Expert Review of Neurotherapeutics

ISSN: 1473-7175 (Print) 1744-8360 (Online) Journal homepage: informahealthcare.com/journals/iern20

Prevalence, clinical features and potential therapies for fibromyalgia in primary headaches

Marina de Tommaso

To cite this article: Marina de Tommaso (2012) Prevalence, clinical features and potential therapies for fibromyalgia in primary headaches, Expert Review of Neurotherapeutics, 12:3, 287-296, DOI: 10.1586/ern.11.190

To link to this article: https://doi.org/10.1586/ern.11.190

Published online: 09 Jan 2014.

EXPERT REVIEWS

Prevalence, clinical features and potential therapies for fibromyalgia in primary headaches

Expert Rev. Neurother. 12(3), 287–296 (2012)

Marina de Tommaso

Neurological and Psychiatric Sciences Department, University of Bari Aldo Moro, Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy
Tel.: + 39 080 547 8565
Fax: +39 080 547 8532
m.detommaso@neurol.uniba.it

Fibromyalgia (FM) syndrome is predominantly related to generation and persistence of central sensitization, which is an aggravating factor for chronic headaches. This review aims to examine the last 11 years of studies on FM and primary headache comorbidity, focusing on prevalence, clinical features and treatments. Chronic forms of migraine and tension-type headache show a high frequency of FM comorbidity. The symptoms characterizing headache patients presenting with FM comorbidity are high headache frequency, poor sleep quality, pericranial tenderness, anxiety and reduction of physical performances. The effects of headache-preventive drugs on factors favoring FM comorbidity were poorly evaluated. Nonpharmacological approaches such as transcranial magnetic stimulation may be an option for treatment of chronic migraine associated with FM.

Keywords: fibromyalgia • migraine • tension-type headache • therapeutic options

Medscape EDUCATION

Medscape: Continuing Medical Education Online

This activity has been planned and implemented in accordance with the Essential Areas and policies of the Accreditation Council for Continuing Medical Education through the joint sponsorship of Medscape, LLC and Expert Reviews Ltd. Medscape, LLC is accredited by the ACCME to provide continuing medical education for physicians.

Medscape, LLC designates this Journal-based CME activity for a maximum of 1 ***AMA PRA Category 1 Credit(s)***™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

All other clinicians completing this activity will be issued a certificate of participation. To participate in this journal CME activity: (1) review the learning objectives and author disclosures; (2) study the education content; (3) take the post-test with a 70% minimum passing score and complete the evaluation at http://www.medscape.org/journal/expertneurothera; (4) view/print certificate.

Release date: February 24, 2012; Expiration date: February 24, 2013

Learning objectives

Upon completion of this activity, participants will be able to:

- Describe the prevalence and underlying pathophysiology of FM comorbid with headache
- Describe the clinical characteristics of FM comorbid with headache
- Describe available treatments for FM comorbid with headache

 10.1586/ERN.11.190 ISSN 1473-7175

Financial & competing interests disclosure
Editor
Elisa Manzotti, *Editorial Director, Future Science Group, London, UK*
Disclosure: *Elisa Manzotti has disclosed no relevant financial relationships.*
CME Author
Laurie Barclay, *Freelance writer and reviewer, Medscape, LLC*
Disclosure: *Laurie Barclay, MD, has disclosed no relevant financial relationships.*
Authors
Marina de Tommaso, *Neurological and Psychiatric Sciences Department, University of Bari Aldo Moro, Policlinico, Piazza Giulio Cesare 11, 70124 Bari, Italy*
Disclosure: *Marina de Tommaso, MD, has disclosed no relevant financial relationships.*

Possible causes of comorbidity between fibromyalgia & primary headaches

Fibromyalgia (FM) is a chronic pain syndrome of unknown etiology characterized by diffuse pain over more than 3 months and tenderness in at least 11 tender point sites out of 18 [1]. The diagnostic criteria have recently been revised in view of the full consideration of the complexity of symptoms associated with generalized pain, including nonrestorative sleep, fatigue and cognitive dysfunction, with less importance attributed to the number of painful tender points [2].

The causes of FM are still unresolved. However, the most supported hypothesis suggests an enhanced mechanism of central sensitization as the cause of muscle skeletal pain persistence [3]. Central sensitization is a phenomenon present in any type of pain, nociceptive or neuropathic, where a noxious stimulus, able to recruit the C and A-δ sensory fibers, reduces in a short time the pain threshold in the primarily involved areas, a phenomenon known as hyperalgesia, while in the adjacent zones any mechanical input becomes painful, as an effect of the so-called 'allodynia' [4]. In this sense, central sensitization is an epiphenomenon of tissutal or nervous damage: in FM, peripheral changes at the muscular or cutaneous level induces increased noxious input and permanent changes to the nociceptive pathways toward chronic and disabling pain. In migraine, the activation of the trigeminovascular system induces the so-called 'sterile inflammation' [5], followed by peripheral and central sensitization, with diffusion of pain from the vessel and meningis to the skin and the muscles, and occurrence of allodynia [6]. Central sensitization is further responsible for migraine pain persistence toward chronic pain [7]. In this sense, both migraine and FM may be characterized by a nociceptive inflammatory pain that, whatever its generation, may persist for central sensitization phenomena. Other chronic pain syndromes, such as irritable bowel or chronic lower back pain, may share this abnormal amplification of noxious inputs coming from visceral or local musculoskeletal structures [8]. What is common in these diseases, which greatly differ with regards to their pain origin, is the amplification of pain at a central level and its persistence despite the cessation of the initial cause, which may account for the mutual comorbidity of these syndromes. There are some mechanisms of pain modulation that are dysfunctional in these diseases. Neurophysiological techniques contributed to show several pain processing abnormalities, which are common across migraine, FM and other models of chronic non-neuropathic pain. Reduced habituation to repetitive painful stimuli may subtend an increase of noxious information at the cortical level, favoring central sensitization [9]. This pattern was detected in migraine and FM [9,10], as well as in other syndromes characterized by the absence of tissutal damage and self-generating pain, such as cardiac X syndrome [11]. In FM, the cortical activation induced by painful stimulation appeared to be increased, as well as in migraine patients during the acute phase [12,13]. In addition, there is some evidence of a pattern of hypervigilance to multimodal stimuli, revealed by a reduction in acoustic intensity-dependent changes, which was often described in migraine patients [14,15]. These common mechanisms of altered central modulation of multimodal and especially painful stimuli may be a basis for both diseases and a reason for their coexistence. Reduced habituation to painful heat and cold stimuli was found to be correlated with anxiety, depression, fatigue and pain [9,16]. Chronic migraine is particularly associated with FM [17,18], suggesting that factors facilitating the worsening of migraine may also predispose to diffuse musculoskeletal pain. Chronic tension-type headache showed the most frequent comorbidity with FM [18]. It seems to be caused by peripheral myofascial structures at the pericranial level, which start to become painful for different reasons, such as postural or dental factors, determining central sensitization. In these patients, measurements of pain tolerance thresholds and suprathreshold stimulation have shown the presence of generalized hyperalgesia, and in addition diffuse noxious inhibitory control function has been shown to be reduced [7]. A common disequilibrium between inhibitory and excitatory modulatory control on pain transmission may subtend these syndromes, so whatever the initial cause of nociceptive inputs, either a self-activation of the trigeminovascular system with consequent sterile inflammation in migraine or pericranial myofascial tenderness in tension-type headache, central sensitization persists toward chronic forms [19]. In the same patients, FM may complicate their syndrome when initial nociceptive inputs start from diffuse musculoskeletal points. The reason for the diffusion of central sensitization outside the pericranial site into the entire body may be an epiphenomenon of the sensitization processing of headache episodes. Studies suggested that during a migraine attack, transformation of headache into whole-body allodynia/hyperalgesia may be mediated by sensitization of thalamic neurons [20]. Contemporary causes of musculoskeletal pain, such as ostheoarthrosis or postural abnormalities, may lead to chronic diffuse somatic suffering in patients with a dismodulation of nociceptive processing, as apparent in individuals with chronic migraine and chronic tension-type headache.

