HUMAN PSYCHOPHARMACOLOGY
Hum. Psychopharmacol Clin Exp 2009; **24**: S19–S23.
Published online in Wiley InterScience
(www.interscience.wiley.com) **DOI**: 10.1002/hup.1028

SUPPLEMENT ARTICLE

Functional magnetic resonance imagery (fMRI) in fibromyalgia and the response to milnacipran

Yves Mainguy*

Pierre Fabre Médicament, Boulogne-Billancourt, France

Functional imaging has been used to study response to pain in fibromyalgia patients. Functional magnetic resonance imagery (fMRI) which tracks local changes in blood flow has a higher spatial and temporal resolution than other techniques such as positron emission tomography (PET) or single-photon emission tomography (SPECT). fMRI studies in fibromyalgia patients suggest that similar levels of subjective pain result in similar central nervous system (CNS) activation in both fibromyalgia patients and controls. For a similar stimulus, however, fibromyalgia patients have a greater subjective sensation of pain. This increased sensitivity is accompanied with a decreased activity in brain regions implicated in the descending pain inhibitory pathways. The hypothesis that increased sensitivity to pain is due to decreased activity of the descending inhibitory pathways is supported by results with milnacipran. Fibromyalgia patients treated with the serotonin and noradrenaline reuptake inhibitor, milnacipran, exhibited a reduction in pain sensitivity and a parallel increase in activity in brain regions implicated in the descending pain inhibitory pathways compared to placebo-treated patients. Copyright © 2009 John Wiley & Sons, Ltd.

KEY WORDS — fibromyalgia; neuroimaging; SNRI

FUNCTIONAL IMAGERY STUDIES IN FIBROMYALGIA

The pathophysiology of fibromyalgia has been suggested to involve abnormalities of central pain processing (Bennett, 2005) possibly through a dysfunction of the serotonin and noradrenaline neurons in the basal ganglia which modulate the inhibitory descending pathways.

Functional imaging has been used to investigate abnormalities in the central nervous system (CNS) function in response to pain (Peyron *et al*., 2000) in general and more specifically in fibromyalgia patients (Williams and Gracely, 2006). Both single-photon emission tomography (SPECT) imaging (Kwiatek *et al*., 2000) and positron emission tomography (PET) (Lekander *et al*., 2000) have been used. These techniques use radioactive tracers to measure regional cerebral blood flow (rCBF) in different brain areas. PET uses radioactive tracers with a shorter half-life than SPECT, which results in an improved temporal resolution (Alavi and Hirsch, 1991).

Studies suggest that fibromyalgia patients may have reduced rCBF in one or both thalami (Kwiatek *et al*., 2000; Mountz *et al*., 1995). The cause of this decrease is unknown but inhibition of activity in this region may be the result of prolonged excitatory nociceptive input (Iadarola *et al*., 1995). The lower resting rCBF in the thalamus is consistent with a tonic inhibition in response to a persistent excitatory input associated with widespread chronic pain which is characteristic of fibromyalgia.

Functional magnetic resonance imagery (fMRI) is a technique that directly tracks local changes in blood flow (through changes in water molecule density) (Gracely *et al*., 2002). fMRI has a higher spatial and temporal resolution than PET or SPECT (Detre and Floyd, 2001).

A study using fMRI investigated differences in cortical activation between fibromyalgia patients and controls while they underwent thumbnail pressure testing (Gracely *et al*., 2002). In fibromyalgia subjects, the fMRI was performed while they were subjected to 'moderately painful' pressure. The control subjects were scanned under two conditions, 'stimulus pressure control' which used the same level of mechanical pressure as the fibromyalgia patients and 'subjective pain control' which used a degree of mechanical

* Correspondence to: Y. Mainguy, Pierre Fabre Médicament, 45, Place Abel Gance, 92100 Boulogne-Billancourt, France.
E-mail: yves.mainguy@pierre-fabre.com

Received 21 March 2009
Accepted 21 March 2009

pressure that resulted, as in the fibromyalgia patients, in moderate pain. The levels of cortical activation seen in fibromyalgia patients and the controls under the 'subjective pain control' condition were similar. However, fMRI scans of control subjects under the 'stimulus pressure control' condition showed no significant activation.

