The Placebo Effect and Its Determinants in Fibromyalgia

A systematic review and meta-analysis of randomised controlled trials

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Abstract

Introduction: Placebo has been proven effective in many diseases but whether it is effective in the treatment of fibromyalgia, a chronic widespread pain condition affecting 2% of general population, is unknown.

Objectives: [1] to determine whether placebo is effective for fibromyalgia; [2] to identify the possible determinants of the placebo effect [3] to gain knowledge around placebo effect, including nocebo effect and placebo response in difference conditions.

Method: Literatures were searched for randomised controlled trials that included placebo as a treatment or comparator in people with fibromyalgia. The placebo effect was measured as the improvement of pain and other outcomes from baseline. The effect was compared with no treatment control group or waiting list group. Meta-analysis was undertaken to combine data from different studies. Subgroup analysis was conducted to identify possible determinants of the placebo effect.

Results: 3375 studies were found from the literature search. After scrutiny, 204 trials met the inclusion criteria. Participants who took placebo in the trials had significant improvement in pain, fatigue, sleep quality, physical function, and other main outcomes, while participants in the no treatment controlled group stayed unchanged. The effect size of placebo in pain relief is clinically moderate (ES=0.47, 95%CI 0.37 to 0.56). The effect increased with the strength of the active treatment in the trials, participants' age and baseline pain severity, but decreased in women and with longer duration of disease.

Conclusion: Placebo per se is effective in the treatment of fibromyalgia. The effect varies upon context, suggesting that the

treatment effect in fibromyalgia depends on context which may be enhanced with the alternation of non-specific or contextual factors.

Acknowledgement

Completing my PhD degree is probably the most challenging activity of my first 29 years in life. The best and worst moments of my doctoral journey have been shared with many people. It has been a great privilege to spend several years in the Arthritis Research UK Pain Centre, Department of Rheumatology, Orthopaedics and Dermatology of Nottingham University, and its members will always remain dear to me.

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Chapter 1 Introduction

I'll discuss the current understanding of fibromyalgia (FM), including definition, epidemiology, diagnosis, and treatment. I'll then discuss the history and definition of placebo, possible mechanisms, clinical evidence of its therapeutic effect in general and placebo analgesia in musculoskeletal disorders to justify this study. Finally, the aims and objectives of the thesis will be stated.

1. Introduction to fibromyalgia

1.1 Definition and history

Fibromyalgia is a disorder characterised by chronic widespread musculoskeletal pain, fatigue, non-restorative sleep and widespread lowered pain threshold, (Pozgain et al., 2014)

Historically the condition has been recognised under different diagnostic labels. The earliest descriptions that were identified in European literature in the late 16th century described it as widespread musculoskeletal "aches and pains" (Inanici and Yunus, 2004). Early definitions of this condition were vague with almost no distinction between generalised and localised pain syndromes.

The term “fibrositis” was first used for FM by the British neurologist Sir William Gowers in 1904 (Gowers, 1904). However, the concept of fibrositis was not clearly defined and in fact overlapped with many other rheumatic conditions (Table 1-1). In the mid-1970s, Smythe and Moldofsky defined fibrositis as a generalised pain syndrome, accompanied by fatigue, poor sleep, morning stiffness, aggravating and relieving factors, emotional distress, and multiple hyperalgesic tender points (Smythe and Moldofsky, 1977). The change of the name was inspired by the increasing evidence that there was no inflammation in the connective tissues of individuals with this condition. In 1990, the American College of Rheumatology (ACR) further developed this concept by publishing criteria for the diagnosis of FM (Harth, 2013). One of the unique features of the ACR criteria is the requirement of a hyperalgesic wince-withdrawal response to pressure in at least 11 out of 18 defined “tender points” in all four quadrants of the body (Figure 1-1).

Table 1-1 Development of the concept of FM

Study	Name used	Definition/Description
Gowers, 1904	Fibrositis	“We are thus compelled to regard lumbago in particular and muscular rheumatism in general, as a form of inflammation of the fibrous tissues of the muscles… (And thus)...we may conveniently follow the analogy of ‘cellulitis’ and term it ‘fibrositis’.”
Smythe, 1989	Fibrositis syndrome	A generalized pain syndrome, along with fatigue, poor sleep, morning stiffness, aggravating and relieving factors, emotional distress, and multiple tender points.

Wolfe, 1990	Fibromyalgia	Widespread pain for longer than three months with pain on palpation at 11 or more of 18 specified tender points.
Clauw, 2001	Fibromyalgia	Individuals with chronic widespread musculoskeletal pain, fatigue and lowered pain threshold for which no alternative cause can be identified.

Following widespread use of the ACR criteria it was realised that the criteria did not always perform appropriately. Data from both British and American studies showed that about 20% of the population that suffered with FM did not fulfil the ACR criteria. Conversely, some individuals had sufficient tender points for diagnosis but their pain distribution was not sufficiently widespread (Chaitow, 2009).

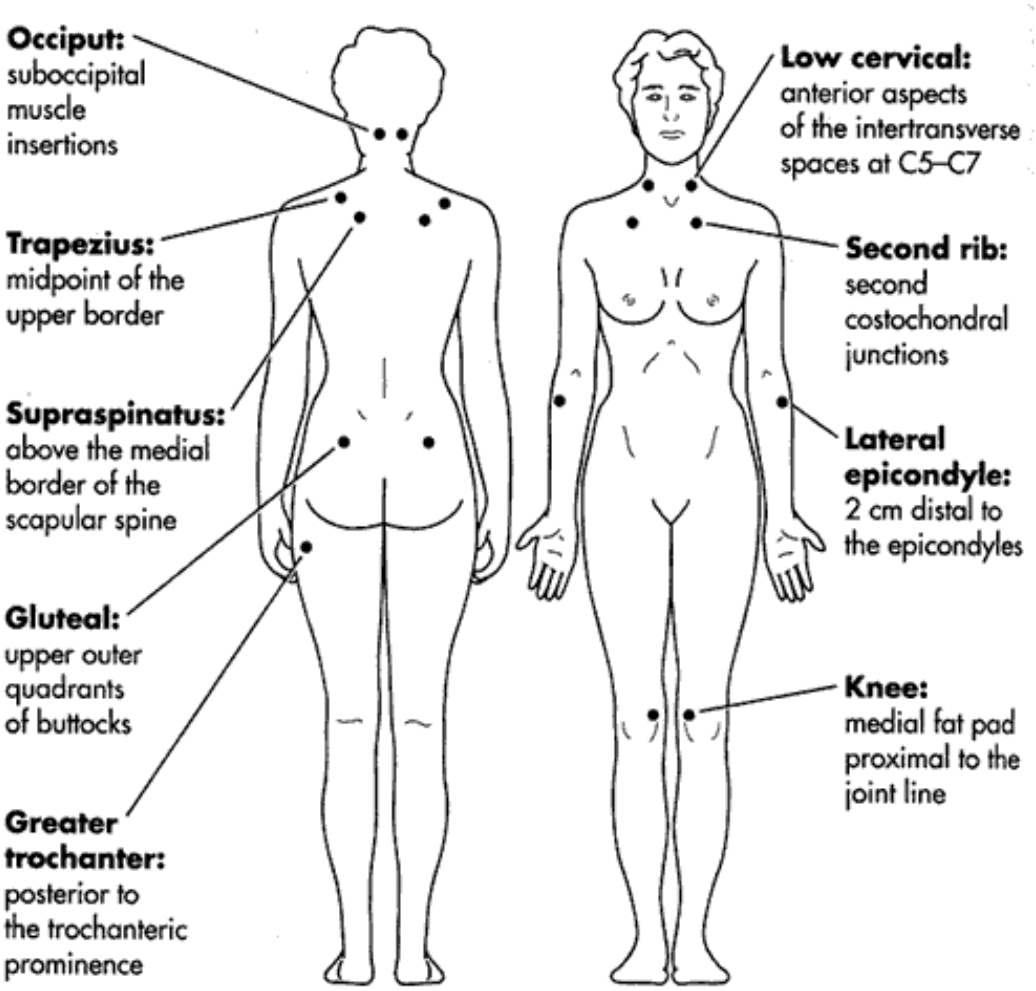


Figure 1-1 Tender points for FM diagnosis – ACR 1990 criteria

Although the concept of FM has been developed over decades, FM is still a difficult-to-treat disease of unknown etiology and the debate of its existence continues (Harth, 2013). Due to the lack of pathologic evidence, observable deformity, and laboratory testing, FM has always been disbelieved (Blom et al., 2012). Kool used the term “invalidation” to capture this phenomenon which includes non-acceptance by others, misunderstanding, disbelief, rejection, stigmatization and suspicion that the problem is exaggerated (Kool et al., 2009).

FM patients may also have a difficult relationship with their health care providers (Hayes et al., 2010). It has been shown in the result of a qualitative study by Briones-Vozmediano that patients complained about the delay and uncertainty in making a diagnosis, delays in referral to numerous specialists, the inefficacy of treatment and the expense of some treatments (Briones-Vozmediano et al., 2013). Some rheumatologist will not see patients that are referred to them for FM or only see them once to exclude other conditions but not provide ongoing care (Alghalyini and Oldfield, 2008). Health providers also describe their experience with FM patients as difficult (Asbring and Närvänen, 2003). Professionals often experience uncertainty when dealing with this disease because of the lack of knowledge. Therefore, their professionalism and explanations are questioned by the patients (Hellstrom et al., 1998)

Some doctors believe that FM is not a disease, as they often cannot find any underlying structural damage apart from pain. A newspaper article by Alex Berenson casts doubts on the existence and validity of FM. He reported that some doctors and patient advocacy groups hoped news drugs to be approved to legitimize FM but others denied the existence of the disease (Camerlain and Myhal, 2009). Dr. Ehrlich expressed his view on FM as an untenable diagnosis because “no one has FM until is diagnosed”. He argued that the pain may be real but FM isn’t (Ehrlich, 2003). This opinion was seconded by Dr. Hadler,

who argued that people who “have exhausted their wherewithal to cope” may become victims of the iatrogenic medical construct of FM (Hadler, 2003). This was especially true when biological model of medicine was taking place, where a medical diagnosis should be based on biological change (Benedetti et al., 2003). However, FM can be a useful term to describe the complex web of co-morbid symptoms as described above – chronic pain, fatigue, sleep disturbance and cognitive symptoms. It needs to be recognized that this is a very heterogeneous group and different patients may arrive at this symptom complex in different ways (Price et al., 1999).

1.2 Overview of the nature of FM

According to Smythe (Smythe, 1989) FM is a generalized pain syndrome. The most common characteristics of FM include fatigue, sleep disturbance with lack of restoration in the morning, morning stiffness, cognitive difficulties, stress, chronic widespread pain and widespread hyperalgesic tender sites. As with many other medically unexplained somatic symptoms, there is no adequate explanation for FM in terms of damage or inflammation of peripheral tissues. Instead, investigators began to explore central neural mechanisms to explain this condition (Mcbeth et al., 2001b).

Population-based studies have investigated the co-morbidities of FM and found that other conditions may co-exist with FM (**Figure 1-2**). Such co-association could be explained by a shared pathophysiology.

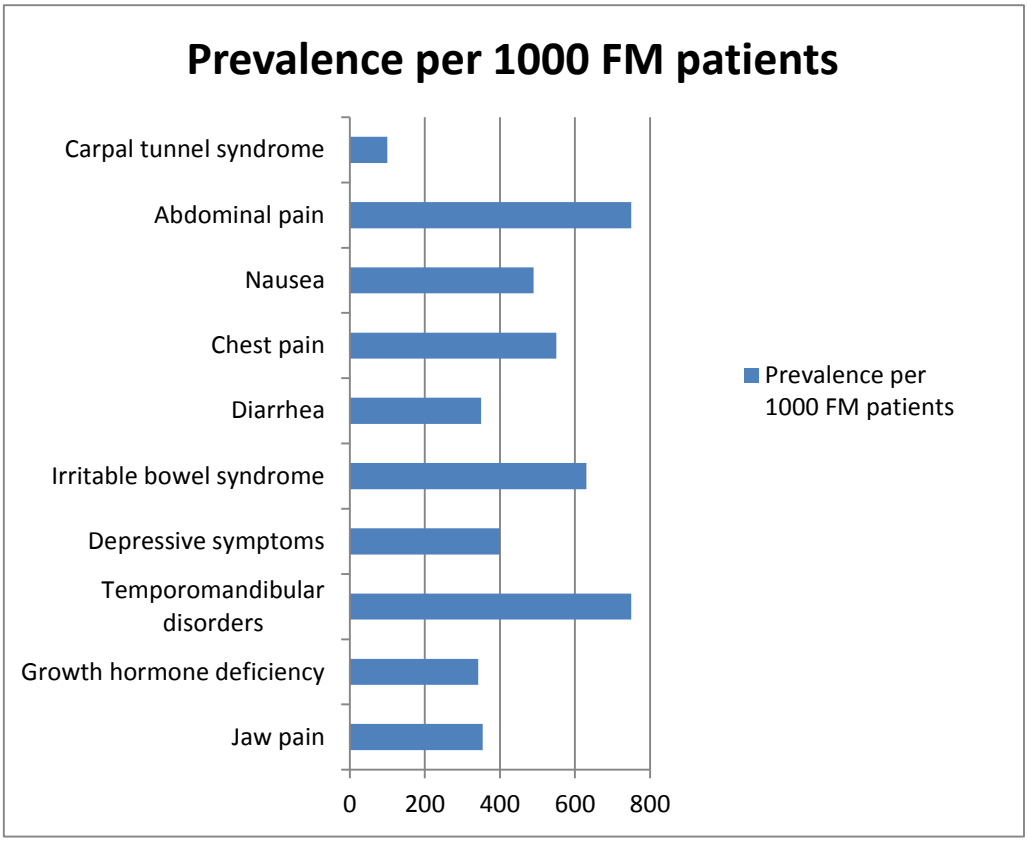


Figure 1-2 Prevalence of main co-morbidities with FM*

*Data collected from (Almansa et al., 2009, Balasubramaniam et al., 2007, Cuatrecasas et al., 2010, Kurland et al., 2006, Sarmer et al., 2002, Toda and Harada, 2010, Wolfe et al., 2005).

1.3 Epidemiology of FM

1.3.1 Prevalence and incidence

1.3.1.1 Prevalence

Population-based epidemiological studies have investigated the prevalence and incidence of FM. It was found that that 2% of the general population met ACR criteria for diagnosis of FM in Wichita,

Kansas, USA and the prevalence was reported to be 2.2% in London, Ontario, Canada (White et al., 1999b). FM is much more prevalent in women (3.4%) than men (0.5%), with a prevalence ratio of 7:1 (White et al., 1999b). Prevalence also increases with age. The Canadian study showed that less than 1% of 18 to 30 year old women suffered from FM but that this figure increased to 8% of women aged 55 to 64 (White et al., 1999b) (**Figure 1-2**).

Similar results were reported in some western European countries. A study in five European countries found that FM prevalence in general population varies from 1.8% (95%CI, 1.7-1.9) in France to 3.8% (95% CI, 3.6-4.0) in Germany (Table 1-2). In the same five countries, the prevalence of FM in hospital clinics was higher, varying from 6% (95% CI, 3.2-9.4) in Spain to 25% (95% CI, 19.6-30.8) in Germany, (Branco et al., 2010).

The socioeconomic, ethnical, environmental and cultural difference among the five countries may have caused the difference in FM prevalence (Sukenik et al., 1999b). Although geographical variations have been observed among patients with chronic pain (Kong et al., 2008), direct comparison between different countries using different epidemiological studies is problematic. This is because these studies might have used different diagnostics criteria, or had different eligible criteria to recruit the participants. The difference in prevalence between countries in the above studies may not necessarily be true

but reflect the differences between studies. A multicentre study using same protocol is still required.

