Factors Associated with Medication-Overuse Headache in Patients Seeking Treatment for Primary Headache

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FACTORs ASSOCIATED WITH MEDICATION-OVERUSE HEADACHE IN PATIENTS SEEKING TREATMENT FOR PRIMARY HEADACHE

A Dissertation
presented in partial fulfillment of requirements
for the Doctor of Philosophy degree
Department of Psychology
The University of Mississippi

By

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ABSTRACT

Although a number of risk factors for medication-overuse headache (MOH) have been identified within the general population, limited research exists examining clinical samples of headache sufferers. Further, prior studies have not assessed the relative influence of risk factors or their utility in combination.

As part of an online survey, 164 headache patients completed a demographic questionnaire, a diagnostic interview for headache, a measure of headache-related disability, measures of psychiatric symptoms, and measures of medication use and substance use. Standardized mean differences were used to quantify differences between patients who met diagnostic criteria for MOH and those who did not across five domains of predictors (demographic characteristics, headache characteristics, psychiatric symptoms, medication use, and substance use). The variables within each domain that best discriminated between those who met criteria for MOH and those who did not were identified using a classification tree approach with Bonferroni corrections. Candidate variables were then entered into a multivariate logistic regression to predict MOH status.

Forty-three of the 164 patients (26.2%) of the sample met diagnostic criteria for MOH. Patients with MOH were more disabled by their headaches (mean [SD]: 67.60 [6.00] vs 63.31 [6.68]) and reported more escape and avoidance behaviors in response to headache pain (14.64 [5.36] vs 10.44 [6.13]. The use of combination medication for the treatment of headache (60.5% vs 33.1%, odds ratio 3.10, 95% confidence interval [CI] 1.51-6.36) was associated with more than a threefold risk of MOH. These three variables were forced into a final multivariate model,
which differentiated well between the two groups (area under the receiver operating characteristic curve = .78; 95% CI .71-.86).

Based on these results, headache-related disability, fear and avoidance of pain-related stimuli, and the use of combination medications for the treatment of headache best predict MOH among treatment-seeking headache sufferers. Brief screening measures that assess relevant risk factors may be used to aid in the identification of headache patients most likely to have MOH and behavioral and cognitive-behavioral interventions may hold promise for the prevention of MOH and the reduction of acute medication use among individuals with MOH.
DEDICATION

This dissertation is dedicated to Rachel Peck. Without my wife’s love and support

I would never have made it this far.
ACKNOWLEDGEMENT

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I. INTRODUCTION

1.1 Headache Diagnoses

Worldwide, 46% of adults suffer from an active headache disorder (Stovner et al., 2007). The International Classification of Headache Disorders 3rd edition-beta version (ICHD-IIIβ) classifies headaches not attributable to identifiable organic pathology as primary headaches. The most common primary headache disorders are migraine and tension-type headache (TTH), which are two of the top three most prevalent medical conditions worldwide (Vos et al., 2012). In contrast, headaches deriving from illness or injury (e.g., trauma, surgery, infection, illicit substance use, and medication overuse; ICHD-IIIβ) are classified as secondary headaches. Primary headaches comprise the large majority of headaches experienced by the population. With the exception of the very rare condition of cluster headache, primary headache disorders are more prevalent in women than in men across cultures (Stovner et al., 2007), making headache a significant women’s health concern.

A recently published meta-analysis indicates that, migraine affects 11.6% of adults worldwide (Woldeamanuel & Cowan, 2017). Migraine attacks typically last between 4 to 72 hours and are characterized by unilateral pulsating head pain of moderate to severe intensity. Migraine may be aggravated by routine physical activity and for diagnosis must produce nausea, vomiting, or both photophobia (sensitivity to light) and phonophobia (sensitivity to sound). In a significant minority of cases, migraine attacks are preceded by aura, a constellation of temporary
focal neurological symptoms that are commonly visual in nature (e.g., seeing spots or zigzag lines, blurry vision). Aura symptoms usually develop gradually over 5-20 minutes and last for less than an hour, after which time the head pain begins (ICHD-IIIβ; Lipton, Scher, Silberstein, Liberman, & Bigal, 2008).

Tension-type headache is the most common type of primary headache, affecting approximately 42% of adults worldwide (Stovner et al., 2007). Tension-type headaches may last anywhere from 30 minutes to 7 days. Unlike migraine, the pain of TTH is characterized as bilateral, pressing or tightening in quality, of mild to moderate severity, and not worsened by routine activity (Rasmussen, Jensen, Schroll, & Olesen, 1991). Nausea and vomiting are not typically associated with TTH, but photophobia or phonophobia (not both) may accompany these headaches, although they are typically of lesser severity compared to that observed in migraine (ICHD-IIIβ; Jensen, 2003).

Cluster headache is a very rare but severe type of primary headache. Approximately 1 in 1000 people suffer from cluster headache (Fischera, Marziniak, Gralow, & Evers 2008). Left untreated, cluster headaches typically last for 15 to 180 minutes. Cluster headache is characterized by unilateral, excruciating pain typically of orbital or supraorbital temporal distribution (ICHD-IIIβ). Attacks are accompanied by ipsilateral autonomic symptoms (e.g., lacrimation, swelling of the orbital socket) and produce restlessness and agitation that often manifest as continuous pacing because of the extreme pain severity (Torelli & Manzoni, 2003). Individuals who suffer from cluster headache often report a significant personal and socioeconomic burden as a result (Jensen et al., 2007).
Migraine and other forms of recurrent headache are among the most common and disabling disorders of the nervous system (Andlin-Sobocki, Jonsson, Wittchen, & Olesen, 2005; Olesen, Gustavsson, Svensson, Wittchen, & Jonsson, 2012; Rasmussen, Jensen, & Olesen, 1992). Due to the financial costs (Hu, Markson, Lipton, Stewart, & Berger, 1999) conferred to both the individual and to society, headache is among the top ten most disabling conditions worldwide (Stovner et al., 2007; Vos et al., 2012) and among the top five most disabling conditions for women (Stovner, et al., 2007). According to the National Ambulatory Care Survey (NAMCS), “pain in the head” was among the top 20 reasons for outpatient doctor’s visits in 2009 (National Center for Health Statistics [NCHS], 2010), and 7.7 million emergency department (ED) visits were attributed to acute headache in 2010 (Mazer-Amirshahi, et al., 2014). Accordingly, head pain is among the top five leading causes of ED visits, accounting for 3.1% of ED visits between 2009 and 2010 (Burch, Loder, Loder, & Smitherman, 2015; Smitherman, Burch, Sheikh, & Loder, 2013).

Most frequently, primary headache disorders occur episodically (< 15 days per month); however, approximately 3-5% of adults in the general population experience “chronic” headache (CH; Castillo, Munoz, Guitera, & Pascual, 1999; Lanteri-Minet et al., 2003; Lu, Fuh, Chen, Juang, & Wang, 2001; Stovner, et al., 2007; Wang, et al., 2000; Westergaard, Glumer, Hansen, & Jensen, 2014). Chronic headache disorders are those with a frequency of 15 or more headache days per month (ICHD-IIIβ). Even though episodic headache (EH) is much more common, individuals with CH make up a large percentage of patients seen in U.S. headache clinics (Mathew, 1993). Compared to individuals with EH, individuals with CH experience lower quality of life, increased disability, reduced work productivity, more frequent and severe psychiatric comorbidities, more and longer hospitalizations, and increased medical costs (Buse,
1.2 Acute Medications as Treatment for Headache

Headache patients commonly use acute medications in order to relieve the pain and disability associated with attacks. As such, headache is among the most common reasons for acute pain medication consumption in the general population (Eggen, 1993; Meskunas, Tepper, Rapoport, Sheftell, & Bigal, 2006; Zwart, Dyb, Hagen, Svebak, & Holmen, 2003). Acute medications prescribed for headache include headache-specific agents (e.g., ergotamine derivatives and triptans), dopamine antagonists (e.g. metochloproamine and prochlorperazine), nonspecific medications (e.g. nonsteroidal anti-inflammatory drugs [NSAIDS]), opioids (e.g., codeine and hydrocodone), barbiturates (e.g., butalbital), and combination analgesics (e.g. aspirin, acetaminophen, and caffeine combinations; Silberstein, Freitag, & Bigal, 2008).

Ergotamine was the first acute medication developed specifically for the treatment of headache. Ergotamine was the treatment-of-choice for migraine until the late 1980s and early 1990s when triptans were introduced and quickly supplanted ergotamine due to superior efficacy and more favorable side effect profiles. Current consensus guidelines recommend triptans as first-line options for the treatment of headache (Marmura, Silberstein, & Schwedt, 2015; Silberstein et al., 2000). As a result, triptans accounted for 80% of the over 6 million prescriptions written for acute migraine medications in outpatient clinics in 2009 (NCHS, 2010). Although triptans are frequently prescribed by headache specialists, prescription practices vary considerably by setting. According to recent analyses of ED prescription practices, triptans are prescribed in few (<2%) ED visits for headache. Instead, opioids (22.8% – 30.5%) and NSAIDS
(16.9% - 31.4%) were far more likely to be prescribed in the ED (Mazer-Amirshahi et al., 2014; McCarthy & Cowan, 2015). Despite consensus guidelines that recommend opioid analgesics and butalbital not be used as first-line agents (Loder, Weizenbaum, Frishberg, & Silberstein, 2013; Silberstein et al., 2000), opioids were more frequently prescribed to treat headache during ED visits in 2010 (35.0%) than in 2001 (20.6%; Mazer-Amirshahi et al., 2014).

Although acute headache medications are vital to the management and treatment of headache, their overuse is frequently associated with CH and may lead to a gradual transformation from EH to CH termed “chronification” (Lipton, 2009; Mathew, 1998). Approximately 30% of individuals with CH (Scher, Midgette, & Lipton, 2008) and more than 70% of individuals treated for CH in headache clinics (Bigal, Rapoport, Sheftell, Tepper, & Lipton, 2004) overuse acute headache medications. On average, individuals with CH use acute headache medications on 18.3 days per month, and 23% report taking acute medications on a daily basis (Scher, Lipton, Stewart, & Bigal, 2010).

1.3 Classification of Medication-Overuse Headache

Frequent use of acute headache medications may produce a form of secondary headache referred to as medication-overuse headache (MOH), which was first described in the 1950s and 1960s when chronic intractable headache was observed among frequent users of ergotamine (Peters & Horton, 1951; Horton & Peters, 1963). Medication-overuse headache currently is defined as CH (headache frequency > than 15 days a month) coinciding with regular overuse of acute headache medications. “Overuse” is quantified as use on 10 or more days per month for triptans, ergotamine, and combination analgesics or 15 or more days per month for simple analgesics and combinations of acute medications, for more than 3 months. Headache typically,
but not always, remits after overuse stops (ICHD-IIIβ), which may require inpatient hospitalization for supervised medication withdrawal. Table 1 displays the ICHD-IIIβ criteria for MOH.

Table 1. The International Classification of Headache Disorders (ICHD-3β) Criteria for Medication-Overuse Headache

| A. Headache occurring on ≥15 days per month in a patient with a pre-existing headache disorder. |
| B. Regular overuse for >3 months of one or more drugs that can be taken for acute, and/or symptomatic treatment of headache. |
| 1. Regular intake of ergotamine, triptans, opioids, or combination analgesics on ≥10 days per month for >3 months. |
| 2. Regular intake of simple analgesics on ≥15 days per month for >3 months. |
| 3. Regular intake of any combination of ergotamine, triptans, simple analgesics, NSAIDS, and/or opioids on a total of ≥ 10 days per month for >3 months without overuse of any single drug or drug class alone. |
| C. Not better accounted for by any other ICHD-3 diagnosis. |


1.4 Medication-Overuse Headache: Prevalence and Epidemiology

The prevalence of MOH is 1-2% within the general population (Colas, Munoz, Temprano, Gomez, & Pascual, 2004; Diener & Limmroth, 2004; Stovner et al., 2007; Westergaard et al., 2014). Despite its relatively low prevalence in population studies, MOH is disproportionally common in pain clinics and specialty headache centers. Schmid and colleagues (2013) reported that 29% of adult pain patients referred to an interdisciplinary pain clinic met diagnostic criteria for MOH. Furthermore, up to 25% of adult headache patients in Europe (Zeeberg, Olesen, & Jensen, 2006) and 50% of adult patients in the United States (Meskunas et al., 2006) present with MOH. Estimates of the mean duration of primary headache among those with MOH are 14.9 – 20.4 years, and the mean duration of medication overuse is 4.0 – 10.3 years (Deiner & Dahlof, 1999; Dong et al., 2015). Overall, MOH is more common in
women than in men (Bigal et al., 2004; Jonsson, Hedenrud, & Linde, 2011; Straube et al., 2010), and mirrors the gender difference in migraine prevalence. It is unclear whether women are actually more likely than men to misuse their medication, or whether gender difference in MOH are a function of disproportionate headache prevalence (Burch et al., 2015; Westergaard et al., 2014). Medication-overuse headache is most prevalent among middle-aged individuals of both genders (D’Amico, Grazzi, Usai, Rigamonti, Curone, & Bussone, 2005; Jensen & Bendtsen, 2008; Westergaard et al., 2014) with mean age of onset at 45 years (Colas et al., 2004). Because MOH onset often occurs during years of peak productivity, MOH imparts a significant burden on patients and society.

