Research Open

Archives of Women Health and Care
Volume 2 Issue 6

Review Article

Migraine, A Review of Basic, Clinical, and Translational Approaches to New Treatment

Jared R Wahl MPH[1], **Todd W Vanderah** PhD[1], **Tally M Largent-Milnes** PhD[1*]

[1]Department of Pharmacology, College of Medicine, University of Arizona Tucson AZ, USA

Corresponding Author: Tally M Largent-Milnes, Department of Pharmacology, College of Medicine, University of Arizona Tucson AZ, USA; **Tel: E-mail:** tlargent@email.arizona.edu

Received: November 07, 2019; **Accepted:** November 18, 2019; **Published:** November 25, 2019;

Abstract

Migraine is a debilitating neurological primary headache disorder characterized by recurring unipolar headaches lasting 4–72 hours with accompaniment of nausea and sensory sensitivities. Migraine is the most common headache disorder resulting in seeking of medical care [1, 2], in addition to being one of the most debilitating chronic disease conditions in terms of both morbidity and lost economic productivity. Migraine incidence has been observed since ancient times to disproportionately affect women, and most current epidemiological assessments put current incidence estimates at 12% overall for US populations, with an incidence of 18% in women and 6% in men when stratified by sex. This dimorphism of incidence is crucial when assessing overall health of a community, specifically when concerning women's health and therefore must be taken into consideration when developing both clinical and basic models of migraine to enact the best possible outcomes of combined translational research efforts. While major recent advances have been made in the field of pharmacologic intervention for migraine with the recent approval of the anti CGRP and anti CGRP receptor antibody medications, prohibitive cost and limited access have made older treatments, such as the triptans and NSAIDs, still the most commonly utilized medications to combat migraine attacks. Current preclinical research models are heavily interested in modulation of the neuropeptide CGRP, and the phenomenon of cortical spreading depression (CSD), believed to be the underlying trigger of migraine with aura, via pharmacological intervention. Modulations of these phenomena has found to be correlated with menstrual events in women, tying back to the overarching theme of higher morbidity in women. With the advent of pharmacogenomics and personalized medicine, a new epoch of potential customizable treatments looms on the horizon, endearing those afflicted with this severely debilitating condition a new glimmer of hope as research progresses into its next phase.

Acronyms: AMPP: American Migraine Prevalence and Prevention study. **NIH:** National Institute of Health. **ICHD-3:** International Classification of Headache Disorders, 3rd edition. **NHIS:** National Health Interview Survey. **NSAID:** Non-Steroidal Anti-Inflammatory Drug. **CGRP:** Calcitonin Gene Related Peptide. **5HT1:** 5-Hydroxytryptamine (Serotonin) Receptor, Subfamily 1. **FDA:** Food and Drug Administration. **CNS:** Central Nervous System. **MOH:** Medication Overuse Headache. **PGE2:** Prostaglandin E2. **CSD:** Cortical Spreading depression. **fMRI:** Functional Magnetic Resonance Imaging. **GWAS:** Genome Wide Association Study. **SNP:** Single Nucleotide Polymorphism.

Background

Migraine is a highly debilitating neurological disorder characterized by recurring unipolar headaches with a duration of 4–72 hours, accompanied by nausea and sensory sensitivities [3]. Migraine is classified as a primary headache disorder, indicating no known underlying cause, and is the most common of all the headache disorders to result in patients seeking medical care [1, 2]. Migraine is also one of the most prevalent and disabling chronic disease conditions, in terms of both individual morbidity and lost economic productivity, with 18% of women and 6% of men in the US suffering from some form of migraine [1], with an incidence in women nearly triple that of men according to the National Health Survey. The economic burden of migraine has been assessed by the American Migraine Prevalence and Prevention study (AMPP) and estimates a mean direct annual healthcare cost burden of $4,144 per chronic migraineur in addition to an average of $5,392.03 of lost economic productivity annually [4]. When quantifying the high degree of morbidity associated with migraine, it quickly becomes evident that the need for better understanding of the underlying pathophysiology be accomplished through basic and clinical research models to aid in ablating the impact of this public health issue.

