated; however, the prescribing information does not disclose which ingredient(s) cause the aversive effects. Morphine ER with sequestered naltrexone is designed so that its opioid effects will be neutralized by naltrexone if it is crushed. This product was approved and then withdrawn from the market owing to issues related to the stability of the formulation. These formulations are not discussed in current guidelines, which were published before any of these formulations received clinical approval or had data supporting their value for preventing abuse. However, early evidence of level 1-4 quality suggests that these formulations may be less easily tampered with and therefore less attractive for abuse than older formulations.

Table 4. Currently available opioids with tamper-resistant features

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Tamper-resistance strategy</th>
</tr>
</thead>
<tbody>
<tr>
<td>OxyContin® (oxycodone CR)</td>
<td>Matrix resists crushing</td>
</tr>
<tr>
<td>Opana® ER (oxymorphone ER)</td>
<td>Forms a viscous gel on dissolution that is difficult to inject</td>
</tr>
<tr>
<td>Nucynta® ER (tapentadol ER)</td>
<td>Sequestered antagonist is released if the product is crushed or dissolved, neutralizing opioid effects</td>
</tr>
<tr>
<td>Embeda® (morphine/naltrexone CR)</td>
<td></td>
</tr>
<tr>
<td>Oxecta® (oxycodone IR)</td>
<td>Aversive ingredients cause mucosal irritation if the product is crushed and abused intranasally</td>
</tr>
</tbody>
</table>

The value of reformulated oxycodone CR, the first tamper-resistant formulation to reach the market, consists of a level 1 randomized, placebo-controlled trial and level 2 postmarketing data. In 19 healthy recreational drug users, reformulated oxycodone CR was associated with lower drug-liking scores compared with oxycodone IR. Oxycodone CR had to be administered at twice the dose to achieve drug-liking scores similar to oxycodone IR. Oxycodone CR and oxycodone IR produced similar drug-liking scores when the tamper-resistance mechanism was defeated by crushing the tablet.

An analysis of data from the National Addictions Vigilance Interventions and Prevention Program (NAVIPPRO) surveillance network on 140,496 patients entering substance abuse treatment found that oxycodone CR abuse declined by 30 percent during the 20 months after introduction of the reformulated tablet. Reductions in the proportion of oxycodone CR abusers who did so by smoking, insufflating, or injecting declined by approximately one-third to one-half. However, during the period that abuse of oxycodone CR declined, the abuse of oxymorphone ER and buprenorphine increased, suggesting that prescription opioid abusers switched to products that were easier to abuse. A survey of 2,566 opioid-dependent patients entering treatment facilities found that a decrease in oxycodone CR abuse after its reformulation was paralleled by an increase in abuse of prescription opioids not formulated to resist tampering and in abuse of heroin (level 2 evidence).

Level 4 evidence, consisting of bench top laboratory experiments and expert opinion, supports the value of reformulated oxymorphone ER for deterring tampering. In laboratory experiments, oxymorphone ER tablets could not be crushed with professional pill crushers or a hammer and could not be successfully dissolved in a variety of solvents. In two studies enrolling experienced recreational drug abusers, participants attempted to crush or dissolve oxymorphone ER tablets using implements and solvents of their choice but were not allowed to consume any drug. Less than 10 percent of participants obtained particles they would be willing to snort, while efforts to dissolve the tablets yielded <2 percent of active drug in an injectable form. Seventy-two percent of participants stated they would pay less for reformulated oxymorphone ER compared with the previous oxymorphone ER tablet, and 28 percent stated they would pay nothing for it.

The abuse liability of oxycodone IR with potentially aversive ingredients was evaluated in a randomized, controlled trial (level 1 evidence) in which 40 experienced recreational drug abusers attempted to crush...
oxycodone IR with aversive ingredients and conventional oxycodone IR tablets and then insufflate the tampered tablets. Subjects gave the oxycodone IR with aversive ingredients lower scores for drug liking and willingness to use it again compared with the standard oxycodone IR tablet. Subjects who attempted to insufflate the powder from the crushed oxycodone IR with aversive ingredients experienced nasal burning and discomfort, and more than 50 percent could not completely insufflate the entire contents of a tablet. Although not mentioned in this study, the inability to snort to the entire contents could be related partly to the mass of the 11-mm diameter oxycodone IR tablet with aversive ingredients compared with the common 6-mm diameter oxycodone IR tablets without aversive ingredients. Approximately 30 percent of subjects said they would not be willing to use oxycodone IR with aversive ingredients again, whereas only 5 percent stated they would not use oxycodone IR again.

Although not currently available, the potential abuse-deterrence of morphine ER with sequestered naltrexone is supported by level 1 evidence. In an RCT conducted in a controlled environment, experienced opioid abusers assigned lower drug-liking scores and reported feeling less high after receiving intravenous morphine plus naltrexone compared with intravenous morphine without naltrexone. Conversely, a level 1 study of oxycodone combined with low-dose naltrexone was not associated with reduced abuse potential compared with oxycodone alone.

Collectively, it would appear that data support the potential for tamper-resistant opioids to have a meaningful positive effect on the problem of opioid abuse. However, the evidence also suggests that the introduction of tamper-resistant opioids has been followed by abusers switching to prescription opioids that are more easily abused, as well as potentially more dangerous substances, such as heroin. It would be speculative to consider whether requiring all opioids to have tamper-resistant formulations would substantially reduce opioid abuse or be accompanied by increased misuse of illegal opioids, which may be more dangerous.

Compliance monitoring

Urine screening is perhaps the most objective tool for monitoring and documenting treatment compliance (level 4 evidence). Other compliance monitoring tools include pill and patch counts, feedback from pharmacy and caregivers, prescription drug monitoring programs (PDMPs) established by US states, and regular physician-patient interaction as a means of follow-up, referral, and discharge.

United States guidelines published jointly by the American Pain Society and American Academy of Pain Medicine in 2009 reported that there is no reliable evidence to support the efficacy of any of these monitoring techniques for detecting, preventing, or modifying aberrant opioid-related behaviors. However, the subsequent ASIPP guidelines state that the evidence for compliance monitoring is good. The Canadian guidelines cite a prospective 100-subject study in which urine drug screening identified substance abuse in 16 percent of opioid-treated patients, and a subsequent study of the same population in which a monitoring protocol that combined urine screening with pill counts, treatment agreements, and patient education reduced substance abuse by 50 percent (level 1 evidence). Level 2 evidence suggests that urine screening will identify opioids in many patients with chronic pain and distinguish between overuse and underuse. However, a systematic review (level 1 evidence) determined that there is relatively weak evidence to support the usefulness of urine drug screening conducted in conjunction with a controlled-substance agreement for reducing the occurrence of opioid misuse. In other words, evidence is stronger that screening identifies misuse than that it prevents or modifies misuse.

Results from a survey of 99 physicians (level 2 evidence) indicated that the majority had a poor understanding of how to interpret urine drug screening results, but that a majority also felt confident about interpreting results; indeed, among male respondents there was an inverse relationship between competence and confidence in one’s interpretation skills. This suggests not only that physicians lack the expertise to conduct urine testing but also that many physicians lack self awareness that a knowledge gap exists. Recognizing the lack of guidelines for urine drug monitoring, an international panel convened to formulate recommendations about how to effectively monitor patients.

State-run PDMPs have been implemented to track patient prescriptions of opioids and other abusable substances, allowing physicians to monitor prior efforts to obtain opioids and prior use. In 2004, the US General Accounting Office noted (level 4 evidence) that the 15 PDMPs implemented as of 2002 differed in their purposes and methodologies, but that these programs appeared to deter diversion and
aid law enforcement in its response to diversion.\textsuperscript{82} Level 2 data suggest that these programs may reduce the occurrence of doctor shopping, diversion, and opioid-related morbidity.\textsuperscript{82-84} An analysis of data from the Researched, Abuse, Diversion, and Addiction-Related Surveillance System revealed that poison center treatment incidents increased by an average of 0.2 percent quarterly in the 44 states where PDMPs have been implemented, compared with an 1.9 percent increase in states without PDMPs. Opioid-related treatment admissions increased by an average of 2.6 percent in states with a PDMP, compared with 4.9 percent in states without a PDMP.\textsuperscript{84} A survey of 1,385 prescribers indicated that physicians are more likely to use PDMPs with online access than those requiring use of the telephone, e-mail, or fax, and that use of PDMPs fosters increased awareness of suspicious opioid-related behaviors.\textsuperscript{83}

Compliance with pain management guidelines

\textbf{Does compliance with clinical guidelines mitigate risk of opioid abuse?} Although current US\textsuperscript{7,9} and Canadian\textsuperscript{6} guidelines include recommendations for a multimodal approach to pain management and the use of compliance monitoring (eg, urine toxicology), there have been few publications on the impact of these strategies on reducing the frequency of aberrant drug-related behaviors. A literature search for articles evaluating the effects of multimodal therapy on the risk of opioid abuse and the frequency of aberrant drug-related behaviors identified no articles. Level 3 evidence suggests that many clinicians do not routinely perform appropriate compliance monitoring in opioid-treated patients to assess whether the opioids are being taken as prescribed or to look for evidence of recreational drug use.\textsuperscript{4,85}

A 2011 study (level 1 evidence) of physicians treating 1,487 patients with moderate to severe chronic pain at 281 primary care treatment centers evaluated physician compliance with pain management guidelines through patient assessment and regular reassessment, controlled-substance agreements, validated risk-screening tools, and three compliance monitoring techniques: cards for obtaining/tracking prescriptions, pill counts, and urine drug screening.\textsuperscript{15} The investigators reported a rate of compliance of only 48 percent (64 percent of physicians complied with the protocol in 75 percent of patients). The screening protocol identified 47 percent of patients as having low risk, 52 percent moderate risk, and 1 percent high risk for opioid misuse. However, during the 4-month follow-up period, many patients with evidence of aberrant drug-related behaviors were improperly categorized as being low risk. These data suggest that clinicians may lack adequate understanding of how to interpret compliance-monitoring results or may not appreciate the relevance of abnormal findings to opioid abuse. For example, did the clinicians consider any recreational drug use (eg, urine positive for cocaine) to be aberrant drug-related behavior for a patient prescribed opioids for chronic pain and not exclusively misuse of opioids?

\textbf{Guideline recommendations on responding to aberrant drug-related behaviors.} Patients exhibiting signs of misuse or a high risk of abuse may be classified in 1 of 4 categories\textsuperscript{17}: 1) patients with a high risk of addiction (eg, history); 2) patients with suspected opioid misuse of intact tablets obtained from a physician, without addiction or abuse of other substances; 3) patients who are suspected of misusing opioids obtained from nonmedical sources, tampering with opioid tablets, and/or being addicted to or misusing other substances; and 4) patients with current opioid addiction (level 4 evidence). Responses to aberrant drug-related behaviors suggestive of abuse in patients in these categories are listed in Table 5.

United States and Canadian guidelines recommend that for patients assessed to have an elevated risk of addiction or misuse, prescribing precautions may include small quantities dispensed at short intervals, avoiding popular drugs of abuse, performing frequent urine testing and pill counts,\textsuperscript{6,7} and level 4 evidence suggests consideration of a tamper-resistant opioid.\textsuperscript{14,86} Guidelines cite weak-to-moderate evidence to recommend that patients with suspected opioid misuse should be administered opioids in a structured trial that includes avoidance of short-acting or parenteral formulations and even more frequent dispensing and monitoring; patients who fail a structured opioid trial, tamper with their opioid, are addicted to other substances, and/or acquire opioids from illegal sources may require referral to a specialty pain clinic for a structured trial of methadone or buprenorphine and formal addiction counseling; patients with current addiction to opioids or other legal or illegal drugs warrants
discontinuation of opioid therapy, often accomplished with a trial of methadone or buprenorphine.6,7,14

Level 2 evidence suggests that the structured opioid trial may resolve aberrant drug-related behaviors in some patients. For example, a retrospective chart review examined outcomes in 195 patients exhibiting aberrant drug-related behaviors who were referred to a specialized “Opioid Renewal Clinic” for structured therapy that included frequent visits, heightened monitoring, adherence to a treatment agreement, opioids prescribed in small amounts, counseling, and education. At 1 year, 89 (45.6 percent) patients resolved their aberrant drug-related behaviors, whereas 106 (54.4 percent) were discharged from the program. Reasons for program discharge included persistence of aberrant drug-related behaviors and unwillingness to accept referral for addiction treatment (n = 61; 31.3 percent), acceptance of addiction treatment (n = 20; 10.2 percent), and inability to follow the structured protocol (n = 25; 12.8 percent).87 These results suggest that structured opioid therapy was useful for improving treatment compliance in patients identified to have

aberrant drug-related behaviors and to identify patients whose risk of misuse was of such concern that opioid therapy was discontinued.

The value of methadone and buprenorphine for patients who are abusing or addicted to opioids has been documented and deserves discussion. Methadone is a pure opioid that has been around for decades and is considered effective as an analgesic (level 4 evidence)88 and for opioid detoxification (level 1 evidence).89 However, abuse of methadone can occur even with the strict supervision usually maintained in specialized clinics (eg, by taking several-days dose at once or obtaining extra doses illegally), leading to a high rate of methadone overdose deaths (level 2 evidence).90

Buprenorphine has proven effective as an analgesic in patients with chronic pain (level 1 evidence),91,92 and formulations combining buprenorphine with naloxone have shown reduced abuse liability compared with buprenorphine (level 1 evidence).93,94 Buprenorphine/naloxone has shown good efficacy for patients undergoing opioid detoxification (level 1 evidence).95-97 Of the two agents,
buprenorphine appears to be associated with more rapid resolution of withdrawal symptoms and a higher rate of complete opioid withdrawal, with less risk of abuse. In a survey of opioid abusers, buprenorphine was abused by approximately 20 percent of opioid abusers for whom it was prescribed, which is less frequent than the corresponding rate for methadone.

Legal and regulatory measures

The US FDA has mandated an ER and long-acting (LA) opioid analgesics risk evaluation and mitigation strategy (ERLA opioid REMS) to be funded and developed by pharmaceutical companies, which includes a medication guide for the opioid and patient education materials to be made available through prescribers. The impact of ERLA opioid REMS on opioid abuse risk has not been measured. However, an FDA advisory committee asked to comment on their value offered several criticisms (level 4 evidence). Committee members noted that medication guides are not likely to have a major impact on abuse rates because many drug companies already routinely offer medication guides and most physicians know the risks associated with opioids. Additional mandatory physician education is not required as part of an ERLA opioid REMS. It was observed that opioids are not abused primarily by people who obtain them via prescription, and that implementation of ERLA opioid REMS is unlikely to reduce abuse by individuals who obtain their opioid from a relative, friend, or other source. On the basis of these limitations, the advisory committee concluded that ERLA opioid REMS as currently conceived are unlikely to significantly reduce abuse. Recommendations for improving them included mandatory prescriber training, use of tamper-resistant prescription pads, and the development of prospective methods for obtaining data about opioid abuse.

Physician surveys (level 4 evidence) suggest that the ERLA opioid REMS may improve patient education and help reduce abuse but may also place demands on physicians that make them less likely to prescribe opioids. For example, in a survey of physicians who currently prescribe opioids (level 4 evidence), nearly half stated that they would discontinue prescribing that same opioid if it meant they would be required to enroll in a 2-hour training session about it. These results suggest that imposition of even modest requirements on physicians may serve as more of a deterrent to legitimate prescribing than it would be to patient abuse.

In absence of federal prescribing regulations to curb abuse, individual US states have begun enacting legislation to restrict opioid prescribing. For example, Washington state has limited the allowable MED to ≤120 mg/d. Florida has passed legislation setting standards of practice for opioid prescribers and placing penalties, some of them criminal, on physicians and pharmacists who inappropriately prescribe opioids. Under the Florida law, law enforcement officials would be able to access prescribing records without a warrant. As with ERLA opioid REMS, it would seem possible that the proposed legal penalties might do more to limit willingness to prescribe opioids legitimately than to curb abuse and that abuse among individuals who do not obtain opioids by prescription would be unaffected. Level 2 evidence shows that the imposition of an opioid dose ceiling in Washington state was followed by a 50 percent reduction in opioid-related mortality. This decline in mortality was associated with more than a one-third reduction in the total number of opioid prescriptions.

CONCLUSIONS

Given the recognized growth in prescription opioid abuse, physicians prescribing opioids for legitimate chronic pain indications for which chronic opioid therapy may be an appropriate option need to prevent, detect, and manage aberrant drug-related behaviors that may indicate opioid misuse and abuse. Guidelines for the use of opioids state that minimizing the risk of opioid abuse requires clearly defined treatment plans and expectations about the course of treatment, careful opioid selection and titration, regular compliance monitoring, and a prespecified protocol for addressing signs of opioid misuse. Guidelines also state that use of a multimodal therapeutic approach that includes counseling, physical rehabilitation, relaxation techniques, and lifestyle modification may allow for reduced opioid consumption or opioid discontinuation for patients deemed to be at high risk of abusing their medication. The quality of evidence used
to support previously published guideline recommendations is generally weak or moderate and has not been supported by additional high-level evidence since their publications. However, the cumulative weight of evidence suggests that routine monitoring during treatment, use of structured opioid therapy, and appropriate opioid selection may decrease the risk of abuse in patients requiring ongoing analgesia. Moreover, there is evidence to suggest that a lack of uniform methodologies with respect to patient assessment, use of controlled-substance agreements, and compliance monitoring may limit their effectiveness, leading to preliminary efforts to formalize abuse-risk management practices. However, there is modest evidence that efforts on the part of regulatory bodies and legislators to reduce risk may decrease physician willingness to prescribe opioids legitimately.

An important development since the publication of US and Canadian guidelines for the safe and effective use of opioids is the introduction of the first opioid formulations designed to be tamper-resistant. Initial epidemiology of abuse data suggests that abuse of specific opioid products declined after they were reformulated to resist certain types of tampering, but overall rates of opioid abuse have been unaffected with substance abusers simply selecting more easily abused alternative products. However, clinicians must be clear that these formulations will probably not deter abuse of intact tablets, and their use may actually have the unintended consequence of prompting a migration of abusers to other drugs and more dangerous substances, such as heroin.

Nevertheless, despite the limitations of current strategies for preventing opioid abuse, it is essential that clinicians use all available tools to prevent and detect aberrant drug-related behaviors during opioid therapy in the hope that their combination will prevent as much opioid abuse as possible. As regulators, legislators, and other interested parties consider implementing their own strategies to limit prescription opioid drug abuse, it will also be essential to ensure that their efforts do not compromise effective pain management and thereby increase suffering.

Given the risks associated with opioid abuse, the general lack of level 1 evidence supporting the use of risk-mitigation tools must be taken in the appropriate context. The Declaration of Helsinki states that clinical research in which a percentage of subjects are denied treatment (eg, a placebo group) should be reserved for conditions for which no proven therapy exists or situations in which denial of therapy will not lead to permanent or serious harm. With opioid therapy, the absence of data from randomized controlled trials assessing available strategies to prevent and identify aberrant drug-related behaviors is likely to persist because a control group cannot be ethically exposed to opioids without the best available precautions. Retrospective data collected from large populations of patients will have to be sufficient to support the use of available risk-mitigation strategies for patients facing the risks associated with exposure to highly abusable substances. Therefore, it is the position of the present paper that all patients seen in clinical practice be treated using these strategies because they are supported by common sense; they do not introduce new risks into treatment; and the likelihood of addiction, abuse, or other serious adverse outcomes would otherwise be too great.

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REFERENCES


Primary care providers’ prescribing practices of opioid controlled substances

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ABSTRACT

Objective: Prescription opioid abuse poses a significant public health concern. House Bill 1 (HB1) was enacted in 2012 to address prescription drug abuse in Kentucky. The authors investigated the impact of HB1 on primary care providers’ (PCPs) prescribing practices of Schedule II controlled substances.

Design: Retrospective evaluation of PCPs’ prescribing practices in an adult outpatient setting.

Methods: A review of the prescribing practices for Schedule II controlled substances written by 149 PCPs. The number of prescriptions for Schedule II controlled substances written by 149 PCPs was compared to the top 10 PCP prescribers. Attention was focused on providers who wrote for oxycodone and/or oxycodone and prescriptions with >90 pills dispensed.

Results: The top 10 PCP prescribers accounted for 38.4 percent of the Schedule II controlled substances and 47.8 percent of the Schedule II controlled substances with >90 pills dispensed. Of the 60 PCPs who prescribed oxycodone and/or oxycodone, the average number of prescriptions was 14.7 compared to 51.0 for the top 10 PCP prescribers. The average percentage of Schedule II controlled substance prescriptions compared to the total number of prescriptions was 27.9 percent for the top 10 PCP prescribers and 7.05 percent of all PCPs. The average percentage of office visits with Schedule II controlled substance prescriptions compared to total office visits was 24.8 percent for the top 10 PCP prescribers versus 7.7 percent for all PCPs.

Conclusions: Further scrutiny is warranted to more closely analyze provider opioid prescribing habits and ensure that the providers at our Institution are prescribing Schedule II controlled substances in compliance with HB1.

INTRODUCTION

Sixty percent of the approximately 38,000 deaths from a drug overdose in the United States in 2010 were attributed to prescription drugs. The number of deaths related to prescription opioids in the United States increased from 4,263 in 1999 to nearly 17,000 deaths in 2011. There has been a 5-fold increase in prescriptions for pain medications without an increase in the painful conditions that warrant them. Physician prescribing practices for potentially lethal pain medications pose a significant dilemma. The majority of individuals who abuse prescription pain medications obtain them at no charge from a friend or relative. The second and third most common means of attaining these drugs is by being prescribed them by more than one doctor and by buying from a friend or relative, respectively. In 2014, the Drug Enforcement Administration reclassified hydrocodone combination drugs such as Vicodin as a Schedule II controlled substance under the Controlled Substances Act, with a high potential for abuse. In addition, patients are only able to obtain these drugs for up to 90 days without receiving a new prescription.
House Bill 1 (HB1), also known as "the pill mill bill," was enacted in 2012 to address the prescription drug abuse dilemma in Kentucky. This bill had two primary goals, specifically, (1) to establish mandatory prescribing, dispensing, and reporting standards and (2) to develop a mandate to licensing boards to establish regulations pertaining to prescribing and dispensing of controlled substances. It required practitioners (eg, physicians, optometrists, and dentists) to utilize Kentucky All Schedule Prescription Electronic Reporting (KASPER) and to link KASPER data with the prescription drug monitoring programs (PDMPs) of ordering states. It focused on Schedule II controlled substances, including morphine, demerol, fentanyl, dilaudid, codeine, oxycodone, hydrocodone, and methadone.

Several new requirements for prescribers and dispensers were inherent in HB1. A practitioner or pharmacist authorized to prescribe or dispense controlled substances was required to register with the Cabinet to use KASPER and maintain this registration continuously during their term of licensure. Prior to the initial prescribing or dispensing of a Schedule II controlled substance to a patient, a practitioner was required to obtain a complete history and physical, query KASPER every 3 months on the patient's personal data, educate patients about the specific drug, develop a written treatment plan, and discuss and obtain written informed consent. Long-term prescribing greater than 90 days demanded random urine drug screen and pill counts as well as consideration of referral to a specialist.

There are no national benchmarks to monitor physicians’ prescribing practices of opioid controlled substances. The present study identified the top 10 PCPs at our Institution who prescribed the greatest quantities of Schedule II controlled substances and compared their prescribing practices to those of the total 149 PCPs. We discuss the effect of HB1 in educating physicians, enhancing physician prescribing practices, and improving documentation with the ultimate goal of curtailing the rampant abuse of Schedule II controlled substances. We also offer numerous suggestions for reducing the reliance on opioid medications and techniques for prescribing opioids.

METHODS

We retrospectively reviewed the PCPs’ prescribing practices of Schedule II controlled substances at our Institution to determine the impact of HB1 in Kentucky. This study consisted of 149 PCPs at 26 adult PCP practices between January 1, 2015 and December 31, 2015. The PCPs included those who treated patients in the adult outpatient setting and wrote three or more orders for Schedule II controlled substances. The Schedule II controlled substance stimulants (methylphenidate and amphetamine) were excluded from the data.

We compared the number of Schedule II controlled substance prescriptions written by all 149 PCPs to those who were the top 10 PCP prescribers. Particular attention was devoted to providers who specifically wrote for oxycotin and/or opana and prescriptions with greater than 90 dispensed. In addition, we compared the CPT codes for back pain (724.2, 724.3, 724.4, and 724.5) and degenerative disc disease (422.4, 722.51, 722.52, and 722.6) between the top 10 PCP prescribers and all 149 PCP providers of Schedule II controlled substances.

RESULTS

The Schedule II controlled substance prescriptions written by PCPs at our Institution are displayed in Table 1. The average number of Schedule II controlled substance prescriptions written was substantially higher for the top 10 PCP prescribers compared to all 149 PCPs. The top 10 PCP prescribers accounted for 38.4 percent of the total number of prescriptions for Schedule II controlled substances (Figure 1).

The top 10 PCP prescribers represented 47.8 percent of the total Schedule II controlled substance prescriptions written with dispense quantities in excess of 90. Sixty (40.3 percent) of the total 149 PCPs prescribed the Schedule II controlled substances opana and/or oxycotin. The average number of prescriptions written for opana and/or oxycotin was 51.0 for the top 10 PCP prescribers compared to 14.7 (representing the 60 PCPs who prescribe these drugs) and 5.9 (all 149 PCPs).

The average number of patients per provider with CPT codes for back pain and degenerative disc...
disease was 570 for the top 10 PCP prescribers of Schedule II controlled substances (total of 5,696 patients) compared to 133 for all 149 PCP prescribers of Schedule II controlled substances (total of 19,815 patients).

**DISCUSSION**

Prescription drug abuse is a dilemma both nationally\(^{10-16}\) and in Kentucky.\(^{9,17-20}\) Prescription rates for hydrocodone and oxycodone in Kentucky increased by 27 and 49 percent, respectively, from 2003 to 2010.\(^{19}\) According to the National Survey on Drug Use and Health in 2008-2009, Kentucky had a higher rate of illicit use of opioid analgesics than the United States for all age groups.\(^{19}\) The highest use was among 18-25-year old’s, with 15.4 percent reporting use compared to 11.9 percent nationally.\(^{19}\)

This was attributed to prescription practices leading to increased drug availability and diversion. The nonmedical use of prescribed controlled substances, in particular opioid analgesics, represents a significant public health concern.\(^{10,11}\) According to the Drug Abuse Warning Network between 1997 and 2001, the use of opioid analgesics substantially increased: morphine by 48.8 percent, fentanyl by 151.2 percent, and oxycodone by 347.9 percent.\(^{11,21}\)

Since the inception of its PDMP in 1999 to monitor the abuse of addictive drugs, Kentucky’s ranking among states with the highest nonmedical use of prescriptions pain medications dropped from second to thirty-first place.\(^{22}\) KASPER is considered the “gold standard” for state PDMPs due to three aspects: (1) legislation that mandates physician and pharmacy compliance; (2) ongoing innovations; and (3) continued cooperation among key stakeholders.\(^{22}\)

The present work highlighting PCPs’ prescribing practices of opioid controlled substances and suggestions for reducing the reliance on opioids represents a timely contribution in the setting of the opioid crisis. In 2012, the American Society of Interventional Pain Physicians provided guidance for the use of opioids for the treatment of chronic noncancer pain with the intention of improving the treatment of chronic noncancer pain and decreasing the incidence of abuse and drug diversion.\(^{23,24}\) In March 2016, the Centers for Disease Control issued 12 guidelines to PCPs for prescribing opioids for chronic pain.\(^{25}\) The guidelines were organized into three areas of practice: (1) when to start or continue opioids for chronic pain; (2) how to select which drug, at what dose, for how long, and when
Numerous positive attributes have been observed following the application of HB1 in clinical practice (Table 2). In the 1 year following the implementation of HB1, there was a noticeable decrease in controlled substance dispensing, with an 8.5 percent decrease among all controlled substances statewide (Figure 2). In addition, a striking increase in the number of KASPER reports requested was observed statewide (Figure 3). This represents the extensive use of the electronic reporting system to closely monitor physicians’ prescribing practices and a patient’s history of controlled substance prescriptions. “Doctor shopping” refers to patients who receive multiple prescriptions from four or more different prescribers that are filled at four or more different pharmacies within a 3-month period.17 HB1 significantly affected “doctor shopping” behavior as there was a greater than 50 percent decrease in the number of patients who met this criterion after the HB1 implementation.17 The use of KASPER limited a patient’s ability to make excessive emergency room visits for nonemergency issues, request early refills, and request replacements for lost medications regularly.18 Of note, between 2011 and 2013, Kentucky’s heroin overdose deaths increased from 3 to 40 percent, the heroin overdose emergency medical services calls increased 700 percent, and heroin trafficking arrests increased 1,300 percent.26

We identified several factors during the investigation of the prescribing practices of the top 10 PCP prescribers at our Institution that may account for their prescribing a greater quantity of Schedule II controlled substances compared to all 149 PCP prescribers. The average number of patients per provider with CPT codes for back pain and degenerative disc disease was 570 for the top 10 PCP Schedule II controlled substance prescribers compared to 133 for all 149 PCP Schedule II controlled substance prescribers. This finding indicates that the

<table>
<thead>
<tr>
<th>Table 2. Positive impact of HB1 in Kentucky</th>
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<tbody>
<tr>
<td>Improved documentation</td>
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<tr>
<td>More thorough patient care</td>
</tr>
<tr>
<td>More screening and education of patients</td>
</tr>
<tr>
<td>Increased partnering of providers with pain management specialists</td>
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<tr>
<td>Providers more selective when accepting patients</td>
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Figures shown in doses dispensed

Figure 2. One-year comparison of Schedule II controlled substances dispensed statewide prior to and following the implementation of HB1 in Kentucky (KASPER data provided by the Cabinet for Health and Family Services, Frankfort, KY).
top 10 PCP prescribers have a considerably higher number of patients with back pain and degenerative disc disease which may necessitate prescribing a greater amount of Schedule II controlled substances compared to all 149 PCP prescribers. Further studies will address additional causes for the differences in prescribing practices of PCPs.

The majority of pain management specialists prefer to focus on procedures such as epidural injections and would prefer not to assume the long-term prescribing of controlled substances which would inevitably increase the quantities prescribed by PCPs. In addition, it is not reasonable for pain management physicians to take over the responsibility of prescribing opioids to patients who should not have been started on opioids, individuals treated with unreasonable dosages, and patients with addiction issues, behavioral issues, and involved in diversion. Pain management practices are under tight scrutiny, and pain physicians are not offered special protection with regards to high-risk patients. Pain physicians strive to reduce the reliance on opioids by implementing several effective strategies (Table 3). Interestingly, we discovered that many PCPs no longer want to prescribe Substance II controlled substances due to the strict regulations inherent in HB1, thus, necessitating one PCP in a practice to prescribe a higher number of Schedule II controlled substances to patients of fellow colleagues. A host of valuable techniques for prescribing opioids are suggested (Table 4).