Thus, similar levels of subjective pain intensity resulted in similar CNS activation in both groups. In contrast the same intensity of pressure stimulation resulted in a more pronounced and bilateral activation of the CNS in fibromyalgia patients compared to healthy controls (Gracely *et al*., 2002). These results strongly support the notion of a lower pain threshold and/or increased gain of the nociceptive system in fibromyalgia patients which is consistent with a model of central sensitization.

A recent fMRI study of experimental tonic (continual) pain found differences between fibromyalgia patients and controls in the activation in the fronto-cingulate cortex, the supplemental motor areas and the thalamus (Burgmer *et al*., 2009) which supports the hypothesis that central mechanisms in the medial pain system, play an important role for pain processing in patients with FMS.

In a study of fibromyalgia patients (selected from a larger multicentre study) and healthy age-matched controls, the pressure stimulus–pain response curve was used to establish pressures giving identical perceived pain levels. These pressures were applied during fMRI scans (Jensen *et al*., 2009). Fibromyalgia patients needed significantly less pressure to experience the same subjective pain level as the controls. In addition fibromyalgia patients had significantly lower activity in the rostral anterior cingulate cortex (rACC) and in the left pulvinar nucleus of thalamus compared to controls. The fMRI response in the brain regions associated with primary sensory or affective representations of pain were identical in the two groups (Jensen *et al*., 2009). Thus there was no evidence of increased activity in emotional areas during processing of noxious input in fibromyalgia patients. In fibromyalgia patients, however, there was a decreased activity in brain regions implicated in the descending pain inhibitory pathways, such as rACC and thalamus, during nociceptive stimulation.

FUNCTIONAL MAGNETIC RESONANCE SPECTROMETRY (fMRI) IN FIBROMYALGIA PATIENTS TREATED WITH MILNACIPRAN

In animal models of chronic pain, the serotonin and noradrenaline reuptake inhibitor (SNRI), milnacipran, has been shown to reverse hyperalgesia and allodynia (Mochizuki, 2004). These effects were observed following oral administration but also via both intracerebral and intrathecal routes, suggesting that the antinociceptive effects are not mediated locally but involve the CNS (Mochizuki, 2004). A number of double-blind placebo-controlled clinical trials have shown milnacipran to produce a significantly greater reduction in pain compared to placebo in patients suffering from fibromyalgia (Branco *et al*., 2008; Clauw *et al*., 2008; Gendreau *et al*., 2005; Mease *et al*., 2009). In addition to reducing pain, milnacipran also reduced fatigue and had a positive effect on patients' global impression of change. The positive effects of milnacipran (and other SNRIs) in fibromyalgia are not related to effects on depression and the studies have shown that response rates were similar in patients with and without co-morbid depression.

fMRI analysis was integrated into a recent double blind, placebo-controlled, multicentre trial (UK, Sweden and Germany), which studied milnacipran over 13 weeks (3-week dose escalation, 9-week fixed dose (200 mg daily = 100 mg b.i.d.), 9-day down titration), with a primary endpoint at 12 weeks (Gracely *et al*., 2008). The patients were 92 women (18–55 years) diagnosed with fibromyalgia according to the American College of Rheumatology classification criteria. They were all right-handed, with no unstable medical disorder. They had all discontinued any psychotropic medication, commonly used for fibromyalgia, for at least 2 weeks. Pain intensity, determined by average weekly recall of pain on a 100 mm visual analogue scale (VAS), was $\geq$40 mm at baseline.

The sensitivity to pain produced by multiple 2.5 s pressure stimuli of supra-threshold intensities randomly applied to the left thumb nail was assessed with a VAS at baseline and after 12 weeks treatment. A stimulus-response curve was constructed for each patient at week 12 and the pressure required to produce a VAS of 50 mm (P_{50}) was derived. Brain activity during pain evoked at P_{50} was determined using fMRI as previously described (Apkarian *et al*., 2005; Ingvar, 1999).

At week 12, there was a 5.2 mm downward VAS shift in mean stimulus-response curve of milnacipran compared to the placebo curve ($p = 0.11$). This occurred over the entire range of applied pressures from pain threshold to pain tolerance threshold (Figure 1).

