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EXPERT REVIEWS

Amitriptyline for the treatment of fibromyalgia: a comprehensive review

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Fibromyalgia is characterized by chronic generalized pain accompanied by a wide range of clinical manifestations. Most clinical practice guidelines recommend multidisciplinary treatment using a combination of pharmacological and non-pharmacological therapies. The tricyclic antidepressant amitriptyline has been most thoroughly studied in fibromyalgia. Amitriptyline has been evaluated in placebo-controlled studies, and it has served as an active comparator to other therapeutic interventions in the treatment of fibromyalgia. In addition, several systematic reviews and meta-analyses have evaluated its efficacy and safety for the treatment of fibromyalgia. Data from individual studies as well as from systematic reviews indicate that low doses (10–75 mg/day) of amitriptyline are effective for the treatment of fibromyalgia and, despite the limited quality of the data, they do not seem to be associated with relevant tolerability or safety issues. Consistent with some clinical guidelines, we believe amitriptyline in low doses should be considered a first-line drug for the treatment of fibromyalgia.

KEYWORDS: amitriptyline • antidepressants • clinical practice guidelines • fibromyalgia management • randomized clinical trials • review • systematic reviews

Fibromyalgia: a complex disease

Fibromyalgia syndrome is characterized by chronic generalized pain that is common to every patient. Other symptoms that frequently present in fibromyalgia patients are sleep disturbances (≥90% of patients) that are generally described as unrefreshing sleep [1], chronic daily fatigue (≈76%) [2], and depressive symptomatology (≈90%) [3]. Additional frequently associated symptoms include cognitive disturbances [4], gastrointestinal manifestations [5] and balance problems [6].

Fibromyalgia is frequently associated with comorbid conditions, including other central sensitivity syndromes such as primary headaches, irritable bowel syndrome, chronic fatigue syndrome, temporomandibular disorder or interstitial cystitis. Moreover, fibromyalgia can coexist with organic diseases, such as rheumatoid arthritis, systemic lupus erythematosus, or hypothyroidism [7].

Fibromyalgia is diagnosed applying the criteria established by the American College of Rheumatology, initially in 1990 [8] and later revised in 2010 [9]. The extent of pain is measured by the widespread pain index that requires a minimum of seven painful body areas, and the amount and severity of associated symptoms are measured by the symptom severity scale (SS); a definite diagnosis of fibromyalgia requires widespread pain index ≥ 7 and SS ≥ 5 or widespread pain index 3–6 and SS ≥ 9 [9].

This complex syndrome is not easy to treat. Currently, most experts and clinical practice guidelines [10,11] recommend a multidisciplinary treatment using a combination of pharmacological with non-pharmacological measures. A review of the pharmacological options for the treatment of fibromyalgia can be found elsewhere [12,13]. Among pharmacological therapies, most of the drugs prescribed for the treatment of fibromyalgia involve the class of antidepressants: tricyclic antidepressants (TCAs), selective noradrenaline and serotonin reuptake inhibitors, and selective serotonin reuptake inhibitors. The TCA amitriptyline has been more thoroughly studied than other antidepressants and is also frequently used as active comparator to assess comparative efficacy. The aim of this article is to provide an

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up-to-date review on what is known about amitriptyline for the treatment of fibromyalgia, including pharmacological data and information from randomized clinical trials (RCTs), systematic reviews, observational studies, and clinical practice guidelines.

Pharmacological profile of amitriptyline

Pharmacokinetics

Amitriptyline is a highly lipophilic drug that undergoes extensive metabolism. The bioavailability of amitriptyline is low (47 ± 11%) after oral administration [14] due to the first-pass effect. Amitriptyline is likely a substrate for the ABCBA1 (P-glycoprotein) transporter at intestinal and hepato-biliary levels [15,16], and this factor, more than metabolic degradation, is likely responsible for its low oral bioavailability.

Amitriptyline terminal half-life values range from 15 to 19 h after intravenous administration [17] and 17 to 26 h after oral administration [18]. Amitriptyline is extensively metabolized, primarily by N-demethylation that creates its active metabolite nortriptyline, and by hydroxylation and N-oxidation to a lesser extent [19]. The production of nortriptyline from amitriptyline shows considerable interindividual variation [20]. Different cytochromes are involved in the metabolism of amitriptyline: CYP2D6 catalyzes amitriptyline and nortriptyline hydroxylation, and CYP2C19 and CYP3A4 are involved in amitriptyline demethylation to nortriptyline [21]. Amitriptyline metabolic pathways are likely clinically relevant because genetic polymorphisms may underlie the higher or lower propensities of adverse reactions [22] and serious potentially life-threatening drug–drug interactions [23–25].

Pharmacodynamics

Amitriptyline is a rather unselective drug compared with newer antidepressants because it has multiple different pharmacological targets. This non-selective nature accounts for its toxicity, but it is also likely responsible for its efficacy in the treatment of chronic pain. It is generally accepted that both the antidepressant and antinociceptive activities of amitriptyline and its active metabolite nortriptyline are primarily, but not exclusively, due to its capacity to bind the noradrenaline and serotonin transporters at central sites [26,27]. Other central and peripheral mechanisms of action that have been postulated to mediate the antinociceptive efficacy of amitriptyline include α_2 adrenergic receptor agonism, 5-HT_2 receptor antagonism, activation of the endogenous opioid system, glutamate NMDA receptor antagonism, $GABA_B$ receptor potentiation, decrease in TNFα and prostaglandin E_2 production, blockade of Na^+ and Ca^{2+} channels activity and K^+ channels activation [26,27].

The side-effect profile of amitriptyline includes dry mouth, constipation and urinary hesitancy due to peripheral anticholinergic activity, sedation and somnolence due to $histamine_1$ receptor antagonism, and drowsiness and orthostatic hypotension due to α_1 adrenergic receptor antagonism. The amitriptyline doses used in the treatment of chronic pain are substantially lower than the doses that are used for the treatment of depression. Therefore, serious dose-dependent adverse events are rarely observed. However, cognitive impairment and tachycardia (both anticholinergic side effects) may be problematic in elderly patients.

Amitriptyline for the treatment of pain

Antidepressants were initially used for treating chronic pain more than three decades ago [28]. TCAs and monoamine-oxidase inhibitors are the oldest antidepressants, and these drugs have been used extensively to treat different pain conditions. Among them, amitriptyline is the most frequently used drug. Amitriptyline was primarily studied in the treatment of different types of neuropathic pain, migraine and tension-type headache (TTH) prevention, and fibromyalgia treatment. One extensive review, published in 1992, that evaluated the analgesic efficacy of antidepressants in the treatment of chronic non-malignant pain, found that amitriptyline had a mean effect size of 0.73 for pain parameters [29].

In 2007, a Cochrane review that analyzed the effectiveness of numerous antidepressants in the treatment of neuropathic pain and included 26 trials performed with amitriptyline versus placebo or an active comparator concluded that TCAs are effective against different types of neuropathic pain [30]. Amitriptyline was clearly effective in diabetic peripheral neuropathy and possibly effective in trigeminal neuralgia and central pain, but it was ineffective against HIV-related neuropathies [30]. The number needed to treat (NNT) value for amitriptyline was 3.1 (95% CI: 2.5–4.2), and the NNH value for amitriptyline was 28 (95% CI: 17.6–68.9) for major adverse events and 6 (95% CI: 4.2–10.7) for minor adverse events. The efficacy of amitriptyline for the treatment of neuropathic pain has been recently revised in a Cochrane review that concluded that evidence of its beneficial effect is low due to the lack of good quality trials but that the drug should be continued to be used although perhaps only a minority of patients will achieve a satisfactory degree of pain relief [31].

A meta-analysis for headaches published in 2010 evaluated 37 clinical trials that investigated TCAs versus placebo or an active comparator in the treatment of migraine, TTH or mixed (migraine + TTH) headache, and 30 (81%) of these trials included amitriptyline [32]. The authors concluded that TCAs effectively reduced the burden both of migraine and TTH with large effects sizes of −1.00 (95% CI: 1.52 to −0.48) and −0.99 (95% CI: −1.66 of −0.32), respectively. TCAs were significantly more effective than selective serotonin reuptake inhibitors for headache improvement, with effect sizes of −0.51 (95% CI: −0.99 to −0.02) for migraine and of −0.80 (95% CI: −1.63 to 0.02) for TTH, but the tolerability of TCAs was lower. The effect of TCAs increased with longer treatment duration.

Amitriptyline also improves the symptoms of irritable bowel syndrome, including pain, which is one of the most relevant symptoms for this condition [33]. The use of amitriptyline was also examined in the treatment of rheumatoid arthritis [34] and the prevention of postsurgical pain [35], but the available evidence does not currently support its efficacy in these indications.

Amitriptyline for the treatment of fibromyalgia

Randomized clinical trials

Efficacy

Placebo-controlled studies

We found 10 placebo-controlled RCTs that used amitriptyline published between 1986 and 2001 [36–45]. Nine trials were short-term studies (4–12 weeks), and one trial was a long-term study [39]. Three trials had a cross-over design [38,41,43]. All trials were double-blinded. A summary of the design and key results of these RCTs appears in Tables 1 & 2, respectively.

All but one trial [40] reported the patient global impression of improvement, and six trials demonstrated positive results (i.e., significantly greater improvement with amitriptyline compared with placebo) [37,38,41–43,45]. Only two trials reported the impact of amitriptyline on the overall symptoms of fibromyalgia, as measured with the total score of the fibromyalgia impact questionnaire (FIQ) [43,45]. Goldenberg *et al.* [43] used a crossover design and found that amitriptyline (25 mg/day) was significantly better than placebo in the improvement of the overall impact of fibromyalgia on the patient. Heymann *et al.* [45] reported a greater improvement of the FIQ total score with amitriptyline (25 mg/day) in a parallel RCT, although this difference did not reach statistical significance ($p = 0.071$ for the group effect).

All but one of these placebo-controlled trials [45] reported results on pain, with a significantly greater improvement of pain scores for amitriptyline compared with placebo reported in five trials [37,38,41–43]. Of the remaining four trials, in two trials, amitriptyline demonstrated significant improvements in pain from baseline to end of treatment, but placebo did not [36,44]. Eight trials reported outcomes for sleep [36,37,39–44], and six of these studies revealed significantly greater benefits for amitriptyline over placebo [36,37,41–44]. Seven RCTs reported the impact of amitriptyline on fatigue [37,39–44], and a significantly greater improvement for amitriptyline compared with placebo was noted in three trials [37,41,42]. Only two RCTs reported the effect of amitriptyline on depressive symptoms, and both studies reported the lack of superiority of amitriptyline over placebo [39,43].

Overall, these results suggest that amitriptyline provides a significant greater overall relief to patients with fibromyalgia compared with placebo. The beneficial effect of amitriptyline on sleep was consistently demonstrated in most trials. Although less consistently, the results also suggest a beneficial effect on pain and, to a lesser extent, on fatigue. There were no effects on depressive symptoms, which was expected because of the low prescribed doses of amitriptyline. Although there were no dose–response studies, efficacy did not appear dose related. Three of the trials that demonstrated consistently negative results across several outcomes used doses of amitriptyline up to 50 mg [36,39,40], which suggests the possible impact of a worse tolerability of higher doses on efficacy results. However, the proportion of dropouts due to adverse events in amitriptyline patients was low and similar to placebo in two of these three trials [36,39]. Another trial that used flexible doses of 10–50 mg/day of amitriptyline reported that 75% of patients reported improvement with amitriptyline and 22% reported improvement with placebo [38].

Clinical studies comparing amitriptyline to other pharmacological interventions

The design and results of the clinical trials comparing amitriptyline with other pharmacological interventions are presented in Tables 1 & 2 for placebo-controlled trials, and Tables 3 & 4 for active-controlled trials.

Amitriptyline has been compared with other antidepressants, including fluoxetine [43], moclobemide [44], and nortriptyline [45] in placebo-controlled trials, and paroxetine [46,47], venlafaxine [48], and reboxetine [49] in active-controlled trials. In addition, we found a RCT comparing fluvoxamine and amitriptyline [50], but we were unable to retrieve the full article; although this study has not been included in the summary tables, available data from the abstract are briefly commented below.