Several interventions have been implemented at our Institution based on the findings in the current work with the primary objective of protecting PCPs and their patients. We have educated PCPs about the significance of HB1 and developed guidelines to apply HB1 into clinical practice. The data collected in this study was shared in a blinded manner with the PCPs to allow them to compare against their peers. In addition, focused attention was directed to the outliers, including auditing their medical charts and providing specific feedback in documentation. Our identified reports were also incorporated into electronic medical record templates. The findings gleaned through the present study permitted our Institution to develop guidelines for PCPs' prescribing practices of opioid controlled substances.

While the ultimate goal of the present work was to ensure PCPs' compliance of HB1, we also stressed the importance of oversight and education of PCPs. This education was focused primarily on determining the objectives of patient treatment with the aim of reducing the quantities of Schedule II controlled substances prescribed and selecting pain medications other than Schedule II controlled substances to treat arthritis and back pain. In addition, PCPs' awareness of HB1
encourages PCPs to evaluate patients in the office on a more frequent basis to discuss their Schedule II controlled substances and associated refills.

From a pharmacy perspective, Betses and Brennan identified high-risk prescribers by comparing them against others in the same geographic region with the same listed specialty using data from submitted prescriptions for hydrocodone, oxycodone, alprazolam, methadone, and carisoprodol. They identified 42 outliers based on the volume of prescriptions for high-risk drugs and the proportion of the prescriber's prescriptions for such drugs. The authors attempted to interview the outliers and subsequently decided not to fill the controlled substance prescriptions for 36 outliers at their pharmacy. Our study closely mimics that of Betses and Brennan's by identifying the top prescribers of controlled substances in a geographical jurisdiction by specialty and then interviewing the outliers to determine the unique characteristics of their practice.

A community in North Carolina focused their prevention program on the education of PCPs in managing chronic pain and safe opioid prescribing. Following an intervention of a tool kit (pain management guidelines, opioid risk assessment tools, sample patient-prescriber agreement [pain contract], and patient education materials) and face-to-face meetings with physicians, the overdose death rate due primarily to opioids dropped from 46.6 per 100,000 in 2009 to 29.0 per 100,000 in 2010. In 2008, 82 percent of overdose decedents received an opioid prescription from a community prescriber compared with 10 percent in 2010. The present study in Kentucky is similar to the community-based opioid prevention program in North Carolina. Both the North Carolina study and the present work emphasize the importance of educating PCPs in safely prescribing opioid medications by means of a tool kit (North Carolina) and through KASPER at our Institution. Similar to the North Carolina analysis, the present study also encourages face-to-face meetings with PCPs. We identified the PCPs with the highest Schedule II controlled substance prescribing practices in an effort to delve into their specific patient population and their particular need to prescribe these medications. The goal of both our study and that in North Carolina was to reduce the quantity of Schedule II controlled substances dispensed by PCPs.

In an effort to curtail the prescription opioid crisis, certain technologies have attempted to develop abuse deterrent formulations. These new extended-release opioids are designed to provide adequate pain control for patients while discouraging prescription opioid abuse. Approved strategies include physical barriers to crushing, chewing, or dissolving, combinations of opioid agonists/antagonists, and the addition of aversive ingredients to opioid tablets.

CONCLUSION

The solution to mitigating the abuse of prescription controlled substances consists of the triad of safe prescribing practices, state policies, and PDMPs. The number of Schedule II controlled substances decreased statewide, and the number of KASPER reports requested increased statewide following the implementation of HB1 in Kentucky in 2012. Future studies will focus on specialists' prescribing practices of Schedule II controlled substances, a patient's diagnosis leading to the prescription of a Schedule II controlled substance, the prevalence of polypharmacy, and physician and patient characteristics. Further analysis is warranted to continue monitoring prescribing practices at our Institution and in Kentucky to elucidate the impact of HB1.

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Determinants of variation in analgesic and opioid prescribing practice in an emergency department

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ABSTRACT

Objective: Adequate treatment of patients’ pain is a top priority for the World Health Organization (WHO), American Medical Association (AMA), and American College of Emergency Physicians (ACEP), but “adequate” is not clearly defined. Most previous studies of emergency department (ED) pain treatments have centered on musculoskeletal pain in terms of rates of analgesia and disparities in treatment based on race and age. This study will examine complaints of pain other than musculoskeletal and will focus on treatment disparities that may result from differences in patient and physician characteristics.

Methods: This retrospective study is of ED patients 18 years and older with nonmusculoskeletal pain who were seen by ED faculty over a period of eight weeks. Logistic regression and χ² tests were performed to quantify effects of doctor, patient, and clinical characteristics on rates of ED analgesia, ED opioids, and analgesic prescriptions at discharge.

Results: A total of 1,360 patients were included. There was wide variation in the type and frequency of ED analgesia depending on the attending doctor. For example, patients seen by one specific ED doctor were less than half as likely to receive any analgesia and seven times less likely to receive an opioid than those seen by another doctor. Age, race, doctor’s training and experience, and whether the patient had chronic pain were important predictors of ED analgesia. There were similar findings for ED opioids and discharge analgesics.

Conclusion: Pain practices in EDs are highly variable and seem inadequate when measured against the goals of WHO, AMA, and ACEP. Patient age, race, and type of pain and the physician’s identity, training, and experience all contribute to practice variation. Further research is needed to identify the causes of these variations, and there is a need to develop interventions to standardize and improve pain assessment and treatment.

Key words: emergency department, pain, pain management, analgesics, opioids

INTRODUCTION

Pain is the most common complaint in general medical practice and is especially common in emergency departments (EDs). Pain management is an increasingly important issue. The World Health Organization (WHO) co-sponsored the first Global Day Against Pain to increase recognition of the fact that pain relief is an integral factor in attaining the highest level of physical and mental health.¹ The American Medical Association (AMA) recently distributed a comprehensive policy statement on pain management involving opioid analgesics. The AMA linked its findings to the Federation of State Medical Boards’ Model Guidelines for the Use of Controlled Substances for the Treatment of Pain and to a joint statement from 21 health organizations and the Drug Enforcement Administration titled Promoting Pain Relief and Preventing Abuse of Pain Medications: A Critical Balancing Act.² The American College of Emergency Physicians’ (ACEP) board of directors approved a strongly worded policy statement in March 2004 advocating safe, rapid, and adequate pain treatment for ED patients and further research into ED pain management.³ Unfortunately, none of these organizations defined adequate pain treatment or established standards for ED pain care.

A number of studies of ED management of specific pain complaints, primarily musculoskeletal, have been published. All report on the quantity of pain treatment but not on quality as judged against an objective standard.⁴ Most assume that pain should be treated and that low rates of ED analgesia represent inadequate care, but
they offer no guidance on what is adequate. Several studies have explored the effects of patient characteristics such as age, race, and gender on ED analgesia practice, with equivocal results. Selbst and Clark studied pain from burns, sickle cell disease, and lower-extremity fractures. Brown et al. studied pain from fractures using the National Hospital Ambulatory Medical Care Survey (NHAMCS), a national weighted sample of ED encounters. Both found that children were less likely to receive ED analgesia and discharge analgesic prescriptions than adults. Raferty et al. found that patient perception of pain was the greatest predictor of the number and strength of analgesics given in the ED and that patient gender was not a predictor of ED analgesic use for patients with headache or back and neck pain. Several studies have attempted to find race-based disparities, with some finding blacks and Hispanics receiving less ED analgesia and others finding no difference, primarily for patients with long-bone fracture. Singer and Thode studied burn patients using NHAMCS and found low rates of analgesia but no disparities based on gender, age, race, ethnicity, or financial status. Tamayo-Sarver et al. also studied NHAMCS looking for racial and ethnic disparities in care provided for migraines, back pain, and long-bone fractures. They found no disparities in ED analgesic use except that blacks were less likely than whites to be prescribed opioids for back pain and migraines.

We found very little research examining the effect of provider characteristics on ED pain practice. Tamayo-Sarver et al. examined pain practice by emergency physicians (EPs) using written case vignettes. They found wide variation in analgesic practice but could not identify any provider characteristics that explained the variations. Todd et al. studied racial disparities in the care of long-bone fractures and statistically controlled for provider differences in their analysis.

Our research group completed a companion study to the one presented here in which we investigated variations in treatment of musculoskeletal pain in the ED. We found that different physician characteristics and wide variation in practice were the only sources of disparities in the prescription of analgesics in the ED. However, the study found patient characteristics including race, age, chronic pain, and trauma influenced prescription for the subgroups receiving opioids in the ED and discharge analgesic prescriptions. No gender or financial status disparities were found. Fewer opioids and discharge analgesics were prescribed for black patients than for whites. Younger patients and those with trauma or chronic pain received more opioids and discharge analgesics than others. Doctors who completed emergency medicine (EM) residencies and those with less than three years of experience prescribed more analgesics in the ED than non-EM-trained physicians and those with more experience.

In summary, current knowledge about ED pain treatment is limited, and there are no valid standards for evaluating the adequacy of treatment. Some patient and doctor characteristics have been identified that predict ED analgesic use, primarily for musculoskeletal pain, but not all relevant contributors to ED pain treatment have been identified.

We sought to describe ED analgesic prescribing practice for painful conditions other than musculoskeletal pain and to investigate whether patient or doctor characteristics would predict variations in ED pain management.

METHODS

Study design and participant selection

After institutional review board approval and waiver of the Informed Consent requirement, we collected chart review data from complete records on all patients 18 years and older with documented pain other than musculoskeletal pain who were seen by our 10 core faculty members and discharged from our ED over an eight-week period in 2004. Our ED is part of an urban, academic medical center with Level 1 trauma designation and an annual census of about 30,000. A pain complaint was defined as any pain or discomfort described with words like ache, sore, tight, hurt, etc. at triage or during physical evaluation or a nonzero pain score on a verbal 0 to 10 scale.

Methods of measurement

Data were collected following the guidelines of Gilbert et al. Chart abstractors were trained on the structure of charts, definitions of study variables, inclusion and exclusion criteria, the printed abstraction tool, and data entry procedures. Frequent discussion among investigators and abstractors via e-mail and in person helped resolve all uncertainties. In addition, random reabstraction of 10 percent of the charts was performed to assess inter-rater reliability by the \( \kappa \) statistic. Abstractors could not be blinded to all study hypotheses.

Patient variables abstracted included age (divided into “under 50” and “50 or older”), sex, race, insurance status (divided into self-pay or insured), location of pain, traumatic mechanism, presence of chronic pain, analgesic given in ED, opioid given in ED, and both analgesic and opioid prescribed at discharge. Because review of ED census data before the study revealed only a small population of patients 65 and older, patients 50 and older were assigned to the “older” group to provide adequate comparative samples based on age. The name of the attending was obtained from the chart. Data on physician gender, type of training, and time in practice were collected by interview.
Pains were described as headache, chest pain, abdominal pain, neuropathic pain, and other. The “other” category included primarily skin and skin structure pain from infection or superficial injury and dental, throat, and ear pain. (As noted earlier, patients with musculoskeletal pain were excluded from this study.) For patients with multiple painful complaints, the patient’s most important single site was recorded. Traumatic mechanism was coded if injury occurred within one week of presentation and no other healthcare had been sought previously for the injury.

No validated definition of chronic pain in EM was found through our literature search. Therefore, we allowed consensus of the investigators to define chronic pain as pain occurring for more than one month and treated with an analgesic on a regular basis before the ED visit.

Definitions of analgesics were broad and specific to pain location. We evaluated only pharmaceutical agents and did not code for analgesia if the only interventions were nonpharmacologic, e.g., ice, elevation, and splinting. Medications treating underlying conditions that might cause pain were not considered analgesics (e.g., antibiotics for a urinary tract infection causing suprapubic pain or for pneumonia causing chest pain, hypoglycemics given to a patient with diabetic neuropathic pain).

Acetaminophen, NSAIDs, and opioids were considered analgesics for all pain sites. For headaches, oxygen was considered an analgesic for cluster headache. Migraine-specific drugs such as prochlorperazine, droperidol, and sumatriptan were coded as analgesics. Tricyclic antidepressants, topical and injected anesthetics, and anti-convulsants such as gabapentin were considered analgesics for neuropathic pain. Nitroglycerin was counted as an analgesic for chest pain. Aspirin was not considered an analgesic for chest pain as it was for all other pain because its use in chest pain is to treat suspected platelet aggregation, an underlying condition causing pain. Antacids, acid suppressors, and antispasmodics were analgesics for abdominal pain. Local anesthesia and procedural sedation for injuries and painful treatments were considered analgesics.

Outcome measures

Primary outcome was analgesic treatment in the ED. Secondary outcomes included ED opioid treatment and discharge opioid and nonopioid analgesic prescriptions.

Primary analysis

We described the range of practice in our group by using frequencies and percentages. We also used SAS 9.1 to perform $\chi^2$ and binary logistic regression analysis to determine the significance of variations in analgesic treatment due to patient demographic and clinical characteristics and doctor identity, training, and experience in pain treatment, while controlling for other variables.

RESULTS

A total of 1,360 patients met inclusion criteria and were included in the analysis. Female patients made up 52.6 percent of the study group, blacks 69.8 percent, and uninsured patients 63.5 percent. The majority of patients (82.1 percent) were < 50 years of age. Other pain and abdominal pain were the most common complaints at
Table 1. Logistic regression results for each outcome

<table>
<thead>
<tr>
<th></th>
<th>Odds ratio interval</th>
<th>95 percent confidence interval</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ED analgesia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50 vs. &lt; 50 years</td>
<td>0.49</td>
<td>0.37-0.66</td>
</tr>
<tr>
<td>White vs. black</td>
<td>1.42</td>
<td>1.12-1.81</td>
</tr>
<tr>
<td>Chronic vs. not</td>
<td>2.36</td>
<td>1.50-3.71</td>
</tr>
<tr>
<td>EM-trained vs. not</td>
<td>1.28</td>
<td>1.02-1.61</td>
</tr>
<tr>
<td>&gt; three years’ experience vs. less</td>
<td>0.66</td>
<td>0.52-0.84</td>
</tr>
<tr>
<td><strong>ED opioid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White vs. black</td>
<td>2.27</td>
<td>1.64-3.16</td>
</tr>
<tr>
<td>Chronic vs. not</td>
<td>1.79</td>
<td>1.07-3.01</td>
</tr>
<tr>
<td>EM-trained vs. not</td>
<td>1.46</td>
<td>1.08-2.04</td>
</tr>
<tr>
<td><strong>Discharge prescription</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 50 vs. &lt; 50 years</td>
<td>0.54</td>
<td>0.40-0.73</td>
</tr>
<tr>
<td>White vs. black</td>
<td>1.47</td>
<td>1.16-1.86</td>
</tr>
<tr>
<td>Chronic vs. not</td>
<td>2.12</td>
<td>1.38-3.23</td>
</tr>
<tr>
<td><strong>Discharge opioid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White vs. black</td>
<td>2.10</td>
<td>1.46-3.02</td>
</tr>
<tr>
<td>Trauma vs. not</td>
<td>1.66</td>
<td>1.05-2.62</td>
</tr>
</tbody>
</table>

39.7 percent and 31.3 percent, respectively. Chest pain accounted for 15.6 percent and headache 12.1 percent of patient pain complaints. In testing for inter-rater reliability of data abstraction, all variables had moderate to near-perfect correlation, with all $\kappa$ values greater than 0.6.

The faculty included five EM-residency-trained physicians and five trained in other specialties but practicing EM full time. Five EPs had less than three years of attending experience, and five had more than three years. In both groups, the number included one female and four male doctors.

Just over half of the patients with pain (51.5 percent) received analgesia in the ED. Of the 700 patients who received ED analgesia, 36.0 percent received opioids. Of the 585 patients who received a discharge prescription, 57.6 percent were prescribed opioids.

Rates of ED analgesia by prescribing doctor are shown in Figure 1 and are primarily remarkable for the wide variation in practice. One specific doctor was less than half as likely to prescribe any ED analgesic and seven times less likely to give ED opioids than the doctor with the highest treatment rates.

An in-depth review of four individual cases of lower molar pain without signs of abscess was performed to illustrate the inconsistency of pain treatment in our ED. All patients reported severe pain (10 out of 10 on a verbal scale). Each was seen by a different doctor. Three patients were black and one white. Two were female, and one was over 50 years old. All were referred to a dentist upon discharge. Patient 1 received nothing in the ED and was given no discharge analgesic recommendation or prescription. Patient 2 received nothing in the ED and was told to take over-the-counter acetaminophen or ibuprofen for pain at discharge. Patient 3 received oral ibuprofen 800 mg in the ED and received a discharge prescription for hydrocodone/acetaminophen 5 mg/500 mg, 10 tablets, with instructions to take one by mouth every six hours as needed for pain. Patient 4 received hydrocodone/acetaminophen 5 mg/500 mg two tablets by mouth in the ED, and the emergency physician performed an inferior alveolar block with bupivacaine 0.5 percent with epi-epinephrine. This last patient also received a prescription for hydrocodone/acetaminophen 7.5 mg/500 mg, 15 tablets, with instructions to take one tablet every four to six hours as needed for pain. No discharge
pain assessments were made, so no inference about adequacy of treatment was available.

The rate of analgesic use varied greatly according to pain location. ED patients with headache received analgesics 63.5 percent of the time, compared to 51.6 percent for abdominal pain, 51.9 percent for chest pain, and 48.0 percent for other pain. Headache and chest pain patients were less likely to receive opioids. Only 18.3 percent of headache and 20.0 percent of chest pain patients received opioids, compared to 49.1 percent of abdominal pain and 38.6 percent of other pain patients.

Logistic regression analysis of the primary and three secondary outcomes demonstrated significant predictors for each outcome (Table 1). For ED analgesia, age, race, chronic pain, and physician characteristics predicted use. Older people were half as likely to receive analgesia as younger patients. The undertreatment of older people continued with regard to discharge analgesics. Whites were 42.0 percent more likely to receive an ED analgesic.

Patients with chronic pain received analgesics, opioids, and discharge prescriptions twice as often as patients without chronic pain. EM-trained physicians were more likely to give analgesics and opioids in the ED than non-EM-trained providers. Physicians with less than three years of experience were more likely to prescribe analgesics in the ED. Blacks were only half as likely to receive ED opioids as whites.

DISCUSSION

Our study is consistent with other studies that have shown low rates of pain treatment in EDs and treatment disparities based on age and race.3-6,8,9,11-14 Nearly half of our patients, with their varied pain complaints, received no analgesia in the ED. Patients 50 or older were less likely to receive analgesia both in the ED and at discharge. Blacks received less pain treatment than whites for all tested outcomes. These findings are statistically, and maybe clinically, significant, but we found that the most important factor determining rates of pain treatment was the identity of the doctor.

The reasons for the wide variation in pain practice by doctors in our ED are not clear and were not within the scope of this study. However, some possibilities could be suggested from our results and from anecdotal evidence from discussions with faculty after the study was completed. For instance, bias related to patient age and race likely plays some role. Fear, on the parts of patients and physicians, of opioid side effects, drug diversion, and addiction promotion also likely contribute to practice variation.

Understanding the factors associated with prescribing behavior and patient analgesic use is a key to providing better pain management in the ED. Our group is currently investigating which knowledge and attitudes of healthcare providers may determine pain management practice.

Studies of patient factors that influence analgesic-taking behavior and desire for pain relief are also needed. Finally, development of systematic interventions to standardize pain practice may reduce inconsistencies in practice and improve satisfaction with care.

Tameo-Sarver et al.11,13 identified wide variation in pain practice by EPs based on written case vignettes but could not find any predictors of that variation, despite their investigation of many doctor characteristics. We found that type of residency training and length of experience significantly influenced rates of ED analgesia but did not influence discharge prescriptions. That EM-trained physicians and recent graduates give more analgesia in the ED makes some intuitive sense, considering the recent emphasis on pain management in the EM literature and by the largest EM professional organization.3,4 In addition, our findings are consistent with a recent systematic review of the effect of years of experience on quality-of-care outcomes which demonstrated that increasing experience resulted in worse quality of care.10

If the finding of lower prescription rates of analgesia by more experienced practitioners is validated in a much larger sample of EPs, peer feedback, continuing education, or other intervention will be needed to overcome this deficiency.

Limitations

Due to the retrospective design, we are limited in our ability to draw firm conclusions about the causes of our findings, despite conscientious efforts to use rigorous chart-review methods to maximize the validity of our results. At best, we can generate useful hypotheses for future study.

Obviously, our EP group and patient list represent a tiny part of EM in the United States, so our findings must be generalized very cautiously. Since we are affiliated with a separate children’s hospital, our patients are almost all adults, so we limited the study to those 18 years and older. Therefore, this study can not infer any conclusions about pain management in children. Also, this study includes no data on follow-up pain assessments or patient satisfaction with treatment, so we can not assess adequacy of treatment. Finally, our definitions of chronic pain and traumatic mechanism were arbitrary, so findings of influence on rates of analgesia require validation in other settings.

CONCLUSION

This study demonstrates that ED pain practices are highly variable and seem inadequate when measured against the goals of the WHO, AMA, and ACEP.1-3 Patient age, race, and type of pain and physician identity, characteristics of training, and experience influence pain
treatment. Further research to identify causes of this variation is needed, and there is a need to develop interventions to standardize and improve pain assessment and treatment.

DISCLOSURE STATEMENT

Ms. Grammas was supported in part by a University of South Alabama (USA) Summer Research Award, and Ms. Huang was a graduate assistant in the USA Department of Mathematics and Statistics. No authors have any commercial affiliations to declare or report any conflicts of interest.

The results described in this paper and other work from our group were presented in abstract form at the 2005 Society for Academic Emergency Medicine Annual Meeting on May 25, 2005, in New York, NY. The abstract was published in the May 2005 issue of Academic Emergency Medicine.

Results of a companion study to the one presented here were recently published. Study cohorts were mutually exclusive, so no data from any patient were duplicated.

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ABSTRACT

Background: Errors may be more common and more likely to be harmful with opioids than with other medications, but little research has been conducted on these errors.

Methods: The authors retrospectively analyzed MEDMARX®, an anonymous national medication error reporting database, and quantitatively described harmful opioid errors on inpatient units that did not involve devices such as patient-controlled analgesia. The authors compared patterns among opioids and qualitatively analyzed error descriptions to help explain the quantitative results.

Results: The authors included 644 harmful errors from 222 facilities. Eighty-three percent caused only temporary harm; 60 percent were administration errors and 21 percent prescribing errors; and 23 percent caused underdosing and 52 percent overdosing. Morphine and hydromorphone had a significantly higher proportion of improper dose errors than other opioids (40 percent and 41 percent compared with 22 percent with meperidine). Hydromorphone errors were significantly more likely to be overdoses (78 percent vs 47 percent with other opioids). Omission errors were significantly more common with fentanyl patches (36 percent compared with 12 percent for other opioids). Wrong route errors were significantly more common with meperidine (given intravenously when prescribed as intramuscular, 34 percent vs 3 percent for morphine). Oxycodone errors were significantly more likely to be wrong drug errors (24 percent vs 11 percent for other opioids), often because of confusion between immediate- and sustained-release formulations.

Conclusions: Reported opioid errors are usually associated with administration and prescribing and frequently cause uncontrolled pain as well as overdoses. These patterns of errors should be considered when using opioids and incorporated into pain guidelines, education, and quality improvement programs.

Key words: opioids, medication errors, medical errors, pain

INTRODUCTION

Opioids are among the most frequently used medications in hospitals and several drugs most commonly involved in error reports are in this class.1 Opioids may be more prone to errors because of factors such as the frequent need to calculate doses and different potencies among opioids and routes of administration. Evaluating and addressing opioid errors is particularly important with the dramatically increased use of these medications over the past decade. Opioid errors are more likely to cause harm or death than errors with many other drug classes, since overdoses can cause symptoms such as respiratory depression.1 Concerns about the possible adverse effects of opioids are important barriers to the use of opioids for both healthcare professionals and patients and families, and errors are a significant factor in the under treatment of pain.2

However, safety issues are rarely addressed in attempts to improve opioid use. In our recent systematic review of quality indicators for pain treatment, most of those we identified were limited to the Institute of Medicine quality domain of effectiveness; only one was related to adverse drug reactions and none were related to medical errors.3 Recommendations or initiatives to decrease errors with opioids have generally been limited to education about pain management and opioid conversions, and specific issues such as eliminating the use of meperidine because of toxicity with higher doses4 and the use of abbreviations for morphine.5 Little evidence is available on patterns of errors with opioids or how best to prevent them; the few previous relevant studies were limited in sample size and scope.6,7

Improving the safety and efficacy of opioids requires better knowledge of patterns of errors. We therefore
analyzed opioid errors in routine inpatient care using a national medication reporting system, MEDMARX®, with the following objectives: (1) Evaluate patterns of opioid medical errors; (2) evaluate differences in these patterns among commonly used opioids; and (3) qualitatively describe issues related to opioid characteristics and specific opioids and formulations.

METHODS

Data source

MEDMARX is a voluntary, anonymous medication error reporting program established in 1998 by the US Pharmacopeia. More than 850 subscribing hospitals and health systems have used MEDMARX, which currently receives approximately 20,000 medication error reports per month. MEDMARX facilities are representative of US hospitals in bed size and include a variety of facility types.1 Reports categorize errors using the National Coordinating Council for Medication Error Reporting and Prevention (NCCMERP) taxonomy (including whether there was harm and the degree of harm).8 Reports contain a number of data fields including the drugs involved, some patient characteristics, type of patient-care unit, error node (prescribing, transcribing/documenting, dispensing, administering, or monitoring), error type (eg, omission, wrong drug, wrong route), causes and factors involved in the error, resulting level of care required by the patient (including whether a narcotic antagonist or antidote was administered), and a free-text error description.

We included error reports mentioning any opioid that was potentially used for treatment of pain, occurring on a patient care unit, and stating that there was patient harm (Categories E-I in the NCCMERP taxonomy). We excluded errors in intensive care units and during surgery or procedures, since patterns of use are different in these settings. We excluded errors associated only with patient-controlled analgesia (PCA) devices or intrathecal or epidural pumps, which are different because of issues such as programming the pumps correctly. We excluded reports that were adverse drug events or otherwise clearly not errors by reviewing the codes and free-text reports that were adverse drug events or otherwise such as programming the pumps correctly. We excluded epidural pumps, which are different because of issues controlled analgesia (PCA) devices or intrathecal or settings. We excluded errors associated only with patient- or procedures, since patterns of use are different in these excluded errors in intensive care units and during surgery (Categories E-I in the NCCMERP taxonomy). We 17 (2 percent) were excluded for other reasons. Therefore, 644 error reports were included in these analyses. Reports came from 222 facilities (149 of which reported only one or two errors), during 1999-2004 (90 percent from 2001 to 2004); 535 (83 percent) were associated with only temporary harm (NCCMERP Category E). The mean patient age was 58; 19 of the 583 reports where age was recorded were in patients younger than 18. Sixty percent were coded as administration errors, 21 percent were coded as prescribing, 12 percent as transcription, and 6 percent as dispensing or monitoring. The errors resulted in overdosing in 53 percent of reports, underdosing in 23 percent, and other adverse effects in 10 percent, such as allergic reactions due to giving an opioid despite a documented allergy. The effect was unclear in the remaining

Error and patient characteristics

From 1998 to 2004, of the 1,082 harmful errors reported from inpatient care units, 353 (35 percent) were related only to use of PCA, 37 (3 percent) were related only to use of epidural or intrathecal catheters, 31 (3 percent) were reported as adverse drug events, and 17 (2 percent) were excluded for other reasons. Therefore, 644 error reports were included in these analyses. Reports came from 222 facilities (149 of which reported only one or two errors), during 1999-2004 (90 percent from 2001 to 2004); 535 (83 percent) were associated with only temporary harm (NCCMERP Category E). The mean patient age was 58; 19 of the 583 reports where age was recorded were in patients younger than 18. Sixty percent were coded as administration errors, 21 percent were coded as prescribing, 12 percent as transcription, and 6 percent as dispensing or monitoring. The errors resulted in overdosing in 53 percent of reports, underdosing in 23 percent, and other adverse effects in 10 percent, such as allergic reactions due to giving an opioid despite a documented allergy. The effect was unclear in the remaining
14 percent of cases. Giving naloxone was reported as an outcome in 22 percent of cases, and in an additional 9 percent, one of the outcomes reported was giving an antidote, which was not always specified. Although some of these were diphenhydramine or other treatments for allergic reactions, many were described as naloxone in the free-text error descriptions.

There were six reported deaths (1 percent of harmful error reports). In one case, a dying, frail, elderly woman with pleural effusions died 2 hours after 10 mg of morphine was administered (the ordered range was 1-3 mg); in another, a morphine drip with 100 mg in 100 mL (usually used for dying patients and intended to be infused over 24 hours) was found to be empty after an hour. Another patient who had undergone hip surgery received 3 mg of morphine intravenously (IV) and became sedated with respiratory depression; a narcotic antagonist did not wake the patient, who was treated with BIPAP but had a do not resuscitate order and subsequently died. In the other three cases, it is unclear how ill the patient was. In one, the error description only states that the patient received 1,050 mg of meperidine and 4 mg hydromorphone IV in a 24-hour period. Another patient received 6 mg of hydromorphone IV; although the dose had been intended as 1 mg, it was transcribed as 6 mg because of misinterpretation of the handwriting. The last death occurred in a postoperative patient who received epidural morphine at a dose higher than ordered in addition to intravenous morphine, which had not been ordered.

**Causes of errors**

Overall, the most commonly reported primary causes of errors were communication, knowledge and performance deficits, not following protocols and procedures, and documentation. Calculation errors (77 percent of which were errors with administration), computer entry, dispensing devices, dosage form, or name confusion were each the primary reported cause in less than 5 percent of reports, and abbreviations, decimal point issues, and verbal orders were the primary cause in less than 1 percent each. Contributing factors of cross coverage, shift change, transfers, range orders, and lack of pharmacy support were all reported in less than 2 percent of cases. Calculation errors were of the administration type in 77 percent of cases (such as performing mg to mL conversion when calculating an intravenous opioid dose or making 10-fold errors), but some were errors of converting one opioid to another or using the wrong mg/kg factor in calculating for a child. There were numerous examples of products with similar names being mistaken for each other (eg, Roxicet/Roxanol).

In the qualitative analysis, there were several other issues identified that were not addressed in the error taxonomy. Use of opioids with multiple other sedating medications was an issue in several cases, as was simultaneous use of more than one opioid or route of administration. Several errors were described as due to overly aggressive treatment of uncontrolled pain, such as exceeding the appropriate or ordered dosing interval or using more than one opioid or route. Harm often occurred after repeated opioid doses over a short period of time. A few reports were related to conversions from one opioid or route to another, including one calculation error and several where the previous medication was not discontinued with the opioid change. Some descriptions mentioned not questioning a physician's order even when the nurse knew it was incorrect.

Several reports noted not double-checking for errors when pain was uncontrolled, stating, for example, that a patient was complaining of severe pain for a period of time before it was recognized that there was an opioid omission. Several noted lack of adequate physician response to uncontrolled pain or other quality issues such as not prescribing a bowel regimen when starting an opioid, resulting in constipation. Finally, a number of errors were related to failure to note medication allergies.

