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# Demographic disparities in studies of acute OTC migraine treatment

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Thesis

**DEMOGRAPHIC DISPARITIES IN STUDIES OF ACUTE OTC MIGRAINE  
TREATMENT**

by

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B.A., Smith College, 2015

Submitted in partial fulfillment of the  
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Master of Science

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# **DEMOGRAPHIC DISPARITIES IN STUDIES OF ACUTE OTC MIGRAINE**

## **TREATMENT**

**LILY MI RONDEAU**

### **ABSTRACT**

This paper explores the existing prevalence data from migraine studies of the efficacy of over-the-counter medications compared to the demographic information from pharmacological studies of migraine medications. A literature review was done using PubMed with keywords related to migraine, over the counter, medication, and prevalence to assess the current research. Studies were then reviewed for demographic data including biological sex, age, socioeconomic status, insurance status, ethnicity, and race. Review of the available literature revealed notable differences in demographic data including biological sex, age, socioeconomic status, insurance status, ethnicity, and race between prevalence in the general American population when compared to demographics from over-the-counter migraine medication studies. The current medical literature on the efficacy of migraine treatment with medication may not be representative of a large portion of migraine sufferers in the United States. Studies of over-the-counter medications should be repeated with a focus on recruiting from yet underrepresented demographic populations, which prevalence data strongly suggest are also suffering from migraine.

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## LIST OF ABBREVIATIONS

AAC	acetaminophen, acetylsalicylic acid, caffeine (Excedrin)
ACEi	angiotensin converting enzyme inhibitor
AE	adverse experiences
ANOVA	Analysis of Variance
APAP	acetaminophen (Tylenol)
ASA	acetylsalicylic acid (Aspirin)
BU	Boston University
CGRP	calcitonin gene-related peptide
CT scan	Computed Tomography scan
DMSS	Defense Medical Surveillance System
ED	Emergency Department
GCSE	General Certificate of Secondary Education
HND	Higher National Diploma
HRQoL	health related quality of life
IB	ibuprofen
ICHD-2	International Classification of Headache Disorders 2nd Edition
IHS	International Headache Society
IRB	Institutional Review Board
ISO	International Standards Organization
MANOVA	multivariate analysis of variance
MAST	Migraine in America Symptoms and Treatment

MeSH	Medical Subject Headings
NSAID	Non-Steroidal Antiinflammatory Drug
OTC	Over the Counter
PAR	pain relief
PCP	Primary Care Provider
PID	pain intensity difference from baseline
RCMP	Royal Canadian Mounted Police
Serotonin 5-HT <sub>1F</sub> receptor .....	serotonin 5-hydroxytryptamine <sub>1F</sub> receptor
SES	Socioeconomic Status
TOTPAR <sub>2</sub>	Total Pain Relief Over 2 Hours Post-dose Period
TOTPAR <sub>4</sub>	Total Pain Relief Over 4 Hours Post-dose Period
UK	United Kingdom
US	United States

## **CHAPTER ONE: INTRODUCTION**

### **Background**

Migraine is one of the most common primary headache disorders along with tension type headache and cluster headache.<sup>1</sup> Migraine primarily affects individuals between the ages of 18-60 and, while not fatal, is a significant cause of disability and is second only to low back pain among all diseases with respect to years of life lived with disability.<sup>2</sup> Migraine affects just over one tenth of the global population and over one sixth of adults in the United States and is about twice as common in women as in men.<sup>3</sup> Migraine headache is prevalent enough in the population that most people know someone who gets them, has migraines themselves, or at the very least, recognizes it as a form of severe headache. Despite migraine being part of general awareness, the scope of who gets migraines as well as how migraines impact an individual's quality of life, socioeconomic status are somewhat less well known to the populace.

### **Statement of the Problem**

Prevalence data suggests that, while migraine affects twice as many females as males, ethnic groups are affected at near equal rates, including White, Black, Native/Pacific Islander, and Hispanic/Latino groups. Migraine also disproportionately affects more people who fall into lower socioeconomic groups, particularly those in "near poor" and "poor", as described by the US census.<sup>2,3</sup>

Despite the socioeconomic and ethnic distribution of migraine, research has historically consistently oversampled populations that are White, female, married, and, often, from more affluent socioeconomic groups.<sup>4-8</sup> This pattern is multifactorial but is heavily influenced by how the data is collected in the study, as well as the level of commitment required from the participants.<sup>9</sup> For example, some studies are performed entirely from patient groups who visit subspecialty clinics, which immediately narrows the demographics to individuals who can afford to pay for specialty care for a non-fatal chronic headache condition.<sup>10</sup> Another study that used surveys noted that the subject pool was disproportionately represented by elderly subjects and White stay at home mothers.

In addition to affecting a large portion of the population, migraine has a significant economic impact not just in healthcare costs but also lost productivity in both education and work.<sup>11</sup> Individuals suffering from migraine report significantly lower health related quality of life compared to those without migraine and those reporting milder headache.<sup>12,13</sup> Individuals who suffer from migraine are also less likely to have completed higher education and make less household income compared to individuals without migraine.<sup>14</sup>

Considering these factors, much of the available data on migraine is not very generalizable to populations not fulfilling the majority demographics in these studies. With new information coming out about subtle differences in drug metabolism found in some ethnic groups,<sup>8</sup> data collected on a population that is

significantly comprised of White, married, affluent, and female is less generalizable to those who do not fall into those demographics and do not have access to the type of care that private insurance can afford, enough disposable income to pay for relatively new and expensive treatment, or the economic flexibility to not work. Although half as many males suffer from migraines compared to females, males also face social and cultural challenges regarding invisible pain syndromes, such as migraine, so their pain may be less likely to be believed or considered seriously and, therefore, may be less likely to receive appropriate attention and treatment.

### **Hypothesis**

Combination acetaminophen, acetylsalicylic acid, caffeine (AAC) for acute treatment of migraine headache has superior analgesia to ibuprofen (IB) alone or placebo. Commonly available over the counter medications may have a different efficacy for treating migraine pain across ethnic groups as defined by the US census.

### **Objectives and Specific Aims**

The objective of this study is to (1) repeat a comparison of a readily available and affordable OTC migraine medication compared to placebo, (2) collect the data from a more representative sample of the United States population, (3) begin to have a better understanding of whether the current understanding of the efficacy of popular OTC medication is as effective in these other populations as the data shows it to be in the oversampled demographics of White, affluent married women.

