

Postamputation Pain and Sensory Changes in Treatment-naïve Patients

Characteristics and Responses to Treatment with Tramadol, Amitriptyline, and Placebo

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Background: Pain after amputation is common but difficult to treat, and few controlled treatment studies exist.

Methods: In the current study, 94 treatment-naïve posttraumatic limb amputees with phantom pain (intensity: mean visual analog scale score [0–100], 40 [95% confidence interval, 38–41]) were randomly assigned to receive individually titrated doses of tramadol, placebo (double-blind comparison), or amitriptyline (open comparison) for 1 month. Nonresponders were crossed over to the alternative active treatment.

Results: After 1 month, phantom pain intensity was 1 (0–2) in the 48 tramadol responders (mean dose, 448 mg [95% confidence interval, 391–505 mg]), 0 (0–0) in the 40 amitriptyline responders (55 [50–59] mg), and 0 (0–0) in the 2 placebo responders, with similar effects on stump pain. Cytochrome P-450 2D6 slow metabolizers derived greater analgesia from tramadol and less from amitriptyline compared with fast metabolizers in the first treatment week ($P < 0.01$). Electrical pain thresholds increased and pain during suprathreshold stimulation decreased markedly on the stump and, to a lesser extent, on the contralateral limb after 1 month of treatment with amitriptyline or tramadol. Adverse effects were minor in all groups, but more common with tramadol.

Conclusions: In treatment-naïve patients, both amitriptyline and tramadol provided excellent and stable phantom limb and stump pain control with no major adverse events. Both drugs demonstrated consistent and large antinociceptive effects on both the stump and the intact limbs.

ABNORMAL sensory phenomena in amputated limbs are very common and can be divided into sensations or pain in the amputated limb (phantom sensation or pain) and pain in the amputation stump (stump or residual limb pain).¹ In addition, there is sometimes persistence of pain existing before amputation in the removed limb. Prevalence of phantom pain generally varies between 50 and 80%, with severe pain being reported in approximately 5% of patients.^{1–7} In a recent survey from Mozambique, the country in which the current study was also performed, 67% of 303 amputees reported pain in the posttraumatically amputated limb.⁸ This type of neuropathic pain usually develops within the first week of

amputation and is predominantly felt distally. Phantom sensations are present almost immediately in all amputees and range from sensations of a normal limb to changes in sensory quality, such as pressure, temperature, touch and anatomy (e.g., length, posture), and movement.¹ Stump pain, defined as localized and exacerbated by mechanical stimulation, predisposes to phantom pain and exists long term in approximately 25–60% of amputees.^{1–7}

Treatment of phantom pain has been attempted at all levels of pain transmission and perception: peripheral, spinal, and central. Medical treatment with membrane-stabilizing, antidepressant, and *N*-methyl-D-aspartate-antagonistic drugs, calcitonin, gabapentin, opioids, and clonidine has shown some success, but controlled studies in larger patient groups are sparse.^{1,9–30} Many patients are not offered any analgesic treatment because of misconceptions about the pain etiology.³ The aim of this randomized and placebo-controlled study was to assess the efficacy of tramadol and amitriptyline in the treatment of phantom limb pain. In addition, the effects on stump pain and on sensory thresholds were investigated. Tramadol has been shown to be effective and well tolerated in many other forms of pain, including neuropathic pain.^{31–36} Amitriptyline is a tricyclic antidepressant, which is a class of drugs with some efficacy in neuropathic pain, and is available in many less-developed countries, including Mozambique.³⁷

Materials and Methods

Amputees aged between 18 and 80 yr were prospectively included in this placebo-controlled, randomized, three-arm study (fig. 1). Recruitment was by word of mouth and the War Veterans Association. Inclusion criteria were presence of phantom limb pain (defined as pain in the amputated limb, not localized in the stump), with or without stump pain (localized in stump), with an average pain intensity of at least 30 on the 100-mm horizontal visual analog scale (VAS) during a 7-day observational run-in period before study enrolment. Only patients with posttraumatic amputations were enrolled. Main exclusion criteria were several successive limb amputations, pregnancy or breastfeeding, significant pain sources besides phantom and stump pain, use of centrally active medication (e.g., antidepressants, opioids, antiepileptics, monoamine oxidase inhibitors, long-

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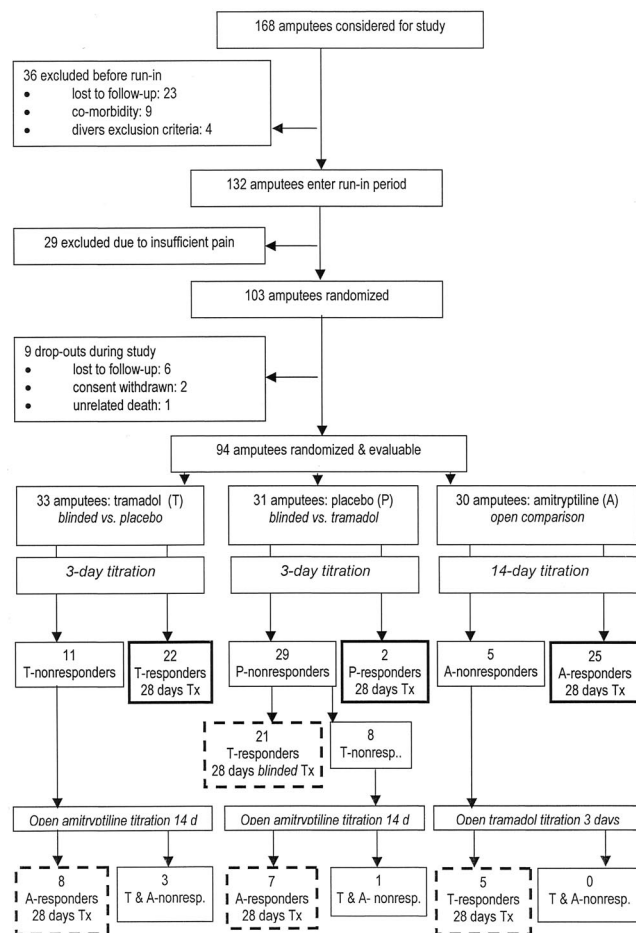