Reduced habituation to pain, common to migraine and FM [9,10], may facilitate central sensitization and myofascial pain persistence in presence of other favoring conditions, such as anxiety and sleep disturbances. A self-outstanding circuit of increased headache frequency, development of pericranial myofascial pain and persisting central sensitization with somatic diffusion of pain may explain FM comorbidity in both chronic tension-type headache and chronic migraine [17,18,21,22].

The present review aimed to examine the last 11 years of studies on the prevalence, clinical features and therapeutic options for headache patients sharing FM comorbidity in order to emphasize present knowledge about their clinical management and the opportunity for further research.

Table 1. Prevalence of fibromyalgia in primary headaches: migraine and tension-type headaches.

Study (year)	Type of study	Population	Type of headache	Prevalence of fibromyalgia (%)	Ref.
Peres *et al.* (2001)	Observational	101 outpatients	Transformed migraine	35.6	[17]
Ifergane *et al.* (2006)	Observational	94 outpatients	Migraine	22.2	[23]
Schur *et al.* (2007)	Large-scale population	3982 twin individuals	Tension-type headache	Odds ratio: 5	[31]
Tietjen *et al.* (2007)	Retrospective	223 outpatients	Migraine	37.21	[24]
de Tommaso *et al.* (2009)	Observational	217 outpatients	Primary headaches	Migraine (including chronic migraine); 28.47; tension-type headache: 59	[18]
Tietjen *et al.* (2009)	Observational	1413 outpatients	Migraine	10	[25]
de Tommaso *et al.* (2011)	Observational	849 outpatients	Primary headaches	Migraine: 17.8; tension-type headache: 35.06	[26]
Le H *et al.* (2011)	Large-scale population	31,865 twin individuals	Migraine	20	[27]

The criteria for inclusion in the review were observational, retrospective, case–control and large-scale population studies published in the years 2000–2011.

Prevalence of FM in primary headache patients

In order to establish prevalence of FM comorbidity in primary headaches, we carried out a search of the PubMed database using the key words FM, migraine, tension-type headache and prevalence. We included original research studies, starting from 2000 up to 2011. With regard to migraine, we found 34 studies, but only a few of them were observational, retrospective or large population studies, the remaining being reviews or case reports. There were six studies on FM prevalence in cohorts of migraine patients (Table 1) [17,18,23–26], while Le *et al.* [27] examined comorbidity between migraine and somatic diseases (including FM) in a large cohort of twins. One study examined migraine prevalence in FM patients [28] and another study dealt with comorbidity between migraine and chronic fatigue syndrome [29], for which the criteria actually largely overlap (Table 2) [2]. The search for tension-type headache retrieved nine results, but only six were original studies, two of them checking FM comorbidity in both types of headaches (Table 1) [18,26] and three evaluating tension-type headache in cohorts of FM patients, chronic fatigue and temporomandibular disorder (Table 2) [28–30]. One study reported inter-relationships among nine medically unexplained and psychiatric conditions, including FM and tension-type headache, in twin samples provided from the primary care setting (Table 1) [31]. In the migraine population, the prevalence of FM ranged from 35.6% in patients with transformed migraine [7] to 22% in episodic migraine [23]. In our cohort of 217 consecutive headache patients, 36.4% of the patients were found to have FM [18]. A recent multicenter study on 1413 migraine patients reported 10% of migraine patients presenting with FM comorbidity, but the features of migraine, with or without aura, or even chronic, were not specified [25]. Our studies showed that FM prevailed in chronic migraine and chronic tension-type headache [7,18]. In our previous study, we found that tension-type headache was the most common primary headache associated with FM, with a 59.0% prevalence compared with episodic and chronic migraine, presenting with 28.8% prevalence. There was no difference between chronic tension-type headache and chronic migraine in FM syndrome prevalence, which suggests that FM is a syndrome that may be associated with these two types of chronic headache [18]. We recently re-evaluated FM prevalence in a larger primary headache sample (1123 consecutive patients screened in a time range of 3 years) (Table 1) [26]. We screened a total of 889 primary headache patients, and FM prevalence was considered in regard to main headache group and type, according to the most recent headache classification [32]. Considering the main headache groups [32], FM prevailed in tension-type headache, followed by the migraine group. Considering the primary headache types, FM was particularly well represented in chronic tension-type headache, followed by chronic migraine. Among FM patients, 13 were males [26].

This latter evaluation accounts for a lower frequency of FM representation in the total headache sample, as previously found in other studies [18]. Other studies on this topic were specifically dedicated to chronic or episodic migraine without aura, with a reported frequency of 35 and 22%, respectively, in the selected populations (Table 1). The frequency of 17.8% that we actually found in the migraine group was almost the same as in a previous study [18], with a minimum frequency in purely migraine with aura and a maximum in chronic migraine. The apparent

Table 2. Prevalence of headache in fibromyalgia and chronic fatigue syndromes.