## **CHAPTER TWO: REVIEW OF THE LITERATURE**

### **Overview**

Migraine headache is an active area of research and the current understanding of the pathophysiology is primary neuronal dysfunction centering around the trigeminovascular system.<sup>15</sup> Migraine usually has four stages: prodrome, aura, headache, postdrome, though many sufferers do not report experiencing aura and many may not report postdrome due to using sleep as part of treatment. Prodrome may be any of several symptoms that occur prior to the onset of a migraine and often signal to that individual that a migraine is incoming. Aura includes a wide variety of transient perceptual, visual, auditory, sensory, and, in rare cases, neurological abnormalities leading up to and sometimes continuing into the headache phase. The pain of migraine is usually considered moderate to severe and is traditionally described as a pulsating headache that begins unilaterally, located behind one eye socket and commonly accompanied by photophobia and nausea. Postdrome is a break or change in the headache pain that, in a somewhat similar fashion to prodrome, signals to that individual that the migraine is finishing.<sup>15</sup> Migraine is also a heritable disorder and common forms of migraine can be attributed to complex genetic disorders, which have not been well described thus far.

Symptomatic or abortive therapy for migraine consists of OTC analgesics, such as NSAIDs and acetaminophen, and prescription medications such as triptans,

antiemetics, and newer agents, such as calcitonin gene-related peptide (CGRP) antagonists, serotonin 5-HT<sub>1F</sub> receptor agonists, and ergot derivatives.<sup>16</sup> First line preventative treatments include nonselective beta-blockers, tricyclic antidepressants, and anticonvulsants. Alternative preventative regimens can include Botox injections and CGRP antagonists. Non-pharmacologic interventions include behavioral therapy and neurostimulation and chronic control can be increased by therapeutic lifestyle changes, as well as identification and avoidance of migraine triggers.<sup>17,18</sup>

Migraine is a clinical diagnosis with imaging and other tests only used to rule out other, more life-threatening causes of acute headache.<sup>15,19</sup> Migraine is known to run in families and often follows known patterns.<sup>15</sup> However, it is also highly individual. Pain syndromes without visible signs carry social stigma, in addition to lost productivity and opportunities for educational and career advancement.

The prevalence of migraine in the American population over the past few decades has been relatively stable across sex, ethnicity, and socioeconomic status.<sup>2,3,8,19,20</sup> People suffer from migraine regardless of their location in the regional United States, though some differences can be found between central and coastal areas.<sup>19</sup> Across both time and space, the prevalence of migraine in females is persistently about twice the prevalence in males.<sup>2,20</sup> The prevalence of migraine is relatively evenly distributed across ethnic groups with a few exceptions, though the gathering ethnic and racial demographics from study subjects has only begun recently and is

not performed in every study. The available data suggests that migraine has an increased prevalence in socioeconomic and educationally disadvantaged groups, as well as primarily affecting individuals during the prime of life and childbearing years. Those who suffer from migraine are also more likely to have government funded insurance or be uninsured and, additionally, be less likely to be prescribed and afford prescription treatment.<sup>2,3,8,19,20</sup>

### **Synthesis of Existing Research**

#### *Migraine Prevalence in Population*

Migraine is the most common chronic headache condition or disease and affects 11% of global population.<sup>3</sup> The prevalence data published in 2015 found that migraine affects about 15.3% of the age adjusted population<sup>20</sup>, 20.2-21.0% among women and 10.2-10.7% among men.<sup>2</sup> The prevalence remained stable from 2016-2018 at between 15.3-15.9% of all adults in the United States suffering from migraine. Migraines accounted for about 4 million emergency department visits in 2016 and continue to be a significant burden on the healthcare system.<sup>2</sup>

The age distribution of migraine is heavily skewed in favor of those under the age of 65; the prevalence is 18.7% in those between the ages 18-44, 15.7% in those between 45-64, and 15.4% among the 65-74 and 75 and up groups, collectively.<sup>2</sup> It is well understood that migraine is most prevalent in females during their reproductive years.<sup>20</sup> The data strongly support the conclusion that migraine has

consistently and continues to affect a significant portion of the overall population, particularly those in their prime working years.

Prevalence has been stable over time. Variations in prevalence may be attributed to methodological or budgetary changes on the part of researchers, which may lead to fluctuations in sample size, possible changes in accuracy, and artificially inflated or decreased prevalence.<sup>19</sup> The female to male ratio has been the most stable and changes are most likely due to changes in prevalence in male migraineurs due to the smaller sample size.<sup>19</sup>

Unsurprisingly, the military is noted to have a significantly lower prevalence of migraine, though the female predominance persists.<sup>19</sup> This reduced prevalence is likely due to multiple factors related to the significant disability associated with migraine. Migraineurs may be less likely to choose to enlist in military service compared to those who do not have a chronic pain disorder. Additionally, the data on migraine prevalence in the military may also be complicated by how the data is recorded. The DMSS database (Defense Medical Surveillance System) only recorded a diagnosis of migraine in those who sought medical attention during the research period and may not have included individuals who did not need medical attention due to sufficient symptomatic control.<sup>19</sup> DMSS data over time suggests that migraine prevalence is increasing but this may merely be a reflection of increased healthcare resource use by existing migraineurs or increase in formal diagnosis of migraine, rather than a true increase in prevalence of migraine.<sup>19</sup> The paper also speculated

that the increase in prevalence in non-migraine headaches after 2005 may be related to an increase in post-traumatic headache coincidental with military deployment.<sup>19</sup>

#### *Migraine Prevalence by Location in US*

Prevalence is noted to be similar on the US coasts with increased prevalence in more central regions. The highest prevalence is in the North Central region, followed by the Mountain region.<sup>8</sup> It is also of note that migraine appears to decrease in prevalence with increasing population density for women but is relatively stable across population density for males.<sup>8</sup> When comparing attack frequency compared to disability by region of the US, females were noted to have generally more frequent attacks but relatively less disability, while males varied widely. With New England used as a reference value, males in the Mountain and South-Central regions were noted to have decreased attack frequency but increased disability, followed by the Pacific region to a lesser degree. The New England and Atlantic regions were noted to have similar degrees of attack frequency and disability and the North central region has a notably increased attack frequency but decreased disability.