Fig. 1. Study flowchart. Responders are defined as those with a decrease of 10 mm or greater from baseline visual analog scale phantom limb pain scores on day 3 of dosing with tramadol or placebo (plus in addition no rescue tramadol on day 3 of dosing) and after 14 days of dosing with amitriptyline (in addition no need for rescue paracetamol on day 14 of dosing). Nonresponders were crossed over to the alternative active treatment [Tx], tramadol to amitriptyline or *vice versa*. Placebo nonresponders were switched to amitriptyline if they did not respond to tramadol rescue on day 3. If they responded to tramadol rescue, they continued on tramadol. See Materials and Methods section for a more detailed description of dose titration.

acting sedatives) within the past 2 weeks, inability to communicate adequately, and participation in another clinical trial within the past month. The protocol was approved by the Ethics Committee of the Medical Faculty of the University of Eduardo Mondlane in Maputo, Mozambique, and all patients gave their written informed consent. All documentation was provided in Portuguese, the common language in Mozambique.

Patients fulfilling the above criteria were randomized to one of three treatment groups, A, B, or C, using a computer-generated list. Group A received 100-mg slow-release tramadol tablets (Tramal retard[®]; Grünenthal GmbH, Aachen, Germany) taken twice daily at 7:30 AM and 7:30 PM. Group B received identical placebo tablets taken twice daily at 7:30 AM and 7:30 PM. In groups A and B, the first drug dose was given in the evening, and

twice-daily dosing began on the subsequent day. Tramadol solution (Tramal[®]; Grünenthal GmbH) was available in doses of 50 mg for rescue analgesia up to once every hour. Adaptation of the next day's regular 12-hourly dose was based on the previous day's rescue dose rounded downward to the nearest full-tablet dose. Medication in groups A and B was administered in a blinded fashion throughout the study. Group C was the open comparator arm and received unblinded 25-mg amitriptyline capsules (Saroten[®]; Lundbeck Pharma AS, Taastrup, Denmark) taken at 7:30 PM. Twenty-five milligrams was given in the evening for the first 2 days and increased to 50 mg on the third day. If pain scores did not decrease after 1 week, the evening dose was increased to 75 mg. Up to three 1,000-mg paracetamol (acetaminophen) tablets daily were available for rescue analgesia. After the 3rd (groups A and B) or 14th (group C) day of titration, an investigator not involved in the treatment or assessments determined the further treatment based on the last day's VAS pain scores and rescue drug use as follows:

- Group A (tramadol): Responders, defined as patients with a decrease of at least 10 mm in VAS phantom pain scores from baseline, were continued on blinded tramadol treatment until the end of the 1-month period. Nonresponders, defined as those with a decrease of less than 10 mm in VAS phantom pain scores from baseline, were switched to the open amitriptyline arm (group C) after a 3-day washout period.
- Group B (placebo): Responders (for definition, see group A in preceding paragraph; in addition, not requiring any rescue medication) were continued on blinded placebo treatment for 1 month. Patients fulfilling the definition of responders but requiring tramadol rescue were classified as tramadol responders and continued on the corresponding blinded dose of twice-daily tramadol for 1 month. Nonresponders, comprising patients whose VAS phantom pain scores did not decrease by more than 10 mm compared with baseline despite tramadol rescue, were switched to the amitriptyline arm (group C) after a 3-day washout period.
- Group C (amitriptyline): Responders (for definition, see group A; in addition, not requiring rescue medication) were continued on amitriptyline for 1 month. Nonresponders were switched to tramadol and dosed according to group A after a 7-day washout period.

All patients received 10 mg metoclopramide twice daily as an antiemetic on the first 3 days of dosing. Patients in all groups were followed up for 1 month of treatment.

The following variables were documented in a specific questionnaire before the start of the study: location, quality, and intensity of phantom and stump pain using descriptors, a body map, and a horizontal, anchored 100-mm VAS (0 = no pain, 100 = worst pain possible); the onset and duration of phantom and stump pain and

sensations; the frequency and intensity of involuntary phantom limb movements; pain before amputation; previous and current pain treatments; the date of and reason for amputation; any operative complications and reoperations; the type and use of prosthesis; and the effect of its use on pain.