1.5 Disability Associated with Medication-Overuse Headache

Medication overuse headache was recently identified as the 18th leading cause of disability worldwide (Vos et al., 2015). Both the individual and society are negatively impacted by MOH due to lost productivity, elevated disability, increased medical costs, and a high burden on health care services (D’Amico et al., 2005; Linde et al., 2012). Moreover, MOH is substantially more disabling than other forms of headache. Individuals with MOH experience considerable work-related impairment, as the number of workdays lost by MOH patients is nearly six times higher than the number of workdays lost by those with episodic migraine (EM; Raggi et al., 2015). The annual personal cost of MOH is 3 times higher than the personal cost of migraine and more than 10 times higher than that of TTH (Linde et al., 2012). Some evidence suggests that MOH may result in even greater reductions in quality of life than other forms of CH (Lanteri-Minet et al., 2011). For these reasons, some have asserted that MOH is prevalent and among the most costly neurological condition known (Russell & Lundqvist, 2012).
1.6 Treatment of Medication-Overuse Headache

The withdrawal of overused medications, either abruptly or via gradual tapering, is the treatment-of-choice for MOH (Evers & Jensen, 2011; Obermann, Bartsch, & Katsarava, 2006). Headache frequency gradually declines over the days and weeks following withdrawal of the overused medication (Katsarava, Fritsche, Diener, & Limmroth, 2001; Relja, Granato, Bratina, Antonello, & Zorzon, 2006). The withdrawal of opioids, barbiturates, and benzodiazepines are often associated with significant withdrawal symptoms (e.g., worsening of headache, nausea, vomiting, restlessness, anxiety, and nervousness); therefore, gradual withdrawal may be the best option for patients overusing these agents. Abrupt withdrawal is the treatment-of-choice for patients who misuse triptans, ergots, combination analgesics, simple analgesics, and NSAIDs, as severe withdrawal symptoms are uncommon with these medications (Evers & Jensen, 2011). Withdrawal symptoms typically last for 2-14 days, and the duration of withdrawal symptoms is typically shorter for patients who overused triptans in comparison to those who overused ergotamine or NSAIDs (Katsarava et al., 2001; Rabe et al., 2013). Initiation of a prophylactic regimen in conjunction with withdrawal of the acute medication is often associated with better outcomes in comparison to acute medication withdrawal alone (Chiang, Schwedt, Wang, & Dodick, 2016). For example, initiation of a prophylactic regimen in conjunction with withdrawal of the acute medication is associated with significant reductions in headache frequency and improvements in quality of life, headache-related disability, anxiety, and depression (Bendtsen et al., 2014; Wallasch & Kropp, 2012; Zebenholzer, Thamer, & Wober, 2012).
1.7 Pathophysiology of Medication-Overuse Headache

The pathophysiology of MOH remains unclear. Given that MOH can be caused by the excessive use of any class of migraine-specific or non-specific acute medication, it is unlikely that MOH is attributable to the action of any specific agent. Rather, it seems more likely that acute pain medications used to treat headache share a common mechanism that is capable of producing headache chronification (Srikiatkhachorn, le Grand, Supornsilpchai, & Storer, 2014). In line with this hypothesis, neuronal hyperexcitability in the cerebral cortex and trigeminal system following the excessive use of acute pain medications, has been identified as a pathophysiological mechanism that may underlie central sensitization and cortical spreading depression (CSD; an analog for migraine aura).

Prolonged exposure to opioids may produce allodynia and hyperalgesia for long periods after the discontinuation of the medication (Ali, 1986; Arner & Meyerson, 1988; De Felice & Porreca, 2009; Johnson, Hutchinson, Williams, & Rolan, 2013). Calcitonin gene-related peptide (CGRP) plays a prominent role in initiating vasodilation of the intracranial blood vessels and is implicated in the pathogenesis of migraine (De Felice & Porreca, 2009) and increased expression of CGRP has been observed in the dorsal root ganglia following chronic administration of opioids (Belanger, Ma, Chabot, & Quirion, 2002; Ma, Zheng, Kar, & Quirion, 2000). Therefore, changes in the expression of CGRP may play a key role in the pronociceptive neural adaptations associated with MOH. In addition to changes in the expression of CGRP, sustained exposure to opioids is also associated with enhanced glutamate release (Gardell et al., 2002), expansion of cutaneous receptive fields, lower thresholds of dura-sensitive medullary dorsal horn neurons (Okada-Ogawa, Porreca, & Meng, 2009), and activation of toll-like receptor-4 on glial cells (De Felice & Porreca, 2009; Johnson et al., 2013). Although hyperalgesia is more commonly
associated with opioid medications, prolonged exposure to triptans can also produce changes in trigeminal pain nociceptive systems. Enduring but reversible cutaneous tactile allodynia has been observed in rats following chronic triptan administration. This change is associated with increased levels of CGRP in afferent trigeminal ganglionic (TG) neurons (De Felice et al., 2010b) and increased expression of nitric oxide synthase in the trigeminal neurons that innervate the dura of rats (DeFelice et al., 2010a). Considered together, this evidence suggests that the overuse of opioids and triptans can produce a persistent proinflammatory state and long-lasting pronociceptive adaptation in trigeminal primary afferent neurons located in the peripheral nervous system.

In addition to sensitization of neurons in the trigeminal system, serotonergic dysfunction has been implicated in the development of MOH as well as the affective disorders that are frequently comorbid with headache and (Atasoy, Atasoy, Unal, Emre, & Sumer, 2005; Hagen, Linde, Steiner, Stovner, & Zwart, 2012). Triptans are presumably effective due to their action as agonists on the serotonergic system. Triptans act on 5-HT\textsubscript{1B/1D} receptors which primarily exert an inhibitory effect. The acute and systematic administration of triptans decreases 5-HT synthesis in brain areas such as the dorsal raphe nucleus. However, chronic administration of triptans produces the paradoxical effect of increasing 5-HT synthesis. Potential mechanisms for this increase in 5-HT synthesis include a down-regulation or desensitization of 5-HT\textsubscript{1} receptors and/or an unmasking of excitatory triptan-sensitive 5-HT receptors (Dobson, Tohyama, Diksic, & Hamel, 2004). Like triptans, acetaminophen acts on the serotonergic system. However, acetaminophen acts on 5-HT\textsubscript{2A} receptors. Unlike to 5-HT\textsubscript{1} receptors, activation of 5-HT\textsubscript{2A} receptors is associated with increased neuronal excitability. The acute administration of acetaminophen is associated with significant increases of 5-HT and a decrease in the number of
5-HT$_2$ receptors available in the cerebral cortex (Pini, Sandrini, & Vitale, 1996). However, chronic administration of acetaminophen to rats has been found to increase the frequency of CSD and CSD-evoked increases of 5-HT2A serotonin receptor expression in the cerebral cortex and trigeminal nucleus caudalis (Supornsilpchai, le Grand, & Srikiatkhachorn, 2010a & Supornsilpchai, le Grand, & Srikiatkhachorn, 2010b).

Impairment of the endogenous 5-HT dependent pain modulation system may underlie the cortical sensitization and pain facilitation associated with MOH. Animal models suggest that decreased availability of 5-HT is associated with upregulations in the expression of pronociceptive 5-HT$_{2A}$ receptors in the cortex and trigeminal system, increased CGRP expression in the TG, and increase susceptibility to CSD (Le Grand, Saengjaroentham, Supronsilpchai, & Srikiatkhachorn, 2010; Maneepak, le Grand, & Srikiatkhachorn, 2009; Saengjaroentham, Supornsilpchai, Srikiatkhachorn, le Grand, 2012; Supornsilpchai, le Grand, & Srikiatkhachorn, 2010a; Supornsilpchai, Sanguanrangsirikul, Maneesri, & Srikiatkhachorn, 2006). These findings suggest that the chronic administration of acetaminophen or triptans may negatively impact central pain modulation systems by either decreasing nociceptive inhibition or by increasing nociceptive facilitation.

In summary, more research is needed in order to better understand the pathophysiology of MOH; however, chronic exposure to acute headache medications such as opioids, acetaminophen, and triptans is associated with increased neuronal excitability in the trigeminal system and cerebral cortex. Increased neuronal excitability in the cortex may increase susceptibility to CSD; whereas, increased excitability of trigeminal neurons may facilitate peripheral and central sensitization. Such neuronal excitability following the overuse of acute headache medications is thought to be secondary to impairment of serotoninergic pain
modulation systems that exert a strong influence on the trigeminal system. The depletion of 5-HT following the excessive use of acute headache medication may be driven at least in part by upregulation of pronociceptive 5-HT$_{2A}$ receptors that increase susceptibility to CSD. Furthermore, low 5-HT levels may also increase the release of CGRP and the subsequent sensitization of trigeminal nociceptors. Therefore, impairment of the serotonin-dependent pain modulation systems subsequent to chronic headache medication may be central to increased pain sensitivity and MOH.

1.8 Medication Use Patterns Associated with Medication-Overuse Headache

All acute medications used for the treatment of headache are capable of causing MOH (ICHD-IIIβ; Obermann et al., 2006), but as prescription practices have changed so have the rates of MOH caused by various medications. Meskunas and colleagues (2006) randomly reviewed the charts of patients seen at a single headache center during the years of 1990, 1995, 2000, and 2005. Between 1990 and 2005 MOH attributed to ergotamine and combination analgesics declined significantly (18.6% to 0% for ergotamine and 42.2% to 13.6% for combination analgesics). Simultaneously, frequency increased significantly for MOH attributed to the overuse of triptans (0% to 21.6%), simple analgesics (8.8% to 31.8%), and for combinations of acute medications (9.8% to 22.7%). Although there was a decrease in MOH associated with opioid overuse during this same period (18.6% to 9.1%), the trend was not statistically significant.

Individuals with CH are more likely to use opioid-combination analgesics in comparison to those with EH or no headache (Bigal & Lipton, 2008; Scher et al., 2010). The use of opioids for the treatment of headache is controversial. Evidence suggests that opioids are likely to sensitize the central nervous system to pain and increase the risk of MOH (Bigal & Lipton, 2008;
Johnson et al., 2013). Compared to individuals using acetaminophen to treat their migraines, individuals using opioids are at an increased risk for migraine chronification (Bigal, Serrano, Buse, Scher, Stewart, & Lipton, 2008; Scher et al., 2010). The management of headache via opiates is not recommended as a first-line treatment option due to relatively lower efficacy in comparison to a number of other acute medications as well as a number of adverse effects including tolerance, dependence, and addiction (Levin, 2014). Further, the critical dose of exposure likely to produce a transition from episodic to chronic headache is low (approximately 8 days per month; Bigal & Lipton, 2008). Despite these adverse effects, opioids are frequently prescribed in clinical practice, particularly in ED settings (Mazer-Amirshahi et al., 2014; McCarthy & Cowan, 2015).

Despite the efficacy and cost-effectiveness of triptans (Asseburg, Peura, Oksanen, Turunen, Purmonen, & Martikainen, 2012; Thorlund et al., 2014), a large proportion (43%) of individuals with chronic migraine (CM) overuse them (Ferrari et al., 2007). As a result, triptans are frequently implicated in the development of MOH. Medication-overuse headache may develop more quickly and at a lower dosage for individuals who are prescribed triptans in comparison to individuals who are prescribed other acute headache medications. The mean critical duration of overuse (calculated by subtracting the duration of MOH from the duration of medication overuse) is shorter for triptans (1.7 years) than for ergots (2.7 years) and simple analgesics (4.8 years). Among patients with MOH, the mean monthly number of doses necessary to produce MOH is lower for triptans (18 doses per month) compared to ergots (37) and simple analgesics (114; Limmroth, Katsarava, Fritsche, Przywara, & Diener, 2002).

Simple analgesics, NSAIDs, and combination analgesics are frequently used to treat headache because they are affordable and readily available over-the-counter (Dong et al., 2015;
Zwart, Dyb, Hagen, Svebak, Stovner, & Holmen, 2004), particularly outside of the United States where triptans are less likely to be prescribed. For instance, two-thirds of a Spanish sample with MOH reported the use of simple analgesics alone or in combination with ergotamine (Colas et al., 2004), whereas combination analgesics were most commonly overused by Chinese patients with MOH (Dong et al., 2015). In the United States, individuals with tension-type headache TTH frequently use over-the-counter medications such as NSAIDS (Lyngberg, Rasmussen, Jorgensen, & Jensen, 2005). NSAIDs have been found to exert a dose-dependent protective effect such that NSAIDs are associated with a decreased risk for MOH among individuals with low to intermediate headache frequency (Bigal & Lipton, 2009; Bigal, et al., 2008; Scher at al., 2010), but increased risk for chronification and MOH among individuals who have 10 or more headaches per month (Bigal & Lipton, 2009). Consequently, patients with chronic tension-type headache (CTTH) are at an increased risk for MOH.

Analgesics are used and overused in attempts to treat a wide variety of chronic pain conditions; therefore, the question has been raised whether the frequent use of analgesics can induce CH in previously headache-free individuals. Medication-overuse headache is most frequently diagnosed in patients with a prior history of migraine (Radat et al., 2008; Zwart et al., 2003) and to a lesser degree TTH (Silberstein, Lipton, & Sliwinski, 1996). Contradictory to long-held clinical lore, patients with cluster headache may also develop MOH; however, cluster headache patients with a personal or family history of migraine appear to be at a much greater risk for MOH than individuals with no personal or family history of migraine (Paemeleire, Evers, & Goadsby, 2008). Although individuals with a history of primary headache may experience chronic pain following the overuse of analgesics prescribed for conditions other than headache, MOH is very rare among individuals without a history of primary headache. For example,
patients with no prior history of primary headache who consumed large amounts of pain medications for the treatment of arthritis and irritable bowel syndrome did not show an increased incidence of CH (Bahra, Menon, & Goadsby, 2003; Lance, Parkes, & Wilkinson, 1988; Wilkinson, Becker, & Heine, 2001). Schmid and colleagues (2013) found that interdisciplinary pain patients with a history of primary headache had 13.1 times greater odds of having MOH than patients without a history of primary headache. However, individuals with primary headache who are diagnosed with comorbid chronic musculoskeletal pain or gastrointestinal complaints appear to be at greater risk for MOH compared to individuals without comorbid pain or gastrointestinal complaints (Hagen et al., 2012). This increased risk may be in part attributable to greater access to pain medications, but it appears unlikely that individuals with no prior history of headache will develop headache “de novo” as a result of medication overuse for another condition.

1.9 Modifiable Risk Factors for Medication-Overuse Headache

In addition to medication-taking behaviors, a variety of other factors are associated with increased risk for MOH. Although some risk factors such as gender and headache diagnosis are not modifiable, others are modifiable and should be emphasized because they are amenable to intervention. Modifiable risk factors include low socioeconomic status (SES), high body mass index (BMI), substance use and abuse, and mood and anxiety disorders.