Amitriptyline and fluoxetine were associated with significantly greater improvement than placebo in overall symptomatology as measured with FIQ, pain, global wellbeing and sleep disturbance in a randomized, double-blinded, crossover clinical trial comparing amitriptyline (25 mg/day), fluoxetine (20 mg/day), the combination amitriptyline/fluoxetine, and placebo [43]. The results of the two active-controlled studies comparing amitriptyline and paroxetine demonstrated inconsistent results [46,47]. While Ataoglü *et al.* [46] reported that paroxetine (20 mg/day) was superior to amitriptyline (100 mg/day) in reducing pain and sleep disturbance, Çapaci *et al.* [47] reported that amitriptyline (20 mg/day) and paroxetine (40 mg/day) exhibited similar reductions in pain, but significantly more amitriptyline-treated patients were without sleep disturbances and fatigue than paroxetine-treated patients. The results reported by Ataoglü *et al.* may be influenced by the lower tolerability of amitriptyline (100 mg/day) than paroxetine (20 mg/day). The number of patients who reported adverse events was much greater in amitriptyline-treated patients (93 vs 38%), and the proportion of dropouts due to adverse event was also greater with amitriptyline 100 mg/day than paroxetine 20 mg/day (15 vs 6%) [46].

In two active-controlled trials, amitriptyline (25–75 mg/day) exhibited similar overall efficacy and beneficial effect on pain and depressive symptoms as venlafaxine (75 mg/day) [48] and reboxetine [49]; but in this latter trial, the reduction in the FIQ total score was significantly greater with reboxetine than with amitriptyline. In a placebo-controlled trial, amitriptyline (25–37.5 mg/day) was not significantly different than moclobemide (450–600 mg/day) in improvements in pain or fatigue, but sleep disturbances were reduced to a significantly greater extent than moclobemide [44]. In another placebo-controlled trial, amitriptyline (25 mg/day) was superior to placebo in reducing the overall symptomatology as measured with the FIQ and the proportion of patients reporting improvement, but nortriptyline (25 mg/day) was not different than placebo [45]. In a

Table 1. Summary of study designs of randomized placebo-controlled pharmacological clinical trials of amitriptyline for the treatment of fibromyalgia.

Study (year)	Design	Comparator groups (n)	Drug dose	Duration (weeks)	Key selection criteria	Ref.
Short-term clinical studies						
Carette *et al.* (1986)	Double-blind, parallel	AMT (n = 34) versus Placebo (n = 36)	AMT: 10–50 mg HS	9	Primary fibrositis (Smythe criteria)	[36]
Goldenberg *et al.* (1986)	Double-blind, parallel	n = 62 equally distributed to: AMT/NP, NP, AMT and placebo	AMT: 25 mg HS NP: 500 mg BID	6	FMS (Modified Yunus *et al.* criteria) Pain (VAS 0–10) ≥ 4 or FMS symptoms (VAS 0–10) ≥ 4	[37]
Scudds *et al.* (1989)	Double-blind, crossover	AMT versus Placebo (n = 36)	AMT: 10 mg HS (wk 1); 25 mg HS (wk 2) followed by 50 mg HS	4 each period	Fibrositis syndrome (Smythe and Moldofsky criteria)	[38]
Kempenaers *et al.* (1994)	Double-blind, parallel	SER282 (n = 12) versus AMT (n = 12) versus Placebo (n = 12)	AMT: 50 mg/day SER282: 20 mg/ml 3 times/wk	8	PFS (Yunus *et al.* criteria) Without severe psychiatric comorbidity	[40]
Carette *et al.* (1995)	Double-blind, crossover	AMT versus placebo (n = 22)	AMT: 10–25 mg HS	8 each period	Age ≥ 18 FMS (ACR 1990) Score of ≥4 on at least 1 of 2 self-administered 10-cm VAS (Pain or global FMS symptoms)	[41]
Ginsberg *et al.* (1996)	Double-blind, parallel	AMT SR (n = 24) versus placebo (n = 22)	AMT SR: 25 mg HS	8	PFS (ACR 1990)	[42]
Goldenberg *et al.* (1996)	Double-blind, crossover	AMT versus FLX versus AMT/FLX versus placebo (n = 31)	AMT: 25 mg HS FLX: 20 mg/day	6 each period	Aged 18–60 FMS (ACR 1990) Pain (VAS 0–100) ≥ 30 HDRS ≤ 18	[43]
Hannonen *et al.* (1998)	Double-blind, parallel	AMT (n = 42) versus MOC (n = 43) versus placebo (n = 45)	AMT: 25–37.5 mg HS MOC: 450–600 mg/day	12	Women aged 18–65 FMS (ACR 1990) A minimum baseline score of 4 (moderate) on at least 3 of 4 10-point VAS (general health, pain, sleep and fatigue) Without depression or psychosis	[44]
Heymann *et al.* (2001)	Double-blind, parallel	AMT (n =40) versus NTP (n = 38) versus placebo (n = 40)	AMT: 25 mg HS NTP: 25 mg HS	8	Women ≥ 18 FMS (ACR 1990)	[45]
Long-term clinical studies						
Carette *et al.* (1994)	Double-blind, parallel	AMT (n = 84) *versus* CYB (n = 82) versus placebo (n = 42)	AMT: 25 mg HS (wks 2–12); 50 mg HS (wks 12–24) CYB: 20 mg HS (wks 2–12); 10 mg in the morning and 20 mg HS (wks 12–24)	24	Age ≥ 18 FMS (ACR 1990) Score of ≥4 on at least 1 of 2 self-administered 10-cm VAS (Pain or global FMS symptoms)	[39]

ACR: American college of rheumatology; AMT: Amitriptyline; BID: Twice daily; cm: Centimeters; CYB: Cyclobenzaprine; FLX: Fluoxetine; FMS: Fibromyalgia syndrome; HDRS: Hamilton depression rating scale; HS: Once nightly; J/cm^2: Joules per square centimeter; kg: Kilogram; mg: Milligrams; MOC: Moclobemide; NP: Naproxen; NTP: Nortriptyline; PFS: Primary fibrositis syndrome; SER282: Antidiencephalon immune serum; SR: Sustained-release; VAS: Visual analogue scale; wk: Week.

Table 2. Summary of results of randomized placebo-controlled pharmacological clinical trials of amitriptyline for the treatment of fibromyalgia.

Study (year)	Outcome measures	Drug groups (dose range/day)				Statistical outcomes	Ref.
Short-term trials							
Carette *et al*. (1986)		AMT (10–50 mg)		Placebo			[36]
	Pain (VAS 0–10) (mean ± SD)	Baseline: 6.3 ± 2.3 Endpoint: 4.3 ± 3		Baseline: 5.8 ± 2.4 Endpoint: 5 ± 3		Inter-group differences: NS between groups Within-group differences: AMT ($p < 0.05$), placebo (NS)	
	Sleep disturbance (% of patients reporting improvement)	70%		40%		Inter-group differences: $p = 0.02$	
	PGI-I (% of patients reporting improvement)	77%		50%		Inter-group differences: NS	
	Number of patients reporting AE (%)	19 (55.8%)		4 (11.1%)			
	Number of dropouts due to AE (%)	2 (5.8%)		2 (5.5%)			
Goldenberg *et al*. (1986)		AMT/NP 25 mg/500 mg BID	NP 500 mg BID	AMT 25 mg	Placebo		[37]
	Pain (VAS 0–10) (Mean)	Baseline: 6.9 Endpoint: 4.7	Reported in a figure	Baseline: 7.3 Endpoint: 5.4	Reported in a figure	Inter-group differences: $p < 0.001$ for AMT groups versus non-AMT groups; NS between AMT groups Within-group differences: $p < 0.05$ for AMT groups	
	Sleep disturbance (VAS 0–10) (Mean)	Baseline: 5.5 Endpoint: 3.6	Reported in a figure	Baseline: 6.9 Endpoint: 3.0	Reported in a figure	Inter-group differences: $p < 0.001$ for AMT groups versus non-AMT groups; NS between AMT groups Within-group differences: $p < 0.05$ for AMT only	
	Fatigue (VAS 0–10) (Mean)	Baseline: 6.7 Endpoint: 4.7	Reported in a figure	Baseline: 7.5 Endpoint: 4.3	Reported in a figure	Inter-group differences: $p < 0.001$ for AMT groups versus non-AMT groups; NS between AMT groups Within-group differences: $p < 0.05$ for AMT groups	
	PGI-I (% of patients reporting improvement)	Reported in a figure	Reported in a figure	Reported in a figure	Reported in a figure	Inter-group differences: More significant improvement in AMT groups versus non-AMT groups ($p < 0.001$)	

AE: Adverse events; AIMS: Arthritis impact measurement scales; AMT: Amitripytiline; ANOVA: Analysis of variance; BDII: Beck depression inventory; BID: Twice daily; CYB: Cyclobenzaprine; FIQ: Fibromyalgia impact questionnaire; FLX: Fluoxetine; HAQ: Health assessment questionnaire; HDRS: Hamilton depression rating scale; hrs: hours; J/cm^2: Joules per square centimeter; mg: Milligrams; MOC: Moclobemide; MPQ: McGill pain questionnaire; NHP: Nottingham health profile; NP: Naproxen; NR: Not reported; NS: Non-significant differences; NTP: Nortriptyline; PGI-I: Patient global impression of change-improvement; QOL: Quality of life; SD: Standard deviation; SE: Standard error; SER282: Antidiencephalon immune serum; TST: Total sleep time; VAS: Visual analogue scale.

Table 2. Summary of results of randomized placebo-controlled pharmacological clinical trials of amitriptyline for the treatment of fibromyalgia. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)				Statistical outcomes	Ref.
Short-term trials (cont.)							
	Number of patients reporting AE	AMT-containing groups: 4	2	AMT-containing groups: 4	2		
	Number of dropouts due to AE	1	0	0	1		
Scudds *et al*. (1989)		AMT (10–50 mg)		Placebo			[38]
	Pain (MPQ)	Reported in a figure		Reported in a figure		Within-group differences: significantly lower levels of pain rating after AMT therapy ($p < 0.05$)	
	PGI-I (% of patients reporting improvement)	75%		22%		Inter-group differences: $p < 0.001$	
	Number of patients reporting AE (%)	NR		NR			
	Number of dropouts due to AE (n)	1		1			
Kempenaers *et al*. (1994)		AMT (50 mg)	SER282 (20 mg 3 times/wk)	Placebo			[40]
	Pain (VAS 0–100) (mean ± SD)	Baseline: 57 ± 23 Endpoint: 32 ± 31	Baseline: 67 ± 18 Endpoint: 63 ± 26	Baseline: 65 ± 20 Endpoint: 37 ± 28		ANOVA for repeated measures: Group effect p: NS; Time effect p = 0.012; Interaction effect p: NS	
	Sleep quality (VAS 0–100) [worst to best] (mean ± SD)	Baseline: 30 ± 8 Endpoint: 47 ± 30	Baseline: 59 ± 39 Endpoint: 36 ± 14	Baseline: 58 ± 7 Endpoint: 60 ± 22		ANOVA for repeated measures: NS differences	
	Fatigue (VAS 0–3) (mean ± SD)	Baseline: 1.5 ± 0.6 Endpoint: 1.2 ± 0.5	Baseline: 2.7 ± 1.5 Endpoint: 2 ± 1	Baseline: 2 ± 1 Endpoint: 2.7 ± 1.5		ANOVA for repeated measures: NS differences; Interaction effect p = 0.05	

AE: Adverse events; AIMS: Arthritis impact measurement scales; AMT: Amitripytiline; ANOVA: Analysis of variance; BDII: Beck depression inventory; BID: Twice daily; CYB: Cyclobenzaprine; FIQ: Fibromyalgia impact questionnaire; FLX: Fluoxetine; HAQ: Health assessment questionnaire; HDRS: Hamilton depression rating scale; hrs: hours; J/cm^2: Joules per square centimeter; mg: Milligrams; MOC: Moclobemide; MPQ: McGill pain questionnaire; NHP: Nottingham health profile; NP: Naproxen; NR: Not reported; NS: Non-significant differences; NTP: Nortriptyline; PGI-I: Patient global impression of change-improvement; QOL: Quality of life; SD: Standard deviation; SE: Standard error; SER282: Antidiencephalon immune serum; TST: Total sleep time; VAS: Visual analogue scale.

