OUTPATIENT OPIOID PRESCRIBING FOR CHRONIC NON-CANCER PAIN:
ASSESSMENT OF INDICATIONS, EFFICACY AND SAFETY

Brittain McJunkin, MD,a Suzanne Kemper, MPH,a Baby Kodali, MD,a Srivani Chunchulu, MD,a
Benjamin Smith, MS 4,a Nirmita Shah, MD a

a Department of Internal Medicine, West Virginia University Health Sciences Center, Charleston
Division/Charleston Area Medical Center

CONTACT INFORMATION: Brittain McJunkin, MD, West Virginia University Health Sciences
Center, Rm 3075, 3110 MacCorkle Ave SE, Charleston, WV, 25314

Email: bmcjunkin@hsc.wvu.edu

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ABSTRACT

The purpose was to evaluate our ongoing outpatient opioid prescribing in regard to indications, efficacy, and safety, and to compare with current guidelines. Records of clinic outpatients were reviewed for year 2014. Demographic and clinical features were compared between opioid and non-opioid treated groups, indications for opioid prescribing, opioids used, doses, efficacy, and safety. Two hundred-thirteen patients were studied (Mean age 54.0 ± 13.0 years, 49.8% male). 153 (71.8 %) had chronic non-cancer pain. Of these, 78 (51.0 %) had been eventually prescribed opioids. Mean daily morphine milligram equivalent dose was 49.6 ± 40.1 mg. Pain appeared satisfactorily controlled in 41 (52.6%), inadequately controlled in 30 (38.5%), and unclear in 7 (9.0%). No overdoses or opioid related deaths occurred. Opioid prescribing was appropriate within most current guideline parameters. A morphine milligram equivalent dose of about 50 mgs daily appears to be a threshold dose which can safely provide adequate analgesia in a significant proportion of patients.
In the late 1990s, several developments resulted in greater use of prescription opioid analgesia. Recognizing inadequacies in the management of chronic non-cancer pain, several pain societies and others advocated a more liberal use of opioids for non-cancer pain.\textsuperscript{1-3} As proposed by the American Pain Society, adoption of pain as the “fifth vital sign” became standard.\textsuperscript{4,5} In addition, long acting oxycodone (OxyContin) was released in 1996 and aggressively marketed as safe and effective with low addictive potential, despite negligible data.\textsuperscript{2} Other pharmaceutical firms followed suit with active promotion of opioids. In 2001, the Federation of State Medical Boards established a policy of no regulatory action for opiate prescribing, and for the first time, recommended that under-treatment of pain may be punishable.\textsuperscript{6,7} Subsequent opioid prescribing for chronic non-cancer pain became accepted and mainstream in primary care to the benefit of many, but rampant prescription opioid overuse developed as an unexpected offshoot. Opioid prescribing has quadrupled since 1999.\textsuperscript{8} This epidemic phenomenon, along with gateway effects into heroin, has resulted in significant societal downsides related to addiction, criminal diversion (selling) of prescription agents, and overdose deaths. In 2014, the rate of US drug overdose deaths attributed to morphine, oxycodone, and hydrocodone increased 9% to 3.8 per 100,000. West Virginia had the highest rate of overdose deaths (35.5 per 100,000), primarily involving opioids.\textsuperscript{8}

In the past several years, government and private sector efforts have been implemented to combat prescription opioid abuse. Among these are several guidelines and publications which are generally in accord, focusing on initial management of pain with non-opioid approaches, and the judicious use of opioid analgesia when prescribed.\textsuperscript{9-16} Particular emphasis has been placed on careful vetting of patients, proper selection of opioids, avoidance of long-acting agents, limitation of concomitant opioids with sedatives, and proposed dosage ceilings (100 to 200 morphine milligram equivalent per day [MME]). The most recent guidelines, from CDC, are more stringent, proposing avoidance of opioid dosing beyond 90 MME.\textsuperscript{9} A three-fold increase in serious overdose events is observed at doses above 50 MME, and events dramatically increase at doses greater than 100 MME.\textsuperscript{17,18}
In 2010, confronting readily apparent local opioid overuse, our program established a more rigorous prescribing policy which was generally in accord with existing and subsequent guidelines proposals. In this current study, to better assess appropriateness of prescribing, we sought to compare opioid treated versus non-opioid treated chronic pain patients in regard to age, medications used, and underlying medical conditions, including specific pain syndromes and psychiatric disease. We also sought to observe how our overall prescribing practices compare presently with guidelines and studies, including the recent CDC guidelines recommendations. Depending on findings, further adjustments in chronic pain management practices would be undertaken.