#### *Migraine Prevalence Across Sex and Ethnicity*

In 1992, a study surveying a representative sample of households in the United States using over 20 thousand mail-in surveys found that the group with the highest prevalence of migraine were females between ages 30-49 from the lowest

income bracket (<\$10,000). The survey suggested that household income was the strongest predictor of migraine prevalence but that severity of disability was not related to gender, age, income, urbanicity, or region of country. Frequency was also inversely related to disability; individuals reporting lower frequency of migraine attacks also reported a higher degree of disability, while those reporting a higher frequency of attacks reported less disability. The study used a market research firm National Family Opinion Inc as the subject pool, which had known demographic biases, such as a skew toward upper-income White households and limited race demographics to White and Black. In addition, the data was self-report by one designated representative in the household. Also of note, the data was collected in 1986 at which point the median household income was \$24,897.<sup>8</sup>

The study attributed the slightly lower prevalence in Black population due to higher platelet level of tyramine conjugating enzyme phenolsulfotransferase, resulting in a proposed protective effect through increased metabolism of proposed dietary triggers of migraine, such as tyramine.<sup>8</sup> Given that, at the time of the study, race demographics collected were limited to White, Black, other and unknown categories, the study did find a slightly higher prevalence in the white group compared to Black group across both females and males with a prevalence of 17.4% of female Black migraineurs compared to 17.6% female White.<sup>8</sup> It is also notable that the number of subjects in each group in the comparison varied widely in this study. Prevalence in White females was slightly higher at 17.6% compared to 17.4%

in Black females but that prevalence of 17.6% in the White female group was composed 1803 subjects, while the 17.4% Black female group only had 67 subjects. Male groups showed similar disparities with a prevalence of 6.1% for the White male group with 561 subjects and 3.3% in the Black male group with only 8 subjects.<sup>8</sup> The small number of subjects in some groups likely contributed to the large differences noted in analyses. Interestingly, while prevalence varies somewhat compared to more recent studies, the trends across racial/ethnic and socioeconomic groups are highly consistent.<sup>2,8,19,20</sup>

The study also found that Black male migraineurs reported more frequent severe headaches but reported less frequent disability from those headaches compared to White males.<sup>8</sup> The data is also notable for similar, though not as striking, inverse patterns of increased disability but decreased attack frequency in males as household income increases.<sup>8</sup>

Studies from 2015, 2018, and 2021 showed relatively stable prevalence across sex with male prevalence between 9.0-10.7% and female prevalence at 18.9-21.0%.<sup>2,19,20</sup> The more recent prevalence studies noted that gradual increases in prevalence across both sexes could be attributed to increases in participation and inclusion of previously underrepresented groups. The prevalence study from 1992 gathered ethnicity data from fewer categories with prevalence of migraine sufferers being 17.6% among White, 17.4% among Black, 12.3% among other, and 15.9% among unknown. It is notable that 1803 subjects identified as White, 67 subjects

identified as Black, 10 identified as other, and 22 identified as unknown.<sup>8</sup> The study from 2015 did not appear to collect ethnicity data.<sup>19</sup> The racial ethnic data collected in the prevalence studies from 2018 and 2021 found 15.2-16.3% among White, 14.6-16.2% among Black or African American, 15.5-22.1% among American Indian or Alaska Native, and 9.8-11.3% Asian.<sup>2,20</sup> The variation in prevalence among minority groups was attributed to greater inclusion of those groups in more recent surveys. The prevalence study from 2018 additionally included the option to identify as Native Hawaiian or Other Pacific Islander among whom there was a 20.3% prevalence.<sup>20</sup> The prevalence data from 2021 had further ethnic breakdown options for Hispanic or Latino origin and race and found a migraine prevalence of 14.0-16% among Hispanic or Latino, 12.6-15.8% among Mexican or Mexican American, 15.5-16.1% among Not Hispanic or Latino, 16.2-16.7% among White (single race), and 14.3-15.6% among Black or African American (single race).<sup>2</sup>

Many migraine studies report that their study pool is a representative sample of migraine sufferers in the United States but comparison of racial and ethnic census data to the demographics of many of these studies suggest otherwise. Recent US census estimates of Race and Hispanic Origin from 2021 support that individuals reporting to be White alone continue to be the ethnic majority at 75.8% of the population, or at least the majority of US census respondents.<sup>21</sup> Additionally, the percentage of the population reporting to be White alone, not Hispanic or Latino is 59.3%. The largest ethnic minority is Hispanic or Latino at 18.9%, followed by

Black or African American alone at 13.6%, Asian 6.1%, American Indian and Alaska Native at 1.3%, and then Native Hawaiian and Other Pacific at 0.3%.<sup>21</sup> Those reporting Two or More Races represent 2.9% of the population. One would expect a representative sample of the United States population to have a study pool with percentage White between 60-75%, rather than the 65.0-93.6%<sup>4-6,12,22</sup> White or Caucasian as seen in many migraine studies that chose to collect racial and ethnic demographic data. Considering the ethnic breakdown from the census, one would also expect a representative sample of the population to have a larger portion of subjects reporting Hispanic or Latino origin followed by Black or African American, Asian, American Indian and Alaska Native, and then Native Hawaiian and Other Pacific Islander<sup>21</sup>.

Many migraine studies included in this literature review, particularly the older ones, did not collect ethnic or racial demographics<sup>19</sup> or only collected White and other,<sup>12</sup> or White, Black, and other.<sup>8,22</sup> Of those studies that collected ethnic and racial demographics, none had demographics that resembled the US census data. Subjects in a study comparing diclofenac combined with caffeine to diclofenac alone to placebo were 77.8% White, 17.7% Black, 1.4% Asian, and 4.2% Other.<sup>4</sup> A study on patterns of use in migraine treatment had a study pool composed of 93.6% Caucasian, 5% African American, and 2% other individuals.<sup>22</sup> A study of a common OTC migraine medication, the study pool was composed of 74.3% white, 20.2% Black, 0.6% Asian, 3.9% Hispanic, and 1.0% other.<sup>5</sup> A repeat study by the same lead

investigator had a study pool of 65.0% White, 28.0% Black, and 6.9% Asian/Hispanic/other.<sup>6</sup> Not only was Black the largest minority, the grouping of Asian, Hispanic, and other as only 6.9% shows that the population of this study was not representative of the population. The population data in these studies demonstrate that the demographics presented as representative of the American population are not quite accurate.