Table 2. Summary of results of randomized placebo-controlled pharmacological clinical trials of amitriptyline for the treatment of fibromyalgia. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)			Statistical outcomes	Ref.
Short-term trials (cont.)						
	Number of patients reporting AE (%)	NR	NR	NR		
	Number of dropouts due to AE (%)	NR	NR	NR		
Carette *et al.* (1995)		AMT (10–25 mg)		Placebo		
	Pain (VAS 0–10) (mean ± SD)	Baseline: 7.1 ± 1.9 Endpoint: 5.1 ± 3.2		Baseline: 7.1 ± 1.9 Endpoint: 7.1 ± 2.4	Inter-group differences: $p < 0.05$ Within-group differences: AMT ($p < 0.05$); placebo (NS)	
	Sleep disturbance (VAS 0–10) (mean ± SD)	Baseline: 7.5 ± 2.8 Endpoint: 3.9 ± 3.1		Baseline: 7.5 ± 2.8 Endpoint: 6.5 ± 2.7	Inter-group differences: $p < 0.05$ Within-group differences: AMT ($p < 0.05$); placebo (NS)	
	Sleep (TST, hrs) (mean ± SD)	Baseline: 6.3 ± 1.1 Endpoint: 6.8 ± 1.2		Baseline: 6.3 ± 1.1 Endpoint: 6.5 ± 1.1	NS differences	
	Fatigue (VAS 0–10) (mean ± SD)	Baseline: 7.8 ± 1.8 Endpoint: 5.6 ± 3.1		Baseline: 7.8 ± 1.8 Endpoint: 7.6 ± 1.8	Inter-group differences: $p < 0.05$ Within-group differences: AMT ($p < 0.05$); placebo (NS)	
	Patient global assessment (VAS 0–10) (mean ± SD)	Baseline: 7.3 ± 1.7 Endpoint: 5.5 ± 3		Baseline: 7.3 ± 1.7 Endpoint: 7.1 ± 2.1	Inter-group differences: $p < 0.05$ Within-group differences: AMT ($p < 0.05$); placebo (NS)	
	Number of patients reporting AE (%)	NR		NR		
	Number of dropouts due to AE (%)	NR		NR		
Ginsberg *et al.* (1996)		AMT (25 mg)		Placebo		[42]
	Pain (VAS 0–10) (mean ± SD)	Baseline: 7.3 ± 1.4 Endpoint: 3.8 ± 2.4		Baseline: 7.1 ± 1.4 Endpoint: 7 ± 1.3	ANOVA for repeated measures: Interaction effect $p < 0.001$; AMT: Significant improvement compared with baseline; placebo: NS compared with baseline	

AE: Adverse events; AIMS: Arthritis impact measurement scales; AMT: Amitripytiline; ANOVA: Analysis of variance; BDII: Beck depression inventory; BID: Twice daily; CYB: Cyclobenzaprine; FIQ: Fibromyalgia impact questionnaire; FLX: Fluoxetine; HAQ: Health assessment questionnaire; HDRS: Hamilton depression rating scale; hrs: hours; J/cm^2: Joules per square centimeter; mg: Milligrams; MOC: Moclobemide; MPQ: McGill pain questionnaire; NHP: Nottingham health profile; NP: Naproxen; NR: Not reported; NS: Non-significant differences; NTP: Nortriptyline; PGI-I: Patient global impression of change-improvement; QOL: Quality of life; SD: Standard deviation; SE: Standard error; SER282: Antidiencephalon immune serum; TST: Total sleep time; VAS: Visual analogue scale.

Table 2. Summary of results of randomized placebo-controlled pharmacological clinical trials of amitriptyline for the treatment of fibromyalgia. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)				Statistical outcomes	Ref.
Short-term trials (cont.)							
	Sleep disturbance (VAS 0–10) (mean ± SD)	Baseline: 5.2 ± 2.5 Endpoint: 2.6 ± 3.1		Baseline: 5.4 ± 3 Endpoint: 5.1 ± 3		ANOVA for repeated measures: Interaction effect p = 0.003; AMT: Significant improvement compared with baseline; placebo: NS compared with baseline	
	Fatigue (VAS 0–10) (mean ± SD)	Baseline: 7.3 ± 1.5 Endpoint: 3.8 ± 2.5		Baseline: 6.7 ± 2 Endpoint: 5.9 ± 2.2		ANOVA for repeated measures: Interaction effect p = 0.001; AMT: Significant improvement compared with baseline; placebo: NS compared with baseline	
	Patient global assessment (VAS 0–10) (mean ± SD)	Baseline: 7.7 ± 1.3 Endpoint: 3.9 ± 2.3		Baseline: 7 ± 1.6 Endpoint: 6.8 ± 1.8		ANOVA for repeated measures: Interaction effect p < 0.001; AMT: Significant improvement compared with baseline; placebo: NS compared with baseline	
	Number of patients reporting AE (%)	7 (29%)		0			
	Number of dropouts due to AE (%)	1 (4%)		0			
Goldenberg *et al.* (1996)		AMT (25 mg)	FLX (20 mg)	AMT/FLX (25 mg/20 mg)	Placebo		[43]
	Overall efficacy (FIQ) (mean ± SD)	Baseline: 54.9 ± 15.4 Endpoint: 52.3 ± 22.9	Baseline: 54.9 ± 15.4 Endpoint: 47.6 ± 19.8	Baseline: 54.9 ± 15.4 Endpoint: 38 ± 21.2	Baseline: 54.9 ± 15.4 Endpoint: 58.5 ± 17.1	ANOVA generalized linear model: AMT: p = 0.03; FLX: p = 0.006; Interaction effect p = 0.94 AMT/FLX significantly better than each alone (p-value NR)	
	Pain (VAS 0–100) (mean ± SD)	Baseline: 70.6 ± 18.4 Endpoint: 64.4 ± 28.3	Baseline: 70.6 ± 18.4 Endpoint: 57.5 ± 25.7	Baseline: 70.6 ± 18.4 Endpoint: 42.9 ± 28.5	Baseline: 70.6 ± 18.4 Endpoint: 81.5 ± 16.5	ANOVA generalized linear model: AMT: p = 0.02; FLX: p < 0.001; Interaction effect p = 0.55 AMT/FLX significantly better than each alone (p-value NR)	
	Depression (BDI) (mean ± SD)	Baseline: 11.7 ± 6.3 Endpoint: 8.7 ± 6	Baseline: 11.7 ± 6.3 Endpoint: 7.8 ± 4.7	Baseline: 11.7 ± 6.3 Endpoint: 7.4 ± 4.4	Baseline: 11.7 ± 6.3 Endpoint: 9.3 ± 6.5	ANOVA generalized linear model: AMT: p = 0.52; FLX: p = 0.35; Interaction effect p = 0.49 Single drug therapy versus combination: NS	
	Sleep disturbance (VAS 0–100) (mean ± SD)	Baseline: 65.8 ± 28.3 Endpoint: 57 ± 34.8	Baseline: 65.8 ± 28.3 Endpoint: 66 ± 26.6	Baseline: 65.8 ± 28.3 Endpoint: 39.9 ± 29.2	Baseline: 65.8 ± 28.3 Endpoint: 74.6 ± 23.9	ANOVA generalized linear model: AMT: p < 0.001; FLX: p = 0.04; Interaction effect p = 0.79 AMT/FLX significantly better than each alone (p-value NR)	

AE: Adverse events; AIMS: Arthritis impact measurement scales; AMT: Amitripytiline; ANOVA: Analysis of variance; BDII: Beck depression inventory; BID: Twice daily; CYB: Cyclobenzaprine; FIQ: Fibromyalgia impact questionnaire; FLX: Fluoxetine; HAQ: Health assessment questionnaire; HDRS: Hamilton depression rating scale; hrs: hours; J/cm^2: Joules per square centimeter; mg: Milligrams; MOC: Moclobemide; MPQ: McGill pain questionnaire; NHP: Nottingham health profile; NP: Naproxen; NR: Not reported; NS: Non-significant differences; NTP: Nortriptyline; PGI-I: Patient global impression of change-improvement; QOL: Quality of life; SD: Standard deviation; SE: Standard error; SER282: Antidiencephalon immune serum; TST: Total sleep time; VAS: Visual analogue scale.

Table 2. Summary of results of randomized placebo-controlled pharmacological clinical trials of amitriptyline for the treatment of fibromyalgia. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)				Statistical outcomes	Ref.
Short-term trials (cont.)							
	Fatigue (VAS 0–100) (mean ± SD)	Baseline: 68.8 ± 23.4 Endpoint: 67.7 ± 29.9	Baseline: 68.8 ± 23.4 Endpoint: 68.6 ± 24.1	Baseline: 68.8 ± 23.4 Endpoint: 57.2 ± 31.6	Baseline: 68.8 ± 23.4 Endpoint: 73.7 ± 25.1	ANOVA generalized linear model: AMT: $p = 0.26$; FLX: $p = 0.22$; Interaction effect $p = 0.88$ Single drug therapy versus combination: NS	
	Patient global assessment (VAS 0–100) (mean ± SD)	Baseline: 66.6 ± 22.8 Endpoint: 61.6 ± 29.5	Baseline: 66.6 ± 22.8 Endpoint: 60.9 ± 24.9	Baseline: 66.6 ± 22.8 Endpoint: 48.2 ± 29.7	Baseline: 66.6 ± 22.8 Endpoint: 76.8 ± 24.8	ANOVA generalized linear model: AMT: $p = 0.02$; FLX: $p = 0.02$; Interaction effect $p = 0.4$ AMT/FLX significantly better than each alone (p-value NR)	
	Number of patients reporting AE (%)	NR	NR	NR	NR		
	Number of dropouts due to AE (n)	0	1	3	1		
Hannonen *et al*. (1998)		AMT (25–37.5 mg)	MOC (450–600 mg)	Placebo			[44]
	Pain (VAS 0–10) (mean ± SD)	Baseline: 6 ± 2.1 Endpoint: 4.5 ± 2.8	Baseline: 5.7 ± 2.1 Endpoint: 4.5 ± 2.7	Baseline: 5.7 ± 2.3 Endpoint: 5.2 ± 2.7		Inter-group differences: NS Within-group differences: AMT ($p < 0.01$); MOC ($p < 0.05$); Placebo (NS)	
	Sleep disturbance (VAS 0–10) (mean ± SD)	Baseline: 5.9 ± 2.2 Endpoint: 3.6 ± 2.8	Baseline: 5.8 ± 2 Endpoint: 5.8 ± 3	Baseline: 5.5 ± 2.7 Endpoint: 4.8 ± 2.9		Inter-group differences: $p < 0.01$ for AMT Within-group differences: AMT ($p < 0.001$); MOC (NS); Placebo ($p < 0.05$) compared with other treatment groups	
	Fatigue (VAS 0–10) (mean ± SD)	Baseline: 6 ± 2.1 Endpoint: 4.7 ± 2.8	Baseline: 5.3 ± 2.3 Endpoint: 4.9 ± 2.7	Baseline: 5.6 ± 2.6 Endpoint: 4.6 ± 2.6		Inter-group differences: NS Within-group differences: AMT ($p < 0.01$); MOC (NS); Placebo ($p < 0.05$)	

AE: Adverse events; AIMS: Arthritis impact measurement scales; AMT: Amitripytiline; ANOVA: Analysis of variance; BDII: Beck depression inventory; BID: Twice daily; CYB: Cyclobenzaprine; FIQ: Fibromyalgia impact questionnaire; FLX: Fluoxetine; HAQ: Health assessment questionnaire; HDRS: Hamilton depression rating scale; hrs: hours; J/cm^2: Joules per square centimeter; mg: Milligrams; MOC: Moclobemide; MPQ: McGill pain questionnaire; NHP: Nottingham health profile; NP: Naproxen; NR: Not reported; NS: Non-significant differences; NTP: Nortriptyline; PGI-I: Patient global impression of change-improvement; QOL: Quality of life; SD: Standard deviation; SE: Standard error; SER282: Antidiencephalon immune serum; TST: Total sleep time; VAS: Visual analogue scale.

