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## Depression and Ambivalence toward Chronic Opioid Therapy for Chronic Non-cancer Pain

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### Abstract

**Objectives**—Chronic opioid therapy (COT) for chronic non-cancer pain (CNCPP) is characterized by both high rates of patient-initiated discontinuation and by perceived helpfulness among those who sustain opioid use. This study examines predictors of the desire to cut down or stop opioid therapy among patients receiving COT who report that opioids are helpful for relieving pain.

**Methods**—We conducted a cross-sectional survey of 1737 selected patients receiving COT for CNCPP who perceived opioids to be helpful in relieving their pain. Ambivalence about opioid use was assessed by agreement/disagreement with a statement indicating that they would like to stop or cut down use of prescribed opioid medications. Depression was measured with the 8-item Patient Health Questionnaire.

**Results**—A high percentage (43.3%) of survey respondents who found opioids helpful also reported the desire to stop or cut down opioids. Half of these patients reporting the desire to stop or cut down were clinically depressed, compared to a third of those not wanting to stop or cut down, a highly significant difference after controlling for covariates ( $p < 0.0001$ ). The group wanting to stop or cut down opioid use also reported significantly higher levels of opioid-related psychosocial problems and opioid control concerns.

**Discussion**—There are high rates of ambivalence about opioid use among COT recipients who consider opioids helpful for pain relief. Depressed patients are more likely to be ambivalent about use of prescribed opioids. Eliciting patient ambivalence may be helpful in patients who are not benefiting from long-term opioid use as an initial step towards consideration of discontinuation.

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**Conflicts of Interest** There are no conflicts of interest.

## Keywords

chronic opioid therapy; chronic non-cancer pain; depression

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## Introduction

Recent years have seen a dramatic increase in the use of chronic opioid therapy (COT) for chronic non-cancer pain (CNCP).<sup>1, 2</sup> The risks and benefits of COT, as well as the issue of patient selection, have been areas of active research. The selection of suitable candidates for COT has been considered the responsibility of the prescribing clinician. It involves identifying those patients with high likelihood of having good analgesia and functional improvement on opioid maintenance, and low risk for addiction, misuse and non-adherence.<sup>3</sup> However, observational studies suggest that a large portion of patients (greater than a third for oral opioids) discontinue opioids within 6 months due to adverse effects or inadequate pain relief.<sup>4</sup> This suggests that self-selection plays an important role in determining who remains on COT. Thus, it is important to understand factors that influence patient desires to stop opioid therapy, beyond perceived adequacy of pain control and drug side effects. This inquiry should help us recognize and understand the patient's role in shared decision-making concerning COT.

In the present study, we investigate predictors of patient desire to stop or cut down opioids among COT recipients who consider opioid therapy helpful for pain relief. We use the term "ambivalence" to describe the conflicting attitudes toward opioid use expressed by those patients who find opioids helpful but also have the desire to discontinue or reduce opioids. We test the hypothesis that ambivalence about opioids is more common among patients with clinically significant depressive symptoms. Even though depression is associated with long-term opioid use<sup>5, 6</sup>, we expected depression to be associated with ambivalence about opioids because prior research on medication adherence has found that depressed patients are more likely to express negative attitudes toward medication use<sup>7</sup>, and that they are less likely to adhere to prescribed medication regimens across a range of chronic conditions.<sup>8-13</sup> A previous study based on the same survey of COT recipients as described in this paper showed that depression is associated with patients experiencing more psychosocial difficulties that they specifically attribute to opioid use.<sup>14</sup> Thus depression increases the likelihood that patients experience more psychosocial dysfunction related to opioid use, and may make it more likely they want to stop or cut down opioids.

## Methods

### 1. Setting and participants

Data described in this paper were obtained as part of the CONSORT study (CONsortium to Study Opioid Risks and Trends) which surveyed adults ages 21 to 80 receiving COT for CNCP. The participants were enrollees of Group Health Cooperative (GHC) of Washington State and Kaiser Permanente of Northern California (KPNC). The two health plans serve about a total of 4 million people.