A study of prevalence from 2018 by NCHS showed percentage of respondents reporting migraine or severe headache across ethnicity and race in the past 3 months were composed of White 15.4%, Black or African American 15.2%, American Indian or Alaska Native 18.4%, Asian 11.3%, Native Hawaiian or Other Pacific Islander 20.3%.<sup>20</sup>

Restrictions, such as limitations of number of attacks per month or severity of headache, also exclude individuals from groups with the highest burden of migraine and reduce the generalizability of that data to those groups. For example, in 2014, Goldstein et al. performed a study of the response to a commonly available OTC medication on severe migraine. While this study's inclusion criteria was less restricted than prior, it still limited participation to those with fewer than 6 migraines per month.<sup>6</sup> According to a MAST study, most sufferers (83.8%) of migraine sufferers have 1-9 headache days per month<sup>14</sup>, so restricting the study pool to 6 or under makes sense. However, that study was also 88.0% White with African American, Asian, or Pacific Islander, Native American, and two or more races

making up the remaining 12%. Contrast this with prevalence data and that shows trends of increased burden of migraine in non-White ethnic groups and the generalizability may begin to falter. Prevalence data gathered from massive population sampling would suggest prevalence of migraine in White populations is closer to 15%, with other ethnic groups such as Black or African American, American Indian or Alaska native having relatively higher burden of migraine, and only Asian populations having a lower burden of migraine compared to White groups.<sup>2</sup> Unfortunately, the number of attacks per month is not available to compare. Additionally, the MAST study did not have headache frequency breakdown by ethnicities so differences in frequency by ethnicity cannot be evaluated. However, considering the low participation by non-White groups, it is possible that there may be statistically significant differences in migraine frequency across ethnicities, which may make studies with restrictive inclusion criteria generalizable to those populations.

Women are more likely to suffer from migraines compared to men. Women are also more likely to seek help and escalate medication compared to men.<sup>23</sup> Women reported more frequent attacks, were more likely to be disabled by attacks, and had higher rates of diagnosis than men. Women are also less likely than men to use preventative medication, consistent with previous research.<sup>14</sup> In a MAST study, 73% of respondents were women which is consistent with the prevalence data showing twice the number of females are affected compared to males.<sup>14</sup> In a study

comparing seeking care for migraine in the UK compared to the US, males in the US were noted to be significantly less likely to seek care for migraine than females and, when they sought care, were more likely to be older in age, whereas no such discrepancy was noted in the UK population.<sup>24</sup>

### *Migraine Prevalence Across Socioeconomics*

Migraine disproportionately affects socioeconomically and educationally disadvantaged populations, as well as the uninsured.<sup>2</sup> Prevalence studies over the years consistently note higher rates of migraine are associated with less education, being on Medicare/Medicaid or uninsured, being near or in poverty, and reporting being unemployed or working part time.<sup>2,19,20</sup> The National Health Interview Survey, in an average of 3 month prevalence between 2016-2018, found that that 18.5% had earned less than a high school diploma, 15.9% had a high school diploma/GED, 17.7% had some college, and 12% had a bachelor's degree or higher.<sup>2</sup> Poverty level data was only available from 49-59% of the study participants. Prevalence was 22.7% for respondents reporting being at or below the poverty level and 19.2% among those reporting that they were "near poor", as determined by the US Census-determined poverty level. Employment status data from 2012-2018 showed, of the 72-82% of respondents with available employment data, between 35-40% reported being unemployed and had never worked or currently unemployed but had previously worked and 40.9% reported at least part time employment.<sup>2</sup>

Migraine remains a high healthcare burden and continue to disproportionately affect vulnerable populations, such as those with low socioeconomic status, the unemployed or part time employed, the uninsured.<sup>19</sup> These are populations that are less likely to have ready access to healthcare, whether it be the time to attend an doctor's appointment or the finances to pay for testing and medication.

The popular belief that migraine is more prevalent in higher socioeconomic group is due to increased incidence of individuals of that group seeking medical help for migraine compared to those in a lower socioeconomic group, since data suggests that prevalence increases with decreased socioeconomic status across all demographics.<sup>8</sup> The core social determinants of health contributing to headache disparities are insurance status, employment status, education level, and income level.<sup>2</sup> Increased prevalence in the lower income group could be due to known effects on health from lower income, such as those on diet, stress, and other factors. Migraine likely interferes with completion of education and maintenance of employment. <sup>2</sup> Increased attack frequency and increased disability burden of migraine is associated with low socioeconomic status and part time and unemployment, as well as government insurance status.<sup>19</sup> Additionally, access to good health care in higher income groups may contribute to decreased duration of illness, as evidenced in age distribution data. <sup>8</sup> The economic impact of migraine can be correlated to the degree of disability, as well as lost time and lost productivity. <sup>25</sup>

Nationwide prevalence data of the United States suggests that migraine impacts people of different ethnic backgrounds, as defined by the US census, relatively equally and disproportionately affected more individuals who report being near poor or below poverty line.<sup>2</sup>

### *Migraine Prevalence and Insurance and Treatment*

Patients without insurance were 45% less likely to receive triptan prescription compared to patients with private insurance.<sup>7</sup> The likelihood of triptan prescription was also lower in patients in low or poor income categories.<sup>26</sup> Less than 5% of migraine sufferers seek care from specialists, such as neurologists, and yet many studies of migraineurs are recruited through subspecialty clinics and, as such, exclude an enormous portion of the affected population.<sup>9,13,19</sup> In data collected between 2009-2018, the percentage of migraineurs who reported having health insurance remained steady. The greatest change was between 15.7% in 2017 and 20.9% in 2011, though insurance patterns did not appear to show a change after introduction of Affordable Care Act in 2012.<sup>2</sup> In the same study, in the 65 and under group, 27.1% of respondents reported having Medicaid, 24.6% reported other and 18.0% reported being uninsured; only 15.3% reported having private insurance.<sup>2</sup> Additionally, the paradigm for treatment is changing from symptomatic (e.g. analgesics, antiemetics, etc.), which includes affordable OTC medications, to more specific therapies (e.g. triptans, anti-CGRP antibodies, etc.) that target the underlying mechanisms of migraine and can be significantly more expensive and

require increased contact and familiarity with the healthcare system, such as referrals to specialists, testing, formal diagnoses, and prescription coverage.<sup>20</sup> The data suggests that just over a quarter of those who suffer from episodic migraine receive minimally appropriate care for their condition and the same historical barriers to care are ongoing.<sup>14</sup>