Table 2. Summary of results of randomized placebo-controlled pharmacological clinical trials of amitriptyline for the treatment of fibromyalgia. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)			Statistical outcomes	Ref.
Short-term trials (cont.)						
	QOL (NHP)	Endpoint: Energy: 24.3 ± 27.5; Sleep: 18.8 ± 25.3; Pain: 36.6 ± 30; Emotion: 2.9 ± 7.7	Endpoint: Pain: 41.4 ± 34.5	Endpoint: Sleep: 32.3 ± 30.3	AMT significantly improved: Energy and sleep ($p < 0.001$), pain and emotions ($p < 0.01$) MOC significantly improved the pain dimension ($p < 0.001$) Placebo significantly improved sleep dimension ($p < 0.05$)	
	Patient global assessment (VAS 0–10) (mean ± SD)	Baseline: 5.8 ± 1.8 Endpoint: 4.4 ± 2.6	Baseline: 6.2 ± 1.8 Endpoint: 5.3 ± 2.4	Baseline: 5.9 ± 2 Endpoint: 5.3 ± 2.5	Inter-group differences: NS Within-group differences: AMT ($p < 0.001$); MOC ($p < 0.01$); Placebo ($p < 0.05$)	
	Number of patients reporting AE (%)	31 (74%) Causal relation with the drug: (43%)	33 (77%) (58%)	36 (80%) (53%)		
	Number of dropouts due to AE (%)	5 (12%)	6 (14%)	5 (11%)		
Heymann *et al.* (2001)		AMT (25 mg)	NTP (25 mg)	Placebo		[45]
	Overall efficacy (FIQ) (mean ± 2 SE)	Baseline: 63.2 ± 4.2 Endpoint: 40 ± 6.5	Baseline: 67.3 ± 4.7 Endpoint: 48.8 ± 7.3	Baseline: 67.4 ± 4.3 Endpoint: 51.7 ± 8	Within-group differences: $p < 0.05$ for all groups ANOVA: group-effect $p = 0.071$; time-effect $p < 0.001$; interaction $p = 0.253$)	
	PGI-I (% of patients reporting improvement)	86.5%	72.2%	54.5%	Inter-group differences: $p = 0.0363$ AMT versus placebo: $p = 0.00981$; NTP versus placebo: NS	
	Number of patients reporting AE (%)	16 (40%)	31 (81.6%)	25 (62.5%)		
	Number of dropouts due to AE (%)	0	1 (2.6%)	2 (5%)		

AE: Adverse events; AIMS: Arthritis impact measurement scales; AMT: Amitripytiline; ANOVA: Analysis of variance; BDII: Beck depression inventory; BID: Twice daily; CYB: Cyclobenzaprine; FIQ: Fibromyalgia impact questionnaire; FLX: Fluoxetine; HAQ: Health assessment questionnaire; HDRS: Hamilton depression rating scale; hrs: hours; J/cm^2: Joules per square centimeter; mg: Milligrams; MOC: Moclobemide; MPQ: McGill pain questionnaire; NHP: Nottingham health profile; NP: Naproxen; NR: Not reported; NS: Non-significant differences; NTP: Nortriptyline; PGI-I: Patient global impression of change-improvement; QOL: Quality of life; SD: Standard deviation; SE: Standard error; SER282: Antidiencephalon immune serum; TST: Total sleep time; VAS: Visual analogue scale.

Table 2. Summary of results of randomized placebo-controlled pharmacological clinical trials of amitriptyline for the treatment of fibromyalgia. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)			Statistical outcomes	Ref.
Long-term clinical studies						
Carette *et al.* (1994)		AMT (10–50 mg)	CYB (10–30 mg)	Placebo		[39]
	Pain (MPQ-rating index) (mean ± SD)	Baseline: 28.2 ± 12.5 Endpoint: 19.5 ± 13.5	Baseline: 28.2 ± 13.2 Endpoint: 19.3 ± 14.8	Baseline: 28.6 ± 12.4 Endpoint: 21.6 ± 14.4	Inter-group differences: NS Within-group differences: AMT and CYB ($p < 0.001$); placebo ($p < 0.05$)	
	Depression (AIMS) (mean ± SD)	Baseline: 3.5 ± 1.9 Endpoint: 2.4 ± 1.9	Baseline: 3.5 ± 1.9 Endpoint: 2.2 ± 1.6	Baseline: 3.8 ± 2 Endpoint: 2.6 ± 1.8	Inter-group differences: NS Within-group differences: AMT and CYB ($p < 0.001$); placebo ($p < 0.05$)	
	Sleep disturbance (VAS 0–10)	Reported in a figure	Reported in a figure	Reported in a figure	Inter-group differences: NS Within-group differences: Significant improvement for AMT and CYB ($p < 0.05$); placebo (NS)	
	Fatigue (VAS 0–10)	Reported in a figure	Reported in a figure	Reported in a figure	Inter-group differences: NS Within-group differences: Significant improvement for AMT, CYB and placebo ($p < 0.05$)	
	HAQ disability index (mean ± SD)	Baseline: 0.7 ± 0.4 Endpoint: 0.6 ± 0.5	Baseline: 0.7 ± 0.4 Endpoint: 0.5 ± 0.4	Baseline: 0.9 ± 0.7 Endpoint: 0.7 ± 0.6	NS	
	Patient global assessment (VAS 0–10)	Reported in a figure	Reported in a figure	Reported in a figure	Inter-group differences: NS Within-group differences: Significant improvement for AMT, CYB and placebo ($p < 0.05$)	
	Number of patients reporting AE (%)	80 (95%)	80 (98%)	26 (62%)	Dry mouth, somnolence, dizziness, and weight gain being the most frequently reported	
	Number of dropouts due to AE (%)	5 (6%)	11 (13.4%)	2 (4.8%)		

AE: Adverse events; AIMS: Arthritis impact measurement scales; AMT: Amitripytiline; ANOVA: Analysis of variance; BDII: Beck depression inventory; BID: Twice daily; CYB: Cyclobenzaprine; FIQ: Fibromyalgia impact questionnaire; FLX: Fluoxetine; HAQ: Health assessment questionnaire; HDRS: Hamilton depression rating scale; hrs: hours; J/cm^2: Joules per square centimeter; mg: Milligrams; MOC: Moclobemide; MPQ: McGill pain questionnaire; NHP: Nottingham health profile; NP: Naproxen; NR: Not reported; NS: Non-significant differences; NTP: Nortriptyline; PGI-I: Patient global impression of change-improvement; QOL: Quality of life; SD: Standard deviation; SE: Standard error; SER282: Antidiencephalon immune serum; TST: Total sleep time; VAS: Visual analogue scale.

Table 3. Summary of study designs of randomized controlled trials comparing amitriptyline with other pharmacological interventions or with non-pharmacological interventions.

Study (year)	Design	Comparator groups (n)	Drug dose	Duration (weeks)	Key selection criteria	Ref.
Isomeri *et al.* (1993)	Open-label, parallel	AMT (n = 17) versus CFT (n = 17) versus AMT/CFT (n = 17)	AMT: 25 mg HS	15	PFS (Yunus *et al.* and Wolfe *et al.* criteria) Able to participate in the heavy physical training	[55]
Ataoğlu *et al.* (1997)	Open-label, parallel	AMT (n = 34) versus PRX (n = 34)	AMT: 100 mg HS PRX: 20 mg/day	6	Women with FMS (ACR 1990) Without previous diagnosis of depression	[46]
Azad *et al.* (2000)	Open-label, parallel	AMT (n = 41) versus Vegetarian diet (n = 37)	AMT: 25–100 mg/day	6	FMS (ACR 1990)	[53]
Çapaci *et al.* (2002)	Rater-blinded, parallel	AMT (n = 20) versus PRX (n = 20)	AMT: 20 mg/day PRX: 40 mg/day	8	FMS (ACR 1990)	[47]
Fors *et al.* (2002)	Factorial, double-blind, parallel	Psychological intervention: PI (n = 17) versus AI (n = 21) versus control (n = 17) Pharmacological intervention: AMT (n = 28) versus Placebo (n = 27)	AMT: 50 mg/day Pleasant imagery or attention imagery: 30 min	4	Women with FMS (ACR 1990)	[56]
Gür *et al.* (2002)	Single-blind, parallel	AMT (n = 25) versus Ga-As laser (n = 25) versus Placebo laser (n = 25)	AMT: 10 mg HS Ga-As laser: 2 J/cm^2 for 3 min at each tender point	AMT: 8 Laser: 2	FMS (ACR 1990) Without recent or Past history of psychiatric comorbidity	[52]
Gulec *et al.* (2007)	Randomized, double-blind, parallel	AMT (n = 28) versus VFX (n = 28)	AMT: 25–75 mg/day VFX: 75 mg/day	8	Women with FMS (ACR 1990) Without severe psychiatric disorders	[48]
Konuk *et al.* (2010)	Open-label, parallel	AMT (n = 11) versus RBX (n = 10)	AMT: 25–75 mg/day RBX: 4–8 mg/day	8	FMS (ACR 1990) Without MDD	[49]
Vlainich *et al.* (2011)	Double-blind, parallel	AMT (n = 15) versus AMT/lidocaine (n = 15)	AMT: 25 mg HS Lidocaine: 240 mg IV once per wk	4	Women aged 18–60 FMS (ACR 1990) Without psychiatric comorbidity	[54]
Calandre *et al.* (2014)	Open-label, parallel, non-inferiority (δ for FIQ score = 8)	AMT (n = 45) versus quetiapine XR (n = 45)	AMT: 10–75 mg HS Quetiapine XR: 50–300 mg HS	16	Adults 18–70 years FMS (ACR 1990) FIQ ≥ 40 BPI-s ≥ 4 Without psychiatric comorbidity except MDD Without severe depression (BDI < 30)	[51]

ACR: American college of rheumatology; AI: Attention imagery; AMT: Amitriptyline; BDI: Beck depression inventory; BPI-s: Brief pain inventory-severity; CFT: Cardiovascular fitness training; FIQ: Fibromyalgia impact questionnaire; FMS: Fibromyalgia syndrome; Ga-As: Gallium arsenide; HS: Once nightly; IV: Intravenous; MDD: Major depressive disorder; mg: Milligrams; PFS: Primary fibrositis syndrome; PI: Pleasant imagery; PRX: Paroxetine; RBX: Reboxetine; VAS: Visual analogue scale; VFX: Venlafaxine; wk: Week; XR: Extended release.

randomized, double-blind, crossover clinical trial, fluvoxamine (50 mg/day) was compared with amitriptyline (25 mg/day) in patients with fibromyalgia without psychiatric comorbidity; except for a greater improvement of anxiety symptoms with fluvoxamine, there were no differences in terms of efficacy between the two drugs [50].

Amitriptyline has also been compared with drugs other than antidepressants, including naproxen [37] and the atypical

Table 4. Summary of results of randomized controlled trials comparing amitriptyline with other pharmacological interventions or with non-pharmacological interventions.

Study (year)	Outcome measures	Drug groups (dose range/day)			Statistical outcomes	Ref.
Isomeri *et al.* (1993)		AMT (25 mg)	CFT	AMT/CFT		[55]
	Pain (VAS 0–100)	Reported in a figure	Reported in a figure	Reported in a figure	Pain VAS scores decreased only in patients treated with AMT and CFT	
	Number of patients reporting AE (%)	NR	NR	NR		
	Number of dropouts due to AE (%)	NR	NR	NR		
Ataoğlu *et al.* (1997)		AMT (100 mg)	PRX (20 mg)			[46]
	Pain (VAS 0–10) (Mean)	Baseline: 7.7 Endpoint: 7.4	Baseline: 7.7 Endpoint: 5.5		Inter-group differences : $p < 0.001$ Within-group differences compared with baseline: AMT ($p < 0.05$) and PRX ($p < 0.001$)	
	Depression (HDRS) (mean ± SD)	Baseline: 9 Endpoint: 7.8	Baseline: 8.2 Endpoint: 6.8		Inter-group differences : NS Within-group differences compared with baseline: AMT and PRX were both statistically significant	
	Sleep disturbance (VAS 0–10) (mean ± SD)	Baseline: 7.9 Endpoint: 7	Baseline: 7.8 Endpoint: 4.8		Inter-group differences : $p < 0.001$ Within-group differences compared with baseline: AMT and PRX were both statistically significant	
	Fatigue (VAS 0–10) (mean ± SD)	Baseline: 7.8 Endpoint: 7	Baseline: 7.9 Endpoint: 7.2		Inter-group differences : NS Within-group differences compared with baseline: AMT ($p < 0.01$) and PRX (NS)	
	PGI-I (% of patients reporting improvement)	37.9%	40.6%		NS	
	Number of patients reporting AE (%)	27 (93.1%)	12 (37.5%)			
	Number of dropouts due to AE (%)	5 (14.7%)	2 (5.8%)			

AE: Adverse events; AI: Attention imagery; AMT: Amitripytiline; ANOVA: Analysis of variance; BDI: Beck depression inventory; BPI-s: Brief pain inventory-severity; CFT: Cardiovascular fitness training; C.I: Confidence interval; FIQ: Fibromyalgia impact questionnaire; Ga-As: Gallium arsenide; HDRS: Hamilton depression rating scale; MCS: Mental component summary of the SF-36; mg: Milligrams; NR: Not reported; NS: Non-significant differences; PCS: Physical component summary of the SF-36; PI: Pleasant imagery; PRX: Paroxetine; PSQI: Pittsburgh sleep quality index; QOL: Quality of life; SD: Standard deviation; SF-36: Short-form health survey; VAS: Visual analogue scale; XR: Extended release.