Patients who had a >30% reduction of pain over the treatment period (measured by average weekly pain intensity on VAS) were defined as pain responders. A subanalysis showed that milnacipran pain responders ($n = 21$) compared to milnacipran pain non-responders

DOI: 10.1002/hup

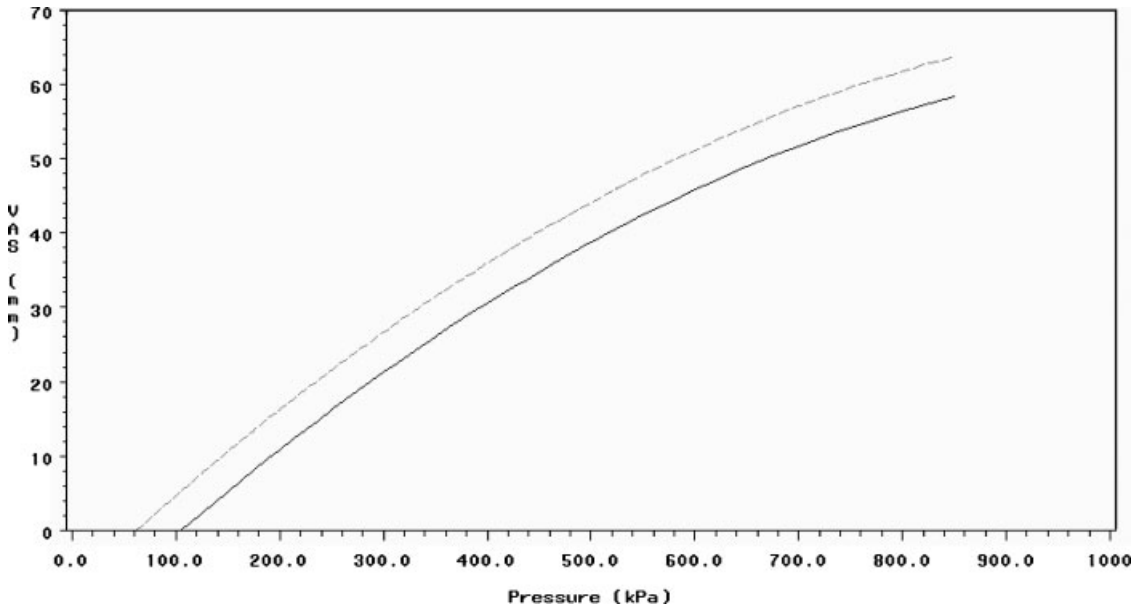

Figure 1. Pain response to pressure stimulus after 12 weeks treatment with milnacipran or placebo. VAS, 100 mm pain intensity visual analogue scale. Dashed line—placebo-treated patients, solid line—milnacipran-treated patients. Taken from Gracely *et al*. (2008)

($n = 23$) had shorter duration of chronic pain at baseline (84.6 and 168.8 months respectively, $p < 0.005$). Pain sensitivity to pressure was determined as the pressure required to produce a pain with an intensity scored 50 mm on the VAS (kPa VAS 50 mm). In pain responders on milnacipran, significantly greater pressure was required to produce the standard level of pain whereas this was not the case in pain responders on placebo (Figure 2). Thus the mechanism of the drug response appears to be different from that of the placebo response indicating a true pharmacological effect of the drug.

Patients who had a >30% reduction of patient global impression of change (PGIC) were defined as PGIC-responders. Pressure pain sensitivity was decreased by treatment in milnacipran PGIC responders but not in placebo PGIC responders nor in milnacipran PGIC non-responders (Figure 3). There was a positive correlation ($p < 0.01$) in milnacipran responders between the decrease in pain intensity and the reduced sensitivity to pressure.

Brain activity in the posterior cingulum and precuneus during repeated painful stimulation was significantly greater ($p < 0.05$) after treatment with milnacipran as compared to placebo (Figure 4). The milnacipran-treated group also exhibited greater activity than the placebo group in the thalamus ($p = 0.057$) and other areas (amygdala, caudatus nucleus, anterior insula) during repeated painful stimulation.

Fibromyalgia patients are highly sensitive to adverse events and 87% of placebo-treated patients and 97.8% of milnacipran-treated patients reported experiencing at least one treatment-emergent adverse event. Most adverse events, however, were of mild or moderate intensity (98 and 93% in the placebo and milnacipran groups, respectively). The most frequently reported events in the milnacipran group corresponded to the well-established safety profile of milnacipran (Stahl *et al*., 2005).