Table 1-2 Prevalence of fibromyalgia in different countries (population-based)

Study	Location	Sample size	Women%	Mean age	Prevalence (95% CI)
Wolfe, 1995	*US*	3006	/	54	2.0 (1.4–2.7)
White, 1999	*Canada*	3395	62	N/A	3.3 (3.2-3.4)
Santos, 2010	*Brazil*	361	64	73	5.5 (5.4-5.7)
Le Lay, 2008	*UK*	1500	51	/	2.8 (1.9-3.6)
Le Lay, 2009	*Russia*	1610	55	/	2.1 (1.4–2.8)
Branco, 2010	*Portugal*	500	51	41	3.6 (2.0-5.2)
	France	1014	52	45	1.4 (0.7-2.1)
	Italy	1000	52	47	3.7 (2.6-4.8)
	Germany	1002	52	45	3.2 (2.1-4.3)
	Spain	1001	52	43	2.3 (1.4-3.2)
Makela, 1991	*Finland*	3775	52	30+	0.75 (N/A)
Lindell, 2000	*Sweden*	2425	/	/	1.3 (0.8-1.7)

1.3.1.2 Incidence

Only two epidemiological studies have studied the incidence of FM. Forseth followed 2498 women in South Norway for 5.5 years and found that the annual incidence of FM in this population was 0.58% (Forseth et al., 1997). Another large population-based study showed an age-adjusted incidence rate of 0.69% among men and 1.13% among women per person-years between 1997 and 2002 (Weir et al., 2006). According to Weir, et al. (2006) the age-adjusted relative risk between women and men was 1.64 (Table 1-3).

Table 1-3 Incidence of FM

Study	Location	Design	Sample (n)	Age range	Women%	FM incidence
Forseth, 1997	Norway	Cohort study	2038	26-55	100	0.58% per year
Weir, 2006	U.S.	Cohort Study	62000	<65	65	0.69% per person-years (M) 1.13% per person-years (F)

1.3.2 Risk factors for developing FM

1.3.2.1 Age

The prevalence of FM increases with age (Pozgain et al., 2014)(**Figure 1-3**). However, the prevalence tails off over the age of 70, sharper in women. There are a few possible explanations for the

age effect. Firstly, FM may remit in elderly people. Secondly, people with FM may be more likely to die than the general population. FM could either be fatal itself (e.g., suicide) or be associated with other potentially fatal illness. Thirdly, the tail-off may be caused by the cohort effect, i.e., different birth cohorts may have been exposed to different risk factors. For example, people born in 1945 in Hiroshima and Nagasaki had greater leukaemia prevalence than those born in 1935 and 1955 because of the atomic bombs (Inaba, 2009). This may cause the prevalence increase in early ages then decrease in the very old people in a cross-sectional survey. This is however unlikely for FM, as a sudden shift of an environmental exposure should affect both men and women. Considering FM as a chronic disease, the “tails off” prevalence in very old women with FM is more likely due to the disease itself, e.g., self-remitted when getting older.

However, FM symptoms decreased with age (Cronan et al., 2002). In their study, older patients reported less pain, depression, illness impact, and better sleep quality (Cronan et al., 2002). This diminution in symptoms may be explained by the fact that older individuals often perceive their health status positively (Cockerham et al., 1983).

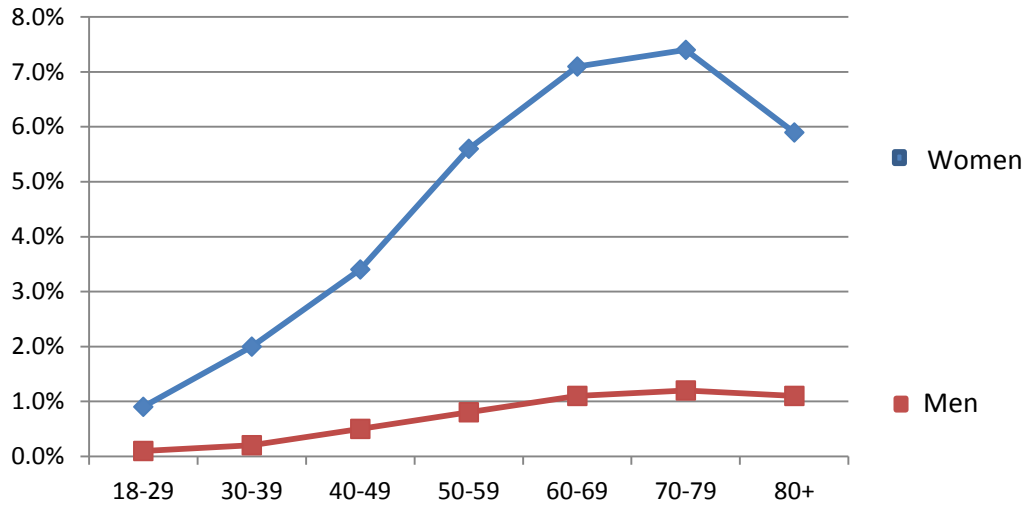


Figure 1-3 Prevalence of FM for both genders

1.3.2.2 Gender

Evidence concurs in every country that the prevalence is higher in women than in men (**Table 1-4**). In addition, women experience longer and more severe symptoms, such as more common fatigue, morning fatigue, hurt all over, total number of symptoms, and significantly more tender points than men. Symptoms for men also last for shorter periods of time and happen less frequently (Yunus, 2001). The role of gender in FM symptomatology and its mechanisms are not fully understood yet, but are likely to involve an interaction between biology, psychology, and sociocultural factors (Yunus, 2002).

Biological aspects of gender difference in FM have attracted much attention from researchers. Genetic studies in animals suggest that the degree of inheritance of genes involved in pain physiology may differ by gender, although much work needs to be done to investigate

such an explanation in humans (Yunus, 2001). In humans, the enzyme catechol-O-methyltransferase (COMT) genetic variations were found to contribute to pain ratings in humans in a sex-specific manner. The haplotype coding for low COMT activity increased capsaicin-induced pain perception in women, but not men (Belfer et al., 2013).

Physiological studies show that woman have greater sensitivity than men to mechanical, electrical, ischaemic and cold stimili (Fillingim and Maixner, 1995). Since FM becomes more prevalent in the post-menopausal years, female hormones could play an important role. Oestrogen is protective against pain (Ma et al., 2011). Oestrogen may affect pain by modulating serotonergic neural functions, cognitive functions and mood (Bethea et al., 1998). Men release endorphins which activate the brain's mu-opioid receptors more effectively than women (Hellstrom et al., 1998). That may partially explain why women in general have a lower pain threshold than men (Bragdon et al., 2002).

Table 1-4 Prevalence by gender in FM

Study	Location	sample size	Women	Mean age	Prevalence	
					Women	Men
Wolfe, 1995	*US*	3006	N/A	54	3.4 (2.3-4.6)	0.5 (0.0-1.0)
White, 1999	*Canada*	3395	62%	/	4.9 (4.8-4.9)	1.6 (1.5-1.8)
Le Lay, 2009	*Russia*	1610	55%	/	2.8 †	1.2†
Branco, 2010	*Portugal*	500	51%	41	5.2 (4.9-5.5)	1.8 (1.6-2.0)
	France	1014	52%	45	2.0 (1.7-2.3)	0.7 (0.7-0.7)
	Italy	1000	52%	47	5.5 (5.3-5.7)	1.6 (1.5-1.7)
	Germany	1002	52%	45	3.9 (3.7-4.1)	2.5 (2.4-2.6)
	Spain	1001	52%	43	3.3 (3.2-3.4)	1.3 (1.2-1.4)

†95%CI not provided in the original study
Citation: (Pozgain et al., 2014, Ernst and Resch, 1995)

Gender is associated with psychological distresses, which have also been shown to be important in pain modulation (Evans et al., 2013). Recent studies have shown that women report greater psychological distress and use more coping strategies than men (Goetz et al., 2008). Pain symptoms are likely to be influenced by socio-cultural factors as well. For example, it is a general belief that men should be more tolerant to pain than women and this belief may encourage men to report less pain to “be manly” (Yunus, 2001).

1.3.2.3 Psychosocial stress

Studies have supported co-morbidity of FM and psychiatric conditions, such as depression, panic disorders, anxiety. It was hypothesized that chronic pain causes depression, or vice versa (Fulda and Wetter, 2008). Population-based studies have shown that psychological distress is a strong risk factor for the future development of FM. It is known that different type of stress, e.g. life stress during adulthood, post-traumatic stress and childhood abuse are all associated with FM (Van Houdenhove et al., 2005, Aaron et al., 1997). However, for each individual type of stress, the magnitude varies (Van Houdenhove et al., 2005).

Although most clinicians consider life stress as an association with FM development, prospective studies did not support this opinion (Van Houdenhove, 2002). Interestingly, one population-based study

suggested that only “idiosyncratic” stressors with a strong personal significance may have strong impact on the development of FM (Van Houdenhove et al., 2002), such as high workload and the experiences of being bullied at work (Kivimaki et al., 2004). Post-traumatic stress remains a controversial factor for FM too, although some evidence shows an association between post-traumatic stress and FM (Cohen et al., 2002). It is found that traumatic stressors superimpose upon a long history of chronic physical and/or psychological burden and post-event worry, catastrophizing and inactivity led by these stressors play an important role in FM (Zautra et al., 2004, Mclean and Clauw, 2004). Childhood victimization is another important type of stress that is highly associated with FM occurrence as an attributive risk. Report rates of emotional neglect or abuse, physical maltreatment, and sexual abuse among FM patients are higher than that of the general population (Mcbeth et al., 2001a, Goldberg et al., 1999). The psychological trait of “somatisation” is a found to be a risk factor for future development, according to McBeth (2001). Subjects who display the process of somatization are at an increased risk of the development of FM (Mcbeth et al., 2001b).

1.3.2.4 Genetic factors

A strong familial component to FM has been identified in several studies (Verhagen et al., 2000, Shleyfer et al., 2009). FM prevalence of interviewed relatives of probands with FM was 18.5% and that of all the relatives of FM probands was estimated to be 6.4%. Both

figures are higher than FM prevalence in the general population (Verhagen et al., 2000). For first-degree relatives of probands with FM, the prevalence was eight-fold higher than that of the general population. Other symptoms that associate with FM, such as irritable bowel syndrome (IBS), temporo-mandibular jaw dysfunction (TMD), “tension” headaches and other regional pain syndromes were also found to be more common in family members of individuals with FM (Verhagen et al., 2000).

Studies of twins have investigated the genetic influence on somatic symptoms and confirmed that these symptoms more strongly co-aggregate in identical compared to non-identical twins and are under strong genetic influence. According to Kato (2006), genetic factors accounted for about half of the risk for developing chronic widespread pain (FM). Furthermore, a comparison between genders in that study showed no significant differences in the magnitude or type of genetic influence. This means that genetic factors may have the same predisposition to development of FM in both men and women (Kato et al., 2006).

Although it is still unclear which specific genetic mechanisms predispose to FM, there are reports that certain polymorphisms of serotonin 5-HT2A (5-hydroxytryptamine receptor 2A), serotonin transporter, dopamine 4 receptor, and COMT (catecholamine O-methyl transferase) genes occur in higher frequency in people with

FM. According to Cohen (2009) carriers of the COMT met/met genotype showed increased sensitivity to pain and this could be one mechanism for the role of this gene in conferring risk for FM (Cohen et al., 2009).

One common feature of all the polymorphisms identified is that they are involved the metabolism or transport of monoamines. These compounds play a critical role in the human stress response and descending inhibition of upward pain neurotransmission. It is likely that there are many other genetic polymorphisms, involving other neuromodulators and monoamines, which in part determine an individual's "set point" for pain and sensory processing (Hochberg et al., 2010).

1.4 Pathogenesis of FM

1.4.1 Altered sleep physiology

Sleep disturbance has been identified as a major complaint for most FM patients, including difficulty getting off to sleep (increased latency), frequent wakening, and poor quality of sleep with lack of restoration (Martinez-Lavin et al., 1998, Roizenblatt et al., 2001). Selective delta sleep deprivation causes reduced pain threshold and development of FM symptoms in normal volunteers (Moldofsky and Scarisbrick, 1976). When deprived from stage-4 sleep, young healthy subjects experienced aching and stiffness and an overnight increase in

dolorimeter scores. The dolorimeter is an instrument that measures pain threshold and pain tolerance. The result shows that deprivation of restorative sleep lowers people's pain threshold and tolerance to pain.

Compared with healthy controls, FM patient suffer from significantly lower sleep quality ($p<0.04$) and experience worsening of pain symptoms after poor sleep (Roizenblatt et al., 2001). Sleep disturbance is also found to be associated with lower energy and fatigue in patients with FM (Bradley, 2009). Frequent alpha wave intrusion during delta sleep (alpha delta intrusion) has been associated with reduced production of growth hormone and insulin-like growth factor 1, which are needed for muscle microtrauma repair (Van Cauter et al., 1998).

The enhanced pain, in turn, contributes to a future worsening of sleep quality, which consequently keeps patients' fatigue at a high level and prolongs the repair of muscle damage (Davies et al., 2008). The correlation between pain and sleep is supported by a large epidemiologic study which found that improvements in restorative sleep were associated with pain relief (**Figure 1-4**). Therefore, therapies which improve sleep quality for patients with chronic pain symptoms may also help reduce the pain (Davies et al., 2008).

1.4.2 Altered pain physiology

Altered processing of pain appears to be a major contributor to FM (Abeles et al., 2007). Accumulating evidence shows that patients with FM have enhanced sensitivity to a wide array of stimuli, such as heat and cold, as well as to mechanical and ischaemic pressure (Carli et al., 2002). Compared with healthy controls, lower stimulus intensity is needed to evoke a pain response in patients with FM, (Gracely et al., 2002). Using subjective scales and spinal nociceptive flexion reflex, a specific physiologic correlate for the subjective evaluation of central nociceptive pathways, Desmueules, et al., found a significant reduction in nociceptive flexion reflex threshold in FM patients (Desmeules et al., 2003).

There is increasing evidence that FM pain is a result of augmentation of sensory input that is mediated by the central nervous system (Nielsen and Henriksson, 2007). More recent studies also found abnormalities in the peripheral nervous system. There is peripheral sensitisation, with resultant allodynia and dermatographism, spinal cord “wind-up”, increased levels of the neurotransmitter substance P in cerebrospinal fluid, and reduced efficiency of descending inhibitory systems that involve the hypothalamo-pituitary axis sympathetic system and the growth hormone somatomedin system (Nielsen and Henriksson, 2007).

Painful symptoms of FM may also involve abnormalities in the descending pain inhibition pathways (Colloca and Miller, 2011). Normal transmission of sensory input to the brain is inhibited by the activation of fibres that descend from brainstem sites to the dorsal horn by releasing neurotransmitters that are associated with variations in pain and mood (Bradley, 2009). However, this function may be impaired in FM patients by a deficiency of these neurotransmitters in the central nervous system (Colloca and Miller, 2011).

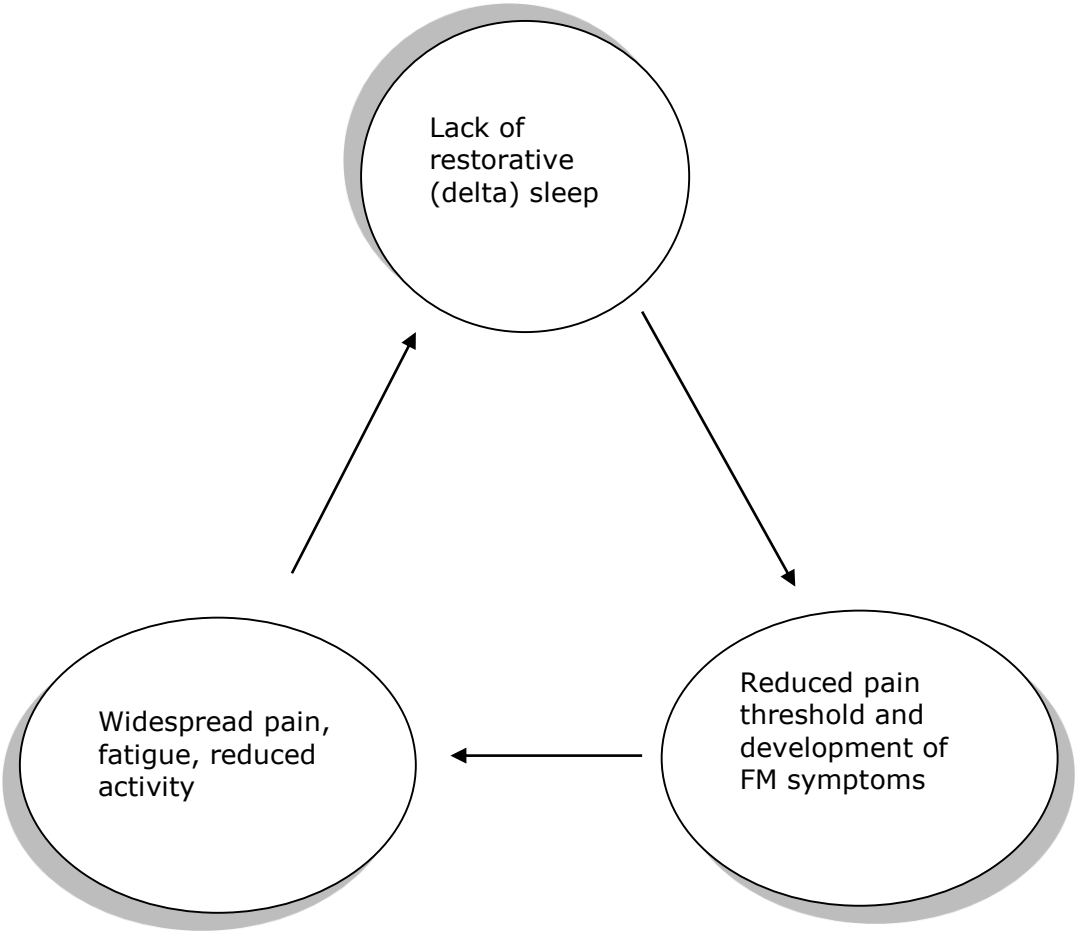


Figure 1-4 Pathogenesis of FM

1.4.3 Psychosomatic issues

As discussed before, FM may be a class of related disorders, which commonly co-occur in individuals. They may share physiologic abnormalities and genetic risks factors (Steinsbekk et al., 2007, Gracely et al., 2002), such as chronic fatigue syndrome, irritable bowel syndrome, migraine, etc. These disorders also encompass a number of psychiatric problems, such as attention-deficit, generalized anxiety disorder major depressive disorder, and obsessive-compulsive disorder, etc (Steinsbekk et al., 2007).