Table 4. Summary of results of randomized controlled trials comparing amitriptyline with other pharmacological interventions or with non-pharmacological interventions. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)		Statistical outcomes	Ref.
Azad *et al.* (2000)		AMT (25–100 mg)	Vegetarian diet		[53]
	Pain (VAS 0–10) (mean ± SD)	Baseline: 6.2 ± 1.9 Endpoint: 2.3 ± 1.3	Baseline: 5.7 ± 1.8 Endpoint: 5 ± 1.8	Inter-group differences: $p < 0.0001$ Intra-group differences: Vegetarian diet ($p = 0.025$); AMT ($p < 0.0001$)	
	Fatigue (%)	Baseline: 100% Endpoint: 7%	Baseline: 97% Endpoint: 92%	Inter-group differences: NR Intra-group differences: vegetarian diet (NS); AMT ($p < 0.0001$)	
	Insomnia (%)	Baseline: 63% Endpoint: 0%	Baseline: 65% Endpoint: 78%	Inter-group differences: NR Intra-group differences: vegetarian diet (NS); AMT ($p < 0.0001$)	
	Non-restorative sleep (%)	Baseline: 78% Endpoint: 0%	Baseline: 73% Endpoint: 78%	Inter-group differences: NR Intra-group differences: vegetarian diet (NS); AMT ($p < 0.0001$)	
	Number of patients reporting AE (%)	NR	NR		
	Number of dropouts due to AE (%)	0	0		
Çapaci *et al.* (2002)		AMT (20 mg)	PRX (40 mg)		[47]
	Pain (VAS 0–10) (Mean)	Baseline: 7 Endpoint: 1.7	Baseline: 7 Endpoint: 1.3	NR	
	% of patients with depressive symptoms	Baseline: 60 Endpoint: 30	Baseline: 70 Endpoint: 30	Inter-group differences: $p = 1$ Within-group differences: AMT($p = 0.031$); PRX ($p = 0.008$)	
	% of patients with sleep disturbances	Baseline: 70 Endpoint: 0	Baseline: 100 Endpoint: 50	Inter-group differences: $p < 0.001$ Within-group differences: AMT ($p < 0.001$); PRX ($p = 0.002$)	
	% of patients with fatigue	Baseline: 100 Endpoint: 20	Baseline: 100 Endpoint: 90	Inter-group differences: $p < 0.001$ Within-group differences: AMT (<0.001); PRX ($p = 0.5$)	

AE: Adverse events; AI: Attention imagery; AMT: Amitripytiline; ANOVA: Analysis of variance; BDI: Beck depression inventory; BPI-s: Brief pain inventory-severity; CFT: Cardiovascular fitness training; C.I: Confidence interval; FIQ: Fibromyalgia impact questionnaire; Ga-As: Gallium arsenide; HDRS: Hamilton depression rating scale; MCS: Mental component summary of the SF-36; mg: Milligrams; NR: Not reported; NS: Non-significant differences; PCS: Physical component summary of the SF-36; PI: Pleasant imagery; PRX: Paroxetine; PSQI: Pittsburgh sleep quality index; QOL: Quality of life; SD: Standard deviation; SF-36: Short-form health survey; VAS: Visual analogue scale; XR: Extended release.

Table 4. Summary of results of randomized controlled trials comparing amitriptyline with other pharmacological interventions or with non-pharmacological interventions. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)			Statistical outcomes	Ref.
	Number of patients reporting AE (%)	NR	NR			
	Number of dropouts due to AE (%)	NR	NR			[56]
Fors *et al.* (2002)	*Effects of psychological interventions*	PI	AI	Control		
	Pain (VAS 0–100) (mean ± SD)	Baseline: 48.5 ± 24 Endpoint: 31.7 ± 22.3	Baseline: 52 ± 19.9 Endpoint: 55.6 ± 21.8	Baseline: 51.2 ± 23.3 Endpoint: 45.7 ± 45.6	Inter-group differences: $p < 0.005$ for PI versus AI and for PI versus control; AI versus Placebo (NS)	
	Number of patients reporting AE (%)	NR	NR	NR		
	Number of dropouts due to AE (%)	NR	NR	NR		
	Effects of pharmacological intervention	AMT (50 mg)	Placebo			
	Pain (VAS 0–100) (mean ± SD)	Baseline: 42.6 ± 26 Endpoint: 39.2 ± 29.1	Baseline: 44.7 ± 23.5 Endpoint: 50.7 ± 24.1		NS	
	Number of patients reporting AE (%)	NR	NR			
	Number of dropouts due to AE (%)	NR	NR			
	Interaction between the two interventions					
	Pain (VAS)				There was no interaction between the psychological and pharmacological interventions ($p = 0.76$)	
Gür A *et al.* (2002)		AMT (10 mg)	Ga-As laser (2 J/cm^2)	Placebo laser		[52]
	Overall efficacy (FIQ) (mean ± SD)	Baseline: 57.7 ± 9.1 Endpoint: 39.8 ± 8.6	Baseline: 56.3 ± 7.6 Endpoint: 33 ± 12	Baseline: 59.9 ± 8.2 Endpoint: 50.3 ± 8.9	Inter-group differences: $p = 0.003$ for AMT compared with placebo; $p = 0.003$ for laser compared with placebo Within-group differences: AMT and laser ($p < 0.001$); Placebo ($p = 0.042$)	

AE: Adverse events; AI: Attention imagery; AMT: Amitripytiline; ANOVA: Analysis of variance; BDI: Beck depression inventory; BPI-s: Brief pain inventory-severity; CFT: Cardiovascular fitness training; C.I: Confidence interval; FIQ: Fibromyalgia impact questionnaire; Ga-As: Gallium arsenide; HDRS: Hamilton depression rating scale; MCS: Mental component summary of the SF-36; mg: Milligrams; NR: Not reported; NS: Non-significant differences; PCS: Physical component summary of the SF-36; PI: Pleasant imagery; PRX: Paroxetine; PSQI: Pittsburgh sleep quality index; QOL: Quality of life; SD: Standard deviation; SF-36: Short-form health survey; VAS: Visual analogue scale; XR: Extended release.

Table 4. Summary of results of randomized controlled trials comparing amitriptyline with other pharmacological interventions or with non-pharmacological interventions. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)			Statistical outcomes	Ref.
	Pain (Likert 0–4) (mean ± SD)	Baseline: 2.9 ± 0.7 Endpoint: 2.1 ± 0.9	Baseline: 3 ± 0.5 Endpoint: 1.2 ± 0.7	Baseline: 3.2 ± 0.9 Endpoint: 2.2 ± 0.7	Inter-group differences: $p < 0.001$ for laser compared with MT and to placebo Within-group differences: $p < 0.001$ in all groups	
	Depression (HDRS) (mean ± SD)	Baseline: 17.6 ± 4.2 Endpoint: 7.2 ± 3.2	Baseline: 19.2 ± 5.9 Endpoint: 11.5 ± 4	Baseline: 18.1 ± 4.1 Endpoint: 15.8 ± 4.1	Inter-group differences: $p < 0.001$ for AMT compared with laser and to placebo Within-group differences: AMT and laser ($p < 0.001$); Placebo ($p = 0.092$)	
	Sleep disturbance (Likert 0–4) (mean ± SD)	Baseline: 2.1 ± 1.3 Endpoint: 0.8 ± 0.7	Baseline: 2.4 ± 1.2 Endpoint: 1.1 ± 1.1	Baseline: 2.1 ± 0.8 Endpoint: 1.8 ± 1.4	Inter-group differences: NS Within-group differences: AMT and laser ($p < 0.001$); Placebo ($p = 0.613$)	
	Fatigue (Likert 0–4) (mean ± SD)	Baseline: 2.9 ± 0.9 Endpoint: 2.5 ± 1.3	Baseline: 3.1 ± 0.8 Endpoint: 1.3 ± 1.1	Baseline: 3 ± 0.7 Endpoint: 2.3 ± 0.9	Inter-group differences: $p < 0.001$ for laser compared with AMT and to placebo Within-group differences: AMT ($p = 0.137$); laser ($p < 0.001$); Placebo ($p = 0.126$)	
	Number of patients reporting AE (%)	NR	NR	NR		
	Number of dropouts due to AE (%)	NR	NR	NR		
Gulec *et al.* (2007)		AMT (25–75 mg)	VFX (75 mg)			[48]
	Overall efficacy (FIQ) (mean ± SD)	Baseline: 56.4 ± 14.1 Endpoint: 43.4 ± 12.6	Baseline: 55.2 ± 13 Endpoint: 41.4 ± 13.6		Inter-group differences: NS Within-group differences: AMT ($p = 0.001$); VFX ($p = 0.001$)	
	Pain (VAS 0–10) (mean ± SD)	Baseline: 5.9 ± 1.9 Endpoint: 3.9 ± 2	Baseline: 5.9 ± 2 Endpoint: 3.7 ± 1.9		Inter-group differences: NS Within group differences: AMT ($p = 0.001$); VFX ($p = 0.001$)	
	Depression (BDI) (mean ± SD)	Baseline: 20.1 ± 10.5 Endpoint: 13.1 ± 9.8	Baseline: 19.3 ± 11.1 Endpoint: 11.5 ± 10.7		Inter-group differences: NS Within group differences: AMT ($p = 0.001$); VFX ($p = 0.001$)	
	Number of patients reporting AE (%)	NR	NR			
	Number of dropouts due to AE (%)	13 (46%)	6 (21%)			

AE: Adverse events; AI: Attention imagery; AMT: Amitripytiline; ANOVA: Analysis of variance; BDI: Beck depression inventory; BPI-s: Brief pain inventory-severity; CFT: Cardiovascular fitness training; C.I: Confidence interval; FIQ: Fibromyalgia impact questionnaire; Ga-As: Gallium arsenide; HDRS: Hamilton depression rating scale; MCS: Mental component summary of the SF-36; mg: Milligrams; NR: Not reported; NS: Non-significant differences; PCS: Physical component summary of the SF-36; PI: Pleasant imagery; PRX: Paroxetine; PSQI: Pittsburgh sleep quality index; QOL: Quality of life; SD: Standard deviation; SF-36: Short-form health survey; VAS: Visual analogue scale; XR: Extended release.