Migraine continues to be a popular reason for healthcare visits across all settings. Most individuals report seeing a primary care provider for their migraine care but 16.7% still present to the Emergency Department for their headache treatment.<sup>19</sup> This is concerning, not just for the higher economic cost of ED visit compared to an office visit with a PCP, but also because migraine care in the Emergency Department setting is suboptimal. Patients presenting with head pain in the ED are more likely to be treated with or prescribed non-migraine specific medications such as opiates, which, not only pose an unnecessary risk of dependence and overuse syndromes, but are also not recommended as treatment for migraine pain.<sup>1,19</sup> Pharmacological trends show that opioid use in the treatment of migraine in emergency departments is increasing.<sup>19</sup>

Men are significantly more likely to use opioids for migraine than women and these are usually drugs originally prescribed for trauma or other pain.<sup>14</sup> Conversely, women were found to be more likely to be prescribed opioids for headache than men.<sup>14</sup> ED treatment of migraine also increases a patient's chance of unnecessarily being exposed to radiation. Imaging is not necessary for a patient

presenting with migraine who has a normal neurological exam and, yet, 8% of ED visits had a CT scan.<sup>19</sup>

### *Demographic Representation in Studies of Migraine Treatment*

Subjects in a study comparing diclofenac combined with caffeine to diclofenac alone and to placebo was 86.1% female and 77.8% white, 17.7% Black, 1.4% Asian, and 4.2% Other.<sup>4</sup> A study looking at the impact of OTC migraine medication program on quality of life also had subject pool demographics, which were heavily skewed. The study demographics were primarily female (87.1%), White (83.2%) with no other races noted, married (70.3%), employed full time (60.6%), and had an income >\$50,000 (62%).<sup>12</sup> In a study of a common OTC migraine medication, the study pool was 78.8% female, 74.3% White, 20.2% Black, 0.6% Asian, 3.9% Hispanic, and 1.0% other.<sup>5</sup> A study on patterns of use in migraine treatment had a study pool composed of 89% female, 93.6% Caucasian, 5% African American, and 2% other.<sup>22</sup>

There is a heavy skew to White, married, middle-aged, well-off women with insurance. Compared to prevalence surveys of the American population, the disproportionately affluent, White study pool does not reflect the majority or the most frequent migraine sufferers, although it does reflect the demographic reporting the greatest degree of disability from surveys of the population in 1992.<sup>8</sup> The differences noted between migraine medication studies and migraine prevalence studies reveals a gap in the literature. More research focusing on

underrepresented minorities, those of low socioeconomic status, and the uninsured is necessary to provide a better understanding of how to improve care for migraine.

## **CHAPTER THREE: METHODS**

### **Study Design**

This proposed study will be a double-blind, randomized, parallel-group, placebo-controlled, single-dose design heavily based on the methods used in Goldstein 2006 and Goldstein 2014.<sup>5,6</sup> There will be three treatment groups each will be provided with one 2-tablet dose of either acetaminophen (Tylenol) 250 mg, acetylsalicylic acid (Aspirin) 250 mg, and caffeine 65 mg combination (AAC), ibuprofen 200 mg (IB), or placebo. Study participants will be instructed to take the single study dose and record their perception of pain relief.<sup>5,6</sup> This study will deviate from the original design using more targeted recruitment to attempt to capture a more ethnically representative population of the American population of migraine sufferers and the use of virtual and smartphone technology to increase accessibility and participation.

### **Study Population and Sampling**

Clinical assessment would be conducted in person or virtually by an investigator and the subject would be included in the study, if they met the criteria for the International Headache Society (IHS) diagnostic criteria for migraine with or without aura, or International Classification of Headache Disorders 2<sup>nd</sup> edition (ICHD-2). Inclusion criteria also include being 18 years or older, being in general good health, and having had at least one migraine in the past two months but no more than six migraines in a single month over the prior year. Patients will not be

excluded from the study if they require bed rest or experience frequent vomiting during a migraine attack. Exclusion criteria includes head pain due to or worsened by recent head or neck injury, known history of cluster headache, history of migraine variants, non-migraine headache, or used analgesic drugs for headache on more than twelve days per month. Potential study subjects will also be screened for history of adverse reactions to the over-the-counter medications that the subject could potentially be exposed to as part of the study to ensure safety of all participants regardless of group placement.

Patients will be surveyed on whether they have a rescue medication or therapy for acute migraine attacks and will be informed that for the purposes of the study, they will be asked to withhold treatment for at least two hours. They will also be informed that if they are unable to wait to take rescue medication for any duration of time, they will be asked to indicate such on their survey the time they took the rescue medication and optionally provide a brief explanation of why. Rescue medication or therapy is defined as any medication, treatment, or intervention that the individual subject normally relies on to treat their migraines.

The Goldstein et al studies from 2006 and 2014 used a 3:3:1 ratio and calculated that they needed 665 subjects per active treatment group and 222 subjects for the placebo group to achieve at least 90% power and an alpha of 0.05. This study will recruit subjects until beyond the minimum number of participants for each of the three principal cohorts has been obtained in anticipation of up to a

potential 15%<sup>6,27</sup> reduction per treatment group due to rescue medication use prior to the 2 hour post dose time, or failure to fill out the surveys.

### **Treatment, Intervention, and Exposure Groups**

Patients meeting the inclusion criteria will be randomly assigned with a 3:3:1 ratio to receive: a single four tablet dose of 2 AAC tablets (acetaminophen (Tylenol) 250 mg, acetylsalicylic acid (Aspirin) 250 mg, caffeine 65 mg) and 2 placebo IB tablets; 2 IB tablets (200 mg ibuprofen) and 2 placebo AAC tablets; or 4 placebo tablets to be taken to treat one headache meeting the symptom profile for migraine and considered moderate to severe in intensity during the study period.<sup>5,6</sup>

This trial includes a placebo arm both to better replicate the methods used by Goldstein et al<sup>5</sup> and due to recommendation by the Guidelines of the International Headache Society for controlled trials of acute treatment of migraine attacks in adults: Fourth edition.<sup>28</sup> Placebo response in trials for acute treatment of migraine are known to vary widely for measures of headache relief from 6-56% and for pain freedom from 6-25%.<sup>28</sup> A placebo arm of a drug trial for treatment of migraine headache is important to be able to be able to rule out the placebo response from the active arms of the trial.<sup>29-31</sup>