During the run-in and 1-month treatment periods, the following variables were documented daily in a specific diary by the patient: phantom and stump pain intensities on the anchored 100-mm VAS at 7:30 AM and 7:30 PM; pain duration in hours; bowel and bladder function; limb prosthesis use; regular and rescue medication use and side effects, specifically nausea and emesis, sedation, and dizziness on a verbal rating scale of 0–3 (0 = not present, 1 = slight, 2 = moderate, 3 = severe). General change in functioning was assessed daily by the question “Today I could do more than yesterday: no, yes.” Before treatment global functioning (no handicap, slight handicap, major handicap, can do nothing) and quality of life (excellent, good, I get by, miserable) were assessed. After 1 month, pain in the fourth treatment week was retrospectively rated as gone, mild, moderate, severe, or unbearable, and quality of life and global functioning were rated as better than, equal to, or worse than before treatment. Electrical sensation (first sensation) and pain tolerance (point where patient terminates the stimulation due to a level of pain he or she is no longer willing to tolerate) thresholds (quantitative sensory testing [QST]) were measured in the area most sensitive to pressure pain on the stump and a similar location on the contralateral limb by slow ramp stimulation (0.2-mA/s increase at 100 Hz with a maximum current of 30 mA; Digistim 3 Plus[®]; Organon Teknika, Durham, NC) before and after 1 month of treatment. Suprathreshold nociceptive stimulation was performed at stimulation currents twice the individual pain tolerance threshold for 120 s, and pain intensity was rated by verbal rating scale (0 = none, 4 = severe).

As both amitriptyline and tramadol are metabolized *via* the polymorphic cytochrome P450 2D6 pathway, the patient’s metabolizer phenotype was assessed using 30 mg oral dextromethorphan as the substrate. Patients collected all urine for 12 h after ingestion of the substrate, and the metabolite dextrorphan was quantified in the urine by high-performance liquid chromatography.³⁸ Cytochrome P450 2D6 slow metabolizers were defined by a dextromethorphan/dextrorphan ratio of greater than 0.3. Neither patients nor investigators were aware of the metabolizer status results until after completion of the entire study.

Statistics

Primary Endpoints. Phantom limb pain intensity during the run-in period and on the last day of 1 month of treatment and the difference between these two time points were compared between treatments by analysis

of variance (Statistica Version 5.0; Statsoft, Tulsa, OK). *Post hoc* comparison of individual time points was performed using the Tukey honest significance difference test. A per-protocol analysis was performed, with patients switching from the ineffective treatment to the alternative active treatment.

Secondary Endpoints. All other variables were compared between groups by analysis of variance and the Tukey honest significance difference test (parametric) or Kruskal-Wallis analysis of variance followed by the Mann-Whitney U test (nonparametric) with a Bonferroni correction, as appropriate. Individual symptom scores were compared on treatment days 1, 7, 14, and 28. The Fisher exact test was used for comparison of group frequencies, and correlations were examined using a linear regression technique.

Power Calculation. A sample size of 25 patients was required to demonstrate a 10% unit reduction in pain intensity using the 100-mm VAS, assuming a mean (SD) pain intensity of at least 30 (± 15) in the run-in period, and α and β errors of 0.05 and 0.1, respectively (dependent, two-tailed testing). At least 90 patients were planned for inclusion in the study to ensure adequate power.

Data are shown as mean and 95% confidence interval or median with interquartile range. Statistical significance was assumed when *P* was less than 0.05.

Results

A total of 168 amputees were considered for participation, of whom 65 were excluded before randomization: 29 had insufficient pain in the run-in period, 23 did not appear for their run-in period, 9 were excluded because of significant comorbidity or other sources of chronic pain, and 4 had other exclusion criteria. There were 9 dropouts during the study: 8 withdrew consent unrelated to analgesic efficacy or toxicity or were lost to follow-up, and 1 died of unrelated causes. A total of 94 patients were therefore randomized (flowchart: fig. 1), 33 to receive tramadol, 30 to receive amitriptyline, and 31 to receive placebo. Patients’ characteristics are shown in table 1. The dominant limb had been amputated in 47 of the patients. None of the included patients had received any previous analgesic treatment.

Pain Intensity and Drug Doses

The numbers of patients responding to the initial treatments (a decrease in phantom pain VAS scores of at least 10 mm compared with baseline; see Materials and Methods section) were 25 with amitriptyline, with a mean dose after 1 month of 56 mg (95% confidence interval, 52–60 mg); 22 with tramadol, with a mean final dose of 523 (452–594) mg; and 2 with placebo. The time course of phantom pain intensity is shown in figure 2A. There

Table 1. Characteristics of Patients Randomly Assigned to Tramadol, Amitriptyline, or Placebo Treatment

	Tramadol (n = 33)	Amitriptyline (n = 30)	Placebo (n = 31)
Age, yr	41 (37–44)	34 (31–38)	37 (33–41)
Male/female	30/3	27/3	27/4
Weight, kg	64 (60–69)	60 (56–64)	60 (56–63)
Years since amputation	12 (10–14)	11 (7–15)	12 (8–16)
Amputated limb			
Right arm/left arm	1/2	1/1	1/1
Right leg/left leg/both legs	14/16/0	12/16/0	11/17/1
Phantom pain intensity before study*	46 (41–51)	46 (39–54)	49 (43–55)
Stump pain intensity before study*	47 (40–55)	44 (36–51)	45 (39–51)
Phantom sensation, yes/no	30/3	28/2	28/3
Phantom movement, yes/no	27/6	29/1	27/4
Quality of life			
Excellent/good/I get by/miserable	0/8/23/2	1/3/21/5	0/7/22/2
Global functioning			
No handicap/slight handicap/major handicap/cannot do anything	1/23/8/1	0/24/5/1	2/21/6/2

Data are presented as mean (95% confidence interval) or total numbers.

* Visual analog scale (0 = no pain, 100 = worst pain possible).

were no significant differences in pain scores between the initial responders groups by analysis of variance.

Five patients were nonresponders to amitriptyline with daily doses of 75 mg and were crossed over to tramadol treatment, to which all patients responded.