Environmental triggers such as exposure to stressors is a factor that contributes to the pathophysiology of FM (Rupp et al., 2006). Physical stressors at work were found to be associated with chronic widespread pain (Wolfe and Michaud, 2007), such as heavy lifting, repetitive motions, or squatting for extended periods (Lawrence et al., 2008). Some psychosocial stressors were also found to predict the development of FM. The effect of mood of reported pain was studied by Davis. In the study, women with FM who underwent negative mood induction reported significantly greater increase in pain. The result suggests that psychosocial stress may affect the severity of pain associated with FM (Davis et al., 2001).

1.5 Diagnosis

1.5.1 ACR criteria

The American College of Rheumatology (ACR) criteria for the classification of fibromyalgia was published in 1990 (Harth, 2013). Since then, ACR criteria have been used widely in clinical and epidemiological studies. The ACR criteria were intended as classification rather than diagnostic criteria, although the criteria could be useful for clinical diagnosis as well. The 1990 ACR criteria emphasised two parameters in their classification: widespread tenderness and chronicity of symptoms. A patient would be diagnosed to have FM when hyperalgesia (i.e. wince/withdrawal response) is present in all four quadrants of the body and in at least 11 out of 18 tender sites when digital palpation with an approximate force of 4kg is performed, and when multiple pain symptoms last for at least three months (Harth, 2013).

There are a few potential pitfalls that need considering when clinicians use the criteria to diagnose patients with FM. First of all, the ACR criteria associate a single non-specific clinical feature, tenderness, with an entire pain syndrome (Cohen, 1993). As suggested in a recent study, the anatomical regions of tenderness are non-specific for describing patients with diffuse pain (Katz et al.,

2006). Secondly, there is a substantial risk of circular reasoning, as the criteria fail to distinguish between cause and effect (Cohen and Quintner, 1998). Thirdly, current understanding of FM as a diffuse disorder of central pain processing is not specific to FM (Cohen and Quintner, 1998).

In 2010, ACR published an updated version of FM diagnostic criteria. New criteria request a patient to satisfy the following three conditions to be diagnosed as FM: 1) widespread pain index (WPI) =>7 and symptom severity (SS) scale score >= 5 or WPI 3-6 and SS scale score =>9, 2) symptoms have been present at a similar level for at least 3 months, 3) the patient does not have a disorder that would otherwise explain the pain. No physical or tender point examination is requested. The WPI scale is the number of areas in which the patient has had pain over the last week and it will be between 0 and 19. The SS scale covers three FM symptoms, fatigue, waking unrefreshed and cognitive symptoms. Each indicates the level of severity over the past week (0-3). The SS scale sums up the severity of the 3 symptoms and the extent (severity) of somatic symptoms in general. The score ranges between 0 and 12.

According to this definition, FM is more than just a high WPI scale but also high score in SS. It also recognizes that high score in symptom severity should be sufficient for diagnosis (Neogi et al., 2009). Comparison of the two classification criteria is summarised in

Table **1-5**. ACR 2010 modification to the FM classification criteria allows their use in epidemiologic and clinical studies without the requirement for an examiner. Compared with 1990 criteria, the 2010 version is simpler to use and administer.

Table 1-5 Comparison of FM classification criteria

	ACR 1990	**ACR 2010**
Hyperalgesia site	In all 4 quadrants of the body and in at least 11 out of 18 tender sites	Not required
Chronicity **Symptom severity**	At least 3 months Not specified	At least 3 month WPI=>7; SS >= 5 or WPI 3-6; SS =>9,
Others	N/A*	The patient does not have a disorder that would otherwise explain the pain

*not applicable

1.5.2 Clinical presentation

Although ACR criteria 1990 require a minimum 11 out of 18 tender points, in clinical practice, patients with less tender points may also have a clinical presentation that is in this spectrum. The 11 point cut-off has been criticised due to its arbitrary nature. Thus, pain and tenderness is more often used as the defining feature of FM (Ablin et al., 2008). Doctors often diagnose someone with FM if they have the right symptoms, i.e. chronic widespread, multiple regional pain with no other explanation and fatigue.

1.6 Management of FM

Up till now, there is no specific or effective medicine or therapy for FM. Doctors may use different ways to manage FM based on the main symptoms that the patients have. In general, all the treatments given to FM patients can be grouped into two categories - pharmacological and non-pharmacological (Table 1-6).

Table 1-6 Treatments for FM

Non-pharmacological	**Pharmacological**
Patient education	Analgesics
Cognitive-behavioural therapy	Antidepressants
Aerobic exercise programme	Medicines that help with sleep
Acupuncture	Muscle relaxants
Herbal medicine	Anticonvulsants
Addressing anxiety and depression	Antipsychotics

1.6.1 Non-pharmacological treatment

1.6.1.1 Patient education

Management of FM symptoms remains a big challenge for health providers as pharmacological interventions have only limited effects on reducing pain and other symptoms of FM (Hammond and Freeman, 2006). On the other hand, non-pharmacological approaches are attracting more and more attention from doctors, general practitioners, and patients themselves. Patient education, by

definition, is a combination of learning experiences which are designed to guide the patients to improve their understanding of the disease, their behaviours and ultimately their health status (Hill, 1997). The goal of patient education is to provide patients with more capacity to manage their condition and to improve their quality of life (Ramos-Remus et al., 2000). Patient education in terms of providing a diagnostic label and explaining the nature of the condition, the relevant risk factors, available treatment options, and prognosis in terms that the individual patient can understand is also a professional responsibility, so should be given to every person with FM (Stewart-Williams and Podd, 2004).

In a randomised controlled trial (Verhagen et al., 2003), FM patients were randomised to an education course group or a control observation group. The education group received information on FM, the role of stress in the development of FM, coping, problem-solving techniques, assertiveness training, relaxation strategies and the importance of physical conditioning while the control group were observed while they were waiting to receive a similar intervention. The results showed that the education group had a better quality of life and self-efficacy outcomes. Helplessness, number of days feeling bad, physical dysfunction, and pain in the tender points decreased significantly.

Another UK study into patient education and FM management showed that FM patients considered this education strategy very helpful. Compared with the controls in a relaxation group, more patients in the FM education group experienced improvement in FM symptoms. Using the Fibromyalgia Impact Questionnaire (FIQ), greater changes were observed at four months for those who considered themselves to have improved (Hammond and Freeman, 2006).

1.6.1.2 Exercise

Aerobic exercise is effective for pain relief, reducing stiffness and fatigue, and improving quality of life and other symptoms of FM (Busch et al., 2007, Assis et al., 2006, Stephens et al., 2008, Richards and Scott, 2002). Aerobic exercise as a treatment, either in combination with other therapies or on its own has been demonstrated to improve FM symptoms (Busch et al., 2007). Tissue oxygenation improvements, increased muscle endurance and high energy phosphate levels are suggested as the main mechanisms of the therapeutic effect of exercises (Valim et al., 2003, Bennett, 1989, O'connor and Youngstedt, 1995). Exercise also increases delta sleep which is reduced in FM patents (Ehrlich, 2003). Therefore a graded increase in aerobic exercise is a simple and very safe intervention that should be routinely prescribed to all FM patients (reference guidelines). In practice, however many patients find it hard to

undertake regular aerobic exercise due to their marked pain and fatigue.

Tai chi is one type of traditional Chinese martial arts, preferentially practised by patients with musculoskeletal disorders and mental health conditions in the US. Tai chi combines meditation with slow, gentle and graceful movements which is thought to stimulate vital energy (qi) movement throughout the body. This complex exercise integrates physical, emotional, psychological, spiritual and behavioural elements (Wang et al., 2010c). Randomized controlled trials have been undertaken to examine the effect of tai chi in the treatment of FM (Wang et al., 2010b, Van Eijk-Hustings et al., 2010, Zhang and Wu, 2010). In one of the studies, the tai chi group had significantly greater improvement in some outcomes: FIQ score, sleep quality, 6-minute walk test and CPSS scores, compared with the wellness education and stretching program control group. The long-term effect for the tai chi group was also superior to the control group. Therefore, tai chi may be a promising treatment for FM (Wang et al., 2010c).

1.6.1.3 Sleep hygiene

Sleep disturbance with non-restorative sleep is a central problem for FM patients. Effective management of sleep disturbance has the potential to improve FM symptoms. Sleep hygiene therapy was examined in one randomized controlled trial. Compared with usual

care control, sleep hygiene therapy is superior in improving patients sleep quality (Edinger et al., 2005a).

1.6.1.4 Cognitive-behavioural therapy

Cognitive behavioural therapy (CBT) was developed in the middle of the 20th century (Rachman, 2009). Research interest in this therapy, which focuses on the role of dysfunctional thought patterns in coping and emotional disorders, has grown rapidly in the past decades. The main therapeutic techniques that are employed in CBT are twofold: firstly, recognising and modifying dysfunctional thought patterns which may interfere with or have negative impacts on the treatment progress; and secondly, encouraging patients to change their behavioural patterns in order to break the vicious cycle between symptoms and patterns of dysfunctional performance (Bennett and Nelson, 2006). With the development of CBT, more methods of treatment have become available, which have made CBT a useful adjuvant therapy for many chronic conditions including FM. However, it is *per se,* a complex intervention which normally requires specific theory and methods to support it and it is not widely available in many settings (Casale et al., 2008)

1.6.1.5 Acupuncture and complementary medicine

Although acupuncture has been found to be effective in the management of pain in general (Eccles, 2007), not many clinical trials have assessed its potential in treating FM. Controversial results were reported in different studies. One randomised controlled trial found that acupuncture, compared with sham acupuncture in the control group, significantly improved symptoms of FM. Symptomatic improvement was not restricted to pain relief and was most significant for fatigue and anxiety (Martin et al., 2006b). Acupuncture is also found to be beneficial as adjunctive treatment to usual care for the FM patient in terms of reduced pain and increased quality of life (Targino et al., 2008). However, the opposite results have been found in other clinical trials. According to Assefi et al., (2005), acupuncture was no better than sham acupuncture at relieving pain in FM (Assefi et al., 2005).

1.6.1.6 Electrotherapy

Different types of electrotherapy have been studied in FM. Passard and colleagues have found that unilateral repetitive transcranial magnetic stimulation of the motor cortex significantly reduced pain and improved several aspects of quality of life including fatigue, morning tiredness, general activity, walking and sleep (Passard et al., 2007a). According to Colbert, sleeping on a magnetic mattress pad

provides significant and clinically relevant pain relief and improved sleep quality in FM patients (Colbert et al., 1999). Low-frequency pulsed electromagnetic field therapy was studied by Sutbeyaz etc. They found that this therapy might improve function, pain, fatigue, and global status in FM patients (Sutbeyaz et al., 2009a).

1.6.1.7 Balneotherapy

Balneotherapy refers to the medical use of spas in hot baths and natural vapour baths as well as the various kinds of mud and sand. Several minerals are commonly found in the spa water, including sodium, magnesium, calcium, and iron etc (Sukenik et al., 1999a). Balneotherapy is known to be successful in the treatment of osteoarthritis and inflammatory rheumatologic disorders (Verhagen et al., 2007, Sukenik et al., 1999b, Verhagen et al., 2003). A few studies have investigated its effect against FM symptoms. Their results have shown that balneotherapy is effective and can be an alternative method in treating FM patients (Camerlain and Myhal, 2009, Fioravanti et al., 2007, Fioravanti et al., 2009, Evcik et al., 2002, Ardic et al., 2007).

1.6.1.8 Summary of non-pharmacological treatments

Several types of non-pharmacological treatments are available to treat FM patients, including educational approach, cognitive-

behavioural therapy, exercise and complementary medicine, etc. Non- pharmacological treatments are effective in reducing pain and improving sleep quality and other self-reported outcomes, such as physical status, FM symptoms, physical function and psychological status. Some studies argue that non-pharmacological treatments are more effective than pharmacological treatments in FM (Lee et al., 2011). Combination therapy that incorporates at least one educational therapy with one exercise therapy offers an advantage. In general, non-pharmacological treatments are safe to use (Millan, 2002).

1.6.2 Pharmacological treatment

Pharmacological treatments of FM have been widely studied in clinical trials, although none of them were specifically developed for FM. Active research into their therapeutic potential is ongoing. Most commonly prescribed drugs can be categorised into anti-depressants or analgesics.

1.6.2.1 Anti-depressants

Different anti-depressants work on different parts of the brain and help to change the brain function in different ways but all to make patients feel less depressed. There are three major classes of anti-

depressants: tricyclics (TCAs), selective serotonin reuptake inhibitors (SSRIs), and serotonin norepinephrine reuptake inhibitors (SNRIs).

A meta-analysis of 18 RCTs of antidepressants including TCAs, SSRIs and SNRIs shows strong evidence for the efficacy of the TCAs in reducing pain, sleeping disorder and fatigue. However, this class of antidepressants do not have a large effect size on reducing depression symptoms. SSRIs are proven to be effective in reducing pain, but the effect on fatigue and depressed mood is small. There was strong evidence for SNRIs in reducing pain and sleeping disorder (Haeuser et al., 2009).

Pain and sleep-related disorders are among the most common complaints of FM patients. Anti-depressant drugs, although typically used for depression, can be also beneficial for FM patients by regulating these symptoms. The idea of helping FM patients with anti-depressants is to interrupt pain cycles and to gain more restorative sleep. Anti-depressant drugs are prescribed at lower doses for FM than for depression. Amitriptyline is a typical TCA that is given at only low dose once at night and at that dose it works on the sleep centre to increase delta sleep, and at the spinal cord to reduce “wind-up” (Goldenberg et al., 1996, Hauser et al., 2009).

1.6.2.2 Analgesics

Chronic widespread pain is a cardinal complaint of all FM patients. Therefore different types of analgesics are given to patients to help with their symptoms. However, evidence to support the use of non-steroidal anti-inflammatory drugs, in FM is not promising (Hayes et al., 2010, Blom et al., 2012). Opioid analgesics like tramadol are considered effective in treating FM pain. Biasi found statistically significant improvements in self-reported pain relief in tramadol versus placebo treated patients (Biasi et al., 1998). The efficacy of tramadol was further supported by Russell who found a significantly lower withdrawal rate due to inadequate pain relief in the tramadol group than in the placebo group (Neogi et al., 2009). Other opioids used in FM include morphine and codeine. However, due to the concerns about abuse, dependency and toxicity, the use of this group of analgesics in FM is limited (Portenoy, 1996).

1.6.2.3 Hypnotics

Altered sleep physiology is the main cause of the development of FM and lack of restorative sleep is a common complaint of FM patients. Drugs that improve patients' sleep quality was proven to be effective as a treatment again FM symptoms (Boonen et al., 2005, Sicras-Mainar et al., 2009). According to Spaeth, sodium oxybate therapy significantly reduced FM patients' pain and fatigue. Improvement in

general health measured by SF-36 was also achieved (Spaeth et al., 2012).