The 2 hour post dose benchmark will be used as the main measure of efficacy both to mirror the measures used in Goldstein et al, but also because most acute treatments of migraine do not have an onset significantly earlier than the 2 hour mark.<sup>5,28</sup> In the original study, onset of meaningful pain relief had a mean of greater

than 2 hours for all groups with AAC having the fastest onset at 128.4 minutes, IB at 147.9 minutes and placebo at 167.1 minutes.<sup>5</sup>

Patients will be asked to refrain from taking rescue treatment for at least 2 hours if possible,<sup>28</sup> and if they choose to take it, they will be asked to record the time.<sup>5,6,27</sup> Those who choose to take rescue medication prior to 2 hours post dose will be considered treatment failure, as well as those who indicate taking the study dose but fail to record at the designated times, as per IHS guidelines.<sup>28</sup> In both cases, post rescue medication PAR scores will all be assigned 0 “no relief” and PID score will automatically assigned “severe pain”.<sup>5</sup> This population of patients will be considered an incidental study cohort. Participants who decide to take rescue medication after 2 hours post dose will be recorded as such, and their data will be included in analysis.

If a participant has not indicated that they have taken rescue medication but fails to fill out a survey at any of the predetermined time intervals, their scores will be filled in with an average of the adjacent scores. Treatment groups will remain blinded until data collection has been completed.

### **Project Variables and Measurement Tools**

The key variable in this study will be meaningful pain relief (PAR) as rated by the patient at 15, 30, 45, 60, 90, 120, 180, and 240 minutes after taking the randomly assigned dose. Time to meaningful PAR will be considered the point in time after taking the study dose when the patient subjectively considers their pain

to be relieved. Total pain relief 2 hours post dose (TOTPAR2) will be considered the primary efficacy time point and total pain relief at 4 hours post dose (TOTPAR4) will be considered a secondary efficacy time point as noted in the Goldstein studies.<sup>5,6</sup>

At each time interval, the smartphone application will automatically prompt the participant at 15, 30, 45, 60, 90, 120, 180, and 240 post-dose to fill out a short questionnaire, providing ratings or attesting to the presence or absence of certain symptoms. Subjects will rate meaningful PAR on a scale of 0 to 4, with 0 being “no relief” and 4 being “total relief”. Subjects will also be asked to rate two additional factors: pain intensity compared to baseline (PID) and functional disability. PID will be on a scale of 0 to 3, with 0 being “no pain” and 3 being “severe pain”, and functional disability to perform usual activities will be on a scale of 0 to 4, with 0 being “no disability” and 4 being “totally unable to perform usual activities”. Subjects will also be asked about the presence or absence of commonly associated symptoms including nausea, vomiting, photophobia, and phonophobia.<sup>5,6</sup>

### **Recruitment**

Study subjects from the Greater Boston Area will be recruited primarily using targeted advertisements on social media. Advertisements will ask for volunteers interested in contributing to research exploring the efficacy of commonly available over the counter medications primarily in ethnic minority groups. Subjects will also be recruited using traditional methods including soliciting community health centers, local primary care offices, and specialists for referrals for this study.

Subjects who express interest will be directed to a website and be asked to fill out an initial screening survey asking about their general symptoms to assess for the major inclusion and exclusion criteria such as frequency of migraine and key clinical features of migraine that differentiate it from other primary and secondary headache disorders. Potential subjects who meet inclusion criteria will be informed of the type of study and that if they wish to proceed, the next step will be to set up an appointment for a more detailed health and safety evaluation, as well as consent to participate, with an in person or virtual interviewer, dependent on their preference.

Potential subjects will also be asked if they have a rescue medication or treatment and will be informed prior to participation in the study that they will be requested as part of the study to refrain from taking their rescue medication for at least two hours after taking the study medication, but they if they are unable to do so, they will be asked to record the time they took their rescue medication. Participants will be given clear assurance that needing to take rescue medication is just as important to the study as measuring the efficacy of study treatment, and to take their rescue medication if they feel that they need it. Participants will be informed that should they be selected for inclusion in the study, they will be given the option to pick up the one dose study medication in person from a designated location or may request to have it mailed to them prior to the start of the study period.

## **Data Collection**

Initial evaluations will be conducted in person or virtually by trained investigators in the Greater Boston area, dependent on patient preference and availability. Participants will be encouraged to download a smartphone application for data collection. The participant will indicate on the application that they have taken their study medication and the application will then automatically prompt the participant to fill out the survey questions at 15, 30, 45, 60, 90, 120, 180, and 240 minutes post dose.

After the participant has completed their single drug trial, the participant will be required to connect to the internet and their data will automatically be sent to the research team. The application will notify the participant when their data has been successfully uploaded, they will be thanked for their participation, and informed that the application is safe to uninstall. The survey on the application will be functional regardless of internet access. Internet access will only be required for initial download of the phone application and uploading of the completed data.

## **Analysis**

The raw data will be downloaded from the cloud and then organized onto a spreadsheet for statistical analysis. First, a Pearson correlation will be used to determine if any of the TOTPAR variables are correlated with PAR. If so, only PAR and PID will be used as dependent variables in MANOVA model. A MANOVA will be run to determine whether there are any differences between intervention, AAC, IB

and placebo cohorts (independent variables) on time to meaningful PAR, PID, TOTPAR2, and TOTPAR4 (dependent variables). MANOVA assumes that the two or more variables are measured at intervals or ratios, and that the independent variable includes two or more independent groups. The methods used in this study would be blinded and no participants will be included in more than one group, and will be recruiting a large number of participants. MANOVA assumes that there are no outliers in each group of the independent or dependent variables, and that there is multivariate normality. It also assumes that there is a linear relationship between each pair of dependent variables of each group of the independent variable, homogeneity of variance-covariance matrices, and no multicollinearity.<sup>32</sup>

A Chi-square test will be used to analyze categorical variables including sex, ethnicity, socioeconomic status, insurance status, employment status, and education to assess whether there is a statistically significant difference between the three treatment groups. The Chi-square assumes that the data is frequencies or number of cases, the levels or categories of the variables are mutually exclusive, each subject contributes only one data point in one treatment group, study groups are independent, and there are two variables and both are measured as categories.<sup>33</sup>

Time to meaningful PAR will be analyzed one way ANOVA to evaluate whether one intervention had an earlier or later average time to meaningful PAR in comparison to the treatment groups. One way ANOVA assumes the dependent variable is continuous, independent variable is two or more categorical independent

groups, that subjects will be included in only treatment group only, that there will be no significant outliers, that the dependent variable is approximately normally distributed for each category of the independent variable, and that there is homogeneity of variances.<sup>34</sup> Considering the changes in recruiting methods compared to prior studies, trends in distribution seen in those studies may not be applicable to those recruited for this study. Additionally, there is a plan to recruit a large number of subjects per cohort, and as a result there is a chance that data may be normally distributed. It is difficult to assume how the data will be distributed prior to data collection, so nonparametric test may be preferred.

