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Etiopathogenesis of medication abuse headache (MOH): abuse of analgesics

Keywords: medication, headache, drug, analgesics

Abbreviations: MOH, medication abuse headache; NSAIDs, non-steroidal anti-inflammatory drugs; NO, nitric oxide.

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Maria del Valle López Martínez,[1] Javier Pareja Román,[2] Maria Dolores Jiménez Hernández,[1] Ceferino Maestu Unturbe,[3] Maria del Carmen Ramirez–Castillejo[2]

[1]Servicio de Neurologia HUVirgen Rocio, Universidad de Sevilla, Spain
[2]Biotecnología-Biología Vegetal ETSIAAB, Universidad Politécnica de Madrid, Spain
[3]Centro de Tecnología Biomédica, UPM, Spain

Correspondence: Maria del Valle López Martínez, Servicio de Neurologia HUVirgen Rocio, Universidad de Sevilla, University in Seville, Spain, Email maria.lpez13@goumh.umh.es
Javier Pareja Román, Research Group on Health Sciences, Biotecnología-Biología Vegetal ETSIAAB, Universidad Politécnica de Madrid, Spain, Email javier.pareja.roman@gmail.com

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Introduction

The abuse of symptomatic medication is the main cause of the chronification of some primary headaches such as migraine as well as the development of medication abuse headache (MOH). It has been considered to be decisive for the transformation of an episodic headache to a chronic headache. Patients with chronic headaches often increase gradually the dose and frequency of the drug until it causes important dependence, considering it as a normal situation and not telling it to the doctor unless they are specifically asked.

The paradoxical effect that analgesics can increase headache frequency has been widely described. The sustained consumption of analgesic drugs leads to the ineffectiveness of the same prophylactic treatments, with a significant improvement of the pain episodes when the treatment is suspended. The most frequent cause of analgesic abuse is the patient's self-medication, whether due to persistent headache, inadequate dosage or prophylactic use of analgesics for fear of pain, all this coupled with the abundant commercial propaganda and the ease of acquiring these drugs.

Symptomatic medication of abuse in headache

Simple analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), triptans, ergotics, opioids, and combined analgesics are drugs highly related to MOH. The type of abused drug is clinically relevant since it is known that some need less exposure time and lower doses to induce MOH. Thus, triptans are the drugs that need less exposure time and fewer doses to induce MOH, followed by ergotics, opioids, and analgesic.[1] It is difficult to identify a single causative substance of MOH, since 90% of patients take more than one drug, and each of these drugs can induce a headache.

Worsening of previous headache conditions in those patients who frequently consumed ergotic was first described by Horton and Peters in 1951, describing an intractable chronic headache in these patients with a history of migraine.[2,3]

In the eighties, different authors[4–6] demonstrated that analgesics also contribute to the development of chronic forms of headache, arising the concept of headache due to abuse of analgesics or rebound headache.[7,8] Abstinence phenomena after drugs abrupt withdrawal and loss of efficacy of preventive medication if abuse persisted were also described.[9,10]

For a long time, ergotics, and analgesic combinations have been considered the most important drugs to induce MOH. However, as the use of triptans has been universalized, it has been seen that they have a greater capacity to cause this problem even earlier and with lower doses than other drugs.[11] Recently, both first and second generation of triptans, an important therapeutic novelty in the treatment of migraine, have also been linked to maintenance and/or aggravation of pre-existing headaches.[12,13]

Katsarava et al.,[14,15] observed that a lower monthly dose of triptans is required to induce MOH when compared to analgesics. The average induction period and the monthly dose necessary to induce MOH are lower in the case of triptans (1.7 years); higher for ergotics (2.7 years) and even higher for analgesics (4.9 years).[16]

Patients who frequently consume acetylsalicylic acid, acetaminophen or ergotic derivatives show a worsening of their headache, which is known as a rebound headache. This headache usually appears in the early morning, mainly in patients who abuse ergotic derivatives, due to the fall of plasma levels. This type of headache occurs only in patients with headache as no rebound headache has been described in patients without a previous history of headache.

Some substances are more likely to cause addiction, either because of the analgesic effect or because of the cephalic reward (providing some sense of well-being), as is the case of barbiturates and opioids.