1.6.2.4 Other drugs

Anaesthetics such as lidocaine may provide small benefit when injected into multiple tender points (Hong and Hsueh, 1996). Corticosteroid is also sometimes recommended but the evidence to support the use of these drugs is sparse (Walsh et al., 2002).

1.6.2.5 Summary of pharmacological treatments

Simple analgesics and antidepressants are the most commonly used drugs for FM. Other drugs including gabapentidiods, dopaminergic agents and sleep modifiers are also used to control symptoms of FM (Hauser et al., 2012b). Combination of treatments is suggested if a single drug is ineffective. Doses may be adjusted if needed to control the symptoms without increasing the side effects (Lee et al., 2011). As most patients with FM may have already been on multiple drugs, careful scrutiny of pharmacotherapy with reduction of excessive medication use should be considered (Schaible et al., 2011).

1.6.3 Economic Burden of FM

With the increasing awareness of FM, a few studies have been conducted to estimate the economic burden of FM in different countries. The first study was done by White and colleagues in Canada in 1999. They found that, compared with people who did not suffer from FM, the ones who had FM used about twice the health services and about twice the costs (White et al., 1999a). In the US, the cost ratio was higher. The total health care cost was estimated as three times higher in FM patients (Berger et al., 2007). A survey in the Netherlands calculated the average annual cost for FM patients as €7,813 (Boonen et al., 2005). In Spain, the total costs for FM patient, including the use of healthcare and nonhealthcare resources were more than €5,000 higher than others. FM patient also displayed a higher prevalence of comorbidities, had more visits to the doctors and missed more days at work (Sicras-Mainar et al., 2009).

FM has also caused considerable financial burden to the UK National Health Service (NHS). A study found that compared with the age and sex matched control patients with no FM from the same GP practice, the FM cohort had put on more burden to the NHS as FM patients had more co-morbidity alongside their condition, such as headache/migraine, depression, and sleep problems and more drug related adverse events. They were also more likely to be referred to

hospitals. Therefore, FM patient present a greater burden to the NHS than patients without FM (Benedetti et al., 2007).

1.7 Measures of FM treatment

1.7.1 Fibromyalgia impact questionnaire (FIQ)

One of the most widely used measures for FM treatment is the Fibromyalgia Impact Questionnaire (FIQ). It was designed by Burckhardt originally and revised by Bennett (Bennett et al., 2009). The goal of this questionnaire is to assess the health status of patients with FM. It can be used for both clinical and research purposes. Concerns about the validity of this instrument include gender bias, because it was developed from a female dominant clinic population, and non-linearity of the scales (De Craen et al., 1999a). However, regardless of its validation caveats, FIQ is a widely used instrument for measuring the impact of FM on patients and shows good responsiveness to change in clinical trials (De Craen et al., 1999a)

1.7.2 Visual analogue scale (VAS) for pain

A visual analogue scale (VAS) is often part of the questionnaires for FM. It is measured along a continuous line between two endpoints, which stand for the two extremes of the measure, eg, pain ranging

from 0 (ie, no pain) to 100 (extreme pain). Participants indicate a position along the line to quantify their pain severity (Pace et al., 1995).

1.7.3 Tender points

Tender points occur at many places throughout the body but for study purposes up to 18 specified points are used for examination for a wince-withdrawal response when a metered pressure is applied. The number of tender points is also used as a measurement of FM changes in clinical trials (De Pascalis et al., 2002).

1.7.4 Quality of life

Quality of Life (QOL) measures the general aspects of well-being, in various domains for patients with FM. QOL may be measured using a generic QOL questionnaire such as SF-36, WHO-QOL and Euro-QOL (Wechsler et al., 2011). It may also be measured using a disease-specific instrument such as FIQ (Enck et al., 2013). While the former is more useful for comparisons between diseases, such as the impairment of QOL between patients with FM versus patients with cancer, the latter is more useful to catch specific outcomes due to FM and therefore more sensitive to change in response to treatments for FM.

1.8 Prognosis

To date, all existing treatments have shown limited effect on FM. For many FM patients, the best thing to do after being diagnosed is to learn how to cope with it. Early intervention possibly could promise a higher chance of good prognosis. Studies show that patients being diagnosed and treated by general practitioners and other primary physicians are more likely to have larger improvement than those diagnosed in hospitals and other tertiary care settings (Goetz et al., 2008). Once the symptoms of FM are severe enough to warrant referral to hospital specialists, improvement may be more difficult. Patients who begin to have symptoms after 40 are less likely to respond to treatment and so are patients with severe mood or behavioural disturbances. A lower education level has also found to be a risk factor for a worse prognosis. In terms of mortality, one study found shorter life expectancy among FM patients as a result of cancer (Macfarlane et al., 2001). This result was supported by who found that patients with widespread pain had an elevated risk of deaths from cancer. Furthermore, they found FM patients had higher risks of death from cardiovascular diseases (Walsh et al., 2002). However, it was not agreed by another study which concluded mortality did not appear to be increased in patients diagnosed with fibromyalgia, but the risk of death from suicide and accidents was increased (Wolfe et al., 2011).

2. Introduction to placebo and the placebo effect

2.1 Definitions and history of placebo

The word placebo, in Latin, means “I shall please”. The meaning of placebo was defined as “a commonplace method or medicine” in the 1785 New Medical Dictionary and later changed to “an epithet given to any medicine adapted more to please than to benefit the patient” in the revised Quincy’s Lexicon-Medicum by Hooper in 1811 (De Craen et al., 1999a). The placebo response is a phenomenon in which an inert treatment can sometimes improve a patient's condition simply because the person has the expectation that it will be helpful. Expectation plays a potent role in the placebo effect (Gensini et al., 2005).

The earliest use of placebo dates back to the 14th century. In medical documents, this word was first used from the late 18th century (Shapiro and Shapiro, 1998). Before the Second World War, placebo was widely used in medical practice (De Craen et al., 1999a) largely because there were very few effective treatments to give patients. However scientific evidence to support the use of placebo as a treatment has only been documented since the middle of the last century (De Craen et al., 1999a).

Placebo was first used in a randomised controlled trial (RCT) in 1945 in an unpublished study funded by the MRC as a standard control to determine the therapeutic effect of streptomycin in pulmonary tuberculosis (Goetz et al., 2008). The assumption of using placebo in RCTs is that placebo has no treatment effect or it is inert to the disease of interest. However, Henry K. Beecher successfully drew attention to placebo response in his classic work entitled “The Powerful Placebo” in 1955. He demonstrated that about 35% of patients with different conditions responded well to the placebo treatment and that this had nothing to do with a lower level of intelligence, as had been suggested previously (Beecher, 1955).

After Beecher’s work, more studies were undertaken to examine the placebo effect and the mechanism of its action in a wide variety of conditions including pain analgesia (Levine et al., 1978), affective disorders (Mayberg, 1997) and Parkinson’s disease (De La Fuente-Fernandez et al., 2001). A meta-analysis of 60 RCTs investigating the treatment of restless legs syndrome found a placebo response rate of 40% with a large effect for the primary outcome in most studies. It means that 40% of participants were much improved by taking placebo, (Fulda and Wetter, 2008) Placebo has also been proven to be effective in the treatment of chronic fatigue syndrome, though with a lower effect size (placebo response, 19.6%, 95%CI, 15.4 to 23.7) than expected and lower than in some other conditions (e.g. major depression, 29.7%, duodenal ulcer, 44.2%, migraine 29.0%, reflux

esophagitis, 26.8%) (Cho et al., 2005, Walsh et al., 2002, De Craen et al., 1999b, De Craen et al., 2000, Pace et al., 1995). In the treatment of depression, the placebo effect accounted for 68% of the treatment effect in studies of various types of antidepressants (Rief et al., 2009b). However, these studies may suffer from the same bias as Beecher's study, since they compared outcomes in the placebo group to those in a treatment group but with no observation group who were receiving neither of these. Without a no-treatment observation control, the results may be confounded by many other factors, such as regression to the mean, natural history of the disease, fluctuation of symptoms, etc (Doherty and Dieppe, 2009, Hrobjartsson and Gotzsche, 2001).

With inclusion of a third group – an observation or "untreated" control - new studies that examined the placebo effect found different results. One landmark meta-analysis of RCTs in 60 conditions that had trials with placebo and untreated control concluded that placebo may have some modest effect in subjective outcomes, including pain, but not in objective outcomes, especially if dichotomised (Hrobjartsson and Gotzsche, 2001). Another more recent meta-analysis showed that placebo was superior to untreated controls in osteoarthritis and that the effect size of placebo was often greater than the additional specific effect of an active treatment (Zhang et al., 2008). Researchers distinguished the true placebo effect from perceived placebo effect by introducing the untreated group because this comparison can tell whether patients get improved by the placebo

effect or other non-specific effects, such as being observed in clinical trials – Hawthorn effect (Mccarney et al., 2007), natural history of disease (Last and Adelaide, 2013) and regression to the mean (Stigler, 1997). In this way, the true placebo effect can be quantified (Ernst and Resch, 1995). More recently, a waiting list group has been added into randomised controlled trials to examine the placebo effect. In this design, people in the waiting list control group are given nothing but wait for the treatment at the end of the study. Using this trial design, Kaptchuk et al (2008) found that placebo acupuncture augmented by the practitioner's warmth, attention and confidence resulted in a significantly larger effect in the treatment of irritable bowel syndrome (IBS) than placebo acupuncture alone (i.e. the "ritual" needling procedure without any patient-practitioner interaction) and that both of these gave far better results than no treatment in an observation group (Kaptchuk et al., 2008a). Kapchuk et al subsequently demonstrated in a small proof of concept study that placebo given without deception could be an effective treatment for IBS (Suokas et al., 2012), possibly getting around the ethical dilemma that although we know that placebos can help patients, in clinical practice it is not acceptable to intentionally lie to a patient. More RCTs that are specially designed to examine such issues related to placebo are warranted.

Different terms have also been used in the past 50 years to describe the effect related to placebo, including placebo response (Enck et al.,

2013), and placebo effect (Wechsler et al., 2011). While there is no clear boundary between these terms, some differences may be observed during the development of the concept. For example, placebo response is normally used to measure the number of people who respond to placebo irrespective of whether the response is due to placebo or other factors, such as regression to the mean or confounding factors (Ernst and Resch, 1995). In contrast, placebo effect is often used in RCTs where there is a control group, eg, no-treatment control (Ernst and Resch, 1995). The effect is therefore more specific and attributable to placebo. Other terms have also been used, eg, non-characteristic (or non-specific) effect (Enck et al., 2008), meaning response (Moerman and Jonas, 2002) and contextual effect, (Paterson and Dieppe, 2005). These are the terms used to generalise the concept of placebo and/or to encourage the development of contextual enhancement benefits in clinical practice (Doherty and Dieppe, 2009). The area is growing and the terminology is still evolving.

2.2 Possible Mechanisms of the placebo effect

Studies have shown that placebo effects exist in possibly all disciplines of medicine and that the mechanisms may vary. Currently, there are several recognised mechanisms to explain the placebo effect, including expectancy, classic conditioning and a

psychoneuroimmunological response (Stewart-Williams and Podd, 2004, Eccles, 2007).

Expectancy refers to an outcome or effect that a patient expects or wishes to receive from a specific intervention. For example, in pain studies, expectancy can be measured by asking the patient about how much pain relief they expect to receive after receiving the intervention. Expectancy is not only influenced by verbal suggestion but also by the previous experience and beliefs of the patient (Voudouris et al., 1989, Montgomery and Kirsch, 1997, Bingel et al., 2011). A study has found that patients expected more pain reduction after being told they were given a strong pain killer. Expectation was lower in the group where patients were told they had a weak pain killer. Although both groups had the same placebo, these expectations were closely related to the magnitude of the placebo effect (De Pascalis et al., 2002). Emotions and anxiety are likely to modulate people's expectancies. Reduction of anxiety is likely to contribute to placebo effect, especially in the pain domain (Murray and Stoessl, 2013). Placebo treatment can significantly influence symptom even without concealment or deception. One study demonstrated that IBS patient given open label placebo had clinically meaningful symptom improvement that was significantly better than the waiting list control (Suokas et al., 2012).

In some studies, researchers have manipulated patient expectation to increase the placebo effect. For example, researchers can pair the inert treatment to lower pain stimuli so that patients come to experience and expect pain relief. The procedure is classified as conditioning (Colloca and Benedetti, 2006). Conditioning can occur with or without a history of actual first-hand experience. Some patients can also build up expectation through observation of others (Colloca et al., 2008) The placebo effect that is produced by conditioning can last a few days. According to Colloca and Benedetti, exposure to effectiveness via conditioning elicited placebo present that were present after a few seconds as well as after a week (Colloca and Benedetti, 2006).

A psychoneuroimmunological response has been suggested to explain certain placebo effects, especially with pain relief (Eccles, 2007). There is some evidence that endogenous opioids are implicated in placebo analgesia. Levine, et al.(1978) successfully demonstrated that the placebo response in pain reduction could be blocked by the opiate antagonist naloxone (Levine et al., 1978). This study result was confirmed by subsequent studies using sophisticated investigations such as neuro-imaging (Levine and Gordon, 1984, Benedetti, 1996, Benedetti et al., 1995). For example, a subset of brain regions have been shown to be affected similarly both by treatment and placebo (Petrovic et al., 2002), and μ-opioid receptor signalling has been demonstrated to be activated by patients'

expectation of pain reduction (Zubieta et al., 2005). Parkinson's disease, that results mainly from low levels of dopamine in the basal ganglia, is another condition that can be improved by a placebo response and in this case placebo associates with the release of dopamine in the striatum (De La Fuente-Fernandez et al., 2001). Some studies argue that personality traits, such as novelty seeking and reward responsiveness, altruism, optimism and empathy also play a role in the magnitude of placebo effect (Schweinhardt et al., 2009, Scott et al., 2008a, Mackenbach, 2005, Geers et al., 2010).

2.3 Placebo Analgesia

Placebo analgesia refers to a situation where the administration of placebo could achieve a pain-relieving effect, which may be a result of the participant's belief in the analgesic effectiveness of an intervention (Levine et al., 1978). One of the reasons why placebo could contain analgesic effect is that cortical areas recruit the opioid dependent descending pain control system in the brainstem, which ultimately inhibits nociceptive processing in the dorsal horn of the spinal cord in a gate-control manner (Eippert et al., 2009). According to Eippert, et al. (2009), psychological factors can influence nociceptive processing in the dorsal horn of the spinal cord. Using neuroimaging techniques, Craggs et al (2008) demonstrated that an increase in neural activity which coincides with placebo analgesia is associated with at least two general mechanisms of pain-modulation.

One of the mechanisms engages affective processes during the whole placebo condition to aid in pain-modulation. The other mechanism engages cognitive processes early in the placebo time course that are involved in context evaluation and feedback to expectation-stimulus correspondence (Craggs et al., 2008).

2.4 The nocebo effect

A substance without medical effect does not only benefit the health status because of the patients' belief that the inert substance is effective, but also cause advert events (Pozgain et al., 2014). The nocebo effect, which is to the opposite of placebo effect, refers to the phenomenon in which a substance without medical effects worsens the health status of the person taking it as a result of negative beliefs (Colloca and Miller, 2011).

The proven mechanisms of the placebo response can also been shared by the nocebo response, including reaction to expectation and learning by Pavlovian conditioning (Enck et al., 2008). Cutaneous hyperalgesia could be induced experimentally through verbal suggestions (Benedetti et al., 2007). According to Klosterhalfen, worsening of symptoms could be conditioned in a learning experiment with health volunteers (Klosterhalfen et al., 2009). From neurobiological perspectives, two neurobiological substrates have been shown to play a part in the nocebo effect. The secretion of

dopamine and endogenous opioids were found to increase in placebo analgesia, while the reaction decreased in placebo hyperalgesia (nocebo effect) (Scott et al., 2008b). Other central process, such as the neurohormone cholecystokinin, may also play a part in the nocebo response since worsening of symptoms is often associated with anxiety (Benedetti et al., 2006).

2.5 Placebo effect in the treatment of osteoarthritis (OA)

A single systematic review has examined the placebo effect in the treatment of OA. The study used Medline (1950–), Web of Science (1960–), EMBASE (1980–), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982–), and Allied and Complementary Medicine (1985–) for literature search and found 4141 relevant citations. After inclusion/exclusion criteria, 198 studies were selected for data analysis.