Phantom pain scores on the last day of amitriptyline titration were 32 (19–47) and decreased to 0 (0–0) after completion of the 1-month treatment with tramadol at a mean dose of 400 (248–552) mg (fig. 2B).

Eleven patients were nonresponders to tramadol at doses of 394 (212–576) mg and were switched to amitriptyline. Eight of these patients responded to amitriptyline at a mean dose of 53 (32–74) mg, and phantom pain scores decreased from 34 (26–43) on the last day of tramadol titration to 0 (0–0) at the end of the 1-month day treatment with amitriptyline (fig. 2B). The three remaining nonresponders to both active treatments had a mean phantom pain score of 35 after amitriptyline titration to 75 mg and median paracetamol rescue doses of 3 g daily.

Two of the 31 patients receiving placebo were responders. Their mean pain scores were 33 (18–44) before and 0 (0–0) after the 1-month dosing. Twenty-one of the patients were placebo nonresponders but responded to the tramadol rescue medication. Mean phantom pain scores at the end of titration were 20 (13–28), with tramadol rescue doses of 171 (138–205) mg. They were switched to regular tramadol treatment and had mean pain scores of 1 (0–3) on 381 (280–482) mg of tramadol after 1 month. The 8 patients with placebo who did not respond to tramadol rescue during titration were switched to amitriptyline treatment, to which 7 patients responded. Pain scores decreased from 37 (31–43) on the last day of placebo with tramadol rescue to 0 (0–0) after 1-month dosing with amitriptyline (mean dose, 50 [50–50] mg) (fig. 2B). The nonresponder to 75 mg amitriptyline had a pain score of 32 despite a daily rescue dose of 3 g paracetamol. No rescue doses were required in any group after day 14 of treatment.

Mean phantom limb and stump pain scores in all responders irrespective of initial response are shown in

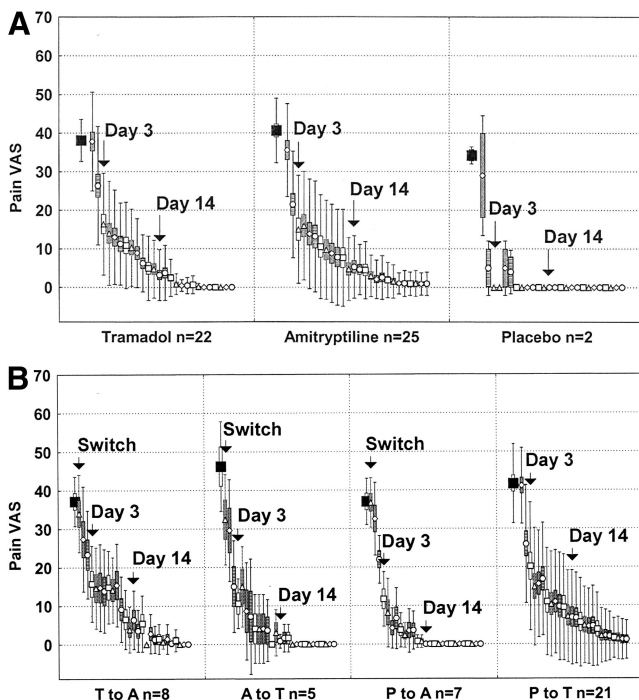


Fig. 2. Daily mean phantom limb pain intensity (95% confidence interval) by visual analog scale (VAS) score (0 = no pain, 100 = worst pain possible) at baseline (solid square) and during 28 days of treatment in responders to initial randomized treatment (A) and in nonresponders switching to alternative treatment after the titration phase (B). Highlighted are pain scores just before treatment switch, after 3 days and after 14 days of treatment. A to T = switch from amitriptyline to tramadol; P to A = switch from placebo to amitriptyline; P to T = switch from placebo to tramadol; T to A = switch from tramadol to amitriptyline. See Materials and Methods section for definitions of responders and treatments.

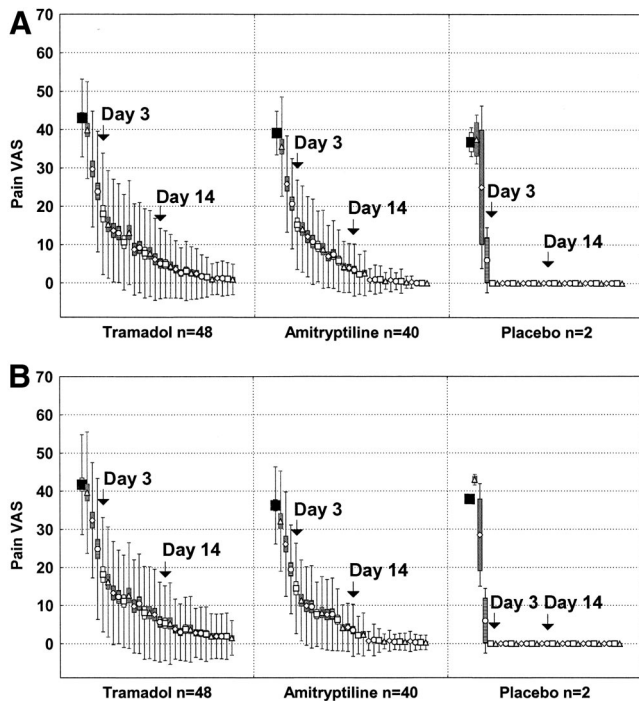


Fig. 3. Mean phantom limb pain (95% confidence interval) (A) and stump pain intensity (visual analog scale [VAS] score [0 = no pain, 100 = worst pain possible]) (B) at baseline and during 28 days of treatment in final responder groups. Pain scores after 3 and 14 days of treatment are highlighted.