METHODS:

Following IRB approval, we conducted a retrospective review of randomly selected patient records from the year 2014 at Charleston Area Medical Center (CAMC) Outpatient Care Clinic, Charleston, WV, which serves as the teaching clinic for the WVU HSC/ Charleston Division Department of Internal Medicine. Inclusion criteria were as follows: age greater than 18 years, routine follow-up as general medicine patients (not subspecialty), documented pain syndrome lasting greater than six months, and no history of malignancy. In addition, if opioids were prescribed, vs the non-opioid management group, the duration of treatment required for inclusion was for greater than six months. We compared the demographic and clinical features between opioid and non-opioid treated groups, opioid agents used, doses, efficacy, and monitoring. Tramadol, a partial µ receptor agonist with different characteristics and lesser abuse potential, has not been considered a “standard opioid.” This agent was evaluated separately in the “non-opioid group” for purposes of this study. Morphine milligram equivalents per day were calculated using NYC Health and Mental Hygiene MME calculator. Risk assessment tools (CAGE-AID, RAFFT) were commonly utilized for patient vetting prior to opioid prescribing. Adequacy of pain control was based on at least a 30% decrease in intensity of pain and reported increase in functional status. Such assessment monitoring was patterned after “The Four A’s” tool per Passik, which includes use of the established Numeric Rating Scale and functionality evaluation. Data analysis was performed using SAS Statistics 17.0. Basic
descriptive statistics, such as means and standard deviations for continuous variables and proportions and frequencies for categorical variables, were used to analyze patient and prescribing characteristics.

RESULTS:

Table 1 summarizes baseline data for all patients. Two-hundred and thirteen patients were studied (Mean age 54.0 ± 13.0 years, 49.8% male). Most patients were uninsured or on Medicaid or Medicare. One-hundred fifty-three (71.8 %) had chronic non-cancer pain. Of these, seventy-eight (51.0 %) had been eventually prescribed opioids on a chronic basis. During the year of review (2014), opioids were initiated in 10 (11.8 %) of all pain patients not previously treated with opioids. Opioid treated patients were older than pain patients not prescribed opioids (56.5 ± 10.9 yrs vs 51.3 ± 13.4 yrs, \( P < 0.02 \)). Seventy-three (93.6%) of opioid patients were over forty years of age. Opioid treated patients showed a trend toward higher burden of medical co-morbidities than non-opioid pain patients (7.6 ± 3.3 vs 6.6 ± 2.8, \( P < 0.06 \)), and significantly greater co-morbidities than all 135 non-opioid patients (7.6 ± 3.3 vs 6.1 ± 2.6, \( P < 0.009 \)). In addition, opioid treated patients were taking more medications (12.5 ± 5.4 vs 9.9 ± 5.5, \( P < 0.004 \)). These patients were more likely to have back pain (39 [50.0 %] vs 23 [30.6 %], \( P < 0.01 \)) and arthritis (38 [48.7 %] vs 17 [22.7 %], \( P < 0.05 \)) than pain patients not treated with opioids, Table 2. Compared to the entire non-opioid group, opioid treated patients had a greater prevalence of psychiatric disease, 27/78 (34.6 %) vs 29/135 (21.4 %), \( P < 0.04 \). Of opioid patients, 68 (87.2%) were prescribed short-acting agents only, 8 (10.3%) were prescribed both long-acting and short-acting agents, and 2 (2.6%) were prescribed long-acting agents alone. Fentanyl patch was prescribed in three patients of the entire opioid group. Other pain modulating agents such as low-dose tricyclic anti-depressants (TCAs), serotonin nor-epinephrine reuptake inhibitors (SNRIs), and gabapentin, were co-prescribed with opioids in 57 (73.1%) vs 32 (42.7 %) of non-opioid treated pain patients \( (P < 0.001) \). Thirty-four (43.6%) opioid patients were prescribed concomitant benzodiazepines. Of opioids used, hydrocodone was prescribed in 60 (76.9%), oxycodone in 18 (23.1%), and other opioid agents in 10 (12.8%). Mean MME was 49.6 ± 40.1 mg qd. Pain appeared to be satisfactorily controlled in 41 (52.6%),
not adequately controlled in 30 (38.5%), and unclear in 7 (9.0%). No overdoses or opioid related deaths occurred, Table 3. Nineteen of 78 non-opioid patients (24.4%) were prescribed tramadol (partial µ receptor agonist) with other agents. Though tramadol MME is not clearly established, estimated MME was 22.9 ± 8.3 mg qd. Pain control appeared to be satisfactory in 10, unsatisfactory in 5, and unclear in 4.