This study was exploratory and not powered to detect a difference in pain sensitivity between the groups. Nevertheless a trend to a reduction of pressure pain sensitivity in the milnacipran-treated fibromyalgia patients compared to placebo group was observed. This result is compatible with a clinically relevant effect of milnacipran in decreasing sensitivity to evoked pain in fibromyalgia patients. The milnacipran group exhibited increased activity in brain regions which are implicated in the descending pain modulation inhibitory network (amygdala, caudate nucleus, anterior insula) (Freund *et al*., 2007; Tracey and Mantyh, 2007), or have previously shown decreased basal and pain-evoked activity in non-treated fibromyalgia patients (thalamus) (Kwiatek *et al*., 2000; Mountz *et al*., 1995). These changes were not found in the placebo group. Increased activity of the posterior cingulum has previously been reported after treatment in chronic pain patients (Niddam *et al*., 2007).

DOI: 10.1002/hup

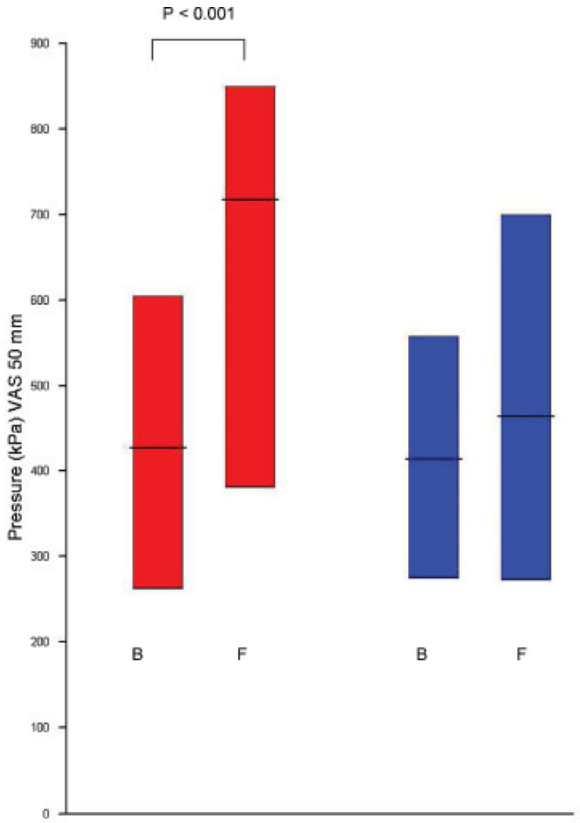

Figure 2. Pressure pain sensitivity in responders before and after treatment with milnacipran or placebo. Pressure (kPa)VAS 50 mm = pressure required to produce a pain with a standard intensity scored as 50 mm on the VAS. Thus increased (kPa)VAS 50 mm values indicate a decreased sensitivity to pain. B = before treatment, F = following treatment. Red bars = milnacipran ($n = 12$), blue bars = placebo ($n = 12$). Taken from Kosek *et al*. (2008)

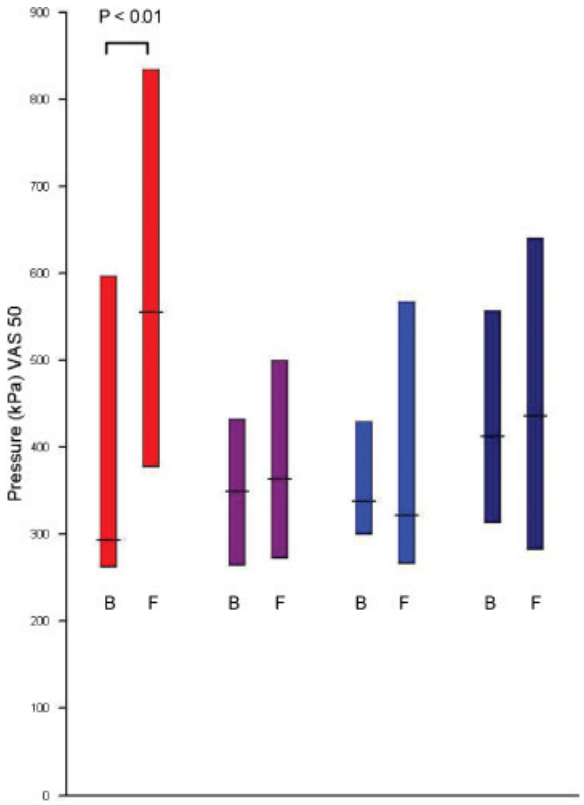

Figure 3. Pressure pain sensitivity in PGIC (patient global impression of change) responders before and after treatment with milnacipran or placebo. Pressure (kPa)VAS 50 mm = pressure required to produce a pain with an intensity scored 50 mm on the VAS. B = before treatment, F = following treatment. Red bars = milnacipran PGIC responders ($n = 19$), mauve bars = milnacipran PGIC non-responders ($n = 17$), lighter blue bars = placebo PGIC responders ($n = 15$), dark blue bars = placebo PGIC non-responders ($n = 23$). Taken from Kosek *et al*. (2008)

