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HEADACHES THROUGH THE PAST OF MEDICINE

Abstract: The understanding of the etiopathogenesis of headache through the evolution of medicine has closely followed the civilizational and social development of the human species – from primitive prehistoric medicine to two medical scientific philosophies, humoral and cellular, which changed countless medical concepts, causes, diagnostic principles and therapeutic bases. The treatment of headaches throughout the history of medicine was based on common principles respecting the symptomatology of the ruling medical philosophies, initially based on the empiricism of folk medicine, including herbal preparations and craniotomy, and then on alchemy and the scientific development of pharmacy.

Keywords: Headache, Migraine, History of medicine, Therapy

Non MeSH: etiopathogenesis

Introduction

The understanding of headache through the evolution of medicine has closely followed the civilizational and social development of the human species – from primitive prehistoric medicine to two medical scientific philosophies, humoral and cellular, which have changed countless medical concepts, causes, diagnostic principles and therapeutic bases.

The original, primordial, demonic-theurgic period of the development of medicine firmly distinguished the influence of nature on health and life, and supernatural forces and demons on disease and death, and it seems that headaches and their forms have been known since the earliest developmental periods of civilizations and medicine, as confirmed by numerous paleoanthropological evidence, especially the millennia-old evidence of skull trepanation (craniotomy), as the first surgical procedures.

The terminology, pathophysiology, diagnostics and treatment of headache are therefore also evident as a monosymptomatic painful condition, as a symptom in polysymptomatic conditions or other systemic diseases or disorders (e.g. fever, meningitis). [1-8]

In this review, we present etiopathogenetic considerations and therapeutic procedures through medical evolution.

Etiopathogenesis of headaches in premodern and modern medicine

The evil spirit “in the head” was the cause of all diseases that originated in the head, including headaches, epilepsy, often associated with psychic components in the period of pre-humoral ancient scientific medical philosophy. Thus, the Sumerians and Babylonians in their tablets from about 5,000 years ago described headaches as a consequence of the action of demonic-magical and theurgic forces. Early civilizations in Mesopotamia from 3000 BC mentioned headaches and eye disease, in what was later known as migraine syndrome, while Egyptian papyri from 1200 BC provide testimony of a migraine attack, “half-head disease”, with described photophobia and visual aura. The ancient Chinese, based on their own philosophy of pentacism and meridians and the vital energy *Qi*, attributed headaches exclusively to women, although they believed that it could also occur in men, albeit very rarely. The ancient Chinese considered sudden and severe, short-term or constant headaches to be the result of excess *Qi*, while chronic and moderate headaches were a sign of an internal *Qi* deficiency. Thus, they distinguished between classic frontal headaches as a disorder of the colon-stomach meridian axis, headaches during sleep as a disorder of the gallbladder meridian, neck pain with headaches as a disorder of the relationship between the bladder and small intestine meridians, and pain during stress due to excess liver and Yang, and the acupuncture treatment was directed accordingly. [1-4]

Disturbed relations between cold and hot, wind and moisture, and the accumulation (*stasis*) of mucus and thickened mucus (*turbid mucus*), as well as blood stagnation, along with other disorders of the organism based on the humoral theory, would for centuries become significant factors in the occurrence of various headaches, including migraines, until the second scientific theory: the cellular theory. [1-8]

Hippocrates (460 BC – 370 BC), based on the teachings of Empedocles, taught that the body contains four bodily fluids or four essences: blood, phlegm, yellow bile and black bile. Thus, the humoral theory, which would be difficult to dispute for centuries, was born, and it would last until the mid-19th century. Hippocrates described headaches and migraines with associated symptoms such as vomiting and nausea, and even fever. Erasistratus blamed excessive eating (*plethora*) for the occurrence of various diseases, including headaches, for which it was believed that harmful essences or their excess accumulated in the head, accompanied with a description of flushed and red plethoric patients, which we see today in a condition often associated with hypertensive crisis. The ancient Greek and Roman physician Galen (129 AD – 200 AD) was first to use the name

hemicrania in his work from 180 AD *De compositione medicamentorum secundum locos*, describing a unilateral headache, migraine, and he interpreted the cause according to the aforementioned Hippocratic humoral theory – the accumulation of excess body fluids in the head. His contemporary, the Cappadocian physician Aretaeus (2nd century AD), mentions the *heterocrania* as the unilateral migraine headache, which is described today in two forms: *cephalalgia*, similar to a sudden attack, and *cephalea*, a chronic tension headache. He describes the severe clinical picture of a migraine attack and “the patient’s desire to die, because it is so hard for them”... [1-8] Avicenna interpreted that migraine can arise from the skull bone, and also intraparenchymally from the skull under the membrane, by the arrival of substances from the painful side or extracranially, or from the brain and meninges. [9,10]