Socioeconomic status is strongly associated with MOH. Compared to individuals without headache and patients with other headache diagnoses, patients with MOH are more likely to report a secondary school education or lower, be unemployed, and have a lower household income (Dong et al., 2015; Jonsson et al., 2011). Despite a clear connection between MOH and
SES, the direction of the relationship is unclear, and longitudinal research is needed to determine whether those with low socioeconomic status are more likely to develop MOH or whether MOH instead limits their professional and economic advancement.

Maladaptive health behaviors and lifestyle factors are frequently associated with headache chronification (Bigal et al., 2008; Scher et al., 2008; Westergaard, Glumer, Hansen, & Jensen, 2016). Among individuals with MOH, 21.9% are obese (Body Mass Index [BMI] ≥30), and individuals with MOH are more likely to be obese than headache-free controls, those with EM, and individuals with chronic headache without medication overuse (Straube et al., 2010; Westergaard, Glumer, Hansen, & Jensen, 2016). Thus, modifiable health behaviors such as diet and physical activity may play a role in the development of obesity and MOH. Hagen and colleagues (2012) provided support for this hypothesis when they found that physical inactivity more than doubled (OR = 2.7) the risk for MOH. Although some people with MOH may adopt a sedentary lifestyle in an attempt to avoid headache pain, prospective data suggest that obesity most often precedes increased headache frequency (Bigal, Liberman, & Lipton, 2006).

In addition to SES and health behaviors, substance-use has also been explored in relation to MOH. Limited evidence suggests that MOH patients are more likely than migraineurs to report a personal history of substance abuse or dependence (OR = 7.6) and a family history of alcohol or drug use disorders (OR = 2.8). Although dependence is seen among who overuse triptans, dependence was most common among individuals who overused opioids (Radat et al., 2005). Specific substances linked to an increased risk for MOH include prescription medications and tobacco. Medication-overuse headache patients were also more likely than headache-free controls and individuals with EM to be active smokers (Straube et al., 2010). Further, a longitudinal population-based study found that individuals who used anxiolytics such as
benzodiazepines were at a five times greater odds (OR = 5.2) and smokers were at a more than doubled odds for developing MOH, in comparison to individuals who did not use these substances (Hagen et al., 2012). By comparison, alcohol use and illicit drug use do not appear to be associated with an increased risk for the development of MOH (Hagen et al., 2012; Westergaard et al., 2016), likely because these substances trigger headache for many individuals. Notably, alcohol consumption is frequently lower among headache patients in comparison to headache-free controls (Straube et al., 2010).

Comorbid psychiatric disorders are reported by a large majority (84%) of patients with MOH (Wallasch & Kropp, 2012). Compared to migraineurs who did not misuse acute headache medications, MOH patients are more likely to suffer from major depressive disorder (OR = 21.8), generalized anxiety disorder (OR = 6.0), panic disorder with or without agoraphobia (OR = 12.1), and social phobia (OR = 4.3; Radat et al., 2005). Thus, symptoms of anxiety and depression may act as risk factors for headache chronification and may predict inadequate response to acute headache medications. Indeed, a longitudinal population-based study found that individuals with elevated symptoms of anxiety and depression were at nearly five times greater odds (OR = 4.7) of developing MOH than individuals who were not anxious or depressed (Hagen et al., 2012). Findings from treatment studies indicate that symptoms of anxiety and depression are reduced in MOH patients who undergo inpatient treatment that includes detoxification and initiation of a preventive headache medication (Zebenholzer et al., 2012). Similar results have been found with outpatient treatment studies, as the number of patients with depression anxiety decreased by 50.7% and 27.1%, respectively (Bendtsen et al., 2014). Taken together, these findings suggest that symptoms of anxiety and depression are closely tied to medication overuse and may influence pain coping abilities. Both psychiatric symptoms and
chronic pain can increase an individual’s perception of and focus on pain. As a result, individuals with headache may become fearful of headache pain and increase their analgesic consumption in an attempt to avoid the experience of pain.

Despite strong evidence that anxiety and depression are associated with MOH, there is a paucity of research examining the role of psychological variables specifically pertaining to the experience of pain, particularly cognitive appraisals of pain such as fear and anxiety. According to the fear-avoidance model of chronic pain (Vlaeyen & Linton, 2000), when pain is interpreted as non-threatening, individuals continue engagement in daily activities and functional recovery is facilitated. However, when pain is interpreted as threatening, individuals may begin to fear pain and engage in escape and avoidance behaviors. In the case of CH, it is not usually possible to avoid pain entirely; however, headache patients are often instructed to take headache medication as early as possible in the headache episode. In the short-term, hypervigilance and the avoidance of pain are adaptive, and the patient is reinforced both negatively (i.e., the headache is prevented) and positively (i.e., the patient is able to engage in daily activities) for taking headache medication at the first sign of headache. However, prolonged hypervigilance may prompt avoidance of physiological sensations and contexts actually unrelated to the experience of headache. As a result, repeated avoidance of headache-related stimuli may have the paradoxical long-term effect of increasing pain sensitivity, health care utilization, suffering, and disability (Asmundson, Norton, & Veloso, 1999; Black, Fulwiler, & Smitherman, 2015; McCracken & Dhingra, 2002; Norton & Asmundson, 2004; Vlaeyen, Snijders, Boeren, & van Eek, 1995). Headache sufferers frequently endorse high levels of pain-related anxiety and fear (Black et al., 2015). As a result, these individuals may begin to engage in a maladaptive pattern of avoidance that manifests as overuse of acute headache medications (Asmundson, Wright, Norton, &
Veloso, 2001) and increased headache frequency (Black et al., 2015). Furthermore, a recent study of migrainerouns found that FOP accounted for more variance in disability than gender, anxiety, and depression combined (Black et al., 2015). In light of these findings, FOP may act as a risk factor for MOH, but it remains under-researched in comparison to other variables.

1.10 Aims of the Present Study

The goal of the present study is to identify demographic, headache, psychiatric, medication use, and substance use variables jointly associated with MOH in a population of adults seeking treatment for primary headache disorders. A large body of research examining the prevalence and predictors of MOH makes clear that gender, headache diagnosis, SES, BMI, substance use, anxiety, and depression are independent risk factors for MOH (Dong et al., 2015; Hagen et al., 2012; Jonsson et al., 2011; Schmid et al., 2013; Straube et al., 2010). However, existing research has not empirically examined the comparative importance of these risk factors, and the overwhelming majority of research on MOH-related variables has been conducted among population samples drawn from outside of the United States. While these endeavors have increased our understanding of MOH, a strong need remains to investigate associated factors comparatively and among clinical samples given their disproportionate use of healthcare services and prevalence among headache specialty clinics (25-50% of patients; Meskunas et al., 2006; Zeeberg et al., 2006). Thus, the present study utilized treatment-seeking headache patients and a statistical approach that permits comparative and combinatorial analyses of variables that best predict MOH status. The current study serves not only to identify variables most strongly associated with MOH among treatment-seeking headache patients in the United States, but to inform the development and refinement of MOH assessment tools. Finally, the current study aids
future MOH prevention and intervention efforts by focusing on modifiable risk factors that are amenable to change.

1.11 Goals & Hypotheses

The following goals and hypotheses were proposed:

*Study Goal 1: Determine the demographic, headache-related, psychiatric, medication-use, and substance abuse variables that best differentiated individuals with MOH from treatment-seeking headache sufferers who did not meet criteria for MOH.*

Hypothesis 1a: Compared to other demographic variables, gender would be most strongly associated with MOH, as women would be more likely to endorse MOH than men.

Hypothesis 1b: Compared to other headache-related variables, headache characteristics commonly associated with migraine would be most strongly associated with MOH, as patients who reported headache duration of 4 hours or longer, patients who endorsed nausea during headache episodes, and patients who were sensitive to light and sound during headache episodes would be more likely to endorse MOH than patients who did not report these symptoms.

Hypothesis 1c: Compared to other headache medications, the use of opioids would be most strongly associated with MOH, as individuals who used opioids for the treatment of headache pain would be more likely to endorse MOH relative to patients who used other medications for the treatment of headache.

Hypothesis 1d: Compared to other psychiatric variables, FOP would be most strongly associated with MOH, as patients who endorsed high FOP would be more likely to meet diagnostic criteria for MOH than patients with low FOP.
Hypothesis 1e: Compared to other substance abuse variables, the use or misuse of opioids, anxiolytics, and sedatives would be most strongly associated with MOH, as patients who used or misused opioids, anxiolytics, and sedatives would be more likely to meet diagnostic criteria for MOH than patients who did not overuse opioids, anxiolytics, and sedatives.

Study Goal 2: Identify the combination of predictor variables that best differentiated MOH patients from treatment-seeking headache sufferers who did not meet criteria for MOH.

Hypothesis 2a: Gender, headache characteristics associated with migraine (headache duration ≥ 4 hours, nausea, photophobia, and phonophobia), the use of opioids for headache pain, FOP, and the use or misuse of opioids, anxiolytics, and sedatives would each be uniquely associated with MOH status.

Hypothesis 2b: In conjunction, gender, headache characteristics associated with migraine (headache duration ≥ 4 hours, nausea, photophobia, and phonophobia), the use of opioids for headache pain, FOP, and the use or misuse of opioids, anxiolytics, and sedatives would best differentiate MOH patients from treatment-seeking headache sufferers who did not meet criteria for MOH.
2. METHODS

2.1 Participants

Participants were patients treated for headache at Oxford Neurology Clinic within the last six years. Oxford Neurology Clinic is located in Oxford, Mississippi and provides care to patients with a variety of diseases of the nervous system, including headache. The clinic offers an array of services including consultation and management of primary headache disorders, and our lab has an existing collaborative research relationship with the owner and chief neurologist, Dr. Malcolm Roland, who is board-certified in both neurology and sleep medicine. Participants were at least 18 years of age and had a previously documented diagnosis of migraine, TTH, or cluster headache. Assuming a medium to large effect size (OR = 3.14), a power level of 0.80, and an alpha level of 0.05, a total sample size of 162 was required (Faul, Erdfelder, Buchner, & Lang, 2009).

2.2 Materials

2.2.1 Demographic Questionnaire

The Demographic Questionnaire was composed of a number of questions assessing basic information such as age, gender, education, socioeconomic status, height, and weight. This measure can be found in Appendix A.
2.2.2 Structured Diagnostic Interview for Headache – 3

The Structured Diagnostic Interview for Headache – 3 (SDIH-3; Andrew, Penzien, Rains, Knowlton, & McAnulty, 1992; Smitherman, Penzien, Rains, Nicholson, & Houle, 2014) is a computer-administered instrument designed to determine the presence of primary headache disorders based on the diagnostic criteria set out by the ICHD-IIIβ (2013). The included 21 items afforded differential diagnosis of primary headache disorders, while also providing qualitative data about headache type, frequency, pain intensity, and duration. Further, the instrument provided information about the experience of aura and cluster headaches, and was used to assess secondary causes such as head injury or trauma and medication overuse. For the purpose of this study, questions related to headache disability and headache triggers were omitted as disability was addressed in a subsequent measure and headache triggers were not relevant to the objectives of the present study. This measure can be found in Appendix B.

2.2.3 Headache Medication Use Questionnaire

Headache medication use (e.g. NSAIDS, triptans, and antiepileptics) and days per month using each headache medication were of particular interest. Medication use data was obtained using items included as part of the American Migraine Prevalence and Prevention (AMPP) study (Lipton, Serrano, Nicholson, Buse, Runken, & Reed, 2013). Respondents were asked to endorse which headache medications they used, the number of days per month of use, and the duration each medication had been used at the current frequency. Given that several preventive medications commonly prescribed for the treatment of headache were originally developed for the treatment of other conditions (e.g. antidepressants and antiepileptics), participants were asked to specify whether they were taking each medication for the treatment of headache. Acute and
preventive medications commonly used for headache were listed in the questionnaire by both brand and generic names. Acute medications classes included commonly used NSAIDS and simple analgesics, ergotamine derivatives, triptans, opioids, and combination analgesics. Preventive medication classes included antidepressants, antiepileptics, beta-blockers, and onabotulinumtoxinA (Botox). This measure can be found in Appendix C.

2.2.4 Headache Impact Test-6

The Headache Impact Test-6 (HIT-6; Kosinski et al., 2003) is a 6-item self-report measure of the impact of headache on an individual’s functioning. The instrument addresses how social functioning, cognitive functioning, and psychological distress are affected by headache. Each question requires the respondent to provide an estimate of frequency of impairment (over the last 4 weeks) on a 5-point Likert-type scale ranging from “never” to “always”. Scores range from 36 to 78 and provide a basis for categorizing headache-related disability into 4 levels of severity: little impact (scores ≤ 49), some impact (50-55), substantial impact (56-59), and very severe impact (scores ≥ 60). The HIT-6 has shown good internal consistency (α= 0.90) and test-retest reliability (r = 0.78) as well as discriminant validity across headache diagnostic groups (Kosinski et al., 2003). This measure can be found in Appendix D.

2.2.5 Patient Health Questionnaire-9

The Patient Health Questionnaire-9 (PHQ-9; Kroenke, Spitzer, & Williams, 2001) is a 9-item self-administered measure of depression severity based on DSM-IV diagnostic criteria. Each question requires the respondent to provide an estimate of frequency of depressive symptoms (over the past two weeks) on a 4-point Likert-type scale. Each item is rated from 0
(not at all) to 3 (nearly every day). Scores range from 0 to 27 and provide a basis for categorizing depressive symptoms into 4 levels of severity. Scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively. The PHQ-9 has shown good construct validity (Kroenke et al., 2001), as well as adequate internal consistency pre- and post-treatment (α = .74 and .81) and convergent/divergent validity (Titov, Dear, McMillan, Anderson, Zou, & Sunderland, 2011). Furthermore, meta-analytic data indicate that the PHQ-9 is externally valid and able to correctly identify (sensitivity = 0.80) and rule-out (specificity = 0.92) major-depressive disorder across a wide range of settings and populations (Gilbody, Richards, Brealey, & Hewitt, 2007). This measure can be found in Appendix E.