figure 3. The mean changes from baseline in phantom limb and stump pain scores after 1 month of treatment are shown in table 2. There were no significant differences in baseline intensities of phantom or stump pain or in changes from baseline at any time between the treatment groups. Phantom and stump pain scores were significantly lower at the end of the 1-month treatment period compared with pretreatment in all groups ($P < 0.0001$). After 6 days of treatment, 50% of the patients in the tramadol and amitriptyline responder groups had phantom pain intensities below 10 mm on the VAS. This threshold was reached in 83% of both groups by day 15 and in 96% and 100% of patients with tramadol and amitriptyline by day 28, respectively. Both placebo responders had pain scores below 10 mm on the VAS by the third day of blinded treatment. There were no significant group differences in any pretreatment variables between tramadol and amitriptyline nonresponders or

between responders and nonresponders in each treatment group.

Pain Duration and Characteristics

The median phantom and stump pain duration changed from “intermittent and long” during the run-in to “no pain” in all groups in the last week of treatment. Phantom pain was described as pins (26%), throbbing (24%), burning (16%), cramps (8%), pressure (7%), cutting (2%), and combinations of these (17%). Pain was worsened by change in temperature (71%) and pressure (1%). Phantom sensations reported in patients were none (6%), hypersensitive (48%), itching (18%), electrical/pins (11%), and combinations of these (17%). Stump pain existed in all patients and was described as pin-pricks (24%), throbbing (19%), burning (13%), pressure (6%), cramps (5%), cutting (5%), and combinations of these (27%). Stump sensations reported were none (7%), itching (27%), numb (21%), electrical/pins (11%), hypersensitive (3%), burning (1%), and combinations of these (30%).

Correlations between Phantom and Stump Characteristics

Pain or sensory characteristics and the reduction in pain scores showed no relevant correlation. Pretreatment phantom and stump pain intensities, as well as their characteristics, correlated significantly ($r = 0.66$, $P < 0.0001$ and $r = 0.60$, $P < 0.0002$, respectively).

Quantitative Sensory Testing

Sensation Thresholds. Electrical sensation thresholds on the stump increased significantly after 1 month of treatment with amitriptyline ($P = 0.002$), but not on the contralateral side ($P = 0.06$) or with tramadol or placebo (fig. 4A).

Pain Tolerance Thresholds. Thresholds increased on the stump and contralaterally after 1 month of treatment with tramadol ($P = 0.0001$ and $P = 0.03$, respectively) and amitriptyline ($P = 0.0001$ and $P = 0.0006$, respectively). In both groups, the increases were greater on the stump than contralaterally ($P < 0.001$) (fig. 4B). Trends were similar in the placebo responder group. The mean absolute differences in pain tolerance thresholds before to after 1 month of tramadol, amitriptyline, or placebo were 4.8 (3.3–6.2), 5.2 (2.7–7.6), and 5 (–32

Table 2. Changes from Pretreatment Baseline in Phantom Limb and Stump Pain after 1 Month of Treatment in Final Responder Groups

	Tramadol (n = 48)	Amitriptyline (n = 40)	Placebo (n = 2)
Δ Phantom pain*	–40 (–43 to –38)	–38 (–39 to –36)	–34 (–54 to –14)
Δ Stump pain*	–38 (–40 to –35)	–35 (–38 to –32)	–39 (–66 to –12)

Data are presented as mean (95% confidence interval). Pain intensity was measured by visual analog scale (0 = no pain, 100 = worst pain possible). No significant differences between treatment groups were observed.

* Baseline minus after 1 month; negative value denotes decreased pain score after 1 month.