This study concluded that placebo is effective in the treatment of OA, especially for pain, stiffness and self-reported function. The size of this effect is influenced by the strength of the active treatment, the baseline disease severity, the route of delivery and the sample size of the study, (Nikolajsen et al., 2006). The positive relationship between the active treatment and placebo effect in this study explains that the magnitude of the placebo effect largely depend on the patient expectation for a treatment. The positive relationship between

baseline level of pain and the placebo effect suggests that placebo analgesia may be linear in mild to moderate pain such as OA. This is in fact more likely to be true as most RCTs for OA included patients with 30-70% pain on VAS 100 to be more sensitive to the minor analgesics tested. Whether placebo works for severe pain such as cancer pain remains unknown. This study also confirmed that needle placebo (e.g. sham acupuncture) produced larger effect size that oral tablet placebo which again relates to the patient expectation (Kaptchuk et al., 2006). Studies with larger sample size tended to give higher placebo effect (Nikolajsen et al., 2006). This may be related to spectrum of participants where the larger sample size may offer wider patient spectrum, hence the difference between individuals.

2.5 Comparison of the placebo effect

Chronic pain conditions are driven by either central mechanism or peripheral mechanisms or both. OA is a typical disease, where pain is originated from peripheral joints and enhanced later by altering central pain mechanism (Klosterhalfen et al., 2009). Rheumatoid arthritis (RA) is another disease which has similar pain mechanism but probably more peripheral contribution (e.g., inflammation). Another type of pain may be caused solely by the alternation/abnormality of pain centre in brain or spinal cord. FM is one of them (Schaible, 2007), which provides a unique pain model in

comparison with OA and RA to examine whether placebo works through central, peripheral or both to achieve its analgesia.

3. Aims and objectives of the thesis

The aim of this thesis is to determine whether the placebo effect exists in the treatment of FM and to identify factors that relate to its magnitude, using a systematic review of RCTs. Also a comparison will be undertaken to compare the placebo response to specific treatments used in FM to the placebo response when the same treatments are used in OA.

The whole study has four main tasks. First of all, a systematic review and meta-analysis is performed to demonstrate the benefit that placebo can bring to FM patients. Secondly, by sub-group analysis and meta-regression, possible determinants of this placebo effect are discussed. Thirdly, adverse effect of placebo is studied to investigate the nocebo effect in FM. The last task is to compare the placebo in FM with the placebo in OA and RA. The results of the each task are presented in chapter 4, 5, 6, and 7, separately. More detailed information on the nocebo effect and different pain mechanisms and the rationales of doing nocebo analysis and comparison study are stated in chapter 6 and 7.

Through literature review, placebo is proven effective in different conditions, so the same result is expected. The size of treatment and route of delivery were found to be determinants of the placebo effect in the OA study, and they are examined as possible determinants in this study too. Other factors are examined based on the data available from all included trials. In the comparison analysis, the hypothesis is that placebo might work differently for pain caused predominantly by central mechanisms (FM) than in pain associated with tissue damage and peripheral nociception in OA.

4. Brief summary

This chapter provided a thorough background about FM, from its history, epidemiology, pathogenesis, diagnosis, current management, and prognosis. It is clear that FM is a central driven chronic painful condition. Altered sleep physiology and pain physiology play very important role in the development of FM. Although there is no cure to FM, different treatments have been studied and proven to be effective. Understanding on the placebo and placebo effect was also given in this chapter. Since the placebo is effective as a treatment to different conditions, it naturally brings up the question whether it is also effective in FM and what the determinants of the magnitude of its effect size.

Chapter 2 Methods

This chapter explains the main research methods that were used in this study and the feasibility of choosing the methods, including ways of collecting data, database construction, study quality check and statistical analysis.

In this study, a systematic review and meta-analysis was undertaken, which focused on the identification and analysis of RCTs of treatments in FM that included placebo and/or untreated arms.

2.1 Systematic literature search

2.1.1 Databases

Electronic databases were used for the literature search, specifically Medline (1950–), Web of Science (1960–), EMBASE (1980–), Cumulative Index to Nursing and Allied Health Literature (CINAHL) (1982–), and Allied and Complementary Medicine (1985–). For Medline, both PubMed and OVID databases were searched. Each database was searched from the date when it was initially established. Google search was also undertaken for specific therapies in FM, and the first 100 hits were examined WZ. The search was updated in Feb, 2014 to identify new studies.

2.1.2 Search terms and strategies

The search strategies included: [1] search for fibromyalgia; [2] search for randomised controlled trials (RCTs). Terms used for FM include fibromyalgia/ chronic widespread pain/ fibrositis. Terms used for RCTs included: randomised controlled trial; clinical trial; double blind method; single blind method; comparative study; placebo. Searches were combined between FM and RCTs to produce relevant citations. Systematic reviews and meta-analysis were searched as well to identify any additional studies (Appendix 1 Searching strategy).

2.1.3 Other searches

References from retrieved systematic reviews and RCTs were examined to identify studies relevant to this project. Published abstracts were also searched through national and international societies such as European League Against Rheumatism (EULAR), American College of Rheumatology (ACR) and British Society of Rheumatology (BSR).

2.2 Study selection

Citations were imported into Endnote X7 to remove duplications. Titles and abstracts were read to judge whether the studies met the inclusion criteria. Full papers were obtained for further scrutiny of

relevant studies according to the following inclusion and exclusion criteria.

2.2.1 Inclusion criteria

Studies meeting the following criteria were included:

- RCTs with placebo and/or untreated group
- Studies of participants with FM
- Studies investigating clinical outcomes such as pain, fatigue, sleep quality, physical function and quality of life
- Full reports

2.2.2 Exclusion criteria

The following studies were excluded

- RCTs without placebo or no-treatment control
- RCTs with non-clinical outcome measures, eg, biochemical measures
- Duplicated publications
- Reviews, editorials or commentaries
- Animal experiments

2.3 Quality assessment

2.3.1 Quality of studies

The Jadad score is a widely used checklist to assess the quality of a clinical trial. It covers three aspects, namely randomization, blinding and withdraws/dropouts. The Jadad score varies between zero (very poor) and five (rigorous). Another well-established and commonly used quality assessment tool is the Cochrane Collaboration's tool for assessing risk of bias, which does not use the scoring but categorical system, (Benedetti et al., 2006) .

Although Jadad score has been well accepted in medical research and widely used, it has been criticised for being over-simplified and placing too much emphasis on blinding and low consistency between different reviewers. Allocation concealment is not included which is regarded as paramount to avoid bias by The Cochrane Collaboration (Alexopoulos et al., 2007).

In this study, the Jadad checklist (Table 2-1) was used for two purposes, 1) to evaluate the general quality of all the included trials; 2) to categorise the trials into different quality groups for subgroup analysis. To compensate the drawback of the Jadad score, allocation concealment was added. Blinding was future broken into healthcare

provider blinding, patient blinding and assessor blinding to gain better understanding of the placebo effect and its determinants.

Details of randomisation, allocation concealment, blinding and withdrawal dropouts were added to the checklist for more detailed quality assessment (Table 2-2).

Table 2-1 Quality of trial (Jadad's checklist) Total score:

Question	Yes	No	Unknown/NA
1. Was the study described as randomised (This includes the use of words such as randomly, random, and randomisation)?	☐1	☐0	
2. Was the method of random allocation appropriate (eg, table of random numbers, computer generated, etc)?	☐1	☐-1	☐0
3. Was the study described as double blind?	☐1	☐0	
4. Was the method of double blind appropriate (eg, identical placebo, active placebo, dummy, etc)?	☐1	☐-1	☐0
5. Was there a description of withdrawal and drop-outs?	☐1	☐0	

Table 2-2 Further quality assessment

	Random number	Allocation concealment	Blind care provider	Blind patient	Blind assessor	Intention to treat analysis
Yes	☐	☐	☐	☐	☐	☐
No	☐	☐	☐	☐	☐	☐
Unknown	☐	☐	☐	☐	☐	☐

2.3.2 Risk of Bias

Selection bias: All studies retrieved from the literature search were included regardless of the quality to avoid selection bias. Studies of different qualities were analysed separately if necessary.

Language bias: Non-English language databases were not searched. However, there was no language restriction for the studies obtained through the databases listed above. Any study meeting the inclusion criteria were included regardless of language to minimise language bias. Translations were undertaken if needed.

Publication bias: Cochrane registration (Cochrane) Clinical trials registration (Cochrane) and other national and international trial registration databases were searched for unpublished trials. A funnel plot was used to examine the possibility of publication bias in each

analysis. The Egger statistic was used for asymmetry of the funnel plot (Egger et al., 1997).

Heterogeneity: I^2 was used to measure study heterogeneity (Higgins et al., 2003). It is a measure for inconsistency among studies ranging from 0% to 100%. The larger the I^2 the greater is the inconsistency or heterogeneity of study results. The Q test was applied to determine whether any heterogeneity was statistically significant (Whitehead, 2002).

2.4 Data extraction

2.4.1 Development of the customised data extraction form

A data extraction form was developed for the review which was used to collect data from each of the included studies (Appendix 2 Data extraction form). The information for each study was extracted according to the study level demographics (design, setting, year of publication, sample size, mean age, gender ratio, funding body etc), the quality assessment (randomisation, concealment, blinding, withdrawal, intention-to-treat analysis etc), and the outcomes (pain, sleep, fatigue etc).

2.4.2 Database development

A database was developed using Microsoft Excel. Information concerning the study level characteristics, the quality of study and the outcomes was entered in the database. Different tables and spreadsheets were used to accommodate this information. A unique study ID was assigned to each study across tables, which allowed querying and selection of studies for further analysis.

2.5 Data validation

The data were extracted by one reviewer (X.C.) from all the selected studies using the data extraction form. A second reviewer (K.Z.) randomly chose 10% of the studies and extracted the data independently. Agreement was examined between the two data extractions by another two researchers (M.D. and W.Z.). Less than 5% disagreement was found. The threshold of 5% was based on our experience under the assumption of no significant change for the conclusion between data with 5% disagreement and the data with full (100%) agreement.

2.6 Outcome measures

2.6.1 Primary outcomes

Primary outcomes of the study included pain, fatigue, sleep quality and physical function. The visual analogue scale (VAS) was commonly used to measure pain reduction. In fatigue measurement, The Multidimensional Fatigue Inventory (MFI) was the most commonly used tool. MFI is a 20-item self-report instrument designed to measure fatigue. It covers the following dimensions: general fatigue, physical fatigue, mental fatigue, reduced motivation and reduced activity (Ingham et al., 2011). Pain, fatigue and sleep quality measured by VAS were taken if reported. Other scales such as Likert scale and categorical scale were used when VAS was not available. Standardized mean difference was calculated in the meta-analysis to avoid heterogeneity that was caused by the usage of different measurement tools for the same outcome. Commonly used measurement tools are summarised in **Table 2-3**.

Table 2-3 Summary of commonly used measurement tools

Outcome	Measurement tool	Ref
Pain	Visual analogue scale	Carleton 2011
	FIQ pain	Deluze 1992
	Numerical rating scale	Arnold 2010
	Brief Pain Inventory	Ginsberg 1996
	McGill Pain Questionnaire Pain rating index	Arnold 2007
Fatigue	Multi-dimensional fatigue inventory	Arnold 2004
	FIQ Fatigue	Chappell 2008
	Visual analogue scale	Kiyak 2009
Function	SF-36	Bennett 2003
	FIQ Function	Hammond 2005
	Visual analogue scale	Tomas-Carus 2009
Sleep	Numerical rating scale	Martin 2006
	FIQ sleep disturbance	Nelson 2010
	Visual analogue scale	Almeida 2003
	Medical outcomes study sleep problems index score	Hargrave 2012
Depression	Beck's depression inventory	Branco 2010

2.6.2 Secondary outcomes

Secondary outcomes included quality of life (QOL), patients and doctor's assessment of overall wellbeing, and other measurements. The FIQ and SF36 were normally used as disease-specific and generic QOL instruments respectively in FM. Other QOL measurements were also included.

FIQ is composed of 10 items. The first item contains 11 questions related to physical function. Each question is rated on a 4 point Likert type scale (0-3). Average score of all the answered questions in this item will be the patient's physical impairment score. Items 2 and 3 ask the patient to mark the number of days they felt well and the number of days they were unable to work (including housework) because of

the fibromyalgia symptoms. The rest 7 items all use horizontal linear scale (0-10), on which patient rates pain, fatigue, depression, etc. After the initial scoring is completed, the first three item scores are subjected to normalization so that all scores range from 0 to 10. Therefore, the maximum possible total score of FIQ is 100.

2.7 Statistical analysis

Effect size (ES), that is the standardised mean difference (SMD), was calculated for each outcome measure. The ES standardises the difference using the pooled within study standard deviation (SD) between groups, and therefore normalises the measure across studies which permits the combined analysis. However, unlike the natural measure of the outcome such as pain on VAS (pain ranges from 0 to 100 mm), ES measured the size of effect in the unit of SD. According to Cohen's definition, ES=0.2 (i.e., 20% of SD) suggests a small effect, ES=0.5 (i.e., 50% of SD) indicates a moderate effect, and ES=0.8 (80% or more of SD) means a large effect (Cohen, 1988). Hedges (1982) method was used to calculated ES and its 95% confidence intervals (CI) (Hedges, 1981). ES from baseline to the endpoint was calculated for each arm in the included RCTs. The placebo effect was defined as the difference between the ES for placebo and the ES for untreated control, (Nikolajsen et al., 2006). Heterogeneity was assessed (please see the section Risk of bias, page 51, for further details). A random effects model was used to

combine the results when heterogeneity was high, (Inaba, 2009). Sensitivity analysis was undertaken according to types of intention and type of control (placebo control, no treatment control or both).

Meta-regression is a tool used in meta-analysis to examine the impact of moderator variables on study effect size using regression-based techniques (Borenstein et al., 2009). In this study, it was used after subgroup analysis to examine the possible determinants of the placebo effect.

2.8 Brief summary

Research methods in this study were explained in this chapter. Systematic review and meta-analysis was chosen as the main research methods. Effect size of placebo was calculated as the standard mean difference between baseline and endpoint within the placebo control groups. Subgroups analysis is the main methods to look at the possible determinants of placebo effect and meta-regression is further used to confirm the results.

Chapter 3 Study Characteristics

This chapter covers all study characteristics of the included trials. The procedure of studies selection will be explained in details. Demographic characteristics of participants will be summarised at study level. Different treatments that were used in the trials will be grouped together and the quality of trials will be reported.

3.1 Systematic literature search and study selection

The literature search was completed and updated in February 2014. The type of treatment was not restricted in the search to bring out as many as possible trials that used different treatments. After summarising all treatments that were tested in the trials, each specific treatment was added to the search and re-run to find any missing trials.

In total, 3375 citations were retrieved from the databases. After removing duplicates, 3286 citations remained. Full citations, including abstracts were imported into EndNote X7 and examined. 257 studies appeared relevant by reading abstracts and the full papers on these were retrieved. Subsequently, 204 of these were deemed appropriate and included for meta-analysis (Figure 3-1).

