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Time-Scheduled versus Pain-Contingent Opioid Dosing in Chronic Opioid Therapy

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Abstract

Some expert guidelines recommend time-scheduled opioid dosing over pain-contingent dosing for patients receiving chronic opioid therapy (COT). The premise is that time-scheduled dosing results in more stable opioid blood levels and better pain relief, fewer side effects, less reinforcement of pain behaviors, and lower addiction risk. We report results of a survey of 1781 patients receiving COT for chronic non-cancer pain, in which 967 reported time-scheduled opioid dosing only and 325 reported pain-contingent opioid dosing only. Opioid-related problems and concerns were assessed with the Prescribed Opioids Difficulties Scale. We hypothesized that respondents using time-scheduled opioid dosing would report significantly fewer problems and concerns than those using pain-contingent dosing. Patients receiving time-scheduled dosing received substantially higher average daily opioid doses than those using pain-contingent dosing (97.2 vs. 37.2 milligrams average daily dose morphine equivalents, $p < .0001$). Contrary to expectation, time-scheduled opioid dosing was associated with higher levels of patient opioid control concerns than pain-contingent dosing (6.2 vs. 4.8, $p = .008$), after adjusting for patient and drug regimen differences. Opioid-related psychosocial problems were somewhat greater among patients using time-scheduled dosing, but this difference was non-significant after controlling for patient and drug regimen differences (5.9 versus 5.0, $p = .14$). Time-scheduled dosing typically involved higher dosage levels and was associated with higher levels of patient concerns about opioid use. Controlled comparative effectiveness research is needed to assess benefits and risks of time-scheduled opioid dosing relative to pain-contingent opioid dosing among COT patients in ambulatory care.

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Keywords

Opioids; Chronic pain; Chronic opioid therapy; Adverse effects

Expert guidelines of the Canadian Pain Society on use of opioid analgesics for chronic non-cancer pain (CNCP) [9] state, “When prescribing an opioid analgesic for around-the-clock pain, it should also be dosed around-the-clock in a pharmacologically appropriate, time-contingent dosing schedule.” Guidelines for managing persistent pain of the American Geriatric Society also recommend time-scheduled opioid dosing [1]. Possible advantages of time-scheduled dosing cited by these guidelines include: more stable opioid blood levels, increased tolerance to side-effects, lower addiction risk, reduced reinforcement of pain behaviors, and improved pain control. In contrast, chronic opioid therapy (COT) guidelines of the American Pain Society [5] do not make a recommendation regarding either pain-contingent (as-needed) or time-scheduled dosing.

Empirical research on time-scheduled opioid dosing has largely concerned postoperative pain management. A structured review on time-scheduled opioid dosing for post-operative pain management [12] concluded that there is “sparse empirical work warranting endorsement of this dosing regimen.” Subsequently, several trials of time-scheduled opioid dosing reported benefits relative to pain-contingent dosing in postoperative pain management [6,7,11,19]. Whether findings for time-scheduled opioid dosing in post-operative pain management translate to COT in ambulatory care settings has not been examined.

Lack of evidence regarding the effectiveness of time-scheduled opioid dosing in ambulatory care is particularly salient given the dramatic increase in use of COT in community practice settings [3,17]. While COT is advocated by expert guidelines [1,5,9], the supporting evidence is limited to short-term trials characterized by guideline reviews as providing low quality evidence [1,5]. Opioid dosing regimens may influence COT benefits and risks, so there is a need to understand the clinical implications of differences in how patients administer opioid analgesics for chronic non-cancer pain. Although time-scheduled opioid dosing has been recommended in several guidelines, time-scheduled dosing could possibly result in more frequent opioid administration, higher cumulative opioid dose and thereby greater potential for inducing tolerance, hyperalgesia and other dose-related adverse effects.

We used data from a large survey of COT recipients to assess whether there were differences in problems attributed to use of opioids depending on method of administration—time-scheduled versus pain-contingent. We hypothesized that CNCP patients using only time-scheduled opioid dosing would report lower levels of opioid-related psychosocial problems and would be less worried about their ability to control use of opioid medications. CNCP patients receiving COT who employed pain-contingent versus time-scheduled opioid dosing were compared on measures of pain status, opioid use (e.g. dose), perceived helpfulness of opioid analgesics, and patient-reported problems and concerns attributed to use of opioids.

