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Use of amitriptyline for the treatment of chronic tension-type headache. Review of the literature

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Abstract

Amitriptyline is a tricyclic antidepressant, considered the treatment of choice for different types of chronic pain, including chronic myofascial pain. Its antinociceptive property is independent of its antidepressant effect. Although its analgesic mechanism is not precisely known, it is believed that the serotonin reuptake inhibition in the central nervous system plays a fundamental role in pain control. Although this medication is widely used in the prevention of chronic tension-type headache, few studies have investigated the efficacy of this treatment and the published results are contradictory. The objective of this article was to review the literature published on the use of amitriptyline in the prophylactic treatment of chronic tension-type headache, considering the level of scientific evidence of the different studies using the SORT criteria. From this review, 5 articles of evidence level 1, and another 5 articles of evidence level 2 were selected. Following analysis of the 10 studies, and in function of their scientific quality, a level A recommendation was made in favor of using amitriptyline in the treatment of chronic tension-type headache.

Key words: *Chronic tension-type headache, amitriptyline.*

Introduction

Tension-type headache (TTH) is described as a dull, non pulsatile pain, affecting the entire head, of oppressive and progressive character, moderate or severe intensity, variable duration (up to several days) and lacking the typical features of migraine. In 90% of cases the pain is bilateral, the typical location being in the occipital, parietal, temporal and frontal areas. Occasionally nauseas, photophobia or phonophobia can appear, with or without associated dysfunction of the pericranial muscles. Although the duration and intensity of the pain is variable, this headache is not as debilitating as migraine, and sufferers are usually able to continue their daily activities. It is considered that migraine and TTH constitute the same physiopathologic process, but with different clinical manifestations. Migraine possibly represents a painful condition with an important vascular component, while TTH represents a painful condition with a greater myofascial component. The episodic nature of TTH has an average duration of 12 hours, although this can vary from 30 minutes up to 72 hours. Chronic tension-type headache (CTTH) is present for at least 15 days a month during a 6-month period (1,2).

Although TTH is the most frequent type of primary headache (two thirds of the population have suffered an episodic TTH and 3% suffer from CTTH), its physiopathology is still the cause of controversy within the scientific community.

For many years it has been thought that TTH was directly related with muscular tension. However, more recently it has been postulated that although muscular tension is usually present in most cases, it is possible that the origin is more central, due to the hyperexcitability of the trigeminal caudal nucleus and of other structures of the central nervous system (CNS) that register, modulate and interpret head pain. This abnormality can reduce the pain threshold and make the patient perceive pericranial musculature contraction as painful. Precipitating factors of TTH have been identified as those that interact with the limbic system, and myofascial, or vascular structures; the most frequent being emotional stress, anxiety, depression and myofascial pain (3,4). This pathology type may also be induced, intensified or made chronic by analgesic abuse (5,6).

Amitriptyline (AMT) is a tricyclic antidepressant possessing an analgesic effect, and is therefore prescribed for different types of chronic pain, its analgesic property being independent of its antidepressive effect (7-10). However, the analgesic mechanism is not precisely known. Probably, serotonin (5-HT) and noradrenaline reuptake inhibition of the CNS plays a fundamental role in the control of the pain. CTTH is one of the chronic disorders in which AMT seems to have a positive effect (5,8,11).

The objective of this article was to review the literature published on the use of AMT in the treatment of CTTH, taking into account the level of scientific evidence and following the principals of evidence-based dentistry.

Material and Method

A PubMed-MEDLINE search was carried out of articles published from 1966 to 2006. The MeSH (Medical Subject Heading) keywords and headings were used for "CTTH" (chronic tension-type headache) to obtain a primary bank of articles on this pathology. The identified literature was then limited to studies in humans and articles written in English. A similar search was made for AMT (amitriptyline). Both search types were in turn merged by means of the boolean operator "AND", thus linking the articles for CTTH and AMT. Two authors analyzed the searched articles to verify their pertinence to the topic under study. The irrelevant articles were discarded. Next, two of the authors stratified the scientific articles separately according to their level of scientific evidence using the SORT criteria (Strength of Recommendation Taxonomy) (tables 1, 2 and 3). Subsequently, the authors compared their results and, in the event of disagreement, the results were discussed. When it was not possible to achieve a consensus regarding the level of scientific evidence of a certain article, a third author was included in the discussion. Subsequently, and in accordance

Table 1. Strength of Recommendation Taxonomy (SORT).