2.2.6 Generalized Anxiety Disorder 7-Item Scale

The Generalized Anxiety Disorder 7-Item Scale (GAD-7; Spitzer, Kroenke, Williams, & Lowe, 2006) is a seven item self-administered measure of anxiety symptoms. Each item requires respondents to rate the frequency of anxiety symptoms (over the past two weeks) on a 4-point Likert-type scale that ranges from 0 (not at all) to 3 (nearly every day). Scores range from 0 to 21 and scores of 5, 10, and 15 represent mild, moderate, and severe anxiety symptoms, respectively. The GAD-7 has excellent internal consistency (α= 0.92) and test-retest reliability (r = 0.83), as well as convergent, construct, criterion, procedural, and factorial validity for the diagnosis of generalized anxiety disorder (Spitzer et al., 2006). The GAD-7 also performs well as a screening tool for other anxiety disorders such as post-traumatic stress disorder, panic disorder, and social anxiety (Kroenke, Spitzer, Williams, Monahan, & Lowe, 2007). This measure can be found in Appendix F.
2.2.7 Pain Anxiety Symptoms Scale-Short Version

The Pain Anxiety Symptoms Scale (PASS-20; McCracken & Dhingra, 2002) is a condensed 20-item version of the 40-item PASS (McCracken, Zayfert, & Gross, 1992). The PASS-20 is a self-administered measure designed to assess FOP. Each item requires the respondents to rate how frequently they engage in specific thoughts and behaviors related to the experience of pain on a 6-point Likert-type scale that ranges from 0 (never) to 5 (always). The PASS-20 is divided into four 5-item subscales that measure cognitive anxiety responses, escape and avoidance, fearful thinking, and physiological anxiety responses. Subscale scores range from 0-25 and total scores range from 0-100. Individuals with scores greater than 30 are classified as having high FOP (Abrams, Carleton, & Asmundson, 2007). The PASS-20 has shown excellent internal consistency (α = 0.91; Abrams et al., 2007; McCracken & Dhingra, 2002), good test-retest reliability (r = 0.68; Coons, Hadjistavropoulos, & Asmundson, 2004), as well as concurrent validity with other related measures (Abrams et al., 2007). This measure can be found in Appendix G.

2.2.8 Medication Use/Misuse Questionnaire

Similar to the measure used by Meisel and Goodie (2015), respondents were asked to endorse whether they had a current prescription for the following non-headache medications: stimulants (i.e., Ritalin, Adderall, Dexedrine), opioids (not for the treatment of headache; i.e., Vicodin, Oxycotin, Percocet), anxiolytics (i.e., Xanax, Valium, Klonopin), and sedatives (i.e., Ambien, Halcion, Restoril). Prescription misuse was assessed by asking respondents to endorse whether they had used any of these medications without a prescription during the past 12
months. For each medication they endorsed misusing, participants were asked to endorse the average number of days per month of use. This measure can be found in Appendix H.

2.2.9 Substance Use/Abuse Questionnaire

Similar to the measure used by Meisel and Goodie (2015), respondents answered questions related to the frequency of their alcohol, tobacco, caffeine, and marijuana use during the past 12 months. For each substance they endorsed, frequency of use was assessed by asking respondents to report the average number of days per month of use. Respondents were also asked whether they had used cocaine, methamphetamine, ecstasy, heroin, inhalants, or hallucinogens during their lifetime. Additional items queried whether or not they had experienced symptoms of dependence and whether they or a family member had been diagnosed or treated for a substance use disorder. This measure can be found in Appendix I.

2.3 Procedure

Patients treated at Oxford Neurology Clinic consent to being contacted and having their data used for research purposes as part of the clinic intake procedures. Medical chart reviews were conducted on May, 24, 2016 by the chief neurologist in order to identify eligible participants treated for headache within the past six years (e.g., between March, 1, 2010 – May, 24, 2016). Electronic records were searched using the following diagnostic terms: “drug-induced”, “migraine”, “cluster”, “tension”, and “headache”. Between June 2016 and February 2017, all eligible patients who had email addresses on file were emailed an invitation to participate in the study, and a random sample of patients without email addresses who had been seen in the clinic since January, 1, 2012 were sent mailed invitations to participate. Each invitation included a link to a computer-administered Qualtrics survey that included the
aforementioned measures. When eligible participants visited the link, they were provided with information about study procedures and associated risks and benefits. Prior to beginning the survey, informed consent was obtained electronically. Patients who completed the questionnaire received a $10 Amazon gift card for participating. Patients who reported that they no longer suffered from headache were excluded from the study, as were patients who had less than 80% complete data (in total and on each individual measure), failed to answer headache-relevant items, or endorsed headache resulting from head injury/trauma.

2.7 Statistical Analysis

Analyses were conducted with SPSS 22.0 (IBM, Inc., Chicago, IL, USA). Descriptive statistics are presented using frequency counts, percentages, means, and standard deviations. Odds ratios (ORs) with 95% confidence intervals (CIs) and $p$-values are also presented for interpretive convenience. To avoid the common problem of inflated Type 1 error rates often associated with analyses involving numerous predictor variables, standardized mean differences (SMDs; Austin, 2011) were calculated to quantify the size of any observed differences between MOH and non-MOH groups. Standard mean difference functions as a measure of effect size between groups that is calculated in relation to the two groups’ pooled variability (i.e., SD). Similar to Cohen’s D (Cohen, 1992), SMDs of 0.2-0.49 are interpreted as small effects, 0.5-0.79 as medium effects, and $\geq 0.8$ as large effects.

Combined theory- and data-driven approaches were used to examine the characteristics independently (i.e., one predictor alone) and uniquely (i.e., after controlling for other predictors) associated with MOH. To reduce the potential number of predictors into discrete subsets for subsequent analyses, predictor variables were aggregated into five domains based on theoretical
consistency: 1) demographic variables, 2) headache characteristics (including pain quality, headache frequency, and headache-related disability), 3) psychiatric variables, and 4) headache medication use, and 5) substance use variables. Next, a regression classification tree selection strategy was utilized separately within each domain to identify the candidate predictors that best differentiated between those with and without MOH. For this approach, the chi-square automatic interaction detection (CHAID) algorithm (Kass, 1980) was used to select the optimal combination of candidate predictors of MOH within each domain after adjusting the required statistical significance by the number of candidate predictors in each domain with a Bonferroni correction ($p$-value = .05/number of predictors within domain). The CHAID algorithm was selected because it is a non-parametric recursive partitioning model that tests which predictor variables are most strongly associated with a dichotomous outcome. As such, the CHAID algorithm is an empirically-based means of selecting candidate predictors for inclusion in a multivariate model.

Subsequently, all candidate predictors selected from each domain analysis were simultaneously forced into a multivariable logistic regression model with MOH status as the dichotomous outcome variable. The calibration of this model was assessed using a Hosmer and Lemeshow test, and the predictive utility was assessed using the area under the curve (AUC) of a calculated receiver operating characteristic curve. Because the final model was the result of many data-driven inferences, the 95% CIs of the parameter estimates were re-estimated for confirmation using bootstrapping of 500 samples of the dataset with replacement.
3. RESULTS

3.1 Participant Demographics and MOH Prevalence

Two-thousand nine hundred and fifty-three eligible patients (i.e., adults with tension-type headache, migraine, or cluster headache) were identified from the Oxford Neurology Clinic database. A total of 1,656 patients were sent invitations to participate in the study, 646 via email and 1,010 via mail. A total of 198 patients responded to the invitation (12.0% response rate). Twenty patients failed to complete the entire survey and were excluded from analyses, as were three patients who denied headache and 11 patients who reported headaches deriving from a head injury or trauma.

The analyzed sample consisted of 164 headache patients (87.8% female) with a mean age of 40.14 years ($SD = 13.80$). The majority (82.9%) of the sample was Caucasian, 14.6% were African-American, 1.2% were Hispanic/Latino, 0.6% were Asian, and 0.6% identified as multiracial. With regard to headache diagnosis, 43 patients (26.2%) met ICHD-III criteria for MOH, 21 (12.8%) met criteria for CM without MOH, 6 (3.7%) met criteria for CTTH, 70 (42.7%) met criteria for EM (34 [20.7%] without aura and 36 [22%] with aura), 23 (14%) met criteria for episodic tension-type headache, and 1 (0.6%) met criteria for cluster headache. On average, participants reported experiencing headache 12.48 days per month ($SD = 8.10$), and average headache severity for the sample was 6.42 out of 10 ($SD = 1.78$). Participants reported a
mean score of 64.44 ($SD = 6.76$) on the HIT-6, with 79.3 % scoring at or above the cutoff for very severe headache disability.

3.2 Determinants of MOH Status

3.2.1 Demographic Characteristics

As expected, the patients who met diagnostic criteria for MOH experienced more headache days per month on average (20.58) in comparison to patients who did not meet criteria for MOH (9.60; $p < .001$). Table 2 displays additional demographic characteristics of the sample by MOH status. The two groups were evenly balanced (SMD < 0.15) on all demographics except age, marital status, and BMI. On average, MOH patients were five years older (43.86 vs. 38.82; SMD = 0.37), less likely to be married (18.6% vs. 33.9%; SMD = 0.30), and reported a greater BMI (32.56 vs. 28.83; SMD = 0.48) relative to the non-MOH control group. Although age, marital status, and BMI differentiated between the two diagnostic groups in the univariate analyses, none of the demographic variables were significant within the classification tree model.
Table 2. Participant Demographic Characteristics by MOH Status.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>MOH (N = 43)</th>
<th>No MOH (N= 121)</th>
<th>OR</th>
<th>95% CI</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>43.86 (14.65)</td>
<td>38.82 (13.30)</td>
<td>1.03*</td>
<td>1.00-1.05</td>
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<tr>
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<td></td>
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<td>0.37-3.16</td>
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<tr>
<td>Male</td>
<td>5 (11.6%)</td>
<td>15 (12.4%)</td>
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</tr>
<tr>
<td>Female</td>
<td>38 (88.4%)</td>
<td>106 (87.6%)</td>
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<tr>
<td>Ethnicity</td>
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<td>0.42-2.76</td>
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<tr>
<td>White</td>
<td>36 (83.7%)</td>
<td>100 (82.6%)</td>
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<td>Non-white</td>
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<td>Marital Status</td>
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<td>0.19-1.05</td>
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<td>41 (33.9%)</td>
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<td>Not Married</td>
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<td>80 (66.1%)</td>
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<td>0.37-1.51</td>
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<td>&lt; Bachelor’s</td>
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<td>56 (46.3%)</td>
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</tr>
<tr>
<td>degree</td>
<td>20 (46.5%)</td>
<td>65 (53.7%)</td>
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<td>Income</td>
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<td>0.39-1.65</td>
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<td>&lt; $50,000</td>
<td>26 (61.9%)</td>
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<td>52 (43.3%)</td>
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</tr>
<tr>
<td>Employed</td>
<td>24 (57.1%)</td>
<td>73 (60.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unemployed</td>
<td>18 (42.9%)</td>
<td>48 (39.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>32.56 (9.15)</td>
<td>28.83 (7.14)</td>
<td>1.06**</td>
<td>1.02-1.11</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Note. Values are frequency counts (%), except for age which is displayed as a mean (standard deviation). MOH = medication-overuse headache, OR = odds ratio vs No MOH group, CI = confidence interval, SMD = Standardized mean difference, BMI = body mass index.

*p < .05. **p < .01.

3.2.2 Headache Characteristics

Table 3 displays the headache characteristics between groups. A small effect was observed between groups on headache severity (SMD = 0.46) and a medium effect was observed in headache-related disability (SMD = 0.61). These univariate outcomes indicated that patients with MOH experienced more severe headaches and greater headache-related disability in comparison to non-MOH patients. In the classification tree, only headache-related disability (HIT-6) scores significantly discriminated between groups, \( \chi^2 (1) = 17.64, p < .001 \). Moreover,
the classification tree indicated that a HIT-6 score of 67 made the best distinction between the
two groups such that individuals who obtained scores greater than 67 on the HIT-6 were more
likely to meet criteria for MOH in comparison to individual who reported scores equal to or less
than 67. Selection of additional predictors within this domain did not significantly improve the
prediction afforded by headache-related disability alone.

Table 3. Headache characteristics by MOH Status.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>MOH (N = 43)</th>
<th>No MOH (N = 121)</th>
<th>OR</th>
<th>95% CI</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache Duration</td>
<td></td>
<td></td>
<td>2.40</td>
<td>0.86-6.65</td>
<td>0.27</td>
</tr>
<tr>
<td>&lt; 4 hours</td>
<td>5 (11.6%)</td>
<td>29 (24%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 4 hours</td>
<td>38 (88.4%)</td>
<td>92 (76%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain Quality</td>
<td></td>
<td></td>
<td>1.28</td>
<td>0.62-2.62</td>
<td>0.10</td>
</tr>
<tr>
<td>Throbbing</td>
<td>26 (60.5%)</td>
<td>80 (66.1%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tight Pressure</td>
<td>17 (39.5%)</td>
<td>41 (33.9%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache Location</td>
<td></td>
<td></td>
<td>0.95</td>
<td>0.45-2.02</td>
<td>0.02</td>
</tr>
<tr>
<td>Unilateral</td>
<td>30 (69.8%)</td>
<td>83 (68.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bilateral</td>
<td>13 (30.2%)</td>
<td>38 (31.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
<td></td>
<td>1.93</td>
<td>0.78-4.76</td>
<td>0.23</td>
</tr>
<tr>
<td>Yes</td>
<td>36 (83.7%)</td>
<td>88 (72.7%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>7 (16.3%)</td>
<td>33 (27.3%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Photophobia</td>
<td></td>
<td></td>
<td>3.35</td>
<td>0.74-15.16</td>
<td>0.26</td>
</tr>
<tr>
<td>Yes</td>
<td>41 (95.3%)</td>
<td>104 (86%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2 (4.7%)</td>
<td>17 (14%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phonophobia</td>
<td></td>
<td></td>
<td>2.68</td>
<td>0.58-12.32</td>
<td>0.21</td>
</tr>
<tr>
<td>Yes</td>
<td>41 (95.3%)</td>
<td>107 (88.4%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>2 (4.7%)</td>
<td>14 (11.6%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aura Symptoms</td>
<td></td>
<td></td>
<td>1.61</td>
<td>0.79-3.28</td>
<td>0.21</td>
</tr>
<tr>
<td>Yes</td>
<td>27 (62.8%)</td>
<td>62 (51.2%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16 (37.2%)</td>
<td>59 (48.8%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache Severity</td>
<td></td>
<td></td>
<td>1.34*</td>
<td>1.07-1.69</td>
<td>0.46</td>
</tr>
<tr>
<td>(HIT-6)</td>
<td>7.02 (1.47)</td>
<td>6.21 (1.83)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache Disability</td>
<td></td>
<td></td>
<td>1.12**</td>
<td>1.05-1.20</td>
<td>0.61</td>
</tr>
<tr>
<td>(HIT-6)</td>
<td>67.60 (6.00)</td>
<td>63.31 (6.68)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note. Values are frequency counts (%), except for headache severity and headache disability
which are displayed as a mean (standard deviation). MOH = medication-overuse headache, OR =
odds ratio vs No MOH group, CI = confidence interval, SMD = Standardized mean difference,
HIT-6 = Headache Impact Test-6.