Methods

Setting and participants

The NIDA-funded CONSORT study (CONsortium to Study Opioid Risks and Trends) was initiated to study long-term use of opioids for non-cancer pain among adults age 18+ in Group Health Cooperative (located in Washington State) and Kaiser Permanente of Northern California [20]. These two health plans serve about four million persons--over one-

percent of the U.S. population. CONSORT research plans were reviewed and approved by the Institutional Review Boards of both health plans. Participants in the analyses reported here were COT patients who completed a telephone interview about opioid use.

Automated pharmacy and medical encounter data

Both health plans maintain automated pharmacy and medical encounter data for all covered services, including services provided directly by the health plans and services rendered by other providers who bill the health plans. The pharmacy files contain one record per drug dispensed including generic drug name, strength, directions for use, date dispensed, quantity dispensed, days supply, prescriber identification number, and National Drug Code. Kaiser Permanente and Group Health pharmacies are conveniently located in relation to clinics. Surveys at both health plans have consistently found that more than 90% of enrollees obtain almost all of their prescription medications through health plan pharmacies [15,16].

Opioid use variables

Based on electronic pharmacy data, descriptors of opioid use were estimated using methods described elsewhere [20]. Average daily dose was estimated by the total morphine equivalent dose (MED) during the 90 days prior to the interview date of each subject, divided by 90. Opioids were classified into two major groups: long-acting opioids and short-acting opioids. Subjects were classified as predominate users of either short- or long-acting opioids depending on which type had the larger total days supply in the 90 days prior to their interview date. That is, the total days supply of short-acting and long-acting opioids dispensed to each individual patient was determined, and each patient was classified as predominately using long-acting or short-acting opioids based on which medication class had the greatest days supply. In case of ties, the opioid type with the larger MED was chosen.

Eligibility and exclusion criteria

Health plan enrollees age 18 years or older were eligible if they had filled an opioid prescription within 30 days of the sample selection date, and had filled at least 10 opioid prescriptions and/or received at least 120 days supply in a one-year period prior to the sample selection date, with at least 90 days between the first and last opioid dispensing in that year. These criteria for COT have been shown to predict a high probability of sustained opioid use one year later [20]. Additional eligibility criteria included continuous enrollment in the health plan for at least one year prior to sampling. We excluded patients who had received a cancer diagnosis (except for non-melanoma skin cancer) in local cancer registries or who had two or more cancer diagnoses in automated visit records in the year prior to sampling.

Sampling

We selected patients for the survey using stratified sampling, selecting an equal number of patients within three dosage strata (1–49 milligrams, 50–99 milligrams, and 100+ milligrams, MED). This approach oversamples survey respondents receiving higher dosage levels because most COT patients receive relatively low dosage levels [3]. For data analysis, observations were weighted by the inverse of the probability of selection to obtain estimates representative of the population of long-term opioid users from which the sample was selected.

Field work

At Group Health, interviews began in June 2008 and ended in November 2008. At Kaiser Permanente, interviews began in January 2009 and ended in October 2009. Potentially

eligible patients were mailed a letter explaining the study. At Group Health, a two dollar bill was included as a pre-incentive, while at Kaiser Permanente a \$5 gift card was included for a national retail store. Experienced lay survey interviewers working for the survey research centers in the collaborating health plan research centers then called potential participants. Interviews were conducted using Computer-Assisted Telephone Interview technology. Patients were asked to participate in a 25–30 minute telephone interview and to allow the study to access their electronic health care data from the time they enrolled in the health plan until three years after the date of the interview. Patients who completed the interview were mailed a \$20 cash reimbursement at Group Health and a \$50 gift card reimbursement at Kaiser Permanente Northern California. The differential in incentive payments was based on prior experience in the two populations suggesting incentive payments needed to achieve an acceptable response rate.

Study measures

Self-report information on opioid self-administration was obtained to augment information from the health plan electronic pharmacy data.