The use of drugs that lead to MOH varies substantially from one country to another and is influenced by cultural factors. In a study carried out in the USA in 1990, analgesics containing butalbital (a short-acting barbiturate), caffeine and aspirin with or without codeine were found to be the main inducers of MOH.[8] In 1993, Robinson et al. conducted a study in Canada and estimated that 90% of migraine patients abused medications, and rebound headache appeared in 1.5% of them, due to excessive use of analgesics or ergotics.[17] Until the mid-nineties, the combination of analgesics containing codeine or caffeine, or ergotics combined with codeine were the most common headache therapy in many European countries,[18–20] but it changed with the introduction of triptans and the withdrawal of ergotic in some countries. Headache due to sumatriptan abuse was observed in patients who had previously abused ergotamne,[13,21] and was later reported in patients taking naratriptan, zolmitriptan or rizatriptan.[22,23]

Today there is no doubt that all triptans can cause MOH. A prospective study of 96 patients with MOH in Germany, showed that the abuse of triptans caused MOH in more cases than the abuse of ergotics.[16] Several studies carried out in different countries have shown how the majority of MOH patients abused simple analgesics, followed by ergotics, opioids, triptans and combined drugs.[24–28]

Triptans

Although a multitude of hypothetical pathophysiological mechanisms has been suggested for cephalea, including cortical depression, vasodilation, extravasation of plasma proteins, sensitization of dural nociceptive afferences, the pathophysiology of this disorder remains unclear.[29–32] Studies in migraine patients showed that headache crisis can be induced by nitric oxide (NO) donor compound such as nitroglycerin, and this process is accompanied by an increase of peptide related to the calcitonin gene (CGRP) in blood levels, which is directly related to the severity of pain.[33–35] There is substantial evidence that NO is an important mediator that contributes to the pathogenesis of migraine.[36–38] Nitric oxide is synthesized by three different isoforms of nitric oxide synthase (NOS): neuronal, endothelial and inducible isoform,[39] being the neural one responsible for the presence of NO in the central and peripheral nervous system.[40] The increased synthesis of NO by the neuronal NOS in the spinal cord induces spinal sensitization, which enhances the activity of the spinal pathways of pain.[41–44] On the other hand, many studies have shown that inhibition of neuronal NOS reduces central sensitization in animal models of neuropathic pain and inflammation.[45–48]

Regardless of the mechanism of initiation of migraine attacks, it is thought that the activation of primary afferent neurons mediates pain and initiates the process that leads to cephalic and extracephalic allodynia, often observed in patients.[49–51] The sensitization of postsynaptic cells in the pain pathways can explain the skin allodynia associated with migraine, which occurs in regions outside the craniofacial area.[49,52,53] Although the mechanisms underlying MOH are unknown, the evidence indicates that it must be associated with central sensitization.[15,54] In this sense, cutaneous allodynia represents an important clinical marker of this sensitization.[55–57] Migraine patients have a higher prevalence of cutaneous allodynia than patients with other non-migraine headaches.[59] Besides, patients with MOH and chronic migraine show a higher prevalence of allodynia compared to episodic migraine patients.[59,60]

Triptans are often the treatment of choice for moderate to a severe migraine. They are mainly agonists of the serotonin 5-HT1B/1D receptors, but they may have less activity on serotonin 5-HT1A and 5-HT1F receptors, and they have three basic pharmacological effects: a) vasoconstriction of cerebral blood vessels, which reverses the vasodilation that induces migraine pain; b) peripheral neuronal inhibition and c) inhibition of neuropeptides release and neurogenic inflammation in the trigeminal cervical complex. It is unknown which of these effects is the main responsible for antimiginous activity.[61–63]

As we have said, it has been suggested that triptans inhibit the secretion of pronociceptive neurotransmitters, including the calcitonin gene-related peptide (CGRP), through presynaptic serotonin (5-HT) 1B/1D receptors in trigeminal afferences, so they can prevent the development of central sensitization if they are administered in the early course of the headache crisis.[54,64–67]