Migraine Types/Epidemiology

Migraine has been classified into several categories depending on the clinical presentation and description of the patient, these are 1) migraine without aura, 2) migraine with aura, this class includes hemiplegic migraine (including familial and sporadic), migraine with brainstem aura, retinal migraine and aura without headache. 3) chronic migraine (CM), which is defined by 15 or more "headache days" per month, for three months, in absence of medication overuse. Aura is described as a temporary visual disturbance appearing as zigzag lines, flashing lights, or temporary visual loss according to the NIH. Episodic migraine (EM) is classified as having less than 15 headache days per month for three months according to the ICHD-3. While precise estimates of migraine incidence can be difficult to ascertain due to differences in study methodology, the most recent and largest of these was the AMPP, a longitudinal study focused on

120,000 surveyed US households with recipients based on US census data. Overall incidence of migraine was reported as 12%, with 18% of women and 6% of men reporting experiencing at least one migraine attack in the previous year. Upon stratifying by gender, 17.4% of women and 5.7% of men had EM, while 1.29% of women and 0.48% of men meet diagnostic criteria for CM [5]. The disease burden of migraine is carried much more heavily by women.

Sexual dimorphism in migraine presentation: Often, migraine begins at menarche for girls, and continues until approximately age 40, at which symptomology levels off [1, 2]. It was also noted that women experience more severe pain intensity and associated disability when compared to men [6, 7]. This finding is highly significant as these are the most economically productive years for an individual woman and instantiates an even higher degree of cost burden when factoring in the higher observed incidence rate of migraine in women. Coupled to this phenomenon is the degree to which female sex hormone fluctuation during the menstrual cycle, pregnancy, and post-partum periods has been positively observed to impact not only incidence of migraines attacks, but also perceived severity [6, 7]. This chronic level of unpredictability can cause a severe amount of stress and disability at a time in a woman's life when she is expected to be at her peak performance, both economically and in terms of social and familial commitments. For those women with children, the crippling effect of chronic or episodic migraine attacks is a cost burden most simply not afford, and those suffering under the severe duress from a typical migraine attack will still be expected to perform career duties, child care duties, social duties etc. The crippling morbidity of this condition cannot be understated, as the buildup of chronic stress due to migraine results in lost economic productivity, lost time to care for offspring, lost ability to invest in pleasurable activities, which can all contribute to a noticeable decline in long term mental health. It doesn't take long to connect the dots here and realize the agonizingly debilitating effect this condition has on the nearly one fifth of women who suffer from it, and why addressing it is a grave public health concern to society. While studies in the US have found an inverse relationship between income and migraine [8], European studies have been more nebulous about this association, failing to replicate the results seen in the US [6].

Migraine and Race: Migraine incidence varies by race in the US, according to the AMPP study white women and men had the highest incidence (20.4%, 8.4%), followed by African Americans (16.2%, 7.2%), and lowest among Asian Americans (9.2%, 4.2%) [9]. Further surveys of underrepresented populations undertaken by the NHIS indicate highest prevalence in American Indians and Alaska Natives (19.2%), followed by whites (15.5%), African Americans (15%), Hispanic and Latinos (14.9%), Native Hawaiians and Pacific Islanders (13.2%) and Asians (10.1%) [6]. Overall, migraine is a functional pain disorder that disproportionally impacts women during their most productive years, regardless of race.

Clinical Aspects

Diagnostic criteria for the several subtypes of migraine are laid out in the ICHD-3 manual. For use as a type example, the diagnostic criteria for migraine with aura is as follows: Recurrent attacks, lasting minutes, of unilateral fully-reversible visual, sensory or other central nervous system symptoms that usually develop gradually and are usually followed by headache and associated migraine symptoms. Diagnoses of migraine invariably depend on self report by patients, and therefore accurate estimation of true disease prevalence can be difficult [10]. Patients suffering from migraine are currently treated with a host of pharmaceutical agents developed to either abort an acute migraine attack, or act as a prophylactic treatment against future attacks [11].