**Issues more common with specific drugs or formulations**

Additional characteristics of opioid errors and differences between the most commonly used opioids are listed in Table 1. Morphine and hydromorphone errors were significantly more likely to be improper dose/quantity than other opioids (40 percent and 41 percent vs 31 percent, p ≤ 0.01). Hydromorphone errors, but not morphine errors, were significantly more likely to be overdoses than other opioids (78 percent vs 52 percent, p < 0.001). Particularly for hydromorphone, but also for morphine and sometimes other opioids, harm often occurred because the initial dose given for a patient was higher than the recommended range. The pattern of these errors, both in administration and prescribing, suggests that they were often due to lack of familiarity with the differences in potency between hydromorphone and morphine and between intravenous and oral forms, as the dose given would have been appropriate for the other situation (such as 4 mg of hydromorphone as a starting intravenous dose for an opioid-naïve patient rather than 0.2 mg).

Errors with fentanyl occurred almost exclusively with transdermal patches. These errors were significantly more likely to be errors of omission (36 percent vs 15 percent, p < 0.001) and underdoses (46 percent vs 20 percent, p < 0.001) than other opioids. A number of cases were due to not changing patches at the recommended time or not realizing that a patch was on or that the previous patch had not been removed. Errors with meperidine were significantly more likely to be wrong
route errors (34 percent vs 2 percent, $p < 0.001$) and overdoses (65 percent vs 50 percent, $p < 0.005$) than other opioids. These mainly involved meperidine that was prescribed intramuscularly (IM) but administered IV; there were only a few cases of this occurring with other opioids. There were also numerous cases of seizures or other central nervous system complications related to meperidine, often with higher-than-recommended total doses due to repeated administration. In one case, the patient’s condition was recognized only after a special meperidine quality team recognized the symptoms. Errors with oxycodone were significantly more likely to be errors of omission (24 percent vs 14 percent, $p < 0.05$) or unauthorized/wrong drug errors (24 percent vs 11 percent, $p < 0.005$) than with other drugs. In particular, confusion between sustained-release and immediate-release versions was commonly noted, with one being given instead of the other. In a few cases, sustained-release oxycodone was crushed and given to the patient.

There were also several issues with specific opioid formulations. There were multiple cases of wrong administration of the concentrated opioid solutions frequently

| Table 1. Most commonly reported primary error types and effects, by most commonly prescribed opioids ($n = 644$) |
|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|-----------------------------------------------------|
| Opioid                                              | Morphine ($n = 201$), percent                         | Hydromorphone ($n = 102$), percent                     | Fentanyl ($n = 90$), percent                          | Meperidine ($n = 80$), percent                        | Oxycodone ($n = 67$), percent                         | Other* ($n = 123$), percent                          |
| Type of error                                       |                                                     |                                                     |                                                     |                                                     |                                                     |
| Improper dose/quantity                              | 40$^\dagger$                                       | 41$^\dagger$                                       | 29                                                   | 23                                                   | 19                                                   | 19                                                   |
| Omission                                            | 13                                                   | 4                                                   | 36$^\dagger$                                        | 3                                                    | 24$^\dagger$                                        | 15                                                   |
| Prescribing error                                   | 11                                                   | 8                                                   | 11                                                   | 15                                                   | 6                                                    | 23                                                   |
| Unauthorized/wrong drug                             | 10                                                   | 15                                                  | 4                                                    | 9                                                    | 24$^\dagger$                                        | 19                                                   |
| Wrong route                                         | 3                                                    | 5                                                   | 0                                                    | 34$^\dagger$                                        | 0                                                    | 2                                                    |
| Extra dose                                          | 5                                                    | 6                                                   | 4                                                    | 4                                                    | 3                                                    | 6                                                    |
| Wrong administration technique                      | 3                                                    | 4                                                   | 3                                                    | 5                                                    | 4                                                    | 2                                                    |
| Drug prepared incorrectly                           | 2                                                    | 6                                                   | 1                                                    | 1                                                    | 4                                                    | 4                                                    |
| Other$^\ddagger$                                    | 13                                                   | 11                                                  | 12                                                   | 16                                                   | 16                                                   | 10                                                   |
| Effect of error                                     |                                                     |                                                     |                                                     |                                                     |                                                     |                                                     |
| Overdose                                            | 55                                                   | 78$^\dagger$                                        | 47                                                   | 65$^\dagger$                                        | 39                                                   | 52                                                   |
| Underdose                                           | 23                                                   | 8                                                   | 46$^\dagger$                                        | 6                                                    | 30                                                   | 23                                                   |
| Other                                               | 12                                                   | 9                                                   | 1                                                    | 19                                                   | 4                                                    | 13                                                   |
| Unclear                                             | 10                                                   | 5                                                   | 6                                                    | 10                                                   | 27                                                   | 12                                                   |

*Error reports where none of the five most commonly used opioids were mentioned; most common other products were acetaminophen/oxycodone, acetaminophen/hydrocodone, methadone, and acetaminophen/codeine. Twenty-two reports had more than one of these five most commonly used opioids involved in the error.

$^\dagger$Significantly greater at $p < 0.05$ ($\chi^2$ compared with all other opioids; some cells with small numbers). Results were similar when only the commonly used opioids were included in the comparisons.

$^\ddagger$Error types reported for $\leq 5$ percent of any of the common opioids included wrong dosage form, wrong patient, wrong time, deteriorated or expired product, and mislabeling.
used in hospice care, such as 20 mg/mL morphine. In many of these cases, the mg dose was confused with the mL dose (eg, patient given 5 mL instead of 5 mg, which would have been 0.25 mL). There were multiple cases of morphine drips administered over an hour instead of a 24-hour period, such as a 50 mg/50 mL solution that was administered over an hour rather than at a rate of 1 mg (or 1 mL) per hour. There were also issues with combinations of opioids with other analgesics, often apparently related to use of the brand name and not recognizing the ingredients or doses of the component drugs. In some cases, patients received a medication included in the drug that they were allergic to, which was not recognized because of use of the brand name. In others, formulations containing acetaminophen were given too frequently and the patient received more than the recommended daily dose of acetaminophen.

**DISCUSSION**

In this study of harmful opioid errors from a national, anonymous reporting system, more than half were reported as administration errors and an additional 20 percent were related to prescribing. Half of the errors caused overdoses, many of which required naloxone administration, and about a quarter caused underdosing and uncontrolled pain. Most errors were reported as related to issues with communication, knowledge, or performance deficits, not following protocols or documentation. Issues related to specific opioids included inappropriately high starting doses, particularly with hydromorphone but also with morphine, mostly due to administration errors; administering meperidine IV rather than IM; incorrectly changing fentanyl patches; and confusing sustained-release and immediate-release preparations, particularly with oxycodone. Issues with specific formulations included confusion about ingredients in combination products including opioids and other analgesics.

Several previous studies have evaluated opioid errors from different perspectives. A medical record review of 22 opioid overdoses requiring naloxone found that only 64 percent were due to an apparent error in prescribing, administration, or compounding, and 18 percent involved more than one opioid. Evaluating errors through retrospective medical review may yield different information; few of these overdoses were reported as incident reports or adverse drug reactions. Much of the information on errors and causes available through reporting systems is usually not documented in medical records, and opioid overdoses may be difficult to distinguish from other clinical causes of patient decompensation. In another series of 43 hospitalized patients who received naloxone for suspected overdose, only 65 percent had rapid improvement of symptoms and were defined as an overdose in an independent medical record evaluation by two investigators. Pulmonary, neurologic, and other causes were frequently misdiagnosed as opioid overdoses.

A study of clinically significant prescribing errors identified through pharmacist screening found that opioids had the highest percentage (92 percent compared with 64 percent overall) considered to be likely or possibly preventable with computerized order entry. Prescribing errors due to lack of knowledge or easy reference to dosing recommendations, miscalculations, or conversion to different opioids or formulations might all be preventable with computerized systems. Underdosing errors (such as not treating uncontrolled pain), as well as the majority of errors that we identified due to administration, may be difficult to address with this approach. Errors of omission or underdosing involving opioids may be more likely to be reported than errors associated with many other drug classes, as the clinician can often observe the direct consequence—uncontrolled pain.

Researching errors with anonymous reporting systems data has many advantages but also has limitations, particularly the inability to evaluate data validity and issues with both underreporting and overreporting. Although MEDMARX is an anonymous reporting database, reporters may be less willing to enter errors associated with serious harm or death (or these may be addressed as sentinel events in their hospitals), and the proportion of these errors in the database may therefore be artificially low. Since we cannot describe the frequency and patterns of opioid use with these data, our results cannot be used to determine the relative safety of one opioid compared with another. Although the relative frequency of types of errors for different types of opioids is affected by how they are used, we were able to confirm specific issues through qualitative review of the brief error descriptions.

Our results identify potentially important issues with specific opioids and formulations, in addition to general safety concerns. Reducing the frequency of inappropriately high doses, particularly with hydromorphone but also with other opioids, might be helped by computerized order entry and availability of appropriate quantities in intravenous unit doses. Confusion between the abbreviations “IM” vs “IV,” no suffix vs “SR” (sustained-release), and similar brand names and combination medications might be helped by clearer prescribing or medication documentation systems. Use of morphine infusions and concentrated morphine solutions may require special attention and care, such as writing out doses in both mg and mL. Our results also underscore the importance of considering errors as a potential etiology when patients are sedated or do not appear to be responding to prescribed opioids. Finally, educational and safety programs and practice guidelines should include information designed to address these types of errors.
ACKNOWLEDGMENTS

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REFERENCES

Patterns of illicit drug use and retention in a methadone program:  
A longitudinal study

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ABSTRACT

Objective: This study aimed to analyze illicit drug use of participants in a methadone treatment program in relation to methadone dose, counseling, and retention.  
Methods: This was a longitudinal study of a cohort of 204 heroin-dependent subjects admitted for the first time to a methadone program in Stockholm. The patients were admitted between 1995 and mid-2000 and were followed until December 2000 or discharge. Up to June 11, 1998, individual psychosocial counseling was provided, after this date individual counseling was replaced with group counseling. Clinical data were collected from patient records and from a laboratory database. Rates of drug-positive urine analyses during different time periods were measured.  
Results: The mean observation time was 2.5 years for all patients. The one-year retention rate was 84 percent, and the two-year rate was 65 percent, with no major differences between the two counseling groups. Almost all patients relapsed to illicit drug use. Discharged patients had a significantly higher rate of positive urine samples (21 percent versus 9 percent) than patients who remained in treatment. Also, low methadone dose and younger age predicted discharge from treatment.  
Conclusion: The frequent urine monitoring showed that illicit drug use was rather common, even in a program with structured psychosocial interventions, although it was lower than in other studies. This testing policy can be used for early identification of patients at risk for drop-out or discharge who should be offered complementary interventions.  
Key words: methadone maintenance treatment, urine samples, drug abuse patterns, discharge, drug abuse, methadone dose

INTRODUCTION

Methadone maintenance treatment (MMT), generally used in combination with psychosocial services, is a well-documented treatment for opiate addicts. It offers a number of reported positive effects, such as reduced opiate and other illicit drug use,\textsuperscript{1,2} decreased risk for needle sharing and HIV transmission,\textsuperscript{3,5} reduced risk of premature death,\textsuperscript{6} reduced criminal behavior,\textsuperscript{7} improved quality of life,\textsuperscript{8} social rehabilitation, and reduced costs for society.\textsuperscript{1,4,5,9,10} Illicit drug use is one of the most common reasons for clients’ leaving MMT prematurely\textsuperscript{11} and is related to the methadone dose\textsuperscript{12} and level of psychosocial services\textsuperscript{1,13} provided. Moolchan and Hoffmann\textsuperscript{14} proposed a four-phase model with successively decreasing treatment interventions in relation to increased performance. The question of whether the impact of group-based counseling differs from that of individual counseling warrants study.  
Information about illicit drug use during MMT can be obtained through interviews alone\textsuperscript{1,15} or in combination with urine drug screening.\textsuperscript{10,17} However, the validity of interview data is uncertain, as patient reports may be influenced by recall difficulties and perceived risk of negative sanctions if illicit drug use is exposed.\textsuperscript{18,19} Magura and Lipton\textsuperscript{20} concluded that urinalysis is the most objective measure for evaluating patients’ illicit drug use, as well as for making clinical decisions during treatment. Studies employing data from both interviews and urine testing have focused on changes in illicit drug use during treatment periods shorter than one year.\textsuperscript{10,17}  
The Methadone Maintenance Treatment Programmes (MMTP) in Sweden were regulated by the National Board of Health and Welfare,\textsuperscript{21} in accordance with Dole and Nyswander’s initial model, until January 2005. The national goal of a drug-free society led to close scrutiny of MMTP,
and the maximum number of patients allowed in the treatment programs at the same time was limited (500 patients 1994 through 1996,22 600 patients 1997 through 1998,23 800 patients 1999 through 2003,24 and 1200 in 200425). The inclusion criteria were a minimum of four years of addiction involving compulsive intravenous opiate use, an age of at least 20 years, failed individual rehabilitation by drug-free treatment, absence of advanced polydrug use, and the patient’s free choice to enter the program.21 The two-year retention rate was 80 percent for all 655 patients in MMTP in Sweden until 1993, which is markedly higher than in most other reported studies.20

The Stockholm MMTP expanded from 100 patients in 1988 to 271 patients in 1994, to 310 patients in 2000. After detoxification, MMT was initiated in ward or at the outpatient clinic and, at least during the following three months, supervised daily intake of methadone and routine urine sampling were obligatory. Approximately every second urine specimen was selected for laboratory analysis. The methadone dose was increased for all patients—up to 50 to 60 mg—during the first three months; after this point doses were individually adjusted (usually increased) if a patient reported withdrawal symptoms and/or if the plasma methadone concentration was lower than 200 to 400 ng/mL.27 If the patient used illicit drugs, a drug-free period of four weeks was demanded before dose adjustment. A positive urine sample resulted in daily testing until a negative sample was produced. If the rehabilitation progressed positively, urine sampling became more infrequent (usually two to four times a month), take-home doses were allowed, and psychosocial services were gradually decreased. Decisions regarding involuntary discharge were made after discussion and evaluation of the patients’ treatment performance and potential to benefit from further treatment. The criteria for inevitable involuntary discharge were threat of violence, criminal acts leading to a prison sentence, drug dealing, providing or smuggling narcotic substances and/or methadone, tampering with a urine specimen, and, from 1997 on, not taking methadone according to prescription.

MMTP thus made use of frequent monitoring of illicit drug use through urine testing. The existence of well-documented data about urine test results, methadone doses, and discharges dating back to 1995 permitted a more detailed analysis of illicit drug use during MMT than reported in other studies, and this is the rationale for this report. The aim of this study was to analyze the following:

- whether initial individual or group counseling is related to illicit drug use, methadone dose, and retention; and
- the roles of illicit drug use and age at discharge.

The study was approved by the Research Ethical Committee at Karolinska Institutet on November 5, 2001 (Dnr: 01-310).

**METHODS**

During the period from January 1, 1995, to June 30, 2000, 225 heroin-dependent subjects with no prior experience with MMT were admitted to MMTP. This study is based on 204 of these patients, as 21 were excluded because of transfer to another MMTP (six subjects), lack of urinalysis results (four), or no participation in “The New Team” (11 subjects). The subjects were followed until December 31, 2000. The observation period ranged from six months to six years.

The psychosocial intervention was based on structured individual counseling (here referred to as “The Old Team”) until June 1998, when a more structured group treatment program was introduced (here referred to as “The New Team”) based on Moolchan and Hoffman’s14 model, with mandatory activities for about 15 hours each week during the first three months or until negative urine samples were obtained. After this first treatment phase, patients were transferred to one of four other outpatient clinics for continued treatment based on individual counseling, urine screening, and cooperation with the social service agencies.

**Data collection**

Information about illicit drug use was obtained from the laboratory database. The exception was alcohol consumption, regarding which we lacked sufficiently detailed information. The urine samples were analyzed using routine immunochemical screening methods for methadone, opiates, benzodiazepines, amphetamines, cocaine, cannabis, barbiturates, LSD, and propoxyphene. Confirmation analyses by gas chromatography and mass spectrometry were undertaken if a positive screening result was refuted by the patient; these tests were performed in about 10 percent of all positive cases. The number of urine samples analyzed per person was 122 during the first year and decreased successively over time to 55 during the fifth year for patients with at least four years of treatment. Positive test results were grouped into relapse periods, each consisting of one or more sequential positive results and ending with the first negative result. All data concerning time in treatment, methadone dose, reasons for discharge, and patient characteristics were abstracted from patient records.
Statistical analysis

This study includes nearly all first-time patients admitted to MMTP during the study period. The power is 100 percent when we look at illicit drug use in relation to treatment status, but power has not been calculated for other analyses, as the numbers of patients are too low in the subgroups. Statistical analysis of illicit drug use during different periods after entry into MMTP was performed for all positive urine samples combined and separately for opiates, amphetamines, benzodiazepines, and cannabis. The differences were analyzed by $\chi^2$ test. Results were considered significant for $p < 0.05$. Poisson regression was used to adjust for differences in follow-up time among subjects when calculating the number of relapse periods in relation to time at risk (time with drug abuse excluded). The incidence rate (number of relapse periods per person and year) was calculated as the total number of relapses divided by the total time in treatment for all persons during relevant time periods.28 The relationships between illicit drug use and methadone dose, gender, age, and initial psychosocial treatment were compared for subjects who were in treatment on December 31, 2000, and for those who were discharged before the end of the study period. The Wilcoxon signed-rank test and Spearman rank-order correlations were calculated for bivariate correlations. The last adjusted methadone dose before three and six months in treatment, at one year, at 435 days (representing the median time in treatment for the 84 discharged patients), and each following year were compared between the patients in treatment and those who were discharged. The relative risk for relapse to drug use for the discharged patients in comparison to those in treatment was calculated from the incidence of relapse periods for each group. SAS software packet 9.0 was used for data analysis.

RESULTS

Subjects

The study cohort comprised 147 men (72 percent) and 57 women (28 percent). The median age at admission was 36 years (range of 21 to 66 years) for the men and 34 years (range of 24 to 50 years) for the women. The majority (54 percent) of patients had nine years or less of schooling, and only 5 percent had studied at a university. All patients had been detoxified in inpatient care at least once, and 40 percent more than 10 times. The mean number of prior residential treatment episodes was 2.4. At admission, 74 percent of patients were unemployed, 22 percent were receiving disability pension or were sicklisted, and 4 percent were employed, self-employed, or students. The mean number of years of intravenous opiate use was 11, and use of other illicit drugs had usually occurred for several years.

Mean observation time and retention

Of the 204 patients, 120 patients (89 men, 31 women) remained in treatment and were followed until December 31, 2000, and 84 patients (58 men, 26 women) were followed until discharge. The mean time in treatment was 869 days (2.4 years) for all patients, 1,084 days (3 years) for patients who remained in treatment, and 561 days (1.5 years) for discharged patients. Two patients were discharged during the first three months. The one-year retention rate was 84 percent. The discharged patients were significantly younger (median age of 33 years; $p < 0.05$) than the patients who remained in treatment (median age of 37 years).

Results from urine screening

Illicit drug use was detected at least once in 13 percent (5,666) of 45,431 analyzed urine samples, corresponding to 3 percent of all 231,073 drug analyses (some tests did not involve all nine substances). Discharged patients had a significantly higher rate of positive urine samples (21 percent versus 9 percent) than patients who remained in treatment. Only nine of all 204 patients had no positive tests. Of all positive urine samples, 50 percent were positive for opiates, 49 percent for benzodiazepines, 16 percent for amphetamines, 8 percent for cannabis, and 2 percent for cocaine. There was no gender difference.

Illicit drug use after entry

The total number of relapse periods was higher for those who were discharged during all time periods. During the first three months, 51 percent (104 patients) of all 204 patients relapsed at least once; this value represents 47 percent (56) of the 120 patients in treatment and 57 percent (48) of the 84 discharged patients, resulting in a nonsignificant difference ($p = 0.14$). Figure 1 shows that 78 percent (81) of the 104 patients had at least one urine sample positive for opiates; 43 percent (45) had taken benzodiazepines, 20 percent (21) amphetamines, 9 percent (9) cannabis, and only 2 percent cocaine. Illicit use of amphetamines was significantly more frequent in the discharged group (31 percent, or 15 patients) than among those who remained in treatment (11 percent, or six patients; $p < 0.01$).

About 12 percent (24) of the 204 patients left urine samples that were positive for both opiates and benzodiazepines, but there was no significant relationship between these results and discharge ($p = 0.35$). The mean number of relapse periods per person during the first three months of treatment was 4.6 for discharged patients, compared to 3.4 per person and year among patients in treatment at the end of the observation period.


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(p = 0.02); in this area there was a statistically significant difference for men (p = 0.04) but not for women. Discharged patients also had significantly more relapse periods per person and year during the first six months and each year thereafter (up to and including the third to fourth years: p < 0.0001; fourth to fifth years: p = 0.05) (Table 1).

The overall relative risk for illicit drug use for patients who were discharged was 2.3 (95 percent CI 2.0 to 2.4) in comparison to those who remained in treatment; for men the risk was 2.2 (95 percent CI 2.0 to 2.4) and for women 2.9 (95 percent CI 2.5 to 3.5). The relapse rate among discharged patients decreased with longer treatment periods for both groups with regard to opiates, cannabis, and amphetamines, but not for benzodiazepines (Table 2).

**Methadone dose in relation to relapse with opiates and retention**

The rate of relapse to opiates during the observation period was negatively associated at the last adjusted methadone dose (r = -0.22; p < 0.05) and also at 435 days of treatment (r = -0.19; p < 0.05). The mean last adjusted dose was significantly lower for discharged patients than for those who remained in treatment: 63 versus 67 mg at three months (p < 0.05), 70 versus 76 mg at six months (p < 0.0001), 75 versus 84 mg at one year (p < 0.0001), and 81 versus 87 mg at two years of treatment (p < 0.05).

**Association between counseling, illicit drug use, and methadone dose**

Of the 204 patients, 131 (93 men and 38 women) were admitted to The Old Team (through June 11, 1998) and 73 (54 men and 19 women) to The New Team (from June 12, 1998, to June 30, 2000). Overall, men and women from The Old Team had significantly more relapse periods than those from The New Team for the first two years of treatment (p < 0.0001). The number of relapse periods per person per year for patients in The Old Team was 5.9, versus 4.4 for patients in The New Team, and 8.4 versus 7.3 for discharged patients from the two teams, respectively. The last methadone dose before the end of the first year of treatment was significantly higher in The New Team than in The Old Team (83 mg versus 77 mg; p = 0.0052), especially among men (83 mg versus 75 mg; p = 0.0006), which may account for some of these differences. The one- and two-year retention rates were 85 and 66 percent in The Old Team and 83 and 63 percent in The New Team.

**Reasons for involuntary discharge**

Thirty-eight of the 84 involuntarily discharged patients (45 percent) were discharged because of illicit drug use, mostly in combination with some other discharge criteria. They had an average of 7.1 relapse periods per person per year, versus 6.6 for those who were discharged for other reasons (p = 0.25). About 30 percent of the discharged patients were women—the same proportion of females as in the entire study population. The proportion of discharged patients declined with age; 55 percent of patients ≤ 30 years of age were discharged, versus 23 percent of patients ≥ 41 years of age.
Table 1. Number of relapse periods per person and year among patients who remained in treatment (Tx) or were discharged (Dis)

<table>
<thead>
<tr>
<th>Observation period</th>
<th>Time in treatment</th>
<th>0 to 6 months</th>
<th>6 to 12 months</th>
<th>1 to 2 years</th>
<th>2 to 3 years</th>
<th>3 to 4 years</th>
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<td>Dis (n = 29)</td>
<td>Tx (n = 24)</td>
<td>Dis (n = 10)</td>
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<td>8.8</td>
<td>3.6</td>
<td>6.5</td>
<td>2.5</td>
<td>3.9</td>
<td>4.4</td>
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<td>8.0</td>
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<tr>
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<tr>
<td>4 to 5 years</td>
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<td>5 to 6 years</td>
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</table>

DISCUSSION

No other reports seem to exist about MMT programs utilizing such frequent urine analyses. Most of the patients left at least one positive urine sample, and almost all patients relapsed to opiates, but of the total taken only 13 percent of the urine samples were positive. In a study by Saxon et al., 40 percent of urine samples collected weekly during an 18-month period were positive for opiates; about 38 percent were positive for cocaine, 7 percent for benzodiazepines, and about 30 percent each for propoxyphene, barbiturates, and amphetamines. These percentages are much higher than in our study, but the mean methadone dose was lower in the Saxon et al. study. It was expected that discharged patients would have a significantly higher rate of positive urine samples than patients who remained in treatment (21 percent versus 9 percent), as this is a common reason for discharge. At the same time, the analyses show that patients with (even repeated) illicit drug use during treatment can stay in treatment after an overall assessment of their situation. This is contrary to a belief expressed in a sometimes polarized discussion of MMT in Sweden and in the past has been seen as controversial.

The policy of urine screening remained unchanged. A limitation of the study is the decreasing number of urine specimens with time in treatment. 30 We do not know whether we would have found a higher level of drug use with more frequent urine testing or with complementary self-reports. A combination of the two methods is considered to be more effective than either method used alone. 31–33 The 120 patients in treatment at the end of the study period had begun treatment with histories of significantly less drug abuse, and their lower rates of abuse persisted during all observation periods in comparison to the 84 discharged patients. Although relapses occurred late in treatment as in other studies, 1 the relapse periods decreased with time in treatment. 1,34 Patients yielding the most frequent positive urine samples were discharged first, as in the study by Morral et al. 17 All but two patients remained in treatment during the first three months. This differs from several other studies where about 30 percent, if not more, left treatment during this period. 35–38 The high retention rate seen in this study may be related to strict admission criteria, a long admission procedure including social and medical treatment planning, and time spent on a waiting list; this combination of factors has probably led
to priority being given to subjects with higher motivation, as well as to a high perceived risk of involuntary discharge following positive urine tests. The retention rate could also be related to methadone dose, medical or psychosocial treatment, and social interventions such as the availability of lodging in a boarding house.

The patients often used benzodiazepines, a finding reported in other studies.39,40 This was more common in the discharged group and may be due to a generally more dysfunctional life,39 a greater need to reduce withdrawal from or enhance the effect of the primary drug,41 and/or benzodiazepine dependence.32 Amphetamine use was significantly related to discharge even during the first three months, especially for men. Bykvist,43 in a study of polydrug use among Swedish drug abusers in the early 1980s, found that amphetamines and cannabis were the most common second-choice drugs for drug users whose primary drugs were opiates (benzodiazepines were not included in the study). The discharged patients were about six times more likely to use cannabis during treatment than those who remained in treatment. We found a negative relationship between methadone dose and opiate relapse, which corresponds with earlier research.1,14-46 The discharged patients had lower methadone doses, possibly due to a delayed increase in methadone dose because of illicit drug abuse, leaving treatment because of withdrawal symptoms, or dissatisfaction with the methadone dose level. Hiltunen et al.27 found that dissatisfied patients who received a dose increase stopped their illicit drug use. This poses the question of whether the schedules for reaching stabilization levels and the policy for adjusting methadone doses were sufficiently adapted to individual needs. We also must question whether a delayed dose increase due to positive urine tests increased the risk of relapse and involuntary discharge. The lower relapse rate among the patients in The New Team compared to patients in The Old Team is probably partly due to significantly higher methadone doses during the first year, but it could also be due to the stricter deterrent policy of discharge after two positive urine samples. During the first three months, the levels of attendance and counseling were high in both teams, and we feel these are important predictors of treatment retention.38 Aberg et al.47 reported that Swedish methadone patients considered psychosocial interventions very important. No differences in retention rates were observed between the two teams, which suggests that the level of counseling in both teams contributed equally well to retention. Illicit drug use was the most frequent administrative reason for discharge, which corresponds to the results of other Swedish studies.26,48 In other countries, loss of contact, loitering, noncompliance with program rules, voluntary drop-out, arrest, and incarceration seem to be more common reasons for discharge1,37,49; these outcomes may be explained by different program policies.

**CONCLUSION**

The generality of this study is limited with regard to methadone programs with less restrictive admission criteria. Although the subjects in this study had long histories of drug abuse, the retention rates were high. Almost all patients relapsed into illicit drug use at least once, but the proportion of positive urine tests was low, although comparisons with other programs are difficult due to their lower rates of urine testing. Illicit drug use decreased during the follow-up period but was the most frequent reason for discharge. Methadone dose was related to illicit drug use and discharge, and there is some question as to whether the policy of not increasing the methadone dose in patients with a positive urine sample contributed to further relapse

<table>
<thead>
<tr>
<th>Type of drug</th>
<th>Time in treatment (years)</th>
<th>0 to 1</th>
<th>1 to 2</th>
<th>2 to 3</th>
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<tr>
<td></td>
<td>Tx (n = 15)</td>
<td>Dis (n = 34)</td>
<td>Tx (n = 25)</td>
<td>Dis (n = 29)</td>
</tr>
<tr>
<td>Opiates</td>
<td>2.8</td>
<td>5.0</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>1.1</td>
<td>3.4</td>
<td>2.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Cannabis</td>
<td>0.0</td>
<td>0.7</td>
<td>0.0</td>
<td>0.3</td>
</tr>
<tr>
<td>Amphetamines</td>
<td>0.8</td>
<td>1.9</td>
<td>1.3</td>
<td>1.8</td>
</tr>
</tbody>
</table>
and involuntary discharge. Further research is needed to identify factors that reduce the risk for illicit drug use during treatment and to develop ways of using this knowledge to improve treatment and to better adapt it to individual needs.

ACKNOWLEDGMENTS

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REFERENCES

Psychological factors as predictors of opioid abuse and illicit drug use in chronic pain patients

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ABSTRACT

Background: Psychopathology (depression, anxiety, somatization disorder) and substance abuse (opioid misuse and illicit drug use) are common in patients with chronic pain and present problems for public health and clinical management. Despite a body of literature describing various methods for identifying psychopathology, opioid misuse, and illicit drug use in chronic pain patients, the relationship between psychopathologies, substance abuse, and chronic pain has not been well characterized.

Methods: This report describes a total of 500 consecutive pain patients prescribed and receiving stable doses of opioids. The patients were evaluated for psychopathology, opioid abuse, and illicit drug use during the course of regular pain management treatment. The relationships between psychopathology and drug abuse and/or illicit drug use in chronic pain patients were examined, and psychological evaluation for depression, anxiety, and somatization disorder was performed.

Results: Depression, anxiety, and somatization disorder were documented in 59, 64, and 30 percent of chronic pain patients, respectively. Drug abuse was significantly higher in patients with depression as compared to patients without depression (12 percent with depression versus 5 percent without). Current illicit drug use was higher in women with depression (22 percent) than women without depression (14 percent) and in men with or without depression (12 percent). Current illicit drug use was also higher in men with somatization disorder (22 percent) than men without (9 percent).

Conclusion: This study demonstrated that the presence of psychological features of depression and somatization disorder may be markers of substance abuse diathesis in chronic pain patients.