Strength of Recommendation	Definition
A	Recommendation based on consistent and good-quality, patient-oriented evidence (1)
B	Recommendation based on inconsistent or limited-quality, patient-oriented evidence (1)
C	Recommendation based on consensus, usual practice, opinion, disease-oriented evidence (2), or on case series for studies of diagnosis, treatment, prevention or screening

(1) Patient-oriented evidence considers the following objectives: reduction of mortality and morbidity, improvement of the symptoms, better quality of life, reduced costs.
(2) Disease-oriented evidence comprises intermediate, histopathologic, physiologic and other surrogate or potentially useful results for improving the patient's quality of life (blood sugar, blood pressure, etc.) that may or not reflect the patient's actual improvement.

Table 2. Levels of scientific evidence. Abbreviations: SR = systematic review; RCT = randomized clinical trial.

Study quality	Diagnosis	Treatment/prevention/ screening	Prognosis
Level 1 - good-quality, patient-oriented evidence	- SR/meta-analysis of high-quality studies - High-quality diagnostic cohort study	- SR/meta-analysis of RCTs with consistent findings - High quality individual RCT - All or none studies*	- SR/meta-analysis of good-quality cohort studies - Prospective cohort study with good follow-up
Level 2 - limited-quality, patient-oriented evidence	- SR/meta-analysis of low-quality studies or studies with inconsistent findings - Cohort study or low-quality case control study	- SR/meta-analysis of low-quality clinical trials or of studies with inconsistent findings - Low-quality clinical trial - Cohort study - Case control study	- SR/meta-analysis of lower-quality cohort studies or with inconsistent results - Retrospective cohort study or prospective cohort study with poor follow-up - Case-control study - Case series
Level 3 - other evidence	- Consensus guidelines, extrapolations from bench research, usual practice, opinion, disease-oriented evidence, or case series to study diagnosis, treatment, prevention or screening		

* All or none: the treatment causes a dramatic change in the outcomes (such as antibiotics for meningitis or surgery for appendicitis).

Table 3. Consistency across studies. Abbreviation: SR = systematic revision.

Consistent	- Most studies found similar or at least coherent conclusions (coherence means that the differences are explainable) or -The high-quality meta-analysis and SR support the recommendation
Inconsistent	- Considerable variation among study findings and lack of coherence - If high-quality SR or meta-analyses exist, they do not find consistent evidence in favor of the recommendation

Table 4. Level 1 and 2 studies that analyze the use of amitriptyline in prophylactic treatment of chronic tension headache.

Authors and year	Journal	Scientific Evidence
Bendtsen and Jensen (2000) (16)	Cephalalgia	Level 1
Mitsikostas et al. (1997) (15)	Acta Neurol Scand	Level 1
Bendtsen et al. (1996) (8)	J Neurol Neurosurg Psychiatry	Level 1
Pfaffenrath et al. (1994) (14)	Cephalalgia	Level 1
Nappi et al. (1990) (12)	Headache	Level 1
Bettucci et al. (2006) (28)	J Headache Pain	Level 2
de Tommaso et al. (2005) (18)	Neurol Sci	Level 2
Rampello et al. (2004) (13)	Neuro-psychobiology	Level 2
Holroyd et al. (2001) (25)	JAMA	Level 2
Göbel et al. (1994) (5)	Pain	Level 2

with the level of scientific evidence of the analyzed articles, a recommendation level was declared in favor of, or against the use of AMT for the treatment of CTTH.

Results

The PubMed-MEDLINE search provided 1148 articles on AMT and 194 articles for CTTH. As mentioned previously, both search strategies were interleaved. This provided a bank of 20 articles. The articles obtained were then analyzed to determine if they were pertinent to the topic under study. Articles with significant methodological errors such as an insufficient patient sample, inadequate sample selection criteria, imprecise definition of the study groups, inadequate description of the analyzed variables, or incomplete and/or inadequate presentation of the results obtained in the study were discarded. Articles were also discarded with scientific evidence level 3.