Treatment and sex sensitivity: Currently, the US headache consortium has outlined a 6 point objective plan to help guide physicians in treating acute migraine attacks. These are 1) treat attacks rapidly and consistently without recurrence; 2) restore patient's ability to function; 3) minimize the use of back-up and rescue medications; 4) optimize self-care and reduce subsequent use of resources; 5) to be cost-effective for overall management; 6) have minimal or no adverse events, however achieving all of these is typically not possible with available treatments. Treatment criteria also differs by region, as some pharmaceuticals are approved in one are while others are not (ergotamines). NSAIDs and acetaminophen, with or without caffeine, are typically first line treatment for a migraine attack [12], due to their easy availability and lack of harmful side effects from frequent use. These are typically used for a mild to moderate migraine sufferer. Triptans are the current first line medications for treating moderate to severe migraine [12], they have agonist activity at the 5HT1 receptors and are believed to work through suppression of CGRP release. They are well-tolerated and demonstrate efficacy in 68% of patients in one meta-analysis [13, 14]. Use of triptans, however, are limited to a maximum use limit of 8–9 doses per month, due to fear of medication overuse headache and the potential of serotonin syndrome [15]. Some first line combination agents exist, such as sumatriptan-naproxen to maximize efficacy of both compounds. Recently on the market are the anti CGRP monoclonal antibodies and anti CGRP receptor monoclonal antibodies. These drugs have yet to be classified in this hierarchy of use, due to their prophylactic nature (once monthly/quarterly administration) and prohibitive cost (estimated cost for erenumab, $6900 annually). While considered safe by the FDA, utilization of any monoclonal antibody does carry some degree of risk of autoimmune induction. This is a relevant point here as CGRP has been shown to have immune function in both the CNS and periphery [16]. However due to the very recent availability of these drugs some time must pass before an in depth analyses can be made. A more cost effective and longer standing approach to migraine prophylaxis lies in the application of the beta blocker drug class. Being the first in their class in terms of application towards migraine treatment, they are still extensively utilized as a prophylactic treatment with the benefit of a much lower cost and tolerable side effect profile [17]. Second line drugs for acute migraine treatment include those of the anti-emetic class, such as promethazine and chlorpromazine. Last resort agents include opiates, barbiturates, ergotamines and valproate, due to either contradicting results, abuse potential, risk of medication overuse headache, or lack of current approval. Medication overuse headache (MOH) is a phenomenon observed from overuse of migraine and pain disorder medications [13, 14]. the ICHD-3 defines MOH as headache occurring on 15 or more days per month, for three months

due to over-usage of acute or symptomatic headache medication. The prevalence of MOH is 1–2% globally, however it is one of the costliest neurological disorders known due to its extremely debilitating effects and treatment resistance [18]. A variety of medication have been observed to cause MOH, however findings have specifically found analgesics such as opioids to be the highest risk class for causing MOH, with triptans being at most equal to opiates for relative risk of developing MOH [13, 14]. Demonstration of not only lack of efficacy of classic analgesics, but the ability for them to increase relative risk for MOH demonstrates the pertinent need for new therapeutics.

Divergence in Female Treatment Response Sensitivity: While the current literature is somewhat lacking in this study metric, fitting within the narrative of this review it would be prudent to assess relevant clinical observational data that is currently available. While many studies have been performed assaying treatment efficacy, there seems to be an overall dearth of results stratified on gender in respect to observed efficacy of pharmaceutical migraine treatment. However, studies have observed a higher female preponderance to developing medication overuse headache; this could be an artifact of the higher overall incidence of migraine in women, higher usage of medication by women, and higher seeking of medical care by women vs men, and underdiagnosing of migraine in men [10]. Moreover, specific agents that induce MOH were not discussed. A recent study has outlined differences in pharmacokinetics in women vs men for the triptan drug class, particularly noting the substantially higher peak plasma concentration of triptans observed in women, which can have far reaching effects on the differences observed in treatment response in men vs women [10]. Regarding the new anti CGRP drugs, studies are under way to assess different response in women and men when treated. However, the few studies that have been done have not been able to definitively state a difference in response to the monoclonal antibodies [19].