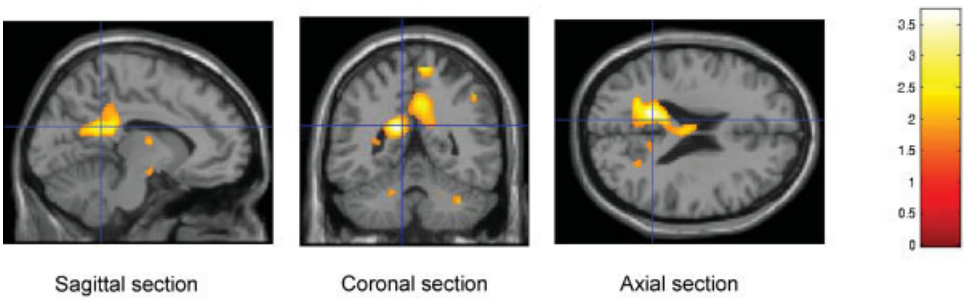

Figure 4. An example of increased fMRI activity evoked by painful stimulation after milnacipran treatment as compared to placebo treatment. The precuneus is indicated by the intersecting blue lines in the sagittal, coronal and axial sections. Quantification of activity (increasing from dark red, through orange to yellow) is shown in the bar on the right. Taken from Gracely *et al*. (2008)

CONCLUSIONS

The various fMRI studies carried out in fibromyalgia patients to date all suggest that similar levels of subjective pain intensity result in similar CNS activation in both fibromyalgia patients and controls. The same intensity of pressure stimulation, however, results in a more pronounced subjective sensation of pain and in greater brain activation in fibromyalgia patients than in controls (Gracely *et al*., 2002; Jensen *et al*., 2009). This increased sensitivity is not due to increased activity of areas involved in emotional

DOI: 10.1002/hup

reactions (Jensen *et al*., 2009). Fibromyalgia patients do, however, appear to have decreased activity in brain regions implicated in the descending pain inhibitory pathways, such as rACC and thalamus (Jensen *et al*., 2009). These results strongly suggest that the lower pain threshold of the nociceptive system in fibromyalgia patients is due to decreased activity of the descending inhibitory pathways. This hypothesis is supported by the results with milnacipran, which has been demonstrated to produce clinically relevant pain reduction in fibromyalgia patients (Spaeth and Briley, 2009). Fibromyalgia patients treated with milnacipran who exhibited a reduction in pain sensitivity showed an increased activity in brain regions implicated in the descending pain inhibitory pathways compared to placebo-treated patients (Gracely *et al*., 2008).

These studies demonstrate the potential of fMRI in investigating the neuronal pathways involved in the enhanced sensitivity to pain in fibromyalgia. In addition it is clearly a valuable technique for demonstrating the objective effects of drugs in the treatment of fibromyalgia and in elucidating their mechanism of action.

CONFLICT OF INTEREST

Yves Mainguy is employed by Pierre Fabre Médicament. He has received no honoraria, grants from any other source. He does not hold shares in any pharmaceutical company

REFERENCES

Alavi A, Hirsch LJ. 1991. Studies of central nervous system disorders with single photon emission computed tomography and positron emission tomography: evolution over the past two decades. *Semin Nucl Med* **21**: 58–81.

Apkarian AV, Bushnell MC, Treede RD, Zubieta JK. 2005. Human brain mechanisms of pain perception and regulation in health and disease. *Eur J Pain* **9**: 463–484.

Bennett R. 2005. Fibromyalgia: present to future. *Curr Rheumatol Rep* **7**: 371–376.

Branco JS, Perrot S, Bragee B, *et al.* 2008. Milnacipran for the treatment of fibromyalgia syndrome: a European multicentre, randomised, double-blind, placebo-controlled trial. *Poster presented at Annual European Congress of Rheumatology (EULAR 2008)*, Paris, June 2008.

Burgmer M, Pogatzki-Zahn E, Gaubitz M, Wessoleck E, Heuft G, Pfleiderer B. 2009. Altered brain activity during pain processing in fibromyalgia. *Neuroimage* **44**: 502–508.

