Significantly Associated and Prognostic Factors of Long-Term Opioid use in Patients with Low Back and Non-Cancer Pain

Greg Howell

The opioid epidemic in the United States continues to be a pervasive problem, will death tolls as a result of opioid related overdoses rising over the last 15 years ¹. In fact, prescription opioid drug overdose deaths have guintupled since 1999², with over 42,000 overdose deaths occurring in 2016 as a result of opioids ^{3,4}. Long-term opioid use is often associated with an increased risk for drug-overdose ^{5,6}, as well as an increased risk of dependency ^{5,7}, adverse events including substance abuse and mortality ⁵, and development of depression ^{5,8}. In fact, one fourth of individuals prescribed opioids for long-term use (i.e. ≥12-months) struggle with issues of dependency and addiction ⁷. An opioid prescription is common for patients diagnosed with low back pain (LBP) ^{9–11}, with between 4.5-19% of the individuals prescribed opioids for LBP continuing to use them long-term ^{9,11}. This makes back pain the second most commonly cited reason for long-term opioid use amongst chronic opioid users, well ahead of head and neck pain, and second only to joint related pain ¹¹. LBP is not only a significant contributor to long-term opioid use in the general population, but has also been shown to be an issue in military populations. Morasco et al¹² found a strong association between chronic non-cancer related pain and high-dose opioid prescription in the military, with patients diagnosed with low back pain being nearly twice as likely to receive higher doses of opioids (i.e. ≥180 mg/day). In fact, military veterans have been shown to be nearly twice as likely to suffer opioid related overdoses than non-military members ¹³. It has been speculated that psychosocial and demographic differences between the military and non-military populations, as well as increased access to medications and the effects of combat exposure could be contributing towards these observed differences ¹³. However, conclusive findings that fully explain these differences have yet to be determined.

Over the last several years conservative treatment approaches, common with physical therapy, have been strongly advocated for as alternatives to opioid therapy for the treatment and management of chronic non-cancer pain ^{14,15}. However, few clinically useful tools and little information has been presented to help guide clinicians in their ability to screen for individuals whom may be at an increased risk for long-term opioid use. This expanded literature review serves to highlight several of those factors, which are related to, and potentially predictive of long-term opioid use in patients with non-cancer pain. It will highlight the impact of opioid exposure as it relates to pain and disability outcomes in patients with LBP. And will serve to inform analyses of a military data set involving opioid use in patients with LBP. This review will conclude with a synthesis of the information presented, as well as recommendations for continued research efforts in areas with reduced empirical support.

Associated and Prognostic Factors of Long-Term Opioid Use

Gender

Gender is an easily identified and dichotomized factor that has been heavily explored in the long-term opioid use literature, in order to determine its impact on prevalence and incidence rates. Recent findings have suggested that women are more likely to be prescribed opioids at higher rates¹⁶ and higher doses when compared to their male counterparts ¹⁷. Several studies have noted increased incidence and prevalence rates of long-term opioid use in women compared with men for the treatment of non-cancer pain^{18–20}, including LBP ²⁰. However, other findings do not reflect these trends, with contradictory evidence suggesting that being male is a significant predictor of both past year non-medical opioid use²¹, prescription opioid use in patients with non-cancer pain²⁴, including LBP²⁵, found that gender is not a significant predictor of long-term opioid use. Despite the higher instances of long-term opioid use in women noted in the literature, it is inconclusive whether or not gender is a significant prognostic factor of long-term opioid use.