Opioid use—Whether patients used opioids on a pain-contingent (as-needed) or a time-scheduled basis was determined by self-report. Participants were asked whether they agreed or disagreed with the following two statements: 1) “I usually take opiate pain medicines at about the same time each day, on a regular schedule, no matter what my pain is like”; and, 2) “I usually wait until my pain gets really bad before taking an opiate pain medicine”. Participants who agreed with the first statement were classified as employing time-scheduled opioid use, while those who agreed with the second statement were classified as using pain-contingent opioid use. Some agreed with both statements and others agreed with neither. We report descriptive data for all four of these groups, but the main analyses in this paper include persons who endorsed only time-scheduled or only pain-contingent opioid use, but not both. Patients were also asked on how many days they used opioids in the prior two weeks, and how many times per day they took these medications on days they used opioid medications.

Problems and concerns related to opioid use—Patient problems and concerns attributed to opioid use were measured using the Prescribed Opioid Difficulties Scale (PODS) [2,18]. PODS has one subscale measuring psychosocial problems attributed to opioids and a second sub-scale measuring opioid control concerns. The PODS scales focus on recent problems and concerns related to opioid use from the patient’s perspective (in the past two weeks for common problems, in the past month or year for less common problems). The Problems sub-scale includes the following 8 difficulties attributed to opioid use: loss of interest in usual activities; trouble concentrating or remembering; feeling slowed down, sluggish or sedated; feeling depressed, down or anxious; interference with work, family or social responsibilities; difficulty thinking clearly; feeling sleepy or less alert when driving or doing something where you needed to be alert; and a rating of the bothersomeness of side effects. The Concerns sub-scale includes the following 7 difficulties: preoccupation with use of opioids; feeling unable to control use of opioids; needing a higher dose to get the same effect; worry about being dependent on or addicted to opioids; wanting to stop or cut down use of opioids; opioid-related problems with family, friends or co-workers; and, patient report that family or friends perceived an opioid dependence or addiction problem. Patients were also asked to rate how helpful opioids were for pain control [2]. The validity and clinical relevance of the PODS sub-scales has been established, as reported elsewhere [2,18].

Pain intensity was measured using a 0–10 average pain intensity rating scale from the Graded Chronic Pain Scale [21,22]. A *Pain Impact Scale* [22] consisting of 11 yes-no items concerning effects of pain in the last two weeks (e.g., staying in bed more, avoiding jobs around the house, doing fewer social activities) was also included. The severity of depressive symptoms was measured with the 8 item version of the *Patient Health Questionnaire*, a validated and widely used self-report measure of depressive symptoms [10]. *Body mass index* (BMI) was calculated from self-reported weight and height. Chronic disease comorbidity was assessed using the Romano version of the *Charlson comorbidity score* [13].

Analyses

Only interviewees who reported having used opioid medications in the two weeks prior to the interview were included in the analyses reported here. In order to ensure that persons included in the analyses were experiencing daily or near-daily pain, analyses were limited to persons reporting pain on at least 155 days in the prior six months, corresponding to pain on at least 6 days per week. Analyses used SAS PROC SURVEYMEANS or PROC SURVEYREG software to account for the stratified random sampling approach, providing estimates for the population surveyed. These analyses weight respondents based on their probability of selection to obtain estimates representative of the population sampled. We used basic statistics (proportions, means and standard deviations) to describe patients in the population surveyed. Between group differences in proportions were tested using chi-square statistics. We examined the association between type of dosing (pain-contingent or time-scheduled) and PODS subscales using linear regression models to adjust for potential confounders. We used a hierarchy of models, sequentially adding relevant confounders. An initial model adjusted only for health plan. A second model adjusted for health plan, patient characteristics (age, gender, BMI, education), pain characteristics (average pain intensity, pain days) and opioid use variables (average daily opioid dose, predominant use of long-acting opioids, number of days in the prior two weeks opioids were used, and number of times per day opioids were used in the prior two weeks). A third model adjusted for the same variables as the second model and for pain impact score and for the Charlson comorbidity score. A final model added adjustment for PHQ-8 depression score and self-report history of alcohol or drug problems as well as all other variables included in the third model. PROC SURVEYREG was used to estimate confidence intervals and test statistics for the adjusted regression models taking the stratified random sampling approach into account.