*p < .05. **p < .01.
3.2.3 Psychiatric Symptoms

Table 4 displays scores on the self-report measures of psychiatric symptoms by diagnostic status. A medium-sized effect was observed on PHQ-9 (SMD = 0.64), as patients with MOH reported moderate levels of depressive symptomatology compared to those without MOH, who instead on average reported mild levels of depressive symptomatology. Furthermore, a small between-group difference was observed on the GAD-7 (SMD = 0.46), such that patients with MOH reported more severe symptoms of relative to individuals who did not meet diagnostic criteria for MOH. Medium differences (SMDs = 0.54-0.78) were also obtained for all four PASS-20 subscales. Relative to treatment-seeking patients who did not meet criteria for MOH, patients in the MOH group reported higher levels of cognitive anxiety (15.93 vs. 11.38), escape and avoidance behaviors (14.64 vs. 10.44), fearful appraisals (8.26 vs. 4.96), and physiological anxiety (10.49 vs. 7.33). For this domain, the PASS-20 escape and avoidance subscale was the only variable selected in the classification tree as a significant predictor of MOH status, \( \chi^2 (1) = 19.24, p < .001 \). The classification tree indicated that a PASS-20 escape and avoidance subscale score of 12 made the best distinction between the two groups.
Table 4. Self-reported Psychiatric Symptoms by MOH Status.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>MOH (N = 43)</th>
<th>No MOH (N = 121)</th>
<th>OR</th>
<th>95% CI</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHQ-9 Total Score</td>
<td>12.63 (6.76)</td>
<td>8.31 (6.71)</td>
<td>1.09**</td>
<td>1.04-1.15</td>
<td>0.64</td>
</tr>
<tr>
<td>GAD-7 Total Score</td>
<td>9.30 (6.08)</td>
<td>6.55 (5.95)</td>
<td>1.08*</td>
<td>1.02-1.14</td>
<td>0.46</td>
</tr>
<tr>
<td>PASS-20 Total Score</td>
<td>50.14 (18.92)</td>
<td>34.11 (20.96)</td>
<td>1.04***</td>
<td>1.02-1.06</td>
<td>0.78</td>
</tr>
<tr>
<td>Cognitive Anxiety Subscale</td>
<td>15.93 (6.52)</td>
<td>11.38 (7.00)</td>
<td>1.10**</td>
<td>1.04-1.17</td>
<td>0.66</td>
</tr>
<tr>
<td>Escape &amp; Avoidance Subscale</td>
<td>14.64 (5.36)</td>
<td>10.44 (6.13)</td>
<td>1.12***</td>
<td>1.05-1.19</td>
<td>0.71</td>
</tr>
<tr>
<td>Fear Appraisal Subscale</td>
<td>8.26 (5.62)</td>
<td>4.96 (4.96)</td>
<td>1.12**</td>
<td>1.05-1.19</td>
<td>0.64</td>
</tr>
<tr>
<td>Physiological Anxiety Subscale</td>
<td>10.49 (6.31)</td>
<td>7.33 (5.68)</td>
<td>1.09**</td>
<td>1.03-1.16</td>
<td>0.54</td>
</tr>
</tbody>
</table>

Note. Values are displayed as a mean (standard deviation). MOH = medication-overuse headache, OR = odds ratio vs No MOH group, CI = confidence interval, SMD = Standardized mean difference, PHQ-9 = Patient Health Questionnaire-9, GAD-7 = Generalized Anxiety Disorder 7-Item Scale, PASS-20 = Pain Anxiety Symptoms Scale-Short Version.

*p < .05. **p < .01. ***p < .001.

3.2.4 Medication Use

Rates of headache medication use by diagnostic status are displayed in Table 5. None of the patients included in the sample reported the use of ergotamine for the treatment of headache. However, meaningful differences between groups were observed for the use of many of the acute headache medications. In comparison to non-MOH controls, patients who met diagnostic criteria for MOH were more likely to use NSAIDs (72.1% vs. 60.3%), opioids (25.6% vs. 11.6%), antidepressants (32.6% vs. 18.2%), and beta-blockers (23.3 vs. 7.4%) for the treatment of headache. Patients who met diagnostic criteria for MOH were also more likely to have received a Botox treatment within the past six months (27.9% vs. 14.0%) in comparison to non-MOH controls. A
medium-sized difference (SMD = 0.51) was observed for the use of combination medications (e.g., acetaminophen/aspirin/caffeine, codeine with acetaminophen, hydrocodone with acetaminophen), with 60.5% of MOH patients reporting use of these medications in comparison to 33.1% of patients who did not meet criteria for MOH. Of these differences, only the use of combination medications was selected into the classification tree to discriminate between the groups $\chi^2 (1) = 9.10, p = .002.$

<table>
<thead>
<tr>
<th>Predictor</th>
<th>MOH (N = 43)</th>
<th>No MOH (N = 121)</th>
<th>OR</th>
<th>95% CI</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs</td>
<td>31 (72.1%)</td>
<td>73 (60.3%)</td>
<td>1.70</td>
<td>0.80-3.63</td>
<td>0.22</td>
</tr>
<tr>
<td>Triptans</td>
<td>18 (41.9%)</td>
<td>60 (49.6%)</td>
<td>0.73</td>
<td>0.36-1.48</td>
<td>0.14</td>
</tr>
<tr>
<td>Opioids</td>
<td>11 (25.6%)</td>
<td>14 (11.6%)</td>
<td>2.63*</td>
<td>1.09-6.35</td>
<td>0.35</td>
</tr>
<tr>
<td>Combination Medications</td>
<td>26 (60.5%)</td>
<td>40 (33.1%)</td>
<td>3.10**</td>
<td>1.51-6.36</td>
<td>0.51</td>
</tr>
<tr>
<td>Botox</td>
<td>12 (27.9%)</td>
<td>17 (14.0%)</td>
<td>2.37*</td>
<td>1.02-5.49</td>
<td>0.32</td>
</tr>
<tr>
<td>Anti-depressants</td>
<td>14 (32.6%)</td>
<td>22 (18.2%)</td>
<td>2.17</td>
<td>0.99-4.78</td>
<td>0.31</td>
</tr>
<tr>
<td>Beta-blockers</td>
<td>10 (23.3%)</td>
<td>9 (7.4%)</td>
<td>3.77**</td>
<td>1.41-10.05</td>
<td>0.45</td>
</tr>
<tr>
<td>Anti-epileptics</td>
<td>14 (32.6%)</td>
<td>31 (25.6%)</td>
<td>1.40</td>
<td>0.66-2.99</td>
<td>0.14</td>
</tr>
</tbody>
</table>

Note. Values are frequency counts (%). MOH = medication-overuse headache; OR = odds ratio vs No MOH group; CI = confidence interval; SMD = Standardized mean difference, NSAIDs = nonsteroidal anti-inflammatory drugs.

*p < .05. **p < .01.

### 3.2.5 Substance Use

Rates of prescription medication use and substance use are displayed in Table 6. Very few patients reported the misuse of medications prescribed for the treatment of medical conditions other than headache. A total of four patients reported that they used opioids prescribed for conditions other than headache without a physician’s prescription. In addition, six patients reported the misuse of anxiolytics and two patients reported the misuse of sedatives.
Given that the rate of medication misuse was so low, between-group comparisons were not conducted for medication misuse variables.

In addition to low rates of prescription medication misuse, patients included in the sample reported low rates of illicit drug use. The majority of patients (n = 156) reported that they had not used illicit substances other than marijuana at any point in their life. Of the patients who endorsed illicit drug use, five patients reported cocaine use, two patients reported crack cocaine use, three patients reported methamphetamine use, two patients reported ecstasy use, two patients reported inhalant use, and four patients reported hallucinogen use at some point during their lifetime. In terms of substance use disorder (SUD) symptomatology, three patients reported that they were unable to stop using substances when they wanted to and three patients reported that they experienced withdrawal symptoms after they stopped using a substance at some point in their life. Once again, between-group comparisons were not conducted for illicit substance use variables other than marijuana because symptoms of SUD were infrequently reported by patients included in the sample.

Although medication misuse and a personal history of illicit substance use were very rare in the current sample, significant proportions of patients reported the prescribed use of medications for other medical conditions, a family history of substance abuse, and/or the use of alcohol, tobacco, caffeine, and cannabis. Accordingly, between-group analyses were conducted for prescription drug use, a family history of substance abuse, and the use of alcohol, tobacco, caffeine and cannabis. Small but meaningful differences (SMD = 0.20-0.28) between groups were observed in current prescriptions for opioids for conditions other than headache, current prescriptions for anxiolytics, and a family history positive for SUD. As such, patients who met diagnostic criteria for MOH were more likely to be prescribed opioids for pain conditions other
than headache (9.3 vs. 4.1%), have a current prescription for anxiolytics (30.2 vs. 17.4%), and to have a family member with a SUD (32.6% vs. 19.8%) in comparison to patients who did not meet criteria for MOH. Despite these small univariate differences, none of the substance use variables were independently selected as significant predictors of MOH status in the classification tree model.

### Table 6. Self-Reported Substance Use by MOH Status.

<table>
<thead>
<tr>
<th>Predictor</th>
<th>MOH (N = 43)</th>
<th>No MOH (N = 121)</th>
<th>OR</th>
<th>95% CI</th>
<th>SMD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulant Rx</td>
<td>3 (7.0%)</td>
<td>10 (8.3%)</td>
<td>0.83</td>
<td>0.22-3.18</td>
<td>0.04</td>
</tr>
<tr>
<td>Opioid Rx (not for Headache)</td>
<td>4 (9.3%)</td>
<td>5 (4.1%)</td>
<td>2.38</td>
<td>0.61-9.31</td>
<td>0.20</td>
</tr>
<tr>
<td>Anxiolytic Rx</td>
<td>13 (30.2%)</td>
<td>21 (17.4%)</td>
<td>2.06</td>
<td>0.92-4.61</td>
<td>0.28</td>
</tr>
<tr>
<td>Sedative Rx</td>
<td>8 (18.6%)</td>
<td>14 (11.6%)</td>
<td>1.75</td>
<td>0.68-4.51</td>
<td>0.18</td>
</tr>
<tr>
<td>Alcohol Use (past 12 months)</td>
<td>24 (55.8%)</td>
<td>75 (62.0%)</td>
<td>0.78</td>
<td>0.38-1.57</td>
<td>0.11</td>
</tr>
<tr>
<td>Tobacco Use (past 12 months)</td>
<td>9 (20.9%)</td>
<td>27 (22.3%)</td>
<td>0.92</td>
<td>0.39-2.16</td>
<td>0.03</td>
</tr>
<tr>
<td>Caffeine Use (past 12 months)</td>
<td>42 (97.7%)</td>
<td>112 (92.6%)</td>
<td>3.38</td>
<td>0.42-27.46</td>
<td>0.19</td>
</tr>
<tr>
<td>Cannabis Use (past 12 months)</td>
<td>2 (4.7%)</td>
<td>11 (9.1%)</td>
<td>0.49</td>
<td>0.10-2.30</td>
<td>0.15</td>
</tr>
<tr>
<td>Family History of SUD</td>
<td>14 (32.6%)</td>
<td>24 (19.8%)</td>
<td>1.95</td>
<td>0.90-4.25</td>
<td>0.27</td>
</tr>
</tbody>
</table>

Note. Values are frequency counts (%). MOH = medication-overuse headache, OR = odds ratio vs No MOH group, CI = confidence interval, SMD = Standardized mean difference, Rx = Prescription, SUD = substance use disorder.

#### 3.3 Final Multivariable Model

Table 7 displays the three selected predictors (headache-related disability, escape and avoidance subscale of the PASS-20, and the use of combination medications for the treatment of headache) that were forced into the final multivariable model using the classification tree approach, along with 95% CIs as estimated through bootstrapping using 500 samples with replacement. The omnibus model differentiated well between the two diagnostic groups $\chi^2(3) = 28.86$, $p < .001$, and the Hosmer-Lemeshow test confirmed an absence of differences between
observed and predicted participant classifications $\chi^2(8) = 3.66, p = .887$. Figure 1 graphically displays the predictive utility of this 3-variable model, which had an AUC = 0.78 (95% CI = 0.71–0.86). Headache disability and the consumption of combination medications for the treatment of headache were uniquely associated with MOH diagnosis after controlling for the other predictors and after bootstrapping confirmation. Specifically, patients prescribed combination medications for the treatment of headache were approximately three times as likely to have MOH as patients who were not prescribed these medications. Likewise, odds of meeting diagnostic criteria for MOH increased 9% for each 1-point increase on the HIT-6. Further, the effect of the PASS-20 fell just short of significance after controlling for the other predictors included in the final model. For every 1-point increase on the PASS-20 escape and avoidance scale, odds of meeting diagnostic criteria for MOH increased by 7%.