### 2. Inclusion/Exclusion

To be eligible for the survey, health plan enrollees must have filled at least 10 opioid prescriptions or received at least 120 days supply in a 1-year period prior to the sample selection date, with at least 90 days between the first and last opioid dispensing in that year. Opioid usage was verified via GHC's and KPNC's electronic pharmacy databases where members obtain over 90% of their prescription medications. 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 were excluded.

The sample for this paper was restricted to patients who reported using opioids everyday in the last 2 weeks and rated their opioids as moderately, very or extremely helpful. COT patients who did not find opioids helpful were excluded from our analyses to identify those who were ambivalent about opioid use among those who found opioids helpful in relieving their pain. Thus 1737 subjects were included and 426 subjects were excluded.

### 3. Sampling

Because most patients receiving COT receive less than 20mg morphine equivalent dose (MED) per day, we used stratified sampling to select an equal number of survey respondents within three dosage strata (1–49mg, 50–99mg, and 100+mg, MED). This way, patient subgroups using opioids at higher dosages were oversampled to ensure greater precision in data analysis. Observations were then weighted within dosage strata by the inverse probability of selection to obtain survey estimates representative of the population from which the sample was selected.

### 4. Telephone survey

Telephone interviews were carried out between June to November 2008 at GHC, and from January to October 2009 at KPNC. A letter explaining the study was sent to potentially eligible patients. A two dollar bill was enclosed with the letter to potential GHC participants and a five dollar gift card for a national retail store to potential KPNC participants. Experienced survey interviewers working for the collaborating health plan research centers then called potential participants and asked them to participate in a 25–30 minute telephone interview which was conducted using Computer-Assisted Telephone Interview technology. Survey respondents were also asked to allow study staff to access their electronic healthcare data from the time they enrolled in the health plan until three years after the date of the interview. GHC participants who completed the interview received a \$20 cash reimbursement and KPNC participants received a \$50 gift card. The different incentive payments were based on the researchers' prior experience with achieving acceptable response rates at their respective institution. All study procedures were approved by the Institutional Review Boards at both health plans.

### 5. Study measures

**5.1 Depression**—The severity of depressive symptoms was measured using the 8-item version of the Patient Health Questionnaire (PHQ-8), a validated and widely used self-rated measure of depression<sup>15</sup>. Based on recommended cutpoints for PHQ-8<sup>15</sup>, scores below 5 were classified as non-depressed, 5–9 as mild depression, and 10+ as clinically significant depression.

**5.2 Problems and concerns related to opioid use**—Fourteen items from the survey were selected to measure recent problems and concerns patients attributed to opioid use (in the past two weeks for common problems, in the past month or year for less common problems).<sup>16</sup> Psychosocial problems patients attributed to opioid use were measured with the following 8 items: loss of interest in usual activities; 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 alertness is needed; and bothersomeness of side effects. Opioid control concerns were assessed with the following 6 items: 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; having opioid-related problems with family, friends or co-workers; and patient report that family or friends perceived an opioid dependence or addiction problem.

**5.3 Opioid helpfulness**—Patients were asked to rate, on a 5-point Likert scale, how helpful they found opioids were for relieving their pain in the past month. Possible ratings include “not at all”, “a little”, “moderately”, “very”, and “extremely” helpful.

**5.4 Desire to stop or cut down opioid use**—Desire to stop opioids or cut down on the amount of opioid use was measured by patient agreement with the statement “In the past year I have wanted to stop using opiate pain medicines or to cut down on the amount of opiate medicines that I use.” Responses were recorded on a 5-point Likert scale ranging from “strongly disagree to “strongly agree.” Persons who strongly agreed or agreed with this item were classified as having the desire to stop or cut down. Those who strongly disagreed, disagreed or were neutral were classified as not having the desire to stop or cut down.

**5.5 Pain intensity and impact**—Pain intensity was measured using a 0–10 pain intensity rating scale from the Graded Chronic Pain Scale<sup>17</sup> that rates average pain in the prior 3 months. A Pain Impact Scale<sup>18, 19</sup> consisting of 11 yes-no items concerning effects of pain on daily activities in the past 2 weeks was also included.