Statistical significant will be considered when P is less than or equal to 0.05.<sup>5,6</sup>

### **Timeline and Resources**

During Winter 2022, a smartphone survey application will be selected for the study, and then assessed for security and HIPPA compliance. Then, in the Spring 2023, the study will be submitted for IRB approval. Advertisement, recruitment, and evaluation of potential participants will occur over Summer 2023. In Fall 2023 during a 3 month period, participants will be eligible to take the single dose and record their experience on the phone application. In Winter 2023 after the study period, the data will be pooled for analysis.

This study will need at least 10 trained interviewers who will be tasked with evaluating potential study subjects for inclusion and exclusion criteria. A clinical

coordinator, statistician, and an office space for in person interviews will also be needed. IT support will be needed as well as internet access, a server with the capacity to have one account per participant, and cloud storage for the data. A preexisting survey smartphone application can be used or altered for the purposes of this study.

### **IRB**

This study is modeled from Goldstein et al. 2006 and 2014 which were both IRB approved at each site where the study took place. IRB approval will be sought through Boston University. Potential subjects will be screened for known adverse reactions to the medications used in the study to decrease the potential risk to the participants. After meeting inclusion criteria, data will be collected anonymously through virtually available survey. Because the drugs in this study are not part of an investigational new drug application under 21 CFR part 312, this study falls under the exception which allows for expedited review.

## CHAPTER FOUR: CONCLUSION

### Discussion

Migraine is a common primary headache disorder that affects a not insignificant portion of the population worldwide and is an active area of research. Migraine disproportionately affects females, those of low socioeconomic status, and those with government insurance and the uninsured.<sup>2,11,19,20</sup> Additionally, the data suggests that migraine affects ethnic and racial groups at a similar prevalence, which has also been stable over the past several decades.<sup>2,20</sup> However, there appears to be a significant gap in the literature regarding the representation of individuals of color, those with low socioeconomic status and the uninsured. The etiology of the gap is multifactorial and subjects may be excluded due to recruiting from specialty clinics that by nature cater to those with private insurance, reduced use of medical services by minority groups, or subjects may not be inclined to answer medical surveys.<sup>7,22,26</sup> Traditional recruitment methods such as random number dialing, referral from specialty clinics, referral from private practice favor the inclusion of subjects who are more likely to be home and answer the phone, have a home phone, or have a cultural inclination to participate in studies at all. To better understand whether commonly available, affordable medications are as effective in other groups as they are documented to be in the studied population of White females, more data must be collected that includes more of these underrepresented groups.

This study design has several strengths. This study method or very similar methods have already been used multiple times<sup>5,6</sup> so data gathered using these methods will be more attributable to the target population but will also increase the study's generalizability. Overall time commitment is reduced to the evaluation for inclusion and the endpoint 4 hours from taking the study medication for one migraine which may encourage individuals with less free time to participate. A smartphone application does not restrict the movement of the study participant and with the ubiquity of smartphones a user friendly and convenient application is an easier commitment. Another strength of a smartphone application is the ability to program timed survey prompts so that participants do not have to keep track of timing intervals themselves. Wireless data upload to cloud storage means that large volumes of data can be collected remotely. Use of virtual meetings and smartphone technology for data recording and collection increases the flexibility and privacy of study subjects and may encourage participation in populations who have less free time.

A study of this magnitude and focus on inclusion of specific groups will have many limitations. The model methods for this study had three groups with a 3:3:1 ratio, and recruited over 1700 subjects for a goal of 665 patients for the two active treatment groups, and a goal of 222 patients for the placebo group.<sup>5</sup> This will be a challenge to recruit and retain enough subjects to obtain a statistically significant result, as well as collect and organize data from so many subjects. In mimicking the

methods of the Goldstein et al<sup>5</sup> this study does not address limitations brought up by the original study surrounding the increased placebo response rate likely due to the high randomization ratio used in these studies. Research has shown that placebo response rates increase when subjects are more likely to believe that they will receive the active medication<sup>5</sup> in addition to the traditionally high placebo response rates seen in headache research in general.<sup>28</sup> A migraine attack is unpredictable in onset so the study could possibly run longer than expected if an insufficient number of subjects have submitted their data by the study timeline. In addition to the challenge of recruiting the target subject demographics, the portion of subjects who will answer all the questions at the appropriate times and complete the study will certainly not be 100%. The requirement to use a smartphone application will likely limit participation to those comfortable with technology, though this may primarily exclude those at the upper end of the age range. Migraine is well known to be significantly more prevalent in those under the age of 65 of both sexes,<sup>3,8,20</sup> so exclusion due to technology fluency may not result in a large bias. Unfortunately, without further restricting the inclusion criteria, there is poor control over potential overrepresentation of certain groups that are historically known to participate in research, though the strategic placement of advertisements in public spaces or targeted advertisements social media may work somewhat to counteract this.

There is also a limitation regarding the potential for non-adherence to the study guidelines and requirements. Patients who will report their data outside of a

clinical setting have less oversight and may not record their results accurately or may fail to report taking rescue treatment prior to the 2 hour post dose timeline. Use of rescue medication prior to the 2 hour post dose point will be considered treatment failure for that intervention group. Patients must be allowed access to rescue medication and participants will be encouraged to take their rescue medication if they feel that they need it and will be encouraged to do so prior to agreeing to participate in the study. Previous studies that used similar methods reported a portion of participants who used rescue medication prior to the 2 hour post dose time, or failed to answer the survey questions, but none noted that this was a significant portion of the study pool.<sup>5,6,27</sup> Rescue medication use rates ranged were up to 10% prior to 2 hours post dose and up to 15% between the 2 hour post dose and 4 hour post dose times.<sup>6,27</sup> It is possible that a higher than expected proportion of participants might use rescue medication and this could result in reduced power. This would also increase the proportion of participants reporting severe pain compared to mild or moderate pain since that individual will automatically be given a “severe pain” score for PID.