Table 7. Final Multivariable Prediction Model

<table>
<thead>
<tr>
<th>Predictor</th>
<th>$\beta$</th>
<th>Bootstrapped 95% CI</th>
<th>OR</th>
<th>95% CI</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache Disability (HIT-6)</td>
<td>0.09</td>
<td>0.17-0.21</td>
<td>1.09</td>
<td>1.01-1.18</td>
<td>.022</td>
</tr>
<tr>
<td>PASS-20 Escape &amp; Avoidance Score</td>
<td>0.07</td>
<td>0.01-0.15</td>
<td>1.07</td>
<td>1.00-1.15</td>
<td>.051</td>
</tr>
<tr>
<td>Combination Medications</td>
<td>1.13</td>
<td>0.37-1.98</td>
<td>3.09</td>
<td>1.42-6.73</td>
<td>.004</td>
</tr>
</tbody>
</table>

Note. Omnibus model $\chi^2(3) = 28.86, p <.001$, Hosmer-Lemeshow $\chi^2(8) = 3.66, p = .887$, bootstrapped estimate from 500 sample replications. $\beta$ = estimated multinomial logistic regression coefficient, CI = confidence interval, HIT-6 = Headache Impact Test-6, PASS-20 = Pain Anxiety Symptoms Scale-Short Version.
Figure 1. Receiver operating characteristics (ROC) curve of multivariable prediction model of medication-overuse headache status. Area under the curve: 0.78 (95% confidence interval 0.71-0.86), $p < .001$. 
4. DISCUSSION

The present cross-sectional analysis is among the first to examine the comparative importance of factors associated with MOH among treatment-seeking headache sufferers in the United States. In this sample, the factors most strongly associated with MOH included headache-related disability, attempts to escape and avoid painful stimuli, and the use of combination medications for the treatment of headache. In conjunction, these three variables accurately distinguished between those with and without MOH.

4.1 Demographic and Headache Characteristics

Contrary to hypotheses, women were no more likely than men to meet diagnostic criteria for MOH. These findings suggest that demographic characteristics may not be particularly relevant to the identification of headache patients who are currently overusing acute pain medications. Although some studies have found that women are more likely to develop MOH (Jonsson et al., 2011), others have suggested that the preponderance of women with MOH simply reflects the fact that women are much more likely than men to suffer from headache (Burch et al., 2015; Westergaard et al., 2014). The findings of the current study support the latter conclusion and suggest that headache treatment history, behavioral responses to pain, and psychiatric variables are more relevant in the identification of patients with medication overuse.
Patients with a history of migraine typically experience unilateral pulsating pain (ICHD-IIIβ), and previous research suggests that patients with MOH typically report a history of migraine (Mathew, 1982; Radat et al., 2008). Although patients with TTH may also overuse acute headache medications, TTH is less frequently associated with MOH in comparison to migraine (Silberstein et al., 1996). Despite the association between migraine and MOH, pain quality and location frequently change following the onset of MOH (Tepper, 2012) and may differ by medication type (Limmroth et al., 2002). Thus, it is more difficult to identify the primary headache diagnosis while the patient continues to overuse acute headache medications (Diener, Holle, Solbach, & Gaul, 2016). In contrast to previous studies that identified headache characteristics and diagnoses most closely associated with the development of MOH, the current study examined whether headache characteristics could differentiate between patients with MOH and non-MOH controls. Results indicated that patients with MOH did not differ significantly from non-MOH controls in terms of pain location or quality. Thus, patients who report unilateral pulsating migraine pain may be more likely to develop MOH relative to TTH patients who report bilateral tightening pain; however, headache characteristics such as pain quality and location do not appear to reliably differentiate between patients already with MOH and those without MOH.

4.2 Headache-Related Disability

The finding that headache patients who met criteria for MOH were significantly more disabled in comparison to non-MOH control patients adds to a large body of research indicating that MOH is significantly more disabling than most other forms of headache (Lanteri-Minet et al., 2011; Linde et al., 2012; Raggi et al., 2015). In addition to previous estimates of the societal burden and monetary cost associated with MOH (D’Amico et al., 2005; Linde et al., 2012; Vos
et al., 2013), the present findings highlight the personal costs associated with MOH. Specifically, individuals with MOH are more likely to experience negative cognitive, social, and psychological outcomes in comparison to patients seeking treatment for other headache conditions. In the univariate analysis, individuals with MOH reported HIT-6 scores that were 4.29 points higher on average relative to non-MOH controls. Moreover, the multivariable model indicated that for every 1-point increase on the HIT-6, the odds of meeting criteria for MOH increased by 9%, even after controlling for scores on the escape and avoidance subscale of the PASS-20 and the use of combination medications. Extrapolating this finding using the four levels of severity specified by the HIT-6, an individual who scored a 60 on the HIT-6 (e.g., “very severe” headache-related disability) was at approximately two times greater odds of meeting diagnostic criteria for MOH in comparison to an individual who scored a 49 on the HIT-6 (e.g., “little impact” of headache on disability). Although HIT-6 scores were associated with MOH, headache-related disability is conceptualized as a consequence of MOH (Linde et al., 2012) rather than a predictor of maladaptive medication use behaviors. Therefore, headache-related disability is rarely conceptualized as a risk factor for MOH. As such, the HIT-6 and other brief measures of headache-related disability may be most useful for identifying patients who are currently overusing their headache medications and for monitoring treatment progress.

4.3 Escape and Avoidance Behaviors

Although previous studies have indicated that repeated engagement in escape and avoidance behaviors in the presence of pain-related stimuli is associated with increased disability and the use of acute headache medications (Asmundson et al., 2001; Black et al., 2015), the present study is among the first study to examine FOP as a predictor of MOH using ICHD-IIIβ
diagnostic criteria. Patients who met diagnostic criteria for MOH were more likely to engage in escape and avoidance behaviors (e.g. avoiding important activities due to pain, cessation of activities at the first sign of pain, and taking medications at the first sign of pain) relative to patients with other headache conditions. Individuals with MOH obtained PASS-20 escape and avoidance subscale scores that were on average 4.20 points greater than those of non-MOH controls. Moreover, the multivariable model indicated that for every 1-point increase on the PASS-20 escape and avoidance subscale, the odds of meeting criteria for MOH increased by 7%, even after controlling for headache-related disability and the use of combination medications.

The finding that pain-related escape and avoidance is strongly associated with MOH has significant clinical implications. Historically, headache patients have been advised to identify and avoid headache triggers (World Health Organization, 2006). Presumably, this advice is given under the notion that avoidance of triggers should confer reduction in headache. However, there is very little empirical or theoretical support for this strategy (see Martin & MacLeod, 2009). Instead, a prolonged pattern of escape and avoidance in response to headache triggers and headache pain is often maladaptive and associated with a number of negative consequences stemming from increased sensitivity to the avoid trigger, including increased pain, disability, and the excessive use and misuse of analgesics (Asmundson et al., 1999; Asmundson et al., 2001; Black et al., 2015; McCracken & Dhand, 2002; Norton & Asmundson, 2004; Vlaeyen et al., 1995). Based on these findings and psychological research in the area of stress and emotion regulation (Meichenbaum, 1985; Blackledge & Hayes, 2001), an emerging body of research suggests that progressive exposure to triggers, similar to that used for the treatment of anxiety disorders, is effective in reducing nociceptive response and sensitivity to headache triggers (Martin, 2001; Martin, Lae, & Reece, 2007; Martin, Reece, & Forsyth, 2006). In these studies,
individuals were exposed to commonly identified headache triggers (e.g., “visual disturbances”, noise, and stress) for varying durations. In all three studies, a curvilinear relationship was identified between the length of exposure to a trigger and sensitivity to the trigger, such that longer exposure produced decreased sensitivity. Based on these findings, a recent randomized controlled trial (RCT) found that a behavioral intervention that included graduated exposure to relevant headache triggers produced significant improvements in headache and reductions in medication consumption (Martin et al., 2014). In conjunction with these findings, the current study suggests that headache patients who are highly fearful of pain may engage in consistently avoidant patterns of behavior and are thus more likely to meet diagnostic criteria for MOH. Exposure-based treatment, such as that developed by Martin and colleagues (2014), may hold particular promise for individuals who are highly fearful of pain and patients who meet diagnostic criteria for MOH. Nonetheless, carefully controlled research is needed before such conclusions can be drawn.

4.4 Other Psychiatric Symptoms

Although the escape and avoidance subscale of the PASS-20 was the only psychiatric variable chosen for inclusion by in the classification tree, several other measures of psychiatric symptoms were significantly associated with MOH status in univariate analyses. As reported elsewhere (Hagen et al., 2012; Radat et al., 2005), anxiety and depression are associated with subsequent development of MOH and may serve as predictors for deleterious outcomes. Consistent with these findings, patients in the present study who met diagnostic criteria for MOH obtained scores on the PHQ-9 and GAD-7 significantly greater than those of patients without MOH. Though is well established that psychiatric disorders are commonly comorbid with
headache (Kalayadjian & Merikangas, 2008), findings of this and other studies indicate that psychiatric comorbidities are even more prevalent among individuals with MOH. For example, Radat and colleagues (2005) found that individuals suffering from MOH were more likely to report anxiety and mood disorders in comparison to migraineurs, and that these conditions were far more likely to precede than to follow MOH. As such, psychiatric conditions are conceptualized risk factors for MOH rather than the result of MOH. The self-medication model of substance use disorders (Khantzian, 1997) suggests that individuals abuse substances in an attempt to avoid, escape, or relieve distress evoked by negative affective states. Accordingly, future studies should examine to what extent this model applies to individuals with MOH and whether behavioral and cognitive-behavioral interventions (e.g., exposure-based interventions for anxiety and behavioral activation for depression) targeting anxiety and depression are effective for preventing the development of MOH or reducing the frequency of acute medication use.

4.5 Medication Use

As predicted, use of medications with higher potential for abuse and misuse (e.g. opioids and combination medications, which included those containing opioids) was associated with higher odds of meeting criteria for MOH. Although use of opioid medications significantly predicted MOH in univariate analyses, the use of combination medications was the strongest predictor of MOH status, and use of opioids did not improve the classification afforded by use of combination medications. After controlling for headache-related disability and escape and avoidance behaviors, patients using combination medications were still at approximately three times greater odds to meet the diagnostic criteria for MOH relative to patients not using these
medications. The current findings support the recommendation that opioids and opioid-combination analgesics should generally not be prescribed for headache (Loder et al., 2013). All acute headache medications have the potential for overuse; however, headache-specific medications such as triptans and non-specific medications such as NSAIDS were associated with much lower odds (0.73 and 1.70, respectively) for MOH.

Combination medications that contain NSAIDs have demonstrated consistent and impressive evidence for the treatment of migraine (Gatoulis, Voelker, & Fisher, 2012; Loder, 2005). However, many authors suggest that opioid-combination analgesics should be used on a limited basis (Levin, 2014; Loder, 2005; Loder et al., 2013). Although many opioids and opioid-combination analgesics are superior to placebo for the treatment of headache (Kelley & Tepper, 2012; Loder, 2005), the frequent use of opioids and opioid-combination analgesics for the treatment of headache pain is contraindicated due to a high risk for headache chronification, pronociceptive effects, tolerance, overuse, and addictive behaviors, as well as decreased effectiveness of other acute medications (Bigal et al., 2008; Katzung, Masters, & Trevor, 2012; Levin, 2014; Kelley & Tepper, 2012). For example, Bigal and colleagues (2008) documented the association between opioid use and the rapid progression of migraine even for minimal use. Similar concerns have been raised in reference to the use of opioid-combination analgesics, as the regular use of opioid-combination analgesics is associated with chronic headache (Scher et al., 2010). Accordingly, more research regarding the safety and tolerability of these drugs is warranted. Given the sparse evidence for efficacy and the high risk for tolerance and overuse, opioids and opioid-combination analgesics should only be used the treatment of headache when all other options have been exhausted. Practice guidelines and recommendations promote triptans for patients who respond poorly to NSAIDS and daily preventive medications for patients who
overuse their acute headache medications (Loder et al., 2013). The findings of the current study add to concerns regarding the efficacy and safety of combination medications as patients who used these medications were at a more than a three times greater risk for MOH in comparison to patients who did not use these medications.

The fact that the use of opioids for the treatment of headache was not chosen for inclusion in the final multivariable model was unexpected and may be at least partially attributable to the small number of patients (n = 25) who reported the use of opioids for the treatment of headache. Relative to population samples that include patients treated in a variety of settings, patients recruited for the present study may have been less likely to receive a prescription for opioids because they were receiving treatment from a headache specialist familiar with headache treatment guidelines. Ongoing research efforts are needed to monitor and examine prescription practices across a wide variety of settings. Specifically, a focus on ED settings seems prudent as opioids remain commonly prescribed in these settings (Mazer-Amirshahi et al., 2014; McCarthy & Cowan, 2015) and may reflect prescribers’ unfamiliarity with headache treatment guidelines. In addition to well-documented legislation and public health reform, efforts aimed at curbing the prescription of opioids for chronic pain, additional efforts should be aimed at making headache treatment guidelines readily available in ED settings.

4.6 Substance Use

Contrary to expectations, substance use and prescription misuse were relatively uncommon and did not differentiate between patients who met diagnostic criteria for MOH and those who did not. The relationship between MOH and problematic substance use is unclear and complex. Medication overuse headache has previously been depicted as a part of a broader
pattern of substance abuse and addictive behaviors (Radat et al., 2008; Radat et al., 2005). Patients with MOH have exhibited higher rates of abuse and misuse of substances such as tobacco, caffeine, sedatives, and anxiolytics; however, only a small percentage of individuals reported problematic alcohol use or illicit drug use (Hagen et al., 2012; Radat et al., 2008; Radat et al., 2005). In light of the current findings and findings drawn from previous research, the function of substance use and medication misuse behaviors should be examined further among individuals with headache. Although some headache patients may engage in problematic substance use and medication misuse with the goal of “getting high”, it may be the case that the majority of headache patients overuse analgesics and use other substances in an attempt to self-medicate headache pain and psychiatric distress. The finding that there was no association between MOH and problematic alcohol use or illicit drug use is consistent with previous findings (Hagen et al., 2012; Westergaard et al., 2016). A significant proportion of headache patients abstain from alcohol (Panconesi, Franchini, Bartolozzi, Magnai, & Guidi, 2013), possibly because alcohol is among the most commonly identified dietary headache triggers (Kelman, 2007). Despite these findings, medication class should be examined a moderator of this relationship. A large number of patients included in the present study overused over-the-counter medications, but problematic substance use has been documented most extensively among chronic pain patients who misuse opioids (Ives et al., 2006).