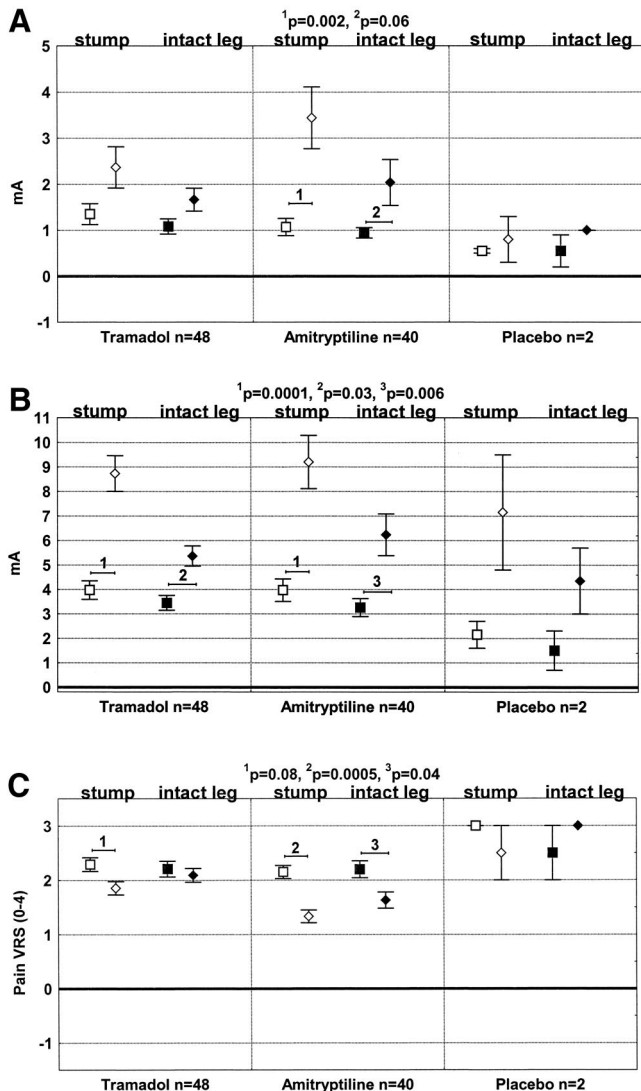


Fig. 4. Sensation (A) and pain tolerance (B) electrical thresholds and pain during suprathreshold stimulation (C) on stump and contralateral limb before (squares) and after 28 days of treatment (diamonds) in final tramadol, amitriptyline, and placebo responders. Data are shown as means (95% confidence interval). VRS = verbal rating scale.

to 42) mA on the stump and 1.9 (1.2–2.7), 3.0 (1.1–5.0), and 2.9 (–4 to 10) mA contralaterally, respectively.

Suprathreshold Stimulation. Mean pain ratings during suprathreshold electrical stimulation decreased during amitriptyline treatment on the stump ($P = 0.0005$) and contralaterally ($P = 0.04$). There was a trend to diminished stump pain ratings with tramadol ($P = 0.08$) (fig. 4C).

Correlations between QST and Pain

Pretreatment pain tolerance thresholds correlated inversely with changes in pain tolerance thresholds from baseline after 28 days of treatment both on the stump and contralaterally (both $R = -0.34$, $P = 0.001$), *i.e.*, patients with high pretreatment thresholds showed a small posttreatment increase in thresholds, whereas

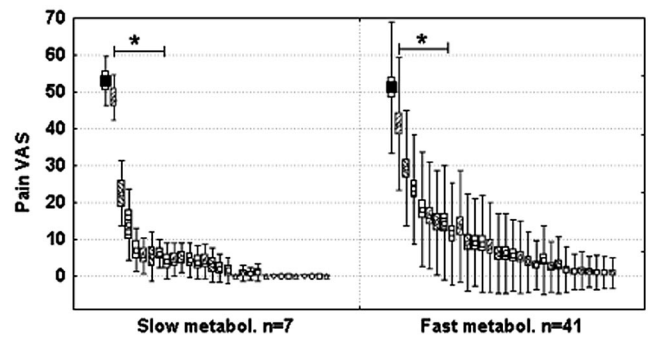


Fig. 5. Mean phantom limb pain (95% confidence interval) and stump pain intensity (visual analog scale [VAS] score [0 = no pain, 100 = worst pain possible]) at baseline and during 28 days of treatment in slow and fast cytochrome P450 2D6 metabolizers receiving tramadol. * $P < 0.01$ fast versus slow metabolizers in first week by analysis of variance between groups (analysis of variance).

those with low baseline thresholds demonstrated a large increase with treatment. Pretreatment suprathreshold pain ratings during electrical stimulation also correlated inversely and closely with the change from baseline in these pain ratings after 28 days treatment on the stump ($R = -0.66$, $P < 0.00001$) and contralaterally ($R = -0.62$, $P < 0.00001$).

Further Parameters

Influence of Amputated Limb Dominance. Phantom limb pain was higher in an amputated dominant limb at baseline (mean [95% confidence interval], dominant: 43 [39–48], nondominant: 34 [30–39]; $P = 0.03$), and the decrease in phantom limb pain intensity was greater (dominant: -42 [–45 to –41], nondominant: -39 [–42 to –36]; $P = 0.03$) when compared with nondominant limb amputations, with no differences in stump pain. In addition, pain intensity during suprathreshold stimulation on the stump, but not contralaterally, was higher in amputees of the dominant limb (2.4 [2.2–2.7]) compared with the nondominant limb (2.0 [1.8–2.2]; $P = 0.03$).

Influence of Cytochrome P450 2D6 Metabolizer Phenotype. Slow (poor) metabolizer phenotype for cytochrome P450 2D6 was present in 14% of patients who received tramadol, 5% who received amitriptyline, and none who received placebo. With amitriptyline, phantom and stump pain intensity scores in slow (poor) metabolizers were significantly greater than in fast (extensive) metabolizers during the first week of treatment ($P < 0.01$) but not during later weeks or at baseline. Respective average daily doses were 50 (50–50) and 54 (49–54) mg. Slow metabolizers given tramadol demonstrated lower phantom and stump pain scores in the first week of treatment but not later or at baseline ($P < 0.01$; fig. 5). Respective average tramadol doses on day 28 were 383 (215–551) and 445 (377–513) mg (not significant). There were no significant differences in the inci-

Table 3. Patients with Adverse Effects during the Dose-titration and Steady-dose Treatment Phases with Tramadol, Amitriptyline, and Placebo

Adverse Effect	Tramadol (n = 48)		Amitriptyline (n = 40)		Placebo (n = 2)	
	Titration	Treatment	Titration	Treatment	Titration	Treatment
Nausea	18 (38%)	16* (33%)	7 (18%)	1 (3%)	1	1
Vomiting	13* (27%)	7* (15%)	1 (3%)	0	1	1
Tiredness	32 (67%)	29* (60%)	22 (55%)	7 (18%)	1	1
Dizziness	21* (44%)	19* (40%)	9 (23%)	6 (15%)	0	1
Constipation	5 (10%)	17* (35%)	6 (15%)	4 (10%)	0	1
Headache	5 (10%)	21* (44%)	4 (10%)	6 (15%)	1	1
Difficult micturition	2 (4%)	4 (8%)	0	0	0	0
Itching	4 (8%)	3 (6%)	0	0	0	1
Other	7 (15%)	25* (52%)	10 (25%)	10 (25%)	1	1

Data are presented as number (%).