Key words: psychopathology, substance abuse, opioid abuse, illicit drug use, MCMI, P3, DSM-IV-TR, endophenotype

INTRODUCTION

Pain is defined as both a physiological sensation and a psychological condition or state.¹ Thus, the neural event of pain is in many ways inextricable from the psychological or phenomenal experience of pain.² Chronic pain in particular manifests a psychological constellation of cognitive, emotional, and behavioral characteristics.³ There is extensive literature associating chronic pain and psychological disorders.²-²⁸ Numerous studies have shown that a significant proportion of pain patients present with depression, anxiety, and somatization disorder, either alone or in combination.⁴-²⁸ In studies that have evaluated chronic pain patients, the comorbidity of major depression ranged from 15 percent to 56 percent, significantly higher than the occurrence of major depression within the general (i.e., non–chronic pain) population, which ranged from 5 percent to 10 percent. Similarly, the occurrence of somatization disorder ranged from 20 percent to 31 percent in chronic pain patients, compared to 1 percent to 4 percent in the general population. Thus, it becomes evident that 1) psychological factors are reciprocally interactive in the initiation and expression of the pathology of chronic pain; 2) unrecognized and untreated psychopathology may increase pain intensity, disability, and exacerbation of environmental influences; 3) this reflects the truly biopsychosocial dimensionality of chronic pain, and, therefore, 4) such dimensions must be considered in any meaningful paradigm for chronic pain management.⁵-⁸

A considerable amount of research has been devoted to profiling the psychological and behavioral characteristics of chronic pain patients in an attempt to accurately
identify strategies and tactics of effective co-management of psychological and physical symptoms and the combined effects of disability (e.g., anxiety has been shown to decrease patients’ pain threshold and tolerance, and both anxiety and depression have been associated with magnification of medical symptoms). Yet a persistent problem is the overuse/abuse of both prescription drugs and illicit agents in this patient population. Surveys have shown that persons with a history of at least one major depressive episode within the past year were significantly more likely to have used illicit drugs during that time period compared to those persons without a major depressive episode (28.8 percent versus 13.8 percent), and substance dependence or abuse was more prevalent among persons with a major depressive episode than among nondepressed persons (22.0 percent versus 8.6 percent). Similarly, serious psychological distress was highly correlated with substance dependence or abuse: 21.3 percent (4.6 million) of adults with serious psychological distress were shown to be dependent on or to have abused alcohol or illicit drugs in 2004, as compared to only 7.9 percent of adults without serious psychological distress. Similarly, the risk and prevalence of substance abuse has been associated with pre- and comorbidity of psychological disorders in patient populations receiving controlled substances. Regier et al. demonstrated that patients with a lifetime mental disorder present with more than twice the risk of having an alcohol disorder and over four times the risk of having (another) substance abuse disorder. Webster and Webster have shown that depression is a risk factor for opioid abuse (as ascertained by the Opioid Risk Tool), although Ives et al. failed to reveal a direct correlation between depression and opioid misuse.

The potential magnitude of this problem becomes evident when one considers that, according to the 2004 National Survey on Drug Use and Health, there were 35.1 million (14.7 percent) persons aged 12 or older who had had at least one major depressive episode in their lifetime. Of these, 19.3 million persons (8.1 percent of the population) had had a major depressive episode in the past 12 months, including 2.2 million youths (aged 12 to 17) and 17.1 million adults (aged 18 or older). This survey also estimated the prevalence of serious psychological distress, defined as a high level of distress due to any type of mental problem. In 2004, there were 21.4 million adults with serious psychological distress, representing 9.9 percent of all adults.

Despite the noted increase in the prevalence of pain, psychological, and substance abuse disorders and the growing body of evidence to support the comorbidity (and putative relationship) of these disorders, there is sparse literature addressing the viability of psychological factors as predictors of opioid abuse and/or illicit drug use in chronic pain patients. Controlled substance abuse among chronic pain patients is common. The prevalence of prescription drug overuse and abuse has been reported to be between 9 and 41 percent for patients receiving opioids for chronic pain. This is particularly significant, given that as many as 90 percent of patients in pain management settings receive opioids for chronic pain. Our work has revealed that pain resulting from motor vehicle accidents, involvement of multiple painful sites, and a past history of illicit drug use were all significant risk factors. In addition to these variables, Ives et al. identified past cocaine abuse, drug or DUI conviction, and past alcohol abuse as predictors of misuse.

In light of the fact that drug use represents a significant epidemiological problem, compounds the impact of chronic pain and psychological conditions, and considerably complicates (if not impedes) effective care, tactics for the detection and reduction/prevention of continued drug misuse/abuse assume an important place in the initiation of therapeutic intervention. Multiple investigators have described screening instruments to detect opioid abuse or misuse in chronic pain patients. However, most of the screening instruments currently in use have not included or accounted for psychological variables.

Our earlier work evaluated depression as a variable. However, our study was limited in that it did not consider the broader effects of pain and comorbid psychopathologies as part of a spectrum disorder (or disorder continuum), and therefore did not examine patterns or the role of anxiety and somatization disorder as covariates in drug misuse/abuse in chronic pain patients. The hypothesis that chronic pain and these disorders may be covariant is strengthened by the findings of Dersh et al., according to which chronic pain patients were 10.2 times more likely than persons in the general population to have a major Axis I psychiatric disorder. The Dersh et al. evaluation of Axis I disorders included drug abuse and alcohol abuse/dependence, as well as major depression, dysthymia, any anxiety disorder, and panic disorder. Their study showed that drug abuse and dependence were present in 10.7 percent of the patients. There was a correlation between the occurrence of pain and several types of pathologies classified in the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV-TR), most notably major depressive disorder, drug abuse/dependence, and personality disorders, although anxiety disorders were less frequent than major depressive disorders.

Therefore, given that pain is by definition both a physiological and psychological event, and considering the reported relationship between particular Axis I psychological disorders (e.g., depression, anxiety, somatization)
and substance abuse, we pose the question of whether
determination of psychological presentation (i.e., the
presence of co- and/or premorbid psychological disor-
ders) may have some value toward predicting (or alert-
ing to) the predisposition/sensitivity to substance abuse
in chronic pain patients. Thus, this study investigated
the pattern of depression, anxiety, and somatization disorder
in chronic pain patients who were either misusing op-
oids or using illicit drugs in an attempt to correlate these
findings and better clarify the value of psychological condi-
tion as a predictor of substance abuse among chronic
pain patients in interventional pain management settings.

METHODS

This article reports the results of routine psychological
testing for 500 consecutive patients taking prescribed
opioids for pain management through a private practice
in an interventional pain management setting. All patients
provided valid and informed consent for obtaining infor-
mation on drug use, random drug testing, and confiden-
tial publication of results. Appropriate precautions were
taken to protect the privacy and confidentiality of
patients participating in this evaluation. All patients also
signed agreements that included permission to contact
pharmacies and physicians and to perform random drug
screening. All patients in this study were receiving stable
doses of hydrocodone, oxycodone, methadone, or mor-
phine in pharmacologic support of interventional pain
management techniques. In this way, opioid use consti-
tuted supplemental pain management and was not the
mainstay of the treatment protocol. Inclusion criteria for
data evaluation required that patients were willing to par-
ticipate, were in stable condition, and were in a pain
management program encompassing interventional tech-
niques and opioid drug administration. Exclusion criteria
were defined as an inability to understand the consent,
refusal to sign the consent, refusal to follow the terms of
the agreement, refusal to submit to random drug testing,
and unstable pain control.

Upon inclusion, initial evaluation consisted of monitoring
controlled substance intake—with special focus upon exter-
nally provided drugs—and documentation of past history of
illicit drug use. History of illicit drug use was determined
from patients’ reports of such use/activity.

Data collected included information from records,
pharmacies, referring physicians, and all physicians
involved in patient treatment. Data were collected using a
preprinted format including demographic information
and drug history and were compared with all acquired
information.

Rapid urine drug screening (Instant Technologies,
iCup®, Norfolk, VA) was performed on all the patients
participating in the study. The rapid drug screen is a one-
step, lateral-flow immunoassay for the simultaneous
detection of up to nine drugs via urinalysis. Each analysis
occupies a separate channel intended for use in the qual-
itative detection of various drugs.

Psychological evaluation focused on signs and symp-
toms that were representative of the DSM-IV-TR charac-
terizations of depression, anxiety, and somatization disor-
der. Psychological status was evaluated by obtaining a
psychological history using a DSM-IV-TR criteria-based
questionnaire, followed by a physician-conducted in-
terview and/or administration of the Million Clinical
Multiaxial Inventory (MCMI-II or MCMI-HD) and/or
administration of the Pain Patient Profile (P-3).18,56 Evaluation
using the DSM-IV-TR criteria-based question-
naire involved multiple questions with content validity
for determinations of clinically relevant features of
depression, anxiety, and somatization disorder.4,58

The MCMI is a 175-question psychological tool that
does not require administration by a psychologist, is
commonly utilized to evaluate psychological involve-
ment in various medical syndromes, and is easily admin-
istered in outpatient interventional pain practices.59 The
MCMI evaluates personality disorders and various clinical
syndromes including depression, generalized anxiety,
and somatoform disorder.

The P-3 is a 34-item instrument for briefly assessing
psychological characteristics known to affect the pain
perception and treatment response of pain patients.60 It is
somewhat specifically used to evaluate comorbidity of
depression, anxiety, and somatization in pain patients.

A prospective evaluation of the effectiveness of the
DSM-IV-TR questionnaire, pain management question-
naire, and clinical interview showed these techniques to
reliably assess depression and anxiety in an interven-
tional pain management setting.4 Therefore, diagnostic
impressions of psychological conditions were based on
the results of these tests throughout the (opioid) treat-
ment period.

Substance abuse was operationally defined as occur-
ring 1) when patients received controlled substances
from any place or source other than the prescribing
physician, with the exception of the short-term use of
controlled substances for acute injury/insult and/or emer-
gency, and/or 2) when patients escalated the use of con-
trolled substances beyond the dose(s) and schedule pre-
scribed. Drug trafficking was defined according to the
legal determination as described by statute and in courts
of law. Past history of illicit drug use was based on
patient report/history and/or information afforded by the
patient’s medical record.

All patients underwent rapid urine drug testing.
Patients were considered positive for current illicit drug
use if one of the monitored illicit drugs (including
cocaine, marijuana [THC], amphetamines, or metham-
phetamine) was detected by urinalysis, with the qualify-
ing conditions that 1) positive results for the presence of
<table>
<thead>
<tr>
<th>Table 1. Demographic characteristics</th>
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<tr>
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<tr>
<td>Age (years)</td>
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<td>45 to 64</td>
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<td>≥ 65</td>
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<td>Range</td>
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<td>Mean ± SE</td>
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<tr>
<td>Duration of pain (years)</td>
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<td>&lt; 5</td>
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<td>5 to 9</td>
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<tr>
<td>≥ 10</td>
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<tr>
<td>Range</td>
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<td>Mean ± SE</td>
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<td>Mode of onset</td>
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<td>Motor vehicle accident</td>
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<td>Other incident</td>
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<td>Work-related injury</td>
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<td>two regions</td>
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<tr>
<td>three regions</td>
</tr>
<tr>
<td>History of previous spine surgery</td>
</tr>
<tr>
<td>Insurance status</td>
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<tr>
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<td>Medicare with/without third-party support</td>
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<td>Medicare and Medicaid</td>
</tr>
<tr>
<td>Medicaid</td>
</tr>
<tr>
<td>Past history of illicit drug use</td>
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</table>

* Indicates a significant difference between male and female patients.
Table 2. Psychological characteristics

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th></th>
<th>Anxiety</th>
<th></th>
<th>Somatization disorder</th>
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<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Male (n = 205)</td>
<td>111 (54%)</td>
<td>94 (46%)</td>
<td>119 (58%)</td>
<td>86 (42%)</td>
<td>55 (27%)</td>
<td>150 (73%)</td>
</tr>
<tr>
<td>Female (n = 295)</td>
<td>185 (63%)</td>
<td>110 (37%)</td>
<td>200 (69%*)</td>
<td>95 (32%)</td>
<td>96 (32%)</td>
<td>199 (68%)</td>
</tr>
<tr>
<td>Total (N = 500)</td>
<td>296 (59%)</td>
<td>204 (41%)</td>
<td>319 (64%)</td>
<td>181 (36%)</td>
<td>151 (30%)</td>
<td>349 (70%)</td>
</tr>
</tbody>
</table>

* Indicates a significant difference between male and female patients.

cocaine (and its metabolites) was considered definite by rapid urine drug screen, and 2) positive identification(s) of methamphetamine, amphetamine, and/or marijuana were checked for false positives with a follow-up laboratory evaluation and exclusion of drugs causing false-positive results. For example, tentatively positive THC results were confirmed with secondary laboratory testing if a patient was on pantoprazole (Protonix®) or denied using marijuana. All results confirmed by secondary laboratory evaluation were considered final.

Data were tabulated using Microsoft Access® 2003, and SPSS (version 9.0) was used to generate frequency tables. The $\chi^2$ statistic was used to determine significant differences between groups. Fisher’s exact test was used post hoc (wherever the expected value was less than five). Student’s t-test was used to determine significant sex-based differences. All results were considered statistically significant at $p < 0.05$.

RESULTS

Patient flow

Data were evaluated for the prevalence of opioid abuse and illicit drug use in 500 patients. Initially, 566 patients were eligible, but 66 patients refused to participate in the study. All patients were evaluated for opioid abuse and underwent urinalysis for cocaine, amphetamines, methamphetamine, and marijuana (THC).

Demographic characteristics

Table 1 illustrates the demographic characteristics of age, duration of pain, mode of onset of pain, number of body regions involved, history of previous spine surgery, insurance status, and past history of illicit drug use among male and female patients.

The proportion of female patients was higher in the age group of those younger than 45 years (42 percent versus 32 percent), whereas the proportion of male patients was higher in the 45-to-64 age group (59 percent versus 45 percent). Mean age was slightly higher for males (49.5 years versus 48.0 years).

The duration of pain was evaluated in three groupings: less than five years, five to nine years, and 10 years or longer. Overall, 75 percent of the patients had had pain for more than five years, and 47 percent had had pain for more than 10 years. Mean duration of pain was longer in males (11.6 years versus 10.1 years).

Thirty-seven percent of patients reported pain to be of gradual onset without injury. A significantly higher proportion of female patients presented with gradual-onset pain (44 percent versus 28 percent). The study also showed a significantly greater proportion of males than females with work-related injuries (30 percent versus 13 percent).

The number of body regions involved was different between males and females. Among males, 46 percent had involvement of one body region; a greater proportion of females than males presented with involvement of two or more body regions (72 percent versus 54 percent).

A history of previous spine surgery was present in 35 percent of the patients. Surgery was more common among males (47 percent versus 27 percent).

Insurance status showed significant differences. A greater proportion of males than females were covered by Medicare with or without third-party insurance (39 percent versus 25 percent). Overall, 38 percent of patients were covered by third-party insurance, 31 percent were covered by Medicare with or without third-party supplemental insurance, 17 percent were covered by Medicare and Medicaid, and 14 percent were covered by Medicaid only. A total of 48 percent of patients were covered by Medicare, and 31 percent had Medicaid coverage.

Psychological characteristics

Psychological characteristics are illustrated in Table 2. Overall, depression, anxiety, and somatization disorder
Table 3. Prevalence of drug abuse and illicit drug use

<table>
<thead>
<tr>
<th>Drug abuse</th>
<th>Male (n = 205)</th>
<th>Female (n = 295)</th>
<th>Total (N = 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Doctor shopping</td>
<td>9 (4.4 percent)</td>
<td>16 (5.4 percent)</td>
<td>25 (5 percent)</td>
</tr>
<tr>
<td>95 percent CI</td>
<td>(2 percent, 7 percent)</td>
<td>(3 percent, 8 percent)</td>
<td>(3 percent, 7 percent)</td>
</tr>
<tr>
<td>Trafficking</td>
<td>12 (6 percent)</td>
<td>9 (3 percent)</td>
<td>21 (4 percent)</td>
</tr>
<tr>
<td>95 percent CI</td>
<td>(3 percent, 9 percent)</td>
<td>(1 percent, 5 percent)</td>
<td>(2 percent, 6 percent)</td>
</tr>
<tr>
<td>Total opioid abuse</td>
<td>20 (10 percent)</td>
<td>26 (9 percent)</td>
<td>46 (9 percent)</td>
</tr>
<tr>
<td>95 percent CI</td>
<td>(6 percent, 14 percent)</td>
<td>(6 percent, 12 percent)</td>
<td>(7 percent, 12 percent)</td>
</tr>
</tbody>
</table>

Illicit drug use

<table>
<thead>
<tr>
<th>Drug</th>
<th>Male (n = 205)</th>
<th>Female (n = 295)</th>
<th>Total (N = 500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marijuana</td>
<td>15 (7 percent)</td>
<td>39 (13 percent*)</td>
<td>54 (11 percent)</td>
</tr>
<tr>
<td>95 percent CI</td>
<td>(4 percent, 11 percent)</td>
<td>(9 percent, 17 percent)</td>
<td>(8 percent, 14 percent)</td>
</tr>
<tr>
<td>Cocaine</td>
<td>10 (5 percent)</td>
<td>14 (5 percent)</td>
<td>24 (4.8 percent)</td>
</tr>
<tr>
<td>95 percent CI</td>
<td>(2 percent, 8 percent)</td>
<td>(2 percent, 7 percent)</td>
<td>(3 percent, 7 percent)</td>
</tr>
<tr>
<td>Methamphetamine/amphetamines</td>
<td>2 (1 percent)</td>
<td>9 (3 percent)</td>
<td>11 (2 percent)</td>
</tr>
<tr>
<td>95 percent CI</td>
<td>(0 percent, 2 percent)</td>
<td>(1 percent, 5 percent)</td>
<td>(1 percent, 4 percent)</td>
</tr>
<tr>
<td>Total illicit drug use</td>
<td>25 (12 percent)</td>
<td>55 (19 percent)</td>
<td>80 (16 percent)</td>
</tr>
<tr>
<td>95 percent CI</td>
<td>(8 percent, 17 percent)</td>
<td>(14 percent, 23 percent)</td>
<td>(13 percent, 19 percent)</td>
</tr>
</tbody>
</table>

* Indicates a significant difference between male and female patients.

were documented in 59, 64, and 30 percent, respectively. A greater proportion of female than male patients were diagnosed with anxiety (69 percent versus 58 percent). There were no significant differences noted between male and female patients with depression or somatization disorder.

Opioid abuse/misuse and illicit drug use

A past history of illicit drug use was identified by self-report in 16 percent of patients. Table 3 illustrates drug abuse and illicit drug use characteristics. A total of 9 percent of patients were either “doctor shopping” or trafficking in opioids. While there were no significant differences noted between males and females, there was an insignificant trend among male patients for trafficking and among female patients for doctor shopping.

Table 3 also illustrates illicit drug use. Overall, the prevalence of illicit drug use was 16 percent—19 percent among females and 12 percent among males. Marijuana use was significantly higher in females than in males (13 percent versus 7 percent).

Drug abuse and illicit drug use characteristics by psychological status

Table 4 illustrates drug abuse and illicit drug use characteristics based on psychological diagnosis. There were no differences in current illicit drug use noted with regard to depression, anxiety, or somatization disorder. However, drug abuse was significantly higher in patients with depression than in those without (12 percent).

Table 5 shows drug abuse and illicit drug use characteristics based on psychological diagnosis and gender. Current illicit drug use was more frequent in women with depression than without (22 percent versus 14 percent) and more prevalent in depressed women than men (22 percent versus 12 percent). Prescription drug abuse was
also higher in women with depression (11 percent versus 4 percent). Current illicit drug use was highest in males with somatization disorder (22 percent versus 9 percent without).

**DISCUSSION**

This study showed a high prevalence of depression (59 percent), anxiety (64 percent), and somatization disorder (30 percent) in patients with chronic pain. Female pain patients presented with comorbid anxiety more often than male pain patients. Depression was shown to be a predictor of comorbid substance abuse, with 12 percent of depressed chronic pain patients showing substance abuse, versus 5 percent of pain patients without depression. Current illicit drug use was shown to be significantly higher in patients with depression than without and among females as compared to males. In this latter regard, subset analysis factoring for gender revealed that 22 percent of women with depression were using illicit drugs. Female patients with depression also showed a significantly higher prevalence of drug abuse (11 percent versus 4 percent). In contrast, male patients with somatization disorder showed a significantly higher prevalence of current illicit drug use compared to male patients without somatization disorder. These results are consistent with those of other studies that have shown an increased prevalence of depression, anxiety, somatization, and substance abuse/dependence disorders in chronic pain patients as compared to the general population.1-28,30,61,62 Furthermore, given the correlation between chronic pain, patterns of emotional reactivity (to internal and external environmental stimuli evidenced in the presented psychopathologies), and substance abuse, the findings of the current study strengthen our previous work, which demonstrated that other biopsychosocial factors (such as pain subsequent to motor vehicle accidents, involvement of multiple anatomic regions, and past history of illicit drug use) are predictive for substance abuse in chronic pain patients.38 Although our study did not demonstrate a clear association between current illicit drug use or drug abuse and anxiety or somatization disorder in women, this could be because the clinical testing instruments used were not sufficiently sensitive to detect such relationships. On the other hand, in regard to illicit drug use and abuse in the population of pain patients studied here, anxiety and somatization behaviors may have been nested within the features of depression.

To date, there is a relative paucity of valid measures that specifically address the predictive correlation between psychopathological variables and the potential for substance abuse in chronic pain patients. Of those in existence, most notable is a preliminary validation of the Opioid Risk Tool, in which Webster and Webster25 identified five factors—family history of substance abuse, personal history of substance abuse, age of 45 years or younger, history of preadolescent sexual abuse, and the presence of particular psychological disorders (i.e., attention deficit disorder, obsessive-compulsive disorder, unipolar depression or bipolar disorder, or schizophrenia)—as potential risks for opioid abuse. Most other studies have not focused upon the role of psychological comorbidity in substance abuse in chronic pain patients; instead, they have tended to examine reactivity to and influence of environmental and circumstantial factors as possible risk predictors.

Chabal et al.35 developed a prescription abuse checklist consisting of five criteria—overwhelming focus on opioid issues persisting beyond the third clinic treatment session; a persistent pattern of early refills; multiple telephone calls or office visits requesting more opioids; reports of consistent problems associated with the opioid prescription (including but not limited to lost, spilled, and/or stolen medications); and opiates obtained from multiple providers, emergency rooms, or illegal sources—that might be indicative of a high(er) substance abuse risk. Compton et al.49 identified three items that were particularly viable in identifying misuse of opioids; these included belief of addiction by the patient, increasing analgesic dose or frequency, and route of administration preference. Passik et al.50 developed a questionnaire that was employed among a small group of cancer and HIV patients to evaluate medication use, present and past.

<table>
<thead>
<tr>
<th></th>
<th>Depression</th>
<th>Aniety</th>
<th>Somatization disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Current illicit drug use</td>
<td>53 (18%)</td>
<td>27 (13%)</td>
<td>18 (15%)</td>
</tr>
<tr>
<td>Drug abuse</td>
<td>35 (12%)</td>
<td>11 (5%)</td>
<td>35 (11%)</td>
</tr>
</tbody>
</table>

* Indicates significant difference.
Table 5. Drug abuse and illicit drug use based on psychological diagnosis and gender

<table>
<thead>
<tr>
<th>Drug abuse</th>
<th>Depression</th>
<th>Anxiety</th>
<th>Somatization disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Male (n = 205)</td>
<td>12 percent (13/111)</td>
<td>12 percent (12/94)</td>
<td>14 percent (17/119)</td>
</tr>
<tr>
<td>Female (n = 295)</td>
<td>22 percent** (40/185)</td>
<td>14 percent (15/110)</td>
<td>20 percent (41/200)</td>
</tr>
<tr>
<td>Male (n = 205)</td>
<td>15 percent (14/111)</td>
<td>6 percent (6/94)</td>
<td>11 percent (13/119)</td>
</tr>
<tr>
<td>Female (n = 295)</td>
<td>11 percent* (21/185)</td>
<td>4 percent (5/110)</td>
<td>11 percent (22/200)</td>
</tr>
</tbody>
</table>

* Indicates significant differences between women with or without depression and men with or without somatization disorder.
** Indicates significant differences between men and women with and without depression.

drug use, patients’ beliefs about addiction risk, and aberrant drug-taking attitudes and behaviors.

Atluri and Sudarshan44 developed a screening tool for detecting the risk of inappropriate prescription opioid use in chronic pain patients that identified six clinical criteria: patient focus on procuring opioids, opioid overuse, other substance use, nonfunctional exaggeration of pain, and unclear and/or improbable pain etiology. Manchikanti et al.52 evaluated the instrument developed by Atluri and Sudarshan44 and specifically identified three primary factors that appeared to reliably predict potential substance abuse: excessive opiate needs, deception or lying to obtain controlled substances, and doctor shopping. Holmes et al.50 developed and introduced the Pain Medicine Questionnaire (PMQ) to assess the risk for opioid medication misuse in chronic pain patients. The PMQ is a 26-item questionnaire that evaluates various dimensions of chronic pain and attempts to isolate pain-related variables and factors that may suggest abuse liability. Savage57 suggested that opioid addiction and/or its potential might be reflected or revealed through behaviors such as an unwillingness to taper opioids or try alternate pain treatments, decreased levels of function despite seemingly appropriate analgesia, and frequent requests for medication refills before renewal is due.

Clearly, the relationship between psychological state/condition (e.g., the presence or absence of psychopathology, as either directly indicated [as by Webster and Webster29] or implied through patterns of reactivity, behaviors, etc.), chronic pain, and the potential for substance abuse is strong, and we concur with the opinion raised in several studies that this reflects a biological basis for the comorbidity of certain psychopathologies (including substance abuse disorders) and chronic pain.20,58-62 This thesis is fortified by the demonstrated co-involvement of several neuropharmacologic systems (e.g., serotonin, norepinephrine, dopamine, glutamate, gonadal steroids) and anatomical structures (namely the thalamo-cortical-limbic pathway) common to these disorders.63,64

It may be that the neural and/or glial chemistry, micro- and macrostructural anatomy of brain regions that are involved in mediating intero- and exteroceptive sensory (i.e., noxious) input, and the associative and emotive aspects of reinforcement and/or reward are disrupted or dysfunctional.65 Underlying these neural (and possibly glial) phenotypic variations might be genetic variations that could potentially induce pleiotropic effects upon several substrates of neural and/glial function (e.g., alterations in transmitter, receptor, and/or effector-signaling molecule synthesis or expression; expression of variant membrane constituents, including differentially sensitive ionic channels; etc.) to alter the pattern(s) of activity at brain loci that are involved in establishing “common neural bases” that predispose one to (or directly subserve) chronic pain, depression, somatization, and substance abuse.66 Recent studies have shown that these loci include (but are not limited to) the parabrachial nucleus, amygdala, nucleus accumbens, and cingulate and frontal cortices as target zones of ascending sensory and internal associative/regulatory pathways.67 The affective components operative in chronic pain (i.e., pain as protracted disease process and illness, affective pain) are akin to those of mood disorder and somatic sensitization.69

Particular individuals are predisposed to the development of neural sensitization within these pathways as a consequence of overreactivity to insult and trauma, inflammation, or aberrant response to environmental input. The overexpression of neural substrates that subserve algesia or distress, together with a suppression or underexpression of pain-modulating, reinforcement, and reward substrates, might induce pathologic patterns of sensory hyperreactivity, altered cognitive processing and emotional responses, and loss of impulse control. In this way, persistent pain, psychopathology, and substance
abuse may be correlated and reflect related mechanistic processes. As Koob and Le Moal note, persistent pain involves “sensitization . . . that is defined by enhanced responsiveness to incoming signals . . . in the peripheral and central nervous system . . . . [A]ddiction also can be considered a type of chronic pain syndrome characterized by emotional pain, dysphoria . . . and interpersonal difficulties . . . . Drugs can be . . . self-medication for such pain.”

Chromosomal quantitative trait loci (QTL) that affect neural phenotypes relevant to types of pain and certain psychopathologies including substance abuse have recently been identified. These QTLs can either operate singly or multiply to affect particular phenotypes. Most surely, the phenotypes for pain, psychopathology, and substance abuse are multifactorial; therefore, it is likely that such QTLs establish a probabilistic basis for the (co)occurrence of these phenotypes along a continuum, while the actual expression of phenotypes as clinically relevant disorders is epigenetically influenced by the central nervous microenvironment and/or effects incurred by ongoing interactions between internal and external environments throughout the lifespan. Variant patterns of these conditions appear to validate this possibility.

Tsan et al. showed that genetic influence in the abuse of marijuana, stimulants, and sedatives is shared across drugs. Thus, an abuser of one drug is more likely than nonabusers to go on to abuse a different category of drug. However, it has been shown that the genetic influence for heroin/opioid abuse is specific to heroin/opioids and is not shared with other drugs. Thus, the high probability of genetic influence on opioid abuse fortifies the repeated finding that familial and personal history of opioid drug abuse is heavily weighed in risk analyses of opioid misuse. Taken together, such findings suggest that genotypic variants might predispose either 1) a “generalized” pattern of diathesis, in which neural substrates of environmental sensitivity, responsivity, reinforcement, and reward are altered to affect interpretive/ associative aspects of bodily sensations (including discomfort and pain), appetitive drives, and emotionality; or 2) more “specific” diatheses, in which particular neural phenotypes are affected which directly correlate to certain forms of pain and/or psychopathology and substance dependency. Albeit speculative, it is tempting to postulate that genetic alteration in the expression of opioid, glutamate, and/or GABAergic receptors (or receptor-linked mechanisms) and/or cation-channel expression might underlie sensitivity to pain, development of particular types of pain (e.g., neuropathic syndromes), the constellation of somatic and cognitive features found in forms of depression and somatization disorder, and decreased viability of opioid-dependent neuromodulation, therefore impacting predisposition to escalative misuse of opioids.

If we consider that these comorbidities may represent environmentally dependent, differential expression of neural and behavioral phenotypes that are established by a relatively confined set of genomic influences, then we may view chronic pain as a spectrum disorder that may co-manifest (other) neuro- and psychopathological effects/conditions. Working from the concept that chronic pain and psychological disorders may be correlated along a neuropathological continuum, it becomes important to recognize that 1) these disorders represent underlying genomic diatheses, and the expression of phenotypic substrates is differentially dependent upon particular interactions with internal and external environmental factors; 2) it is possible—and likely—that such genetic-environmental covariance sustains that comorbidity; 3) this covariance is equally likely on several dimensions of cause and effect; and 4) these effects may be manifested in the co-terminal expression of chronic pain and mood, somatization, and substance abuse disorders. Thus, it may be that (clinically relevant) depressive and somatization signs and symptoms are viable psychological endophenotypes that have predictive value for the substance abuse potential of chronic pain patients, particularly if viewed alongside other identified biopsychosocial risk factors.