It was known that the German nun, healer and herbalist St. Hildegard of Bingen (1098-1179) believed that severe headaches could not occur on both sides of the head, but only on one side. She had severe migraines with auras, manifesting her visions inspired by God, which provided afflatus to write her works. So, based on her example and other cases, doctors and medical historians of the time put forward the psychogenically (mentally) conditioned theory of migraine. And later, over the centuries until today, there were numerous cases of patients suffering from severe headaches who had a religious – fanatical perception of suffering, due to sins committed. [11-13]

In the book *De cerebri morbis* from 1549, Jason Pratensis (1486-1558) describes migraine headaches, which he interpreted according to the theory of the accumulation of black bile and mucus, and he believed that the meninges are the cause of headaches. The famous British neuroanatomist Thomas Willis (1621-1675) gives a vascular theory of the origin of migraine, formulated in the chapter *De Cephalalgia* of his book *De anima brutorum* from 1672, on the basis of neuropathological autopsy findings of unilateral vasodilatation of cerebral blood vessels. He thought that they irritate the meninges and cause headaches. However, he continues to associate the Hippocratic cerebral stagnation of mucus and hyperaemia with the onset of migraine, as well as emotional tension and excitement, and brain injury. The Swiss physician Johann Jakob Wepfer (1620-1695) explained migraine as a relaxation of cerebral vessels with increased pulsations, i.e., rhythmic increase and decrease in blood vessel volume, thus supporting the vascular theory. However, there are other descriptions of the etiopathogenesis of migraine that are the result of the transformation of medicine during the Enlightenment, such as the French physician Samuel Tissot (1728-1797) who expounded that irritation of the stomach, which reaches the eye via nerve fibres, irritates the brain via supraorbital nerves, so this paradoxical theory is actually neurogenic. Tissot thus distinguished between true migraine (*migraine vraie*) and secondary migraine (*migraine accidentale*) as a sign of a disease of the viscerocranium, nasal mucosa, or eye. [2,4,13,14]

During the development of neurology at the beginning of modern medicine, various vascular theories were supported. In 1850 Peter Mere Latham (1789-1875) believed that

migraine was the result of narrowing of the arteries in the area of the posterior cerebral artery. In 1860 Hughlings Jackson (1834-1911) interpreted migraine as a separate form of epilepsy, and Emil du Bois-Reymond (1818-1896) as spasms of vascular muscles and thus prepared a two-phase theory of pain formation due to intravascular pressure according to Wolff, with initial vasoconstriction and secondary vasodilation. However, in 1886, William Gowers (1845-1915) opposed vascular etiopathogenesis and supported neurogenesis, explaining disturbed activity of nerve cells in the brain in his research, while in 1873, Edward Liveing (1832-1919) described such events in the thalamus and interpreted migraine as a “nerve storm”, an attack that affects autonomic nerve fibres, which in turn affect the reactivity of blood vessels. The British physician Thomas Lauder Brunton (1844-1916) in his 1883 book *On the Pathology and Treatment of Some Forms of Headache* interpreted headache as a warning sign for the patient to stop bad habits before it is too late, emphasizing headache as a possible occurrence of other intracranial processes, and not just a monosymptomatic painful condition. [13-15]

These two theories of 19th century scientists support the statements of unfortunate patients suffering from various types of headaches, most notably migraines, who described their experiences as: “a red-hot, writhing snake dancing on a reel” (1809); “as if a red-hot knife was piercing or twisting into the flesh” or “like hot tongs for tearing bones...” (1816). The following experiences and descriptions of headaches during the 19th century are also mentioned: “...as if a hundred windmills were turning in a circle..”, “.....like the top of the head is being unscrewed....”, “....that the eyes will fall out of the head...”, “... that the headache is sparkling how awful it is...” [2,4,13,14,15]