**5.6 Opioid dosing**—Average opioid daily dose and predominant opioid type (long-acting vs. short-acting) for the 90-day period prior to the survey were obtained using electronic pharmacy data. Average daily dose was estimated by the total morphine equivalent dose divided by 90. Dose was converted to milligrams morphine equivalents according to previously described methods.<sup>20</sup> The predominant opioid type was defined as the type with the largest dispensed days supply during the time period.

## 6. Analyses

SAS PROC SURVEYMEANS or PROC SURVEYREG software was used for the analyses to account for the stratified random sampling approach, providing estimates for the population surveyed. Basic statistics, including proportions, means and standard deviations, were used to describe patients surveyed. Between group differences in proportions were tested using chi-square statistics.

We examined the association between patient desire to stop or cut down opioid use and PHQ-8-depression score using logistic regression models to adjust for potential confounders. Covariates included patient characteristics (age, gender, BMI, education), pain characteristics (mean days in pain in prior 6 months, average pain intensity, mean pain impact score), opioid use variables (average daily opioid dose, predominant use of long-versus short-acting opioids), self-reported substance abuse problem (past and present), Charlson co-morbidity score<sup>21</sup>, and health plan site. We also described differences in other patient problems and concerns with opioids between those who wanted to stop or cut down opioid use relative to those who did not. These descriptive analyses did not control for patient covariates.

## Results

### 1. Sample characteristics

A total of 3790 patients were approached (2185 at GHC and 1605 at KPNC), of which 185 were ineligible (76 at GHC and 109 at KPNC). 2163 completed the interview (1191 at GHC and 972 at KPNC), for an overall response rate of 60% (57% at GHC and 65% at KPNC).

The response rate difference between sites was presumably due to lower incentive payments at GHC. Response rates were higher for patients over the age of 65 in both health plans (65% at GHC and 68% at KPNC), but there were little gender differences in response rates. Response rates increased with average daily opioid dose at KPNC (58% for <50mg MED, 66% for 50 to <100mg MED, 71% for 100+mg MED), but not at GHC (58%, 57%, 55%, respectively for the three dosage strata).

Among the 2163 survey respondents, analyses were restricted to those who reported having used opioids in the past 14 days and rated opioids as moderately, very, or extremely helpful, resulting in inclusion of 1737 (80%) patients in the analytic sample. As shown in Table 1, the percentage of the patients in the sample who endorsed having wanted to stop or cut down their opioids was 43.3% (N=795). Thus, among the patients who found opioids helpful in relieving their pain, nearly half said they would like to stop or reduce opioid usage.

## **2. Comparison between patients who had the desire to cut down opioid use and those who did not**

Patients reporting the desire to stop or cut down opioid use were, on average, younger than those who didn't want to cut down (Table 1). The two groups were similar in gender, BMI, and education attainment. Patients with the desire to stop or cut down were also receiving higher average daily dose of opioids, whereas the two groups did not differ significantly in the predominant type of opioids they used, or the number of times per day they took opioids in the last two weeks. Both groups had an average greater than 90 days supply of opioids in the last 90 days according to automated pharmacy data, indicating that these patients were typically daily opioid users, consistent with their self report of daily opioid use in the prior two weeks.

The two groups were also similar in their average pain intensity and the number of days they had pain in the prior 6 months. However, the group wanting to stop or cut down opioids had higher mean Pain Impact scores. It is important to note that the two groups did not differ significantly in the percentage of patients perceiving opioids as very or extremely helpful versus only moderately helpful. There was also no significant difference between the two groups in Charlson co-morbidity score or self-reported history of substance abuse problems.

## **3. Depression and the desire to cut down opioid use**

A significantly greater percentage of patients who reported the desire to stop or cut down opioid use had either mild (PHQ-8 scores 5–9) or clinically significant depression (PHQ-8 scores 10 or higher), compared with the group that didn't endorse the desire to reduce opioid use. The group wanting to stop or cut down opioids also reported higher mean levels of depression symptoms (Table 2). We further divided PHQ-8 symptoms into two domains: a Cognitive-Affective sub-scale (“Little interest or pleasure in doing things”, “Feeling down, depressed, or hopeless”, “Feeling bad about yourself”, and “Trouble concentrating on things”), and a Somatic sub-scale (“Trouble falling or staying sleep, or sleeping too much”, “Poor appetite or overeating”, “Feeling tired or having little energy”, and psychomotor changes). Table 2 shows that the group wanting to stop or cut down opioids scored higher in both domains than the comparison group.