Table 4. Summary of results of randomized controlled trials comparing amitriptyline with other pharmacological interventions or with non-pharmacological interventions. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)		Statistical outcomes	Ref.
Konuk *et al.* (2010)		AMT (25–75 mg)	RBX (4–8 mg)		[49]
	Overall efficacy (FIQ) (mean ± SD)	Baseline: 47.6 ± 9.6 Endpoint: 28.5 ± 7	Baseline: 53.2 ± 8.2 Endpoint: 21.7 ± 3.7	Inter-group differences: $p < 0.05$ ANOVA: time-effect $p = 0.009$	
	Pain (VAS 0–10) (mean ± SD)	Baseline: 7.2 ± 1.7 Endpoint: 3.6 ± 1.2	Baseline: 8.1 ± 1.4 Endpoint: 3.3 ± 0.9	Inter-group differences : NS ANOVA: time-effect $p = 0.0001$	
	Depression (BDI) (mean ± SD)	Baseline: 11 ± 8.5 Endpoint: 4.8 ± 2.7	Baseline: 12.8 ± 3.7 Endpoint: 2.9 ± 1.9	Inter-group differences: NS Within-group differences: significant decrease with both drugs	
	Depression (HDRS) (mean ± SD)	Baseline: 17.4 ± 9.8 Endpoint: 7.5 ± 4	Baseline: 13.1 ± 6.3 Endpoint: 5.2 ± 2.3	Inter-group differences: NS Within-group differences: significant decrease with both drugs	
	Number of patients reporting AE (%)	NR	NR		
	Number of dropouts due to AE (%)	2 (18%)	2 (20%)		
Vlainich *et al.* (2011)		AMT (25 mg)	AMT/lidocaine (25 mg/4–8 mg)		[54]
	Pain (VAS 0–10) (mean ± SD)	Baseline: 7 ± 1.2 Endpoint: 4 ± 2.1	Baseline: 7.6 ± 0.8 Endpoint: 4.1 ± 2.3	Inter-group differences: NS Within-group differences: $p < 0.05$ in both groups	
	Number of patients reporting AE (%)	NR	NR		
	Number of dropouts due to AE (%)	NR	NR		
Calandre *et al.* (2014)		AMT (10–75 mg)	Quetiapine XR (50–300 mg)	Difference in mean change (80% C.I.) [P-value]	[51]
	Overall efficacy (FIQ) (mean change ± SD)	−13.9 ± 16.7	−9.8 ± 15.5	4.14 (−0.70, 8.98) [0.373]. Non-inferiority ($\delta = 8.0$) not shown	
	Pain (BPI-s) (mean change ± SD)	−1.2 ± 1.9	−1.2 ± 2.0	[0.620]	

AE: Adverse events; AI: Attention imagery; AMT: Amitripytiline; ANOVA: Analysis of variance; BDI: Beck depression inventory; BPI-s: Brief pain inventory-severity; CFT: Cardiovascular fitness training; C.I: Confidence interval; FIQ: Fibromyalgia impact questionnaire; Ga-As: Gallium arsenide; HDRS: Hamilton depression rating scale; MCS: Mental component summary of the SF-36; mg: Milligrams; NR: Not reported; NS: Non-significant differences; PCS: Physical component summary of the SF-36; PI: Pleasant imagery; PRX: Paroxetine; PSQI: Pittsburgh sleep quality index; QOL: Quality of life; SD: Standard deviation; SF-36: Short-form health survey; VAS: Visual analogue scale; XR: Extended release.

Table 4. Summary of results of randomized controlled trials comparing amitriptyline with other pharmacological interventions or with non-pharmacological interventions. (cont.).

Study (year)	Outcome measures	Drug groups (dose range/day)		Statistical outcomes	Ref.
	Depression (BDI) (mean change ± SD)	−4.2 ± 7.6	−2.1 ± 7.9	[0.250]	
	Sleep disturbance (PSQI) (mean change ± SD)	−3.8 ± 4.1	−3.9 ± 4.3	[0.624]	
	QOL (SF-36 PCS) (mean change ± SD)	0.9 ± 6.6	2.3 ± 7.3	[0.375]	
	QOL (SF-36 MCS) (mean change ± SD)	5.5 ± 11.7	5.3 ± 11.9	[0.940]	
	Number of patients reporting AE (%)	42 (93.3%)	45 (100%)		
	Number of dropouts due to AE (%)	3 (6.7%)	14 (31.1%)		

AE: Adverse events; AI: Attention imagery; AMT: Amitriptytiline; ANOVA: Analysis of variance; BDI: Beck depression inventory; BPI-s: Brief pain inventory-severity; CFT: Cardiovascular fitness training; C.I: Confidence interval; FIQ: Fibromyalgia impact questionnaire; Ga-As: Gallium arsenide; HDRS: Hamilton depression rating scale; MCS: Mental component summary of the SF-36; mg: Milligrams; NR: Not reported; NS: Non-significant differences; PCS: Physical component summary of the SF-36; PI: Pleasant imagery; PRX: Paroxetine; PSQI: Pittsburgh sleep quality index; QOL: Quality of life; SD: Standard deviation; SF-36: Short-form health survey; VAS: Visual analogue scale; XR: Extended release.

antipsychotic quetiapine [51]. Amitriptyline (25 mg/day) was superior to naproxen (500 mg b.i.d.) in the reduction of pain, fatigue, and sleep disturbance in a placebo-controlled trial [37]. Quetiapine (50–300 mg/day) was unable to demonstrate the non-inferiority to amitriptyline (10–75 mg/day) in terms of the reductions of the overall symptomatology, as measured by the FIQ [51].

Clinical studies comparing amitriptyline to non-pharmacological interventions

The design and results of the trials that compared amitriptyline with other non-pharmacological interventions are presented in Tables 3 & 4, respectively. The administration of a gallium-arsenide laser was superior to amitriptyline (10 mg/day) for the amelioration of pain and fatigue, but amitriptyline was superior to the laser therapy in the reduction of depressive symptoms [52]. Amitriptyline was superior to a vegetarian diet in the reduction of pain, the proportion of patients with fatigue, insomnia, and non-restorative sleep [53]. In a placebo-controlled trial (Tables 1 & 2), Amitriptyline (50 mg/day) was not different from an anti-diencephalon antibody (SER282) in reducing the core symptoms of fibromyalgia [40].

Combination studies

Amitriptyline has been evaluated in combination with other drugs and non-pharmacological interventions. In a placebo-controlled trial (Tables 1 & 2), the combination of amitriptyline (25 mg/day) with naproxen (500 mg b.i.d.) did not provide any additional benefit over amitriptyline alone [37]. In contrast, in a placebo-controlled trial, the combination of amitriptyline (25 mg/day) with fluoxetine (20 mg/day) was significantly better than either treatment alone in the improvement of overall symptomatology, both as evaluated with the FIQ and a patient global assessment, and pain and sleep measures [43]. Finally, in an active-controlled trial (Tables 3 & 4), the combination of amitriptyline (25 mg/day) with lidocaine (4–8 mg) was not significantly different than the administration of amitriptyline alone in the reduction of pain [54].

Cardiovascular fitness training in combination with amitriptyline (25 mg/day) was superior to either treatment alone in reducing several measures of pain, but overall pain, as measured with a visual analog scale was only improved in the combination group [55]. Fors *et al.* [56] randomized patients to receive a relaxation technique in combination with imagery methods. Patients were further randomized to receive amitriptyline (50 mg/day) or placebo. The use of amitriptyline did not add any additional benefit to the administration of the psychological intervention [56]. The design and detailed results of these two trials are summarized in Tables 3 & 4, respectively.

Tolerability and safety

The limited methodological quality of many of the clinical studies that examined amitriptyline use in fibromyalgia greatly influences evaluations of its tolerability and safety. The lack of a systematic approach in the collection and, especially, reporting of adverse events is notable in many of the placebo-

Table 5. Pooled tolerability data of eight placebo-controlled trials with amitriptyline for the treatment of fibromyalgia.

Studies[†]		Carette *et al.* (1986) [36]	Goldenberg *et al.* (1986)[‡] [37]	Scudds *et al.* (1989) [38]	Carette *et al.* (1994) [39]	Ginsberg *et al.* (1996) [42]	Goldenberg *et al.* (1996) [43]	Hannonen *et al.* (1998)[§] [44]	Heymann *et al.* (2001) [45]	
Adverse event	Groups	N								Total *(%)[¶]
	AMT	34	31	36	84	24	31	42	40	322
	PBO	36	16	36	42	22	31	45	40	268
Agitation	AMT	–	–	–	–	–	–	–	–	
	PBO	–	–	–	–	–	–	–	–	
	D/O AMT	1	–	–	–	–	–	–	–	1 (0.3)
	D/O PBO	0	–	–	–	–	–	–	–	0 (0)
Dizziness	AMT	–	–	–	Freq.	–	–	–	2	2/40 (5)
	PBO	–	–	–	Freq.	–	–	–	4	4/40 (10)
	D/O AMT	–	–	–	0	–	–	–	–	0 (0)
	D/O PBO	–	–	–	1	–	–	–	–	1 (0.4)
Drowsiness	AMT	Freq.	1	–	–	–	–	–	1	2/71 (2.8)
	PBO	Freq.	0	–	–	–	–	–	2	2/56 (3.6)
	D/O AMT	1	1	1	4	–	–	–	–	7 (2.2)
	D/O PBO	1	0	1	1	–	–	–	–	3 (1.1)
Headaches	AMT	–	–	–	–	–	–		0	0/40 (0)
	PBO	–	–	–	–	–	–	Freq.	2	2/40 (5)
	D/O AMT	–	1	–	–	–	–	–	–	1 (0.3)
	D/O PBO	–	0	–	–	–	–	–	–	0 (0)
Neuropsychiatric	AMT	–	–	–	–	2	–	–	–	2 (1.5)
	PBO	–	–	–	–	0	–	–	–	0 (0)
	D/O AMT	–	–	–	–	1	–	–	–	1 (0.3)
	D/O PBO	–	–	–	–	0	–	–	–	0 (0)

[†]Two studies, missing safety outcomes, were not included [40,41].
[‡]In the study conducted by Goldenberg *et al.* [37], 62 patients were equally randomized to four groups (the exact disposition of patients was not reported), as such we assumed that 31 patients were randomized to amitriptyline-containing groups and 16 patients randomized to placebo.
[§]One patient placed on AMT had serious AE of vasovagal collapse; hospitalized and D/C treatment.
[¶]The total number of patients used in the calculation of each adverse event frequency was pooled from the studies reporting the occurrence of the specific event; Scudds *et al.* [38] and Goldenberg *et al.* [43] clinical studies were not included in the calculation of the total frequency of patients reporting AEs due to missing data; the total number of patients used to calculate the percentage of drop outs due to each adverse event was pooled from all the clinical studies included in the table.
[#]Gastrointestinal manifestations encompassed: dyspepsia, constipation, diarrhea, nausea and abdominal and epigastric pain.
D/O: Dropouts; AMT: Amitriptyline; PBO: Placebo; AE: Adverse events; D/C: Discontinued; Freq.: Frequent adverse events with no specific frequencies being reported; N: Number of randomized patients; NR: Not reported.
–: Indicate the lack of any data being reported.

Table 5. Pooled tolerability data of eight placebo-controlled trials with amitriptyline for the treatment of fibromyalgia. (cont.).

Studies[†]		Carette *et al.* (1986) [36]	Goldenberg *et al.* (1986)[‡] [37]	Scudds *et al.* (1989) [38]	Carette *et al.* (1994) [39]	Ginsberg *et al.* (1996) [42]	Goldenberg *et al.* (1996) [43]	Hannonen *et al.* (1998)[§] [44]	Heymann *et al.* (2001) [45]	
Adverse event	Groups	N								Total *(%)[¶]
Vertigo	AMT	–	–	–	–	1	–	–	–	1/24 (4.1)
	PBO	–	–	–	–	0	–	–	–	0/22 (0)
	D/O AMT	–	–	–	–	–	–	–	–	
	D/O PBO	–	–	–	–	–	–	–	–	
Palpitations and dyspnea	AMT	–	–	–	–	–	–	–	0	0/40 (0)
	PBO	–	–	–	–	–	–	–	2	2/40 (5)
	D/O AMT	–	–	–	–	–	–	–	0	0 (0)
	D/O PBO	–	–	–	–	–	–	–	1	1 (0.4)
Ventricular arrhythmias	AMT	–	–	–	–	–	–	–	0	0/40 (0)
	PBO	–	–	–	–	–	–	–	1	1/40 (2.5)
	D/O AMT	–	–	–	–	–	–	–	0	0 (0)
	D/O PBO	–	–	–	–	–	–	–	1	1 (0.4)
Gastrointestinal[#]	AMT	–	0	–	Freq.	2	–	–	5	7/95 (7.3)
	PBO	–	2	–	Freq.	0	–	–	7	9/78 (11.5)
	D/O AMT	0	0	–	1	1	–	–		2 (0.6)
	D/O PBO	1	1	–	0	0	–	–		2 (0.7)
Dysgeusia	AMT	–	–	–	–	–	–	–	2	2/40 (5)
	PBO	–	–	–	–	–	–	–	1	1/40 (2.5)
	D/O AMT	–	–	–	–	–	–	–	–	
	D/O PBO	–	–	–	–	–	–	–	–	

[†]Two studies, missing safety outcomes, were not included [40,41].
[‡]In the study conducted by Goldenberg *et al.* [37], 62 patients were equally randomized to four groups (the exact disposition of patients was not reported), as such we assumed that 31 patients were randomized to amitriptyline-containing groups and 16 patients randomized to placebo.
[§]One patient placed on AMT had serious AE of vasovagal collapse; hospitalized and D/C treatment.
[¶]The total number of patients used in the calculation of each adverse event frequency was pooled from the studies reporting the occurrence of the specific event; Scudds *et al.* [38] and Goldenberg *et al.* [43] clinical studies were not included in the calculation of the total frequency of patients reporting AEs due to missing data; the total number of patients used to calculate the percentage of drop outs due to each adverse event was pooled from all the clinical studies included in the table.
[#]Gastrointestinal manifestations encompassed: dyspepsia, constipation, diarrhea, nausea and abdominal and epigastric pain.
D/O: Dropouts; AMT: Amitriptyline; PBO: Placebo; AE: Adverse events; D/C: Discontinued; Freq.: Frequent adverse events with no specific frequencies being reported; N: Number of randomized patients; NR: Not reported.
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Table 5. Pooled tolerability data of eight placebo-controlled trials with amitriptyline for the treatment of fibromyalgia. (cont.).