However, its frequent use can induce headaches due to medication abuse (MOH) and it has been shown to have a high risk for the transformation of episodic to chronic migraine.[68–72] Patients with triptans overuse generally develop a MOH identical to their episodic migraine attacks previous, or simply report an increase in the frequency of crisis.[16]

Several studies relate the triptans overuse with the chronicity of migraine and the development of MOH. Thus, for example, De Felice et al demonstrated that persistent exposure of rats to sumatriptan or naratriptan for a period of 6-7 days leads to a state called "latent sensitization induced by triptans", which is characterized by a persistent increase of the peptide related to the calcitonin gene (CGRP) and substance P, at the level of innervation of the dura mater. On the other hand, they explored the possibility that exposure to triptans could modulate the expression of neuronal NOS in dural afferents and that the activity of this enzyme induced the increased excitability observed in rats with latent sensitization induced by triptans.

They observed that sumatriptan exposure increased the expression of neuronal NOS by trigeminal neuronal lines, which was particularly evident in dural afferents that also express CGRP. The upregulation of neuronal NOS in trigeminal dural afferents lasted beyond the period of treatment with triptans, suggesting that these persistent neuroplastic changes should promote the increased neuronal excitability.[73] Perhaps, the most important fact is that this neuronal NOS increase induced by triptans was markedly located in fibers expressing CGRP, suggesting a potential functional nexus between the activity of this neuropeptide and that of the neuronal NOS enzyme at the level of dural afferents.

This observation is consistent with the hypothesis proposed by Olesen, which suggests a causal role for NO in the initiation and maintenance of migraine.[74] These data suggest that the transformation of episodic to chronic migraine involves sensitization of trigeminal sensory pathways, and that the abuse of symptomatic medication such as triptans is not only a risk factor for this transformation, since the mechanisms that induce MOH may be similar to those of migraine chronification.

Opioids

Opioids are used to suppress the pain of moderate to severe intensity and they act in the central nervous system. In addition to their analgesic properties, they have euphoric properties, which contribute to the analgesic effect. They are usually divided into naturally occurring alkaloids, opium derivatives, semisynthetic agents, and synthetic compounds. They interact with opioid receptors, which are of various types: mu, delta and kappa and are located in the central nervous system (brain, brainstem, and medullary areas), peripheral sensory pathways, and other areas. At the level of afferent central pathways, the activation of opioids spinal receptors (laminal neurons I and V and primary somatosensory terminations of the posterior horn) inhibits the entry of impulses from somatosensory afferent fibers (C fibers). The activation of supraspinal receptors in the bulb (raphene nucleus) and mesencephalon (gray periaqueductal substance), inhibits afferent activity carried by the spino-mesencephalic pathways.

At the level of efferent central pathways, at the presynaptic terminals of the Rolando gelatinous substance, the activation of the opioids receptors inhibits the release of glutamate, ATP, peptide related to the calcitonin gene and substance P. In postsynaptic terminals, the activation of the opioids receptors increases conductance for K^+ (postsynaptic terminal hyperpolarization) and inhibits the activation of second-order neurons, inhibiting upward transmission.[75,76] Besides, by activating the receptors of the limbic system and adjacent cortex,

opioids decrease the ability to integrate the subjective emotional component that accompanies the pain. It is well known that tolerance and dependence develop after prolonged exposure to opioids and we have an extensive literature of the neuronal mechanisms involved in these phenomena.[77–80] Recently, an undesired consequence of the use of opioids has been described, hyperalgesia induced by opioids (HIO), which could reduce its effectiveness.[81] A reduction of the pain threshold after prolonged exposure to opioids has also been described in preclinical animal studies.[82] In the clinical context, it would be translated as increased sensitivity to painful stimuli or a general exacerbation of pain in the absence of new tissue damage, as a consequence of opioid overuse.[81] It has been seen that neuro-immune activation and neuro inflammation play an important role in the pathogenesis of HIO.[83]

Traditionally, the phenomenon of pain has focused almost exclusively on neurons, since neuronal circuits are fundamental in the processing, integration, and transmission of nociceptive signals.[84] Recognizing the importance of neuro-immune interactions has been an advance in the understanding of nociceptive processing.[85] In the last two decades, new evidence has shown that astrocytes and microglia, together with neurons, play a vital role in pain modulation.[86–88] The activation of astrocytes and/or microglia results in an increase in the production of inflammatory mediators such as pro-inflammatory cytokines, interleukins, tumour necrosis factor, prostaglandins ..., which will increase neuronal excitability both directly and indirectly, since these pro-inflammatory mediators will also stimulate more glial cells, generating a positive feedback effect.[89]