To be sure, these conclusions are highly speculative, and multiple issues may be raised regarding methodology and the relevance and relativity of definitions of opioid abuse, illicit drug use, doctor shopping, and drug trafficking. We posit that the sampling methodology we used was appropriate for the type of evaluation, and that the methods of psychological evaluation were also appropriate to context, setting, and applicability to intervention/pain management. In this latter regard, it has been shown that the psychological diagnostic impressions achieved by utilizing DSM-IV-TR criteria were superior to self-report questionnaires or loosely structured interviews. In the present study, we have included patients who have been characterized with depressive features by evaluation of past psychological history, DSM-based questionnaire, and use of the MCMI; thus, the number of patients presenting with such operationally defined depression may be higher than in our previous work. However, we believe that this multifocal assessment approach has higher sensitivity and therefore more reliably captured depression within this patient population.

The major purpose of this study was to evaluate and address the predictive value of multiple risk factors for drug abuse and illicit drug use in chronic pain patients. Therefore, the present study is an extension of our previous work, which identified physical factors predisposing subjects to substance abuse. By now evaluating and
identifying psychological factors, we move toward a biopsychosocial approach to assessment, upon which a more comprehensive scope and trajectory of care might be conceived and implemented.

Clearly, our knowledge of pain, psychological conditions, and substance abuse influence the epistemic basis of both medical practice and the ethics that guide such care.\(^{57,58}\) An understanding of the neurobiology of these disorders allows us to view them as pathological processes ascribed to a disease model. But this remains a double-edged sword, for while we adopt an integrative-approach disease model of assessment, we often continue to adhere to an older, more Cartesian, dualistic (body versus mind) approach to care, which can foster clinical disregard of psychological disorders—including substance abuse—as being “only in the mind.” However, nesting neurobiology within a biopsychosocial framework allows for insight into the mechanisms and effects of genetic, phenotypic, and environmental interactions in the expression of disease and manifestation of illness, and it equally compels the use of a biopsychosocial approach to treatment of these disorders.\(^{89,91}\) In sum, the better we understand how genetics and neurobiology affect individual patients, the better we will be able to adapt clinical practice to meet the complex individual medical needs of each person in pain.

CONCLUSION

This study demonstrated that 1) the presence of psychological features of depression and somatization may be endophenotypes of substance abuse diathesis in chronic pain patients, and 2) these psychological features are reasonable predictors of substance abuse in chronic pain patients. These conclusions are based upon both the quantitative analyses of specific data and reflection upon the most contemporary understanding of the neurogenetics of these pathologies, hypothesized herein to be components of a neuropathological spectrum disorder. This provides a basis for both theoretical and predictive contextual knowledge, and we advocate that such knowledge should inform and sustain the ethical practice of pain medicine.\(^ {92,93}\) A deepened understanding of pain, psychopathology, and addiction allows for an enhanced ability to treat, heal, and care as necessary. Ongoing work by our group is dedicated to continued research to advance this approach.

ACKNOWLEDGMENTS

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REFERENCES


LEGAL PERSPECTIVE

Medicolegal rounds: Medicolegal issues and alleged breaches of standards of medical care in a patient motor vehicle accident allegedly related to chronic opioid analgesic therapy

David A. Fishbain, MD, FAPA
John E. Lewis, PhD
Brandly Cole, PsyD
Renné Steele Rosomoff, BSN, MBA
Hubert L. Rosomoff, MD, DMedSc, FAAPM

ABSTRACT

The objective of this medicolegal case report is to present the details of the case of a chronic pain patient (CPP) who was placed on chronic opioid analgesic therapy (COAT) and was involved in a motor vehicle accident, alleged in litigation to be related to COAT. COAT standards are in a process of evolution, and this process is influenced by recent literature developments. We aim to present both the defendant’s and plaintiff’s expert witnesses’ opinions on whether the defendant’s physician fell below the “standard” in allowing the CPP to drive. Both the methadone and the driving literature are utilized to explain the defendant’s and plaintiff’s experts’ opinions and the differences between them. Based on these opinions, we have attempted to develop some recommendations on how pain physicians should approach the problem of deciding whether patients should be allowed to drive when on COAT.

Key words: chronic pain, intractable pain, opioids, chronic opioid analgesic therapy, driving, motor vehicle accidents, standards of medical care, informed consent, breaches of standards, methadone

INTRODUCTION

Chronic opioid analgesic therapy (COAT) for chronic, benign, nonmalignant pain, although still controversial, has become part of the pain physician’s armamentarium and has recently been adopted as a treatment by other specialties, such as family medicine. The acceptance of COAT as a potential treatment option for chronic, benign, nonmalignant pain is the result of a number of pain medicine developments that began to surface in the early 1980s. The first and most important of these was the appearance of published studies claiming success in treating intractable chronic pain patients (CPPs) with COAT without the development of significant addiction. Second, COAT treatment for pain was demonstrated to be efficacious. Recently, this literature has been compiled and analyzed in two meta-analyses and in one evidence-based, structured review. Both meta-analyses (of over 40 double-blind, placebo-controlled studies) showed opioids to be more effective than placebo, and one demonstrated improvement in functional outcomes. A significant body of literature developed which spoke to the chronic undertreatment of pain by healthcare professionals, and research studies reported that some physicians were prejudiced against the use of opioids (“opiophobia”) because of fears of iatrogenic addiction. In the late 1990s, the chronic undertreatment of pain led state licensing boards to begin to develop policies that supported appropriate opioid prescribing, rather than policies that hindered opioid prescribing. Early in this century, the Joint Commission on Accreditation of Healthcare Organizations incorporated the adequate treatment of pain as a patient right. Finally, in the 1980s drug technology developed a number of controlled-release opioids, which were believed to control pain in a more effective manner than the immediate-acting opioids.

In response to the widening use of COAT and publicity over the abuse of medically prescribed opioids, state medical boards developed state-specific physician practice guidelines for the appropriate utilization of COAT; these plans were based on some of the model guidelines developed by the American Academy of Pain Medicine and the American Pain Society. The widening literature on how to “do COAT” and the development of the aforementioned guidelines then led to their application as “standards” in malpractice cases related to COAT. Some
of these cases have been reported and explored in reference to pseudoaddiction, suicide related to unmanaged chronic pain, and methadone use.\textsuperscript{10,11} An issue that has not yet been explored in the COAT/medicolegal/opioid-prescribing literature is that of the medicolegal standard for COAT in relation to driving rights. The medicolegal case discussed in this article addresses this issue.

CASE REPORT

Mr. X was a 45-year-old white male who presented to a pain physician's office with a chief complaint of chronic low back pain. His pain had started after a lifting injury at work when he was 40 years old. Subsequent surgery for an L5-S1 disc rupture had not relieved his pain. As a result, he was not working, had settled his workers' compensation case, and was on Social Security. Since the surgery, Mr. X's pain had worsened. He was prescribed hydrocodone (four 5 mg tablets per day), but the medication was yielding unsatisfactory pain control (pain levels over a 24-hour period ranged from 7 to 9 out of 10). No further surgery was indicated, and the current working diagnosis was degenerative disc disease and myofascial pain syndrome. Mr. X had also failed physical therapy but had not undergone any interventional procedures. He was referred by his family doctor for evaluation for the possibility of an epidural.

Mr. X denied any previous psychiatric treatment or any current psychiatric symptoms such as depression or anxiety. In addition, Mr. X denied ever having been a smoker, having a previous history of alcohol abuse/addiction, and any illicit drug use or treatment. There were no other medical problems, and he was not taking any medications other than the hydrocodone. Mr. X had a standard physical examination, and his recent imaging studies were reviewed. It was concluded that Mr. X was unlikely to benefit from epidurals and was offered COAT as an alternative. Mr. X consented and signed the standard COAT agreement. He was then placed on methadone 2.5 mg BID and was advised to discontinue hydrocodone use. In addition, he was started on tizanidine 4 mg HS for spasms. A follow-up appointment was scheduled for two weeks in the future, and Mr. X was provided with a call number. On the second day after the initiation of methadone treatment, Mr. X advised the prescribing office that he had been involved in a motor vehicle accident (MVA) (he had hit a tree) and that he thought this had happened because of the medication. He claimed that his low back pain was now worse. Two years later, the office received a letter from Mr. X's lawyers initiating a malpractice suit.

In the litigation discovery process for medical malpractice cases, the plaintiff's lawyer is allowed to name an expert who can determine whether the defendant (in this case the pain physician) fell below the standard of care in the plaintiff's treatment (that which a reasonably prudent and competent physician with the same or similar training would do in the same or similar circumstances).\textsuperscript{10} If that expert finds that the plaintiff's care was below the standard, then in all likelihood the malpractice case will proceed. Similarly, upon receipt of the complaint the defendant's lawyer is able to name an expert who will then respond to all the allegations of falling below the standard as opined by the plaintiff's expert. Table 1 presents the opinions of the plaintiff's and the defendant's medical experts on the alleged breaches of the standard of medical care in Mr. X's case. As can be seen, the plaintiff's expert found eight alleged breaches of standards. The defendant's medical expert disagreed and absolutely refuted allegations 1, 3, 4, 7, and 8. He also partially refuted allegation 2. According to the record provided, he could not refute allegations 5 and 6. The eventual legal outcome of this case was that it was settled for much less than the requested amount.

DISCUSSION

The defendant's expert's responses to the allegations of the plaintiff's expert (Table 1) will be discussed below.

Allegation 1

In administering COAT and selecting CPPs for COAT, it is important to remember that most state practice guidelines indicate that CPPs selected for COAT should have intractable chronic pain and should have failed to find relief through other methods of pain treatment. This information should be documented to allow prescribers to avoid or refute this allegation.

Allegation 2

In a recent evidence-based, structured review, Fishbain et al.\textsuperscript{12} examined the epidemiological evidence regarding whether opioids are associated with intoxicated driving, MVAs, or MVA fatalities. The evidence they found indicates that opioids are probably not associated with intoxicated driving, are not associated with MVAs, and are probably not associated with MVA fatalities. In another evidence-based review, Fishbain et al.\textsuperscript{13} examined the evidence for opioid-related driving-skill impairment in opioid-dependent/tolerant patients. They found moderate, generally consistent evidence that there is no impairment of psychomotor abilities in patients on chronic opioid therapy. Their study reports strong, consistent evidence that there is no greater incidence in motor vehicle violations/ MVAs in such patients versus comparable controls, and they present consistent evidence that no impairment has been measured in driving simulators for off- or on-road driving. It is to be noted that Mr. X had
<table>
<thead>
<tr>
<th>Allegation</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. There was no indication or reason to place Mr. X on COAT. Thus, this action is below the standard.</td>
<td>1. Mr. X’s history indicated that he suffered from chronic pain that was not responsive to other forms of treatment, making him an “intractable” CPP. According to the state practice guidelines for COAT, this made Mr. X a candidate for COAT. Thus, no standard was breached here.</td>
</tr>
<tr>
<td>2. Mr. X’s accident was related to his taking methadone.</td>
<td>2. Based on the literature, there is a reasonable degree of medical certainty that Mr. X’s accident may not have been related to the opioid (methadone). In contrast, the accident could have been related to other issues, e.g., patient characteristics, inattention, etc.</td>
</tr>
<tr>
<td>3. The defendant negligently prescribed methadone.</td>
<td>3. The defendant prescribed a very low starting dose of methadone that, according to equivalency tables, was approximately equivalent to or less than the dose of hydrocodone that the patient had been taking. Thus, no standard was breached here.</td>
</tr>
<tr>
<td>4. The defendant was negligent in that he failed to advise the plaintiff not to drive while on opioids.</td>
<td>4. There is a reasonable degree of medical certainty, as demonstrated in the literature, that patients taking opioids on a routine basis can drive safely.</td>
</tr>
<tr>
<td>5. The defendant was negligent in that he failed to obtain informed consent from the plaintiff regarding the possibility that methadone could, under certain circumstances, be sedating, and could thus interfere with the plaintiff’s ability to drive.</td>
<td>5. There is no evidence of this type of informed consent being obtained or requested in the defendant’s notes or in the COAT agreement.</td>
</tr>
<tr>
<td>6. The defendant was negligent in that he failed to advise the plaintiff or seek informed consent regarding the possibility that methadone could, under certain circumstances, interact with other drugs (such as tizanidine) and thereby cause increased sedation.</td>
<td>6. There is no evidence of this type of informed consent being obtained or requested in the defendant’s notes or in the COAT agreement.</td>
</tr>
<tr>
<td>7. The defendant was negligent in that he did not monitor the plaintiff closely enough after methadone treatment was initiated.</td>
<td>7. The defendant placed the plaintiff on methadone and tizanidine and scheduled a two-week follow-up appointment. The defendant was also available to the plaintiff by phone for advice regarding changes in medication dosages. If the plaintiff was feeling sedated on the new medication, a call should have been placed to the defendant.</td>
</tr>
<tr>
<td>8. The defendant was negligent in that he chose to place the plaintiff on methadone rather than another long-acting opioid with fewer side effects.</td>
<td>8. There is currently no absolute contraindication noted in the literature to utilizing methadone in COAT as a first-line drug. Although this literature may be developing, the defendant did not fall below the standard here.</td>
</tr>
</tbody>
</table>

Previously been exposed to hydrocodone and was presumably tolerant to that opioid. Thus, he should have been partially tolerant to the effects of methadone. Based on the information in the two above-mentioned reviews, the defendant’s expert concluded that Mr. X’s accident may not have been related to methadone.

**Allegation 3**

When changing from one opioid to another, equivalency tables should be utilized, and the calculated dose of the new opioid should be documented in the patient’s chart. This was done by the defendant, and the very low dose of methadone utilized in a non-opioid-naïve subject essentially negates the possibility that this standard was breached in this case.

**Allegation 4**

It is clinical lore that patients on psychotropic medications should be advised not to drive or should be warned about driving. However, according to the studies described above regarding allegation 2, this clinical lore may be incorrect in reference to opioids.12,13 The
reviewed literature indicates that patients on opioids can drive safely, especially when they have developed a tolerance to the sedating effects of the medication.\textsuperscript{12,13} Thus, the defendant’s expert concluded that there was no breach here.

**Allegation 5**

Although the evidence in the two cited evidence-based reviews indicates that patients stabilized on COAT and tolerant to opioids can be advised that they can drive,\textsuperscript{12,13} Fishbain et al.\textsuperscript{13} present some caveats to this possibility.

First, patients placed on long-term opioid treatment should be advised of the current status of this driving research. They should then be advised that whether they do or do not drive should be based on this information, but that it is their own personal decision. Third, they should be advised that if they choose to drive, they should obey the following rules:

- After beginning opioid treatment or after a dose increase, the patient should not drive for four to five days.
- Patients should not drive if they feel sedated.
- Patients should report sedation/unsteadiness/ cognitive decline immediately to their physicians so that a reduction in dosage can be initiated.
- Under no circumstances should patients use alcohol or other illicit drugs such as cannabinoids and then drive.
- Patients on opioids should avoid taking any over-the-counter antihistamines.
- Patients should not make any changes in their medication regimens without consulting with their physician.

A final issue pointed out by Fishbain et al.\textsuperscript{13} relates to what the physician should do if he or she is requested to complete paperwork where questions are asked about a patient’s driving ability. For this problem, the same type of approach was recommended. The physician should explain the current status of the relevant research in the paperwork. In addition, the physician should also report whether he or she has noted any opioid side effects that might interfere with driving (or the absence of such effects). However, if a specific question relating to whether the patient can or can not drive is encountered, that status should be marked as unknown. More specifically, the physician should state that he or she does not have knowledge of the patient’s ability to drive, as that can only be determined via a driving simulator and/or on-road/off-road driving tests.

According to the above recommendation, some form of informed consent in reference to the risks of driving concurrent with opioid use should have been obtained from Mr. X. Ideally, COAT agreements could be utilized for this issue.

**Allegation 6**

Unfortunately, there are large variations in the pharmacokinetics of methadone from one individual patient to the next, and this makes it a difficult drug to use.\textsuperscript{11} Methadone is characterized by a slow elimination phase, which can vary from 4.2 to 130 hours.\textsuperscript{11} Thus, variations in the elimination phase could lead to accumulation toxicity in some patients. In addition, methadone may interact with other drugs, as it particularly inhibits the CYP2D6 isoenzyme systems. This inhibition can affect the levels of drugs metabolized by CYP2D6.\textsuperscript{14} Tizanidine is 95 percent metabolized in the liver, and therefore any inhibition of liver metabolism could cause decreased tizanidine metabolism, resulting in increased sedation. Thus, there is a possibility that methadone, in spite of the low dose used, accumulated in the plaintiff and/or interacted with tizanidine, causing sedation. As noted in the allegations, no informed consent for these possibilities was furnished. It has been recommended that when mixing drugs, the patient should be educated about all potential problems.\textsuperscript{15}

**Allegations 7 and 8**

It is recommended that the physician remain available for patient monitoring when a patient is placed on a new medication.\textsuperscript{15} The defendant, by the nature of his situation, did not fall below the standard here. In reference to allegation 8, physicians can utilize whichever drug they wish over any other drug. This applies as long as the side-effect profile of the chosen drug is not so burdensome that there is a specific contraindication for use in the patient in question.

**CONCLUSIONS**

This case is interesting and instructive for a number of reasons. First, it outlines the process by which allegations are generated by the “experts.” Second, it outlines how experts utilize the current literature in arriving at their opinions. Third, this presentation outlines the importance of the agreed-upon standards of care and how they are applied utilizing current literature. It is to be noted that there is an intimate relationship between the current literature and the development of the standards.
However, when a standard of care is in the process of being developed, such as with recent research reports, most jurisdictions recognize the “respectable minority” defense. This defense applies when a standard of care is in a transitional phase, as are those being developed for COAT, and it may apply here to allegations 5 and 6. A “respectable minority” of physicians may not have provided informed consent for methadone in circumstances such as Mr. X’s because this information was not widely disseminated. In that case, this alleged breach would not necessarily be deemed negligence by the courts. Finally, this case brings to light a potential area of malpractice liability for physicians administering COAT: patient driving risk.

Physicians utilizing COAT should remain abreast of the developing COAT literature. This can be an effective method for improving COAT patient care and decreasing liability risk.

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Science at the mercy of the mob:  
Dr. Hurwitz’s legal problems in perspective

Siobhan Reynolds, MA, MFA

Socrates is an evil-doer, and a curious person, who searches into things under the earth and in heaven, and he makes the worse appear the better cause; and he teaches the aforesaid doctrines to others.

—Socrates in Plato’s Apology

As most members of the pain management community are aware, Dr. William Hurwitz’s drug-trafficking conviction was recently overturned in the Fourth Circuit, after it was proven that the jury had not been correctly instructed on the issue of “good faith” related to the prescription of controlled substances. This was hailed at the time as a victory for all of us. When the legal implications are examined, however, one can see the victory unearths more problems than it solves.

Mainstream legal thinkers laud the Fourth Circuit’s ruling because they expect Dr. Hurwitz’s retrial to provide the pain management community with the opportunity to overcome future government accusations by successfully asserting its own medical standards. This didn’t occur in the first trial, and those following the case are mistaken if they think the inclusion of a good faith jury instruction will make the difference this time around.

In Dr. Hurwitz’s case, as well as in each of the other cases that my organization, Pain Relief Network, has assisted on, the defense teams have presented overwhelming evidence that the accused physician’s conduct fell well within the medical standard of care. Regardless of the issuance of a good faith jury instruction, such testimony has had no positive effect on the outcome in any of our other cases. Jurors are routinely convinced by the government’s accusation—despite what defense experts say to the contrary—that what the doctor did was criminal in nature. This is because the government’s characterization is consistent with the layman’s view of how opioids ought to be prescribed, i.e., rarely or never.

The average American doesn’t view opioids as “real” medicines like antidepressants or insulin. Rather, he or she imagines them to be substances imbued with evil powers that enslave their victims, transforming them into drug-addicted, crime-committing zombies. Such a powerful and irrational image can not be entirely defeated by reason or science. To believe that Dr. Hurwitz’s retrial will be fair is to utterly fail to grasp the profound disadvantage that medical science suffers in federal criminal courts under the existing statutory scheme.

The Controlled Substances Act (CSA) was never intended to create a “battle between experts” such as we saw in Dr. Hurwitz’s first trial, as well as in all the other cases currently making their way up through the appellate process. Justice Kennedy addressed this issue when he wrote for the majority in Gonzales v. Oregon. While this case was ostensibly about physician-assisted suicide, it more importantly defined the limits of the attorney general’s authority over medical practice: “The statutory references to ‘control’ . . . [make] clear that the Attorney General can establish controls against diversion . . . but do not give him authority to define diversion based on his view of legitimate medical practice.”

So the arguments currently being had in Federal courts all over the country as to whether or not the medicine practiced by the defendant doctor was “legitimate” or not are, quite simply, badly off point. Kennedy adds further, “Congress regulates medical practice in so far as it bars doctors from using their prescription-writing powers as a means to engage in illicit drug dealing and trafficking as conventionally understood . . . [The Act] manifests no intent to regulate the practice of medicine generally, which is understandable given federalism’s structure and limitations.

One might ask how, given these limitations, we arrived at a point so profoundly disadvantageous to the autonomy of medical practitioners, as this was clearly not the intent of the authors of the CSA. As it turns out, the Department of Justice itself added the phrase “legitimate medical purpose” to the federal rule giving force to the CSA, thereby accomplishing an end run around the restrictiveness of the statute they were purporting to merely interpret.
Effectively, government lawyers during the Nixon administration wrote themselves a new power—namely, to criminally prosecute physicians whose practices they believed were inconsistent with how they thought pain management ought to be practiced. In other words, they empowered themselves to establish standards for the practice of medicine based on their own preferences, rather than on medical science or compassion. Blessedly, the Supreme Court in Gonzales v. Oregon disallowed the Justice Department’s attempt to outlaw physician-assisted suicide, which was premised on the same expansive legal theory. Justice Kennedy devoted quite a bit of his argument to this problem, using extremely strong and precise language in denouncing the government’s exercise of its power under these terms:

By this logic, however, the Attorney General claims extraordinary authority. If the Attorney General’s argument were correct, his power to deregister necessarily would include the greater power to criminalize even the actions of registered physicians, whenever they engage in conduct he deems illegitimate. This power to criminalize—unlike his power over registration, which must be exercised only after considering five express statutory factors—would be unrestrained. [Italics added for emphasis.] It would be anomalous for Congress to have so painstakingly described the Attorney General’s limited authority to deregister a single physician or schedule a single drug, but to have given him, just by implication, authority to declare an entire class of activity outside “the course of professional practice” and therefore a criminal violation of the CSA.

Unfortunately, the court has yet to apply this analysis to delimit the power of federal prosecutors in the cases of pain-treating physicians, and, oddly, mainstream legal thinkers do not seem to perceive the legal connection between the Gonzales case and the government’s misconduct in its pursuit of pain-treating physicians.

The Fourth’s concession that Dr. Hurwitz’s good faith was indeed relevant to whether or not he had committed a crime demonstrates just how far down the rabbit hole pain doctors and their patients really are after nearly four decades of case law developed on what amounts to no more than a rhetorical sleight of hand. When we are dependent upon courts to rule that actual innocence might reasonably figure into a jury’s deliberations in deciding the fate of a man who no one disputes was practicing medicine in good faith, we have no reason for celebration.

Mainstream legal thinkers in this area need to take off their rose-colored glasses and take a hard look at the CSA and how it actually functions. Because if, as Justice Kennedy noted in the Gonzales opinion, “[t]he CSA’s structure and operation presume and rely upon a functioning medical profession regulated under the state’s police powers,” then it is incumbent upon the pain-treating community to ask itself whether working in terror, prescribing “anything but opioids,” and allowing patients to deteriorate in order to “stay under the radar” really constitutes a functioning medical profession. Dr. Hurwitz was applying the current science in his ethical practice of clinical medicine to patients in chronic pain, and it was this behavior which provoked the wrath of the mob. That he did so in good faith is not likely to protect him from further punishment.

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REFERENCES
ABSTRACT

Background: The intraoperative combination of volatile anesthetics with opioids is a well-accepted technique because of its hemodynamic stability and side effects. This study in adults was designed to determine the pharmacodynamic interactions between different dosages of remifentanil and desflurane in response to skin incision.

Methods: A total of 60 patients were enrolled in this study. Patients were prospectively randomized to receive 0, 0.1, 0.15, or 0.25 μg/kg/min remifentanil. Anesthesia was induced with remifentanil, propofol, and succinylcholine. Thereafter, a group-specific desflurane concentration was administered using Dixon’s up-and-down technique. After a “wash out” and equilibration period, patients were observed for defense movements up to 1 minute after skin incision. Mean arterial pressure and heart rate were recorded before induction of anesthesia (baseline), at surgical incision, as well as 2 and 4 minutes thereafter. Time until extubation was assessed after stopping desflurane and remifentanil at the end of the surgery.

Results: Remifentanil at 0.1, 0.15, or 0.25 μg/kg/min reduced desflurane requirements by 74, 83, and 90 percent, respectively. The time course of mean arterial pressure did not differ between the study groups. However, compared with the group without remifentanil, heart rate was significantly lower in patients receiving 0.15 or 0.25 μg/kg/min remifentanil. No difference between the groups was observed with regard to extubation time.

Conclusion: Remifentanil reduces in a dose-dependent manner the desflurane requirements for skin incision without increasing recovery time. An infusion rate higher than 0.1 μg/kg/min results in a significantly decreased heart rate.

Key words: remifentanil, desflurane, pharmacology, drug interaction, surgery

INTRODUCTION

Desflurane, a methyl-ethyl ether halogenated exclusively with fluorine, has some advantageous characteristics including little or no metabolic breakdown. Blood solubility far lower than those of other potent volatile anesthetics1 allows rapid adjustments in the depth of anesthesia and a quicker time to awakening.2 The minimum alveolar concentration (MAC) of desflurane has been shown to decrease with anesthetic adjuvants such as nitrous oxide, midazolam, and fentanyl.3–5

However, limited clinical data are available about dose adjustments for desflurane, in combination with the ultra-short acting opioid remifentanil.6 Because a combination of two short acting agents such as desflurane and remifentanil seems to be advantageous with regard to cardiovascular stability and rapid recovery, ie, in day-case surgery, we designed this study to generate clinical data for a more rational combination of remifentanil and desflurane.

MATERIALS AND METHODS

After approval of the institutional review board, informed written consent was obtained from 60 outpatients with an age ranging from 32 to 66 years. All patients were classified as American Society of Anesthesiologists (ASA) physical status 1 or 2. They were scheduled for elective abdominal day-case surgery under general anesthesia requiring at least 5-cm skin incision. Patients scheduled for endoscopic surgery were not included in the study.

Patients were randomly assigned to four treatment groups receiving no remifentanil (group A) or remifentanil as continuous infusion at 0.1 μg/kg/min (group B), 0.15 μg/kg/min (group C), and 0.25 μg/kg/min (group D).

On the morning of surgery, the patients were premedicated with oral midazolam 0.1 mg/kg. Anesthesia was
induced with iv bolus of propofol (2 mg/kg) and the group-dependent dosage of continuous remifentanil infusion. No additional remifentanil bolus was given for induction. Tracheal intubation was facilitated by succinylcholine (1.5 mg/kg). The patients lungs were ventilated (FeCO₂: 30-35 mmHg) using a volume-controlled mode (Julian anesthesia ventilator, Drägerwerk, Lübeck, Germany) with 35 percent oxygen in air. Desflurane was added by a Devapor vaporizer (Drägerwerk, Lübeck, Germany) immediately after tracheal intubation, and patients received the predetermined end-tidal anesthetic concentration up to the time of surgical incision. A minimum time interval of 15 minutes was given to allow wash-out for propofol and succinylcholine and an adequate equilibration time for desflurane. 

Dixon’s up-and-down method was used to reduce the number of individuals included in the study. This Staircase bioassay has been described in detail elsewhere. The first patient randomized to one of the treatment groups received a predefined target end-tidal concentration of 6.0, 5.0, 3.0, and 2.0 percent desflurane, respectively. If the first patient did not move at skin incision, the next patient in this group received a 0.5 percent decreased end-tidal concentration of desflurane. The desflurane concentration was increased by 0.5 percent in the subsequent patient if skin incision provoked movements. Patients were allocated until each group had five to six independent pairs with one patient moved and the next not (crossover). The average crossover midpoints were calculated for each group.

Patients were observed up to 1 minute after skin incision by a blinded observer (RN). Any purposeful defense movement of an extremity or the head in response to surgical incision was considered as a movement. Coughing, chewing, or swallowing were not considered being movements. If the patient was moving, intravenous midazolam (2.5-5 mg) was administered as rescue medication. Group-dependent anesthesia was continued until skin closure. Thereafter, the anesthetic circuit was flushed with oxygen and the time until extubation was determined.

Patient monitoring consisted of a lead II and V electrocardiogram, noninvasive blood pressure measurement, pulse oximetry, and temperature measurement. Throughout the study, the inspiratory and expiratory concentrations of carbon dioxide and desflurane were measured continuously using infrared spectrometry (PM 8050, Drägerwerke, Lübeck, Germany) calibrated to desflurane. The sampling line of the airway gas analyzer was connected to the proximal end of the endotracheal tube. The sampling flow was set at 60 mL/min.

**Statistical analysis**

Dixon’s up-and-down method was used to determine desflurane concentration to avoid movements in response to surgical incision. Results between groups were compared by ANOVA. A logistical regression analysis was performed because Dixon’s up-and-down method uses not the full data set. Based on these results, the probability of the movement can be estimated. The demographic data were compared using Kruskal-Wallis tests or χ-square tests as appropriate. Time intervals and hemodynamic variables were analyzed using ANOVA and repeated measures ANOVA. Results are reported as mean and range unless otherwise noted. A p value < 0.05 was considered significant. It has been reported that, with a sample size of 20 subjects, the standard deviation of the MAC for desflurane is 0.5 Vol %. We therefore estimated that a total of 60 patients would provide a 90 percent power for detecting a difference in the desflurane MAC of 1 Vol %.

**RESULTS**

A total of 60 patients of both genders were enrolled in the study. There was no difference among the four study groups with respect to demographic data and ASA status, “wash out” interval, and extubation interval (Table 1).

Dixon’s up-and-down method was applied in five to six pairs of data sets. The average desflurane concentration (mean ± SD) to prevent movements in 50 percent of patients was 7.2 ± 0.5 Vol % in group A. Remifentanil at 0.1 µg/kg/min (group B), 0.15 µg/kg/min (group C), and 0.25 µg/kg/min (group D) reduced the required desflurane concentration to 3.5 ± 0.8 Vol % (p < 0.001), 1.1 ± 0.5 Vol % (p < 0.001), and 1.2 ± 0.5 Vol % (p < 0.001), respectively. The individual end-tidal concentrations in the different groups are presented in Figure 1. Using logistic regression analysis without the independent variable remifentanil, we observed a reduction in desflurane requirements to 1.91 Vol %, 1.24 Vol %, and 0.72 Vol % with remifentanil at 0.1, 0.15, and 0.25 µg/kg/min, respectively (Table 2). Hemodynamic variables are presented in Figure 2. Mean arterial pressure decreased after induction of anesthesia, but no difference between the study groups could be observed. In contrast, heart rate was significantly lower in patients receiving remifentanil at 0.15 and 0.25 µg/kg/min compared with the group receiving desflurane alone.