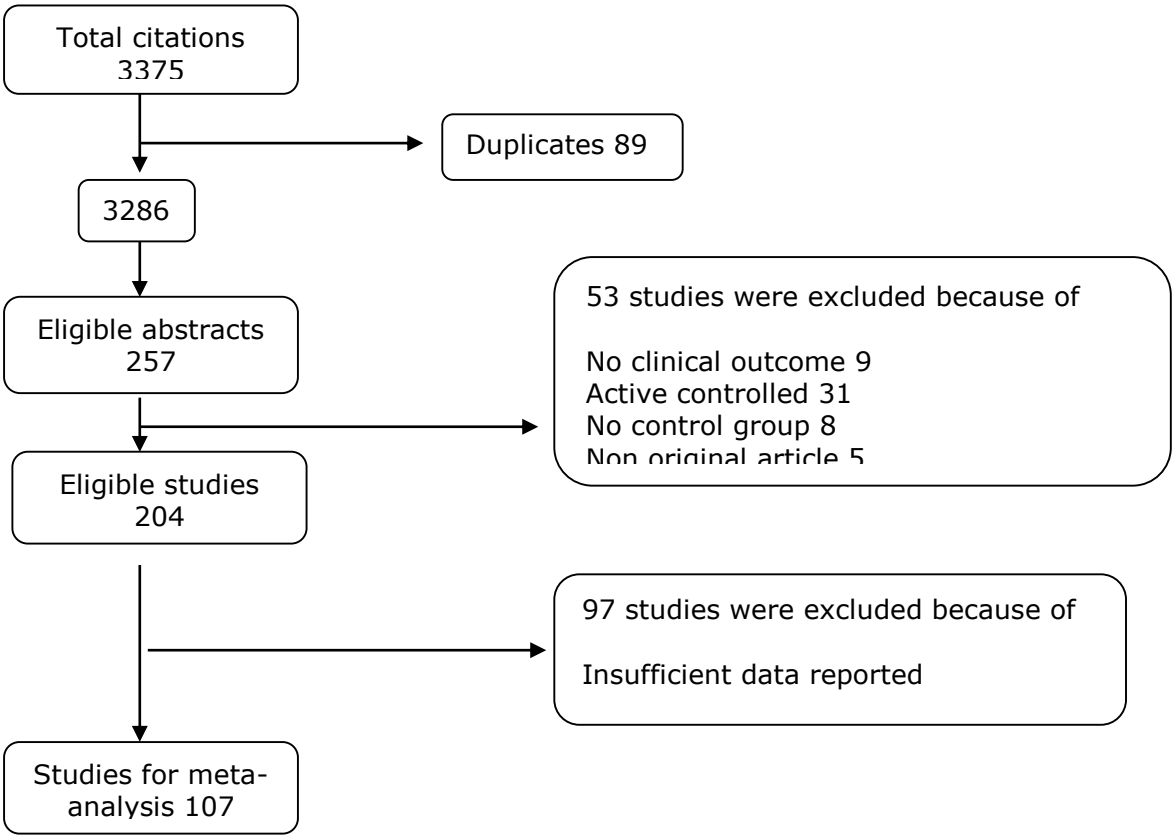


Figure 3-1 Flowchart of literature search

Of the 53 studies which were excluded from the 257 eligible abstracts, 9 did not have any clinical outcome, 31 used active interventions in the control groups and 8 did not have any control group. The final 5 studies were excluded because they were secondary analysis of the trials whose primary outcome had already been published somewhere else.

In order to perform meta-analysis, both the means and standard deviations of each outcome measure are needed. Trials that failed to provide suitable data were not able to enter this review. A total of 97 eligible trials could not be included in the final data selection because

of the lack of suitable data. Therefore, 107 trials remained for meta-analysis.

Data from all included studies were extracted using a pre-defined data extraction form and validated by another researcher (NA). All studies used either placebo or untreated group as control. One study that investigated magnetic therapy for FM used both placebo and untreated control groups (Alfano, 2001) but in the demographics section it is only counted once in the placebo controlled group to avoid duplication.

3.2 Demographic characteristics of included studies

Of the 107 trials included in the review, 63 used placebo and 44 used an untreated group as control. In total there were 10,980 participants in placebo controlled trials and 3,078 participants in untreated group controlled trials. Both placebo controlled trials and untreated group controlled trials had participants of a similar age range and similar percentage of women (Table 3-1).

Table 3-1 Demographic characteristics of included trials

	Total	Control	
		Placebo	Observation
No. of trials	107	63	44
No. of participants	13968	10980	3078
Mean age, range (yr)	49.2 (29.4, 59.0)	49.0 (29.4, 59.0)	49.4 (40.8, 58.5)
Women%	95.4 (63.7, 100)	94 (63.7, 100)	100 (74, 100)
No. of trials reporting outcomes for			
Pain	81	47	34
Physical function	28	14	14
Fatigue	45	30	15
Sleep quality	30	18	12

The main symptoms of FM, such as pain, physical function impairment, fatigue, and sleep disturbance, were all measured in both placebo controlled trials and untreated group controlled trials.

3.3 Geographic distribution and recruitment

The USA had the largest number of trials (41/107), followed by Spain (12), Canada (10) and Turkey (6). All except one trial (Finchk, 2005) used a parallel group study design. All trials after 1990 used the American College of Rheumatology FM classification criteria. Trials that were conducted earlier than the ACR 1990 criteria used diffuse pain, fatigue and multiple hyperalgesic sites for FM diagnosis. Both criteria were considered appropriate in this review.

Participants were recruited entirely from the community in 17 trials, from general practice in 2, from hospital outpatient clinics in 53 and from FM Society patient groups in 4. Participants were recruited from two sources in 7 trials (outpatient and community, outpatient and patient society) and 22 trials did not specify where they recruited their participants. More characteristics of the included trials are summarised in Table 3-2.

Table 3-2 Summary of other study characteristics

	Total	Control	
		Placebo	Observation
Existing therapy			
Continued	30	14	16
Stopped	32	31	1
Unclear	45	18	27
No. of study centres			
Single	39	19	20
Multiple	34	31	3
Unclear	34	13	21
Route of delivery			
Oral	38	38	0
Physical touch	17	17	0
Needling*	8	8	0
Others	44	0	44
Funding body			
Industry	31	31	0
Non-industry	27	8	19
Unclear	49	24	25

*Needling included needle injection and acupuncture

3.4 Types of interventions

Both pharmacological and non-pharmacological interventions were tested in the included trials. Antidepressants were the most common pharmacological intervention and exercise was the most common non-pharmacological intervention. Other commonly investigated treatments included cognitive behavioural therapy (CBT), balneotherapy and magnetic and electrical stimulation (Figure 3-2).

All pharmacological trials used placebo as control. Some physical intervention trials also used sham treatment as control. These interventions included acupuncture, magnetic field, laser, ultrasound and electrical current stimulation. In these studies similar technology was used but without the active component (e.g. electrical machines were turned off, non-magnetic devices were used, acupuncture needles did not penetrate or were used in non-acupuncture sites).

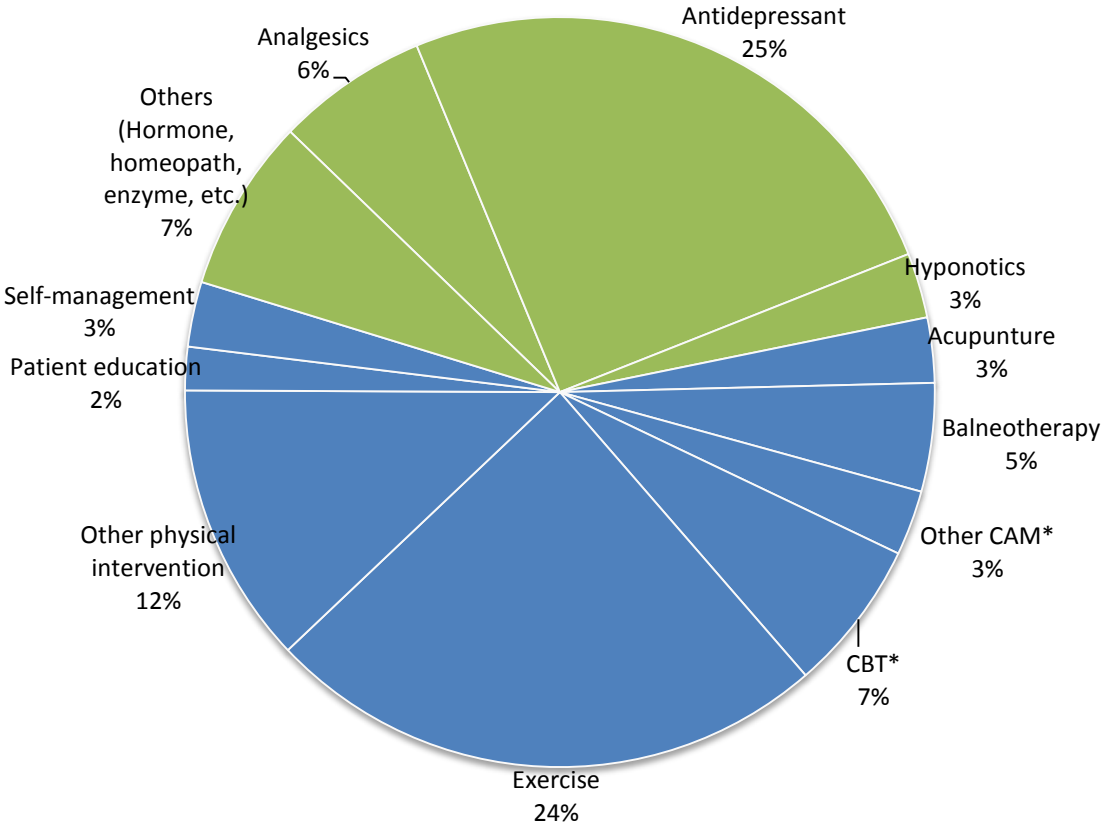


Figure 3-2 Types of treatments
*CBT, cognitive-behavioural therapy; CAM, complementary and alternative medicine

Pharmacological treatments were further categorised according to mechanism of action such as analgesics, antidepressants and hypnotics. Non-pharmacological therapies were further categorised as self-management, education, physical therapies (eg, exercise and balneotherapy), psychological therapy (eg, CBT) and complementary and alternative therapy (eg, herbs and acupuncture). Many therapies were only studied in one trial while others were studied in just a few trials (Table 3-3).

Table 3-3 Summary of treatment used in all included trials

	Category	**Treatments in included trials (No. of trials)**
Non-pharmacological	Self-management	Self-management (3)
	Patient education	Patient education (2)
	Exercise	Exercise (26)
	Balneotherapy	Thermal bathing (3), SPA (1), Phytothermotheray (1), Mud pack bath (1)
	Other physical intervention**	Current stimulation (2), Neurofeedback (3), Farabloc (1), Ultrasound and current (1), Magnetic field (5), Laser (1)
	CBT*	CBT (7)
	Acupuncture**	Acupuncture (3)
	Other CAM*	CAM (3)
Pharmacological	Analgesics**	Carisoprodol, paracetamol & caffeine (1), Nabilone (1), pregabalin (4), Gabapentin (1) and Tramadol & acetaminophen (1).
	Antidepressants**	Fluoxetine (2), Duloxetine (5), Milnacipran(5), Esreboxetine (2), Amitriptyline (5), Terguride (1), Tropisetron (3), Moclobemide (1), Citalopram (1), Dolasetron (1) and Paroxetine (1)
	Hyponotics**	Sodium oxybate (3)
	Others**	Cyclobenzaprine (1), Growth hormone(1), Dehydroepiandrosterone (1), Pyridostigmine (1), Alpha1-antitrypsin (1) Homeopath (2)

*CAM, complementary and alternative medicine; CBT, cognitive-behavioural therapy
** Placebo controlled trials

3.5 Quality assessment

3.5.1 Jadad score

Quality assessment was undertaken using the Jadad checklist. Randomization was undertaken adequately in all trials. All placebo controlled trials claimed to be blinded. However, two of them were judged not to be truly blinded based on the description in their methods section. Due to the nature of study, no-treatment controlled trials were not able to blind the participants or care providers. Most included trials (90%) had Jadad score >=3. More placebo controlled trials passed that threshold than no-treatment controlled trials (93.5% vs. 84.4%).

3.5.2 Other quality aspects

Only around half of the included trials clearly stated that they used intention to treat (ITT) analysis for their outcome measures. Less than 50% (47/107) of trials had clear allocation concealment, of which 37 were placebo controlled, and 10 were untreated group controlled trials. Over half of the trials (58%) contained participants who were blinded to treatment and all of these were placebo controlled (Table 3-4). Of the 63 placebo controlled studies, the majority (68.2%) maintained blinding of patients, care provider and assessors.

Table 3-4 Additional assessment of study quality

	Total	Control	
		Placebo	Observation
ITT*			
Yes	56	35	21
No	24	11	13
Unknown	27	17	10
Allocation concealed			
Yes	47	37	10
No	13	5	8
Unknown	47	21	26
Random number			
Yes	49	34	15
No	6	3	3
Unknown	52	26	26
Blinded to:			
Patient	58	58	0
Care provider	43	43	0
Assessor	60	49	11

*ITT, intention to treat analysis

3.5.3 Publication bias

Funnel plots were used to detect potential publication bias for the reporting of all major outcomes. Overall, the funnel plots are symmetrical for pain, fatigue, sleep, depression and FIQ total score, suggesting that there is no significant publication bias for these outcomes (Appendix 4 Publication bias). These were supported by the Egger test where the asymmetric tests for the 6 outcome measures were insignificant, (Table 3-5). The only exception was physical function (Figure 3-3), where the funnel plot was asymmetric (p=0.0486), that is, trials with smaller placebo effects were more likely

to be published. These trials normally had larger standard error (i.e., smaller sample size).

Table 3-5 Summary of publication bias in main outcome measures

Outcome	Egger test (95%CI)	P value
Pain reduction	-0.94 (-2.0, 0.14)	P = 0.0859
Fatigue	-0.30 (-1.10, 0.50)	P = 0.4522
Physical function	-1.47 (-2.93, -0.01)	P = 0.0486
Sleep quality	-0.90 (-1.89, 0.08)	P = 0.0704
FIQ total score	0.69 (-0.75, 2.13)	P = 0.3331
Depression	0.06 (-2.17, 2.28)	P = 0.9544
Number of hyperalgesic tender sites	1.64 (-0.90, 4.17)	P = 0.1939

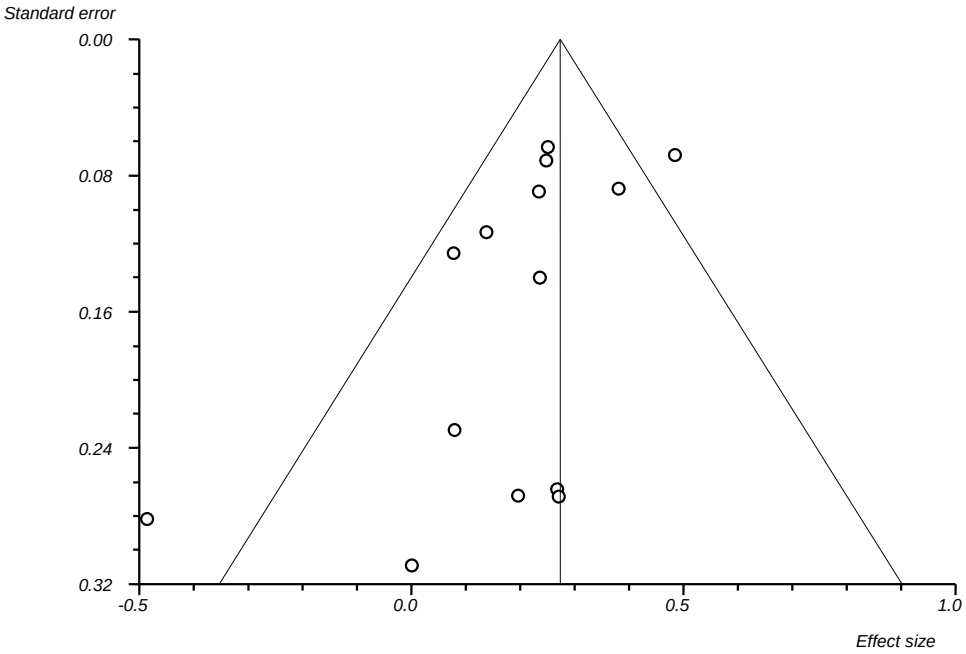


Figure 3-3 Funnel plot: physical function

3.6 Brief summary

One hundred and seven trials were included in this study. The majority of participants in these trials were middle age and women. Various types of treatments were tested and both placebo control group and untreated control group were used in the trials. The quality of study was assessed as good in general. It all provided a great base for a systematic review and meta-analysis.

Chapter 4 Is Placebo Effective in the Treatment of Fibromyalgia?

In this chapter, the first main research question, whether placebo is effective as a treatment to FM will be answered. A direct comparison between the placebo group and untreated group from the same trials will be presented. However, the number of three arm trials which allow direct comparison is very limited. Indirect comparison of the placebo groups and untreated groups from different trials will also be used to demonstrate the placebo effect. The placebo effect will be examined in all main outcome measures to prove the existence of placebo effect.

4.1 Direct comparison between placebo and untreated control

Only one trial with three arms (active intervention, placebo and untreated control group) was found from the literature, (Alfono, 2001). In this trial, participants were randomised into a static magnetic fields treatment, sham treatment or untreated control - usual care (Table 4-1).

