ORIGINAL ARTICLE

Adverse effects and cognitive function among primary care patients taking opioids for chronic nonmalignant pain

Randall T. Brown, MD
Megan Zuelsdorff, BS
Michael Fleming, MD, MPH

ABSTRACT

Chronic opioid therapy is commonly prescribed for chronic nonmalignant pain. Few published data describe the adverse effects experienced by patients with chronic nonmalignant pain being treated by primary care physicians. A prevalence study was conducted on a sample of 1,009 patients (889 receiving chronic opioids) being treated by 235 primary care physicians. Standardized questionnaires and medical record reviews were used to assess rates of addiction, pain diagnosis and severity, opioid adverse effects, and mental health. The mean daily dose of opioids was 92 mg using a morphine-equivalent conversion. Side effects included constipation (40 percent), sleeping problems (25 percent), loss of appetite (23 percent), and sexual dysfunction (18 percent), with patients on daily opioids experiencing more side effects than subjects on intermittent medication. The Medical Outcomes Study Mental Health Inventory (MOS-MHI) cognitive functioning scale indicated poorer cognitive function in the overall sample of chronic pain patients as compared to a general clinical sample ($\Delta \bar{x}$ 95 percent CI = 9.28, 13.76). However, there were limited differences in MOS scores between chronic pain subjects on daily opioids vs. intermittent opioids vs. no prescription opioids. A regression model suggests that psychological measures and pain severity are more predictive of decrements in cognitive function than specific opioid preparations or daily opioid dose. Physicians should closely monitor patients for adverse effects and adequacy of pain control when using chronic opioid therapy for chronic pain treatment. Psychological health, an important predictor of cognitive dysfunction, is a particularly important measure to actively monitor and manage.

Key words: opioids, adverse effects, chronic nonmalignant pain, primary care physicians

INTRODUCTION

It has been estimated that 50 million Americans suffer from chronic nonmalignant pain (CNMP).[1,2] Opioids are the most effective analgesics available, but their use in CNMP continues to be controversial. While published guidelines advocate the use of long-acting opioid analgesics in the management of CNMP,[3-7] care providers have expressed reluctance in survey-based studies to prescribe these agents chronically due to concern that adverse effects may precipitate functional decline.[8-11]

Opioid adverse effects are generally dose-related, but severity varies between individuals. Systems affected include the central nervous (sedation, respiratory depression, and cognitive impairment), gastrointestinal (nausea, vomiting, and constipation), and the skin (pruritus).[8,12] Though most studies have observed no significant cognitive impairment with long-term opioid use,[13-16] others have raised the concern that adverse effects with long-term use may contribute to serious adverse events, such as falls and hip fractures[17,18] and impairment of judgment and reaction time necessary for safe driving.[19] Randomized clinical trials have found that opioids improve pain relief in the setting of CNMP but with the trade-off of more frequent adverse effects (primarily constipation, sedation, dizziness, and nausea).[20-23]

The findings of previous clinical trials, of 14 weeks or less in duration, may not generalize to clinical settings where opioid analgesics are commonly used over the longer term. The current study sought to determine the prevalence of adverse effects, the level of cognitive dysfunction, and patient factors and prescribing practices associated with these adverse effects in a primary care sample with CNMP patients taking opioid analgesics for three months or more. We hypothesized that, when controlling for important covariates, long-term daily opioid use, particular opioid analgesic preparations, and higher daily doses would not be predictors of greater levels of cognitive dysfunction. We further hypothesized that adverse effects would be more strongly associated with intermittent, or as-needed, use than with daily scheduled use of opioid analgesics.

METHODS

Detailed study methods have been published elsewhere[24] and will be summarized here.

Setting and dates

Subjects were recruited with the help of 235 primary care physicians. These physicians were members of five healthcare systems: the UW Medical Foundation, Dean Clinics, Group Health Cooperative, Aurora Health Care, and Mercy Health Care. Interviews were conducted in a variety of settings including primary care clinics and research offices. The interviews were conducted by one of four researchers. Study recruitment and data collection took place from July 2002 to July 2004.

Procedures followed were in accordance with the Helsinki Declaration of 1975 as revised in 1983. The study protocol was reviewed and approved by the University of Wisconsin—Madison Health Sciences Institutional Review Board.

Sample

An interview study was conducted with a convenience sample of 1,009 subjects being treated for CNMP. Chronicity was defined as pain that has persisted every day for at least three months. Inclusion criteria for the primary group of interest included 1) age between 18 and 81, 2) a diagnosis of CNMP, and 3) current treatment by a primary care physician including chronic opioid therapy.

Overall response rate was over 85 percent, with some variation by physician and clinic. Primary reasons given for nonparticipation included lack of time, employment time conflicts, childcare responsibilities, confidentiality issues related to chronic pain treatment, and transportation problems.