**DISCUSSION**

In this study, we determined the desflurane requirements for skin incision in adults when remifentanil was administered at various doses. Remifentanil at a dosage of 0.1 µg/kg/min decreased desflurane requirements by 74 percent. At a dosage of 0.25 µg/kg/min, only a slight reduction in desflurane requirements to 90 percent was observed. Several variables affect MAC in humans: aging decreases MAC of desflurane as well as the concomitant use of nitrous oxide or intravenous fentanyl. As
Table 1. Biometric data, ASA classification, and time intervals for propofol and succinylcholine “wash out” and from discontinuing desflurane and remifentanil until extubation

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Group 3</th>
<th>Group 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(no remifentanil)</td>
<td>(0.1 µg/(kg min) remifentanil)</td>
<td>(0.15 µg/(kg min) remifentanil)</td>
<td>(0.25 µg/(kg min) remifentanil)</td>
<td></td>
</tr>
<tr>
<td>Age, years*</td>
<td>54(38-63)</td>
<td>49(33-62)</td>
<td>41(32-66)</td>
<td>49(34-64)</td>
<td>46(34-63)</td>
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<tr>
<td>Height, cm*</td>
<td>172(165-178)</td>
<td>1,729(164-178)</td>
<td>174(164-183)</td>
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<td>Weight, kg*</td>
<td>84(72-90)</td>
<td>80(65-88)</td>
<td>82(64-89)</td>
<td>73(69-88)</td>
<td>78(69-89)</td>
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<tr>
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<td>5</td>
<td>7</td>
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<td>10</td>
<td>8</td>
<td>36</td>
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<td>ASA I, n</td>
<td>8</td>
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<td>5</td>
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<tr>
<td>ASA II, n</td>
<td>7</td>
<td>13</td>
<td>10</td>
<td>11</td>
<td>41</td>
</tr>
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</table>

Time interval, min (mean ± SD)

| “Wash out” time  | 20.5 ± 6.3                     | 21.6 ± 6.0                    | 24.2 ± 8.4                    | 23.7 ± 9.9                    | not applied |
| Extubation time  | 8.8 ± 4.2                      | 7.9 ± 3.4                    | 8.7 ± 4.2                     | 8.9 ± 5.5                     | not applied |

*Mean (range).

Figure 1. The individual end-tidal concentrations of desflurane tested in the four study groups, receiving no remifentanil (group A) or remifentanil as continuous infusion at 0.1 µg/kg/min (group B), 0.15 µg/kg/min (group C), and 0.25 µg/kg/min (group D), respectively. Points above the horizontal lines indicate movement in response to skin incision, whereas points below this lines indicate no movement. The triangles indicate the mean analyzed by Dixon’s method.
previously shown with fentanyl, small doses of remifentanil appear to have large effects on desflurane’s MAC. We found that recovery from anesthesia was not extended by remifentanil. This is consistent with the results of a recent study by Billard et al. who analyzed the effects of various remifentanil dosages in combination with desflurane and N₂O. In patients receiving low-dose remifentanil infusion (0.07 µg/kg/min) to supplement desflurane-N₂O anesthesia for laparoscopic surgery, recovery was even facilitated compared to desflurane-N₂O anesthesia. Sebel et al. investigated the effects of a single bolus of fentanyl on recovery in patients receiving desflurane or isoflurane. They found that in patients with similar fentanyl concentrations at the end of surgery, recovery was always faster in patients who received desflurane than in those who receiving isoflurane.

From the data of those patients who did not receive remifentanil, we determined a median desflurane concentration of 7.2 Vol % to avoid movements in response to surgical incision. Using a comparable study design, Rampil et al. reported a MAC for desflurane in oxygen of 7.2 Vol % in 18- to 30-year-old patients compared with 6.0 Vol % in 30- to 65-year-old patients. In this study, our patients’ age ranged from 32 to 66 years. Although we started with an end-tidal concentration of 6.0 Vol %, the dosage for subsequent patients in the subgroup without remifentanil had to be adjusted to 7.2 Vol %. It remains unclear why our results differ from those reported by Rampil et al. Differences in pain sensitivity (ie, gender, age, and ethnic groups) may account for these findings.

No adverse effect on mean arterial pressure and heart rate were observed in this study. However, heart rate was reduced by remifentanil in a dose-dependent manner. This reduction in heart rate may be advantageous because increasing desflurane concentrations results in greater sympathetic nervous system activation compared with other inhaled anesthetics.

Attention should be paid to some limitations of the study. MAC determinations are usually performed after inhalational induction. However, intravenous induction has been used previously as well, because in current clinical practice this is the preferred induction technique. We believe that the effects of propofol and succinylcholin were minimal because MAC determinations were performed after a mean “wash out” period of more than 20 minutes. Furthermore, the high desflurane MAC of 7.2 Vol % without remifentanil (group A) makes major effects of the intravenous induction technique unlikely. All patients were premedicated with oral midazolam and this may theoretically interfere with the results of this study. However, it was the intention of our study to analyze the effects of the combination of desflurane and remifentanil in a real-world setting. Furthermore, Brosius et al. reported no difference in intraoperative BIS values and recovery parameters between premedicated (oral midazolam) and unpremedicated patients after sevoflurane-nitrous oxide anesthesia.

MAC reduction findings are important for two reasons. First, it gives an example how initial target concentrations should be set. This helps to reduce side effects or adverse effects. It also gives the opportunity to use minimal flow systems to reach target end tidal concentrations. The favorable pharmacokinetic of desflurane and remifentanil, which result in short recovery times, enables a

<table>
<thead>
<tr>
<th>Remifentanil dosage, µg/((\text{kg min}))</th>
<th>Estimated MAC-value desflurane, percent</th>
<th>MAC-reduction for desflurane, percent</th>
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</thead>
<tbody>
<tr>
<td>0.0</td>
<td>7.30</td>
<td>Not applied</td>
</tr>
<tr>
<td>0.1</td>
<td>1.91</td>
<td>74</td>
</tr>
<tr>
<td>0.15</td>
<td>1.24</td>
<td>83</td>
</tr>
<tr>
<td>0.25</td>
<td>0.72</td>
<td>90</td>
</tr>
</tbody>
</table>

Figure 2. Course of mean arterial pressure (upper curve) and heart rate (lower curve).

Table 2. Estimated MAC value and reduction of MAC desflurane with increasing dosages of remifentanil by logistic regression

Figure 2. Course of mean arterial pressure (upper curve) and heart rate (lower curve).
potential economic benefit by the rationale use of a combination of these anesthetics.

In summary, we have shown that the combination of desflurane with remifentanil results in a dose-dependent reduction of desflurane requirements with stable hemodynamics and without a prolonged recovery from anesthesia in a real-world setting.

ACKNOWLEDGMENTS

Support was provided solely from departmental sources. The work has been presented in parts at the German National Congress of Anesthesiology (DAK) 2001 in Nuernberg, Germany.

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ABSTRACT

Objective: The severity of self-reported withdrawal symptoms varies during detoxification of opioid-dependent patients. The aim of this study is to identify subgroups of withdrawal symptoms within the detoxification trajectory and to predict the severity of withdrawal symptoms on the basis of drug-related and sociodemographic characteristics.

Design and setting: A prospective study carried out in an in-patient setting in four addiction treatment centres in the Netherlands.

Participants: Two hundred opioid-dependent patients who participated in a randomized controlled trial and completed more than 75 percent of the administrations of the subjective opioid withdrawal scales during rapid detoxification.

Intervention and main outcome measure: Main outcome measure was the severity of opioid withdrawal as measured by the subjective opioid withdrawal scale during detoxification (18 measurements). Predictor baseline data were obtained on sociodemographic background, severity of addiction, psychopathology, personality disorder, and craving.

Statistics: Those variables found to be statistically significant in univariate analyses were entered into multivariate regression models to predict the severity of subjective withdrawal.

Results: No distinct subgroups could be identified despite substantial individual variability throughout the detoxification trajectory. The multiple regression results showed only four variables to predict the severity of withdrawal symptoms: baseline withdrawal symptoms, intravenous heroin use in the last 30 days, anxiety, and cluster C personality disorder. The variance explained by these sociodemographic variables was low while the largest amount of variance was explained by baseline withdrawal symptoms (27 percent).

Conclusions: The results of the present study provide evidence that the severity of withdrawal symptoms during detoxification treatment is moderately predicted by the baseline severity of their withdrawal symptoms and not by drug- and patient-related characteristics.

Key words: substance dependence, opioid, detoxification, withdrawal, prediction

INTRODUCTION

Detoxification is the first step in the treatment of opiate dependence and is part of a total treatment program aimed at the maintenance of abstinence. Different kinds of detoxification methods are available for opioid-dependent patients. One of the most widely studied detoxification methods during the last decade is rapid detoxification. The benefit of rapid detoxification is that a higher number of successful detoxifications is attained relative to standard detoxification but without greater intensity of withdrawal symptoms. Substantial individual variability in the intensity of withdrawal symptoms has nevertheless been found.

Rapid detoxification can be undertaken with minimal sedation but also under general anaesthesia. General anaesthesia has been called into question because of the potential of adverse life-threatening events and the expensive cost. In addition, the results of rapid detoxification either with or without anaesthesia have been shown to be comparable in terms of withdrawal severity, abstinence outcome, and rates of naltrexone induction.

In the study of De Jong et al., clinicians observed totally different degrees of severity for the withdrawal symptoms during rapid detoxification. The question arose as to whether different subgroups of withdrawal symptoms can possibly be identified along the detoxification trajectory and whether the severity of withdrawal symptoms can be predicted on the basis of drug-related and sociodemographic characteristics. Should this be possible, then clinicians are placed in a position to improve the individual treatment of withdrawal symptoms and plan treatment better.

Factors influencing the severity of opioid withdrawal symptoms have only been examined in a few studies. Most of the predictors examined in these opioid detoxification
studies can be divided into drug-related or person-related factors. Examples of the first are the type of opioid, \( t^1 \) opioid dose, \( t^1, t^8 \) duration of opioid use, \( t^9, t^{10} \) method of heroin intake (intravenous vs. smoking), \( t^8 \) and acute versus chronic cocaine use. \( t^{11}, t^{12} \) The number of previous detoxifications has only been found to be a significant predictor in alcohol studies. \( t^{13}, t^{14} \) A clear-cut relation between severity of dependence and severity of withdrawal has not been found, \( t^8, t^9 \) and no sociodemographic characteristics of users have been found to relate to withdrawal symptoms. Such person-related factors as anticipation of withdrawal severity and neuroticism have been found to be associated with withdrawal symptoms. \( t^{10} \) Both these factors are anxiety related and may therefore amplify withdrawal symptoms. In subjects with an antisocial personality disorder, withdrawal symptoms have also been found to be significantly higher than in other subjects. \( t^{15} \) Although no studies have examined the associations between opioid withdrawal and craving, it is generally assumed that opioid withdrawal is accompanied by a persistent desire to obtain opioids. \( t^{16}, t^{17} \)

The aim of the present study was twofold: To identify subgroups of withdrawal symptoms within a detoxification trajectory and to predict the severity of withdrawal symptoms on the basis of drug-related and sociodemographic characteristics.

METHODS

Participants

Participants were opioid-dependent inpatients of four addiction treatment centres who participated in a randomized controlled trial in which the add-on effect of general anaesthesia was examined during rapid detoxification induced by naltrexone. \( t^2 \) The study was approved by the Dutch Ethical Assessment Committee for Experimental Investigations on People. The participants met the following criteria: diagnosed as opioid-dependent according to DSM-IV criteria, several previous unsuccessful attempts to become abstinent, clear wish to become abstinent expressed, older than 18 years, familiar with the Dutch language, and at least one nonopioid user in the social network. Exclusion criteria were: severe somatic diseases or psychiatric disorders, pregnancy, AIDS, doubts about the patient’s willingness to cooperate, and contraindications for general anaesthesia. Dependence on other drugs or drug abuse did not constitute exclusion factors, but withdrawal symptoms from other drugs were not expected. Smokers were premedicated with transdermal nicotine for nicotine withdrawal. In cases of benzodiazepine dependence, benzodiazepine use was stabilized before and during opioid detoxification. Alcohol withdrawal symptoms were treated with additional benzodiazepines prior to the start of opioid detoxification. If the patient had used cocaine 48 or fewer hours prior to detoxification, treatment was not initiated because of the unpredictable effects of cocaine on the cardiovascular system during detoxification.

Instruments

13-item subjective opioid withdrawal scale (13-item SOWS). The 13-item SOWS is a shorter version of the SOWS by Handelsman et al. \( t^{18} \) and measures common direct related motoric, autonomic, gastrointestinal, and musculoskeletal symptoms using 13 items divided across four subscales. \( t^{19} \) Participants rate the presence and intensity of opiate withdrawal symptoms at the time of administration across a scale of 0 to 4 \( (0 = \text{not at all}, 1 = \text{a little}, 2 = \text{moderate}, 3 = \text{quite a bit}, 4 = \text{extreme}) \). The sum of the scores for the different items constitutes the total SOWS score with a minimum of 0 and a maximum of 52.

EuropAddiction severity index (EuropASI). The Dutch ASI \( t^{20} \) measures severity of addiction in eight domains (physical health, work/education/income, alcohol, drugs, legal problems, family/social relationships, psychological/emotional complaints, gambling).

Symptom checklist-90 (SCL-90). The Dutch version of the SCL-90 \( t^{21} \) provides an estimate of experienced pathology (ie, mental health state) in terms of eight dimensions: agoraphobia (range 7-35), anxiety (range 10-50), depression (range 15-75), somatization (range 12-60), insufficiency of thinking/acting (range 9-45), interpersonal sensitivity (range 18-90), hostility (range 6-30), and sleeping problems (range 3-15). The total “psychoneuroticism” score can range from 95 to 450.

Structured Interview for DSM-IV personality (SIDP-IV). The SIDP-IV is a semistructured interview that uses nonpejorative questions to assess personality traits and disorders in terms of the DSM-IV. \( t^{22} \) The SIDP-IV has been shown to have good interrater reliability and construct validity for opioid-dependent patients. \( t^{23}, t^{24} \)

Visual analogue scale craving (VAS craving). Using a VAS, participants are asked to rate the extent of craving for drugs along a 100-mm horizontal line with the left pole representing no craving at all and the right pole representing extreme craving. The result is a score along a continuous scale ranging from 0 to 100.

Desires for drug questionnaire (DDQ). The DDQ assesses the degree of desire triggered by both internal and external drug-related cues (ie, instant craving) along a seven-point scale. The total score is the sum of the scores for 14 items and can thus range from 14 to 98. \( t^{25} \)
**Obsessive compulsive drug use scale (OCDUS).**
The OCDUS measures the obsessive-compulsive aspects of drug use and the experienced general desire for use of the drug of choice throughout the previous week (general craving) along a five-point scale. The total score is the sum score for 13 items and can thus range from 13 to 65.25

**Procedure**

Participants were randomly assigned to rapid detoxification either with or without general anaesthesia. With the exception of some differences in the naltrexone schedule and, of course, the general anaesthesia procedure, all of the patients were treated for withdrawal signs and symptoms using the same medication, dosages, and schedule for three detoxification days. Medication was given to sedate; reduce inner restlessness in muscles; alleviate abdominal discomfort, cramps, and spasms; prevent high blood pressure, nausea, vomiting, and diarrhoea; and control anxiety (see Table 1 for medication schedule). During the subsequent three days of recovery, the patients were treated on a symptom-triggered basis.2

Both the 13-item SOWS and the VAS craving were administered twice at baseline (ie, at 12.00 AM and 7.00 PM), three times on each day of detoxification (ie, at 8.00 AM, 10.00 AM and 7.00 PM), twice during each day of recovery (ie, at 8.00 AM and 7.00 PM), and also upon discharge (ie, at 2.00 PM). The EuropASI was administered before admission and the SCL-90, DDQ, and OCDUS were administered upon admission.

**Analysis**

Only those participants who completed the EuropASI and the SOWS on at least 75 percent of the occasions on which it was administered (ie, on at least 14 of 18 occasions) were included in the present study. This meant 200 of the original 272 participants. When more than 75 percent of the SOWS scale was completed on a particular occasion, missing SOWS item scores were imputed using expectation maximization (EM) techniques.26 After that, missing SOWS total scores were imputed using EM because imputation of total scores allows for individual curve. Analyses were only conducted on the data involving a fixed treatment schedule and therefore up to the first day of recovery.

Descriptive statistical analyses were previously undertaken with respect to the sociodemographic characteristics of the patients and their withdrawal symptoms. No statistically significant differences were found between various sociodemographic characteristics and severity of the withdrawal symptoms for those participants who received general anaesthesia versus those who did not.2 This meant that the two groups could be merged for subsequent analysis.

![Table 1. Fixed medication schedule during three detoxification days](image)

<table>
<thead>
<tr>
<th>Time</th>
<th>Medication</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.00 AM</td>
<td>Clonidine 0.3 mg</td>
</tr>
<tr>
<td></td>
<td>Diclofenac 50 mg</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 4 mg</td>
</tr>
<tr>
<td></td>
<td>Diazepam 10 mg</td>
</tr>
<tr>
<td></td>
<td>Transdermal nicotine (30 mg/20 cm²)</td>
</tr>
<tr>
<td>9.00 AM</td>
<td>Naltrexone</td>
</tr>
<tr>
<td>9.15 AM</td>
<td>Octreotide 0.3 subcutaneous</td>
</tr>
<tr>
<td>10.00 AM</td>
<td></td>
</tr>
<tr>
<td>11.00 AM</td>
<td>Clonidine 0.3 mg</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 4 mg</td>
</tr>
<tr>
<td></td>
<td>Butylscopolamine 20 mg</td>
</tr>
<tr>
<td></td>
<td>Diazepam 10 mg</td>
</tr>
<tr>
<td>3.00 PM</td>
<td>Clonidine 0.3 mg</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 4 mg</td>
</tr>
<tr>
<td></td>
<td>Butylscopolamine 20 mg</td>
</tr>
<tr>
<td>7.00 PM</td>
<td>Clonidine 0.3 mg</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 4 mg</td>
</tr>
<tr>
<td></td>
<td>Butylscopolamine 20 mg</td>
</tr>
<tr>
<td>11.00 PM</td>
<td>Clonidine 0.3 mg</td>
</tr>
<tr>
<td></td>
<td>Ondansetron 4 mg</td>
</tr>
<tr>
<td></td>
<td>Butylscopolamine 20 mg</td>
</tr>
<tr>
<td></td>
<td>Diazepam 10 mg</td>
</tr>
<tr>
<td>If necessary</td>
<td>Haloperidol 1-3 mg (against severe anxiety)</td>
</tr>
<tr>
<td>If necessary</td>
<td>Midazolam 5-10 mg (against insomnia)</td>
</tr>
</tbody>
</table>

A basic mathematical routine (ie, singular value decomposition: SVD) was used to identify subgroups during the detoxification trajectory.27 Four outcome variables measuring severity of opioid withdrawal were defined in the following manner (see Figure 1):

1. The rate of increase of withdrawal symptoms from baseline to the maximum score. The increase is the gradient and expressed in degrees.
2. The peak of withdrawal symptoms after naltrixone induction.

3. The rate of decrease of withdrawal symptoms from the maximum score to the first day of recovery. The decrease is the gradient and expressed in degrees.

4. The extent of withdrawal symptoms experienced was calculated as the total area under the curve (AUC) from baseline to the first day of recovery.

The measures listed in Table 3 were derived from the different instruments and constituted the independent variables. To minimize the effects of any outliers, mean baseline SOWS and VAS craving scores were calculated on the basis of the two baseline measures and one measure prior to the administration of the naltrixone on the first day of detoxification (ie, T3, T4, and T6, see Figure 2).
The number of predictor variables was reduced by testing for significant differences in withdrawal severity (ie, increase$_{\text{grad}}$, peak, decrease$_{\text{grad}}$, and AUC) in univariate regression analyses. Dichotomous variables were entered as dummy variables. Variables with a p-value of <0.05 in the univariate analysis were then entered into a stepwise multivariate regression analysis to evaluate the importance of each predictor variable (variables entered model at p < 0.05 and stayed at p < 0.1, two-tailed). According to Green et al.29 our sample size meets the minimum requirement for multiple regression analysis (>109), which depends upon the number of predictor variable. The statistical software package SPSS 14.0.2 was used for all the computations.

RESULTS

Participant characteristics

Participants were 200 opioid-dependent patients (82.0 percent men), with a mean age of 36.0 years (SD = 6.5). Most of the participants were never married (69.5 percent) and had no education (19.0 percent) or only lower education (50.5 percent) while 50.3 percent had a full-time job.

Course of withdrawal symptoms

The mean baseline SOWS level (ie, average for T3, T4, and T6) was 6.35 (SD = 4.86). The peak of withdrawal severity was reached after the administration of the naltrexone on the first day of detoxification (T7: 19.4 (SD = 10.1); T8: 19.3 (SD = 8.7). The patients were discharged from the addiction centre with a mean SOWS score of 9.1 (SD = 7.7). The standard deviations on all of the measurement occasions were large, which indicates substantial individual variability (Figure 2). And, as already mentioned, no substantial differences were found between those participants who were given general anaesthesia and those who were not; in fact, the group receiving general anaesthesia showed significantly more withdrawal symptoms than the group not receiving general anaesthesia on two of the 18 measurement occasions although this finding must be interpreted with caution due to repeated analysis.

Outcome measures for severity of withdrawal

Subgroups of participants with different SOWS patterns during the detoxification trajectory could not be detected using SVD. SVD revealed only one important component for the course of withdrawal symptoms, comparable with the mean of measurements. The intercorrelations between the four outcome measures for severity of withdrawal—the increase$_{\text{grad}}$ (M = 61.05, SD = 46.07), the peak (M = 25.74, SD = 8.92), the decrease$_{\text{grad}}$ (M = 61.05, SD = 46.07), and the AUC (M = 49.01, SD = 22.04)—are presented in Table 2.

Factors associated with severity of withdrawal

In Table 3, the associations between the independent variables and outcome measures of withdrawal severity are presented. Variables significantly associated with one of the outcome measures were as follows: mean years of heroin use, intravenous heroin use, anxiety, Cluster C personality disorders, baseline VAS craving, DDQ total score, and baseline withdrawal symptoms. The multiple regression model revealed significant contributions of baseline withdrawal symptoms (R$^2$ = 0.18), intravenous heroin use during the last 30 days (R$^2$ = 0.04), and Cluster C personality disorders (R$^2$ = 0.04) to the increase$_{\text{grad}}$ of withdrawal symptoms while anxiety and mean years of heroin use were excluded (see Table 4). The peak for the withdrawal symptoms was found to be associated with baseline withdrawal symptoms (R$^2$ = 0.08) while anxiety and VAS craving no longer played a significant role in multiple regression analysis. The univariate regression analysis showed only one variable to predict the decrease$_{\text{grad}}$ of withdrawal symptoms, namely anxiety (R$^2$ = 0.03). Finally, AUC was associated with both baseline withdrawal symptoms (R$^2$ = 0.27) and anxiety (R$^2$ = 0.02) in the multiple regression analysis; VAS craving and DDQ total score no longer played a role.

Two variables predicting the increase$_{\text{grad}}$ of withdrawal symptoms were dichotomous variables. Patients using intravenous heroin during the last 30 days prior to admission showed a smaller increase$_{\text{grad}}$ (M = 23.94; SD = 82.28) than patients not using intravenous heroin during the last 30 days (M = 62.60; SD = 43.63). The same was found for patients with a Cluster C personality disorder (M = 34.28; SD = 62.35) as opposed to patients with no such personality disorder (M = 63.54; SD = 43.84).

Table 2. Intercorrelations between outcome measures of withdrawal severity (AUC = area under curve) (n = 200)

<table>
<thead>
<tr>
<th>Withdrawal severity</th>
<th>Increase$_{\text{grad}}$</th>
<th>Peak</th>
<th>Decrease$_{\text{grad}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak*</td>
<td>0.16(†)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decrease$_{\text{grad}}$</td>
<td>0.11</td>
<td>-0.09</td>
<td></td>
</tr>
<tr>
<td>AUC</td>
<td>-0.05</td>
<td>0.74(‡)</td>
<td>-0.08</td>
</tr>
</tbody>
</table>

*Most of patients had their peak at T7 (36.1 percent), T8 (25.5 percent), or T9 (12.0 percent).
†Correlation is significant at the 0.05 level (two-tailed).
‡Correlation is significant at the 0.01 level (two-tailed).
Table 3. Descriptive statistics for independent variables and univariate associations* with outcome variables of increase$_{\text{grad}}$, peak, decrease$_{\text{grad}}$, and area under curve (AUC)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n</th>
<th>AUC</th>
<th>Peak</th>
<th>Increase</th>
<th>Decrease</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD)</td>
<td>36.00 (6.47)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Male (percent)</td>
<td>82.0</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Baseline withdrawal symptoms, mean (SD)</td>
<td>6.35 (4.86)</td>
<td>200</td>
<td>0.00</td>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>Drug use in years, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean years heroin</td>
<td>12.09 (5.69)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>0.02</td>
</tr>
<tr>
<td>Mean age at first heroin use</td>
<td>20.93 (5.22)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mean years methadone</td>
<td>7.14 (5.51)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Mean years cocaine</td>
<td>5.39 (5.73)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Drug use last 30 days, mean (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heroin</td>
<td>18.20 (12.20)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Methadone</td>
<td>23.04 (10.97)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Cocaine</td>
<td>3.97 (7.29)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Alcohol</td>
<td>3.57 (8.81)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Benzodiazepine</td>
<td>6.20 (11.37)</td>
<td>196</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Heroin use in gram, mean (SD)$^\dagger$</td>
<td>0.81 (0.68)</td>
<td>67</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Methadone use in mg, mean (SD)$^\dagger$</td>
<td>35.78 (27.98)</td>
<td>67</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Opioid use in mg, mean (SD)$^\ddagger$</td>
<td>52.39 (44.53)</td>
<td>67</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Intravenous heroin use last 30 days (percent)</td>
<td>4</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>0.02</td>
</tr>
<tr>
<td>Number of previous drugs detoxifications, mean (SD)</td>
<td>2.64 (2.88)</td>
<td>200</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Anxiety (SCL-90), mean (SD)</td>
<td>16.38 (6.59)</td>
<td>200</td>
<td>0.00</td>
<td>0.02</td>
<td>0.00</td>
</tr>
<tr>
<td>VAS Craving</td>
<td>22.32 (23.08)</td>
<td>195</td>
<td>0.00</td>
<td>0.02</td>
<td>ns</td>
</tr>
<tr>
<td>DDQ total score</td>
<td>32.43 (14.71)</td>
<td>199</td>
<td>0.03</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>OCDUS total score</td>
<td>34.42 (10.92)</td>
<td>199</td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Personality characteristics (SIDP-IV) (percent)</td>
<td>148</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cluster A presence</td>
<td>3.4</td>
<td></td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Cluster B presence</td>
<td>29.1</td>
<td></td>
<td>ns</td>
<td>ns</td>
<td>ns</td>
</tr>
<tr>
<td>Cluster C presence</td>
<td>12.8</td>
<td></td>
<td>ns</td>
<td>0.01</td>
<td>ns</td>
</tr>
</tbody>
</table>

* p is significant at the 0.05 level (two-tailed).
$^\dagger$ Doses are derived from meetings between physician and participant before admission.
$^\ddagger$ 1 mg of heroin use is translated into 65 mg of oral methadone (1 g of street heroin is roughly equivalent to 50-80 mg oral methadone$^{28}$).
The aim of this study was to identify subgroups of withdrawal symptoms during an opioid detoxification trajectory and to predict the severity of withdrawal symptoms on the basis of drug-related and sociodemographic characteristics. No distinct subgroups could be identified despite substantial individual variability throughout the detoxification trajectory. Opioid withdrawal severity was measured in terms of the rate of increase for the withdrawal symptoms, the peak of the withdrawal symptoms, the rate of decrease for the withdrawal symptoms, and the extent of the withdrawal symptoms. The highest level of withdrawal (peak) generally occurred on the first day of administration of the opioid antagonist and was found to last at least a few days, which is in keeping with the findings of Gowing et al.30 Multivariate regression analyses showed only five independent variables to predict one or more of the four severity of withdrawal measures. Patients who used heroin intravenously during the last 30 days prior to admission showed a smaller rate of increase in their withdrawal symptoms than patients who had not. This is in contrast to the findings of Smolka and Schmidt,8 who found greater severity and duration of total and maximum withdrawal symptoms in injectors when compared to smokers. A possible explanation for these contradictory findings may lie in the relatively small percentage of intravenous heroin use in the Netherlands (10 percent of all opioid users) or in the wide range of medication used in this study instead of abruptly withdrawn as studied by Smolka and Schmidt.8

The severity of the withdrawal symptoms at baseline predicted the rate of increase, peak, and extent of the withdrawal symptoms. Higher baseline withdrawal severity predicted higher peak symptoms and a greater extent of withdrawal symptoms but lower rates of increase for the withdrawal symptoms, which can be explained by the fact that an increase in withdrawal symptoms is limited by definition in patients with already higher baseline levels to start with.

Experienced anxiety predicted the extent of the withdrawal symptoms, which is in accordance with Philips et al.10 Contrary to this was the observation of a relatively faster rate of decrease in the symptoms of withdrawal in patients with a higher anxiety level at baseline. On the analysis for peak of the withdrawal symptoms and rate of increase in withdrawal symptoms, anxiety was dropped from the multiple regression analyses while the severity of withdrawal symptoms at baseline remains. This seems attributable to the strong relation between these two variables (R = 0.47). The presence of personality pathology reflecting the anxious-fearful cluster of the DSM-IV (ie, Cluster C) was associated with a smaller rate of increase in the withdrawal symptoms of the participants.