Study (year)	Type of study	Populations	Type of diffuse pain or somatic symptoms syndrome	Prevalence of headache (%)	Ref.
Aaron *et al.* (2000)	Observational	20 outpatients	Fibromyalgia	Tension-type headache: 4	[30]
		25 outpatients	Chronic fatigue syndrome	Tension-type headache: 23	
Marcus *et al.* (2005)	Observational	100 outpatients	Fibromyalgia	Tension-type headache: 76 (Migraine: 34; tension-type headache: 18; combined: 16; post-traumatic: 4; medication overuse headache: 6)	[28]
Ravindran *et al.* (2011)	Case–control	21 healthy subjects	Chronic fatigue syndrome	Migraine: 16 Tension-type headache: 28 Both types of headache: 11	[29]
		68 outpatients		Migraine: 84 Tension-type headache: 81 Both types of headache: 67	

The criteria for inclusion in the review were observational, retrospective, case–control and large-scale population studies published in the years 2000–2011.

discordance of FM prevalence across studies may be due to variability in applying FM diagnostic criteria, or to the difficulty in assessing FM diagnosis in headache centers. The FM diagnostic criteria are not devoid of problems, and the American College of Rheumatology has proposed to expand the symptoms useful for diagnosis [2]. Interestingly, our last evaluation indicated that FM comorbidity was absent in patients presenting exclusively with migraine with aura attacks, an element that deserves further evaluation in a larger sample. In the study by Ravindran *et al.* on chronic fatigue syndrome, 24% of patients reporting fatigue presented with aura symptoms. However, in that study, a restricted sample of headache patients was fully evaluated, and a syndrome similar to FM was considered [29]. In the study by Tietjen *et al.*, the exact number of migraine with aura patients presenting with FM was not reported [25].

The studies performed on FM or similar syndrome cohorts indicated that headache is common among these patients. Tension-type headache was significantly more represented in a group of FM patients than in controls (Table 2) [30]. In a study of 100 patients with FM, recurring headache occurred in 76%, and predated the onset of FM symptoms by an average of 7 years [28]. In the study by Ravindran *et al.* on chronic fatigue syndrome, migraine was found in more than 80% of the patients affected by fatigue versus 5% of 21 healthy subjects, and tension-type headache was found in 81% of patients and 45% of controls [29].

The search into the prevalence of FM in other primary headache forms gave no results, except for our recent study in which we found a very low representation of FM patients in the other primary headache groups (trigeminal autonomic cephalgias and other forms) [26]. In light of our and previous results, no definitive conclusion about FM comorbidity could be reached in primary headache forms other than migraine and tension-type headache, but rather an impression is evident of a low FM representation even in types with high headache frequency, such as chronic cluster headache, paroxysmal migraine and hemicrania continua. In this sense, the frequency of headache should be the main but not the exclusive factor favoring FM, as specified below.

Clinical features of FM in primary headache patients

Females largely predominated in patients with both primary headache and FM [18], as both conditions are more represented in females [33,34]. These data are consistent with the well-known interactions between gonadal hormones, brain functions and pain processing, supporting the different expression of pain symptoms between sexes [35]. The frequency of both FM and headache in females is fully recognized [36]. In the study by Tietjen *et al.*, central sensitization symptoms were significantly associated with female gender in the considered cohort of migraine patients [25].

Our recent evaluation in 889 consecutive outpatients [26] largely confirmed the results of our previous study [18] with regards to the phenotype expression of headache patients with FM comorbidity, including higher headache frequency, anxiety, pericranial tenderness, reduced physical performance and sleep disturbances.

Pericranial tenderness is considered to be a consequence of chronic headache [37], as a sign of permanent sensitization at cervical and trigeminal second-order nociceptive neurons, subtended by a pathogenic process similar to that which causes pain at tender points [38]. Reduced habituation to pain, common to migraine and FM [9,10], may facilitate central sensitization and myofascial pain persistence in the presence of other favoring conditions, such as anxiety and sleep disturbances. A self-outstanding circuit of increased headache frequency, development of pericranial myofascial pain and persisting central sensitization with somatic diffusion of pain may explain FM comorbidity in both chronic tension-type headache and chronic migraine, where the persistence of pericranial tenderness contributes to the transformation from the episodic into the chronic form [21]. Sleep disturbance

is a well-recognized factor in FM syndrome [39], and our results confirm that in headache patients it favors generalized myofascial pain. The total number of sleep hours are not dissimilar between FM and non-FM patients, while the quality of sleep seems to be the discriminating factor for FM in our headache series [18,26]. Clinical and preclinical data concur that sleep disruption causes hyperalgesia, and despite the widely distributed and overlapping neural networks that regulate states of sleep and pain, the brain mechanisms through which sleep and pain interact remain poorly understood [40,41]. A significant association of severe sleep disturbances and chronic headache [42,43] with central sensitization [44] has also been reported. Poor quality of sleep promotes diffusion of myofascial pain in headache patients, but which sleep phase is more involved in the generation of widespread pain remains to be clarified. Despite FM patients exhibiting higher depression and anxiety levels, it was anxiety levels that best discriminated patients with diffuse pain among our headache population. [18]. Mongini *et al.* found that the presence of anxiety considerably increases the level of muscle tenderness in the head and, even more, in the neck, and as such might facilitate the evolution into chronic headache forms [45]. In this way, anxiety may also facilitate diffuse myofascial pain and FM comorbidity in headache patients presenting with higher pericranial muscle tenderness. FM patients were also characterized by a reduced functioning in daily living, particularly in daily living that required physical activity [18]. This may suggest that persistent pericranial and somatic myofascial pain have an impact on motor performances and that physical inability mainly compromises quality of life in patients sharing FM comorbidity. As we previously showed [18] and further confirmed in a larger headache sample [26], a combination of symptoms is needed to favor FM comorbidity, with headache frequency being the main, although not the only, cause. In fact, patients with other primary headache types, such as cluster headache, hemicrania continua or parossistic migraine, presented with high headache frequency and low probability of sharing symptoms favoring FM comorbidity. However, owing to the low numbers of patients included in these groups of primary headache sufferers, these findings deserve further confirmation in a larger series. Patients presenting exclusively with migraine with aura, had a low probability of sharing FM clinical profile, but the coexistence of migraine with and without aura in the same patient determined the presence of symptoms, such as anxiety or sleep disturbances, characterizing FM syndrome. Tietjen *et al.* recently found that the presence of aura seemed not to be a protective factor against FM comorbidity in patients presenting with both types of migraine [25]. Acute central sensitization phenomena were first described as a development of migraine aura [6] and allodynia has been confirmed as an usual symptom in this type of migraine [25]. Moreover, acutely occurring allodynia does not account for FM comorbidity [18], which is present when central sensitization persists outside attacks and determines pericranial tenderness. In our opinion, this argument needs further evaluation in order to specify whether the prevalent presence of aura characterizes a migraine phenotype with a low predisposition to chronic pain.