Of the 1,009 recruited subjects, 889 were receiving opioid medications on an intermittent (n = 98) or chronic daily (n = 791) basis. Chronic daily use was defined as having taken prescription opioids for at least 20 days in a 30-day time period in at least one of the previous three months. More than 95 percent of subjects in this group were using prescription opioids daily during the previous three months. Intermittent users were characterized by having taken opioids on fewer than 20 days of any 30-day period during the last three months but having taken opioids for pain at some time during the last six months. Opioid use was determined by an initial screening interview and later confirmed by an inventory of the patient's medication bottles, completed during the interview. Ultimately, all analyses were conducted using opioid-intake information from this medication inventory, as it was assumed to be more current.

Subject recruitment

The first step was to identify patients of individual physicians being treated for chronic pain. Physicians used a number of strategies to identify subjects, including clinic logs of persons on opioids, billing records using ICD-9 codes of chronic pain diagnosis, pharmacy records, and electronic medical record searches. The second step was to mail each potential subject a letter of invitation from his or her primary care physician.

Measurements

Once subjects had completed consent forms, the interview resumed with a medication checklist, the Medical Outcomes Study Mental Health Inventory (MOS-MHI) cognitive functioning scale,[25] the Substance Dependence Severity Scale (SDSS),[26-28] the Addiction Severity Index (ASI),[29,30] the Neighborhood Disorder Scale (NDS),[31] and the Pain Inventory Survey.[32] For further previous studies validating these instruments, the authors refer the reader to the study's primary methodological paper.[24]

The subject and interviewer reviewed all medications and dosages. Patient self-report on the type, dose, and frequency of pain medication was confirmed by medical and pharmacy records when available. Disagreements between these reports were resolved by the PI survey, with patient self-report being the primary source of the data used. Until we have reliable statewide pharmacy-reporting mechanisms, patient self-report of pain medication will be the most valid source of medication usage; physician and pharmacy records are often incomplete and may not reflect what patients are actually using. Medical records were also used for determination of the subjects' pain diagnoses.

The primary outcome of cognitive function was assessed using the MOS-MHI cognitive functioning scale. The scale consists of six questions using a Likert scale to quantify six possible responses, ranging from Never to Always. These items generate a score on a 100-point scale, with a lower score indicating greater dysfunction. Questions address experiences over the last 30 days, such as:

1. How often have you had difficulty reasoning and solving problems?

2. How often have you had difficulty with concentration and thinking?

3. How often have you had episodes of confusion?

4. How often have you had short-term memory problems?

Table 1. Demographics of sample*			
Variable		**n**	**Percent of total subjects (N = 889)**
Gender	Male	277	30.7
	Female	612	69.3
Age (years)	18 to 30	43	4.8
	31 to 40	132	14.8
	41 to 50	329	37.0
	51 to 60	275	30.9
	More than 60	110	12.4
Race	White, non-Hispanic	673	75.7
	Black, non-Hispanic	201	22.6
	American Indian	7	0.8
	Asian/Pacific Islander	1	0.1
	Hispanic - Mexican	3	0.3
	Hispanic - Puerto Rican	2	0.2
	No answer	2	0.2
Marital status	Married	267	30.0
	Remarried	116	13.0
	Widowed	49	5.5
	Separated	53	6.0
	Divorced	227	25.5
	Never married	176	19.8
	No answer	1	0.1
Employment status (usual)	Full time	266	29.9
	Part time regular	75	8.4
	Part time irregular	34	3.8
	Student	9	1.0
	Retired/disability	408	45.9
	Unemployed	96	10.8
	No answer	1	0.1
Substance abuse or dependence present	Yes	116	13
	No	773	87
* Current substance abuse or dependence status (yes/no) is per the Substance Dependence Severity Scale.			

Table 2. Opioid analgesics used by study sample					
Drug	**Frequency of prescription (n)**	**Percentage of subjects (out of 889)**	**Range of dosage***	**Mean dosage***	**Standard deviation**
Oxycodone	441	49.6	3 to 640	66.41	89.96
Hydrocodone	254	28.6	1 to 120	21.89	17.87
Morphine	142	16	1 to 800	123.93	152.48
Codeine	88	9.9	2.51 to 80.16	22.12	18.48
Fentanyl	68	7.6	5 to 800	138.46	141.46
Methadone	61	6.9	30 to 1,020	257.95	208.53
Propoxyphene	51	5.8	5 to 55	15.66	13.02
Demerol	12	1.3	6 to 120	32.14	29.90
Dilaudid	11	1.2	10 to 720	115.45	203.19
Overall	**1,128****		**2 to 1,020**	**92.26**	**136.46**

* All doses and ranges are in morphine milligram equivalents; ** Total prescriptions exceed sample size due to 239 subjects taking more than one opioid analgesic.

5. How often have you had difficulty focusing attention on a single activity? and

6. How often have you had slow reactions to things?

In creating a summary score, each item is weighted equally and rescaled to range from 0 to 100. The item responses are then averaged to create an overall score of 0 to 100.