DISCUSSION:

Opioid use in chronic non-cancer pain currently has come under stern scrutiny due to unexpected prescription opioid abuse over the past few decades. Yet despite controversy, those “in the trenches” of primary care with pain management experience will acknowledge the value of judicious opioid treatment in carefully selected patients, for example those with multiple compression fractures or severe deforming arthritis. With these issues, we established a more rigorous policy in 2010, primarily regarding the initiation of opioids. As in many general medicine clinics in the past few decades, a large proportion of patients had been unwittingly initiated on longstanding relatively high doses of opioids prior to realization of prescribing issues, often with insufficient initial documentation of pain syndromes. Tapering of opioids and establishing rehabilitation in these cases is often extremely challenging due to several factors, including limited resources. In addition to general efforts in this regard, our current approach has mainly focused on careful vetting of new patients, commonly using risk assessment tools, mandatory review of outside records and documentation of pain syndromes, depression screening (PH Q-9), baseline urine drug screening, and prescription drug monitoring review, all prior to considering initiation of opioids. Further, a revised comprehensive controlled substances agreement is reviewed in depth with patients when opioids are prescribed, and periodically thereafter. In addition, emphasis is placed on a dosage ceiling of no greater than 90 MME, curtailed use of oxycodone, minimal opioid prescribing in younger patients, and limited use of long-acting agents or opioid/sedative combinations. In general, opioid use is minimized in patients with central sensitization presentations such as chronic headache and fibromyalgia. Didactic sessions and updates on pain management are routinely provided to faculty and house-staff.
When benchmarked with guidelines, ongoing opioid prescribing practices here have been maintained within most parameters, with what appears to be acceptable pain control (see below). Opioid treated patients were older and more ill than untreated patients. Prescriptions to younger patients have been maintained at a low level (6.4% of opioid treated patients were less than 40 years of age), concurrent with literature recommendations warning of greater abuse risk in this age category. The most commonly treated medical conditions were musculoskeletal, primarily relating to spinal disorders and/or arthritic conditions.