We used logistic regression to estimate odds ratios for PHQ-8 score and other variables in predicting wanting to stop or cut down opioid use. Results are shown in Table 3. Among the independent variables tested, greater depression severity (i.e., higher PHQ-8 score) and younger age were associated with increased likelihood of wanting to stop or reduce opioid use.

#### 4. Problems and concerns patients attribute to opioid use

We compared the group that wanted to stop or cut down with those who did not on 14 items assessing problems and concerns that patients had regarding their opioid use. As shown in Table 4, wanting to stop or cut down opioid use was associated reporting more psychosocial problems with opioid use and with having more opioid control concerns.

### Discussion

Among patients receiving chronic opioid therapy and reporting it helpful in relieving their pain, nearly half expressed a desire to stop or cut down their opioid use. This conflicting attitude about opioid use was not associated with the degree of helpfulness opioids were perceived to have. Ambivalence was also not related to pain control, as average pain intensity ratings were identical in the two groups. Patients who desired to stop or cut down reported more psychosocial problems related to opioid use and had more concerns about controlling their use of opioids. They were also receiving higher opioid doses. Thus, even COT recipients who find opioids helpful for pain relief may be ambivalent about continuing on opioid therapy, especially among those who experience more psychosocial difficulty attributed to opioid use. This suggests that at least some patients receiving COT do recognize the problems with staying on opioids, and that they may be more open to discussions of opioid tapering or discontinuation than is generally assumed.

Of note, Pain Impact score, a measurement of effects of pain on daily activities, was correlated with the desire to stop or cut down opioid use in the analysis shown in Table 1, but not in the analysis in Table 3 where depression indicator is included as a covariate. This difference can be accounted for by the fact that depression was correlated with high pain impact (data not shown). Similarly, the differential statistical significance in Tables 1 and 3 of opioid dose in its relation to the desire to stop or cut down opioid use can also be explained by the relationship between depression and high opioid doses (data not shown).

As hypothesized, we found that patient ambivalence was associated with depression. Depression is a robust predictor of poor adherence to drug regimens in other chronic conditions.<sup>7</sup> In the case of chronic pain and opioid therapy, there are a number of potential reasons for the link between depression and ambivalence about opioid use. First, opioids might have been used by patients as a de facto, but imperfect, treatment for depression. Depression has been associated with more pain complaints and higher pain severity.<sup>22, 23</sup> This may be why depressed patients are more likely to receive opioid therapy than their non-depressed counterparts.<sup>5, 6</sup> Although opioids might, in the short term, be helpful in relieving depressive symptoms<sup>24</sup>, their long-term effect on mental health outcomes remains untested. Depression was found to be associated with reduced opioid analgesia in discogenic back pain.<sup>25</sup> Thus, depressed patients might seek relief of their painful symptoms through opioids, but then find this relief incomplete or inadequate, leading to ambivalence about using opioids. Second, depressive symptoms overlap with potential side effects of chronic opioid use, including sedation, decreased concentration and memory, and loss of interest in usual activities. Depressed patients might interpret their depressive symptoms as opioid side effects, leading to the desire to cut down. Third, due to the dual mechanism of higher baseline pain<sup>22, 23</sup> and decreased opioid analgesia<sup>25</sup>, depressed patients might be more likely to end up on higher doses of opioid medications. In fact, a previous report from the CONSORT study did find an association between depression and receiving higher doses of opioids for chronic non-cancer pain.<sup>26</sup> The same report also noted an association between younger age and higher opioid dose, which may help account for the significant link between younger age and the desire to cut down identified in the present study. Higher opioid dosing can potentially cause more bothersome side effects and opioid-related psychosocial difficulties that increase patient ambivalence about opioid use.