4.7 Limitations and Future Directions

Strengths of the current study included the examination of a treatment-seeking sample of headache patients, the consideration of relevant MOH risk factors in conjunction, and the use of a conservative and empirical approach designed to avoid Type I error inflation when selecting
variables for the final multivariable model. Despite these strengths, some limitations are worth bearing in mind. First, the present study was cross-sectional; therefore, significant associations between variables should be interpreted as correlational rather than causal due to uncertainty regarding the temporal ordering of variables. For example, it is assumed that psychiatric symptoms predict medication overuse (Radat et al., 2005; Schmid et al. 2013) and negatively influence pain coping abilities (Asmundson et al., 2001; Black et al., 2015). However, we did not assess order of occurrence, and psychiatric symptoms could develop or worsen subsequent to the overuse of acute headache medications. The temporal ordering of variables has significant theoretical implications as the function of medication overuse is often ignored. Based on theoretical models such as the fear-avoidance model of chronic pain (Vlaeyen & Linton, 2000) and the self-medication model of substance use disorders (Khantzian, 1997), headache patients who overuse their medications may do so in an attempt to avoid pain and feared pain-related stimuli or to self-medicate symptoms of anxiety and depression. However, causality cannot be assumed until this study is replicated longitudinally. Studies that concurrently monitor headache frequency, medication use, psychiatric symptoms, and other medical and psychosocial variables over time would provide valuable data related to the directionality and causality of relationships between variables and could inform the development of future assessment measures and intervention efforts.

Second, though the sample was unique in that it was composed of individuals seeking treatment for headache, patients were all treated by the same physicians and drawn from a limited geographic area. Despite this limitation, the rate of MOH in the present study (approximately 26%) closely resembles that from previous studies (Schmid et al., 2013). Individuals who met criteria for MOH also reported 20.58 (SD = 5.39) headache days per month
on average and were very severely impaired due to headache pain. Thus, the nature of their
headache characteristics also closely resemble treatment-seeking samples used in previous
studies (Schmid et al., 2013; Usai, Grazzi, D’Amico, Andrasik, & Bussone, 2008). In
conjunction, the similarity between the present and prior samples increases confidence that the
current findings are likely generalizable to clinical samples of headache patients. Nonetheless,
replication efforts are needed with more diverse patients drawn from a variety of locations and
clinics.

Third, assessment of substance use and medication misuse was limited in two ways. First,
substance use and medication use variables were based solely on self-report, and biological
measures were not collected. As part of informed consent, patients were instructed that their
responses would remain entirely confidential and would not impact the treatment that they
received from their healthcare provider. Nonetheless, patients may have been reluctant to
disclose information related to the use of illicit substances or the misuse of prescription
medications. Second, in order to reduce the burden on participants and increase participation in
the study, a large number of headache medications were collapsed into a smaller number of
categories. For example, combination medications consisted of over-the-counter medications
such as Excedrin and highly potent opioid-combination medication such as Lortab. Given the
risks associated with the use of opioids for headache (Levin, 2014), there are likely to be
differences between individuals who overuse acetaminophen combinations and individuals who
overuse opioid-combination medications. Thus, future studies should consider more precise and
specific definitions of medication class and utilize biological markers of illicit drug use and
prescription medication misuse.
Finally, low base rates of medication misuse and substance abuse limit the conclusions that can be drawn with regard to the relation between these specific agents and MOH. Similarly, univariate analyses did not reveal any significant interactions between examined variables. Sample size constraints may have prohibited the assessment of interactive effects with sufficient power. Despite the absence of significant interaction effects with this class of predictors, the CHAID algorithm afforded valuable empirically-based decisions regarding which variables to include in the multivariate model. Statistical approaches similar to CHAID algorithm implemented in the present study may prove useful in the development of brief screening measures that can be readily administered in busy primary care and emergency care settings. Such measures could endeavor to include the three variables retained in the final multivariable model herein and could also be helpful for identifying patients who would benefit from preventive treatment efforts.

In summary, the current study is a first step in an effort to more effectively identify and treat headache patients who are overusing prescription pain medications. Based on these findings, a relatively focused number of variables can be assessed to identify patients most likely to meet diagnostic criteria for MOH. Although a great deal of research has been aimed at developing screening measures to identify patients at risk for opioid abuse and misuse in broader populations (Butler, Budman, Fernandez, Franciullo, & Jamison, 2009; Butler, Budman, Fernandez, & Jamison, 2004; Webster & Webster, 2005), MOH has received less attention. Future studies may build on the present study by applying similar analytic approaches longitudinally in order to identify headache patients at risk for medication overuse prior to the onset of maladaptive medication use behaviors. In addition to the development of screening measures, the findings that escape and avoidance behaviors were strongly predictive of MOH has
significant clinical implications as headache patients are often instructed to avoid headache triggers whenever possible. Future research should also examine whether exposure-based treatments that facilitate engagement with headache triggers and other feared headache stimuli can reduce the risk for MOH and whether previously developed interventions (Martin et al., 2014) can be modified and abbreviated for effective implementation in clinical settings where these challenging patients are commonly treated.
LIST OF REFERENCES


Vos, T., Barber, R. M., Bell, B., Bertozzi-Villa, A. Biryukov, S., Bolliger, I…Murray, C. J. L. (2015). Global, regional, and national incidence, prevalence, and years lived with


LIST OF APPENDICES
APPENDIX A: DEMOGRAPHIC QUESTIONNAIRE
DEMOGRAPHIC QUESTIONNAIRE

Please tell us a little bit about yourself. This information is of course completely confidential.

How old are you (in years)?: __________

Gender: __________ (male/female/trans)

Race: (check one)
   _____ Caucasian
   _____ Black/African-American
   _____ Hispanic/Latino
   _____ Asian
   _____ Asian or Pacific Islander
   _____ Native American or Alaskan Native
   _____ Native Hawaiian or Pacific Islander
   _____ Multiracial

What was your highest level of education? (check one)
   _____ 8th grade or less
   _____ some high school
   _____ high school diploma
   _____ some college/university
   _____ bachelor’s degree
   _____ master’s degree
   _____ doctoral or professional degree

Marital status: (check one)
   _____ single (never married)
   _____ married
   _____ divorced
   _____ separated
   _____ widowed

Employment status: (check one)
   _____ unemployed
   _____ home maker
   _____ part time
   _____ full time

Yearly household income: (check one)
   _____ < $10,000
   _____ $10,000 - $20,000
   _____ $21,000 - $30,000
   _____ $31,000 - $50,000
   _____ $51,000 - $100,000
>$100,000

How tall are you? (in feet AND inches): _____ Feet & _____ Inches

How much do you weigh (in pounds)?: _____ Pounds
1. Do you ever get headaches?
   a. Yes  b. No

2. On average, how many DAYS PER MONTH do you have a headache (enter one number between 0 and 30)?
   _____ days per month with headache

3. If 0 is no pain, 5 is moderate pain, and 10 is the worst pain imaginable, what is the average pain intensity of these headaches (enter one number between 0 and 10)?
   _____ average pain intensity

4. If left untreated or unsuccessfully treated, about how long would these headaches usually last?
   a. less than 30 minutes
   b. at least 30 minutes but less than 2 hours
   c. at least 2 hours but less than 4 hours
   d. between 4 hours and 3 days
   e. between 3 days and 7 days
   f. longer than 7 straight days

5. For approximately how long have you been having these headaches?
   a. Less than 3 months
   b. 3 months
   c. 4 months or more

6. About how many of these headaches have you had in your life?
   a. Less than 5
   b. 5 – 9
   c. 11 – 20
   d. More than 20

7. Which of the following best describes your pain?
   a. Pulsating/Throbbing  b. Tight pressure (non-pulsating)

8. Is the pain typically experienced on one side or both sides of your head?
   a. Typically one side  b. Typically both sides

9. Is the pain made worse by routine physical activities or cause you to avoid routine physical activities (like walking, bending over, or climbing stairs)?
   a. Yes  b. No

10. Do you often feel nauseous or sick to your stomach during these headaches?
    a. Yes  b. No

11. Do you often vomit or throw up during these headaches?
12. Are you often sensitive to light during these headaches?
   a. Yes           b. No

13. Are you often sensitive to sound during these headaches?
   a. Yes           b. No

14. Do you often experience any symptoms shortly before the headache pain actually begins, such as changes in your vision (blurry vision, seeing spots or zigzag lines), changes in your sensation (numbness, tingling), or changes in your speech?
   a. Yes
   b. No

15. How many times have you experienced these symptoms before having a headache?
   a. 1
   b. 2 – 5
   c. 6 – 10
   d. More than 10

16. Do you use any medications to treat these headaches?
   a. Yes
   b. No

17. How many days per week do you use any type of medication to treat your headaches?
   a. Less than 1 day per week
   b. 1-2 days per week
   c. 3 days per week
   d. 4 or more days per week

18. How long have you been using these medications at this frequency?
   a. 3 months or less
   b. More than 3 months

19. Did your headache develop or get worse when you started using these medications at this frequency?
   a. Yes
   b. No

20. Did this headache develop shortly after a head injury or head trauma?
   a. Yes
   b. No

21. Have you ever been diagnosed with cluster headaches?
   a. Yes
   b. No
APPENDIX C: HEADACHE MEDICATION USE QUESTIONNAIRE
HEADACHE MEDICATION USE QUESTIONNAIRE

1. Are you currently taking NSAIDS or simple analgesics (e.g. aspirin [Bayer, Excedrin], ibuprofen [Advil, Motrin], naproxen sodium [Aleve], Anaprox) for the treatment of your headaches?
   a. How many days during the previous month did you use NSAIDS or simple analgesics for the treatment of your headaches?
   b. How long have you used NSAIDS or simple analgesics at this frequency?

2. Are you currently taking ergotamine for the treatment of your headaches?
   a. How many days during the previous month did you use ergotamine for the treatment of your headaches?
   b. How long have you used ergotamine at this frequency?

3. Are you currently taking triptans (e.g. sumatriptan [Imitrex], naratriptan [Amerge], zolmitriptan [Zomig], rizatriptan [Maxalt], almotriptan [Axert], frovatriptan [Frova], eletriptan [Relpax]) for the treatment of your headaches?
   a. How many days during the previous month did you use triptans for the treatment of your headaches?
   b. How long have you used triptans at this frequency?

4. Are you currently taking opioids (e.g. codeine, hydrocodone, merperdine [Demerol], oxycodone [Oxy IR], dilaudid, morphine) for the treatment of your headaches?
   a. How many days during the previous month did you use opioids for the treatment of your headaches?
   b. How long have you used opioids at this frequency?

5. Are you currently taking combination medications (e.g. acetaminophen/aspirin/caffeine [Excedrin Migraine, BC Powder, Goody’s Powder], codeine with acetaminophen [Tylenol #3], hydrocodone with acetaminophen [Lortab, Vicodin], merperdine with promethazine [Mepergan], oxycodone with aspirin [Percodan], oxycodone with acetaminophen [Percocet]) for the treatment of your headaches?
   a. How many days during the previous month did you use combination medications for the treatment of your headaches?
   b. How long have you used combination medications at this frequency?

6. Are you currently taking antidepressants (e.g. amitriptyline [Elavil], venlafaxine [Effexor]) for the treatment of your headaches?
   a. How many days during the previous month did you use antidepressants for the treatment of your headaches?
   b. How long have you used antidepressants at this frequency?
7. Are you currently taking antiepileptic drugs (e.g. divalproex sodium [Depakote], sodium valproate [valproate], topiramate [Topamax]) for the treatment of your headaches?
   a. How many days during the previous month did you use antiepileptic drugs for the treatment of your headaches?
   b. How long have you used antiepileptic drugs at this frequency?

8. Are you currently taking beta-blockers (e.g. metoprolol [Lopressor], propranolol [Inderal], timolol [Timoptic]) for the treatment of your headaches?
   a. How many days during the previous month did you use beta-blockers for the treatment of your headaches?
   b. How long have you used beta-blockers at this frequency?

9. Have you received onabotulinumtoxinA [Botox] within the past 6 months for the treatment of your headaches?
APPENDIX D: HEADACHE IMPACT TEST-6
**HIT-6™**
*(VERSION 1.1)*

This questionnaire was designed to help you describe and communicate the way you feel and what you cannot do because of headaches.

To complete, please circle one answer for each question.

1. **When you have headaches, how often is the pain severe?**
   - Never
   - Rarely
   - Sometimes
   - Very Often
   - Always

2. **How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?**
   - Never
   - Rarely
   - Sometimes
   - Very Often
   - Always

3. **When you have a headache, how often do you wish you could lie down?**
   - Never
   - Rarely
   - Sometimes
   - Very Often
   - Always

4. **In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?**
   - Never
   - Rarely
   - Sometimes
   - Very Often
   - Always

5. **In the past 4 weeks, how often have you felt fed up or irritated because of your headaches?**
   - Never
   - Rarely
   - Sometimes
   - Very Often
   - Always

6. **In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities?**
   - Never
   - Rarely
   - Sometimes
   - Very Often
   - Always

To score, add points for answers in each column.

**Total Score**

Higher scores indicate greater impact on your life.