An Adverse Medication Checklist was developed based on the SAFTEE[33-40] and contains 18 items addressing 18 potential opioid adverse effects. On each item patients indicated 1) whether they had experienced specific side effects and 2) whether they felt that these effects were due to opioid analgesics.

The PI survey includes 16 questions that inquire about pain location, pain diagnosis, pain severity, onset of pain problems, opioid efficacy, and patients' concerns about opioids. Questions assess pain severity on a 0 to 10 scale for worst pain, average pain, and least pain experienced.

The SDSS uses DSM-IV and ICD-10 criteria to give a diagnosis of current alcohol or drug dependence. The schedule specifically asks about alcohol, heroin, cocaine, hallucinogens, sedatives, stimulants, pain killers, and methadone. The SDSS was used rather than other diagnostic schedules (e.g. SCID, CIDI) to try to separate patients with true opioid addiction from patients physically dependent on appropriate doses of prescription opioids.

The ASI is a questionnaire containing seven subscales (medical, employment, alcohol, drugs, legal, social, and psychiatric). The depression and anxiety measurements of this instrument were used to control for the effects of these disorders in regression modeling.

The NDS consists of 14 questions and uses a Likert scale of strongly agree, agree, disagree, and strongly disagree. The instrument was included to assess health disparities due to community-level stressors among patients being treated for chronic pain.

The total daily dose of opioids for each patient in the sample was based on a 24-hour morphine sulfate equivalent. The dose equivalents chosen were based on a number of sources, including American Pain Society guidelines, a recent systematic review of clinical guidelines, primary research, and personal communication with pharmacologists and clinicians with expertise in pain management.[41-47] There have been limited empirical studies comparing opioids in noncancer chronic pain samples. For oral morphine medications such as Kadian, MS Contin, immediate-release (IR) morphine, and sustained-release (SR) morphine, we considered the mg dose of each medication as a 24-hour equivalent—10 mg of MS Contin was considered the same as 10 mg of IR morphine; 3 mg of oxycodone was considered equal to 4 mg of morphine.[46,48] A 50-µg/hour fentanyl patch was considered equal to 140 mg of morphine,

Table 3. Frequencies of primary diagnoses among subjects taking pain medication		
Primary diagnostic category	**Number of subjects**	**Percent of subjects (N = 889)**
Arthritis	212	23.8
Chronic low back disorder	189	21.3
Migraine	81	9.1
Neuropathy NOS	48	5.4
Trauma and other injuries	35	3.9
Fibromyalgia	34	3.8
Cervical spine disease	27	3.0
Diabetic neuropathy	25	2.8
Rheumatoid arthritis	24	2.7
Lupus	23	2.6
Chronic abdominal disorder NOS	20	2.2
Myofascial syndrome	19	2.1
Chronic pancreatitis	17	1.9
Spinal stenosis	17	1.9
Shoulder disorder NOS	11	1.2
Headaches NOS	9	1.0
Herniated lumbar disc	9	1.0
Lumbar disc disease and nerve compression	9	1.0
Reflex sympathetic dystrophy	7	0.8
Sickle cell anemia	7	0.8
Avascular necrosis of hips	6	0.7
Knee disorder NOS	6	0.7
Scoliosis	5	0.6
Restless leg syndrome	4	0.4
TMJ	4	0.4
Carpal tunnel syndrome	3	0.3
Other	38	4.3
Total	**889**	**99.7***
* Total percentage at 99.7 rather than 100.0 due to rounding.		

Table 4. Average scores for MOS-MHI 6-item cognitive functioning subscale and mean differences between groups*				
	Group 1 - Chronic opioids (n = 790)	**Group 2 - Intermittent opioids (n = 98)**	**Group 3 - No opioids (n = 115)**	**General clinic population (n = 2,469)**
Total score - Mean (SD)	70.82 (22.42)	71.33 (21.45)	66.96 (20.72)	82.4 (16.5)
Mean differences, 95% CI				
vs. Group 1		0.51 (-3.86, 4.88)	3.86 (-0.48, 8.20)	11.58 (9.30, 13.86)
vs. Group 2	0.51 (-3.86, 4.88)		4.37 (-1.30, 10.04)	11.07 (7.30, 14.84)
vs. Group 3	3.86 (-0.48, 8.20)	4.37 (-1.30, 10.04)		15.44 (11.92, 18.96)
vs. General population	11.58 (9.30, 13.86)	11.07 (7.30, 14.84)	15.44 (11.92, 18.96)	

The six items on the subscale address experiences over the last 30 days: 1) How often have you had difficulty reasoning and solving problems, 2) How often have you had difficulty with concentration and thinking, 3) How often have you had episodes of confusion, 4) How often have you had short-term memory problems, 5) How often have you had difficulty focusing attention on a single activity, and 6) How often have you had slow reactions to things. Answers are on a 6-point Likert scale ranging from "never" to "always." In creating a summary score, each item is weighted equally and rescaled to range from 0 to 100. The item responses are averaged to create an overall score of 0 to 100.