The 19th century witnessed the rising popularity of theories of psychogenic etiopathogenesis, which were at that time associated with the French neurological authority Jean Martin Charcot (1825-1893) and his research on hysteria and neurosis. He interpreted migraine as a disease of a hysterical nature which only occurred in women, thus actually drawing on Hippocraticism and its theory of hysteria from 2000 years ago. However, during the 20th century, there were also reports of psychopathological personality traits in patients with migraines, as well as headaches in mental disorders, so these psychogenic and sexological theories would obviously persist in the collective neuropsychiatry of the past. Thus, Harold Merskey (born 1929) reported in 1968, based on the facial expressions of women suffering from neuralgia, that the typical patient was a “lower-middle-class working woman, perhaps once beautiful and attractive, never satisfied with her sex life, and now faded and sad...” [13,14,15]

In 1937, Graham and Wolff interpreted the neurovascular theory of migraine by combining previous experiences and obtained results from the treatment of migraine attacks with ergotamine, which will be the accepted theory of migraine origin today, along with the genetic one. However, bad habits and a disordered lifestyle have been considered a significant risk factor for the occurrence of various forms of headaches from Hippocratic times to neo-Hippocratism, as well as today. [13-16]

Table 1. Theories of etiopathogenesis and headache therapy throughout the past

Period of medical evolution	Theories of the etiopathogenesis of headaches throughout the past	Therapeutic modalities
Premodern medicine	Humoral	Trepanation Natural opioids (opium from poppy, cocaine from coca)
Modern medicine	Psychogenic Vascular Neurogenic Neurovascular Genetic	Herbal preparations of analgesics / analeptics Opioids Ergotamine derivatives Triptans

Headache treatment in premodern and modern medicine

Various methods were often prescribed as a monotherapeutic approach, intertwined and combined depending on civilizational, religious, cultural and social customs. For example, there is evidence from the earliest periods of civilization and medicine, that craniotomy was a ritual method of exorcism. These were:

- spiritualistic and mythological non-medical therapy, worship of Deities (shamanism, religious rituals, exorcism)
- dietary and natural healing factors (heliotherapy, thalassotherapy, thermal springs and medicinal waters), electrical energy
- ethnopharmacological (mainly herbal medicine with animal and mineralogical preparations)
- surgical methods (trepanation – craniotomy, extension methods, evacuation methods) [1-16]

Although the ancient Egyptians were familiar with poppy and opium, they often resorted to prayer rituals and the worshiping the Gods, including the God Horus, who suffered from “one-sided headaches,” according to legends. Prayers included wishes “that heaven sends him [a patient] a replacement head, as he greatly suffered from headaches”. Also, a good-natured crocodile with grain in its mouth was placed next to the sick person’s pillow, on which there was a sheet with names of the Gods: that was supposed to drive away evil spirits. Ancient Greek mythology provided countless historical data, including the legend that Zeus suffered from unbearable headaches, so he asked to have his head split open with an axe. It was done and, at the same time, Athena was born from his head, a scene which was illustrated by numerous painters. [1-8, 12-15]

Traditional Chinese medicine used all of the above-mentioned methods of treating headaches and migraines, using numerous dietary and phytotherapeutic preparations, along with the use of acupuncture, auriculoacupuncture, acupressure and moxibustion methods. The psychological and somatic exercises are still used today in the system of

ancient Chinese traditional medicine that was transferred to modern medicine, along with the indispensable craniotomy of the ancient Chinese era. About 3,000 years ago, the Chinese “yellow emperor” Huang Ti published *Ling Shu*, the second volume of the *Nei-Jing*, in which he mentions acupuncture treatment – the oldest record of this method. Treatments for headaches and their types are described in detail in traditional Chinese textbooks in which acupuncture is recommended as monotherapy, or with other listed components of traditional Chinese medicine. [1-6, 11-15]

Craniotomy (trepanation) was performed for three reasons: therapeutic (in the case of headaches, brain and skull injuries), magical-ritualistic (demonistic–exorcistic) and combined therapeutic–magical reasons, according to the medical knowledge and understanding of the time (treatment of headaches and epilepsy as a consequence of the actions of evil spirits). It was performed as a literal opening of a painful or diseased skull, without any intervention on the brain. Thus, as mentioned, craniotomy has survived as an indispensable operation from prehistoric times and the exorcism of spirits, to today’s modern neurosurgical stereotaxic operations on individual focal lesions in the brain that are associated with the outbreak of attacks of certain types of headaches. Celsus described trepanation in his works, and Aretaeus shaved the hair and cauterized the muscles up to the skull bones in severe migraine attacks. Hippocrates treated headaches, migraines, and epilepsy with diet therapy, herbal remedies, and craniotomy for severe headaches. The headaches of the Roman emperor Claudius were treated with a quivering eel that produced electricity in contact with the skin, and this method was also used for centuries by ancient African peoples. [3-10, 13-15]