Potential therapies for FM in primary headaches

Few studies focused on the influence of FM comorbidity on preventive treatment of primary headaches. We performed a PubMed search using the keywords migraine, FM, tension-type headache and therapy. We considered only original research, and we did not consider case reports or reviews. The search retrieved only two results on nonpharmacological treatments (see below) [46,47]. We further examined the evidence for the efficacy of treatments recommended for headache or FM on the comorbid condition (e.g., efficacy of drugs for prevention of migraine and tension-type headache in FM, and the opposite for treatments recommended for FM, where effects on migraine and tension-type headache were considered). We examined data from the most representative original and retrospective studies, meta-analyses and reviews.

We limited the present review to preventive treatment for migraine and tension-type headache, although the effect of acute treatments on the development of central sensitization phenomena should be taken into account in future studies on factors predisposing to FM comorbidity [48].

Antidepressants

Amitriptyline is a first-choice drug for tension-type headache and migraine [49] and there is evidence of it having a positive effect in FM syndrome [50]. It has mixed serotonergic and noradrenergic reuptake inhibitor properties, which may exert a variety of inhibitory effects on disturbed neurotransmission [51]. Bendtsen and Jensen found that amitriptyline seemed to elicit its analgesic effect on chronic myofascial pain by reducing the transmission of painful stimuli from myofascial tissues, probably via a segmental reduction of central sensitization in combination with a peripheral antinociceptive action [52], an effect that may be able to reduce pericranial tenderness, very frequently associated with FM comorbidity [18]. However, the methodological reliability of studies on amitriptyline in FM was limited, while that of duloxetine and milnacipran was high [50,53,54]. In fact, both drugs were approved by the FDA for FM treatment. However, the significant effects of amitriptyline and duloxetine were small, as well as those obtained by milnacipran, although all of these antidepressants showed slight efficacy in improving sleep, fatigue and quality of life [50]. However, there is little evidence for efficacy of duloxetine in migraine and tension-type headache prevention [55], and its efficacy on migraine frequency also to be appeared reduced in chronic migraine patients presenting with FM comorbidity [56]. Milnacipran has also been poorly evaluated in cases of migraine and tension-type headache suffering [57].

β-blockers

β-blockers are the most widely used class of prophylactic migraine drug, being more than 50% effective at producing a >50% reduction in attack frequency [51]. Adverse effects, such as drowsiness, fatigue, lethargy, sleep disorders, nightmares, depression, memory disturbance and hallucinations [51], may reduce their efficacy in migraine patients with FM comorbidity. However, there are few evidences in favor of a beneficial effect of acute propranolol on adrenergic dysregulation in patients with FM [58,59].

Calcium-channel blockers

Calcium-channel blockers were originally tested in migraine to reduce vasoconstriction and maintain a cerebral vasodilatory tone. The efficacy of calcium-channel blockers is actually attributed to their actions on many other mechanisms in the migraine cascade [51]. For example, verapamil blocks hyperalgesia, thereby inhibiting neuronal nitric oxide synthase, potentiates analgesia from opioids and acetaminophen [51] and may reduce nociceptive input from the trigeminal nucleus modulating P/Q calcium channels [60]. Although their mechanism of action includes effects on hyperalgesia and trigeminal nociceptor activation, no studies have clarified the effects of these drugs on the severity of central sensitization symptoms and FM comorbidity, and evidence is lacking in regard to their use in chronic musculoskeletal pain. Depression,which is a factor favouring FM comorbidity in chronic headache patients [18,26,61], may be induced or aggravated by flunarizine treatment [62].

Antiepileptic drugs

Antiepileptic drugs (AEDs) were extensively studied, and in some cases recommended, in migraine and FM. Topiramate was originally marketed for the treatment of epilepsy, but is now approved by the FDA for migraine prevention based on controlled clinical trials [63–65]. Besides the effects on cortical-spreading depression [66] and trigeminal neuron activation [67], there are additional data, mainly from animal models, that outline the action of topiramate on central sensitization [68]. However, when considering migraine in humans, the efficacy of topiramate is based on headache frequency. No data are available regarding its possible effect on cutaneous allodynia during the attacks, or on factors favoring chronic migraine, such as sleep disorders or psychiatric symptoms. In addition, the effects of topiramate on anxiety and depression, factors that may exacerbate migraine and FM comorbidity [18,26], have not been fully clarified [69]. Evidence with regards to effects of topiramate on FM symptoms is not currently available [70].

Consistent evidence supports the efficacy of different formulations of valproate in preventing migraine [71]. Its effects on factors potentially favoring migraine severity, such as anxiety and depression, are well known [72]. However, its use in migraine is actually supported by a modulating action on abnormal cortical excitability subtending migraine onset [51], while the potential efficacy in reducing central sensitization and psychopathological features in migraine patients remains quite obscure. The effects of valproic acid on chronic pain, such as neuropathic pain, is well supported [73], but no study is available on the effects of valproate in FM.

Pregabalin was initially developed as an anticonvulsant medication but became the first FDA-approved drug for the treatment of FM [74]. The effect of this adjuvant analgesic is exerted by binding to, and decreasing the activity of, the α-2-δ subunit of the voltage-gated calcium ion channel, which plays an integral role in nociceptive transmission, especially in the development and maintenance of nociceptive hypersensitivity, which, in turn, has a role in fibromyalgic pain [75]. There are no data on the effects of pregabalin in tension-type headache, and very little data are available on its effect on migraine frequency [76].

Botulinum toxin

Botulinum toxin has been reported to relieve pain associated with a variety of conditions, including migraine headache. The presumed mechanism for headache prophylaxis is blockade of peripheral signals to the CNS, which inhibits central sensitization. Recently, its efficacy has been confirmed in chronic migraine [77,78], while its effect on associated FM symptoms remains quite uncertain. Less evident is the efficacy of botulinum toxin in chronic tension-type headache [30] and FM [79], although the challenge in the near future will be to increase our understanding of the botulinum toxin mechanism and its eventual action on central sensitization progression.