assuming that 1) 50 µg/hour fentanyl = 2 mg morphine IV, and 2) the oral bioavailability of morphine is 35 percent.[46,49] 10 mg of methadone was treated as equal to 30 mg of morphine. Analysis was also undertaken with a conversion of 1 mg morphine = 10 mg morphine, given controversy surrounding a consistent conversion ratio for all dosage levels of methadone:morphine.[46,50] Tylenol #3 was considered equal to 5 mg of morphine. Similarly, the total daily dose of benzodiazepines for each patient was based on a 24-hour diazepam equivalent[51,52]: diazepam 10 mg = alprazolam 1 mg = lorazepam 2 mg = clonazepam 4 mg.

Analysis

Data were entered into an Access database and transferred to SPSS version 12.0 statistical software for analysis. The data were assessed for skewness and kurtosis. The average daily mg equivalents demonstrated a high degree of rightward skew for both morphine and diazepam mg equivalents. The natural log of these values exhibited near-normal distribution and was used for purposes of regression modeling.

The type of opioid medication was also examined as a potential contributor to cognitive dysfunction in regression modeling. Dummy variables were created for each medication, and the interaction term for medication X average daily dose was created and included in stepwise regression. The log of average daily dose in morphine mg equivalents for each opioid was also used in this portion of the analysis to more closely approximate normal distribution.

Independent sample t-testing was performed comparing the frequency of adverse effects among those taking opioid analgesics only intermittently vs. that among those taking opioids on a scheduled daily basis. Levene's test for equality of variance was performed, and, when appropriate based upon this test, variance was assumed equal between these groups for the purposes of t-testing.

Due to the small number of subjects in ethnic categories other than White and African American/non-Hispanic, race was included in final analyses as a binary variable (White/non-White). Dummy variables were created for the categories of marital status and employment status. These dummy variables were then retained for analysis of nonparametric bivariate correlations and for stepwise regression analysis if statistically significant Spearman correlations were observed.

Regression analysis was hypothesis-driven and proceeded as follows for modeling of cognitive function score. Medication X dose interaction terms for each opioid analgesic were entered into an initial model to examine dose-response effects by medication on cognitive function. Covariates were then entered into the model via stepwise regression after examination of bivariate analysis of covariates and their correlations with cognitive function. Pearson correlation coefficients were used for

