obtained from the scans will be independently reviewed and compared in order to evaluate the reproducibility of the micro-MRA technique. The study has been approved by the local institutional review board (IRB) and informed consents have been obtained from all participants. Based on our preliminary results on four healthy volunteers (all females, mean ± s.d. age 53.3 ± 8.2 yrs) and one primary Raynaud’s subject (female, age 55 yrs), the reproducibility of all three measurements is consistent. The Pearson’s correlations for both digital artery area and number of veins measurements are 0.99 and Cohen’s-k of the vascular score measurement is 0.69. The Bland–Altman plot for the vascular area measurement is shown in Fig. 1.

We also agree that environmental factors are key issues which may influence scanning measurement results. All the scans described in the original study were conducted in the same environment. The scanning room has a constant temperature of 24°C controlled by a thermostat. In the discussion and planning of the original experiments, temperature control came up often. We did our best to ensure that the scanning suite would be comfortable for the SSc patients, who had to remain motionless for relatively long periods. We agree that the understanding of vascular response to temperature change is clinically meaningful. A follow-up investigation into the role of temperature in digital vasculature is planned and will be conducted in the near future for a better understanding of this issue.

In terms of the vasospasm status in early and evolving pre-SSc subjects discussed by Dr McKay et al. [1], we would like to point out that significant differences were found for both early and long-term patients when compared with their matched controls. This indicated that clinically meaningful morphological differences can be visualized and quantified by the micro-MRA technique, despite the vasospastic status of each SSc subject. The original study was performed in order to learn the feasibility of using the micro-MRA technique to study SSc disease, rather than to explore the physiological and pathological background of the observed results.

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Fig. 1. Bland–Altman plot of the difference vs the mean of the digital artery lumen area obtained in the same subject at two time points. TP1 and TP2 are measurements obtained at time point 1 and time point 2, respectively.

Sir, The reviews of Perrot et al. [1] and Nishishinya et al. [2] brought new information about the usefulness of anti-depressants in rheumatic conditions, especially fibromyalgia syndrome (FMS). Many publications have recently emphasized the well-known association between old and newer anti-depressants and chronic pain relief [3–5]. For a long time, debate has existed upon how anti-depressants alleviate symptoms in chronic pain patients. Are they truly analgesic, or is their effect on higher cognitive pain-associative phenomena? Data from clinical and basic research have corroborated the first option: drugs that inhibit reuptake of catecholamines (noradrenaline and serotonin, sometimes dopamine) may have indeed an analgesic effect [5–8]. While the Perrot et al. and Nishishinya et al. data seem discordant, one must take care in drawing any analysis. Recently, the issues of long-term efficacy and tolerability have surfaced as critical when judging anti-depressant effectiveness as a whole and as analgesic drugs [9, 10]. Although previous data supported the indication of tricyclic anti-depressants (TCAs) as front-line pharmacological treatment for FMS, there was little information about the duration of its effect and tolerability issues seemed to be a major drawback [1, 5]. The review of Nishishinya, coupled with the recent clinical results of newer anti-depressants in FMS and neuropathic pain [4, 6], indicates that it is time to change the primary pharmacological indication for anti-depressants as analgesics from TCA to the serotonin and noradrenergic reuptake inhibitor (SNRI) class. This opinion is also supported by the Perrot review. This field is growing rapidly, and newer drugs are being developed that show better analgesic effect, exploring the same mechanism of anti-depressants: catecholamine reuptake inhibition. Particularly, it has recently been demonstrated that a triple reuptake inhibition mechanism may lead to more potent analgesic effect [11]. What may we conclude from this?

(i) Anti-depressants are good analgesics in selected chronic pain disorders. Their analgesic effect is not associated with their anti-depressant effect, but depends also on their catecholamine reuptake inhibition properties.

(ii) There were recently reported caveats of tolerability and long-term efficacy for anti-depressants in general, and in their use for relief of chronic pain. Therefore, one must carefully design and analyse clinical trials of chronic pain drugs for inclusion of these as primary or secondary end-points.

(iii) The recommended front-line anti-depressants for FMS treatment must be SNRI in the place of TCA. The use of the latter may even be discouraged in the face of its lack of long-term efficacy and excess of adverse events.

(iv) As a pharmacological group, anti-depressants are frequently used as treatment for chronic pain in various diseases, although there is little evidence for many of these uses.


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Comment on: Is there any evidence to support the use of anti-depressants in painful rheumatological conditions?

Systematic review of pharmacological and clinical studies & Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy
It would probably be better to develop newer drugs that have the mechanism of action of the anti-depressants in nociception but lack any effect in mood (and, therefore, have less side-effects).

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**Comment on:** Is there any evidence to support the use of anti-depressants in painful rheumatological conditions?

Systematic review of pharmacological and clinical studies; reply

Sir, We thank Dr Fontenele and colleagues [1] for their interesting comments on our recent article [2] and on a recent review on amitriptyline [3]. In fact, our results were in accordance with those reported by Nishishinya and colleagues [3] and our conclusions are also consistent with those of another recent review on anti-depressants in fibromyalgia (FMS) [4]. We confirm that amitriptyline demonstrates analgesic effects at low doses (25–50 mg) in FMS, without any improvement of these effects at higher doses, and no dose-related effects. However, there are no published trials comparing tricyclic anti-depressants (TCAs) and newer anti-depressants like serotonin and norepinephrine reuptake inhibitors (SNRIs). Most trials on amitriptyline in FMS are not as long as trials with SNRIs, with the exception of that reported by Carette et al. [5], and the methodological quality of the trials is weaker, as studies are not so recent. Other drugs like cyclobenzaprine (structurally similar to amitriptyline, differing by only one double bond) have also demonstrated interesting effects in FMS [6]. Thus, the use of TCAs should not be discouraged in FMS treatment, in the face of an absence of long-term efficacy and an excess of adverse events, as declared by Fontenele and colleagues [1]. Indeed, studies not only directly comparing SNRIs with TCAs but also those making a comparison with anti-convulsants are now mandatory, to establish a rational algorithm for the pharmacological treatment of FMS.

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Advance Access publication 23 December 2008

**Comment on:** Amitriptyline in the treatment of fibromyalgia: a systematic review of its efficacy; reply

Sir, As Fontenele and colleagues [1] point out, the results of our review [2] show that there is no objective evidence supporting the long-term efficacy of amitriptyline at a dose of 25 mg/day in treating patients with fibromyalgia syndrome (FMS). This conclusion was reached because of an absence of data rather than data demonstrating no effect. Without evidence of efficacy, the potential for adverse effects from long-term use of tricyclic anti-depressants (TCAs) should be carefully considered by clinicians. Nevertheless, there is no strong evidence suggesting major safety concerns with the use of amitriptyline at a dose of 25 mg/day, although the data regarding safety in the trials selected in

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