This detailed analysis provided a total of 10 relevant articles. These articles were critically analyzed, and classified according to their level of scientific evidence. This analysis revealed 5 articles with level of scientific evidence 2 and another 5 articles with level of scientific evidence 1 (table 4).

In accordance with the principals of evidence-based dentistry, the analysis of the results revealed a type A recommendation in favor of the use of AMT in the treatment of CTTH.

Discussion

It is currently considered that CTTH is related with an alteration in serotonin (5-HT) reuptake. In patients with CTTH a higher reuptake of this amine has been found, with a consequently lower concentration in plasma and platelets. Although the exact mechanism of tricyclic antidepressants is unknown, especially AMT, they are effective in the prophylactic treatment of CTTH, serotonin uptake inhibition is considered an important factor in its therapeutic action (12-14). This fact has motivated the study of different selective serotonin inhibitors, such as ritanserin, buspirone or citalopram, among others (8,12,13,15-17).

Nappi et al. (12) compared the efficacy of AMT with ritanserin, a long-acting, selective antagonist of 5-HT2 receptors, in patients with depression coexisting with CTH. From the study results they concluded that the two drugs were effective in reducing pain. They found no statistically significant differences between either treatment, except in the first month of treatment in the AMT group who consumed less analgesics than the ritanserin group ($p<0.005$). Very similar results are found when comparing AMT with buspirone, an agent that selectively interacts with an area different to the serotonin receptors, specifically 5-HT1A (15). Rampello et al. (13) carried out a randomized study, finding that AMT was more effective than citalopram, a selective reuptake inhibitor of this amine having better tolerance than AMT in the prophylactic treatment of

CTTH. Nevertheless, they recorded more adverse effects in the group treated with AMT that in that treated with the other drug. These were especially prominent in the first week of treatment, reducing gradually over the remainder of the follow-up period. Those patients that did not respond satisfactorily to the monotherapy (AMT or citalopram) achieved a significant reduction, both for intensity and frequency of attacks, when both drugs were administered together (13). Bendtsen et al. in various publications (8,16,17), conclude that AMT significantly reduces CTTH when compared to a placebo. However, no significant clinical improvement was obtained in patients with CTTH who were administered citalopram. These authors (16), as well as Göbel et al. (5), observed that AMT is also able to significantly reduce pain on palpation of the pericranial musculature.

From the results of various studies (8,12,13,15-17), it has been deduced that since tricyclic antidepressants were more effective in controlling chronic pain than the selective serotonin reuptake inhibitors, the effect of AMT cannot be explained solely by its serotoninergic action, but that possibly it is also related with its wide pharmacodynamic spectrum (adrenergic, cholinergic and histaminergic action). On the other hand, the effectiveness of the merged treatment (AMT and citalopram) obtained by Rampello et al. (13) in their study, may be explained by the probable synergic action of the two substances, potentiating the serotoninergic transmission.

In agreement with the hypothesis of Bendtsen and Jensen(16), pain on palpation of the pericranial musculature may initiate a self-perpetuating cycle, in which the prolonged nociceptive afferent stimuli originating from the affected myofascial tissue create a central sensitization at the level of the dorsal horn of the trigeminal nucleus. This will cause a supraspinal sensitization and a greater stimulation of the nociceptive cortical areas, that will contribute to increasing the pericranial muscular activity and the afferent painful stimuli. Based on this theory, de Tommaso et al. (18), carried out a case control study, concluding that both central (AMT) and peripheral (occlusal ferule) treatments were able to break this cycle and improve the symptomatology of CTTH. On the other hand, they recorded a statistically higher reduction in pain on pericranial muscular palpation, in those patients treated with an occlusal ferule than in those treated with AMT. It would have been interesting if this authors (18) had also combined both therapeutic approaches, as the results would probably have been better than those obtained separately.

Some authors (19-21) have suggested that the duration of the final period of exteroceptive suppression (ES2) of the temporal muscle activity is reduced in patients with CTTH, and that ES2 is partially controlled by the serotoninergic neuronal mechanisms. The results of an investigation published by Bendtsen et al. (17), in which they evaluated the effect of AMT and citalopram in CTTH, demonstrated that only AMT significantly reduced ES2. However, Göbel et al. (5), were unable to detect any correlation between the duration of ES2 and treatment of CTTH with AMT. In any case, many studies (17,22-24) have questioned the importance of ES2 in CTTH, since they have found no significant correlation between the duration of ES2 and the clinical characteristics of this type of headache.