Nonpharmacological approaches

The utility of nonpharmacological treatments, specifically consisting of physical therapy, psychological therapy and acupuncture, is indicated in chronic tension-type headache [30] as well as in FM [54], where the comorbidity for headache did not reduce the efficacy of an 8-week acupuncture trial [46]. Previous experiences of the application of a self-management program, including stretching and exercise to decrease strength and flexibility of muscles of the cervical and dorsal spine, compared with duloxetine treatment, showed that in patients with chronic migraine, the comorbidity with FM may alter the outcome of pharmacological and nonpharmacological treatments on headache [56].

Another interesting standpoint in headache and FM treatment is the modulation of pain perception by the stimulation of the motor or dorsolateral prefrontal cortex, or the improvement of occipital cortex hyperexcitability using single or repetitive transcranial magnetic or direct current stimulation. The safety of transcranial magnetic stimulation (TMS) and transcranial direct current stimulation in clinical practice has been recognized [80,81], and single-pulse TMS delivered over the occipital cortex was suggested as a safe nonpharmacologic, nonbehavioral acute therapeutic alternative to the currently prescribed drugs for patients who suffer from migraine with aura [82]. The modulation of cortical excitability by low-frequency repetitive TMS of the vertex did not show efficacy in migraine prevention [83]. Repetitive TMS of the left prefrontal cortex also displayed a positive effect in chronic migraine [84]. The analgesic effects induced by neurostimulation of the motor cortex have shown efficacy in FM [85,86], while the effects induced by dorsolateral prefrontal cortex modulation are quite uncertain [87]. No data are available on the possible efficacy in patients sharing FM and chronic headache, although the positive effects on psychiatric symptoms of right and left dorsolateral prefrontal cortex neuromodulation may support its potential efficacy on factors favoring comorbidity [88,89].

Occipital nerve stimulation is a neuromodulation technique currently under study to treat various migraine headache disorders [90]. In 12 patients sharing migraine and FM, the C2 area stimulation technique resulted in a global improvement of pain and associated symptoms [47].

Expert commentary

Many studies support a common pathophsyiological basis for chronic headache and FM. Central sensitization, favored by anxiety

and bad sleep, cause the persistence of pericranial tenderness, the chronicization of headache and the spreading of myofascial pain in the body. Migraine without aura and tension-type headache are particularly associated with FM, although this association is often misdiagnosed and rarely considered in clinical practice. Factors facilitating FM comorbidity are headache frequency, anxiety, pericranial tenderness, poor sleep quality and physical disability. No preventive headache treatment has proven efficacy on FM comorbidity and its facilitating factors. First-choice drugs in migraine prevention, such as amitriptyline, β-blockers, calcium-channel blockers and AEDs, such as sodium valproate and topiramate, have limited evidence of efficacy in FM. Evidence is also lacking with regards to possible effects of milnacipran, duloxetine and pregabalin in migraine and tension-type headache prevention. Botulinum toxin showed efficacy in chronic migraine but scarce effects in FM. Future trials might be designed in order to evaluate the effects of AEDs or antidepressants on factors favoring central sensitization and FM comorbidity. Nonpharmacological approaches such as neuromodulation may be another set of techniques used to investigate future trials in chronic migraine associated with FM.

Five-year view

In the near future, the clinical approach to primary headache should include full consideration of the main causes of comorbidities, aiming to globally improve the patient's quality of life. The evidence for mutual interference between headache and FM would suggest the opportunity for studies focusing on the effects of first-choice drugs for primary headache on factors favoring FM comorbidity, such as anxiety, sleep disturbances and pericranial tenderness. The challenge for the coming years will be the discovery of specific pharmacological and nonpharmacological interventions useful to improve pain modulation in patients sharing headache and somatic pain.

Key issues

- Reduced habituation to pain and central dismodulation of pain control may subtend the association between migraine, tension-type headache and fibromyalgia (FM).
- Migraine without aura and tension-type headache present with the highest probability of sharing FM comorbidity.
- Other primary headache types, such as migraine with aura or cluster headache, are rarely associated with FM.
- High headache frequency, pericranial tenderness, anxiety, poor sleep quality and reduced physical performance characterize headache patients with comorbidity for FM.
- To date, no pharmacological or non-pharmacological treatment is indicated in headache patients with associated fibromyalgic symptoms.

References

Papers of special note have been highlighted as:
• of interest
•• of considerable interest

1 Wolfe F, Smythe HA, Yunus MB *et al.* The American College of Rheumatology 1990 criteria for the classification of fibromyalgia. Report of the Multicenter Criteria Committee. *Arthritis Rheum.* 33, 160–172 (1990).

2 Wolfe F, Clauw DJ, Fitzcharles MA *et al.* The American College of Rheumatology preliminary diagnostic criteria for fibromyalgia and measurement of symptom severity. *Arthritis Care Res.* 62, 600–610 (2010).

3 Staud R, Rodriguez ME. Mechanisms of disease: pain in fibromyalgia syndrome. *Nat. Clin. Pract. Rheumatol.* 2, 90–98 (2006).

•• **Outlined the central origin of pain in fibromyalgia.**

4 Treede RD, Meyer RA, Raja SN, Campbell JN. Peripheral and central mechanisms of cutaneous hyperalgesia. *Prog. Neurobiol.* 38, 397–421 (1992).

5 Moskowitz MA. Basic mechanisms in vascular headache. *Neurol. Clin.* 8, 801–815 (1990).

6 Burstein R, Yarnitsky D, Goor-Aryeh I, Ransil BJ, Bajwa ZH. An association between migraine and cutaneous allodynia. *Ann. Neurol.* 47, 614–624 (2000).

7 Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Frequency of headache is related to sensitization: a population study. *Pain* 123, 19–27 (2006).

8 Staud R, Spaeth M. Psychophysical and neurochemical abnormalities of pain processing in fibromyalgia. *CNS Spectr.* 13, 12–17 (2008).

9 de Tommaso M, Federici A, Santostasi R *et al.* Laser evoked potentials habituation in fibromyalgia. *J. Pain* 12, 116–124 (2011).

• **Showed the common neurophysiological basis for migraine and fibromyalgia.**

10 Valeriani M, de Tommaso M, Restuccia D *et al.* Reduced habituation to experimental pain in migraine patients: a $CO(_2)$ laser evoked potential study. *Pain* 105(1–2), 57–64 (2003).

11 Valeriani M, Sestito A, Le Pera D *et al.* Abnormal cortical pain processing in patients with cardiac syndrome X. *Eur. Heart J.* 26, 975–982 (2005).