Studies[†]		Carette *et al.* (1986) [36]	Goldenberg *et al.* (1986)[‡] [37]	Scudds *et al.* (1989) [38]	Carette *et al.* (1994) [39]	Ginsberg *et al.* (1996) [42]	Goldenberg *et al.* (1996) [43]	Hannonen *et al.* (1998)[§] [44]	Heymann *et al.* (2001) [45]	
Adverse event	Groups	N								Total *(%)[¶]
Xerostomia	AMT	Freq.	4	–	Freq.	3	–	Freq.	4	11/95 (11.5)
	PBO	Freq.	0	–	Freq.	0	–	–	1	1/78 (1.3)
	D/O AMT	–	–	–	–	–	–	–	–	
	D/O PBO	–	–	–	–	–	–	–	–	
Rash	AMT	–	–	–	–	–	–	–	–	
	PBO	–	–	–	–	–	–	–	–	
	D/O AMT	–	–	–	1	–	–	–	–	1 (0.3)
	D/O PBO	–	–	–	0	–	–	–	–	0 (0)
Weight gain	AMT	–	–	–	Freq.	–	–	–	1	1/40 (2.5)
	PBO	–	–	–	Freq.	–	–	–	0	0/40 (0)
	D/O AMT	–	–	–	1	–	–	–	–	1 (0.3)
	D/O PBO	–	–	–	0	–	–	–	–	0 (0)
Total number of drop outs due to AE (%)	AMT	2 (5.8%)	1 (3.2%)	1 (2.8%)	5 (6%)	1 (4.1%)	3 (9.6%)	5 (12%)	0	18/322 (5.5%)
	PBO	2 (5.5%)	1 (6.25%)	1 (2.8%)	2 (4.8%)	0	1 (3.2%)	5 (11%)	2 (5%)	14/268 (5.2%)
Total number of patients reporting AE (%)	AMT	19 (55.8%)	4 (12.9%)	NR	80 (95%)	7 (29%)	NR	31 (74%)	16 (40%)	157/255 (61.5%)
	PBO	4 (11.1%)	2 (12.5%)	NR	26 (62%)	0	NR	36 (80%)	25 (62.5%)	93/201 (46.2%)

[†]Two studies, missing safety outcomes, were not included [40,41].
[‡]In the study conducted by Goldenberg *et al.* [37], 62 patients were equally randomized to four groups (the exact disposition of patients was not reported), as such we assumed that 31 patients were randomized to amitriptyline-containing groups and 16 patients randomized to placebo.
[§]One patient placed on AMT had serious AE of vasovagal collapse; hospitalized and D/C treatment.
[¶]The total number of patients used in the calculation of each adverse event frequency was pooled from the studies reporting the occurrence of the specific event; Scudds *et al.* [38] and Goldenberg *et al.* [43] clinical studies were not included in the calculation of the total frequency of patients reporting AEs due to missing data; the total number of patients used to calculate the percentage of drop outs due to each adverse event was pooled from all the clinical studies included in the table.
[#]Gastrointestinal manifestations encompassed: dyspepsia, constipation, diarrhea, nausea and abdominal and epigastric pain.
D/O: Dropouts; AMT: Amitriptyline; PBO: Placebo; AE: Adverse events; D/C: Discontinued; Freq.: Frequent adverse events with no specific frequencies being reported; N: Number of randomized patients; NR: Not reported.
–: Indicate the lack of any data being reported.

controlled studies and the studies that compared amitriptyline with other therapeutic interventions in fibromyalgia. Therefore, the information provided in this section should be considered cautiously.

Several clinical studies failed to report tolerability and/or safety outcomes. Two placebo-controlled studies [40,41] did not report the percentage of patients who experienced adverse events or dropout rates due to adverse events. Two placebo-controlled studies [38,43] only reported dropout rates due to adverse events without referring to the percentage of patients who reported adverse events. Five clinical studies that compared amitriptyline with other therapeutic interventions [47,52,54–56] failed to report any type of tolerability or safety parameters, and three studies [48,49,53] only reported dropout rates due to adverse events without revealing the total percentage of patients who experienced adverse events.

Table 5 shows the pooled data of tolerability and safety derived from eight placebo-controlled studies that reported some tolerability data. The total number of dropouts due to adverse events caused by amitriptyline ranged between 0 and 12% in the eight placebo controlled trials that reported this outcome, with a pooled dropout rate reaching 5.5% [36–39,42–45]. The corresponding figures for placebo were 0, 11 and 5.2%, respectively [36–39,42–45].

In six placebo-controlled trials reporting this information, the overall percentage of patients who experienced adverse events in amitriptyline-treated patients ranged between 13 and 95% with a pooled frequency of 62% [36,37,39,42,44,45]. The corresponding figures for placebo were 11 and 80% with a pooled percentage of 46%. The most commonly reported adverse events caused by amitriptyline in placebo-controlled trials included xerostomia, gastrointestinal manifestations, dizziness, and dysgeusia. Common adverse events in placebo-treated patients included gastrointestinal manifestations, dizziness, headaches, palpitations and dyspnea.

Concerning the safety of amitriptyline, the occurrence of serious adverse events was reported in only one placebo-controlled study in which one of the patients placed on amitriptyline therapy (25–37.5 mg/day) experienced vasovagal collapse that led to hospitalization and treatment discontinuation [44]. Calandre *et al.* [51] reported the influence of amitriptyline on vital signs (i.e., Electrocardiogram and blood pressure), and no relevant changes were reported.

Comparisons of amitriptyline to other therapeutic interventions demonstrated that the dropout rates in patients placed on amitriptyline therapy ranged between 0 and 46% [46,48,49,51,53]. Gulec *et al.* [48] reported the highest dropout rate due to adverse events of amitriptyline (46%). However, the specific adverse events that led to treatment withdrawal were not reported, and the average dose administered by patients who withdrew was not highlighted. This clinical study adopted a flexible dose of amitriptyline that ranged between 25 and 75 mg/day. Only two clinical studies [46,51] reported the percentage of patients who experienced adverse events following amitriptyline, and nearly equal figures were reported (93.1% in the former study and 93.3% in the latter study).

The general perception of poor tolerability of amitriptyline in fibromyalgia is not supported by concrete scientific evidence, despite the limited quality of many of the clinical studies that evaluated amitriptyline in fibromyalgia. Despite limitations, data suggest that amitriptyline is well tolerated because the pooled dropout rates due to adverse events caused by amitriptyline were comparable with placebo, and only a single case of a serious adverse event was reported. A recently published meta-analysis that evaluated the efficacy and safety of amitriptyline in fibromyalgia demonstrated that all-cause withdrawals rates were similar in amitriptyline and placebo groups (17 vs 22%, respectively; risk ratio: 0.77, 95% CI: 0.53–1.1), with similar withdrawal rates due to adverse events in both groups (8% in amitriptyline vs 9% in placebo; risk ratio: 1.03, 95% CI: 0.49–2.2) [31], which is consistent with our outcomes. In the latest meta-analysis of placebo-controlled trials of antidepressants for the treatment of fibromyalgia, Häuser *et al.* [57] reported a RR of dropouts due to adverse events for tricyclics of 0.84 (95% CI: 0.46, 1.52). Another meta-analysis that compared the efficacy and acceptability of amitriptyline, duloxetine and milnacipran in fibromyalgia demonstrated no significant differences in the acceptability (dropout rates) between the three drugs with an adjusted relative risk of dropouts for any cause of 0.77 (95% CI: 0.48, 1.25) for amitriptyline compared with duloxetine and 0.74 (95% CI: 0.47, 1.17) for amitriptyline compared with milnacipran [58].

Systematic reviews & meta-analyses

Several systematic reviews that included amitriptyline among the study drugs under evaluation for their use in fibromyalgia have been performed between 2008 and 2015 [31,57–62].

Nishishinya *et al.* [59]. identified 10 RCT that compared amitriptyline with placebo, but they found a substantial heterogeneity that precluded a meta-analysis. They found that amitriptyline 25 mg/day (six RCTs) in short-term trials was superior to placebo in improvements of pain, sleep, fatigue, and overall patient and investigator global impression. However, they could not reach any conclusion about drug tolerability because of inconsistencies in the data across studies. The quality of the trials was moderate-to-high according to the Jadad scale. The authors concluded that no definitive recommendation for the efficacy of amitriptyline could be made, but there was some evidence to support the efficacy of amitriptyline 25 mg for the short-term treatment of patients with FM.

A meta-analysis of antidepressants for the treatment of FM, published in 2008, included 13 RCTs with amitriptyline (25–50 mg/day) and found that the drug improved pain significantly, with a moderate effect size on fatigue, depressive symptoms, sleep disturbance, and quality of life [60]. No indirect comparisons with other antidepressants were performed. The quality of trials varied from study to study. One year later, the same group published another meta-analysis of placebo-controlled trials with antidepressants and found strong evidence

for the efficacy of amitriptyline (12.5–50 mg/day) in improving pain, fatigue, and sleep disturbances, all of them with a large effect size [61]. They also found a non-significant effect on depressive symptoms and a significant, but doubtfully relevant, effect on the quality of life. Three of the seven studies with amitriptyline were categorized as high quality using the Jadad scale, three studies were moderate, and one study was poor quality [61]. This research group subsequently performed an indirect comparison of amitriptyline, duloxetine, and milnacipran for fibromyalgia in 2011 [58] and found that the three drugs were superior to placebo, except duloxetine for fatigue, amitriptyline for quality of life, and milnacipran for sleep disturbance. In this indirect comparison, amitriptyline was superior to duloxetine and milnacipran in the improvement of pain, sleep disturbances, and limitations of quality of life. There were no significant differences in the acceptability of the drugs as evaluated with overall dropout rates [58].

In a systematic review of pharmacological treatment of fibromyalgia published in 2011, an indirect comparison found that amitriptyline was similar to duloxetine, milnacipran, and pregabalin on outcomes of pain and fatigue, with insufficient data to evaluate other outcomes [62]. Notably, pregabalin, duloxetine and milnacipran exhibited a significant increase in overall adverse events and withdrawals due to adverse events compared with placebo, but amitriptyline was no different than placebo in either outcome. However, there was insufficient evidence to draw any conclusion about the tolerability of amitriptyline compared with the other drugs [62].

In 2012, Hauser *et al.* [57] reported that tricyclics (nine RCTs with amitriptyline and two RCTs with other tricyclics) significantly improved pain, sleep, fatigue and quality of life, with moderate effect sizes on pain and sleep and small effect sizes for fatigue and quality of life in a recent systematic review of antidepressants for fibromyalgia. The NNT for a 30% reduction of pain compared with placebo was five for tricyclics. The relative risk of dropouts due to adverse events for triicyclics compared with placebo was 0.84 (95% CI: 0.46–1.52) [57]. These authors concluded that amitriptyline, duloxetine and milnacipran are first-line options in the treatment of fibromyalgia.