Once the painful stimulus disappears, experimental evidence suggests that the microglia remains "prepared" in a state of sensitization, in which they do not actively produce pro-inflammatory substances, however, they have an increased response to later stimuli, increased cytokine release, causing exaggerated pain.[90–92] Toll-like receptors TLR) are a family of recognition pattern receptors in innate immunity, which respond to a wide variety of ligands related to tissue damage and pathogen molecules.[93] TLR-4 is expressed primarily in microglia and contributes to the activation of these cells.[94] There is clear neuronal-glial signalling through TLR-4, which must have a causal role in the initiation and maintenance of pain.[95–98] Emerging evidence suggests that chronic human pain is associated with increased sensitivity to TLR-4.

Opioid exposure causes glial activation, which is known to be opposite to opioid analgesia and increases adverse effects such as tolerance, dependence and respiratory depression. Interestingly, this opioid-mediated glial activation occurs through the activation of TLR-4 receptors.[89] Preclinical studies have shown that the administration of morphine produces analgesia through neuronal m-opioid receptors, and on the other hand, it activates glial cells through TLR-4 receptors, promoting the production of neuro-excitatory mediators.[99]

We know that headache resulting from opioid abuse is a specific complication for patients with pre-existing headache. The vast majority of patients with MOH have first suffered episodic migraine or tension headache, as opposed to other primary headaches. It is postulated that this selective propensity to develop MOH in these patients may be due to an alteration of the pro-inflammatory immune central signalling, or the presence of underlying central sensitization, which makes them particularly susceptible to the effects of opioid-induced glial activation.[100–102]

In preclinical study models we observe an important role of neuronal interactions to glia in migraine pain, since during the painful process, glial cells secrete a whole range of inflammatory cytokines, such as IL-1b, IL-6, and fractalkine, when exposed to the peptide related to the calcitonin CGRP gene (product secreted by neurons during these crises). Glial activation resulting from CGRP secretion and opioid exposure is probably greater than that caused only by CGRP action, which explains the exacerbation of migraine pain due to opioid abuse.[103] The secretion of cytokines and other pro-inflammatory mediators by this glial activation seems to have a fundamental role in the transformation of episodic to chronic headache in general, and in the development of MOH in particular.[104] It is likely that opioid abuse headache is related to HIO, due to glial activation in susceptible population, and that opioid abuse leads to chronic headache only in patients with pre-existing headache, since glial cells of patients with headache they must be prepared for activation, either by repeated exposure to nociceptive signals characteristic of that headache condition, or by an underlying abnormal immunity.

Analgesics

The non-steroidal anti-inflammatory drugs (NSAIDs) constitute the first step in the pharmacological treatment of headaches. All of them inhibit the synthesis of prostaglandins (blocking the activity of cyclooxygenases) and neurogenic inflammation of the tri-gemino-vascular system. However, chronic consumption of these drugs can cause paradoxical deterioration of migraine and the development of analgesic-induced headaches.

Serotonin is the main pain-modulation neurotransmitter. Its secretion through the raphe nuclei and subsequent distribution through the spinal cord is thought to play an important role in central control of pain. Some studies indicate that the antinociceptive efficacy of several analgesics, both narcotic and non-narcotic, depends on the integrity of the central serotonergic system. An increase in tissue serotonin levels has been observed following analgesics administration. Pini et al. showed that the administration of paracetamol could increase serotonin levels in the cerebral cortex.[105,106] Besides, this same tissue increase in the spinal cord has been observed after the systemic administration of diclofenac.[107]