12 de Tommaso M, Guido M, Libro G *et al.* Abnormal brain processing of cutaneous pain in migraine patients during the attack. *Neurosci. Lett.* 15, 29–32 (2002).

13 Gibson SJ, Littlejohn GO, Gorman MM, Helme RD, Granges G. Altered heat pain thresholds and cerebral event-related potentials following painful CO_2 laser stimulation in subjects with fibromyalgia syndrome. *Pain* 58, 185–193 (1994).

• **Significantly contributed to support for the central origin of pain hypothesis in fibromyalgia.**

14 Hollins M, Harper D, Gallagher S *et al.* Perceived intensity and unpleasantness of cutaneous and auditory stimuli: an evaluation of the generalized hypervigilance hypothesis. *Pain* 141, 215–221 (2009).

15 Ambrosini A, Schoenen J. The electrophysiology of migraine. *Curr. Opin. Neurol.* 16(3), 327–331(2003).

16 Smith BW, Tooley EM, Montague EQ, Robinson AE, Cosper CJ, Mullins PG. Habituation and sensitization to heat and cold pain in women with fibromyalgia and healthy controls. *Pain* 140, 420–428 (2008).

17 Peres MF, Young WB, Kaup AO, Zukerman E, Silberstein SD. Fibromyalgia is common in patients with transformed migraine. *Neurology* 57, 1326–1328 (2001).

18 de Tommaso M, Sardaro M, Serpino C *et al.* Fibromyalgia comorbidity in primary headaches. *Cephalalgia* 29, 453–464 (2009).

• **Evaluated fibromyalgia comorbidity in a cohort of primary headache patients.**

19 Tracey I, Mantyh PW. The cerebral signature for pain perception and its modulation. *Neuron* 55, 377–391 (2007).

•• **Described the complexity of the pain control system.**

20 Burstein R, Jakubowski M, Garcia-Nicas E *et al.* Thalamic sensitization transforms localized pain into widespread allodynia. *Ann. Neurol.* 68(1), 81–91 (2010).

21 Kitaj MB, Klink M. Pain thresholds in daily transformed migraine versus episodic migraine headache patients. *Headache* 45, 992–998 (2005).

22 Hudson JI, Goldenberg DL, Pope HG, Keck PE Jr, Schlesinger L. Comorbidity of fibromyalgia with medical and psychiatric disorders. *Am. J. Med.* 92, 363–367 (1992).

23 Ifergane G, Buskila D, Simiseshvely N, Zeev K, Cohen H. Prevalence of fibromyalgia syndrome in migraine patients. *Cephalalgia* 26, 451–456 (2006).

24 Tietjen GE, Herial NA, Hardgrove J, Utley C, White L. Migraine comorbidity constellations. *Headache* 47(6), 857–865 (2007).

25 Tietjen GE, Brandes JL, Peterlin BL *et al.* Allodynia in migraine: association with comorbid pain conditions. *Headache* 49(9), 1333–1344 (2009).

• **Showed the influence of central sensitization on the symptoms complicating migraine.**

26 de Tommaso M, Federici A, Serpino C *et al.* Clinical features of headache patients with fibromyalgia comorbidity. *J. Headache Pain* 12(6), 629–638 (2011).

27 Le H, Tfelt-Hansen P, Russell MB, Skytthe A, Kyvik KO, Olesen J. Co-morbidity of migraine with somatic disease in a large population-based study. *Cephalalgia* 31(1), 43–64 (2011).

28 Marcus DA, Bernstein C, Rudy TE. Fibromyalgia and headache: an epidemiological study supporting migraine as part of the fibromyalgia syndrome. *Clin. Rheumatol.* 24, 595–601 (2005).

29 Ravindran MK, Zheng Y, Timbol C *et al.* Migraine headaches in chronic fatigue syndrome (CFS): comparison of two prospective cross-sectional studies. *BMC Neurology* 5, 11–30 (2011).

30 Aaron LA, Burke MM, Buchwald D. Overlapping conditions among patients with chronic fatigue syndrome, fibromyalgia, and temporomandibular disorder. *Arch. Intern. Med.* 24, 221–227 (2000).

31 Schur EA, Afari N, Furberg H *et al.* Feeling bad in more ways than one: comorbidity patterns of medically unexplained and psychiatric conditions. *J. Gen. Intern. Med.* 22(6), 818–821 (2007).

32 Headache Classification Committee. The International Classification of Headache Disorders II. *Cephalalgia* 24, 24–136 (2004).

33 Wolfe F. Fibromyalgia: the clinical syndrome. *Rheum. Dis. Clin. North Am.* 15, 1–18 (1989).

34 MacGregor AE. Oestrogen and attacks of migraine with and without aura. *Lancet Neurol.* 3, 354–361 (2004).

35 Aloisi AM, Bonifazi M. Sex hormones, CNS and pain. *Horm. Behav.* 50(1), 1–7 (2006).

36 Yunus MB. Gender differences in fibromyalgia and other related syndromes. *J. Gend. Specif. Med.* 5(2), 42–47 (2002).

37 Buchgreitz L, Lyngberg AC, Bendtsen L, Jensen R. Increased pain sensitivity is not a risk factor but a consequence of frequent headache: a population-based follow-up study. *Pain* 137, 623–630 (2008).

38 Fernández-de-las-Peñas C, Schoenen J. Chronic tension-type headache: what is new? *Curr. Opin. Neurol.* 22(3), 254–261 (2009).

39 Silverman SL, Harnett J, Zlateva G, Mardekian J. Identifying fibromyalgia-associated symptoms and conditions from a clinical perspective: a step toward evaluating healthcare resource utilization in fibromyalgia. *Pain Pract.* 10(6), 520–529 (2010).

40 Lautenbacher S, Kundermann B, Krieg JC. Sleep deprivation and pain perception. *Med. Rev.* 10, 357–369 (2006).

41 Watson SL, Watson CJ, Baghdoyan HA, Lydic R. Thermal nociception is decreased by hypocretin-1 and an adenosine A1 receptor agonist microinjected into the pontine reticular formation of Sprague Dawley rat. *Pain* 11(6), 535–544 (2010).

42 Rains JC, Poceta JS. Sleep and headache. *Curr. Treat. Options Neurol.* 12(1), 1–15 (2010).

43 Ødegård SS, Engstrøm M, Sand T, Stovner LJ, Zwart JA, Hagen K. Associations between sleep disturbance and primary headaches: the third Nord-Trøndelag Health Study. *J. Headache Pain* 11(3), 197–206 (2010).