RESULTS

Survey participation

At Group Health Cooperative (GHC), 2185 persons were sampled for the survey, among which 76 were ineligible. Among the 2109 eligible patients, interviews were completed with 1191. At Kaiser Permanente of Northern California (KPNC), 1605 persons were sampled for the survey, among which 109 were ineligible. Among the 1496 eligible patients, interviews were completed with 972. The total number of completed interviews was 2163, with an overall response rate of 60%. Because response rates differed between the two health plans (65% at KPNC vs. 57% at GHC), possibly due to the difference in incentive payments, we examined response rates by subject characteristics available at the time of sample selection. At both health plans, response rates were higher among persons over the age of 65 (68% at KPNC, 65% at GHC), but gender differences in response rates were small. At GHC, response rates did not differ appreciably by average daily opioid dose (58% for <50 mg. MED; 57% for 50 to <100 mg. MED; and 55% for 100+ mg. MED), while at KPNC response rates increased with average daily opioid dose (58% for <50 mg. MED; 66% for 50 to <100 mg. MED; and 71% for 100+ mg. MED).

Descriptive results

Among the 2163 survey respondents, analyses were restricted to persons who had used opioids in the prior two weeks and who reported daily or near daily pain over the prior six months, resulting in inclusion of 1781 (82%) of the survey respondents in the analytic sample. As shown in Table 1, the estimated percentage of patients with only pain-contingent opioid dosing was 25.6% (N=325), while the estimated percentage with only time-scheduled opioid dosing was 44.8% (N=967). About ten percent reported both pain-contingent and time-scheduled opioid dosing (N=180), and 20% reported neither pain-contingent nor time-scheduled opioid dosing (N=309), based on the questions asked in this survey.

Differences between patients with pain-contingent and time-scheduled opioid dosing

Patients with exclusively pain-contingent opioid dosing were, on average, younger and somewhat more likely to be female than patients reporting only time-scheduled opioid dosing (see first two columns of Table 1). These two groups did not differ in terms of educational attainment, mean body mass index, days with pain in the prior six months, depression score, or the percent using opioids for more than one pain condition. Patients reporting time-scheduled opioid dosing only were somewhat more likely to report a history of drug or alcohol problems, they used opioids on more days in the prior two weeks, and they reported use more times per day relative to patients reporting pain-contingent dosing only.

There were substantial differences in average daily opioid dose, with patients using solely pain-contingent opioid dosing receiving a mean of 37 mg. MED per day compared to a mean of 97 mg. MED per day for patients using only time-scheduled dosing (Table 1). The two groups did not differ in average pain intensity. Those using only time-scheduled opioid dosing were slightly more likely to rate opioids as very or extremely helpful, but this difference was not statistically significant. As might be expected, the percent receiving predominately long-acting opioids was substantially greater among persons with only time-scheduled opioid dosing than among those with only pain-contingent dosing (43% versus 11%). While patients classified as using time-schedule dosing were substantially more likely to be using long-acting opioids predominately, the majority of patients classified as using time-scheduled dosing were predominately using short-acting opioids. Survey participants with both time-scheduled and pain-contingent dosing had average daily opioid dose levels that fell between daily dose levels for those with time-scheduled dosing only and those with pain-contingent dosing only.

Opioid-related patient problems and concerns

Overall, patients with time-scheduled opioid dosing had somewhat higher levels of psychosocial problems attributed to opioids, as assessed by the Prescription Opioids Difficulties Scale, than patients with pain-contingent opioid dosing ($p=0.04$, row 1 of Table 2). This difference was not statistically significant in models controlling for covariates (rows 2, 3 and 4 of Table 2). Thus, the hypothesis that patients with time-scheduled dosing would have fewer psychosocial problems was not confirmed.

Contrary to hypothesis, patients with only time-scheduled opioid dosing had higher levels of opioid control concerns, as assessed by the Prescription Opioids Difficulties Scale, than patients with pain-contingent opioid dosing (row 1 of Table 3). This difference continued to be statistically significant after controlling for relevant covariates (rows 2, 3 and 4 of Table 3).

As shown in Table 4, the specific control concerns reported more often among patients using time-scheduled dosing were: 1) being preoccupied with opioids; 2) concern about inability

to control how much or how often opioids were used; 3) worry about dependence on or addiction to opioid pain medicines; and, 4) patient report that family or friends were concerned about dependence on or addiction to opioid pain medicines. Table 4 also compares psychosocial problems reported by patients using time-scheduled opioid dosing to those with pain-contingent dosing. Psychosocial problems attributed more often by patients using time-scheduled dosing were that: 1) opioids made it hard to think clearly; and, 2) opioids made the person sleepy or less alert when driving or operating machinery, or doing something requiring alertness. Table 4 also provides the percent of patients reporting opioid control concerns and psychosocial problems attributed to opioids for patients reporting both time-scheduled and pain-contingent opioid use, and for patients reporting neither. For control concerns and psychosocial problems that differed between time-scheduled and pain-contingent dosing, patients reporting both time-scheduled and pain-contingent opioid dosing tended to have levels of control concerns and psychosocial problems more similar to the time-scheduled dosing group, whereas those reporting neither tended to be more similar to the pain-contingent dosing group.