Evacuation methods of treatment were for centuries the favourite methods based on the accumulation of “excess” or “bad mucus” and “bad blood” in the head or body. Venesection (phlebotomy) was also used in the treatment of headaches due to “bloodiness” or “blood congestion of the brain”, the accumulation of harmful blood and mucus in the head and therefore poor blood flow through the brain. In addition to phlebotomy, leeches were also used for the same purpose, as were hot foot baths. Purgatives and enemas were given to expel impurities from the body and “prevent the evaporation of harmful gases towards the head so that it remained cheerful, the mind clear, physical activity complete, the heart healthy and content, the skin colour healthy...” [1-8, 13-15]

However, not all recommendations were effective, as harmful lifestyle habits and overconsumption of food and drink were not eradicated from everyday life, and even medical journalists at the time, at the end of the 19th century, emphasized in the media that “based on their own experiences with headaches, that one should ‘treat’ oneself with lots of soup, steaks and oysters, washed down with good wine or port, and not with alcohol”..... [1-8, 13-15]

Analgesics have been known since the ancient times and were used exclusively from natural sources for painful conditions and during surgical procedures. Later, numerous modern analgesics of various compositions were synthesized and are still used

today, based on centuries of use (mandrake, opium from poppy, salicylates from willow bark, quinine from the cinchona tree). The native Americans and ancient Egyptians knew about the willow bark (lat. *salix*), which they initially used for fevers. Its strong analgesic effect due to salicylates is empirically demonstrated, and it would become an indispensable essence in the production of acetylsalicylic acid (synthesized in July 1899) and numerous preparations that are still used today in the treatment of painful conditions, as well as various types of headaches. Ancient and medieval physicians used mandrake root in sweet wine for pain relief, while Arab physicians prescribed inhalation through a sponge soaked in extracts of hemlock, mandrake, mulberry, wild lettuce, ivy, henbane, and opium (Ar. *afyun*) juice or alcohol. In the post-Columbian period, the importation of numerous herbal cultures launched a new wave of analgesics and antipyretics. Thus, the English physician and pharmacist Nicholas Culpeper (1616–1654) introduced tobacco into medicine and pharmacy, and, in addition to other indications for the treatment of “all diseases,” it was also used to treat headaches and other painful conditions by inhaling, chewing, drinking tinctures and teas, enemas, and even by placing a lit tobacco cigarette in the anus! [1-5, 7-9, 13-15]

During the Enlightenment, which was accompanied by the rise of iatrochemistry, iatrophysics and pharmacy, numerous prescriptions and new synthetic drugs were developed from ingredients that were previously successfully used for centuries as analgesics. Thus, the analgesic prescriptions of Hoffmann's drops (Friedrich Hoffmann, 1660-1742) with the pharmaceutical name *Aethanolum aetheris* (*Solutio aetheris spirituosa*), which consisted of 75 g of 90% alcohol and 25 g of ether, and *Laudanum liquidum Sydenhami* (*tinctura opii crocata*), as a strong opioid analgesic, were extremely well known and used. At the same time, the homeopathic treatment method was also developed (the aforementioned Friedrich Hoffman, Samuel Hahnemann 1755-1843), which uses numerous herbal, animal and mineral preparations in very low concentrations to treat headaches and related conditions. For four thousand years, various prescriptions made from poppy seeds, such as poppy syrup or opium pellets, were given to treat severe pain, and in 1802/1803, the German pharmacist Friedrich Wilhelm Adam Serturner (1783-1841) discovered a crystalline alkaline substance from opium, that he called *principium somniferum* (sleeping substance) and named it *Morphi* (*Morphium*, from the Greek *Morpheus*, dream), and in 1820, Heinrich Emmanuel Merck (1794–1855) began producing and marketing morphine on the world market in various forms, and later in the form of subcutaneous injections. [2-7, 13-15]