It is as important to understand what portion of people a particular intervention is effective for as it is to know how many people report no efficacy. One well known example can be found in the practice guidelines for treating high blood pressure, an extremely common condition.<sup>35</sup> Even today, medical education continues to teach that angiotensin converting enzyme inhibitors (ACEi) are less

effective in patients of African American descent compared to other ethnicities.<sup>35</sup> New studies analyzing this long held claim are beginning to challenge the understanding of the data.<sup>36</sup> Migraine affects a significantly smaller portion of the population compared to high blood pressure, and the volume of data available for analysis is also less. However, analysis of the treatment failure population could begin to reveal demographic patterns that have not been noticed due to the relatively poor inclusion of ethnic minorities seen in previous migraine studies.

### **Summary**

Migraine consistently continues to be a significant medical burden, disability, and lost work time the American population.<sup>2,8,11</sup> Historically, both over the counter and prescription drug studies for treatment of acute migraine have had study populations with heavily skewed demographics and represented primarily by white females of upper socioeconomic status.<sup>4,5,27</sup> Additionally, the current understanding of migraine includes the belief that this demographic is representative of migraine sufferers.<sup>4,5</sup> A comparison of demographic data from migraine prevalence studies to a variety of over-the-counter drug studies revealed a large discrepancy. Migraine prevalence studies would suggest that, while females are about twice as likely to suffer from migraine compared to matched males, migraine is prevalent in most ethnic groups at a similar percentage except for Asian ethnic category, which surveys show a lower prevalence than other groups.<sup>2,20</sup> The prevalence data also suggests that migraine disproportionately impacts those of lower socioeconomic

status and those with migraine are also more likely to have government funded insurance or be uninsured.<sup>2,8,11,19,20</sup>

Although migraine is generally understood to not increase mortality, migraine continues to be a significant cause of disability and can negatively impact an individual's educational or career trajectory, leading to completion of less educational or vocational training and significantly more lost productivity and income from work than those who do not suffer from migraine.<sup>2,11,25</sup>

The population demographics from drug studies in migraine, both OTC and prescription, do not match the population that suffers from migraine in prevalence studies. When comparing the demographics in prevalence studies to drug efficacy studies with populations as determined by the US census that are 80% White, female, and well above poverty level, those studies may not be the most accurate reflection the population of migraine sufferers in the USA.<sup>2,3,8,20</sup> Future studies need to be more inclusive to present an accurate picture of migraine sufferers in the US. Migraine affects a significant portion of the population and disproportionately affects lower income demographics.<sup>8,11</sup> A more accurate understanding of the efficacy of OTC medications is critical for a group with less access to potentially more expensive prescription medications and insurance plans. Affordable and easily accessible pharmacological methods of pain relief are an important concern.<sup>2,11,25</sup> The current literature supports the efficacy of these medications in a very specific group that already has access to alternative means of analgesia.<sup>7,18,22,37</sup> Due to all

these factors, it is a matter of public health to have more accurate representation in studies and to better understand the efficacy of OTC drugs in non-female, non-white, and non-affluent populations.

If we just consider the data from these four studies, Goldstein 2006 and 2014<sup>5,6</sup> and the prevalence data published in 2018 and 2021<sup>2,20</sup>, there is a wildly glaring issue with the ethnic or racial breakdown. The demographic data from the Goldstein studies is a good generalization of the demographic breakdown from most studies on migraine with minimal racial or ethnic divisions with White dominating the study pool. This is considered reflective of the population of the US via census data but surveys of prevalence suggest that White groups are not significantly more affected compared to other racial or ethnic groups and may have lower prevalence compared to certain minority groups.

By not including minorities in studies, patients are prescribed medication with the assumption that what worked for the group studied will work the same for that individual, regardless of the potential differences between the individual and the study pool. Those with access to greater resources often have the privilege of choice and availability of options.<sup>22</sup> Those people can try expensive medications until they find one that works. People who only have access to OTC or who have to weigh the cost of an expensive drug against other essentials should have data representative of people from their group, even if the answer is that it works just the same as in existing studies.

Additionally, prevalence by socioeconomic groups as determined by the US census also suggests that there is no statistically significant difference in prevalence by household income.<sup>2,19,20</sup> With this information, the currently available data is not generalizable to the public. White married women with household income above \$50,000 per year are oversampled in migraine research and, thus, results are not very generalizable.

The level of disability caused by migraine is studied but may not be as well understood or considered acceptable by the public. Culturally, it is possible that it is considered most socially acceptable by White females to address or acknowledge headache as worthy of taking time out of work or education to attend to.<sup>9</sup> Most migraine studies looking at efficacy of OTC medications have subject pools that are nearly all more than 80% female and 70% White.<sup>4-6,8,9,27,38</sup>

Migraine affects a significant portion of the population and disproportionately affects lower income demographics.<sup>2,8,11,19,20,25</sup> A more accurate understanding of the efficacy of OTC medications is more critical for a group with less access to potentially more expensive prescription medications and insurance plans. Affordable and easily accessible pharmacological methods of pain relief are an important concern. The current literature supports the efficacy of these medications in a very specific group that already has access to alternative means of analgesia.

### **Clinical/Public Health Significance**

Migraine is a significant cause of disability and, with a better understanding of readily available and affordable treatment options, healthcare providers would be more readily able to provide more individualized care.<sup>2,11,25</sup> Non-White ethnic groups and those of low socioeconomic status are underrepresented in migraine research<sup>4-7,9,27,37,38</sup> but prevalence data suggests that these groups comprise the bulk of migraine sufferers in the United States.<sup>2,3,20</sup> Repeating medication efficacy studies, but intentionally recruiting as to include a more ethnically and socioeconomically representative population can help increase understanding of whether the current paradigm of care is equally as effective in those groups as it is in the well-studied White female population.

## LIST OF JOURNAL ABBREVIATIONS

Ann Pharmacother	Annals of Pharmacotherapy
Biochem Med (Zagreb)	Biochemia Medica
Cochrane Database Syst Rev	Cochrane Database of Systematic Reviews
Curr Opin Investig Drugs	Current Opinion in Investigational Drugs
Eur J Clin Pharmacol	European Journal of Clinical Pharmacology
JAMA	JAMA: The Journal of the American Medical Association
Neurol Sci	Neurological Sciences

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