Score range is 36-78.
APPENDIX E: PATIENT HEALTH QUESTIONNAIRE-9
### PATIENT HEALTH QUESTIONNAIRE-9
(PhQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✔️" to indicate your answer)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

For office coding: \( 0 + \_\_\_ + \_\_\_ + \_\_\_ \)

=Total Score: \_\_\_\_\

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th></th>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
</table>

85
APPENDIX F: GENERALIZED ANXIETY DISORDER 7-ITEM SCALE
GAD-7 ANXIETY

Over the **last 2 weeks**, how often have you been bothered by the following problems?  
* (Use “✔” to indicate your answer*)

<table>
<thead>
<tr>
<th>Problem</th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Feeling nervous, anxious or on edge</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Not being able to stop or control worrying</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Worrying too much about different things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Trouble relaxing</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Being so restless that it is hard to sit still</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Becoming easily annoyed or irritable</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Feeling afraid as if something awful might happen</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

Column totals: ___ + ___ + ___ + ___ = **Total Score** _____

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th>Difficulty level</th>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>□</td>
<td>□</td>
<td>□</td>
<td>□</td>
</tr>
</tbody>
</table>

From the Primary Care Evaluation of Mental Disorders Patient Health Questionnaire (PRIME-MD PHQ). The PHQ was developed by Drs. Robert L. Spitzer, Janet B.W. Williams, Kurt Kroenke and colleagues. For research information, contact Dr. Spitzer at rls8@columbia.edu. PRIME-MD® is a trademark of Pfizer Inc. Copyright© 1999 Pfizer Inc. All rights reserved. Reproduced with permission
APPENDIX G: PAIN ANXIETY SYMPTOMS SCALE-SHORT VERSION
Individuals who experience pain develop different ways to respond to that pain. We would like to know what you do and what you think about when in pain. Please use the rating scale below to indicate how often you engage in each of the following thoughts or activities. Circle one number from 0 (NEVER) to 5 (ALWAYS) for each item.

<table>
<thead>
<tr>
<th>Item</th>
<th>NEVER</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. I think that if my pain gets too severe, it will never decrease.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>2. When I feel pain, I am afraid that something terrible will happen.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>3. I go immediately to bed when I feel severe pain.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4. I begin trembling when engaged in activity that increases pain.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>5. I can’t think straight when I am in pain.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6. I will stop any activity as soon as I sense pain coming on.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>7. Pain seems to cause my heart to pound or race.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>8. As soon as pain comes on, I take medication to reduce it.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>9. When I feel pain, I think that I may be seriously ill.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>10. During painful episodes, it is difficult for me to think of anything else besides the pain.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>11. I avoid important activities when I hurt.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>12. When I sense pain I feel dizzy or faint.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>13. Pain sensations are terrifying.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>14. When I hurt I think about the pain constantly.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>15. Pain makes me nauseous (feel sick to my stomach).</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>16. When pain comes on strong I think I might become paralyzed or more disabled.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>17. I find it hard to concentrate when I hurt.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>18. I find it difficult to calm my body down after periods of pain.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>19. I worry when I am in pain.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>20. I try to avoid activities that cause pain.</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
</tbody>
</table>

Thank you for completing this questionnaire.  
It will help us to better understand your pain problem.
MEDICATION USE/MISUSE QUESTIONNAIRE

As you answer the following questions pertaining to medication use, medication misuse, and substance use, please keep in mind that all of your data will remain entirely confidential.

1.) Do you currently have a prescription for a stimulants (e.g. Ritalin, Adderall, Dexedrine)?
   a. On average, how frequently have you used stimulants (e.g. Ritalin, Adderall, Dexedrine) prescribed to you during the past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

2.) Do you currently have a prescription for opioids NOT for the treatment of headache (e.g. Vicodin, Oxycotin, Percocet)
   a. On average, how frequently have you used opioids (e.g. Vicodin, Oxycotin, Percocet) prescribed to you during the past 12 months? (Do NOT count opioids used for headache)
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

3.) Do you currently have a prescription for anxiolytics (e.g. Xanax, Valium, Klonopin)
   a. On average, how frequently have you used anxiolytics (e.g. Xanax, Valium, Klonopin) prescribed to you during the past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

4.) Do you currently have a prescription for sedatives (e.g. Ambien, Halcion, Restoril)
   a. On average, how frequently have you used sedatives (e.g. Ambien, Halcion, Restoril) prescribed to you during the past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
4. Once a week
5. Multiple times a week
6. Daily

5.) Have you used stimulants (e.g. Ritalin, Adderall, Dexedrine) WITHOUT a physician’s prescription during the past 12 months?
   a. On average, how frequently have you used stimulants (e.g. Ritalin, Adderall, Dexedrine) WITHOUT a physician’s prescription during past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

6.) Have you used opioids not for the treatment of headache (e.g. Vicodin, Oxycotin, Percocet) WITHOUT a physician’s prescription during the past 12 months?
   a. On average, how frequently have you used opioids not for the treatment of headache (e.g. Vicodin, Oxycotin, Percocet) WITHOUT a physician’s prescription during past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

7.) Have you used anxiolytics (e.g. Xanax, Valium, Klonopin) WITHOUT a physician’s prescription during the past 12 months?
   a. On average, how frequently have you used anxiolytics (e.g. Xanax, Valium, Klonopin) WITHOUT a physician’s prescription during past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

8.) Have you used sedatives (e.g. Ambien, Halcion, Restoril) WITHOUT a physician’s prescription during the past 12 months?
   a. On average, how frequently have you used sedatives (e.g. Ambien, Halcion, Restoril) WITHOUT a physician’s prescriptions during past 12 months?
1. Not in the past year
2. Less than once a month
3. Once a month
4. Once a week
5. Multiple times a week
6. Daily
APPENDIX I: SUBSTANCE USE/ABUSE QUESTIONNAIRE
SUBSTANCE USE/ABUSE QUESTIONNAIRE

1.) Have you used alcohol during the past 12 months?
   a. On average, how frequently have you consumed alcohol during past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

2.) Have you used tobacco during the past 12 months?
   a. On average, how frequently have you used tobacco during past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

3.) Have you consumed caffeine during the past 12 months?
   a. On average, how frequently have you consumed caffeine during past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

4.) Have you used marijuana/cannabis during the past 12 months?
   a. On average, how frequently have you used marijuana/cannabis during past 12 months?
      1. Not in the past year
      2. Less than once a month
      3. Once a month
      4. Once a week
      5. Multiple times a week
      6. Daily

5.) Please indicate whether you have used any of the following substances during your lifetime:
a. “Powder” cocaine  
b. “Crack” cocaine  
c. Methamphetamine (Meth)  
d. Ecstasy (other “club” drugs)  
e. Heroin  
f. Inhalants (cleansers, paint, etc.)  
g. Hallucinogens  

6.) Have you found yourself unable to stop using any of the aforementioned drugs when you wanted to?  

7.) Have you ever experienced withdrawal symptoms (felt sick) when you stopped taking any of the aforementioned drugs?  

8.) Have you ever been diagnosed with a substance use disorder (e.g. alcohol abuse, drug abuse, alcohol dependence, or drug dependence) or treated substance use?  

9.) Has anyone in your immediate family ever been diagnosed with a substance use disorder (e.g. alcohol abuse, drug abuse, alcohol dependence, or drug dependence) or treated for substance use.
VITA

Kelly R. Peck

EDUCATION

Doctoral Student in Clinical Psychology 2011-Present
University of Mississippi, Oxford, MS (APA-accredited)
Title of Dissertation: Factors Associated with Medication-Overuse Headache in Patients Seeking Treatment for Primary Headache
Dissertation Defended: 5/12/2015
Supervisor: Todd. A Smitherman, Ph.D.

Clinical Psychology Predoctoral Internship 2016-Present
University of Mississippi Medical Center/G.V. (Sonny) Montgomery VAMC, Jackson, MS (APA-Accredited)

Master of Arts in Clinical Psychology 2014
University of Mississippi, Oxford, MS (APA-accredited)
Title of Thesis: Moderation and Mediation of Headache-Related Disability: The Roles of Self-Efficacy and Headache Diagnosis
Supervisor: Todd. A Smitherman, Ph.D.

Bachelor of Arts in Psychology, Magna Cum Laude 2010
University of Memphis, Memphis, TN

PUBLICATIONS AND PRESENTATIONS

Publications in Peer-Reviewed Journals


Under Review


In Preparation


Book Chapters


Oral Presentations

98

Peck, K. R. (2017, February) Factors Associated with Medication-Overuse Headache in Patients Seeking Treatment for Primary Headache. Presented at the Annual University of Mississippi Graduate Student Council Research Symposium, University, MS.

Peck, K. R. (2016, October) Medication Overuse Headache. Presented at the University of Mississippi Three Minute Thesis Competition, University, MS.


Zhao, M. S., Peck, K. R., Tynes, B. L., Scott, S., & Maack, D. J. (2016, April). Putting the E in Ew! Emotion dysregulation mediates the relation between disgust sensitivity and contamination fear. Presented at the University of Mississippi Conference on Psychological Science, University of Mississippi, University, MS.


Poster Presentations


Peck, K. R. (2012, August). *Center for Epidemiologic Studies Depression Scale (CES-D) and Middle-Eastern populations*. Poster presented at the annual convention of the Mississippi Psychological Association, Gulfport, MS.

Peck, K. R., Buscemi, J., Murphy, J. G., (2010, April). *Exploration of relations between type of residence and alcohol consumption in University of Memphis students*. Poster presented at the annual University of Memphis Student Research Forum, Memphis, TN.


**GRANT FUNDING**

**Funded Grants:**

**SELECTED HONORS AND AWARDS**

John and Lillian Wolfe Graduate Award for Excellence, University of Mississippi, 2015.
Graduate Achievement Award in Psychology, University of Mississippi 2015
Graduate Research Fellowship, University of Mississippi 2011-2016
University of Mississippi Graduate Student Travel Award 2013, 2015, & 2017
St. Jude Children’s Research Hospital Student Travel Award 2012 & 2013
University of Mississippi Medical Center Student Travel Award 2017

EDITING AND REVIEWING

Ad Hoc Reviewer
*Applied Psychophysiology and Biofeedback*
*Headache*

Co-Reviewer
*Addictive Behaviors*
*Alcoholism: Clinical and Experimental Research*
*Behaviour Research and Therapy*
*Cephalalgia*
*Cochrane Collaboration: Pain, Palliative and Supportive Care Review Group*
*Journal of Behavioral Medicine*
*Pediatric Blood and Cancer*

ADMINISTRATIVE AND LEADERSHIP EXPERIENCE

Search Committee for the Chair of the Department of Psychology (2015-2016)
Department of Psychology, University of Mississippi, Oxford, MS

University of Mississippi Conference on Psychological Science Committee (2014-2016)
Department of Psychology, University of Mississippi, Oxford, MS

RESEARCH EXPERIENCE

Pain Management Service
Directors: Jennifer H. Ehrentraut, Ph.D., & Doralina L. Anghelescu, M.D.
Department of Psychology, St. Jude Children’s Research Hospital
Role: Graduate Research Assistant

Reproductive Health Lab
Principal Investigator: James L. Klosky, Ph.D.
NICHD R21 HD061296 & NIH/NCI R01 CA166559
Department of Psychology, St. Jude Children’s Research Hospital
Role: Graduate Research Assistant

Reduction of ETS Exposure in Pediatric Cancer Patients
Principal Investigator: Vida L. Tyc, Ph.D.
2012-2013
Migraine and Behavioral Health Laboratory 2011-present
Supervisor: Todd Smitherman, Ph.D.
Department of Psychology, University of Mississippi
Role: Graduate Research Assistant

CLINICAL EXPERIENCE

Pre-doctoral Psychology Intern Spring 2017
Setting: The University of Mississippi Medical Center/VA Medical Center Consortium, Jackson, MS
Rotations: VA Clinical Neuropsychology
Supervisors: Ted Bennett, Ph.D.
Focus: Neuropsychological Interviewing and Assessment

Pre-doctoral Psychology Intern Spring 2017
Setting: The University of Mississippi Medical Center/VA Medical Center Consortium, Jackson, MS
Rotations: Community-Based Dual Disorders – Prolonged Exposure
Supervisors: Daniel Williams, Ph.D.
Focus: Prolonged Exposure for PTSD, Behavioral Activation for Depression, and Dialectical Behavior Therapy

Pre-doctoral Psychology Intern Winter 2017
Setting: The University of Mississippi Medical Center/VA Medical Center Consortium, Jackson, MS
Rotations: Community-Based Dual Disorders - Motivational Interviewing
Supervisors: Daniel Williams Ph.D., & Scott Coffey, Ph.D.
Focus: Motivational Interviewing, Prolonged Exposure for PTSD, Behavioral Activation for Depression, and Dialectical Behavior Therapy

Pre-doctoral Psychology Intern Fall 2016
Setting: The University of Mississippi Medical Center/VA Medical Center Consortium, Jackson, MS
Rotations: Evidence Based Practice – Behavioral Medicine
Supervisors: Jeanne Gabriele, Ph.D., Kristi Crane, Psy.D., & Lauren Graves, Ph.D.
Focus: Cognitive Behavioral Therapy for Chronic Pain, Cognitive Behavioral Therapy for Insomnia, Tinnitus Management

Pre-doctoral Psychology Intern Summer 2016
Setting: The University of Mississippi Medical Center/VA Medical Center Consortium, Jackson, MS
Rotations: Addictive Disorders Treatment Program
Supervisors: Kevin Connolly, Ph.D., Andrew Voluse, Ph.D., & Amee Patel, Ph.D.
Focus: Cognitive Processing Therapy for PTSD, Relapse Prevention Therapy, and Mindfulness-Based Relapse Prevention

Substance Abuse Therapist 2014-2015
Setting: Haven House, Communicare, Oxford, MS
Supervisors: Scott Gustafson, Ph.D., & John Young, Ph.D.
Focus: Relapse Prevention Therapy for individuals with substance use disorders and comorbid psychiatric diagnoses.

Verification Specialist 2014
Setting: Office of Student Disability Services, University of Mississippi, Oxford, MS
Supervisor: Scott Gustafson, Ph.D.
Focus: Interpretation of psychological assessments in a university setting

Contracted Assessor 2013-2016
Setting: Psychological Assessment Clinic, University of Mississippi, Oxford, MS
Supervisor: Scott Gustafson, Ph.D. & Shannon Sharp, Ph.D.
Focus: Integrated psychological assessment

Graduate Clinician 2012-2016
Setting: Psychological Services Center, University of Mississippi, Oxford, MS
Supervisor: Todd Smitherman, Ph.D., John Young, Ph.D., Stefan Schulenberg, Ph.D. & Scott Gustafson, Ph.D.
Focus: Cognitive Behavioral Therapy, Behavioral Therapy, & Positive Psychology

TEACHING EXPERIENCE

Instructor of Record (Fall, 2015 & Spring, 2016)
University of Mississippi, Oxford, MS
Psy 201: General Psychology