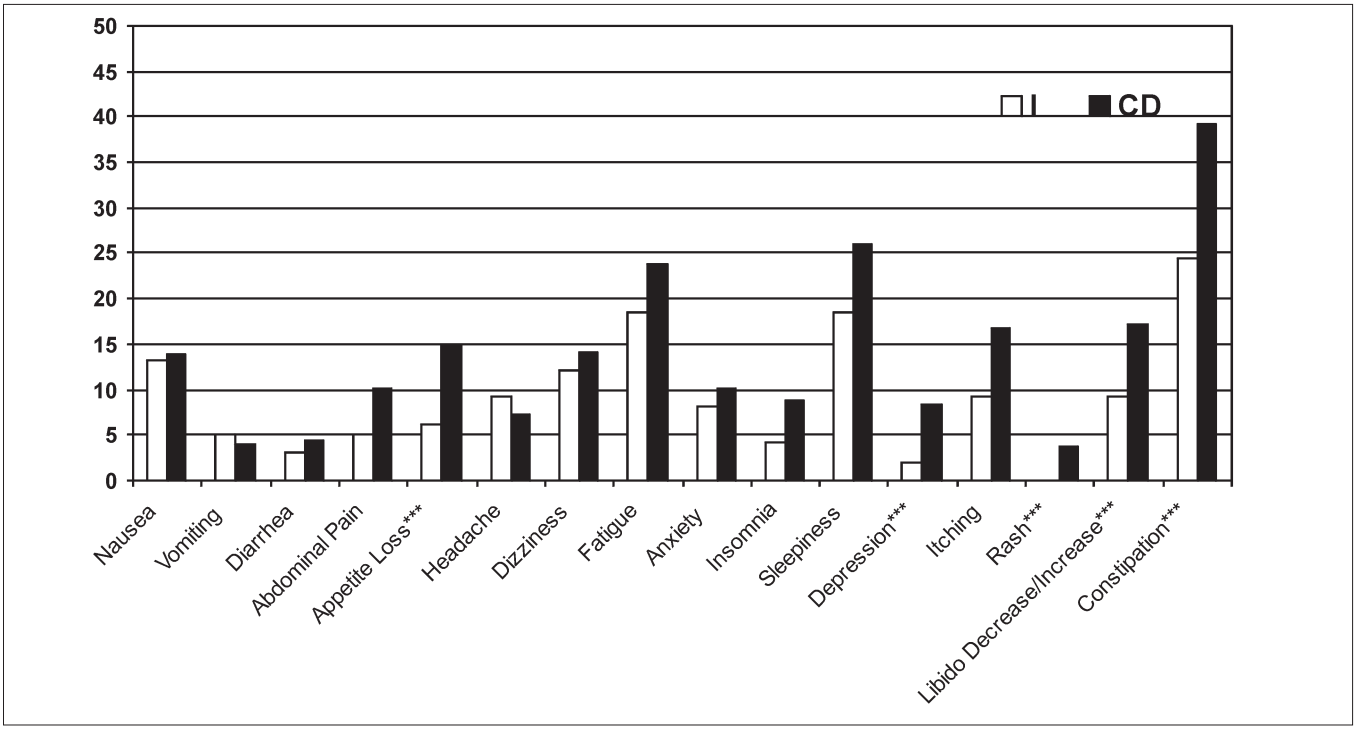

Figure 1: Percentage of subjects reporting side effects due to opioid treatment, by condition. I = intermittent opioids, CD = chronic daily opioids (> three months). * Symptoms with a significant difference between conditions ($p < 0.05$).**

continuous variables and Spearman correlations for categorical variables. Age and gender were retained in the final model for purposes of statistical control for these demographic covariates.

RESULTS

Descriptive statistics

The demographic characteristics of the study sample are detailed in Table 1. As one can see, 30 percent of the sample is male and 22 percent is African American. Other ethnic groups comprised less than 1 percent of the sample, with the next highest category being Native American (0.8 percent). Only 43 percent were currently married, and 20 percent were never married. Thirteen percent of the 889 subjects receiving opioids intermittently or daily met criteria for alcohol or drug dependence.

Table 2 includes relevant information regarding the opioids used by the study population. The most frequently prescribed opioids were the oxycodone family of medications, with nearly half the sample on an oxycodone-based preparation. The second most common were hydrocodones (vicodin and lortabs were the most common preparations). Morphine preparations were third. Prescription methadone was being used by 6.9 percent of the sample for pain control. Propoxyphene continues to be used, with 6 percent of the sample on this medication. The total daily dose in the sample was under 100 mg/day.

Table 3 lists the pain diagnoses for which subjects were being treated. One of the primary challenges in the study was assigning a primary pain diagnosis for each subject. Patient perception and medical records did not always agree, and in some cases it was difficult to find a primary diagnosis in the record. As noted, arthritis and chronic lower back pain were the diagnosis for nearly half the subjects. The next most common diagnoses were migraine headache, trauma, neuropathy, and fibromyalgia.

Means comparisons

Adverse medication effects. Figure 1 reports the frequency of common adverse effects. Constipation was reported as a side effect by 39 percent of the sample on daily opioids. The next most common side effects were fatigue, sleep problems, and loss of appetite. The frequency of adverse effects was much higher in the daily opioid group than in the intermittent medication group. The difference between groups in the overall number of adverse effects experienced also attained statistical significance ($t^{133.6} = -3.047$, $p = 0.003$, equal variances not assumed). While there are multiple other causes for these adverse effects in the sample (e.g. uncontrolled pain, other medications, other chronic medical disorders, lack of exercise) the frequency suggests physicians may want to ask about the effects when using chronic opioids. Six subjects who reported taking opioid medications did not provide information on the adverse

Table 5. Final model of MOS-MHI cognitive functioning score on significant covariates (N = 889)			
	Standardized coefficients β	**t**	**Sig.**
Age in years	-0.06258	-2.2308	0.02594
Gender	0.03568	1.2599	0.20802
ASI Psychiatric Composite	-0.5084	-17.874	< 0.00001
NDS score	-0.1206	-4.2366	< 0.00001
Worst pain level	-0.1015	-3.5637	0.00039

effects they were experiencing and were excluded from this analysis.

Cognitive function

Table 4 compares mean MOS-MHI cognitive functioning scores with 95 percent confidence intervals for the differences between means for the groups in the study and for a general clinical population in prior research.[25] Data on individuals with CNMP taking no opioids are from the current study. The subjects not taking opioids (n = 115) did not complete questionnaires regarding potential opioid adverse effects or opioid dosing. The mean difference in MOS-MHI cognitive functioning score between the overall study population and the general population achieved statistical significance ($\Delta \bar{x}$ 95 percent CI = 9.28, 13.76). Confidence intervals for the differences between the study groups, however, all include 0, and thus do not achieve statistical significance.

Regression modeling

The final model attained via stepwise regression is summarized in Table 5. In addition to the variables listed in Table 5, covariates achieving significance on initial bivariate analysis included monthly income ($p < 0.001$), methadone X dose interaction ($p = 0.022$), and the "least pain" ($p < 0.001$) and "average pain" ($p < 0.001$) measures on the PI survey. The significance of each of these measures, however, disappeared during the course of stepwise regression when covariates were added and partial F-testing performed. The "worst pain" measure provided the greatest statistical significance and the largest effect size of the three pain measures. Formation of a pain index combining the three measures did not improve significance or effect size. The adjusted R-squared for the final model was 0.316.