Age is another widely identified and explored factor in long-term opioid use studies. A younger age, defined as between 18-25 years ²¹ or 18-30 years ^{22,26}, has been shown to be a significant predictor of opioid abuse ^{21,22,26}, as well as a risk factor for opioid misuse and dependence ^{21,22,27}. Increased incidence and prevalence rates of long-term opioid use for the treatment of non-cancer pain, including LBP, have been demonstrated in older populations ^{18,19}. These studies show that incidence and prevalence of long-term opioid use appears to increase with advancing age, whereby individuals aged ≥ 65 years demonstrated the highest relative rates when compared to their younger counterparts ^{18,19}. Despite these findings, older adult individuals have been found to be significantly less likely to suffer from opioid abuse or dependence issues ^{22,28}. Still, other studies have shown that the average age of individuals using opioids long-term for the treatment of non-cancer pain, including LBP, is between 47²⁹ and 50²⁰ vears. Several prognostic studies of long-term opioid use have not found age to be a significant independent predictor of long-term opioid use in these populations ^{24,25}. Inconsistencies in the description of age categorizations as well as in study findings makes the stratification of risk for long-term opioid use based solely upon a patient's age difficult at this time.

Heredity/Family History

A family history of opioid or other form substance abuse has been a commonly cited in the literature as a risk factor for the development of opioid misuse and dependence ^{27,30}. A family history of substance abuse has been described as an influence on future substance use behavior. A family history may influence substance abuse behavior through inherited genetic factors, exposure to specific familial behaviors, and the familial environment ³¹. In fact, these genetic and familial influences have been noted to contribute towards up to 43% of the variance in future opioid dependence ³² and up to 25% of the variance in future drug misuse respectfully ³³. Moreover, individuals with family members who were dependent on or misused opioids were

Age

found to be more than 10 times as likely to go on to become dependent on or misuse opioids themselves ³⁴. Based upon these findings, it is clear that having a familial history of substance abuse, and perhaps more specifically a familial history of opioid dependence, may be a moderate to strong prognostic factor of future opioid dependence and/or long-term use.

Mental Health Disorders

Mental health disorders including anxiety and major depression are very common among persons with chronic non-cancer pain ^{6,35}, opioid dependency^{7,21,36}, and long-term opioid use ^{5,19,37}. Other common mental health disorders attributed to these populations include panic disorder ³⁶, agoraphobia ³⁶, and dysthymia ^{38,39}. In patients with non-cancer pain, presence of a mental health disorder has demonstrated to be a strong prognostic factor of past-year prescription opioid use ^{38,39}, and a mild to strong prognostic factor for opioid dependence ^{21,22,36} or misuse ^{22,40}. Individuals with increased levels of depression have demonstrated to be at an increased risk for taking higher doses of opioids ⁴⁰, and as having an increased likelihood for being prescribed higher doses, receiving more days supply, and receiving stronger classes of opioids to treat non-cancer pain than those without depression ³⁷. Presence of a baseline mental health disorder has demonstrated to be a strong prognostic factor of long-term opioid use in adolescents ⁴¹ and adults ³⁹ with non-cancer pain. Other studies exploring predictors of long-term (i.e. ≥12-month) opioid use in patients with non-cancer pain, including LBP, did not find that either baseline mental health status ²⁵ or baseline depression ²⁴ were significant prognostic factors of long-term opioid use. While evidence from the literature is not definitively conclusive, the majority of studies reviewed agree that the presence of a baseline mental health disorder may be associated with and predictive of longer-term opioid use.

History of Opioid Use

Although a history of substance abuse, including opioid abuse, has consistently shown to be a strong prognostic risk factor for future opioid dependence and abuse in the literature ^{7,22,27,28,42–45}, the prognostic ability of a history of opioid use in predicting long-term opioid use for

patients with non-cancer pain has gone largely unstudied. Findings from Connolly et al. ⁴⁶ revealed that the risk for long-term opioid use following lumbar fusion surgery for the treatment of LBP appeared to be a function of the number of days of opiate use in the year prior to surgery, whereby individuals using opioids on an increasing number of days demonstrated significantly higher risk for continued long-term opioid use when compared with those not receiving an opioid prescription following surgery. Because of the simplicity for dichotomization of this potential risk factor, future prognostic literature could benefit from its inclusion in order to determine whether or not prior opiate use influences future long-term opiate behavior.