Although tricyclic antidepressants, especially AMT, are considered the first line in prophylactic treatment of CTTH; behavioral therapies, relaxation techniques, biofeedback and stress management are also used in the handling of this type of pathology. Holroyd et al. (25), carried out a study examining the possibility that behavioral therapy intensified the results obtained with AMT in CTTH. They evaluated the separate and combined effects of AMT and stress management techniques. The results revealed that both treatments, alone or combined, were effective in reducing both the intensity and frequency of the headaches and analgesic consumption. However, the combination of the two therapies provided a significant reduction (>50%) in the frequency of the headaches in a greater proportion of patients (2/3) than in the groups who only received monotherapy (1/3). Although this finding suggests that combined therapy can improve on the results obtained with monotherapy, it is true that no statistically significant relation was observed in relation to the other variables analyzed. In the group in which only stress management techniques were applied, the reduction in symptoms were not evident until the evaluation at 6 months.

The efficacy of AMT in preventing CTTH does not become evident until 2-3 weeks after commencing therapy. This fact creates a negative psychological impact on the patient during the first phases of treatment. Tizanidine is an $\alpha 2$ agonist that acts as a central muscle relaxant, but also having an antinociceptive effect. Several clinical trials advocate tizanidine as a promising additional drug for the prevention of chronic headaches. However, its use as a monotherapy is not justified (26,27). In a study by Bettucci et al. (28), the combination of tizanidine with AMT provided a significant reduction in frequency, intensity and duration of the symptoms during the first month of treatment when compared to AMT alone. At the end of the treatment (90 days) no significant differences between the two therapies were found. Therefore, the combination of both drugs provided an immediate improvement in quality of life in these patients measured using the HIT6 scale (28). However, some deficiencies in the methodological design of this investigation should be highlighted, such as the small sample size and the fact that the study was not blinded.

Amitriptylinoxide is an antidepressant with a similar sedative effect as AMT on the noradrenergic, serotoninergic and anticholinergic systems in the CNS. In a study by Pfaffenrath et al. (14), the efficacy and tolerance of this

drug was compared to that of AMT (taken as the reference) and a placebo. No statistically significant differences were observed among the three groups with regard to the decrease in intensity, the duration or frequency of the headaches, nor to the adverse effects. However, some authors (5), have criticized the results of this study, considering the parameters used to evaluate the effects of this drug as having little discriminant power.

Selective serotonin reuptake inhibitors have shown a greater tolerance than AMT, although in general, the side effects (xerostomia, drowsiness, nauseas, weight gain or increase in appetite, sleep alterations, vertigo, dizziness, tachycardia or abdominal pain, etc.) are usually slight or decrease gradually over time (12-15,28). However, on comparing AMT with a placebo, no differences between the two have been seen for the majority of adverse effects associated with tricyclic antidepressants; except in xerostomia or drowsiness which were higher in the AMT group (5,25). These data are possibly due to the fact that the dosage of AMT administered in the prophylactic treatment of CTTH is relatively low. The recommended posology oscillates between 10 and 100 mg in a single dose before going to bed. The treatment begins with a low dosage (between 10 and 25 mg/day) increasing gradually until a considerable decrease or the total disappearance of the symptoms presented by the patient is obtained (12-16,18). Its prescription is contraindicated during the immediate recovery period after acute miocardiac infarction. It should be used with extreme precaution in patients with cardiovascular anomalies, convulsive crisis, glaucoma, and hepatic, renal or prostatic dysfunction, its use is also not recommended during the pregnancy (5).

Conclusions

CTTH is difficult to treat since its etiology is still not completely clear. Therefore, although the results obtained have not always been statistically significant for all the evaluated clinical parameters, AMT (10-100mg/day) can be considered as having demonstrated efficacy in the prophylactic treatment of CTTH. Nevertheless, the combination of this treatment with other drugs or with behavioral therapies can provide a greater therapeutic efficacy. The dosage of AMT administered in the treatment of CTTH is low, therefore the majority of patients tolerate the medication well and the adverse effects are negligible.

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