Preclinical Research Models

While the precise mechanisms of Migraine are yet to be elucidated, numerous preclinical and basic research models are available, including *in vitro*, *in vivo*, and *ex vivo* models. While the complete understanding of migraine pathophysiology is beyond the scope of this review, a major recent success has arisen from focusing on the interplay of CGRP, the neurovascular unit, and the trigeminal nerve complex [20]. This has led to the development of several new treatments based on inhibiting activity of CGRP. Current preclinical models include a multitude of models to mirror physiological phenomena believed to be impacted in contributing, all or in part, to overall cellular and neurobiological states resulting in a migraine episode. The inflammatory soup model is one such example. This model is based upon the hypothesis that migraine progression is based upon abnormal functioning of neurons in several brain regions [21]. It is essentially an animal model upon which a cocktail of proinflammatory compounds are introduced into the brain, and fMRI imaging is utilized to map the alterations in brain response, cellularly and chemically, to the introduced disruption [21]. The cocktail itself is an acidic mix of bradykinin, serotonin, histamine and prostaglandin PGE2. This paradigm was conceptualized from samples of inflamed human tissue, utilized to induce a state of allodynia and hyperalgesia in an animal model [22]. Migraine has been observed to be induced by a host of triggers, and in clinical settings it was noticed cardiac angina patients undergoing nitroglycerin therapy demonstrated a high degree of headache incidence from this treatment. This observation led to the development of the use of the NO donor in preclinical studies to serve as a migraine attack trigger in animal and ex vivo models [23], due to the documented vasodilative properties of NO and NO donor chemicals. An interesting observation made in the clinic also found that over 50% of migraine without aura is highly correlated with the menstrual cycle [24]. This has translated into application of progesterone treatment in basic research models, in vitro and animal models to simulate this phenomenon in the laboratory to corroborate possible application of contraceptive medications in pursuit of alleviating menstrual associated migraine without aura with these readily available medications. In addition to many other factors, a major mechanism of action of progesterone only contraceptives are believed to down regulate expression of estrogen receptors in the trigeminal vascular system, thereby reducing nociceptive response to elevated estrogen levels associated with menstrual cycles [24]. in further exploring the myriad of possible triggers producing a migraine response, it would be prudent of the preclinical researcher to investigate inroads into possible environmental triggers of a migraine episode. One such tool developed for this purpose is umbellone, an environmental irritant that has found recent application in studying possible activation of transient receptor potential ankyrin-1 (TRPA1) channels and possible contribution to induction of a migraine event [25].

While a notable amount of current research is being focused on modeling and understanding the cortical spreading depression (CSD) event, it must be noted that it has been observed that not all CSD events result in triggering of migraine event, or any type of headache for that matter. This duality is important to note, as CSD events are hypothesized to be an underlying mechanism for migraine with aura10, direct evidence of this has not yet been fully elucidated and ongoing efforts to model it are being pursued to fully tease out the full impact of a CSD event, as pathological brain conditions other than migraine also demonstrate association with CSD [26]. all of these models and study paradigms have been essential in advancing the field of migraine research in basic and preclinical laboratories in institutions across the globe. As more research is clearly needed to elucidate the sex specific reasons women are affected at a much higher rate with migraine, sex specific models are being developed to further investigate this phenomenon. One immediate and simple method of accomplishing this is by simply including female animals, tissue, or female animal derived primary cell cultures for use in experiments. This paradigm can also be carried further into the clinic for translational studies by the usage of female participants for IRB approved studies. The Dussor research group has developed several models for investigating sex-based differences in progesterone signaling leading to higher incidence of migraines observed in females. An animal model has been developed and utilized by this group to explore the relationship between elevated estrogen levels and specific response patterns to fluctuations of these female sex hormones, further relating

to the translational application of progesterone as a treatment [27]. The Dussor and Russo labs have also investigated the differences of CGRP expression in a female model. Due to the hypothesized impact of CGRP on development of migraine, it would be prudent to assess if a difference in expression patterns of this neuropeptide could be contributing to the observed difference in migraine incidence [28]. while this research is still in its infancy, the new avenues being opened by pharmacogenomic technology and the approach of personalized medicine will potentially allow for a new zenith of breakthroughs, as the apocryphal working hidden within our DNA becomes available for study.

Future Direction of Field and Precision Medicine

The recent development of the new class of anti CGRP and anti CGRP receptor antibodies has been an exciting advance in the field of migraine research, however their high cost makes access to all who could benefit from their use impractical. With the emerging concept of precision medicine and pharmacogenomics becoming more and more optimized and readily available, the possibility of applying these technologies to new treatments looms ever closer on the horizon. Due to the high degree of genetic variation within each migraineur, different variants of the enzymes, transporters, and receptors will be more or less responsive to a unique blend of polytherapy, as coding variants for each of these proteins will respond ever so slightly different to each blend of agent utilized to treat migraine [29]. GWAS analyses is proving to be an extremely powerful tool in analyzing single nucleotide polymorphism (SNP) variants across populations [30, 31]. Emerging research has indicated familial migraine contains a higher pathologic gene load associated with migraine than sporadic cases [32], while another study has begun to map possible loci containing genes involved in migraine pathology, specifically locating 38 new loci [15]. In addition to physiologic aspects, applications of high end computing are being utilized to analyze high volumes of drug safety data [33]. This approach utilizing personalized medicine has already been put into translational studies for cardiovascular anti-coagulant drugs, such as warfarin, which has highly variable therapeutic windows depending on the DNA variants encoding enzymes in its metabolic pathway. Moving forward it is hoped to be able to adapt this individual tailoring approach to create a treatment plan specifically optimized for a given patient. The urgency for this approach is highlighted by the fact that only 50% of migraineurs respond to acute or prophylactic treatment [29]. It is hoped that by moving forward with entrenched research tools in the laboratory, best practices observed in the clinic, and the wealth of knowledge and potential unlocked by pharmacogenomic technology, a new synergistic approach to migraine treatment may be made in order to alleviate this horrifically debilitating condition.