Overall, about 50% of our chronic non-cancer pain patients in this study were prescribed opioids, although in recent years new opioid prescribing is more rigorously overseen due to the ongoing policy changes. In 2014, opioids were initiated in 11.8% of all chronic pain patients not previously on opioids. As we have found no directly comparable US studies, it is unclear how this compares with similar outpatient internal medicine clinics serving a predominantly low-income middle-aged population with multiple significant co-morbidities. One study reported opioid prescribing in 41.6% of patients with chronic spinal disorders. In addition to more careful patient vetting, our current mean MME has been modest (49.6 ± 40.1 mg), concurrent with guideline principles stressing “additional precautions” at doses greater than 50 MME, and recommending a dosage ceiling of no greater than 90 mg MME. Further, our treated population falls primarily within the sixth decade, and thus may be less prone to opioid abuse than significantly younger patients (discussed above), and less prone to fall risk as seen in frail geriatric patients. Nonetheless, we do feel comfortable using low dose opioids in carefully selected older patients, per American Geriatric Society Guidelines. In line with recent CDC guidelines, nearly all opioid patients had been initially placed on trials of non-pharmacologic measures as well as non-opioid analgesia, and/or tramadol trial in full doses prior to commitment to standard opioids. Adjunctive agents such as anti-depressants (usually SNRIs and low-dose TCAs) and gabapentin were also used in most chronic pain patients. We currently minimize use of long-acting agents (12.8%) or oxycodone (23.1%), which appears desirable based on guidelines and regional experience. However, concomitant opioids and sedatives have been prescribed in our clinic at a proportion (43.6%) greater than recommended by
guidelines, possibly enhancing overdose risk.\textsuperscript{10,30,34,35} We presently are modifying these regimens.

At the dosage range used here, pain control appeared to be satisfactory in just over 50% of patients, which does not differ greatly from other studies. It appears that regardless of dosing levels used in chronic pain, the usual acceptable magnitude of pain relief is no greater than about 30%, \textsuperscript{23,24} and up to 40% of patients will continue to report less than desired pain control. \textsuperscript{23, 36,37} Certainly there are no studies confirming superiority of pain control and safety by the use of high dose opioids in chronic non-cancer pain. As discussed, nearly all of our opioid patients had been previously unsuccessfully managed on multiple other analgesics, pain modulators and non-pharmacologic trials prior to initiation of standard opioids. Consultation with a pain specialist had been sought if pain was poorly controlled at doses higher than about 100 MME. Due to limited availability and affordability of many alternative approaches to pain management, including pain specialists, CBT, mindfulness training, and others, it appears unrealistic for primary care providers to completely “re-think” use of opioids, suggested by some as the pendulum now swings in the other direction.\textsuperscript{38} In alignment with CDC concerns regarding doses over 50 MME, the similar MME in this study tends to substantiate 50 mg daily as a dose which can provide satisfactory pain control in a significant proportion of patients, with acceptable safety.

**LIMITATIONS:**

The main limitation in this study has involved assessing adequacy of pain control. Subjectivity of pain perception remains a fundamental issue in reporting pain. We attempted to assess overall pain control by reviewing all visits within the study year with numeric pain scale reports, patient description to physicians regarding degree of discomfort, and reports of activity level and functionality. In addition, requests for opioid dose increases were taken into account. Significant time constraints have appeared to affect quality of pain assessments in this large population of outpatients having numerous co-morbidities. In some cases, due to shortcomings of history taking, adequacy of pain control could not be confirmed and was duly noted as
“unclear.” This study also did not provide comparative data for opioid prescribing prior to and after policy changes. Nonetheless, the main objective of this study was to assess the characteristics of our current practices in regard to adequacy of pain control within a given opioid dosage range, with or without use of other augmentative agents.

Despite no reports of overdose or severe morbidity, a firm conclusion cannot be drawn regarding the safety of opioid use in this study as the numbers are too small. Nonetheless, by prior studies, overdose risk at doses lower than 50 MME is considered to be minimized. 9,17,18

CONCLUSIONS:

In carefully selected middle-aged patients with multiple co-morbidities, chronic non-cancer pain can be managed within most guideline parameters. A morphine milligram equivalent dose of about 50 mgs daily appears to be a threshold dose which can provide adequate pain control in a reasonable proportion of those having significant chronic pain, with acceptable safety. Nonetheless, continued refinement of pain management approaches clearly remains a necessity.