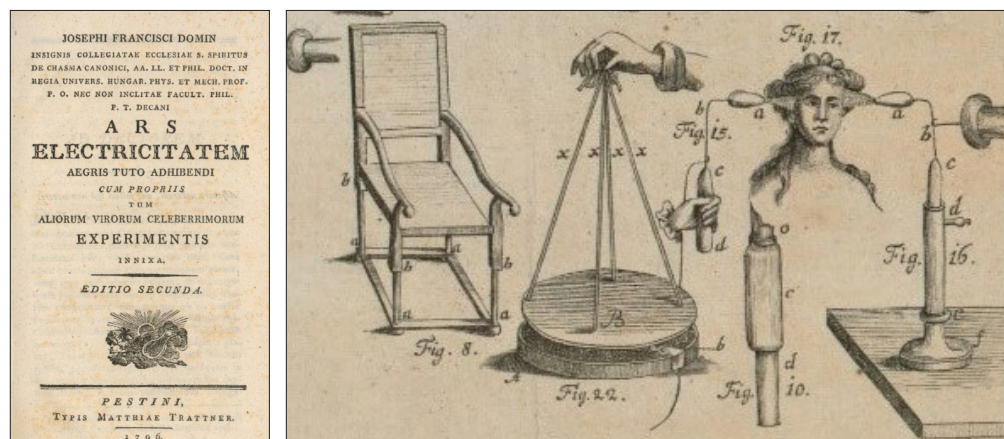
The invention of the electric machine (Benjamin Franklin, 1706-1790) and galvanization (Luigi Galvani, 1737-1798) marked the beginning of the period of use of electrical energy in numerous treatment procedures, which became part of physical therapy. The iatrophysical interpretations of the time believed that electrical fluid activates the nervous fluid, improves circulation and reduces pain. This theory was also followed by the famous Croatian theologian, philosopher, physicist and chemist Josip Franjo Domin

(1754-1819), who began to use electrotherapeutic procedures (as *cura externa*, *stimulantia*) for numerous diseases, especially headaches, migraines, neuralgia, plegia, paresis, febrile conditions in children and adults, rheumatism, arthritis and resuscitation. In his four books, published in the second half of the 18th century, he presented his knowledge and experience of applied medical physics and electrotherapy in the treatment of numerous painful conditions (Figure 1). [4, 13-19]

However, in the world of non-surgical and surgical methods of treating headaches, George P. Hachenberg (1824-1904) mentioned in his textbook (1893) as many as 96 prescriptions for various headaches and another 119 medicines that could be used by headache patients. In 1906, an elixir-laxative called “Bile beans” of unknown chemical prescription was put on sale, composed of Aboriginal ethnoherbals, which were interpreted as being needed in neuralgia precisely because it “nourished and strengthened the blood and kept the nerves healthy”. Therefore, the humoral theory of blood and bile will continue to exist in useless tonics and elixirs of unknown or “secret” chemical composition. [4,11,13-15]

Ergot alkaloids were introduced into migraine therapy by Graham and Wolff in 1937, and triptans in the 1980s. Today’s headache treatment methods are based on holistic principles that were established centuries ago by a different medical philosophy, but with numerous preparations and treatment methods derived from empirical folk medicine that became part of the “evidence-based medicine”, as this chapter has shown. [15,19]

Figure 1. Cover of Domin’s book on electrotherapy, printed in Pest in 1796, showing electrotherapeutic treatment of headaches



Discussion

The humoral (then scientific) theory of centuries-old pre-modern medicine was based on the disruption of bodily fluids and the driving, vital energy (force) in various developments of the medical-historical ribbon of pathophysiology from *spiritus* (Hippocrates, Galen, Arabs), *pneuma* (Diogenes), *ether* and *fire* (Aristotle), vital energy *Qi* (Chinese traditional medicine), *prana* (Indian traditional medicine), *anime* (soul, psyche in various cultures), *archeus* (Paracelsus, Helmont) and *phlogiston* (Lavoisier; the accumulation of harmful fluids and mucus in the head is the main cause of headaches). [4-10] Only the cellular theory of modern medicine from the mid-19th century will explain a different approach by introducing the morphological theory and the discovery of cellular metabolism during the 20th century, and thus the approach to headache and various forms of headaches and the development of numerous pathophysiological theories: psychogenic, pathomorphological (meningeal, vascular, neurogenic, neurovascular) and genetic. [13-15] Thus, various names for headache originate from traditional medical Greek or Latin derivatives based solely on descriptive terms, on the description of painful events “in the head”, and not on a causal diagnosis: *Cephalgia*, *Kephalgia*, *Kephalalgia*, *Cephalaea*, as well as *Heterocrania*, *Migraine* and *Haemicrania* as the most frequently described forms of headache throughout the history of medicine and civilization. [4-10]