* Tramadol vs. amitriptyline, $P < 0.05$.

dence of side effects or in QST between the metabolizer groups for either active treatment.

Gastrointestinal Function. The average number of daily bowel motions before and after 4 weeks of treatment were 0.7 (0.6–0.8) and 0.5 (0.4–0.6) with tramadol ($P = 0.002$), 0.6 (0.5–0.7) and 0.7 (0.6–0.7) with amitriptyline (not significant), and 0.4 and 0.7 in the two placebo responders, respectively. Laxatives were required by one patient in the tramadol group and by none in the other groups.

Use of Prosthesis. There were no significant differences within or between groups regarding use of prosthesis (data not shown).

Daily Functioning Score. With tramadol and amitriptyline, the median response to the global functioning question “Today I can do more than yesterday” changed from no to yes on treatment day 5 and remained yes until day 28. In the two placebo patients, the response changed to yes on day 4.

Final Evaluations. Retrospective analysis showed that pain in the final week was gone, mild, moderate, severe, or unbearable in 45, 3, 0, 0, and 0 patients receiving tramadol; in 40, 0, 0, 0, and 0 patients receiving amitriptyline; and in 2, 0, 0, 0, and 0 patients receiving placebo, respectively. All patients in all groups rated their global function and quality of life as significantly better than before treatment. The quality of pain control was globally rated as excellent, good, or poor after 1 month of treatment by 30, 18, and 0 patients receiving tramadol; by 30, 9, and 0 patients receiving amitriptyline; and by 2, 0, and 0 patients receiving placebo, respectively.

Side Effects. Fifty-six percent of patients receiving tramadol, 54% receiving amitriptyline, and 50% receiving placebo recorded side effects. Individual side effects in responders are listed in table 3. The incidence of side effects in patients not responding to the initial treatment and switching to the alternative drug was similar to those in the initial responders: 48% with tramadol, 45% with amitriptyline, and 40% with placebo. Central side

effects (nausea, vomiting, tiredness, or dizziness) were documented in nonresponders in 55% of the tramadol group, in 48% of the amitriptyline group, and in 38% of the placebo group. This was not significantly different to the incidence in the responder groups (table 3). No patients dropped out because of side effects, and no serious adverse events occurred.

Discussion

This randomized study demonstrated considerable effectiveness of tramadol and amitriptyline in the treatment of long-standing phantom limb and stump pain. Limb pain was almost completely inhibited after initial treatment in 67% of those receiving tramadol, in 83% of those receiving amitriptyline, and in only 3% of those receiving placebo. In the remaining initial nonresponders, similarly good pain relief was achieved after switching to the alternative analgesic. With tramadol or amitriptyline, pain was slight or less in 50% of patients after 7 days and in more than 80% of patients after 14 days of treatment, and no rescue medication was required after this time. Both drugs were well tolerated. Adverse effects were generally mild, somewhat more common with tramadol, and did not lead to treatment discontinuation in any case.

Postamputation phantom and stump pain are generally difficult to treat and are frequently undertreated.^{39,40} Most therapeutic trials have been performed in small, heterogeneous, and heavily selected patient groups, which are often biased toward multimorbid patients not responding to common analgesics. The interventional studies are frequently of short duration and inadequately controlled. The favorable response in the current comparatively large study compared with most previous studies may be explained by the patients' characteristics. The patients in the current trial were treatment naive, otherwise physically healthy, young war veterans with no chronic limb pain before amputation. All amputations

were performed because of trauma. Because there were only two placebo responders in this study, the analgesic effects are robust and cannot be explained by unspecific mechanisms. Unblinding of the active drug as a result of adverse events can occur with centrally active drugs, but this is unlikely to have been a major confounding factor because the side effects reported in the nonresponders in the placebo group were similar to those in the other treatment groups. Both tramadol and amitriptyline have previously been shown to be effective in the treatment of other types of neuropathic pain.^{34,36,37,40-43}

The average daily drug doses after 1 month of treatment were 523 mg tramadol and 56 mg amitriptyline. Nonresponders to either drug did not require higher doses of the alternative drug after switching than first-round responders, implying varying individual sensitivities to different modes of analgesic action. Therefore, in the case of nonresponse to one medication, rotation to the other can be recommended. No baseline characteristics were predictive for nonresponsiveness to either drug. The doses of tramadol required were higher in the current study than in others with diverse types of neuropathic pain, in which an upper limit of 400 mg daily was often observed. We find no other reports of tramadol use in phantom limb pain, and the safe and efficacious results support the use of these higher, individually titrated doses. Even higher doses have been successfully used in other forms of severe pain.³⁶ The amitriptyline dose corresponds to current clinical recommendations and demonstrated rapid onset of effect.^{37,44} There were no signs of drug tolerance within 1 month of treatment, as demonstrated by the stable daily doses and pain scores. Robinson *et al.*²⁷ recently reported a trial comparing amitriptyline and benzotropine mesylate, a central anticholinergic antiparkinson drug combining the effects of atropine and diphenhydramine, as an active placebo. No significant difference in pain intensity was shown between the two treatments after 6 weeks in tertiary care patients. Differences to the current study may be explained by patient characteristics as well as the choice of active placebo.