The role of serotonin in the efficacy of non-narcotic analgesics has been confirmed by observations that interference with the serotonergic system causes a decrease in its efficacy.[105–107] However, the role of the serotonergic system in the efficacy of chronic use of these drugs is still unclear. Srikiatkhachorn et al. observed that platelets of patients with a headache due to abuse of analgesics contained a significantly lower level of serotonin but expressed a higher density of 5-HT2A receptors compared to platelets of patients with migraine.[108,109] The expression of these receptors in these platelets was reduced after the withdrawal of the analgesics. These findings suggest a possible role of serotonin and its receptors in the pathogenesis of headaches due to the abuse of analgesics, and it is crucial to investigate whether these changes also take place in the central nervous system.[110]

Paracetamol intake caused after 15 days a down-regulation of the 5-HT2A receptors as well as an upward regulation of the serotonin transporter in the frontal cortex, and these changes were more evident concerning controls for animals with higher doses of the drug.[111] Interestingly, after 30 days of exposure to paracetamol, the degree of downward regulation of the receptor, as well as upward regulation of the transporter in the frontal cortex became less evident,

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a phenomenon that matches the decrease in analgesic efficacy of paracetamol and on the other hand, platelet serotonin returned to its normal levels. Chronic administration of a non-narcotic analgesic such as paracetamol induces changes in important parameters of the central serotonergic system, depending on the dose and the exposure time. Since it was shown that the changes in the platelet serotonergic system and serotonergic neuronal system are parallel, the changes observed in platelet serotonin should reflect the concurrent change in serotonin levels of the central nervous system.[112]

The nociceptive effect of serotonin may be either of stimulation or of suppression, depending on the type of serotonin receptor on which it acts. Unlike the family of 5-HT1 receptors, which possesses antinociceptive activity, stimulation of 5-HT2A receptors enhances the nociceptive process.[113] Considering the hypothesis of a nociception effect facilitated by 5-HT2A receptors, the reduction of these receptors, as observed in this experiment, could explain the analgesic efficacy of paracetamol.

The observation that the downward regulation of this receptor was limited to the cortex and did not occur in the brain stem may depend on the different density of receptors in these areas and emphasizes the function of the cortex as the objective for the serotonergic antinociceptive system. The mechanism by which paracetamol induces plasticity of the serotonergic system is still unclear. The upregulation in the serotonin transporter contradicts the hypothesis that an increase in the levels of this neurotransmitter is due to a decrease in the re-uptake process. Such changes in the density of 5-HT2A receptors and the serotonin transporter are more likely to be the consequence of changes in the level of serotonin and not the cause.

A direct effect of paracetamol on receptors and serotonin transporters is unlikely since this drug does not have the binding affinity for this type of receptor or transporter. Therefore, we can assume that paracetamol, by indirectly increasing the concentration of serotonin, can induce an adaptive downregulation of postsynaptic 5-HT2A receptors, as well as upregulation of the transporter. These findings can help us understand the pathogenesis of headaches due to the abuse of analgesics. The significant role of serotonin in the pathogenesis of migraine and other headaches is widely accepted, and it has been shown that several changes in this neurotransmitter system take place in headache due to medication abuse. For example, a decrease in platelet serotonin in migraine complicated with MOH has been found, which resulted in an increase in these levels and an improvement in headache after the withdrawal of analgesics.[109,114] This evidence demonstrates an inverse relationship between platelet and cerebral serotonin levels, and the onset of headache, and this could imply a causal relationship between the decrease in serotonin and the onset of headache. These changes induced by the chronic use of analgesics are further complicated by upregulation of 5-HT2A receptors at the central level,[108] which leads to a state of hyperalgesia since this type of receptor is involved in the facilitation of pain.

It is known that headache due to abuse of analgesics may be restricted to those patients suffering from a primary headache, especially migraine, in which abnormalities in the serotonergic system are observed. Suppression due to excessive medication of an already partially depressed serotonin-dependent antinociceptive system may increase‑headache frequency. In certain studies, it has been seen that these 5-HT2A receptors facilitating nociception are upregulated in patients with headache due to medication abuse and could be normalized after the withdrawal of analgesics.

In conclusion, these data prove the evidence of the central serotonin-dependent paracetamol antinociceptive effect. The downregulation of the 5-HT2A receptor in response to serotonin secretion is an important step in the mechanism of analgesia produced by this agent. However, chronic use of paracetamol can result in depletion of serotonin, which, in turn, can cause re-adaptation of the 5-HT2A receptor. The plasticity of this receptor is an important mechanism related to the loss of analgesic efficacy and, to the extreme, should cause pain situations related to the analgesic, for example, headache due to abuse of analgesics. These results provide additional evidence supporting participation of the serotonergic system in the antinociceptive activity of non-narcotic analgesics and, possibly, a revelation in the pathogenesis of migraine and MOH chronification.