44 Lovati C, D'Amico D, Bertora P *et al.* Correlation between presence of allodynia and sleep quality in migraineurs. *Neurol. Sci.* 31(Suppl. 1), S155–S158 (2010).

45 Mongini F, Ciccone G, Deregibus A, Ferrero L, Mongini T. Muscle tenderness in different headache types and its relation to anxiety and depression. *Pain* 112(1–2), 59–64 (2004).

46 Singh BB, Khorsan R, Vinjamury SP. Influence of comorbidities on improvement of fibromyalgia symptoms when treated with acupuncture: a short report. *Altern. Ther. Health Med.* 14(5), 24–25 (2008).

47 Thimineur M, De Ridder D. C2 area neurostimulation: a surgical treatment for fibromyalgia. *Pain Med.* 8(8), 639–646 (2007).

48 Burstein R, Collins B, Jakubowski M. Defeating migraine pain with triptans: a race against the development of cutaneous allodynia. *Ann. Neurol.* 55, 19–26 (2004).

49 Jackson J, Shimeall W, Sessums L, DeZee KJ. Tricyclic antidepressants and headaches: systematic review and meta-analysis. *BMJ* 341, C5222 (2010).

50 Häuser W, Petzke F, Üçeyler N, Sommer C. Comparative efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia syndrome: a systematic review with meta-analysis. *Rheumatology* 50(3), 532–543 (2011).

51 Silberstein SD. Preventive treatment of migraine. *Trends Pharmacol. Sci.* 27, 410–415 (2006).

52 Bendtsen L, Jensen R. Amitriptyline reduces myofascial tenderness in patients with chronic tension-type headache. *Cephalalgia* 20, 603–610 (2000).

53 Di Franco M, Iannuccelli C, Atzeni F *et al.* Pharmacological treatment of fibromyalgia. *Clin. Exp. Rheumatol.* 28, S110–S116 (2010).

54 Staud R. Pharmacological treatment of fibromyalgia syndrome: new developments. *Drugs* 70(1), 1–14 (2010).

55 Taylor AP, Adelman JU, Freeman MC. Efficacy of duloxetine as a migraine preventive medication: possible predictors of response in a retrospective chart review. *Headache* 47(8), 1200–1203 (2007).

56 de Tommaso M, Sardaro M, Vecchio E, Serpino C, Stasi M, Ranieri M. Central sensitisation phenomena in primary headaches CNS and neurological disorders. *Drug Targets* 7, 1–9 (2008).

57 Leo RJ, Brooks VL. Clinical potential of milnacipran, a serotonin and norepinephrine reuptake inhibitor, in pain. *Curr. Opin. Invest. Drugs* 7(7), 637–642 (2006).

58 Light KC, Bragdon EE, Grewen KM, Brownley KA, Girdler SS, Maixner W. Adrenergic dysregulation and pain with and without acute beta-blockade in women with fibromyalgia and temporomandibular disorder. *J. Pain* 10(5), 542–552 (2009).

59 Gur A, Oktayoglu P. CNS abnormalities in fibromyalgia and chronic fatigue syndrome: new concepts in treatment. *Curr. Pharm. Des.* 14(13), 1274–1294 (2008).

60 Knight YE, Bartsch T, Kaube H, Goadsby PJ. P/Q-type calcium-channel blockade in the periaqueductal gray facilitates trigeminal nociception: a functional genetic link for migraine? *J. Neurosci.* 22, RC213 (2002).

61 Tietjen GE, Brandes J., Digre KB *et al.* High prevalence of somatic symptoms and depression in women with disabling chronic headache. *Neurology* 68, 134–140 (2007).

62 Patten S, Thompson J. Organic depression associated with flunarizine. *Can. J. Psychiatry* 40, 111–112 (1995).

63 Silberstein SD. Topiramate in migraine prevention. *Headache* 45, S57–S65 (2005).

64 Brandes JL, Saper JR, Diamond M *et al.* MIGR-002 Study Group. Topiramate for migraine prevention: a randomized controlled trial. *JAMA* 291, 965–973 (2004).

65 Diener HC, Tfelt-Hansen P, Dahlof C *et al.* Topiramate in migraine prophylaxis – results from a placebo controlled trial with propranolol as an active control. *J. Neurol.* 251, 943–950 (2004).

66 Akerman S, Goadsby PJ. Topiramate inhibits cortical spreading depression in rat and cat: impact in migraine aura. *Neuroreport* 16, 1383–1387 (2005).

67 Storer RJ, Goadsby PJ. Topiramate inhibits trigeminovascular neurons in the cat. *Cephalalgia* 24, 1049–1056 (2004).

68 Codd EE, Martinez RP, Molino L *et al.* Tramadol and several anticonvulsants synergize in attenuating nerve injury-induced allodynia. *Pain* 134, 254–262 (2008).

69 Ettinger AB, Argoff CE. Use of antiepileptic drugs for nonepileptic conditions: psychiatric disorders and chronic pain. *Neurotherapeutics* 4, 75–83 (2007).

70 Krymchantowski AV, Bryson J, Lipton RB, Bigal ME. Neuromodulators for the treatment of headache disorders and fibromyalgia. *Curr. Pain Headache Rep.* 12(5), 333–337 (2008).

71 Freitag FG, Collins SD, Carlson HA *et al.*; ER Migraine Study Group. A randomized trial of divalproex sodium extended-release tablets in migraine prophylaxis. *Neurology* 58, 1652–1659 (2002).

72 Zin CS, Nissen LM, Smith MT, O'Callaghan JP, Moore BJ. An update on the pharmacological management of postherpetic neuralgia and painful diabetic neuropathy. *CNS Drugs* 22, 417–442 (2008).

73 Crofford LJ, Rowbotham MC, Mease PJ *et al.* Pregabalin for the treatment of fibromyalgia syndrome: results of a randomized, double blind, placebo-controlled trial. *Arthritis Rheum.* 52(4), 1264–1273 (2005).

74 Johannessen LC. Antiepileptic drugs in non-epilepsy disorders: relations between mechanisms of action and clinical efficacy. *CNS Drugs* 22, 27–47(2008).

75 Sarchielli P, Di Filippo M, Nardi K, Calabresi P. Sensitization, glutamate, and the link between migraine and fibromyalgia. *Curr. Pain Headache Rep.* 11, 343–351 (2007).