Baseline Dosage

The examination of the effects of baseline opioid prescription characteristics, including prescribed baseline dosages, has been frequently performed in the prognostic opioid literature ^{22,25,47,48}. To standardize dosing, prognostic opioid literature utilizes conversion factors to convert the relative strength of prescribed opioids to the units of morphine equivalent dose (MED)^{25,49} or morphine milligram equivalents (MME) 22,47,48 . Receipt of a baseline MED \geq 120 mg/day has been shown to be a mild to moderate prognostic factor for future opioid dependence and/or abuse ^{45,50}, and has been considered to be "high dose" opioid therapy ⁵¹. A retrospective analysis of medical and pharmacological data from a military data set found that receipt of a daily MED ≥100 mg was a strong prognostic factor for opioid related toxicity or overdose of all factors analyzed ⁴⁹. Edlund et al ²², who studied factors associated with risk for opioid abuse and dependence amongst chronic non-cancer pain patients, found that risk was directly associated with the dose received among "chronic" users. The individuals receiving ≥120 MMEs were more than 8 times as likely to develop opiate abuse or dependence issues when compared with individuals receiving <36 MMEs²². A study by Franklin et al.²⁵ prospectively explored variables associated with long-term (i.e. 12-month) opioid use in a cohort of workers with LBP. The authors found that a total MED ≥900 mg in the first three months, or a daily MED \geq 10 mg, was a strong prognostic factor for continued opioid use at 12-months ²⁵. Increased

baseline prescribed dosage was associated with an increased risk for long-term use ²⁵. A similar dose response relationship between baseline opioid dosing and the risk for long-term opiate use was observed in a study by Deyo et al. ⁴⁸, whereby individuals who received \geq 120 MMEs in the first month were at significantly increased risk for long term use . Individuals who received between 3200-3999 MMEs were sixteen times more likely to continue to use opioids for 12-months, than those prescribed <120 mg during the first month ⁴⁸. In accordance with these findings, Shah et al. ⁴⁷ found that baseline prescription of \geq 90 MMEs was a moderate negative prognostic factor of opioid discontinuation at 12-months in opioid naïve patients. This preponderance of evidence suggests that characteristics of baseline opioid dosing may be a strong predictor of continued long-term opioid use in patients with chronic non-cancer pain including LBP.

Baseline Prescriptions

In addition to baseline dosage, other baseline prescription characteristics including the number of opioid prescriptions filled in the first episode of care has also been explored ^{11,48}. Deyo et al. ⁴⁸ found that filling \geq 2 prescriptions was a moderate to strong prognostic factor of continued long-term opioid use in opioid naïve patients receiving opioids for non-cancer pain. Increasing the number of prescriptions filled directly correlated with an increased risk for long-term opioid use ⁴⁸. These findings seem to be corroborated by those from a study by Shah et al. ¹¹ which longitudinally explored characteristics of initial opioid prescription episodes as they related to long-term (i.e. \geq 12-month) usage. This study found that the probability of continuing prescription opioid use long-term increased exponentially with the receipt of additional opioid prescriptions during the initial episode of care ¹¹. In fact ~14% of individuals who received a refill or second opiate prescription continued to use opioids at 12-months ¹¹. While additional studies will be needed to validate these findings, it may be that receipt of >1 opioid prescription during an initial episode of care is a significant prognostic factor for continued long-term opioid use.

Baseline Days Supply

The association between the initial days supply of prescribed opioids, and its impact on long-term opioid use has also been explored in the literature ^{11,47}. Shah et al. ¹¹ found that the probability of long-term (i.e. ≥12-month) usage increased linearly with an increase in the number of days' supply of the baseline opioid prescription. Notable increases in the probability for longterm opioid use were observed with 5 and 30 days' supply of baseline opioid prescription respectfully, signifying the potential importance of limiting the initial days' supply of prescriptions to below these time points ¹¹. In a follow-up study, Shah et al. ⁴⁷ explored the prognostic ability of initial prescription characteristics in predicting opioid discontinuation at 12-months. Regardless of a patient's pain chronicity or the patient's past year opioid exposure, a significant inverse linear relationship was observed between the initial days' supply of opioids and the discontinuation of opioids at 12-months⁴⁷. The probability of opioid discontinuation significantly decreased with the receipt of additional days' supply of opioids, with individuals receiving between 5-7 days worth of opioids being roughly half as likely to discontinue use at 12-months compared with those who only received 1-2 days' supply ⁴⁷. Moreover, patients who initially received ≥22 days worth of opioids were five time less likely to discontinue using opioids longterm ⁴⁷. Edlund et al ²² found that among non-cancer pain patients, receipt of >90 days supply of opioids significantly increased the odds for developing abuse and dependency issues. Based upon these studies, it may be that receipt of an initial days' supply of ≥ 5 days worth of opioids may be a significant prognostic risk factor for continued long-term opioid use in patients with non-cancer pain, with receipt of >90 days supply exponentially increasing an individuals risk for adverse event.