Discussion

This cross-sectional study found that patients receiving chronic opioid therapy who exclusively used time-scheduled opioid dosing received substantially higher average daily doses than patients who used only pain-contingent opioid dosing. These two groups reported comparable average pain intensity and depression levels, but patients with time-scheduled dosing were somewhat more likely to report a history of alcohol or drug problems (25% versus 16%). Based on expectations that time-scheduled dosing should provide more stable blood levels and analgesia, reduce addiction risks, yield fewer side effects, and be less likely to reinforce pain behaviors [9], we hypothesized that patients using opioids on a time-scheduled basis would report fewer psychosocial problems and opioid control concerns than patients with pain-contingent opioid dosing. Contrary to these hypotheses, patients using exclusively time-scheduled opioid dosing reported similar levels of psychosocial problems attributed to use of opioids and higher levels of opioid control concerns than did patients with pain-contingent opioid dosing, after controlling for patient, pain status, and opioid use variables. Patients using time-scheduled dosing reported being more preoccupied with opioid use, less able to control their opioid use, and were more worried about opioid dependence. They were also more likely to report that family or friends thought that they may be dependent on opioids. These unexpected findings suggest that patients who employ time-scheduled opioid dosing differ from those who use pain-contingent dosing, and/or that hypothesized benefits of time-scheduled opioid dosing may not be realized in clinical practice. Since patients using time-scheduled dosing were managed with much higher dosage levels, and more often used Schedule II extended release medications, it is possible that these differences increase patient concerns about opioid control. Since patients using time-scheduled opioid dosing were also more likely to report a history of alcohol or drug problems, observed differences may be partially explained by pre-existing differences in liability to drug dependence. This cross-sectional study cannot establish the reasons for observed differences. However, these unexpected results do suggest that assumptions about benefits of time-scheduled opioid dosing need to be tested in controlled studies.

It is not particularly surprising that patients using time-scheduled dosing received higher opioid doses than did patients with pain-contingent dosing. These patients took opioids on more days per week, more times per day, and were more likely to use higher potency Schedule II opioids. The differences in dosage levels between time-scheduled and pain-contingent dosing groups may have implications for COT risks, as opioid risks increase with dose [8,14,], although rates of emergency department visits may be higher for persons using short-acting opioids [4].

The cross-sectional data reported from this survey do not shed light on the comparative effectiveness of time-scheduled versus pain-contingent opioid dosing. Evaluation of comparative effectiveness requires a longitudinal design with either randomized assignment to dosing regimens or a valid quasi-experimental comparison. It is possible that higher levels of concerns about opioid use using time-scheduled opioid dosing were due to factors other than dosing regimen. For example, physicians might recommend time-scheduled dosing to patients perceived to have higher addiction risks. Randomized trials that have compared long-acting to short-acting opioids have not been designed to evaluate problems with opioid use in general, nor have they assessed differences between time-scheduled and pain-contingent administration in particular. A trial comparing time-scheduled and pain-contingent opioid use would entail design considerations that differ from conventional double-blind, placebo-controlled trials.