Table 4-1 Demographic characteristics of study population

	Static magnetic field	Sham treatment	Usual care
No. of participants	37	27	17
Mean age (years)	44.0	46.0	44.8
Women (%)	92	96	100
Caucasian (%)	97	100	94

Sham magnetic treatment had a larger effect size on pain reduction and FIQ total score than usual care. The direct comparison showed that the participants in the sham treatment group had greater improvement than those in the usual care group. The effect size (ES) for pain reduction from baseline was 0.54 for the placebo group and 0.06 for the usual care group. The ES for FIQ total score was 1.17 for the placebo group and 0.55 for the usual care group (Figure 4-1).

This direct comparison confirms that placebo is better than untreated control in the clinical trial setting. However, only one study was available for such direct comparison. Due to the small sample size the 95% confident intervals were large.

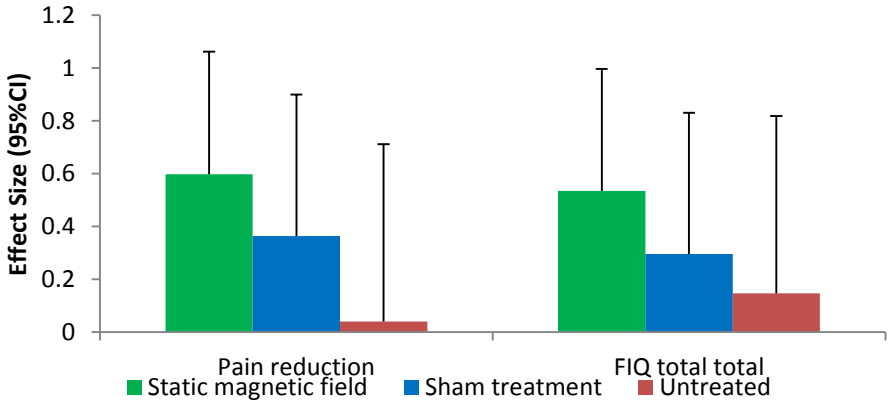


Figure 4-1 Effect size (95% confidence interval) on pain reduction and FIQ total score for treatment, placebo and untreated control groups

4.2 Indirect comparison between placebo and untreated control groups

In addition, we found 62 placebo controlled trials and 44 untreated controlled trials. Outcomes reported in these trials were summarised in **Table 4-2**.

Table 4-2 Number of trials with each outcome measure

Outcome	No. of trials (placebo)	No. of trials (untreated)
Pain reduction	47	34
Fatigue	30	15
Physical function	14	14
Sleep quality	18	12
FIQ total score	33	29
BDI score	9	8
Number of tender points	23	14

The effect sizes (change from baseline) were pooled for placebo and untreated control groups respectively for different outcomes irrespective of whether these two groups were compared in the same trials or not. The results demonstrated that [1] there were substantial improvements from baseline (all statistically significant) for all outcomes in placebo groups; [2] there were, however, very little and non-statistically significant changes from baseline (positive/negative) for pain, fatigue, sleep, BDI and number of tender sites from untreated groups*;* [3] a significant worsening was observed for function score, whereas a significant improvement was observed for FIQ score in untreated control groups; [4] the magnitudes of the effect sizes in

placebo groups were in general significantly greater than those in untreated control groups for all outcomes except for BDI. The comparison was made using the 95%CIs. When the 95%CIs overlapped, the difference between the two groups was not statistically significant (Figure 4-2).

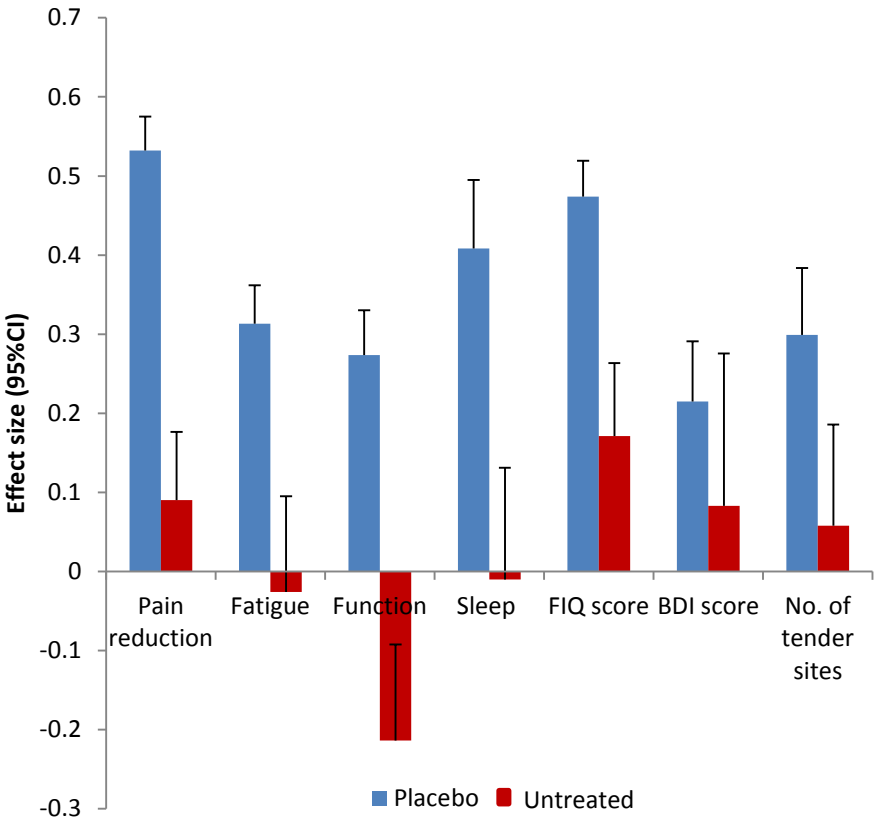


Figure 4-2 Indirect comparison between placebo and untreated control groups

4.3 Placebo effect in main clinical outcomes

As placebo was better than untreated control, the following analyses were based on placebo group only to demonstrate detailed meta-analysis for each clinical outcome.

4.3.1 Pain reduction

Pain reduction is the most commonly examined outcome measure in clinical trials for FM. In this review 47 trials had placebo groups. In total 4,472 participants in the placebo groups were assessed. The average age of participants was 47.8 years, and over 90% of them were women (Table 4-3). A statistical test could not be undertaken as these were study level characteristics.

Table 4-3 Demographic characteristics of pain analysis

	Placebo groups
No. of participants	4472
Mean age	47.8
Women%	91.53

The pain reduction due to placebo varied from study to study. Overall, placebo had a medium mean effect size (ES=0.47, 95%CI 0.37 to 0.56) in reducing pain due to fibromyalgia (Figure 4-3). The placebo effect became more confirmed after 2005 as all studies after that year had positive results. Also, studies in later years had larger sample size and better study quality. Compared with studies that had positive placebo effect, the ones that had negative results had smaller sample size and larger confident interval, which shows studies with better quality are more likely to show the true placebo effect. The studies that were selected for pain reduction analysis were No. 32-39, 43, 44, 50, 52, 54, 60, 61, 63-65, 70-72, 74-79, 80, 82, 83, 86-88, 93, 96, 97, 99, 100, 104-107 in Appendix 3 Full report of study characteristics).

Heterogeneity in these studies was high (I^2=74.3%, P < 0.0001). This might be explained by the fact that data were taken from trials that used different types of treatments. The types of placebos that were included in this analysis were different in shapes, doses, colours and administrated via different routes because they were designed to look exactly the same as the active treatments in order to keep the participants blinded.

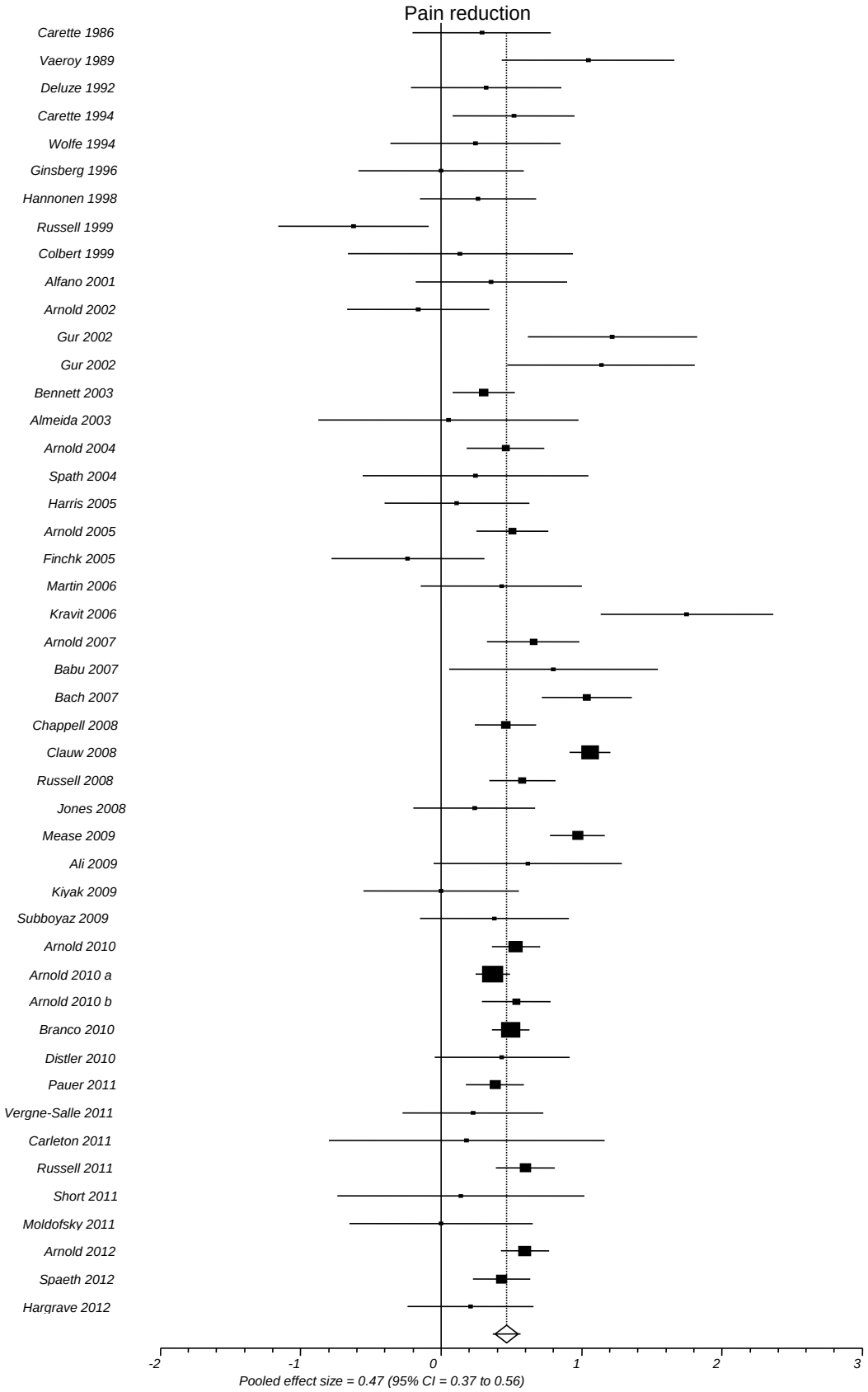


Figure 4-3 Forest plot: effect size of placebo in pain reduction

4.3.2 Fatigue

In total, 30 placebo controlled trials measured fatigue levels. Participants' demographic characteristics (age and gender) were demonstrated (Table 4-4).

Table 4-4 Demographic characteristics of fatigue analysis

	Placebo groups
No. of participants	3456
Mean age (years)	49.2
Women (%)	94.0

A pooled analysis shows that the mean placebo effect size for reduction of fatigue is 0.31 (95%CI 0.26 to 0.36). Three trials had negative results for placebo effect, (Arnold 2002, Moldofsky 2011 and Almeida 2003). However, the other 27 trials all had positive results in reducing the level of fatigue (Figure 4-4). The studies with positive placebo effect had larger sample size and better quality. Low heterogeneity (I^2=25%) was detected for this outcome (p=0.11). The studies that were selected were No. 33, 36, 38-41, 53, 54, 61, 65, 71, 72, 75-78, 82, 86-88, 91, 97, 99, 100, 101, 104, 106, 107 in Appendix 3 Full report of study characteristics.

In contrast, a pooled effect size in the untreated groups was -0.03 (95%CI -0.15 to 0.10), suggesting that there is no improvement for fatigue if there was no treatment in the trials.

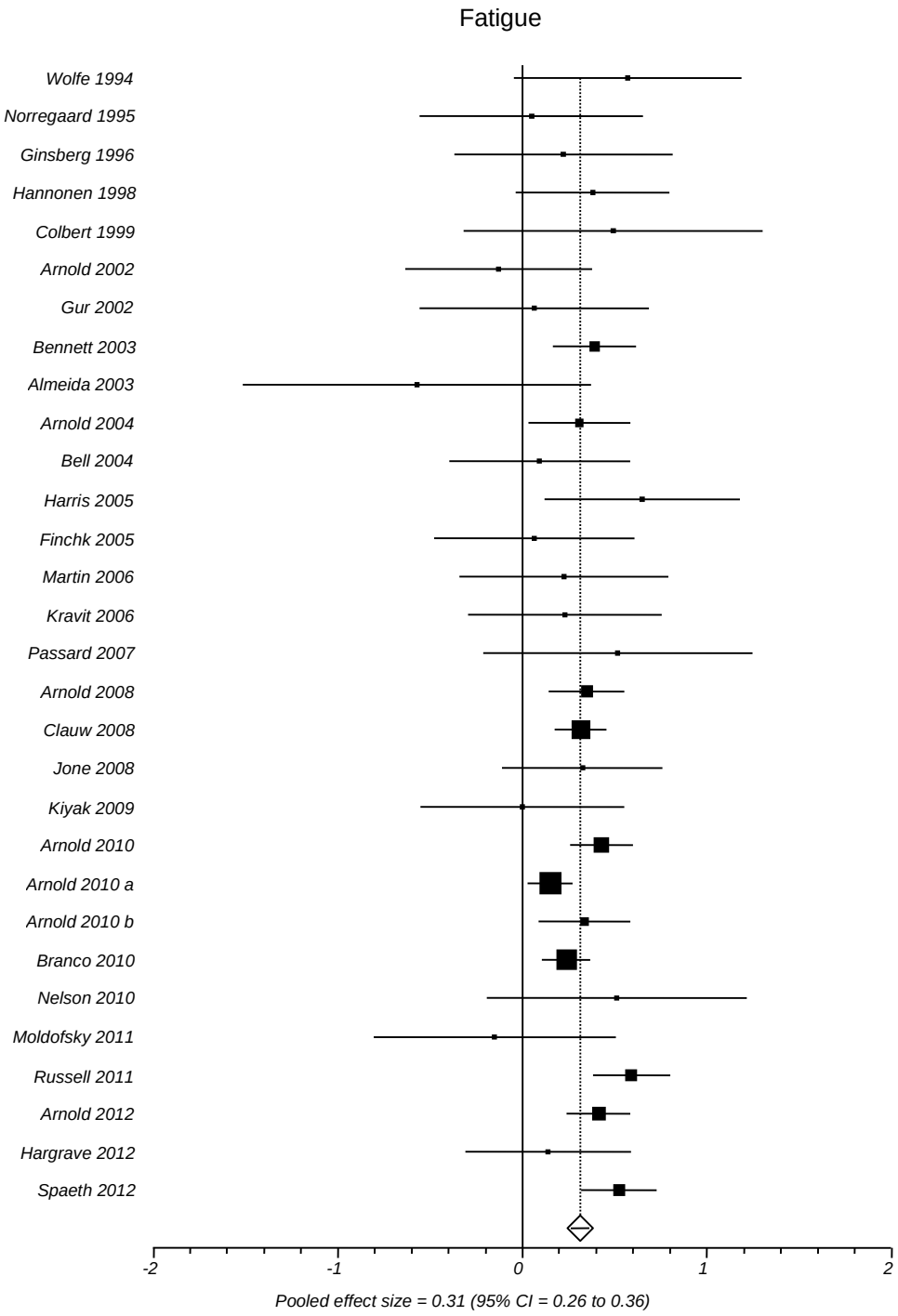


Figure 4-4 Forest plot: effect size of placebo for reduction in fatigue

4.3.3 Physical function

Chronic pain and fatigue in FM is expected to have a negative impact on physical function. 14 trials had placebo groups for physical function (Table 4-5). This was often measured using a VAS scale, or part of the short form 36 and FIQ subscales. Selected studies for this analysis were No. 38, 39, 53, 65, 72, 74-78, 82, 91, 104, 105 in Appendix 3 Full report of study characteristics.