Tobacco Use

Because of the confluence of factors common with addiction and substance abuse ^{52,53}, the association between nicotine and long-term opioid use has been explored ^{53,54}. Two studies directly examining the influence of tobacco use and the risk for long-term opioid use found that

smokers were roughly 2 ⁵⁴ and 4 ⁵³ times as likely to continue to use opiates long-term when compared to non-smokers. Moreover, individuals with either a history of or who are currently smokers appear more likely to be prescribed higher doses of opioids ⁵⁵, for longer terms (i.e. > 90 days) ⁵³. While smoking is known to play a large role in a host of negative health outcomes, based upon these studies it may be at least a moderate risk factor for long-term opioid use. Future studies should continue to explore these relationships, as this factor can be easily dichotomized, and is routinely screened in medical practice.

Baseline Disability Outcome Score

Although disability outcome measures are commonly used to assess a patient's level of perceived functional disability, few studies have explored whether baseline functional disability scores are associated with long-term opioid use. In patients with LBP secondary to lumbar disc herniation or lumbar stenosis, baseline levels of perceived functional disability as assessed with the Oswestry Low Back Disability Index (ODI)⁵⁶ were not found to be predictive of continued opioid use at \geq 12-months ⁵⁴. In workers with LBP, individuals who assessed their baseline level of functional disability in the highest tertile (i.e. 18-22) on the Roland Morris Disability Questionnaire (RDQ) ⁵⁷ were found to be three times more likely to continue using opioids at 12-months than those rating their disability in the lowest tertile ²⁵. Ives et al. ⁵⁸ explored the predictors of opioid misuse in patients with chronic non-cancer pain. Baseline levels of perceived pain disability on the Pain Disability Index (PDI) ⁵⁹ was found to not a significant predictor of opioid misuse in this population ⁵⁸. From these few studies, it is inconclusive as to whether or not baseline levels of perceived functional disability are predictive of long-term or aberrant opioid use. Moving forward, the prognostic literature could benefit by standardizing the disability outcome measures used in developing their multivariate prediction models.

Patient Expectations

Patient expectations with regards to both the likelihood for long-term opioid use and recovery potential have also been explored in the prognostic opiate literature. Thielke et al.²⁴

found that chronic non-cancer pain patients who perceived that it was either "very" or "extremely" likely that they would continue to use opiate medications at least 2-3 days per week in one year were four times more likely to continue using opioids long-term. Even individuals who perceived their likelihood for continued use as "uncertain" or "somewhat" likely were at nearly three times the risk for continuing to use opioids at 12-months ²⁴. Low recovery expectations, or refusing to answer questions with regards to recovery expectations on the Vermont Disability Prediction Questionnaire ⁶⁰ have also been shown to increase the odds for continued long-term opioid use by 2 and 3 times respectfully in patients with LBP ²⁵. While the prognostic literature could benefit by continuing to explore the associations between patient expectations and long-term opioid use, expectations about continued use and/or low recovery expectations may be moderate to strong prognostic factors for long-term opioid use in patients with non-cancer pain.