In addition to the limitations of a cross-sectional survey design, the response rates in this study were less than optimal and differed between the two health plans. Variables related to response rate (age, opioid dose, health plan) were controlled in multivariate analyses. Achieving high response rates among patients receiving COT is difficult. Despite assurances of protection of confidentiality and that no survey information would be communicated to health care providers or placed in the medical record, some participants may have been concerned that providing information could somehow jeopardize access to pain medications. Many patients using opioids long-term are significantly disabled. Functional disability is generally associated with lower response in health surveys. The evaluation of time-scheduled and pain-contingent opioid dosing was based on patient report, which may be subject to measurement error or bias. The questions used to evaluate time-scheduled and pain-contingent opioid use may not have been understood uniformly by respondents, potentially resulting in misclassification of opioid use pattern. Patients reporting time-scheduled dosing were somewhat more likely to have a history of drug or alcohol abuse, suggesting the possibility that physicians may be more likely to prescribe time-scheduled opioids to patients with a history of substance abuse problems. The large difference in predominate use of long-acting medications between the time-scheduled and pain-contingent dosing groups, as determined from electronic pharmacy records, supports the validity of the self-reported dosing classification. However, eleven percent of patients classified as using pain-contingent dosing were predominately using long-acting opioids, although these medications are normally prescribed for time-scheduled use. The reasons for the differences observed in this study cannot be definitively explained—more research on differences between time-scheduled and pain-contingent opioid dosing is clearly needed. In particular, the implications of the observation that patients using time-scheduled dosing received substantially higher opioid dosage levels deserves further investigation. The use of self-report scales to assess opioid-related problems is also a limitation. Further research assessing whether and how objective indicators of opioid-related problems (e.g. positive results on urine drug screening tests, receiving excess days supply of opioids) and physician assessments differ between patients using time-scheduled versus pain-contingent dosing is needed. Objective indicators of opioid-related problems and physician assessments might yield different results.

Summary

In conclusion, time-scheduled dosing was associated with substantially higher average daily opioid doses than pain-contingent dosing, although pain intensity levels in the two groups were similar. Contrary to expectation, time-scheduled opioid dosing was associated with higher levels of patient opioid control concerns and similar levels of psychosocial problems attributed to opioids. This research suggests the need for prospective or experimental

comparative effectiveness research assessing the relative benefits and risks of time-scheduled versus pain-contingent opioid dosing.

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Table 1

Weighted estimates of characteristics of persons using opioids long-term for chronic non-cancer pain by time-scheduled and pain-contingent dosing status. Limited to persons with 155+ days of pain in the prior 6 months.

Variable	A. Pain- contingent dosing only	B. Time- scheduled dosing only	p-value A vs. B	Both A and B	Neither A nor B	All persons
Sample size (unweighted) (Weighted percent)	325 (25.6 %)	967 (44.8 %)		180 (9.5 %)	309 (20.1%)	1781 (100.0 %)
Female (%)	67.7 %	59.5 %	p=.053	49.7 %	71.4 %	63.1 %
Mean age	53.6	56.6	p=.0006	54.5	55.5	55.6
Body Mass Index	32.1	30.9	p=0.10	31.3	29.6	31.0
Some college education (%)	58.7 %	63.9 %	p=.24	51.8 %	59.3 %	60.5 %
Ever had a drug or alcohol problem (%)	16.9 %	25.4%	p=0.02	24.4%	15.1 %	21.0 %
Depression (PHQ-8)	9.4	9.3	p=.0.89	8.8	8.9	9.2
Mean days with pain in prior 6 months	179.5	179.7	p=.44	179.8	179.2	179.5
Using opioids for more than one pain condition (%)	67.1 %	66.1 %	p=.81	59.3 %	62.0 %	64.9 %
Mean number of days used opioids in the prior two weeks	11.7	13.9	p<.0001	13.5	12.5	13.0
Mean number of times per day used opioids	2.5	3.1	p<.0001	2.5	2.9	2.9
Mean opioid dose prior 3 months (SD)	37.2 (71.2)	97.2 (148.3)	p<.0001	74.8 (133.8)	60.9 (174.4)	71.9 (142.8)
Opioid dose level						
< 20 mg/day	46.3 %	18.2 %		31.6 %	38.1 %	30.6 %
20 to < 50 mg/day	36.5 %	32.6 %		35.9 %	35.6 %	35.6 %
50 to <120 mg/day	12.1 %	29.0 %		19.3 %	15.5 %	15.5 %
120+ mg/day	5.2 %	20.3 %	p<.0001	13.1 %	10.9 %	13.8 %
Average pain intensity	5.9	5.8	p=.43	5.9	5.8	5.8
Opioids rated as very/extremely helpful (%)	51.1 %	56.9 %	p=.20	64.8 %	60.7 %	56.9 %

Variable	A. Pain- contingent dosing only	B. Time- scheduled dosing only	p-value A vs. B	Both A and B	Neither A nor B	All persons
Predominate use of long- acting opioids in the prior 3 months (%)	11.4 %	43.2 %	p<.0001	31.4 %	14.8 %	28.3 %

Table 2

Psychosocial problems attributed to opioids (Prescribed Opioids Difficulties Scale): Mean score¹ and standard error of the mean comparing persons with pain-contingent versus time-scheduled opioid dosing among persons with chronic pain. Least square means adjusted for indicated variables.