The final model indicated no significant effect for opioid formulation or dose upon MOS-MHI cognitive functioning score when important covariates were controlled. Though significance was initially observed for a methadone X dose interaction term ($p = 0.022$), the effect size was minimal ($r = -0.077$), and significance disappeared when important covariates were controlled. The presence of a DSM-IV substance-related disorder also failed to achieve statistically significant predictive value for cognitive dysfunction ($p = 0.10$).

DISCUSSION

This paper presents new information on the relationship of opioids to adverse medication effects and cognitive dysfunction in a primary care sample. Chronic daily users of opioid analgesics experienced more medication-associated adverse effects (constipation, depression, sexual dysfunction, rash, and appetite loss) than individuals taking opioids intermittently. This is consistent with the results of previous short-term randomized trials of opioid analgesics in subjects with CNMP.[20-23]

The overall study sample suffered from a greater degree of cognitive dysfunction than general clinical populations.[25] However, we found no significant difference in cognitive function based upon the frequency of opioid use or daily opioid dose. Mental health and stress measures were of greater predictive value. Psychiatric severity accounted for over half of the variation in cognitive function and was followed distantly by neighborhood disorder and pain severity. This finding is consistent with previous studies failing to uncover significant cognitive impairment when daily opioid doses are stable over the long term.[13-15]

With a small negative effect for increasing age ($\beta = -0.06$, $p = 0.026$) on cognitive function, our findings are also consistent with research indicating a potential for some impairment among older individuals with CNMP taking chronic daily opioids.[17,18]

The current study was nonrandomized and cross-sectional. Thus, inferences regarding causality must be made with caution. Unmeasured factors that predate the subjects' pain diagnoses and psychiatric comorbidities may

explain the predictive value of mental health and stress measures for cognitive dysfunction. Associations certainly provide a strong argument, however, for clinical follow-up and concurrent management of these psychosocial issues when managing patients with CNMP.

Strengths of the study include a large sample from a primary care population with prevalent painful conditions and the measurement of and control for numerous potentially important covariates.

These findings present several implications for clinical practice in the primary care management of CNMP. First, adverse effects of long-term opioids are common and should be actively monitored and managed. Primary among these are constipation, depression, sexual dysfunction, loss of appetite, and rash. An appropriate bowel regimen should be routinely recommended to patients on chronic daily opioid analgesics. Patients with CNMP should be routinely assessed for the presence of depression, and appropriate pharmacotherapy and consultation should be arranged. Providers should also assess for sexual dysfunction and initiate an appropriate evaluation. Potential causes include diabetes, atherosclerotic cardiovascular disease, medications (such as antihypertensives and antidepressants), smoking, and psychological causes.[53-55] The presence of decreased libido warrants laboratory evaluation, including measurements of thyroid-stimulating hormone, prolactin, lipids, testosterone, and hemoglobin A1C.

Second, inadequately controlled pain may be of greater concern than opioid prescription when considering the potential impact on cognitive function. Titration of opioid dosing, however, may require greater care in older individuals (over age 60) to reduce what may be an increased risk for impairment, albeit an increase of apparently small magnitude.

This study also confirms the strong associations between psychological well-being and poorly controlled pain. Depression was particularly common in the sample, and psychiatric morbidity was strongly associated with decrements in cognitive function. Additionally, significant association was discovered for community-level stress and cognitive dysfunction. These findings point toward the importance of psychosocial factors in the well-being of patients with CNMP. Clinicians should carefully assess their CNMP patients for psychiatric comorbidity and initiate appropriate management, consultation, and ancillary care.

Randall T. Brown, MD, Assistant Professor, University of Wisconsin, Madison Medical School, Department of Family Medicine, Madison, Wisconsin.
Megan Zuelsdorff, BS, Research Specialist, University of Wisconsin, Madison Medical School, Department of Family Medicine, Madison, Wisconsin.
Michael Fleming, MD, MPH, Professor, University of Wisconsin, Madison Medical School, Department of Family Medicine, Madison, Wisconsin.