Ergotics

Ergotic drugs had been used as the treatment of choice in migraine attacks, before the appearance of triptans. They are non-selective serotonergic agonists, alpha-adrenergic blockers and inhibitors of prostaglandin synthesis, with a potent vasoconstrictor action and elevated blood pressure. This mechanism of action conditions multiple side effects and favours rebound headache, enhancing its abuse.

The antimiginous mechanism of ergotamine is complex. It is one of the alkaloids present in the ergot of rye - a parasitic fungus, Claviceps purpurea - and its chemical structure has some similarity with several neurotransmitters, such as dopamine, adrenaline and, in particular, serotonin, acting in various forms although mostly as an agonist on several receptors of such neurotransmitters in various neural locations. The antimiginous effects appear to be due to the vasoconstriction of the arteries surrounding the brain by binding to the 5-HT1B receptor present in them, and by inhibiting the nerve transmission capacity of the V cranial nerve (trigeminal), involved in the transmission of the Painful signals from the cranial cavity, thanks to the 5-HT1D receptors, which are located in sensory terminations of the trigeminal and their activation causes the inhibition of the release of nociceptive mediators and vasodilators, which are involved in the neurogenic inflammation of meningeal vessels. The main pharmacological actions are due to partial agonist activity in alpha-adrenoceptors and some serotonin receptor subtypes. They can behave as alpha-blockers, while producing intense and lasting vasoconstriction of arteries of the muscular territory, coronary arteries, and extracranial vessels, with elevated blood pressure. It has been suggested that its constricting action in the arteries of the external carotid territory, together with an antagonistic action of the intense constriction that appears in the internal carotid territory, would explain the symptomatic relief that they produce in the acute migraine attack. Dihydroergotamine is less potent than ergotamine, which means that it is less effective, but also that it has fewer adverse effects.

In recent years and with the introduction of triptans, their use has been reduced due to side effects and their tendency to favour headache due to medication abuse.

Discussion

Many studies show that the withdrawal of medication abuse (detoxification) improves the effectiveness of headache treatment, as well as reduces headache crises in quantity and intensity. The treatment of MOH is usually complex and detoxification is recognized as the treatment of choice.[114] This is shown by our yet unpublished research (under editorial revision), since a high percentage of patients who abandoned medication abuse reduced their crisis headache.

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After 23 months of follow-up, we found that, of the 61 patients who abandoned medication abuse, 53 patients (86.9%) reduced their crisis ≥50%.Rapoport[115] observed a substantial improvement in 82% of patients who were detoxified and Mathew[8] reported an improvement of between 72% and 85% of patients with daily or almost daily headaches, thanks to detoxification, compared with only 21% who did not abandon medication abuse. Linton-Dahlof[116] treated 101 patients with detoxification, and 56% experienced a reduction of at least 50% of their crisis. Zed[117] carried out a systematic review of 17 studies of patients with daily chronic headache and detoxification. Summing up these studies, 45% to 60% of patients who were detoxified experienced improvement.

Conclusions

Medication abuse headache (MOH) is a difficult condition, in which the success of treatment depends primarily on the patient's predisposition to abandon medication abuse. The main and most important factor in achieving the success of the preventive treatment is the abandonment of symptomatic medication abuse.

The medical practitioner or specialist must carry out a controlled follow-up of the patient and their medication and inform the patient of the risk of analgesic abuse. The patient should know that he is facing a chronic problem. It is important to explain what his disease consists of and that it does not have radical curative treatment, but that it can undergo a great improvement following a series of guidelines, in which he is a fundamental part, which is indispensable to achieve therapeutic success. There are two fundamental aspects to be transmitted to the patient: the usual taking of analgesics is able to contribute to the development of chronic headache and can prevent or reduce the action of preventive treatments for headache.

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Conflicts of interest

All authors declare no conflict of interest.

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