When depression symptom score was broken down into Cognitive-Affective and Somatic domains, patients who were ambivalent about their opioid use were found to have more severe cognitive and affective symptoms of depressions, as well as somatic symptoms, than those who were not ambivalent. This finding supports the possibility that patient expectation for pain relief and patient attribution of somatic symptoms may both play a part in whether or not they wish to discontinue opioids. Compared to non-depressed patients, those with depression may expect more pain relief from opioids but obtain less, and they experience more somatic symptoms which they may attribute more readily to the opioids. Thus for clinicians initiating opioid therapy, an implication of the finding is that it is important to explore patient expectation about opioid efficacy and understand patient attribution styles as part of obtaining informed consent.

The study has a number of important limitations. Due to the cross-sectional survey design, this study cannot evaluate causal relationships among the variables of interest, including depression, opioid ambivalence, opioid dosing and opioid difficulties. Mental disorders other than depression were not assessed in the survey. These disorders as well as substance use disorders are known to be associated with higher likelihood of receiving COT<sup>6, 27-30</sup>, and therefore possibly play an important role in opioid ambivalence. The survey response rate was not optimal and differed between the two sites. Despite assurances of protection of confidentiality, some patients may have been concerned about providing information that they feel may jeopardize their access to pain medications. Pharmacy data on medications other than opioids was not collected; thus, it was not possible to control for certain potentially confounding variables such as anti-depressant treatment.

The use of long-term opioid therapy for chronic non-cancer pain is controversial, with significant uncertainty remaining about its long-term efficacy<sup>31, 32</sup> and potential harm including misuse and addiction.<sup>33-35</sup> Unintentional overdose from prescription opioids has become a leading cause of accidental death in multiple states<sup>36-38</sup>, drawing scrutiny regarding opioid dosing.<sup>39</sup> Our finding that a significant portion of patients receiving COT actually has the desire to decrease or stop their opioid medications suggests that it may often be possible to reach a mutual decision between the patient and the provider to taper or discontinue opioids when the risks and problems associated with opioid use outweigh the benefits.

In summary, among patients receiving long-term opioid therapy for chronic pain who found opioids helpful, a large percentage (43.3%) thought about quitting or cutting down their opioid medications. Depression was linked to patient ambivalence about opioid use, as were patient-reported opioid-related psychosocial problems and opioid control concerns. These associations between depression and chronic opioid use<sup>5, 6</sup>, and between depression and opioid ambivalence presents a unique challenge to clinicians, especially those working primary care settings, where the large majority of depressed and chronic opioid therapy patients are treated. Depressed patients receiving chronic opioid therapy often continue to have moderate to severe pain and unfavorable functional outcomes. In these patients, optimizing antidepressant therapy could be beneficial.<sup>40</sup> Furthermore, eliciting psychosocial problems that patients relate to opioid use, as well as opioid-related control concerns, may permit discussion of patient ambivalence about long-term use of opioid medications. For chronic pain patients not benefiting from chronic opioid therapy, or who may be misusing prescription opioids, this may provide a basis for considering opioid discontinuation as an option.

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**Table 1**

Comparing characteristics of chronic opioid therapy patients by whether or not have the desire to stop or cut down opioid use.

Variable	Have desire to cut down	No desire to cut down	p-value	All persons
Number of patients	795 (43.3%)	942 (56.7%)		1737
Female	64.6%	61.1%	0.40	62.6%
Mean age (Se)	53.9 (0.6)	57.5 (0.6)	<.0001	55.9 (0.4)
BMI (Se)	30.3 (0.4)	31.1 (0.5)	0.33	30.8 (0.3)
Some college education	59.8%	61.1%	0.73	60.5%
Mean days with pain in prior 6 months (Se)	167.4 (1.7)	167.8 (1.9)	0.84	167.6 (1.3)
Average pain intensity (SE)	5.8 (0.10)	5.8 (0.09)	0.48	5.8 (0.07)
Using opioids for more than one pain condition	64.9%	64.7%	0.54	64.8%
Opioids very/extremely helpful	62.7%	64.1%		63.5%
Predominate use of long-acting opioids in the prior 3 months	32.3%	30.2%	0.32	31.1%
Ever had drug or alcohol problem	22.6%	21.1%	0.92	21.7%
Mean Average daily dose in past 90 days	93.4 (5.8)	69.2 (3.02)	<b>0.03</b>	79.7 (2.7)
Mean days supply in past 90 days	112.5 (2.2)	105.6 (1.8)	0.1	108.6 (1.3)
Mean Charlson score	1.1 (0.09)	1.3 (0.09)	0.71	1.2 (0.06)
Mean Pain Impact score	7.3 (0.16)	6.5 (0.16)	<b>0.003</b>	6.8 (0.12)
Mean # times per day took opioids last 2 weeks	3.1 (0.07)	2.8 (0.06)	0.07	2.9 (0.05)