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27. Clauw DJ, Markman J. Opioids for the treatment of chronic non cancer pain... use or abuse? Program and abstracts of the American College of Rheumatology 2015 Annual Meeting; November 7-11, 2015; San Francisco, California. ARHP Debate.
<table>
<thead>
<tr>
<th>Chronic non-cancer pain patients</th>
<th>Opioid (n = 78)</th>
<th>Non-Opioid (n = 75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (Mean ± SD)</strong></td>
<td>56.5 ± 10.9</td>
<td>51.3 ± 13.4</td>
<td>0.02</td>
</tr>
<tr>
<td><strong>Male sex - n (%)</strong></td>
<td>34 (43.6)</td>
<td>35 (46.7)</td>
<td>0.70</td>
</tr>
<tr>
<td><strong>Medical problems per patient (Mean ± SD)</strong></td>
<td>7.6 ± 3.3</td>
<td>6.6 ± 2.8</td>
<td>0.06*</td>
</tr>
<tr>
<td><strong>Medications per patient (Mean ± SD)</strong></td>
<td>12.5 ± 5.4</td>
<td>9.9 ± 5.5</td>
<td>0.004</td>
</tr>
</tbody>
</table>

**Opioid risk comorbidities - n (%)**

<table>
<thead>
<tr>
<th></th>
<th>Opioid (n = 78)</th>
<th>Non-Opioid (n = 75)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Smoking</td>
<td>55 (70.5)</td>
<td>46 (61.3)</td>
<td>0.48</td>
</tr>
<tr>
<td>Alcohol</td>
<td>9 (12.0)</td>
<td>11 (15.5)</td>
<td>0.79</td>
</tr>
<tr>
<td>Hepatitis C</td>
<td>5 (6.9)</td>
<td>6 (8.7)</td>
<td>0.93</td>
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<tr>
<td>HIV</td>
<td>3 (4.2)</td>
<td>5 (7.4)</td>
<td>0.68</td>
</tr>
<tr>
<td><strong>Psychiatric history - n (%)</strong></td>
<td>27 (34.6)</td>
<td>18 (24.0)</td>
<td>0.15**</td>
</tr>
</tbody>
</table>

**Table 1.** Baseline data for chronic pain patients:  * P < 0.009 for opioid vs. entire non-opioid population (n =135).  ** P = 0.04 for opioid vs. entire non-opioid population (n= 135).
<table>
<thead>
<tr>
<th>Pain presentations</th>
<th>Opioid (n=78) n (%)</th>
<th>Non-Opioid (n=75) n (%)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Back pain*</td>
<td>39 (50.0)</td>
<td>23 (30.7)</td>
<td>0.01</td>
</tr>
<tr>
<td>Neuropathic</td>
<td>10 (12.8)</td>
<td>19 (25.3)</td>
<td>0.05</td>
</tr>
<tr>
<td>Fibromyalgia</td>
<td>3 (3.9)</td>
<td>3 (4.0)</td>
<td>0.96</td>
</tr>
<tr>
<td>Arthritis</td>
<td>38 (48.7)</td>
<td>17 (22.7)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Headache</td>
<td>11 (14.1)</td>
<td>18 (24.0)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

Table 2: Pain presentations: *Spinal disc disease, spinal stenosis, compression fractures, etc.
Opioid treated patients (n = 75) | n (%)  
--- | ---  
Age under 40 yrs | 5 (6.4)  
**Opioids used**  
Hydrocodone | 60 (76.9)  
Oxycodone | 18 (23.1)  
Other | 10 (12.8)  
**Duration of action**  
Short acting agents | 68 (87.2)  
Long acting | 8 (10.3)  
Both long and short acting | 2 (2.6)  
**MME (mean ± SD)** | 49.6 ± 40.1 mg  
**Pain control**  
Satisfactory | 41 (52.6)  
Unsatisfactory | 30 (38.5)  
Unclear | 7 (9.0)  
**Other agents (SNRI, TCA, GABA, etc.)** | 57 (73.1)*  
**Opioids and benzodiazepines** | 34 (43.6)  
**Overdose** | 0 (0.0)  

**Table 3.** Summary of management of opioid treated patients: * 57 (73.1%) vs 32 (42.7%) non-opioid pain pts, (P < 0.001)