REFERENCES

1. Brookoff D: Chronic pain: A new disease? *Hosp Pract (Hosp Ed).* 2000; 7: 1-18.
2. Christo PJ: Opioid effectiveness and side effects in chronic pain. *Anes Clin North Am.* 2003; 21 (December): 699-713.
3. Collett BJ: Chronic opioid therapy for non-cancer pain. *Br J Anaesth.* 2001; 87 (July): 133-143.
4. Evans P: Opioids for chronic musculoskeletal pain. In: Kalso E, McQuay H, Wiesenfeld-Hallin Z (eds.): *Opioid Sensitivity of Chronic Non-Cancer Pain*: IASP Press, 1999.
5. Graven S, De Vet H, van Kleefe M, et al.: Opioids in chronic non-malignant pain: A criteria based review of the literature. Paper presented at: Ninth World Congress on Pain, Progress in Pain Research and Management, 2000.
6. Marcus DA: Treatment of nonmalignant chronic pain. *Am Fam Physician.* 2000; 61: 1331-1338.
7. McCarberg BH, Barkin RL: Long-acting opioids for chronic pain: Pharmacotherapeutic opportunities to enhance compliance, quality of life, and analgesia. *Am J Ther.* 2001; 8 (May-June): 181-186.
8. Bannwarth B: Risk-benefit assessment of opioids in chronic noncancer pain. *Drug Saf.* 1999; 21 (October): 283-296.
9. Coniam S: Prescribing opioids for chronic pain in non-malignant disease. Paper presented at the Edinburgh Symposium on Pain Control and Medical Education, London, 1989.
10. Potter M, Schafer S, Gonzalez-Mendez E, et al.: Opioids for chronic nonmalignant pain. Attitudes and practices of primary care physicians in the UCSF/Stanford Collaborative Research Network. University of California, San Francisco. *J Fam Pract.* 2001; 50: 145-151.
11. Reid MC, Engles-Horton LL, Weber MB, et al.: Use of opioid medications for chronic noncancer pain syndromes in primary care. *J Gen Intern Med.* 2002; 17: 173-179.
12. Reisine T, Pasternak G: Opioid analgesics and antagonists. In: Hardman J, Limbird L (eds.): *Goodman & Gilman's The Pharmacologic Basis of Therapeutics, 9th ed.* New York: McGraw-Hill, 1996.
13. Bruera E, Macmillan K, Hanson J, et al.: The cognitive effects of the administration of narcotic analgesics in patients with cancer pain. *Pain.* 1989; 39: 13-16.
14. Sjogren P, Olsen AK, Thomsen AB, et al.: Neuropsychological performance in cancer patients: The role of oral opioids, pain and performance status. *Pain.* 2000; 86: 237-245.
15. Sjogren P, Thomsen AB, Olsen AK: Impaired neuropsychological performance in chronic nonmalignant pain patients receiving long-term oral opioid therapy. *J Pain Symptom Manage.* 2000; 19: 100-108.
16. Byas-Smith MG, Chapman SL, Reed B, et al.: The effect of opioids on driving and psychomotor performance in patients with chronic pain. *Clin J Pain.* 2005; 21: 345-352.
17. Cumming RG: Epidemiology of medication-related falls and fractures in the elderly. *Drugs Aging.* 1998; 12: 43-53.
18. Shorr RI, Griffin MR, Daugherty JR, et al.: Opioid analgesics and the risk of hip fracture in the elderly: Codeine and propoxyphene. *J Gerontol.* 1992; 47: M111-M115.
19. Vainio A, Ollila J, Matikainen E, et al.: Driving ability in cancer patients receiving long-term morphine analgesia. *Lancet.* 1995; 346: 667-670.
20. Arkinstall W, Sandler A, Goughnour B, et al.: Efficacy of controlled-release codeine in chronic non-malignant pain: A randomized, placebo-controlled clinical trial. *Pain.* 1995; 62: 169-178.
21. Dhaliwal HS, Sloan P, Arkinstall WW, et al.: Randomized evaluation of controlled-release codeine and placebo in chronic cancer pain. *J Pain Symptom Manage.* 1995; 10: 612-623.