p-value controls for age, sex and health plan site

N is unweighted; all percents are weighted

**Table 2**

PHQ-8 depression indicators by whether or not have the desire to stop or cut down opioid use.

Variable	Have desire to cut down	No desire to cut down	p-value	All persons
PHQ 10+ (%)	50.2%	33.8%	<.0001	40.9%
PHQ 5+ (%)	79.5%	65.8%	<b>0.0002</b>	71.7%
Mean PHQ-8 (SE)	10.3 (0.35)	8.0 (0.26)	<.0001	9.0 (0.22)
Mean PHQ Cognitive-Affective symptoms (SE)	4.7 (0.2)	3.4 (0.14)	<.0001	3.9 (0.12)
Mean PHQ Somatic symptoms (SE)	5.6 (0.19)	4.7 (0.15)	<b>.002</b>	5.1 (0.12)

p-value controls for age, sex and health plan site

**Table 3**

OR (95% CI) from multivariable logistic regression predicting wanting to stop or cut down opioid use.

Variable	Odds Ratio (95% CI)	Overall p-value
PHQ-8 0-4 (reference) 5-9 10+	1.0 1.4 (0.9, 2.2) 1.98 (1.3, 3.1)	<b>0.009</b>
Sex Male (reference) Female	1.01 (0.7, 1.4)	0.93
Age	0.98 (0.97, 0.99)	<b>0.003</b>
BMI	0.99 (0.98, 1.01)	0.39
Education 8 <sup>th</sup> grade or less Some HS HS Grad or GED Some voc/trade Some college College grad Post 4-yr college (reference)	0.55 (0.12, 2.6) 0.78 (0.38, 1.63) 0.65 (0.36, 1.2) 0.9 (0.43, 1.9) 0.64 (0.37, 1.09) 0.61 (0.33, 1.12) 1.0	0.61
Mean days with pain in prior 6 months	1.0 (0.995, 1.002)	0.43
Average pain intensity	0.99 (0.92, 1.08)	0.86
Survey site KPNC GH (reference)	1.6 (1.2, 2.1) 1.0	<b>0.003</b>
Pain Impact score	1.0 (0.96, 1.08)	0.64
Self-report Drug or Alcohol Problem No (reference) Yes	1.0 0.96 (0.68, 1.37)	0.83
Charlson score	0.99 (0.91, 1.1)	0.79
Opioid type Predominantly SA Predominantly LA (reference)	1.14 (0.78, 1.7) 1.0	0.50
Dose 120+ 50-120 20-50 < 20 (reference)	1.35 (0.8, 2.27) 1.47 (0.92, 2.3) 1.34 (0.85, 2.1) 1.0	0.42

**Table 4**

Prevalence (%) of problems and concerns related to opioid use by desire to stop or cut down opioids

Problems and Concerns	Have desire to cut down	No desire to cut down	p-value
Lose interest in activity	13.4	4.7	<.0001
Trouble concentrate	21.4	9.2	<.0001
Slowed down/sluggish	23.3	11.0	<.0001
Depressed/anxious	12.1	4.3	<.0001
Interfere w/ work/family/social	30.3	9.6	<.0001
Hard to think clearly	23.0	8.1	<.0001
Less alert	34.7	18.5	<.0001
Bothersomeness of side effect	41.0	21.2	<.0001
Preoccupied with use	13.5	3.5	<.0001
No control over use	6.9	2.7	0.003
Need higher dose	37.9	19.6	<.0001
Worry about dependence	48.1	19.3	<.0001
Caused family problem	8.8	2.3	<.0001
Family/friend thought addicted	22.5	6.9	<.0001

p-value controls for health plan site