As already mentioned, a major association was found between baseline withdrawal symptoms and anxiety in the present study. This presumably reflects the fact that patients may report on not only symptoms of opioid

### Table 4. Results of multiple regression analyses to identify independent predictors of withdrawal severity*

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Predictor</th>
<th>R²</th>
<th>B</th>
<th>SE</th>
<th>β</th>
<th>t</th>
<th>p</th>
<th>95 percent CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increasegrad</td>
<td>Constant</td>
<td>89.93</td>
<td>5.59</td>
<td>16.09</td>
<td>0.00</td>
<td>78.89-100.97</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline withdrawal</td>
<td>0.18</td>
<td>-4.04</td>
<td>0.71</td>
<td>-0.41</td>
<td>-5.68</td>
<td>0.00</td>
<td>-5.45 to -2.63</td>
</tr>
<tr>
<td></td>
<td>Intravenous heroin use</td>
<td>0.22</td>
<td>-48.96</td>
<td>16.01</td>
<td>-0.22</td>
<td>-3.06</td>
<td>0.00</td>
<td>-80.60 to -17.31</td>
</tr>
<tr>
<td></td>
<td>Cluster C personality disorders</td>
<td>0.26</td>
<td>-28.57</td>
<td>10.18</td>
<td>-0.20</td>
<td>-2.81</td>
<td>0.01</td>
<td>-48.69 to -8.46</td>
</tr>
<tr>
<td>Peak</td>
<td>Constant</td>
<td>22.44</td>
<td>1.02</td>
<td>22.10</td>
<td>0.00</td>
<td>20.43 to 24.45</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline withdrawal</td>
<td>0.08</td>
<td>0.53</td>
<td>0.13</td>
<td>0.29</td>
<td>4.16</td>
<td>0.00</td>
<td>0.28 to 0.78</td>
</tr>
<tr>
<td>Decreasegrad</td>
<td>Constant</td>
<td>79.16</td>
<td>3.56</td>
<td>22.24</td>
<td>0.00</td>
<td>72.14 to 86.18</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>0.03</td>
<td>-0.49</td>
<td>0.20</td>
<td>-0.17</td>
<td>-2.43</td>
<td>0.02</td>
<td>-0.89 to -0.09</td>
</tr>
<tr>
<td>AUC</td>
<td>Constant</td>
<td>26.95</td>
<td>3.62</td>
<td>7.44</td>
<td>0.00</td>
<td>19.81 to 34.09</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Baseline withdrawal</td>
<td>0.27</td>
<td>2.00</td>
<td>0.31</td>
<td>0.44</td>
<td>6.38</td>
<td>0.00</td>
<td>1.38 to 2.61</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
<td>0.29</td>
<td>0.58</td>
<td>0.23</td>
<td>0.17</td>
<td>2.50</td>
<td>0.01</td>
<td>0.12 to 1.03</td>
</tr>
</tbody>
</table>

*Note increasegrad (F = 16.89, df = 3/144, p = 0.00); peak (F = 17.28, df = 1/193, p = 0.00); decreasegrad (F = 5.88, df = 1/198, p = 0.02); AUC (F = 39.80, df = 2/191, p = 0.00).
withdrawal but also anticipatory anxiety and a general increase of stress, as Collins et al.\(^3\) have argued. The strong associations between anticipatory anxiety and the individual’s autonomic reaction to stress, on the one hand, and the baseline level of withdrawal severity, on the other hand, also explain why the baseline level of withdrawal severity predicts both the peak and extent of withdrawal symptoms. Higher baseline arousal levels suggest a more sensitive sympathetic nervous system. The stress response during withdrawal may thus be the result of both experienced and expected withdrawal symptoms (ie, pain). Anxiety is further mediated by two systems, the hypothalamic-pituitary-adrenal (HPA) system and the sympathico-adrenomedullary system (SAS), which also mediate the cardiovascular system. In other words, not only subjective experienced anxiety but also the cardiovascular system is acutely activated, which results in increases blood pressure, increased heart rate and dilation of the vascular system. Alcohol and benzodiazepine use before admission did not influence withdrawal severity during baseline and detoxification and did not correlate with anxiety.

In the present study, patients received a wide range of medication to prevent withdrawal symptoms and treat those that occurred. This intervention may explain the low amount of explained variance by the baseline characteristics of the patients for the peak (8 percent) and decrease (3 percent) of withdrawal symptoms scores.\(^3\) In contrast, the explained variance in the increase of withdrawal symptoms and extent of withdrawal symptoms are higher, respectively, 26 percent and 29 percent, mostly due to the baseline withdrawal symptoms (respectively, 18 percent and 27 percent). Considering the range of the SOWS scores from 0 to 52, the withdrawal symptoms during rapid detoxification were rather low.

Collins et al.\(^3\) reported comparable severities of withdrawal for both rapid detoxification (with and without buprenorphine) and clonidine assisted detoxification. This indicates that generalization of the results to patients undergoing other types of opioid detoxification should be possible. Nevertheless, caution should be exercised in generalizing the results of the present study to other types of opioid detoxification because the present study was restricted to patients undergoing rapid detoxification. Another limitation of this study is that most patients are male (82 percent of patients). However, this reflects the opioid dependent population in the Netherlands.\(^32,33\)

In sum, the results of the present study provide evidence that the severity of withdrawal symptoms in patients undergoing opioid detoxification can be predicted by the baseline severity of their withdrawal symptoms but not by other patient characteristics. Given that dilation of the vascular system can cause an increase in the metabolism of medication, the possibility that medication may be less effective for the treatment of withdrawal symptoms should thus be taken into account. Therefore, greater attention should be paid to the identification (eg, assessment) and management of withdrawal symptoms at baseline to improve treatment during opioid detoxification. Higher baseline levels of withdrawal symptoms and anxiety should lead to more rigorous medical treatment to reduce baseline symptoms of withdrawal and anxiety and facilitate their prevention and/or treatment during detoxification. Such an intervention for anxiety reduction may involve the administration of short acting benzodiazepines and the reduction of noradrenergic activity with the administration of clonidine a few days prior to the start of detoxification. Caution is needed to provide short acting benzodiazepines after detoxification, especially when patients are also codependent on alcohol or benzodiazepines.

In closing, only phenotypic predictors were studied in the present study. More research is thus needed in the future on the influences of various endophenotypic factors, anticipatory anxiety, and other stress-related factors on the course of withdrawal symptoms during opioid detoxification.

References

Establishing the safety and efficacy of an opioid titration protocol

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Nancy Yelton, MSN, RN

ABSTRACT

The primary goal of this single-group study was to determine the safety of a standard opioid titration order sheet to manage pain in ambulatory cancer patients. Secondary goals were to examine opioid toxicity and efficacy of this pain protocol.

Twenty-seven patients who required fixed-dose opioids and who had uncontrolled pain were enrolled. All patients had their initial opioid dose titrated by the study physician using the opioid titration order sheet. Data were obtained by the study nurse during a weekly telephone interview and used to determine if pain was controlled. After initial titration, a trained study nurse titrated opioid doses based upon the standing order sheet. At each contact, patients were assessed for adverse effects, pain intensity, and analgesics used.

Patients who completed the four-week trial (n = 17) did not differ from patients who did not complete the trial. No adverse effects were observed in 39 opioid titrations completed by the study nurse. Opioid toxicities, worst pain, usual pain, and pain-related distress declined from baseline to week four. Patients who were adherent to their prescribed medications reported significantly lower pain intensity and distress (p ≤ 0.06).

The opioid titration order sheet, used by a trained nurse, is safe to use in ambulatory cancer patients who have moderate to severe pain. Common opioid toxicities were reduced. The protocol also demonstrated initial efficacy in improving worst and usual pain and pain-related distress. Further research to establish efficacy of the protocol is recommended.

Key words: cancer pain, standing orders, opioid titration

INTRODUCTION

Cancer-related pain has been reported in 50 percent of all patients\(^1\) and more than 85 percent of patients with terminal disease.\(^2\) Given current pharmacological and intervention strategies, the majority of patients should be able to achieve controlled pain. Nonetheless, uncontrolled cancer pain remains a major symptom control issue. Extensive studies have been conducted to identify barriers to uncontrolled pain in order to develop and test interventions. Multiple factors have been identified that contribute to the undertreatment of cancer pain. One commonly cited cause is lack of knowledge by medical staff and patients about cancer pain and its treatment. Eroneous beliefs, particularly about the danger of opioid use, also prevent optimal pain control. One obvious solution to these barriers is pain education. Educational interventions aimed at both medical staff and patients have been tested. While education interventions can improve knowledge and beliefs, they have failed to result in consistent, clinically meaningful improvements in pain outcomes.\(^3\) A more powerful and robust intervention strategy is necessary to effectively reduce cancer-related pain.

Achieving controlled pain is a complex process that requires interaction between healthcare providers (typically physicians and nurses) and the patient-family unit. We developed a conceptual model describing an ideal interaction between healthcare providers and patients that would result in optimal pain control. The ideal interaction involves five steps: 1) the patient effectively communicates pain issues to the provider; 2) the provider assesses current pain, the treatment plan, and reasons for poor pain control; 3) the provider modifies the treatment plan to provide more effective relief; 4) the provider reviews the revised plan with the patient and family; and 5) the patient follows the treatment plan. The first and the last steps in the process are patient driven, while the middle three steps are initiated by the provider (Figure 1). A great deal of work has been done to address the role of patient education to enhance patient adherence and communication with providers about pain control issues. As noted above, these interventions have failed to consistently improve pain control.\(^3\) We chose to develop an intervention that addressed the provider role in pain control.

Based on our conceptual framework, the provider is
| Step 1. | Patient: Patient report of pain |
| Step 2. | Provider: Assessment of pain |
| Step 3. | Provider: Medication modifications |
| Step 4. | Provider: Review of plan with patient |
| Step 5. | Patient: Patient follows treatment plan |

**Figure 1. Critical steps for adequate pain outcome.**

...responsible for three specific tasks: 1) assessing pain control and related issues (such as side effects and adherence), 2) generating a treatment plan, and 3) communicating the plan to the patient. If the provider complies with these steps in the care process, we hypothesize that pain control will be enhanced (i.e., decreased pain intensity and side effects). Furthermore, we posit that the occurrence of a positive pain outcome, which is dependent upon the degree to which the patient follows the treatment plan, will increase the patient’s willingness to report pain at the next healthcare encounter. Conversely, the process can break down if the provider does not follow the steps of the care process. In this instance, the feedback is negative, and patients may be less likely to communicate pain control problems to the provider during the next encounter.

Within our conceptual framework, there are two critical components that determine the healthcare provider’s ability to actualize their pain control tasks: 1) the knowledge base and expertise to allow for adequate assessment and treatment of pain, and 2) the time to obtain pertinent data (pain characteristics, barriers, and side effects) and communicate changes in the treatment plan to the patient. Unfortunately, it is evident that many physicians and nurses lack the skills needed to assess and treat pain. Thus, providers enter practice lacking basic knowledge about how to assess and manage cancer pain. Providers, therefore, learn to manage pain through trial and error, consultation with more seasoned providers, or continuing education. This type of educational process is suboptimal and leads to large gaps in knowledge. One strategy used to reduce knowledge deficits is provider education. Many educational programs for physicians and nurses have demonstrated short-term improvements in knowledge and attitudes. However, this increased knowledge has not resulted in long-term change in assessment and prescribing behaviors or demonstrated a beneficial impact on pain outcomes.

In addition to knowledge deficits, the medical delivery system used by most practicing oncologists prohibits timely and adequate response to cancer-related pain. A high volume of patient care problems and little time to address palliative issues burdens physicians. Lack of time has been identified as a critical barrier to good pain control. In order to save time, most oncologists use nursing staff to assist in symptom control. The use of nurses with advanced training and skills may be an acceptable and appropriate way to ensure timely and adequate control of symptoms. Unfortunately, nurses are usually poorly trained in symptom management and learn these skills on the job. Furthermore, there are few tested guidelines to aid them in this task.

The literature suggests that specific, evidence-based recommendations in the form of pathways, protocols, and algorithms may result in improved clinical outcomes through reducing variation in clinical care. The more specific and accessible the recommendations are, the more likely that providers will adopt new clinical practices. In most instances, successful guideline implementation has incorporated a multifaceted approach with some mix of education, feedback, or monitoring, and patient-provider reminders. We postulated that a well-developed protocol might enhance pain outcomes in the ambulatory cancer patient. We therefore undertook the development of a protocol specifically to address opioid titration. The protocol gives step-by-step instructions to providers, thus allowing providers with a limited knowledge base to use it effectively. In addition, it was designed to be nurse-managed, thus reducing the time required by physicians. The primary goal of this single-group design study was to test the safety of the opioid titration order sheet by examining the occurrence of severe adverse events. In addition, the study examined the efficacy of the protocol in reducing opioid toxicities and selected pain outcomes.

**PATIENTS AND METHODS**

**Sample eligibility**

Patients were recruited from a comprehensive cancer center located in a medical center in the southeastern United States. Eligible patients had: 1) histologically proven cancer, 2) uncontrolled cancer pain requiring opioids on a regular (fixed-dose) schedule, 3) the ability to read and understand English, 4) cognitive ability (Mini-Mental Status Examination [MMSE] > 24), 5) a life expectancy of more than 12 weeks, and 6) an age of 18 years or older. Patients were excluded from the study if they: 1) had pure neuropathic pain; 2) presented in a pain crisis, which is defined as severe pain unresponsive to traditional opioid therapies; or 3) required immediate anesthesia or neurosurgical measures for pain control. Patients were removed from the study if they required hospitalization during the opioid titration trial, if they were transferred to hospice, or if they presented to the clinic or emergency department in a pain crisis. This study was approved by the Institutional Review Board, and all patients provided written informed consent prior to beginning the study.
**Intervention**

Patients who met eligibility criteria and expressed interest in study participation were screened using the MMSE to ensure adequate mental capacity to complete self-report measures. Patients with adequate MMSE scores (≥ 24) were then enrolled in the study. Baseline evaluation included an assessment by a physician in order to adjust medications and to sign the titration order sheet. Patients then completed pain intensity and interference items of the Brief Pain Inventory (BPI), a single-item distress scale, and the Medication Side Effect Checklist (MSEC). Patients and families (when available) underwent a baseline educational program that included a review of medication doses and schedule, written and oral explanation about toxicities, and an assessment of barriers. They were instructed in how to complete the daily diary, which included a daily measure of worst and usual pain and all medications taken to manage pain and side effects. Patients also were instructed to contact the study nurse for any pain related issues. Emergent problems that occurred at night or on weekends were referred to the on-call team.

All follow up was conducted by one study nurse using telephone interviews. Patients were contacted a minimum of once each week for follow-up assessment. Follow-up assessments included an assessment of pain (results of the daily diary were reviewed and recorded), evaluation of adherence and barriers, and an evaluation of toxicity. The physician trained the study nurse in the use of the titration order sheet. The physician reviewed the study nurse dose calculations for the first month to ensure accuracy.

The opioid titration order sheet provides standing orders for opioid dose adjustment based on the level of pain and the use of breakthrough medications. The study nurse used the data obtained from the patient interview to calculate an appropriate dose modification. Once the dose modification was calculated, the patient was told how to take their medications. If adherence barriers were identified (e.g., fear of addiction), the study nurse addressed the barriers and encouraged the patient to take medications as prescribed. If opioid toxicities were identified, standing orders for side-effect management were implemented. Patients who had a dose modification for moderate pain or dose reductions were contacted within 48 to 72 hours after dose titration. Patients who had a dose modification for severe pain were contacted within 24 hours or the next working day. Patients experiencing a pain crisis or who developed new pain of unclear etiology were referred for evaluation by the primary oncologist.

The criteria for dose adjustment were based on pain level and the use of breakthrough medications. The pain level was categorized as mild (1 to 4), moderate (5 to 6), and severe (≥ 7). For the purposes of this study, controlled pain was defined as a usual pain level of 4 or less, with four or fewer rescue doses per 24 hours. To eliminate dose titration based upon transient or isolated activity-dependent pain, the patient must meet the criteria for three consecutive days before titration would be initiated. Patients with severe escalating pain could be titrated more rapidly after consultation with the physician.

Patients who did not meet these criteria for controlled pain were instructed to modify their opioid dose. Patients with mild usual pain (1 to 4) taking more than four rescue doses per day were instructed to adjust their fixed dose by an amount equal to the daily rescue dose in an effort to decrease the frequency of need for breakthrough medications. Patients with moderate pain (5 to 6) were instructed to increase their 24-hour opioid total (fixed dose plus rescue doses taken) by 25 percent. Patients with severe pain (≥ 7) were instructed to increase the 24-hour opioid total by 50 percent. Rescue doses were then recalculated to equal 10 to 15 percent of the new daily fixed-dose opioid total. If a patient met the criteria for controlled pain (usual pain < 4 and use of more than four rescue doses in 24 hours) and desired a decrease in opioid dose, a 25 percent reduction in 24-hour opioid total was prescribed.

**Outcome measures**

The primary outcome measure for this study was adverse events due to opioid overdose. Adverse events were assessed at each follow-up telephone interview. Since toxicities secondary to opioids are common, we clearly defined the parameters that were considered adverse events. These included severe lethargy, obtund sensation, and respiratory depression with a rate less than 8 per minute.

Opioid toxicity was assessed at baseline and during each follow-up interview using the MSEC. Side effects included on the six-item MSEC are those typically associated with opioid use, including constipation, drowsiness, nausea, vomiting, confusion, and dry mouth. The severity of each side effect that had been experienced in the past week was rated on an 11-point Numerical Rating Scale (NRS). Items were averaged to provide a mean weekly side effect score.

Adherence was assessed at each follow-up interview. Adherence to fixed-dose medications and the use of breakthrough dosing for moderate or severe pain was assessed. Patients were categorized as adherent if they: 1) took their fixed-dose opioids as prescribed, and 2) took rescue medications when usual pain was ≥ 4.

Patients completed a daily diary from baseline through week four of the trial. Usual and worst pain, fixed-dose opioid use, rescue medications taken, and other coanalgesics used were recorded in the daily diary. At baseline, week one, and week four, patients completed the interference items from the BPI and the pain-related distress item. Worst and usual pain intensity
and pain-related distress were obtained using 0 to 10 NRSs. Interference because of pain is a seven-item scale, which includes interference with ability to walk, general activity, usual work, mood, sleep, relations with others, and enjoyment in life. Each item was rated on an 11-point NRS, and responses were averaged for a total interference score. All instruments have established reliability and validity.

### Data analysis

The sample size was based upon the ability to detect a 10 percent rate of adverse events. Demographic and clinical variables were examined using descriptive statistics. A weekly average of worst and usual pain was computed from the daily diary. The average number of rescue doses per day was computed. Average scores were computed for the interference and side effects scales. Differences in demographic, clinical, and baseline variables between patients who completed and did not complete the study were examined using $\chi^2$-square for categorical and independent t-test for continuous variables. Toxicities were examined in two ways: 1) the proportion of patients with no toxicities was compared to patients with toxicities using $\chi^2$-square, and 2) the change in mean severity of toxicities was tested using repeated measures analysis of variance (ANOVA). Efficacy of the intervention was examined using a two-factor repeated measure ANOVA. In each analysis, time was the factor within subjects and adherence was the factor between subjects. Dependent variables included worst pain, usual pain (5 data points), pain-related distress, and interference because of pain (3 data points). This type of analysis allowed us to examine main effects for time and adherence and to determine if there were interactions between time and adherence for the selected pain outcomes. Level of significance was $p \leq .10$ for this pilot study. This level of significance was selected to increase our ability to detect differences over time, which may be clinically significant.

### RESULTS

#### Patient characteristics

Out of a total of 27 patients who enrolled in the study, 17 completed the four-week trial (63 percent retention).

![Table 1. Sample description](image-url)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Did not complete study</th>
<th>Completed study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Number of Ss</td>
<td>Percent in group</td>
</tr>
<tr>
<td>Gender</td>
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<td></td>
</tr>
<tr>
<td>Male</td>
<td>8</td>
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</tr>
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<td>25</td>
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<td>Marital status</td>
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<tr>
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<tr>
<td>Single/divorced</td>
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<td>40</td>
</tr>
<tr>
<td>Age in years</td>
<td>57.1</td>
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<tr>
<td>Cancer dx in months</td>
<td>11.3</td>
<td>12.35</td>
</tr>
<tr>
<td>Pain duration months</td>
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<td>13.49</td>
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<td>Mental status</td>
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</tr>
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<td>Worst pain (0-10)</td>
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<td>1.64</td>
</tr>
<tr>
<td>Usual pain (0-10)</td>
<td>5.8</td>
<td>1.03</td>
</tr>
<tr>
<td>Side effects (0-10)</td>
<td>1.96</td>
<td>1.63</td>
</tr>
<tr>
<td>Distress (0-10)</td>
<td>5.9</td>
<td>2.85</td>
</tr>
<tr>
<td>Interference (0-10)</td>
<td>4.38</td>
<td>2.70</td>
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Table 2. Use of rescue medications over time

<table>
<thead>
<tr>
<th></th>
<th>Rescue doses per day</th>
<th></th>
<th>Rescue doses per week</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>Median</td>
<td>Range</td>
<td>Mean</td>
</tr>
<tr>
<td>Week 1</td>
<td>1.79</td>
<td>1.20</td>
<td>0 – 6</td>
<td>12.25</td>
</tr>
<tr>
<td>Week 2</td>
<td>1.82</td>
<td>1.79</td>
<td>0 – 5.29</td>
<td>11.86</td>
</tr>
<tr>
<td>Week 3</td>
<td>2.08</td>
<td>2.07</td>
<td>0 – 5.29</td>
<td>13.0</td>
</tr>
<tr>
<td>Week 4</td>
<td>1.84</td>
<td>1.85</td>
<td>0 – 4.14</td>
<td>12.29</td>
</tr>
</tbody>
</table>

Reasons for discontinuing the study were hospitalization (n = 3), referral to hospice (n = 1), death unrelated to disease progression (n = 1), and loss to follow up (n = 5). There were no significant differences between patients who did and did not complete the study on any baseline variable (Table 1). The final sample (n = 17) was predominantly white and married, with a mean age of 57 years. They had been diagnosed with cancer for 11 months and had experienced pain related to the cancer for nine months. Fifty-nine percent were undergoing active treatment at the time of enrollment.

Adverse events associated with opioid titration

Patients were prescribed a long-acting opioid on a fixed schedule and a rescue medication when entered into the study. The dose range of long-acting opioids was as follows: Duragesic (25 to 400 mcg q 72 h), sustained release morphine (30 to 450 mg qd), and sustained release oxycodone (40 to 271 mg qd). Morphine sulfate immediate release tablets or liquid was the most frequently prescribed opioid for rescue dosing. Over the four-week trial, patients averaged approximately two rescue doses per day, however, there was a high degree of variation across patients in use of rescue medications (Table 2).

All patients had a dose adjustment upon entry into the study. Over the four-week study period, 15 patients (88 percent) had dose escalations: eight patients had one additional dose escalation, and seven patients had between two and five dose escalations. One patient tolerated two dose decreases. One patient required no additional dose modification. Each patient had initial opioids titrated by the physician (27 titrations). The study nurse successfully managed an additional 39 titrations. No patient experienced any adverse effect (severe lethargy, obtund sensation, or respiratory depression) over the course of the trial.

Opioid toxicities

At baseline, less than 20 percent of patients reported no toxicities associated with opioid use (Table 3). Drowsiness and dry mouth were most frequently reported and remained the most frequent toxicities experienced after opioid titration. The proportion of patients with no toxicities gradually rose from week one to week four. Chi-square analyses indicated the proportion with toxicities differed significantly from expected at baseline (p = 0.008), but no significant differences were found after opioid titration (ps > 0.10). The mean score on the MSEC was 1.96 at baseline, with a significant reduction in mean toxicity over time (p = 0.07).

Adherence

Nine patients (53 percent) were adherent to both fixed- and rescue-dose analgesic regimens. The majority of patients took their fixed-dose opioids as prescribed. Nonadherence was primarily related to failure to take rescue doses when usual pain rose above four-tenths on the NRS. When queried about failure to adhere to the breakthrough regimen, most patients replied “the pain wasn’t that bad,” and “they did not need the medication.”

Effect of titration on pain outcomes

The opioid titration order sheet had a beneficial effect on pain outcomes. Repeated measures ANOVA indicated a significant main effect for time on worst pain (p = 0.10), usual pain (p = 0.02), and pain-related distress (p = 0.05). All outcomes showed a decline over time. Interference because of pain did show a slight decline over time, but the change was not statistically significant. A main effect for adherence also was significant for worst pain (p = 0.05), usual pain (p = 0.006), and distress (p = 0.05). As expected, patients who took their medications as prescribed reported lower pain and distress than those who did not. No significant differences were found between patients who were and were not adherent for interference because of pain. No significant interaction between time and adherence was found for any pain outcome.
<table>
<thead>
<tr>
<th>Toxicity</th>
<th>Baseline</th>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constipation*</td>
<td>46.7</td>
<td>21.1</td>
<td>16.7</td>
<td>18.2</td>
<td>7.7</td>
</tr>
<tr>
<td>Drowsiness*</td>
<td>66.6</td>
<td>38.5</td>
<td>59.3</td>
<td>60.0</td>
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</tr>
<tr>
<td>Nausea*</td>
<td>46.7</td>
<td>21.1</td>
<td>33.3</td>
<td>27.3</td>
<td>23.1</td>
</tr>
<tr>
<td>Vomiting*</td>
<td>20.0</td>
<td>21.1</td>
<td>8.3</td>
<td>18.2</td>
<td>15.4</td>
</tr>
<tr>
<td>Confusion*</td>
<td>33.3</td>
<td>21.1</td>
<td>16.7</td>
<td>36.4</td>
<td>23.1</td>
</tr>
<tr>
<td>Dry mouth*</td>
<td>80.0</td>
<td>53.8</td>
<td>75.0</td>
<td>81.8</td>
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Number of toxicities

<p>| | | | | | |</p>
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<tr>
<td>0</td>
<td>17.6</td>
<td>52.9</td>
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<td>1</td>
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<td>2−6</td>
<td>70.6</td>
<td>47.1</td>
<td>42.1</td>
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Severity**

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<tbody>
<tr>
<td>Mean</td>
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<td>0.94</td>
<td>0.99</td>
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</tr>
<tr>
<td>SD</td>
<td>1.63</td>
<td>1.23</td>
<td>1.15</td>
<td>1.10</td>
<td>0.98</td>
</tr>
<tr>
<td>Range</td>
<td>0−5.67</td>
<td>0−3.33</td>
<td>0−3.67</td>
<td>0−3.0</td>
<td>0−3.17</td>
</tr>
</tbody>
</table>

* Percent with toxicity; ** Possible range 0−10.

DISCUSSION

The results of this study confirm the safety of an opioid titration order sheet that is managed by a trained nurse with appropriate physician oversight. The primary outcome measure for this study was adverse events. No adverse events were observed in the 66 titrations completed in this trial. Interestingly, despite the large number of dose titrations during the study period, opioid toxicity decreased over time. This may be related to the aggressive assessment of toxicity coupled with the timely institution of standard therapy to manage opioid side effects.

To capture the effect of the intervention on pain control, it is critical to select appropriate outcome measures. The most commonly used outcome measure for cancer pain is pain intensity. A standard measure of pain intensity in the cancer population is the BPI.\textsuperscript{15,16,20} Usual pain is considered a measure of basal pain, while worst pain reflects breakthrough pain. Results from this pilot trial indicate that opioid titration using the opioid titration order sheet resulted in improvement in usual and worst pain.

Pain, like other symptoms, is characterized by multiple dimensions.\textsuperscript{23} Distress, which is defined as the amount of anguish or bother caused by the symptom,\textsuperscript{23,24} also may have a significant impact on intensity, duration, and secondary outcomes.\textsuperscript{23−25} In previous work, pain-related distress explained a greater proportion of unique variance in interference than pain intensity (worst or usual), mood disturbance, or analgesics used.\textsuperscript{26} Use of the opioid titration order sheet resulted in a significant reduction in distress once the patient had been placed on the protocol and had medications titrated. These findings suggest that distress may be a particularly salient outcome in analgesic trials and merits further study. The lack of effect of the opioid titration protocol on interference because of pain is consistent with previous work,\textsuperscript{27} which is an outcome that may be influenced by a number of factors in addition to adequate pain control. Another explanation is that this scale may not be as sensitive to change as the single item pain intensity and distress items.

In our study, only half of the patients adhered to the prescribed regimen. While most patients took their fixed-dose regimen, adherence to the breakthrough regimen was poor. These results confirm the findings of other investigators. In a study by Miaskowski et al.,\textsuperscript{28} the lack of adherence to medications prescribed to control metastatic cancer pain was substantial. Adherence rates, over a five-week period, were high (90.0 percent) for medications prescribed on a fixed schedule and notably lower for rescue-dose analgesics (24.7 percent). This study
highlights the problem of medication adherence in patients with cancer pain and provides a reasonable explanation for undertreatment.

Furthermore, we demonstrated that patients who adhere to their regimen are more likely to have improved pain outcomes. Our findings also support the work of Du Pen and colleagues,22 who tested a pain algorithm in a randomized clinical trial. Use of the pain algorithm resulted in a significant reduction in usual pain for all patients in treatment and a significant reduction in usual and worst pain for patients who adhered to the prescribed regimen. In their sample, the pain algorithm did not affect symptoms experienced, interference because of pain, or quality of life. Thus, Du Pen and colleagues demonstrated the importance of adherence in achieving improvement in pain intensity when patients are managed with a pain algorithm. Both the pain algorithm and the opioid titration order sheet represent strategies that may produce successful implementation of existing pain guidelines.20-30

Limitations

Several limitations of this study must be noted. Because of the single-group design, we cannot compare the impact of this protocol with standing titration orders to usual care. The ability to generalize the results of this study are limited by the small sample size and attrition of patients from the study. Thus, future research using a randomized design with a usual care comparison group is recommended.

CONCLUSION

The opioid titration order sheet is a clinical tool that addresses the provider-driven steps of our conceptual model. The order sheet specifies the timing and content of pain assessment, the criteria indicating need for opioid dose adjustment, a standing order for dose titration, and an outline for provider communication of the treatment plan to the patient. After initial assessment by the physician, the standing orders can be used by trained nurses, thus reducing the barriers to effective pain management, knowledge deficits, and time constraints. Our pilot study suggests that this type of clinical tool is safe and effective in improving several critical pain outcomes for ambulatory patients with cancer. The protocol with standing orders also addresses barriers to clinical guideline implementation. Because of their level of specificity, algorithms and protocols may be more easily adopted in clinical settings, thus reducing one of the implementation problems inherent in guidelines. To extend this line of research, we need to determine the applicability of a pain protocol with standing orders for dose titration for community-based providers.

ACKNOWLEDGMENTS

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Preliminary findings from the first 17 subjects were presented at the 2001 ASCO scientific meeting. Wells N, Murphy B, Siet D: Standardized opioid titration order sheet (SOTOS) for cancer pain. Proc Amer Soc Clin Oncol. 2001; 20: 2983, abstract #2943. The complete study was presented in poster form at the Pain in Europe conference, September 2003.

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REFERENCES

Monitoring outcomes during long-term opioid therapy for noncancer pain: Results with the Pain Assessment and Documentation Tool

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ABSTRACT
The increasingly common practice of long-term opioid therapy for chronic noncancer pain must be guided by ongoing assessment of four types of outcomes: pain relief, function, side effects, and drug-related behaviors. Our objective was to gather initial pilot data on the clinical application of a specialized chart note, the Pain Assessment and Documentation Tool (PADT), which was developed and tested with 27 physicians. This pilot test provided the means to collect cross-sectional outcome data on a large sample of opioid-treated chronic pain patients. Each of the physician volunteers (located in a variety of settings across the United States) completed the PADT for a convenience sample of personally treated chronic pain patients who had received at least three months of opioid therapy. Completion of the PADT required a clinical interview, review of the medical chart, and direct clinical observation. Data from the PADTs were collated and analyzed. The results suggested that the majority of patients with chronic pain achieve relatively positive outcomes in the eyes of their prescribing physicians in all four relevant domains with opioid therapy. Analgesia was modest but meaningful, functionality was generally stabilized or improved, and side effects were tolerable. Potentially aberrant behaviors were common but viewed as an indicator of a problem (i.e., addiction or diversion) in only approximately 10 percent of cases. Using the PADT, physician ratings can be developed in four domains. In this sample, outcomes suggested that opioid therapy provided meaningful analgesia.

Key words: opioids, noncancer pain, assessment, documentation, outcomes

INTRODUCTION
The use of opioid analgesics is a cornerstone of pain management. Although still controversial, chronic opioid therapy for noncancer pain is becoming a more widely accepted therapeutic option. A large gap exists between the empirical literature on the safety and efficacy of long-term chronic opioid therapy and the expanding use of this approach in clinical practice.