Interestingly, we showed that amputation of the dominant limb resulted in greater baseline phantom limb pain, but not stump pain, and in higher pain intensity during suprathreshold electrical stimulation on the stump compared with amputation of the nondominant limb. The decrease in pain intensity during treatment, however, was also larger, resulting in similar overall pain control independent of limb dominance. Central nervous system reorganization in response to amputation may be asymmetrical and dependent on hemispheric dominance. Increased use of the prosthesis on the dominant side with subsequent effects on pain was not seen and can be ruled out as an explanation.

Approximately half of the patients with either active treatment experienced minor adverse effects. More mi-

nor adverse events were seen with tramadol than with amitriptyline, of which gastrointestinal and central nervous system listings were most common and significant. In previous studies, tramadol has been shown to affect upper and lower gastrointestinal motility significantly less than other opioids, while providing similar analgesia.³⁶

Amitriptyline and tramadol are partly metabolized *via* the cytochrome P450 2D6 pathway, which underlies genetic polymorphism. The few slow metabolizers receiving amitriptyline had significantly slower phantom and stump pain relief than fast metabolizers, probably because of the analgesic potency of nortriptyline, the major active metabolite of amitriptyline.⁴⁵ The trend to less pain despite lower tramadol doses in slow metabolizers indicates the importance of the monoaminergic + and - enantiomers of tramadol in complementing the analgesic action of the opioidergic M1 metabolite in neuropathic pain.³⁴

Quantitative sensory testing revealed a consistent picture of enhanced and powerful antinociception on the stump and a lesser but nonetheless clear effect on the contralateral side. Amitriptyline produced a more profound effect than tramadol. We were unable to investigate whether the patients were allodynic or hyperalgesic on their limbs before treatment, because preamputation data or matched controls with intact limbs were not included in this trial. However, in a prospective study in patients with limb amputations for mainly vascular reasons, most patients demonstrated sensitization in the form of allodynia, hyperalgesia, and "wind-up" pain within 6 months after amputation.⁴⁶ Allodynia and hyperalgesia at a site distant to the site of injury are considered evidence of central (secondary) sensitization, whereas hyperalgesia at the site of injury is due to peripheral (primary) sensitization, both of which develop after limb amputation.^{1,4,24} In the current study, sensitization was assessed by using phasic threshold and tonic suprathreshold electrical stimulation, because the former is more selective for A- δ and the latter is more selective for C nerve fiber effects. As opposed to an acute postoperative pain model, where mainly phasic thresholds were affected, in the current chronic pain setting, analgesia and antinociception were reflected in changes in both phasic and tonic stimulation parameters.^{47,48} Opioids, such as morphine and tramadol, and tricyclic antidepressants have been shown to increase pain thresholds in nonoperative settings and to reduce postoperative sensitization, especially secondary hyperalgesia and allodynia.^{35,48-54} The desensitizing effects after 1 month of treatment with both amitriptyline and tramadol were large on the amputated side and exceeded those contralaterally very significantly. This presumably reflects differential pharmacologic responsiveness of primary and secondary sensitization, which has been demonstrated for opioids and *N*-methyl-D-aspartate antagonists, among other agents. Patients' ratings of

stump and phantom pain intensity did not demonstrate a differential response, either in this study or in a previous study with morphine.²⁸ The lack of correlation between QST and clinical pain scoring indicates that the two measures reflect different aspects of the pain process, as has been shown previously for phantom limb pain and pressure pain thresholds after 6 months.⁵⁵ Pretreatment sensation, pain tolerance, and suprathreshold stimulation pain ratings on both the stump and the contralateral limb correlated significantly and inversely with their respective changes from baseline after 1 month of treatment, as has been previously described in the postoperative setting.⁴⁸ This may indicate different sensory response patterns to analgesics in individuals with high *versus* low baseline sensory thresholds: Patients with low pretreatment thresholds have a large increase in threshold during treatment, whereas those with high baseline thresholds have a small increase. A host of endogenous genetic factors may be implicated in the control of nociception.⁵⁶

This study has several potential limitations. First, we were unable to perform all three arms of the study double blind because of the different pharmacologic properties of amitriptyline and tramadol and the difficulty of performing a double-dummy study in the chosen setting. Blinding in the other two arms throughout the entire treatment period was maintained for the patient and the treating investigators by ensuring that an uninvolved third party made treatment decisions after the titration period. Second, the definition of response as a decrease in pain intensity of at least 10 mm on the VAS was lower than the 20 mm used in several previous studies. The lower threshold for response was chosen to compensate for a relatively short time to response evaluation. *Post hoc* analysis showed that the pain intensity change at the end of 1 month of treatment was similar in patients with a posttitration decrease in pain VAS between 10 and 20 mm and in those with a decrease of more than 20 mm. If the threshold of 20 mm had been chosen in this study, a substantial number of responders would have been incorrectly classified as nonresponders. Third, because there were only two placebo responders, formal statistical analysis of this small group was unreasonable. Last, the good correlation between stump and phantom limb pain intensities may be either a true phenomenon or due to inadequate distinction by patients despite repeated explanatory attempts to encourage differentiation. The application of these results to the commonly studied Western populations should be performed with caution because of the differences in patient characteristics outlined above and possible additional cultural factors affecting reporting.

In summary, in treatment-naïve patients, both amitriptyline and tramadol provided excellent and stable phantom limb and stump pain control, with no major adverse events. QST demonstrated consistent and large antinoci-

ceptive effects of both drugs on both the stump and intact limbs.

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