Variables included in adjustment model	A: Pain-contingent dosing only	B: Time-scheduled dosing only	p-value
1. Unadjusted (except for health plan)	4.2 (0.41)	5.4 (0.34)	0.04
2. Age, Gender, BMI, Education, Average Pain, Pain Days, Average Daily Opioid Dose, Predominant Use of Long-acting Opioids, number of days used opioids in past 2 weeks, number of times per day used opioids in prior two weeks	5.2 (0.46)	5.5 (0.36)	0.71
3. Same covariates as Model 2 plus Pain Impact Score, Charlson Comorbidity Score	5.2 (0.45)	5.8 (0.36)	0.33
4. Same covariates as Model 3 plus Depression (PHQ-8), self-reported history of a drug/alcohol problem	5.1 (0.43)	5.9 (0.35)	0.14

¹ A higher score indicates that patients attributed more psychosocial problems to their use of opioid pain medications.

Table 3

Patient control concerns¹ about opioids, sub-scale (Prescribed Opioids Difficulties Scale): Mean score and standard error of the mean comparing persons with pain-contingent versus time-scheduled opioid dosing among persons with chronic pain. Least square means adjusted for indicated variables.

Variables included in adjustment model	A: Pain-contingent dosing only	B: Time-scheduled dosing only	p-value
1. Unadjusted (except for health plan)	4.0 (0.29)	5.8 (0.32)	<.0001
2. Age, Gender, BMI, Education, Average Pain, Pain Days, Average Daily Opioid Dose, Predominant Use of Long-acting Opioids, number of days used opioids in the past two weeks, number of times per day used opioids in the past two weeks	4.9 (0.36)	5.9 (0.33)	0.05
3. Same covariates as Model 2 plus Pain Impact Score, Charlson Comorbidity Score	4.6 (0.34)	6.2 (0.33)	.01
4. Same covariates as Model 3 plus Depression (PHQ-8), self-reported history of a drug/alcohol problem	4.8 (0.31)	6.2 (0.32)	.008

¹ A higher score indicates that patients reported more control concerns related to use of opioid pain medications.

Table 4

Specific problems and concerns attributed to opioids by patients.

	A: Pain- contingent dosing only	B: Time- scheduled dosing only	p-value (A vs. B)	Both A and B	Neither A nor B
Opioid control concerns					
Preoccupied with opioids	4.4 %	8.7 %	0.03	11.9 %	5.1 %
Could not control opioid use	1.6 %	6.1 %	0.0002	6.5 %	2.0 %
Need higher opioid dose for same effect	25.6 %	28.3 %	0.51	22.5 %	29.9 %
Worry about opioid dependence	15.5 %	35.9 %	<0.0001	33.6 %	23.2 %
Wanted to stop or cut down	43.2 %	43.8 %	0.89	39.8 %	31.4 %
Problems with family-friends- coworkers	3.6 %	5.4 %	0.20	7.8 %	3.4 %
Family/friends thought might be dependent	4.6 %	17.6 %	<0.0001	12.8 %	9.6 %
Psychosocial problems attributed by patient to use of opioids					
Loss of interest in usual activities	8.5 %	6.9 %	0.45	15.9 %	5.6 %
Trouble concentrating or remembering	12.3 %	17.9 %	0.07	14.2 %	7.4 %
Slowed down, sluggish, sedated	17.2 %	18.3 %	0.75	16.2 %	14.4 %
Depressed or anxious	6.5 %	8.9 %	0.27	10.1 %	5.6 %
Interference work-family-social activities	17.8 %	21.9 %	0.22	17.7 %	13.5 %
Hard to think clearly	9.0 %	19.5 %	0.0004	11.2 %	9.3 %
Less alert driving or when needed	19.6 %	30.2 %	0.004	23.8 %	19.2 %
Bothersome side effects	27.4 %	34.1 %	0.10	21.2 %	23.5 %

Patients using time-scheduled dosing received higher opioid dosage than patients using pain-contingent dosing. Time-scheduled dosing was associated with greater opioid control concerns than pain-contingent dosing.