76 Pizzolato R, Villani V, Prosperini L, Ciuffoli A, Sette G. Efficacy and tolerability of pregabalin as preventive treatment for migraine: a 3-month follow-up study. *J. Headache Pain* 12(5), 521–525 (2011).

77 Aurora SK, Dodick DW, Turkel CC *et al.* PREEMPT 1 Chronic Migraine Study Group. Onabotulinum toxin A for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 1 trial. *Cephalalgia* 30(7), 793–803 (2010).

78 Diener HC, Dodick DW, Aurora SK *et al.* PREEMPT 2 Chronic Migraine Study Group. Onabotulinum toxin A for treatment of chronic migraine: results from the double-blind, randomized, placebo-controlled phase of the PREEMPT 2 trial. *Cephalalgia* 30(7), 804–814 (2010).

79 Smith HS, Audette J, Royal MA. Clinical botulinum toxin in pain management of soft tissue syndromes. *J. Pain* 18, S147–S154 (2002).

80 Rossi S, Hallett M, Rossini PM, Pascual-Leone A; Safety of TMS Consensus Group. Clinical safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research *Clin. Neurophysiol.* 120(12), 2008–2039 (2009).

81 Dodick DW, Schembri CT, Helmuth M, Aurora SK. Transcranial magnetic stimulation for migraine: a safety review. *Headache* 50(7), 1153–1163 (2010).

82 Lipton RB, Dodick DW, Silberstein SD *et al.* Single-pulse transcranial magnetic stimulation for acute treatment of migraine with aura: a randomised, double-blind, parallel-group, sham-controlled trial. *Lancet Neurol.* 9(4), 373–380 (2010).

83 Teepker M, Hötzel J, Timmesfeld N *et al.* Low-frequency rTMS of the vertex in the prophylactic treatment of migraine. *Cephalalgia* 30(2), 137–144 (2010).

84 Brighina F, Piazza A, Vitello G *et al.* rTMS of the prefrontal cortex in the treatment of chronic migraine: a pilot study. *J. Neurol. Sci.* 15, 67–71 (2004).

85 Lefaucheur JP. Is rTMS a therapeutic option in chronic pain syndrome? Insights from the treatment of fibromyalgia. *Pain* 152(7), 1447–1448 (2011).

86 Mhalla A, Baudic S, de Andrade DC *et al.* Long-term maintenance of the analgesic effects of transcranial magnetic stimulation in fibromyalgia. *Pain* 152(7), 1478–1485 (2011).

87 Valle A, Roizenblatt S, Botte S *et al.* Efficacy of anodal transcranial direct current stimulation (tDCS) for the treatment of fibromyalgia: results of a randomized, sham-controlled longitudinal clinical trial. *J. Pain Manag.* 2(3), 353–361 (2009).

88 George MS. Transcranial magnetic stimulation for the treatment of depression. *Expert Rev. Neurother.* 10(11), 1761–1772 (2010).

89 Short EB, Borckardt JJ, Anderson BS. Ten sessions of adjunctive left prefrontal rTMS significantly reduces fibromyalgia pain: a randomized, controlled pilot study. *Pain* 152(11), 2477–2484 (2011).

90 Magis D, Schoenen J. Treatment of migraine: update on new therapies. *Curr. Opin. Neurol.* 24(3), 203–210 (2011).

Medscape EDUCATION

Prevalence, clinical features and potential therapies for fibromyalgia in primary headaches

To obtain credit, you should first read the journal article. After reading the article, you should be able to answer the following, related, multiple-choice questions. To complete the questions (with a minimum 70% passing score) and earn continuing medical education (CME) credit, please go to http://www.medscape.org/journal/expertneurothera. Credit cannot be obtained for tests completed on paper, although you may use the worksheet below to keep a record of your answers. You must be a registered user on Medscape.org. If you are not registered on Medscape.org, please click on the New Users: Free Registration link on the left hand side of the website to register. Only one answer is correct for each question. Once you successfully answer all post-test questions you will be able to view and/or print your certificate. For questions regarding the content of this activity, contact the accredited provider, CME@medscape.net. For technical assistance, contact CME@webmd.net. American Medical Association's Physician's Recognition Award (AMA PRA) credits are accepted in the US as evidence of participation in CME activities. For further information on this award, please refer to http://www.ama-assn.org/ama/pub/category/2922.html. The AMA has determined that physicians not licensed in the US who participate in this CME activity are eligible for **AMA PRA Category 1 Credits™**. Through agreements that the AMA has made with agencies in some countries, AMA PRA credit may be acceptable as evidence of participation in CME activities. If you are not licensed in the US, please complete the questions online, print the AMA PRA CME credit certificate and present it to your national medical association for review.

Activity Evaluation
Where 1 is strongly disagree and 5 is strongly agree

	1	2	3	4	5
1. The activity supported the learning objectives.					
2. The material was organized clearly for learning to occur.					
3. The content learned from this activity will impact my practice.					
4. The activity was presented objectively and free of commercial bias.					

1. On the basis of the review by Dr. de Tommaso, which of the following statements about the prevalence and underlying pathophysiology of fibromyalgia (FM) comorbid with headache is **most likely** correct?

- ☐ **A** Cluster headache is the headache type most often comorbid with FM
- ☐ **B** In the author's cohort of 217 consecutive headache patients, about 15% had FM
- ☐ **C** Central sensitization is not involved in neuropathic pain
- ☐ **D** Reduced habituation to pain and central dysmodulation of pain control may underlie the association between headache and FM

2. Your patient is a 36-year-old woman with headache in whom you suspect comorbid FM. On the basis of the review by Dr. de Tommaso, which of the following statements about the clinical characteristics of FM comorbid with headache is **most likely** correct?

- ☐ **A** Depression is more characteristic than anxiety
- ☐ **B** A classic criterion for FM is tenderness in at least 8 of 12 tender point sites
- ☐ **C** Poor sleep quality and reduced physical performance are characteristic
- ☐ **D** Pericranial tenderness is seldom observed

3. The patient described in question 2 is diagnosed with chronic headache and comorbid FM. On the basis of the review by Dr. de Tommaso, which of the following statements about available treatments is **most likely** correct?

- ☐ **A** The best pharmacologic and nonpharmacologic options are well supported by evidence from randomized controlled trials
- ☐ **B** Amitriptyline is a first-choice drug for tension-type headache and may have a positive effect in patients with FM
- ☐ **C** There is excellent evidence that propranolol benefits adrenergic dysregulation in patients with FM
- ☐ **D** Nonpharmacologic approaches play no role in treatment of patients with chronic headache and FM