Clauw DJ, Mease P, Palmer RH, Gendreau RM, Wang Y. 2008. Milnacipran for the treatment of fibromyalgia: a multicenter, double-blind, randomized clinical trial. *Clin Ther* **30**: 1988–2004.

Detre JA, Floyd TF. 2001. Functional MRI and its applications to the clinical neurosciences. *Neuroscientist* **7**: 64–79.

Freund W, Stuber G, Wunderlich AP, Schmitz B. 2007. Cortical correlates of perception and suppression of electrically induced pain. *Somatosens Mot Res* **24**: 203–212.

Gendreau RM, Thorn MD, Gendreau JF, Kranzler JD, *et al*. 2005. Efficacy of milnacipran in patients with fibromyalgia. *J Rheumatol* **32**: 1975–1985.

Gracely R, Jensen K, Petzke F, *et al*. 2008. The effect of milnacipran on pain modulatory systems in fibromyalgia: an fMRI analysis. *Poster presented at Annual European Congress of Rheumatology (EULAR 2008)*, Paris, June 2008.

Gracely RH, Petzke F, Wolf JM, Clauw DJ. 2002. Functional magnetic resonance imaging evidence of augmented pain processing in fibromyalgia. *Arthritis Rheum* **46**: 1333–1343.

Iadarola MJ, Max MB, Berman KF, *et al*. 1995. Unilateral decrease in thalamic activity observed with positron emission tomography in patients with chronic neuropathic pain. *Pain* **63**: 55–64.

Ingvar M. 1999. Pain, functional imaging. *Philos Trans R Soc Lond B Biol Sci* **354**: 1347–1358.

Jensen KB, Kosek E, Petzke F, *et al*. 2009. Evidence of dysfunctional pain inhibition in Fibromyalgia reflected in rACC during provoked pain. *Pain* (in press).

Kosek E, Carville S, Choy E, *et al*. 2008. All responders are not the same: distinguishing milnacipran- from placebo-responders using pressure pain sensitivity in a fibromyalgia clinical trial. *Poster presented at 12th World Congress on Pain*, Glasgow, June 2008.

Kwiatek R, Barnden L, Tedman R, *et al*. 2000. Regional cerebral blood flow in fibromyalgia: singlephoton-emission computed tomography evidence of reduction in the pontine tegmentum and thalami. *Arthritis Rheum* **43**: 2823–2833.

Lekander M, Fredrikson M, Wik G. 2000. Neuroimmune relations in patients with fibromyalgia: a positron emission tomography study. *Neurosci Lett* **282**: 193–196.

Mease PJ, Clauw DJ, Gendreau RM, *et al*. 2009. The efficacy and safety of milnacipran for the treatment of fibromyalgia. Results of a Randomized, double-blind, placebo-controlled trial. *J Rheumatol* **36**: 398–409.

Mochizuki D. 2004. Serotonin and noradrenaline reuptake inhibitors in animal models of pain. *Hum Psychopharmacol Clin Exp* **19**: S15–S19.

Mountz JM, Bradley LA, Modell JG, *et al*. 1995. Fibromyalgia in women. Abnormalities of regional cerebral blood flow in the thalamus and the caudate nucleus are associated with low pain threshold levels. *Arthritis Rheum* **38**: 926–938.

Niddam DM, Chan RC, Lee SH, Yeh TC, Hsieh JC. 2007. Central modulation of pain evoked from myofascial trigger point. *Clin J Pain* **23**: 440–448.

Peyron R, Laurent B, García-Larrea L. 2000. Functional imaging of brain responses to pain. A review and meta-analysis. *Neurophysiol Clin* **30**: 263–288.

Spaeth M, Briley M. 2009. Fibromyalgia: a complex syndrome requiring a multidisciplinary approach. *Hum Psychopharmacol Clin Exp* **24**(Suppl. 1): S3–S10.

Stahl SM, Grady MM, Moret C, Briley M. 2005. SNRIs: their pharmacology, clinical efficacy, and tolerability in comparison with other classes of antidepressants. *CNS Spectr* **10**: 732–747.

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

Williams DA, Gracely RH. 2006. Biology and therapy of fibromyalgia. Functional magnetic resonance imaging findings in fibromyalgia. *Arthritis Res Ther* **8**: 224.

DOI: 10.1002/hup