22. Peloso PM, Bellamy N, Bensen W, et al.: Double blind randomized placebo control trial of controlled release codeine in the treatment of osteoarthritis of the hip or knee. *J Rheumatol.* 2000; 27: 764-771.
23. Peloso PM, Fortin L, Beaulieu A, et al.: Analgesic efficacy and safety of tramadol/acetaminophen combination tablets (Ultracet) in treatment of chronic low back pain: A multicenter, outpatient, randomized, double blind, placebo controlled trial.[see comment]. *J Rheumatol.* 2004; 31: 2454-2463.
24. Fleming MF, Mundt MP, Balousek S, et al.: Chronic pain, addiction and opioids in a primary care sample; Submitted to *JAMA.* September 2005.
25. Stewart A, Ware J, Sherbourne C, et al.: Psychological distress/well-being and cognitive functioning measures. In: Stewart A, Ware J (eds.): *Measuring Functioning and Well-Being: The Medical Outcomes Study Approach.* Durham, NC: Duke University Free Press, 1992.
26. Miele GM, Carpenter KM, Cockerham MS, et al.: Substance Dependence Severity Scale: Reliability and validity for ICD-10 substance use disorders. *Addict Behav.* 2001; 26: 603-612.
27. Miele GM, Carpenter KM, Smith Cockerham M, et al.: Concurrent and predictive validity of the Substance Dependence Severity Scale (SDSS). *Drug Alcohol Depend.* 2000; 59: 77-88.
28. Miele GM, Carpenter KM, Smith Cockerham M, et al.: Substance Dependence Severity Scale (SDSS): Reliability and validity of a clinician-administered interview for DSM-IV substance use disorders. *Drug Alcohol Depend.* 2000; 59: 63-75.
29. Leonhard C, Mulvey K, Gastfriend D, et al.: The Addiction Severity Index: A field study of internal consistency and validity. *J Subst Abuse Treat.* 2000; 18: 129-135.
30. McLellan AT, Kushner H, Metzger D, et al.: The Fifth Edition of the Addiction Severity Index. *Journal of Substance Abuse Treatment.* 1992; 9: 199-213.
31. Ross CE, Mirowsky J: Neighborhood disadvantage, disorder, and health. *J Health Soc Behav.* 2001; 42: 258-276.
32. Adams NJ, Plane MB, Fleming MF, et al.: Opioids and the treatment of chronic pain in a primary care sample. *J Pain Symptom Manage.* 2001; 22: 791-796.
33. Rabkin JG, Markowitz JS, Ocepek-Welikson K, et al.: General versus systematic inquiry about emergent clinical events with SAFTEE: implications for clinical research.[see comment]. *J Clin Psychopharmacol.* 1992; 12: 3-10.
34. Jacobson AF, Goldstein BJ, Dominguez RA, et al.: Interrater agreement and reliability measures of SAFTEE: General inquiry vs. systematic inquiry. *Psychopharmacol Bull.* 1987; 23: 97-101.
35. Guy W, Wilson WH, Brooking B, et al.: Intra-interrater reliability of SAFTEE using videotape interviews and clinical trial data. *Psychopharmacol Bull.* 1987; 23: 93-96.
36. Markowitz JS, Rabkin JG, Stewart J, et al.: Validity assessment of SAFTEE: A preliminary report. *Psychopharmacol Bull.* 1987; 23: 102-105.
37. Guy W, Wilson WH, Brooking B, et al.: Reliability and validity of SAFTEE: Preliminar analyses. *Psychopharmacol Bull.* 1986; 22: 397-401.
38. Rabkin JG, Markowitz JS: Side effect assessment with SAFTEE: Pilot study of the instrument. *Psychopharmacol Bull.* 1986; 22: 389-396.
39. Jacobson AF, Goldstein BJ, Dominguez RA, et al.: Interrater agreement and intraclass reliability measures of SAFTEE in psychopharmacologic clinical trials. *Psychopharmacol Bull.* 1986; 22: 382-388.
40. Levine J, Schooler NR: SAFTEE: A technique for the systematic assessment of side effects in clinical trials. *Psychopharmacol Bull.* 1986; 22: 343-381.
41. American Pain Society: *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 4th ed.* Glenview, IL, 1999.
42. Dahl J: Personal communication. 2005.
43. Fleming M: Personal communication. 2005.
44. Krause C: Personal communication. 2005.
45. Foley KM, Houde RW: Methadone in cancer pain management: Individualize dose and titrate to effect. [comment]. *J Clin Oncol.* 1998; 16: 3213-3215.
46. Pereira J, Lawlor P, Vigano A, et al.: Equianalgesic dose ratios for opioids. A critical review and proposals for long-term dosing. *J Pain Symptom Manage.* 2001; 22: 672-687.
47. American Pain Society: *Principles of Analgesic Use in the Treatment of Acute Pain and Cancer Pain, 5th ed.* Glenview, IL, 2003.
48. Bruera E, Belzile M, Pituskin E, et al.: Randomized, double-blind, cross-over trial comparing safety and efficacy of oral controlled-release oxycodone with controlled-release morphine in patients with cancer pain.[see comment]. *J Clin Oncol.* 1998; 16: 3222-3229.
49. Watanabe S, Pereira J, Hanson J, et al.: Fentanyl by continuous subcutaneous infusion for the management of cancer pain: A retrospective study. *J Pain Symptom Manage.* 1998; 16: 323-326.
50. Bruera E, Pereira J, Watanabe S, et al.: Opioid rotation in patients with cancer pain. A retrospective comparison of dose ratios between methadone, hydromorphone, and morphine. *Cancer.* 1996; 78: 852-857.
51. Ballenger J: Benzodiazepines. In Schatzberg A, Nemeroff C (eds.): *The American Psychiatric Press Textbook of Psychopharmacology, 2nd Edition.* Washington DC: American Psychiatric Press, 1998.
52. Charney D, Mihic J, Harris R: Hypnotics and Sedatives. In Hardman J, Limbird L (eds.): *Goodman & Gilman's The Pharmacological Basis of Therapeutics, 10th ed.* New York: McGraw-Hill, 2001.
53. Bodie J, Lewis J, Schow D, et al.: Laboratory evaluations of erectile dysfunction: An evidence based approach. *J Urol.* 2003; 169: 2262-2264.
54. Johnson A, III, Jarow J: Is routine endocrine testing of impotent men necessary? *J Urol.* 1992; 147: 1542.
55. Lue TF. Male sexual dysfunction—how little do we know? *J Urol.* 2003; 169: 2265.