To use opioids safely and effectively, candidates for therapy should be appropriately selected, drug administration should be optimized, and ongoing monitoring should provide detailed information in multiple domains. Based on extensive clinical experience, four domains have been proposed as most relevant: pain relief, side effects, physical and psychosocial functioning, and the occurrence of any potentially aberrant (or nonadherent) drug-related behaviors. These domains have been summarized as the “Four As” (analgesia, activities of daily living, adverse side effects, and aberrant drug-taking behaviors). The monitoring of these outcomes over time should inform therapeutic decision-makers and provide a framework for documentation of the clinical use of these controlled drugs.

Suboptimal physician monitoring and documentation during opioid therapy is a significant problem and may have adverse clinical, medicolegal, and regulatory implications. In an effort to improve the approach to monitoring and simultaneously provide a standardized chart note for the purposes of documentation, a brief, physician-rated Pain Assessment and Documentation Tool (PADT)
was developed and successfully field tested.\textsuperscript{10} The PADT was developed from a series of questions and checklists that together assessed each of the Four As.

PADT items that evaluated pain relief and function were modeled on the Brief Pain Inventory,\textsuperscript{11} a validated patient-rated instrument. Side effects were tabulated. A list of potentially aberrant drug-related behaviors was developed from descriptions in the medical literature\textsuperscript{3} and clinical experience. The list included drug-related behaviors that are illegal (e.g., altering of prescriptions, lying to obtain a controlled substance, drug diversion), those that strongly suggest addiction (e.g., continued use despite harm), and those that raise concern about drug abuse or addiction but are not, in themselves, diagnostic (e.g., multiple requests for higher doses, repeated visits to an emergency room).

The process by which the PADT was developed and refined, using application of the tool clinically by physicians, has been described previously.\textsuperscript{10} The pilot clinical application itself yielded outcomes data on a large and diverse patient sample. These data, described later, reflect the perceptions of treating physicians pertaining to a broad set of outcomes achieved by a selected population of opioid-treated chronic pain patients. As such, they represent a type of survey data that has not heretofore been explored as a means to define the spectrum of responses observed in clinical practice. Our objective was to gather initial pilot data on the clinical application of a specialized chart note, the PADT, which could then be used in the design of future validation and reliability trials.

\textbf{METHODS}

\textbf{Procedure}

Twenty-seven physicians attending a training program for a pain-oriented speakers' bureau were recruited to participate in the pilot study. The physicians practiced in all regions of the continental United States and spent at least part of their clinical practice time caring for patients with chronic noncancer pain. They were chosen for their collective expertise in pain management and their ready access to patients with chronic pain issues being maintained on opioid therapy. Although this is a potential source of bias, it was felt that having physicians with interest and expertise in pain administer the PADT was important for gathering initial data on the tool.

The physicians were given the checklists that together constituted the first draft of the PADT and were asked to identify patients from their practices who had been receiving opioid therapy for a period of at least three months. They were then instructed to obtain the information necessary to complete the PADT from a clinical interview, review of the medical chart, and direct clinical observation.

A total of 388 patients with a diverse assortment of pain syndromes and a wide variety of opioid and adjuvant medications were interviewed for the study. As stated previously, all patients with chronic noncancer pain were eligible to be selected as long as they had been on opioids for a period of three months or longer. This selection criterion was chosen in the hopes of obtaining a patient sample that was not new to the various physicians so they could render judgments based on some established relationship. In addition, it was hoped that this time period would also maximize the chance that any “dose-finding” for opioids would be well underway or stable in those who were selected. After the checklists were completed by the physician, the forms underwent removal of identifying information and were sent to the lead investigator for analysis.

\textbf{Study Instrument}

The PADT was developed by the investigators with input from a group of experts in pain and addiction medicine.\textsuperscript{10} The tool has four sections: physician demographics, patient demographics, assessment of the Four As, and the physician’s diagnostic impression of the patient. The physician demographics section includes information such as age, mode of practice, practice location, and the number of prescriptions written for opioids in the last month. The patient demographics section includes gender, ethnicity, employment status, pain diagnosis, and medical history.

The section on the Four As requires the physician to rate the effectiveness of the analgesic regimen, the presence of side effects and their severity, the current impact of the pain on function, and the presence of any aberrant drug-taking behaviors. The last section, physician impression, asks the physician to note whether aberrant drug-related behaviors, if present, most likely owed to addiction, unrelieved pain, criminal intent (diversion), or nonaddiction-related psychiatric disturbance (e.g., depression, anxiety, personality disorder).

\textbf{Analysis plan}

The goal of the study was to characterize the impressions of physicians who were treating patients on chronic opioid regimens according to the PADT. To this end, the data analysis plan was to collate and describe the participating physicians and the patients they interviewed. A series of descriptive analyses was conducted, including frequency and mean calculations. Overall, the objective was to simply tally and report the findings from the clinical application of the PADT. However, we were also interested in some exploratory areas that might lead to future research questions. Exploratory analyses were conducted on how each of the Four As related to each
other and to demographic information through a series of Pearson correlations and t-tests. To accomplish this, global scores for each of the Four As were created by summing the items from each section of the instrument. As a final analysis, a series of one-way analysis of variance (ANOVA) tests was conducted to determine whether or not the opioid regimen chosen for the patient had an effect on any of the Four As.

**RESULTS**

**Physician data**

A total of 27 physicians volunteered to participate in the trial. Physicians interviewed an average of 14.4 patients, for a total sample of 388 patients (described later). The majority of physicians were in the 41- to 50-year-old range (n = 15, 55.6 percent), followed by those in the 51- to 60-year-old range (n = 6, 22.2 percent), and then the 30- to 40-year-old range (n = 5, 18.5 percent). Specific ages were not requested to avoid potential identification of the physicians, given the small physician participant pool. Most were male (n = 21, 77.8 percent), and all were board certified (n = 27, 100 percent) in their specialty areas. The most common mode of practice was family practice (n = 10, 45.5 percent), followed by anesthesia (n = 7, 31.8 percent), and neurology (n = 2, 9.1 percent).

Most physicians were located in an urban setting (n = 18, 69.2 percent), followed by those in suburban (n = 7, 26.9 percent) and rural settings (n = 1, 3.9 percent). Most practice settings were in an office (n = 10, 50 percent) or university hospital (n = 5, 25 percent). The physicians reported an average of 14 years in practice (SD = 10.6). Most stated that more than one-half of their patients had chronic pain (mean = 62.7 percent, SD = 36.6); overall, they treated an average of 912.6 patients per year with chronic pain (SD = 1,211.9).

The physicians reported that they managed more than one-half of their chronic pain patients with an opioid regimen (50.6 percent, SD = 31.3), and that they treated an average of 576.9 patients per year with opioids (SD = 927.2). Table 1 lists the estimated number of prescriptions for opioids that were written by the physicians during the month prior to completion of the PADT. Oxycodone-containing products (mean = 39.2, SD = 71.9), hydrocodone-containing products (mean = 31.9, SD = 37.2), and methadone (mean = 16.4, SD = 27.6) were the most frequently prescribed opioid analgesics.

**Patient data**

A total of 388 chronic pain patients were interviewed and rated by the physicians. The sample was comprised of 233 women (63.7 percent) and 133 men (36.3 percent), and had a mean age of 50.1 years (SD = 13.6, range = 21 to 87 years, median = 47.0). Most were white (n = 322, 84.1 percent), followed by African American (n = 29, 7.6 percent) and Hispanic (n = 23, 6.0 percent). Most had some college experience (n = 115, 30.5 percent), followed by those who were high school (n = 93, 24.7 percent) or college (n = 63, 16.7 percent) graduates. Many were disabled (n = 160, 41.2 percent), while others were working full-time (n = 80, 20.6 percent), or retired (n = 60, 15.5 percent). Before their pain diagnosis, most of the patients were working full-time (n = 250, 67.4 percent) or part-time (n = 32, 8.6 percent). They were most likely to be married (n = 218, 56.2 percent), followed by divorced (n = 76, 19.6 percent), single (n = 47, 12.1 percent), and widowed (n = 32, 8.3 percent). Most lived with a spouse (n = 208, 53.9 percent) and the next largest group lived alone (n = 95, 24.6 percent).

Nearly one-half of the sample (n = 178, 45.9 percent) reported only one source of chronic pain; the remainder endorsed two or more causes of pain. Somatic pain was documented for 291 patients (75 percent), followed by mixed/other sources (n = 160, 41.2 percent), neuropathic pain (n = 125, 32.2 percent), and visceral pain (n = 37, 9.5 percent). Only 17.8 percent of the sample (n = 69) stated that the pain was related to a past job, and an additional 4.4 percent (n = 17) stated that the pain was related to their current job.

**Outcomes: The Four As**

**Analgesia.** On a scale of 0 to 10 (0 = no pain, 10 = worst pain imaginable), patients rated their average pain for the prior week as 5.4 (SD = 2.2) and their worst pain during that time as 7.9 (SD = 2.1). When asked what percentage of pain had been relieved since starting treatment, the average response was 57.8 percent (SD = 24.4). More than three-fourths of the patients (n = 301, 77.6 percent) stated that they had a meaningful degree of pain relief, and 85.1 percent of the physician responses (n = 330) also indicated that they believed the degree of pain relief from the analgesic regimen was clinically meaningful.

**Activities of daily living.** Physicians rated aspects of functioning as “better,” “same,” or “worse” compared to a baseline defined as before the current opioid therapy (Table 2). Overall, physicians rated their patients’ physical (n = 307, 79.1 percent), psychological (n = 250, 64.4 percent), and social functioning (n = 214, 55.2 percent) as improved since starting their current regimen.

An index of declining function was created by adding all the domains of function that were scored by the physician as declining since the opioid regimen was begun. The domains included physical functioning, mood, family relationships, social relationships, sleep pattern, occupational functioning, and overall functioning. Therefore, a range of 0 to 7 was possible for domains that had worsened. Overall, only 16.3 percent (n = 63) of the sample
was rated as worsening in one or more domains of function. This was broken down as follows: one (n = 31, 8 percent), two (n = 9, 2.3 percent), and three (n = 15, 3.9 percent).

**Adverse effects.** The most common side effects and ratings of their severity by the patients are listed in Figure 1. A total of 132 (34 percent) patients required treatment for constipation, 23 (5.9 percent) for nausea, 14 (3.6 percent) for sedation, and seven (1.8 percent) for mental clouding. Forty-nine patients (12.6 percent) stated that side effects forced them to cut down their medications, and five (1.3 percent) stated that they had to stop taking the medications entirely. Ninety percent (n = 349) considered the side effects of the medications tolerable.

Only 32.8 percent (n = 127) of the sample rated one or more of the possible adverse side effects as moderate or severe in nature. Most reported only one (n = 97, 25 percent) or two side effects (n = 25, 6.4 percent) as being moderate or severe.

**Potentially aberrant drug-related behaviors.** When asked whether there was concern about a patient's responsibility in the use of the current analgesic regimen, physicians reported 71 times (18.3 percent) that they were concerned, 299 times (77.1 percent) that they were not concerned, and 13 times (3.4 percent) that they were uncertain. When asked whether the patients' families

Table 1. Frequency of opioids prescribed in the past month

<table>
<thead>
<tr>
<th>Item</th>
<th>n</th>
<th>Mean (SD)</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morphine products</td>
<td>27</td>
<td>14.50 (18.00)</td>
<td>8</td>
<td>0 – 80</td>
</tr>
<tr>
<td>Oxycodeine-containing products</td>
<td>27</td>
<td>39.23 (71.85)</td>
<td>15</td>
<td>0 – 350</td>
</tr>
<tr>
<td>Fentanyl patch</td>
<td>27</td>
<td>15.54 (25.62)</td>
<td>5</td>
<td>0 – 125</td>
</tr>
<tr>
<td>Methadone</td>
<td>27</td>
<td>16.42 (27.55)</td>
<td>6.5</td>
<td>0 – 100</td>
</tr>
<tr>
<td>Hydromorphone</td>
<td>27</td>
<td>5.50 (6.49)</td>
<td>3.5</td>
<td>0 – 20</td>
</tr>
<tr>
<td>Tylenol #3</td>
<td>27</td>
<td>3.92 (3.43)</td>
<td>3</td>
<td>0 – 10</td>
</tr>
<tr>
<td>Tylenol #4</td>
<td>27</td>
<td>1.27 (2.44)</td>
<td>0</td>
<td>0 – 10</td>
</tr>
<tr>
<td>Hydrocodone-containing products</td>
<td>27</td>
<td>31.85 (37.23)</td>
<td>15</td>
<td>0 – 125</td>
</tr>
<tr>
<td>Tramadol</td>
<td>27</td>
<td>12.92 (16.02)</td>
<td>5</td>
<td>0 – 50</td>
</tr>
<tr>
<td>Levorphanol</td>
<td>27</td>
<td>0.15 (0.46)</td>
<td>0</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Dihydrocodeine</td>
<td>27</td>
<td>0.08 (0.27)</td>
<td>0</td>
<td>0 – 1</td>
</tr>
<tr>
<td>Butorphanol</td>
<td>27</td>
<td>0.35 (0.69)</td>
<td>0</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Pentazocine</td>
<td>27</td>
<td>0.31 (0.68)</td>
<td>0</td>
<td>0 – 2</td>
</tr>
<tr>
<td>Others</td>
<td>27</td>
<td>0 (0)</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SD, standard deviation.

In a series of related questions, physicians rated the degree to which they suspected problematic behaviors on the part of their patients. Table 3 lists the behaviors as well as the physicians’ impressions. Overall, the physicians believed that their patients answered clinical questions in a completely truthful (n = 308, 79.4 percent) or somewhat truthful (n = 74, 19.1 percent) manner. In only two cases (1.0 percent) was it felt that their patients were “not at all truthful.” In 46 cases (11.9 percent), physicians concluded that their patients had exhibited worrisome aberrant drug-taking behaviors, and in 40 cases (10.3 percent) they felt that the aberrant behavior was related to unrelieved pain.

Nearly one-half of the sample (n = 173, 44.6 percent) was rated as having engaged in at least one of the 29 listed aberrant drug-related behaviors. The range of aberrant behaviors was from 0 to 17, with a mean of 1.48 behaviors per patient (SD = 2.65). Most often, patients engaged in one (n = 62, 16 percent) or two (n = 36, 9.3 percent) aberrant drug-related behaviors. When examining the percentage of patients engaging in multiple behaviors, 19.3 percent of the sample engaged in three or more potentially aberrant behaviors, with 10.8 percent of the
Table 2. Results of patient interviews and physician impressions on activities of daily living (N = 388)

<table>
<thead>
<tr>
<th></th>
<th>Better</th>
<th>Same</th>
<th>Worse</th>
<th>Missing</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient interview</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>303 (78.09)</td>
<td>67 (17.27)</td>
<td>14 (3.61)</td>
<td>4 (1.03)</td>
</tr>
<tr>
<td>Mood</td>
<td>368 (69.07)</td>
<td>96 (24.74)</td>
<td>22 (5.67)</td>
<td>2 (0.52)</td>
</tr>
<tr>
<td>Family relationships</td>
<td>219 (56.44)</td>
<td>151 (38.92)</td>
<td>16 (4.12)</td>
<td>2 (0.52)</td>
</tr>
<tr>
<td>Social relationships</td>
<td>194 (50.0)</td>
<td>171 (44.07)</td>
<td>20 (5.15)</td>
<td>3 (0.77)</td>
</tr>
<tr>
<td>Sleep pattern</td>
<td>226 (58.25)</td>
<td>129 (33.25)</td>
<td>30 (7.75)</td>
<td>3 (0.77)</td>
</tr>
<tr>
<td>Occupational functioning</td>
<td>155 (39.95)</td>
<td>176 (45.36)</td>
<td>19 (4.90)</td>
<td>38 (9.79)</td>
</tr>
<tr>
<td>Overall functioning</td>
<td>289 (74.48)</td>
<td>81 (20.88)</td>
<td>12 (3.09)</td>
<td>6 (1.55)</td>
</tr>
<tr>
<td>Physician impression</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical functioning</td>
<td>307 (79.12)</td>
<td>64 (16.49)</td>
<td>13 (3.35)</td>
<td>4 (1.03)</td>
</tr>
<tr>
<td>Psychological functioning</td>
<td>250 (64.43)</td>
<td>112 (28.87)</td>
<td>22 (5.67)</td>
<td>4 (1.03)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>214 (55.15)</td>
<td>137 (35.31)</td>
<td>29 (7.47)</td>
<td>8 (2.06)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percentages.

sample having engaged in five or more of these behaviors.

Table 4 indicates the aberrant drug-related behaviors recorded by the physicians and the average number of occasions on which a behavior occurred. Because this was a cross-sectional survey, physicians noted the number of times an aberrant behavior occurred over the course of treating the given patient. Requests for frequent early renewals (n = 69) and insisting on a particular medication (n = 65) were the most common potentially aberrant behaviors. Five patients (1.3 percent) had been arrested or detained by the police, four (1.0 percent) had associates who were arrested or detained by the police, and six (1.5 percent) were victims of abuse or violence.

Exploratory analyses of the Four As

It was of interest to determine whether the Four As were correlated and how they were associated with psychological, alcohol, or drug problems or demographic variables. For purposes of determining analgesia level, the question pertaining to the percentage of pain relieved was selected for the analysis. For the remaining domains, summary scores (i.e., total score of each item in that domain) were used as global representations of outcome. Only the activities of daily living domain was significantly related to the other three. Decreased functioning as measured by activities of daily living was associated with a smaller degree of reported pain relief (r = -0.20, p < 0.01), as well as more problems with side effects from medications (r = 0.17, p < 0.01) and a greater number of aberrant drug-related behaviors being endorsed (r = 0.10, p < 0.05).

Several other relationships were significant and noteworthy. Concerning the demographic variables, gender was associated with reported pain relief (t1, 361 = 2.09, p < 0.05), with women (mean = 55.8 percent, SD = 25.5) experiencing a lesser percent of pain relief from treatment than men (mean = 61.4 percent, SD = 22.3). Younger age was also found to be significantly related to an increase in the number of aberrant drug-related behaviors recorded (r = -0.21, p < 0.01).

With regard to psychiatric issues, a past psychiatric history of any kind was associated with engaging in more aberrant drug-related behaviors (r = -0.14, p < 0.01). A final set of interesting correlations concerned the smoking status of the patients. A history of having smoked cigarettes was associated with poorer functioning in their activities of daily living (r = -0.14, p < 0.01). Current smoking activity was associated with a greater number of aberrant drug-related behaviors (r = -0.17, p < 0.01).

Exploratory statistics based on medication

Another key area of interest concerned the effect of
medication choice on the Four As. Using the summary scores and analgesia items mentioned in the previous section, a series of one-way ANOVAs was conducted to compare long- and short-acting opioids. Long-acting opioids were associated with more adverse side effects than short-acting opioids (F1, 381 = 11.86, p < 0.01). There were no significant differences between these categories of opioids concerning percent pain relief, number of impairments in activities of daily living, or number of aberrant drug behaviors exhibited.

**DISCUSSION**

The use of opioids for noncancer pain must be accompanied by a careful and ongoing assessment of outcomes supported by documentation. In this work, we examined outcomes using a tool designed to guide this assessment and generate a comprehensive note to improve record-keeping. We attempted to put this tool into the hands of busy clinicians and examine perceptions of outcome. It is important to note that these results do not represent an epidemiological survey of outcome in chronic opioid therapy—it was neither designed (i.e., sampling) nor powered to be interpreted in this fashion.

Thus, it is important to recognize the limitations of this design to better appreciate what can be learned from such a naturalistic cross-sectional observation of pain therapy with opioids. The physicians who took part in this study were not selected at random, and all had some expertise and familiarity with chronic pain management. Indeed, chronic pain patients made up more than one-half of their respective medical practices. In addition, the patient sample was one of convenience, needing to be on an opioid regimen for a period of at least three months. In addition, the physicians interviewed the patients directly and completed all of the assessment, which could lend to a bias for under-reporting on the part of patients, especially concerning the aberrant drug-taking behaviors. Indeed, we should expect that the patients were not totally forthcoming to their physicians, although a number of aberrant behaviors were reported. Thus, the data reported in this paper are subject to multiple selection biases and may not be representative of outcome in chronic opioid therapy; in this respect, it is not terribly different from many short, often industry-sponsored, community-based studies of opioid therapy in the extant literature. However, this type of design does involve a naturalistic look at pain practice as opposed to a more contrived clinical trial and also offers some insight into how doctors perceive outcomes in their long-term opioid-treated patients.

The PADT does appear to describe outcome in a comprehensive fashion and might prove to be a useful addition to record-keeping in chronic opioid therapy. It may also aid in improving the adherence to guidelines for opioid use and the safe use of opioids for noncancer pain. However, replication studies focusing on more stringent reliability and validity data for the tool are needed. We conclude that this study is an important first step toward creating a clinically applied tool for documentation.

In describing outcomes in these patients, the PADT helps to explicate the Four As of pain outcomes. The patients described in this study overall were assessed as having moderate to severe pain while on opioid therapy. Their degree of pain relief is best described as modest, but meaningful, in that it was overwhelmingly felt to make “a real difference” in patients’ lives. The actual degree of relief noted was a diminution of approximately 58 percent from baseline pain. This is an important and telling observation, one that says much about the need to set appropriate expectations for opioid therapy. With most patients attaining this level of pain relief, a figure which compares favorably with those previously reported in the literature,

![Figure 1. Side effect severity of opioid therapy (N = 388).](image1)

![Figure 2. Total number of aberrant behaviors endorsed by each patient (N = 388).](image2)
this degree of relief are probably fairly uncomplicated and could be considered for opioid therapy in routine medical management settings. Patients who do not functionally improve with this degree of relief are likely to have other clinical problems, such as comorbid psychiatric issues (i.e., depression, anxiety, secondary gain issues, a deep-seated need to stay in the sick role), and would require specialized attention for a satisfying outcome to be realized.

Additionally, nearly four of five patients were seen as improved in overall functioning with this rather gross approach to assessment and documentation. This is an important consideration in the wake of the negative attention focused on opioid therapy owing to OxyContin abuse.14-15 There is a suggestion of the validity of these ratings given that most of the improvement comes in the areas of physical functioning and mood where opioids have their most direct impact.

Opioid side effects were common in this study, but overwhelmingly seen as tolerable and manageable by patients and physicians. Constipation was the most common side effect and was severe in one-third of patients, which is similar to results found elsewhere.16, 17 Side effects can detract from ability to function and must be aggressively managed.

The results from this study in the area of aberrant drug-related behavior, should they be replicated in an adequately designed and powered epidemiological survey, are powerful. For many years, pain experts have argued that addiction is rare in people receiving adequate and appropriate opioids as part of the medical management of pain.16, 19 While this may be true, large-scale studies are, in fact, lacking.

Addiction may not be the central issue facing pain clinicians. In the phenomenology of the pain clinician, the management of noncompliance behavior arising from multiple causes is the central issue. These results suggest that noncompliance is fairly common and challenges the clinician to note, understand, and react to it in nearly 50 percent of patients. Noncompliance has a complex “differential diagnosis,” including addiction, uncontrolled pain (pseudoaddiction), self-medication of psychiatric and physical symptoms other than pain and situational stressors, family dysfunction, and diversion.6, 20-22 The clinician must know how to assess and come to decisions about the meaning of this behavior and importantly, document about it. Physicians noted noncompliance in 45 percent of patients but considered it worrisome only one in 10 times, and so must have a repertoire for responding to psychiatric and other causes of noncompliance.

Behaviors varied tremendously in their frequency. The very aberrant and illegal behaviors were rare and occurred in less than 2 percent of patients overall. The less obvious behaviors were common, seen in the cases of nearly one in five patients in some instances. Most behaviors were seen in approximately 6 percent of

<table>
<thead>
<tr>
<th>Behavior</th>
<th>Yes</th>
<th>No</th>
<th>Do not know</th>
</tr>
</thead>
<tbody>
<tr>
<td>Opioid prescription abuse/addiction</td>
<td>23 (5.95)</td>
<td>342 (88.14)</td>
<td>18 (4.64)</td>
</tr>
<tr>
<td>Prescription opioid dependence</td>
<td>92 (23.71)</td>
<td>261 (67.27)</td>
<td>19 (4.90)</td>
</tr>
<tr>
<td>Prescription drug abuse/addiction</td>
<td>11 (2.84)</td>
<td>358 (92.27)</td>
<td>9 (2.32)</td>
</tr>
<tr>
<td>Prescription drug dependence</td>
<td>6 (1.55)</td>
<td>349 (89.95)</td>
<td>10 (2.58)</td>
</tr>
<tr>
<td>Alcohol abuse/addiction</td>
<td>5 (1.29)</td>
<td>364 (93.81)</td>
<td>11 (2.84)</td>
</tr>
<tr>
<td>Alcohol dependence</td>
<td>9 (2.32)</td>
<td>349 (89.95)</td>
<td>12 (3.09)</td>
</tr>
<tr>
<td>Other illicit drug abuse/addiction</td>
<td>7 (1.80)</td>
<td>356 (91.75)</td>
<td>17 (4.38)</td>
</tr>
<tr>
<td>Any illicit drug dependence</td>
<td>0</td>
<td>351 (90.46)</td>
<td>15 (3.87)</td>
</tr>
<tr>
<td>Drug-taking behavior related to criminal intent</td>
<td>2 (0.52)</td>
<td>367 (94.59)</td>
<td>10 (2.58)</td>
</tr>
<tr>
<td>Drug-taking behavior resulting from family dysfunction</td>
<td>16 (4.12)</td>
<td>346 (89.18)</td>
<td>17 (4.38)</td>
</tr>
<tr>
<td>Has a psychiatric disorder that may be causing or contributing to aberrant drug-related behavior</td>
<td>21 (5.41)</td>
<td>344 (88.66)</td>
<td>16 (4.12)</td>
</tr>
</tbody>
</table>

Numbers in parentheses are percentages.
<table>
<thead>
<tr>
<th>Behavior</th>
<th>n</th>
<th>Mean number of occasions noted per patient (SD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requests frequent early renewals</td>
<td>69</td>
<td>2.88 (2.35)</td>
</tr>
<tr>
<td>Asks for medication by name</td>
<td>63</td>
<td>2.68 (1.79)</td>
</tr>
<tr>
<td>Increases dose without authorization</td>
<td>51</td>
<td>2.59 (2.38)</td>
</tr>
<tr>
<td>Requests higher dose in a worrisome manner</td>
<td>33</td>
<td>3.29 (2.45)</td>
</tr>
<tr>
<td>Reports lost/stolen prescriptions</td>
<td>32</td>
<td>1.36 (0.54)</td>
</tr>
<tr>
<td>Oversedation</td>
<td>31</td>
<td>4.92 (13.12)</td>
</tr>
<tr>
<td>Negative mood change</td>
<td>30</td>
<td>3.05 (2.23)</td>
</tr>
<tr>
<td>Attempts to obtain medication from other doctors</td>
<td>30</td>
<td>1.98 (1.33)</td>
</tr>
<tr>
<td>Successfully obtains medications from other doctors</td>
<td>27</td>
<td>1.80 (1.13)</td>
</tr>
<tr>
<td>Misses appointments except for medication renewal</td>
<td>22</td>
<td>2.23 (1.57)</td>
</tr>
<tr>
<td>Does not comply with other recommended treatments</td>
<td>21</td>
<td>3.26 (2.65)</td>
</tr>
<tr>
<td>Reports no effect of other medications</td>
<td>18</td>
<td>2.78 (1.77)</td>
</tr>
<tr>
<td>Uses medication for purpose other than described</td>
<td>17</td>
<td>2.21 (1.10)</td>
</tr>
<tr>
<td>Declining physical function</td>
<td>16</td>
<td>2.38 (1.82)</td>
</tr>
<tr>
<td>Declining social function</td>
<td>13</td>
<td>2.15 (1.63)</td>
</tr>
<tr>
<td>Declining psychological function</td>
<td>13</td>
<td>2.04 (1.51)</td>
</tr>
<tr>
<td>Intoxicated seeming</td>
<td>13</td>
<td>2.62 (1.82)</td>
</tr>
<tr>
<td>Contact with street culture</td>
<td>13</td>
<td>1.31 (0.63)</td>
</tr>
<tr>
<td>Abusing alcohol or street drugs</td>
<td>11</td>
<td>1.27 (0.47)</td>
</tr>
<tr>
<td>Staff splitting</td>
<td>10</td>
<td>2.70 (1.64)</td>
</tr>
<tr>
<td>Involved in motor vehicle or other accident</td>
<td>7</td>
<td>1.14 (0.38)</td>
</tr>
<tr>
<td>Increasingly unkempt or impaired</td>
<td>6</td>
<td>2.33 (1.21)</td>
</tr>
<tr>
<td>Hoarding of medications</td>
<td>6</td>
<td>2.00 (1.67)</td>
</tr>
<tr>
<td>Worrisome drug effects</td>
<td>5</td>
<td>2.30 (1.72)</td>
</tr>
<tr>
<td>Changes route of administration</td>
<td>4</td>
<td>3.50 (2.89)</td>
</tr>
<tr>
<td>Engaging in the sale of sex to obtain drugs</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

SD, standard deviation.
patients, an interesting observation in that the rate of substance abuse/addiction in the United States is thought to be approximately 6 to 10 percent of the population, and recent reports in chronic pain populations have ranged from 3 to 18 percent. Thus, if this observation is replicated in larger epidemiologic surveys, it suggests that the subgroup of patients expected to be problematic on opioids could have been predicted from the baseline population norms.

Inter-relationships between the Four As and other patient variables

It is interesting that there was not a greater degree of intercorrelation among the Four As. Although they tap vastly different areas, overall we expected that the chronic pain experience would lend an overarching thread to combine these four important areas. Indeed, only the second “A,” activities of daily living, was significantly correlated to the other aspects of the chart note. This may suggest a rather important role for paying attention to the functionality of patients being treated for chronic pain. Poor functioning in this sample was related to lesser amounts of pain relief, more adverse side effects, and a greater number of aberrant drug-related behaviors being engaged by patients. It might be that assessing functionality is a rather innocuous means of getting a global impression of the patient and whether or not he or she is going to ultimately respond to opioid therapy. This notion has been at least initially supported by a recent study of 158 patients treated in an inpatient chronic pain setting.

Regarding aberrant drug-related behaviors, it is important to highlight the predictors that were significant in this study. Those who were younger, had a psychiatric history of any kind, and were current smokers were all more likely to engage in a greater number of aberrant drug-related behaviors. Further assessment of psychiatric history, addiction history, and smoking status and the ability of these factors to predict aberrant behavior is warranted.

CONCLUSION

We attempted to implement a new documentation aid, the PADT, in a naturalistic study of outcomes in opioid therapy. Although subject to the types of selection biases that are common in the field of community-based trials in pain management, the study does suggest that the measure records a comprehensive view of outcomes. The study also suggests that, in general, patients on ongoing opioid therapy were seen as having favorable outcomes by their treating physicians. Future trials are needed to explore the factor structure, reliability, and validity of the tool.

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