Finally, Moore *et al.* [31] in a meta-analysis published in 2015, evaluated the analgesic efficacy of amitriptyline for the treatment of fibromyalgia. They did not find data that met the current best standards of quality. Combining nine studies undertaken in 649 patients with fibromyalgia, they found that significantly more amitriptyline-treated patients (25–50 mg/day) achieved a 50% reduction of pain compared with placebo (36 vs 11%, respectively; risk ratio: 3, 95% CI: 1.7–4.9); NNT 4.1 (2.9–6.7; according to the authors, very low quality evidence) [31]. The authors did not find consistent differences between amitriptyline and placebo or active comparators in the improvement of fatigue, sleep disturbances or quality of life. More amitriptyline-treated patients experienced at least one adverse event (78 vs 47%; NNH 3.3; 95% CI: 2.5–4.9), but total and adverse event withdrawals were not different from placebo [31]. These authors concluded that amitriptyline is an option for the treatment of fibromyalgia, although only a minority of patients will obtain a substantial reduction of pain [31].

Other studies

In 2015, Kim *et al.* [63] used data from the claims of a US commercial health insurance plan and compared the health care utilization pattern of patients who initiated treatment with amitriptyline, duloxetine or gabapentin with patients who initiated treatment with pregabalin. The cohorts were matched with a propensity score for controlling confounding by indication, and amitriptyline, at a median initial dose of 25 mg/day, was associated with fewer hospitalizations and physical therapy visits during the 180 days follow-up than pregabalin initiators (median initial dose 75 mg/day). Notably, only 13.9% of the pregabalin initiators who remained on treatment increased the dose compared with 5.7% of patients who received amitriptyline. The patients were receiving a mean number of approximately 8.0 prescription drugs, which may explain the use of the low doses of pregabalin and the lack of an increase in dose in most patients. The authors used pregabalin as the reference drug, and they did not report any comparisons of amitriptyline with drugs other than pregabalin.

Fibromyalgia treatment guidelines

The role of amitriptyline in the treatment of fibromyalgia differs across clinical practice guidelines. The German guideline from 2008 states that amitriptyline should be the first step in the pharmacological treatment for this condition [64]. The EULAR guideline from 2008 includes amitriptyline with other antidepressants (e.g., fluoxetine, duloxetine, milnacipran, moclobemide, and pirlindole) as a recommended pharmacological treatment to reduce pain and improve function [65]. The Spanish guideline from 2010 recommends the following three alternatives in patients with moderate levels of depression and anxiety: a selective serotonin reuptake inhibitor and evaluate the possibility of combining it with low dose of amitriptyline, pregabalin, cyclobenzaprine, etc.; a serotonin reuptake inhibitor and its potential association with other drugs except tricyclics; and amitriptyline at antidepressant doses but assuming a greater risk of adverse reactions [66]. The Spanish guideline recommends a serotonin reuptake inhibitor in patients with high levels of depression and elevated values of catastrophism and notes that tricyclics have a similar efficacy, but they are associated with multiple side effects and drug interactions. The Canadian guideline of 2013 states that regular physical exercise is the best treatment option for the management of fibromyalgia, and it suggests that several pharmacological treatments (e.g., tricyclics, other antidepressants, gabapentinoids, dopaminergic agents, and sleep modifiers) may also be useful in some patients [67].

Expert commentary

Amitriptyline is more extensively studied for the treatment of fibromyalgia than other drugs. However, the quality of many of the trials performed with this drug is low to moderate,

mainly due to the fact that many of them were performed many years ago. An important concern is the small sample size of most trials, which increases the likelihood of random error and makes the interpretation of individual trials difficult. Fortunately, several systematic reviews with amitriptyline have been performed, which have helped overcome these difficulties. Another important issue is that tolerability was poorly reported in several early trials. However, data from placebo-controlled trials appear to indicate that amitriptyline effectively reduces pain, fatigue, and sleep disturbances. The results of several meta-analyses confirm these beneficial effects of amitriptyline and show that the effect on pain is clinically relevant because an NNT of 5 was found for a reduction of 30% in the pain intensity in a meta-analysis of studies performed in patients with fibromyalgia [57] and for a reduction of 50% in pain intensity in another meta-analysis of studies performed in patients with fibromyalgia or neuropathic pain [68]. The beneficial effect on sleep is also clinically relevant, as reflected by the moderate-to-large effect sizes found in some meta-analyses of placebo-controlled trials [57,58,61]. The clinical relevance of its effect on fatigue is unclear with meta-analyses showing effect sizes which were small [58], moderate [57], or large [61]. The effect on quality of life was investigated on only a few occasions, but the effect seems small [57,58,61]. Amitriptyline had no significant and/or relevant effect on depressive symptoms at the doses used in fibromyalgia trials.

There are no direct comparisons of amitriptyline with the drugs licensed for the treatment of this condition (i.e., pregabalin, duloxetine and milnacipran). However, two indirect treatment comparison meta-analyses suggest that amitriptyline is at least as effective as pregabalin, duloxetine, milnacipran in improving pain, fatigue and sleep [58,62].

Some experts stated that the tolerability of amitriptyline in patients with fibromyalgia may be an issue, especially when used at antidepressant doses [66]. However, amitriptyline, as detailed below, is not commonly used in fully antidepressants doses for the treatment of fibromyalgia nor in the treatment of other types of chronic pain. As mentioned above, tolerability was poorly reported in the RCTs with amitriptyline. However, the data presented herein and from systematic reviews show that the proportion of dropouts due to adverse events was generally low and did not differ from placebo [57,62], which suggests that this drug is not associated with relevant tolerability issues at the low doses that are used in patients with fibromyalgia. No serious adverse events were reported in amitriptyline-treated patients in the trials included in this review. Regarding contraindications and warnings, the package insert indicates that amitriptyline should not be used in patients under treatment with monoamine oxidase inhibitors and during the acute recovery phase after myocardial infarction. Amitriptyline should be used with caution in patients with cardiovascular disorders, in patients with history of seizures, urinary retention, angle-closure glaucoma or increased intraocular pressure, hyperthyroid patients or patients receiving thyroid medication, patients with elevated or lowered glycemia, and impaired liver function.

Regarding the dose, there are no dose–response trials with amitriptyline in this population; therefore, no definitive recommendations can be made regarding this issue. The data presented in this review suggest that higher doses are not associated with better treatment outcomes. However, doses up to 75 mg/day do not seem to be associated with an unacceptable proportion of dropouts due to adverse events. One study using 25–75 mg/day reported the highest dropout rate due to adverse events (46%), but the proportion of patients who dropped-out due to adverse events with amitriptyline (10–75 mg/day) was 6.7% in a larger study [51]. Doses of 100 mg/day were scarcely investigated. Overall, we suggest that amitriptyline may be used in a dose range of 10–75 mg/day, with an individual adjustment of the dose to the lowest effective dose. Treatment should be started using the lowest available dose and titrated up slowly, similarly to other drugs for the treatment of fibromyalgia, to improve tolerability.

What is wrong with amitriptyline? The major problem of amitriptyline for the treatment of fibromyalgia may be that the many of the RCTs were performed 15–20 years ago using quality standards that are different than currently applied RCT standards; in fact, several of the placebo-controlled trials were published before of the publication of the CONSORT statement in 1996 [69]. We agree with Moore *et al.* [31] who stated, "Amitriptyline has been a first-line treatment for fibromyalgia for many years. The fact that there is no supportive unbiased evidence for a beneficial effect is disappointing, but has to be balanced against years of successful treatment in many patients with fibromyalgia."

Overall, we agree with some clinical practice guidelines [64] and the opinion of some experts [12,70] that amitriptyline should be considered a first-line option for the pharmacological management of fibromyalgia. Moreover, in the current setting of budgetary restrictions of most, if not all, national health systems, we think that low doses of amitriptyline (10–75 mg/day) should be tried first in every patient who requires pharmacological treatment, with the exception of patients exhibiting any contraindication for its use. It is important to note, however, that despite its well-established use in the clinical practice setting and its inclusion as first-line drug in most of the clinical practice guidelines for the treatment of a number of chronic painful conditions, including neuropathic pain and fibromyalgia, neither fibromyalgia nor any other painful condition is included among the indications of amitriptyline in its package insert; therefore, the prescription of amitriptyline for fibromyalgia must be considered an off-label drug use.

Five-year view

There are some issues that would deserve further research with amitriptyline in the coming years.

First, although unlikely to be conducted, a direct randomized comparison with pregabalin, duloxetine, and/or milnacipran is needed to better position amitriptyline among these drugs. Interestingly, this comparison was performed in patients with diabetic neuropathy [71]. The study used a randomized,

double-blinded, placebo-controlled design to compare amitriptyline (50–75 mg/day), duloxetine (60–120 mg/day), and pregabalin (300–600 mg/day), and amitriptyline exhibited similar efficacy results as the other two drugs, and it showed at least a similar overall tolerability [71].

Second, the role of amitriptyline as a combination therapy should be further evaluated. The efficacy results of the placebo-controlled trial evaluating the combination of fluoxetine/amitriptyline and either drug alone are encouraging [43]. In fact, some experts actually recommend this combination as a possible second step when amitriptyline has failed [11]. Combination therapy for fibromyalgia has been only scarcely explored in clinical studies although careful planned polytherapy seems a sensible option for many patients [72]. Recent findings in the treatment of neuropathic pain have shown that polytherapy can be a worthy alternative [73–75]. When considering a suitable drug to combine with amitriptyline for the treatment of fibromyalgia, both the pharmacological profile of this drug and the knowledge of its benefits and shortcomings on fibromyalgia symptomatology must be considered to optimize the potential usefulness of the combination. Complementary mechanisms of action, lack of overlapping side effects, and efficacy against different fibromyalgia symptoms should be the ideal targets of the combination. In addition, drug–drug interactions may be an issue when combining antidepressants. Fluoxetine, paroxetine, and duloxetine are at least moderate inhibitors of CYP2D6, and fluoxetine also inhibits CYP3A4. As both isoenzymes are involved in the metabolism of amitriptyline, there is the potential for drug interactions, whereby the inhibition of the metabolism of amitriptyline could be associated with an increase of plasma levels of this drug and a greater risk of side effects. In the fluoxetine/amitriptyline combination trial, the highest number of dropouts due to adverse events was seen during the combination treatment period. Therefore, when combining amitriptyline with other antidepressants for the treatment of fibromyalgia, a careful dose-titration of amitriptyline should be exercised. It would be interesting to evaluate the combination of amitriptyline and pregabalin or gabapentin, which is an association with a lower risk of drug–drug interactions.

Finally, it would also be of interest to evaluate whether amitriptyline produces any additional relevant benefit in combination with exercise, cognitive behavioral therapy, or both.

Regardless of whether these studies are finally conducted, we believe amitriptyline, as part of a pharmacological armamentarium for the treatment of fibromyalgia, is here to stay for many years.

Financial & competing interests disclosure

F Rico-Villademoros has served as a freelance consultant for Almirall, AstraZeneca, Eli Lilly, GSK, Lundbeck, Pfizer, Roche and Sanofi-Aventis. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Key issues

- Fibromyalgia is a disabling and difficult to treat chronic painful condition.
- The management of fibromyalgia involves, in most patients, the combination of non-pharmacological and pharmacological interventions.
- Amitriptyline is an antidepressant with an unselective mechanism of action, responsible for its poor tolerability profile but also for its efficacy for the treatment of some chronic painful conditions.
- We reviewed 10 placebo-controlled pharmacological trials, 11 active-controlled trials or comparison with non-pharmacological interventions, seven systematic reviews, and four clinical practice guidelines involving the study of amitriptyline for the treatment of fibromyalgia.
- The quality of many of the randomized controlled trials with amitriptyline was low to moderate.
- Randomized clinical trials and systematic reviews indicate that, in patients with fibromyalgia, amitriptyline reduces pain and sleep disturbances to a clinically relevant extent.
- Despite the limited quality of data, they suggest that amitriptyline at low doses is not associated with major tolerability or safety issues.
- Overall, we think that amitriptyline at low doses (10–75 mg/day) should be considered a first-line option for the treatment of fibromyalgia.

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