References

1. Lipton RB, Munjal S, Alam A, Buse DC, Fanning KM, et al. (2018) Migraine in America Symptoms and Treatment (MAST) Study: Baseline Study Methods, Treatment Patterns, and Gender Differences. *Headache: The Journal of Head and Face Pain* 58: 1408–1426. [crossref]
2. Lipton RB, Munjal S, Buse DC, Alam A, Fanning KM, et al. (2019) Unmet Acute Treatment Needs From the 2017 Migraine in America Symptoms and Treatment Study. *Headache* 59: 1310–1323. [crossref]
3. Schwedt TJ, Alam A, Reed ML, Fanning KM, Munjal S, et al. (2018) Factors associated with acute medication overuse in people with migraine: results from the 2017 migraine in America symptoms and treatment (MAST) study. *J Headache Pain* 19: 38. [crossref]
4. Messali A, Sanderson JC, Blumenfeld AM, Goadsby PJ, Buse DC (2016) Direct and Indirect Costs of Chronic and Episodic Migraine in the United States: A Web Based Survey. *Headache: The Journal of Head and Face Pain* 56: 306–322. [crossref]
5. Buse DC, Loder EW, Gorman JA, Stewart WF, Reed ML, et al. (2013) Sex differences in the prevalence, symptoms, and associated features of migraine, probable migraine and other severe headache: results of the American Migraine Prevalence and Prevention (AMPP) Study. *Headache: The Journal of Head and Face Pain* 53: 1278–1299. [crossref]
6. Burch R (2019) Epidemiology and Treatment of Menstrual Migraine and Migraine During Pregnancy and Lactation: A Narrative Review. *Headache: The Journal of Head and Face Pain* [crossref]
7. Burch R, Rizzoli P, Loder E (2018) The Prevalence and Impact of Migraine and Severe Headache in the United States: Figures and Trends From Government Health Studies. *Headache: The Journal of Head and Face Pain* 58: 496–505.
8. Lanteri-Minet M (2014) Economic burden and costs of chronic migraine. *Curr Pain Headache Rep* 18: 385. [crossref]
9. Lipton RB, Stewart WF, Diamond S, Diamond ML, Reed M (2001) Prevalence and Burden of Migraine in the United States: Data From the American Migraine Study II. *Headache: The Journal of Head and Face Pain* 41: 646–657. [crossref]
10. van den Maagdenberg AMJM, Nyholt DR, Anttila V (2019) Novel hypotheses emerging from GWAS in migraine?. *J Headache Pain* 20: 5. [crossref]
11. Munakata J, Hazard E, Serrano D, Klingman D, Rupnow MF, et al. (2009) Economic Burden of Transformed Migraine: Results From the American Migraine Prevalence and Prevention (AMPP) Study. *Headache: The Journal of Head and Face Pain* 49: 498–508. [crossref]
12. Mayans L, Walling A (2018) Acute Migraine Headache: Treatment Strategies. *Am Fam Physician* 97: 243–251.
13. Teppe SJ (2019) Acute Treatment of Migraine. *Neurologic Clinics* 37: 727–742. [crossref]
14. Thorlund K, Sun-Edelstein C, Druyts E, Kanters S, Ebrahim S, et al. (2016) Risk of medication overuse headache across classes of treatments for acute migraine. *J Headache Pain* 17: 107. [crossref]
15. Evans RW, Tepper SJ, Shapiro RE, Sun-Edelstein C, Tietjen GE (2010) The FDA alert on serotonin syndrome with use of triptans combined with selective serotonin reuptake inhibitors or selective serotonin-norepinephrine reuptake inhibitors: American Headache Society position paper. *Headache* 50: 1089–99. [crossref]
16. Russell FA, King R, Smillie SJ, Kodji X, Brain SD (2014) Calcitonin gene-related peptide: physiology and pathophysiology. *Physiol Rev* 94: 1099–142. [crossref]
17. Danesh A, Gottschalk PCH (2019) Beta-Blockers for Migraine Prevention: a Review Article. *Curr Treat Options Neurol* 21: 20.
18. Gormley P, Anttila V, Winsvold BS, Palta P, Esko T, et al. (2016) Meta-analysis of 375,000 individuals identifies 38 susceptibility loci for migraine. *Nat Genet* 48: 856–866. [crossref]
19. Melo-Carrillo A, Noseda R, Nir RR, Schain AJ, Stratton J, et al. (2017) Selective Inhibition of Trigeminovascular Neurons by Fremanezumab: A Humanized Monoclonal Anti-CGRP Antibody. *J Neurosci* 37: 7149–7163. [crossref]
20. Loder S, Sheikh HU, Loder E (2015) The Prevalence, Burden, and Treatment of Severe, Frequent, and Migraine Headaches in US Minority Populations: Statistics From National Survey Studies. *Headache: The Journal of Head and Face Pain* 55: 214–228. [crossref]
21. Becerra L, Bishop J, Barmettler G, Kainz V, Burstein R, et al. (2017) Brain network alterations in the inflammatory soup animal model of migraine. *Brain Res* 1660: 36–46. [crossref]
22. De Felice M, Eyde N, Dodick D, Dussor GO, Ossipov MH, et al. (2013) Capturing the aversive state of cephalic pain preclinically. *Ann Neurol* 74: 257–265. [crossref]
23. Ashina, Messoud, Hansen, Jakob Møller Dunga, Bára Oladóttir, et al. (2017) Jes Human models of migraine, short-term pain for long-term gain, Nature Reviews Neurology, Nature Publishing Group, a division of Macmillan Publishers Limited.
24. Allais G, Chiarle G, Sinigaglia S, Airola G, Schiapparelli P, et al. (2017) Treating migraine with contraceptives. *Neurol Sci* 38: 85–89.
25. Edelmayer RM, Le LN, Yan J, Wei X, Nassini R, et al. (2012) Activation of TRPA1 on dural afferents: a potential mechanism of headache pain. *Pain* 153:1949–1958. [crossref]
26. Charles A, Baca S. (2013) Cortical spreading depression and migraine. *Nat Rev Neurol* 9: 637–644. [crossref]
27. Sandweiss AJ, Cottier KE, McIntosh MI, Dussor G, Davis TP, et al. (2017) 17-β-Estradiol induces spreading depression and pain behavior in alert female rats. *Oncotarget* 8: 114109–114122. [crossref]
28. Russo AF. (2015) Calcitonin gene-related peptide (CGRP): a new target for migraine. *Annu Rev Pharmacol Toxicol* 2015 55: 533–552. [crossref]