Influence of Opioid Exposure in Patients with Low Back Pain

Disability Outcomes

Both statistically significant ^{54,61} and clinically significant ⁵⁴ baseline differences have been observed between opiate using and opiate naïve LBP patients on the ODI, in favor of opiate naïve individuals. A systematic review and meta-analysis by Abdel et al. ⁶² on the efficacy of opioid analgesics for LBP found no statistically or clinically significant improvements on disability outcomes (i.e. ODI or RDQ) in patients receiving opioids for LBP in all the studies analyzed. However, the studies assessing the effects of opioids on disability outcomes were few, and of low quality ⁶². Baseline opioid prescription for episodes of acute LBP have been found to be significantly associated with poorer functional disability outcomes at 6-months when compared with patients who did not receive an opioid prescription ⁶³. Lee et al. ⁶⁴ demonstrated that the magnitude of preoperative daily opiate MED was predictive of poorer long-term functional disability in patients who received surgery for spinal pain. More specifically, every 10mg increase in daily MED preoperatively was found to be associated with a 0.5 increase on the

ODI at 12-months, demonstrating a correlation between increased preoperative opioid use and reduced long-term functional disability ⁶⁴. While the long-term impact of opioid exposure on functional disability in LBP has been sparsely studied, findings from Franklin et al. ²⁵ demonstrated that the large majority (i.e. 84%) of individuals taking opioids long-term for LBP did not improve to a clinically meaningful level between baseline and 12-months. These findings seem to suggest that among LBP patients, exposure to opioids does not seem to improve functional disability, and could potentially have a deleterious effect

Pain Outcomes

Opiate medications are prescribed for their ability to reduce pain symptoms in patients with LBP, however their efficacy, especially with regards to longer-term pain management is debated in the literature. Non-statistically significant differences in perceived pain values have been demonstrated between opioid using and opioid naïve back pain patients with similar baseline pain durations ⁶¹. Systematic reviews and meta-analyses analyzing the efficacy of opioid analgesics in the treatment of LBP have found that these medications were effective in reducing pain symptoms from baseline to 3-months ^{62,65}, and between three and 12-months respectfully ⁶². However while statistically significant, these pooled effects were largely small ^{62,65}, and thus unlikely to be clinically meaningful ⁶². Another systematic review and metaanalysis by Martell et al. ⁶⁶ found a non-significant difference in the pooled effect between opioid analgesics and placebo in reducing pain symptoms. A separate analysis demonstrated a nonsignificant difference in pain reduction vs. pain increase for LBP patients taking opioids ⁶⁶. None of the studies included in these systematic reviews evaluated the efficacy of opioids in the longer-term management of LBP. Findings from Franklin et al. showed that only ~25% of LBP patients taking opioids for the long-term for management of their symptoms demonstrated clinically meaningful improvements in pain between baseline and 12-months²⁵. Based upon these findings, opioids may be effective for reducing LBP symptoms in the short to intermediate

terms, but their efficacy in reducing these symptoms in the long-term remains suspect, signifying the potential need for alternative interventions for long-term pain management.

Evidence Synthesis and Recommendations

Screening for prognostic risk factors of long-term opioid use in patients with chronic noncancer pain is important considering the multitude of negative health outcomes and lack of efficacy associated with long-term use. This expanded literature review explored the current evidence with regards to factors associated with or predictive of long-term opioid use in patients with chronic non-cancer pain, including LBP. It was found that factors such as a family history of substance abuse, presence of a baseline mental health disorder, a history of or baseline tobacco use, an increased baseline dosage of opioids, filing >1 prescription during an initial episode of care, being prescribed an initial days supply ≥ 5 days, and patient expectations with regards to continued long-term opioid use may be strong prognostic factors of long-term opioid use. Other factors such as being female, age ≥ 65 years, a history of opioid use, and more severe baseline disability may also be associated with long-term use. Future prognostic research would benefit by establishing a set baseline dosage cut-point using a standardized unit of measure to aid clinicians in more easily identifying at risk individuals. More consistent use of standardized disability outcome measures could also be of benefit, and would help to clarify the predictive relationship between baseline perceived disability and long-term opioid use. Establishing whether or not a prior history of opioid use is a prognostic factor of long-term opioid use could also be beneficial, as this factor can be easily dichotomized, and has gone largely unstudied.

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