Treatment of headaches throughout the history of medicine was based on conventional methods, respecting the symptomatology of the prevailing medical philosophies, initially based on the empiricism of folk medicine, and then on alchemy and scientific evidence of the development of pharmacy. Numerous theriacs and elixirs as omnipotent medicines have been used for centuries as all-powerful healing agents, with panacea-placebo or most often with no effect, a charlatan approach to medicine by numerous quacks, but also doctors of ancient times and the Middle Ages until today. Today's modern approach to treating headaches and migraines is primarily pharmacotherapeutic (medicinal): analgesics from various pharmaceutical groups as monotherapy or polychemotherapy combinations (e.g. paracetamol, acetylsalicylic acid, ibuprofen), various forms of biomodulators (e.g. triptans) are utilised, and the indispensable complementary method of treatment with acupuncture as a proven and recognized treatment method which, like acetylsalicylic acid and opioids, has its roots in the medicines of ancient peoples through thousands of years of medical development.

Rezime

Poimanje etiopatogeneze glavobolje kroz evoluciju medicine čvrsto je pratilo civilizacijski i društveni razvoj ljudske vrste od primitivne prethistorijske medicine pa sve do dvije medicinske znanstvene filozofije, humoralne i celularne, koje su mijenjale bezbroj medicinskih pojmova, uzroka, dijagnostičkih principa i terapijskih osnova. Liječenje glavobolja kroz povijest medicine temeljila su se na uobičajenim načelima poštivajući simptomatologiju vladajućih medicinskih filozofija isprva temeljena na empiriji narodne medicine uključujući herbalne pripravke i kraniotomiju, a potom alkemiji i znanstvenom razvoju farmacije.

Humoralna (tada znanstvena) teorija višestoljetne predmoderne medicine bila je temeljena na poremećaju tjelesnih sokova i pokretačke, životne energije (sile) u raznim razvojem medicinskopovijesne lente patofiziologije od *spiritusa* (Hipokrat, Galen, Arapi), *pneume* (Diogen), etera i vatre (Aristotel), životne energije *Qi* (Kineska tradicijska medicina), *prane* (Indijska tradicijska medicina), *anime* (duša, psiha u raznim kulturama), *archeusa* (Parazelsus, Helmont) te *flogistona* (Lavoisier; nakupljanje štetnih sokova i sluzi u glavi glavni uzrok glavobolja). Tek će celularna teorija moderne medicine od sredine 19. stoljeća objašnjavati drugačiji pristup uvođenjem morfološke teorije i otkrića staničnoga metabolizma tijekom 20. stoljeća, pa tako i pristup glavobolji i raznim oblicima glavobolja te razvitku brojnih patofizioloških teorija: psihogene, patomorfološke (meninge, vaskularna, neurogena, neurovaskularna) i genetske. Tako razni nazivi za glavobolju potječu od medicinsko-tradicijskih grčkih ili latinskih izvedenica temeljenih isključivo deskriptivno, na opisu bolnih zbivanja „u glavi“, a ne kauzalnoj dijagnozi: *Cephalgia*, *Kephalgia*, *Kephalalgia*, *Cephalaea*, te kao i *Heterocrania*, *Migrena* i *Haemicrania* kao najčešće najteži opisivani oblici glavobolja kroz prošlost medicine i civilizacije.

Liječenje glavobolja kroz povijest medicine temeljila su se na uobičajenim načinima poštivajući simptomatologiju vladajućih medicinskih filozofija isprva temeljene na empiriji narodne medicine, a potom alkemiji i znanstvenim dokazima razvoja farmacije. Brojni terijaci i eliksiri kao svemogući lijekovi koristili su se stoljećima kao svemoćna lijekovita sredstva, sa panacejsko-placebo ili najčešće nikakvim učinkom, šarlatanskom pristupu medicini brojnih nadriliječnika, ali i liječnika staroga doba i srednjega vijeka sve do današnjice. Današnji je suvremeni pristup liječenju glavobolja i migrena prvenstveno farmakoterapijski (medikamentozni) analgeticima raznih farmaceutske skupine kao monoterapije ili polikemoterapijske kombinacije (npr. paracetamol, acetilsalicilna kiselina, ibuprofen), raznim oblicima biomodulatora (npr. triptani) te nezaobilazni komplementarni način liječenja akupunkturom kao dokazanom i priznatom metodom liječenja koja, kao i npr. acetilsalicilna kiselina i opiodi imaju temelje u medicinama drevnih naroda kroz tisuće godina razvoja medicine.

Ključne reči: glavobolja, migrena, istorija medicine, terapija, etiopatogeneza

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