29. Daniela Pietrobon, Michael A. Moskowitz (2013) Pathophysiology of Migraine, Journal Article, 2013 Annual Review of Physiology, Annual Review of Physiology February 75: 365.

30. Ayata C, Lauritzen M (2015) Spreading Depression, Spreading Depolarizations, and the Cerebral Vasculature. *Physiol Rev* 95: 953–993. [crossref]

31. Thorlund K, Mills EJ, Wu P, Ramos E, Chatterjee A, et al. (2014) Comparative efficacy of triptans for the abortive treatment of migraine: A multiple treatment comparison meta-analysis. *J Cephalalgia* 34: 258–267 [crossref]

32. de Boer I, van den Maagdenberg AMJM, Terwindt GM. (2019) Advance in genetics of migraine. *Curr Opin Neurol* 32: 413–421. [crossref]

33. Danysz K, Cicirello S, Mingle E, Assuncao B, Tetarenko N, et al. (2019) Artificial Intelligence and the Future of the Drug Safety Professional. *Drug Saf* 42: 491–497. [crossref]

Citation:
Largent-Milnes TM, Wahl JR, Vanderah TW (2019) Migraine, A Review of Basic, Clinical, and Translational Approaches to New Treatment. *ARCH Women Health Care* Volume 2(6): 1–5.