Table 4-5 Demographic characteristics of function analysis

	Placebo groups
No. of participants	2435
Mean age (years)	50.5
Women (%)	93.4

Irrespective of statistical significance, one trial had a negative result on physical function (Finchk 2005) and one trial had a neutral result (Norregaard 1995). The other 12 trials all had positive results. The pooled mean effect size of placebo in improving physical function was 0.27 (95%CI 0.22 to 0.33) which is a small ES (Figure 4-5). Heterogeneity test showed 46.7% inconsistency in this result, (p=0.03).

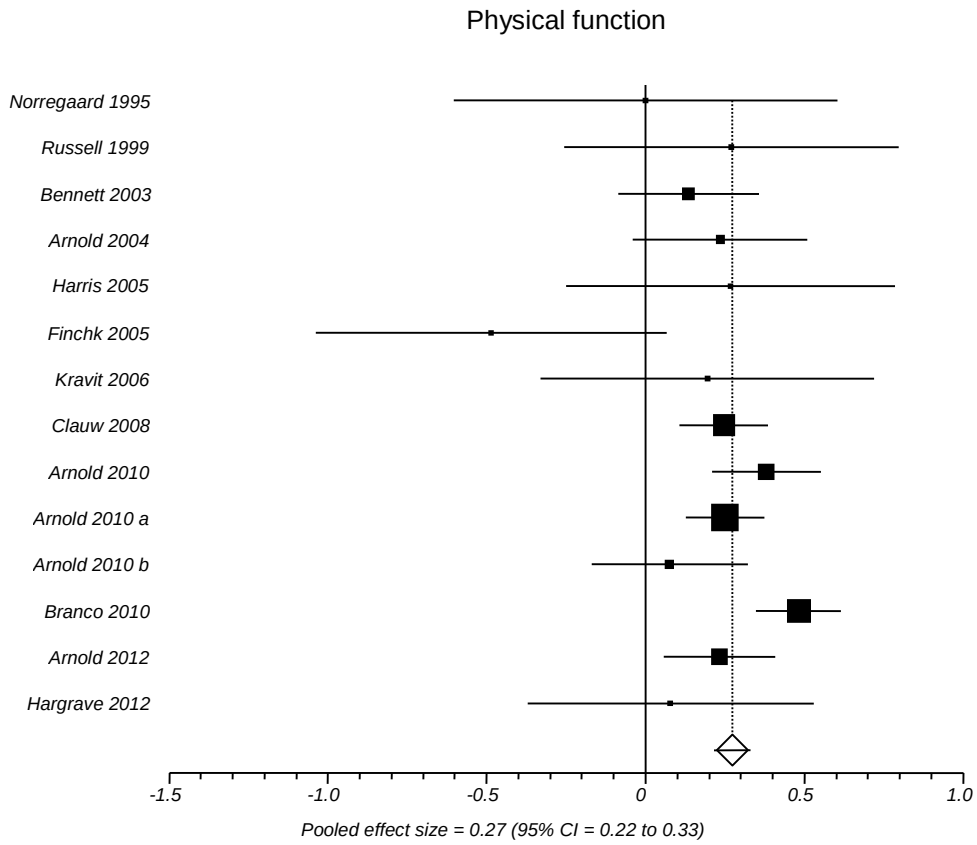


Figure 4-5 Forest plot pooled effect size of placebo in improving physical function

In the untreatment groups, participants' physical function was not improved. The pooled effect size was -0.21 (95%CI -0.34 to -0.09).

4.3.4 Sleep quality

18 trials that had placebo evaluated sleep quality (Table 4-6).

Table 4-6 Demographic characteristics of sleep quality analysis

	Placebo groups
No. of participants	1048
Mean age (years)	50.3
Women (%)	92.5

The pooled mean effect size in the placebo groups in improving patients' sleep quality was 0.41 (95%CI 0.32 to 0.49). Irrespective of statistical significance, two out of 18 trials that measured sleep quality had negative results (Norregaard 1995 and Roizenblatt 2007). The other 16 trials all showed that placebo was effective in improving participants' sleep quality. Negative results only occurred in small studies. There is 0% inconsistency found in this result, (95%CI 0% to 43.7%, p=0.52) (Figure 4-6). The trials selected for this analysis were No. 31, 36, 38, 40, 52, 54, 63, 65, 68, 70, 74, 88, 91, 97, 105, and 106 in Appendix 3 Full report of study characteristics.

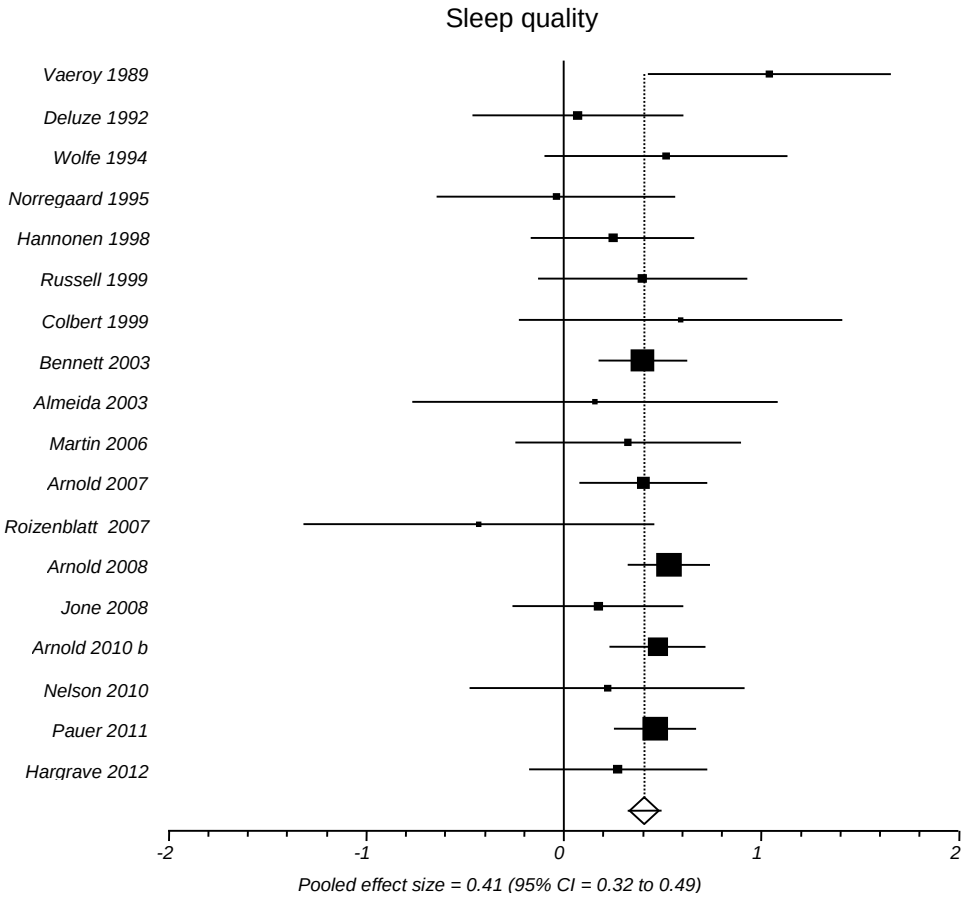


Figure 4-6 Forest plot: pooled effect size for placebo in improving sleep quality

Participants in the untreated groups showed no change in quality of sleep during the study period. The pool effect size was -0.01 (95%CI -0.15 to 0.13).

4.3.5 FIQ total score

Thirty-one trials with placebo controlled in this review reported the FIQ total score (Table 4-7).

Table 4-7 Demographic characteristics of FIQ analysis

	Placebo groups
No. of participants	3897
Mean age (years)	48.3
Women (%)	92.1

The pooled effect size of placebo on FIQ total score was 0.47 (95%CI 0.43 to 0.52). Irrespective of statistical significance, thirty-one trials all had positive results for placebo in terms of improving the FIQ total score. Only two trials with small sample size and large confidence intervals reported negative results (Arnold 2002, Kiyak 2009). Heterogeneity for this result was found to be moderate 64.3% (95% CI 44.6% to 74.8%, $p<0.0001$). Studies that were selected in this analysis were No. 32, 38, 40, 43, 44, 54, 60, 61, 63, 65, 68, 71-78, 82, 83, 89, 93, 96, 99, 100 and 106 in Appendix 3 Full report of study characteristics.

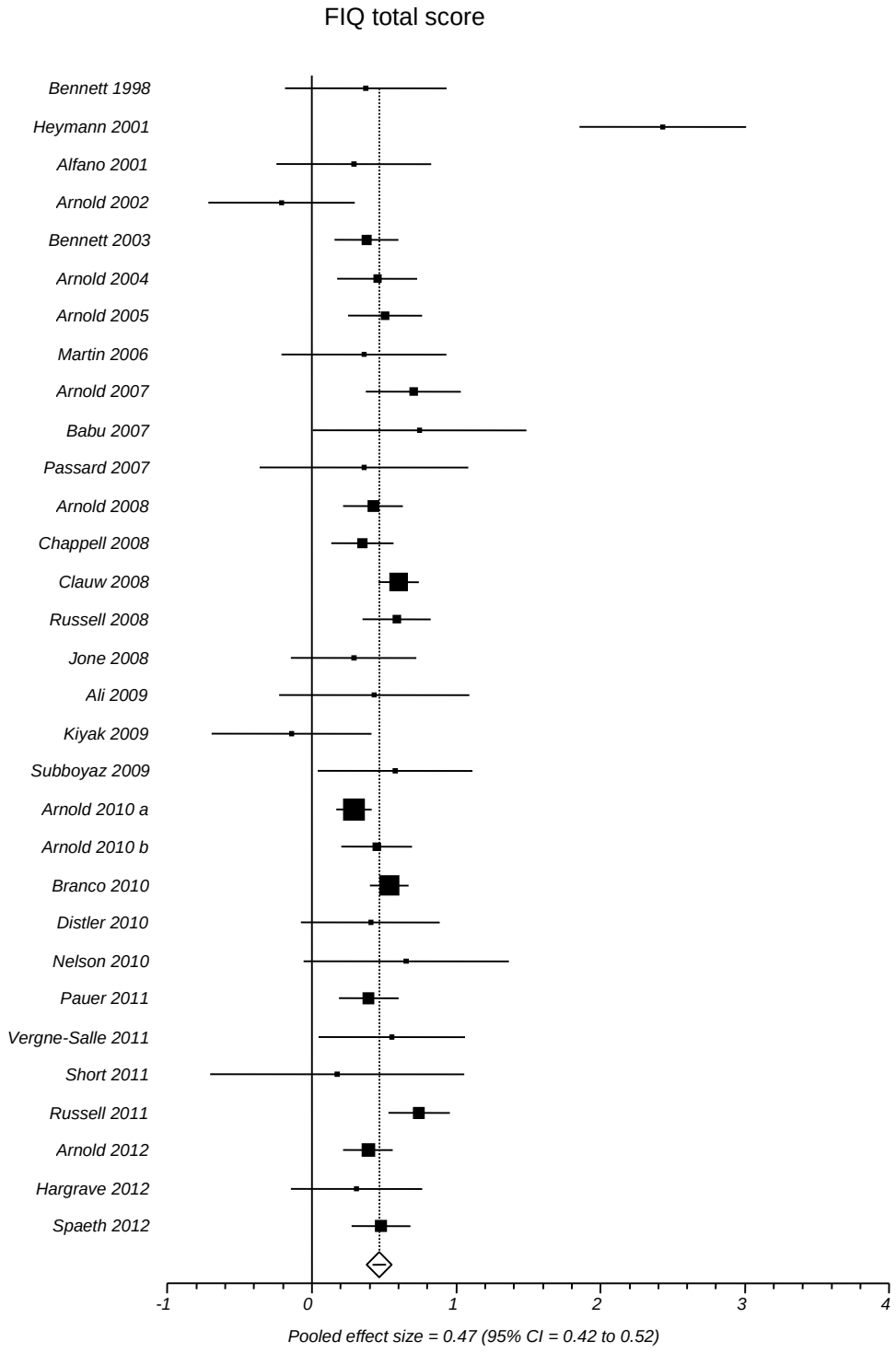


Figure 4-7 Forest plot: pooled effect size of placebo in improving FIQ total score

The effect size is significantly greater than that in the observation groups (pooled mean effect size, 0.17, 95%CI 0.08 to 0.26) (Figure

4-7). Participants in the observation groups had no improvement in FIQ total score.

4.3.6 Depression

Nine trials with placebo controlled groups used the Beck depression inventory (BDI) to measure depression (Table 4-8).

Table 4-8 Demographic characteristics of depression analysis

	Placebo group
No. of participants	1504
Mean age (years)	49.1
Women (%)	91.0

The effect sizes of placebo varied between trials. The heterogeneity was moderate (I2 = 51.7%, 95%CI 0% to 75.6%, p=0.04). The pooled mean effect size of placebo in BDI total score was 0.22 (95%CI 0.09 to 0.36) (Figure 4-8). Selected studies for this analysis were No. 44, 60, 72, 76, 78, 82, 91, 96, and 97 in Appendix 3 Full report of study characteristics.

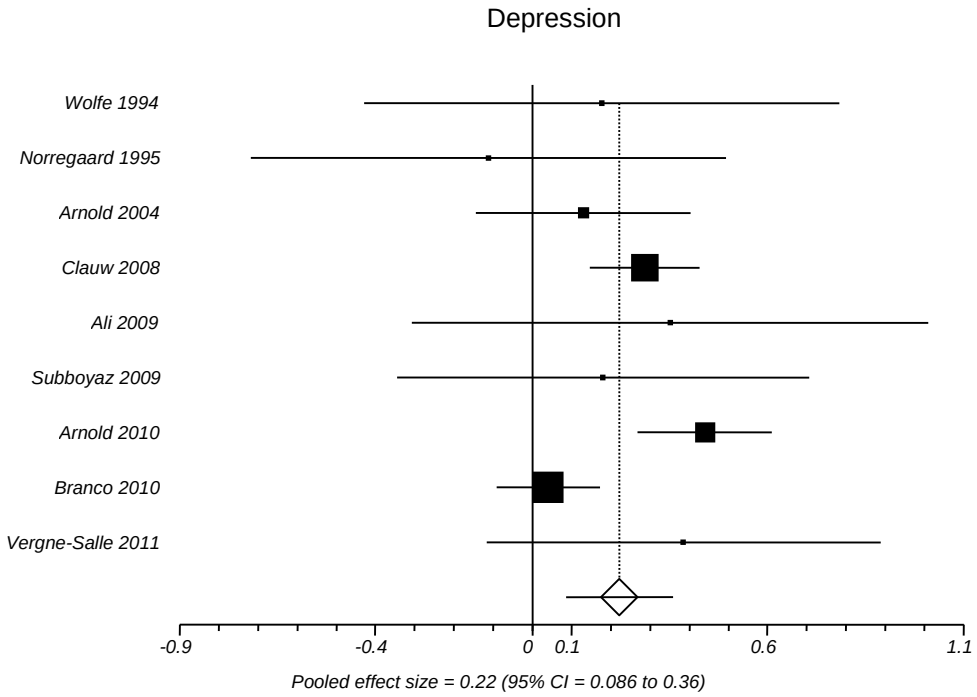


Figure 4-8 Forest plot: pooled effect size of placebo in improving the BDI total score

In contrast, there was no improvement in the untreated groups (pooled effect size, 0.08, 95%CI -0.11 to 0.28), although this was not statistically different from the pooled effect size in the placebo groups (because the two 95%CIs overlapped). The BDI score remained constant in the observation groups.

4.3.7 Number of hyperalgesic tender sites

22 placebo controlled trials measured the change in number of hyperalgesic tender sites. The characteristics of these trials were summarised in Table 4-9.

Table 4-9 Demographic characteristics of tender point analysis

	Placebo groups
No. of participants	1120
Mean age (years)	48.4
Women (%)	91.5

The pooled placebo mean effect size for reducing the number of hyperalgesic tender points was 0.30 (95%CI 0.21 to 0.38) (Figure 4-9). However, large inconsistency was found between trials (I^2 =84.4%, 95%CI 77.7% to 88.4%, p<0.0001). Selected studies for this analysis were No. 32-34, 40-43, 61, 65, 71-73, 84, 86, 87, 89, 91, 94, 97, 101, 103 and 106 in Appendix 3 Full report of study characteristics.

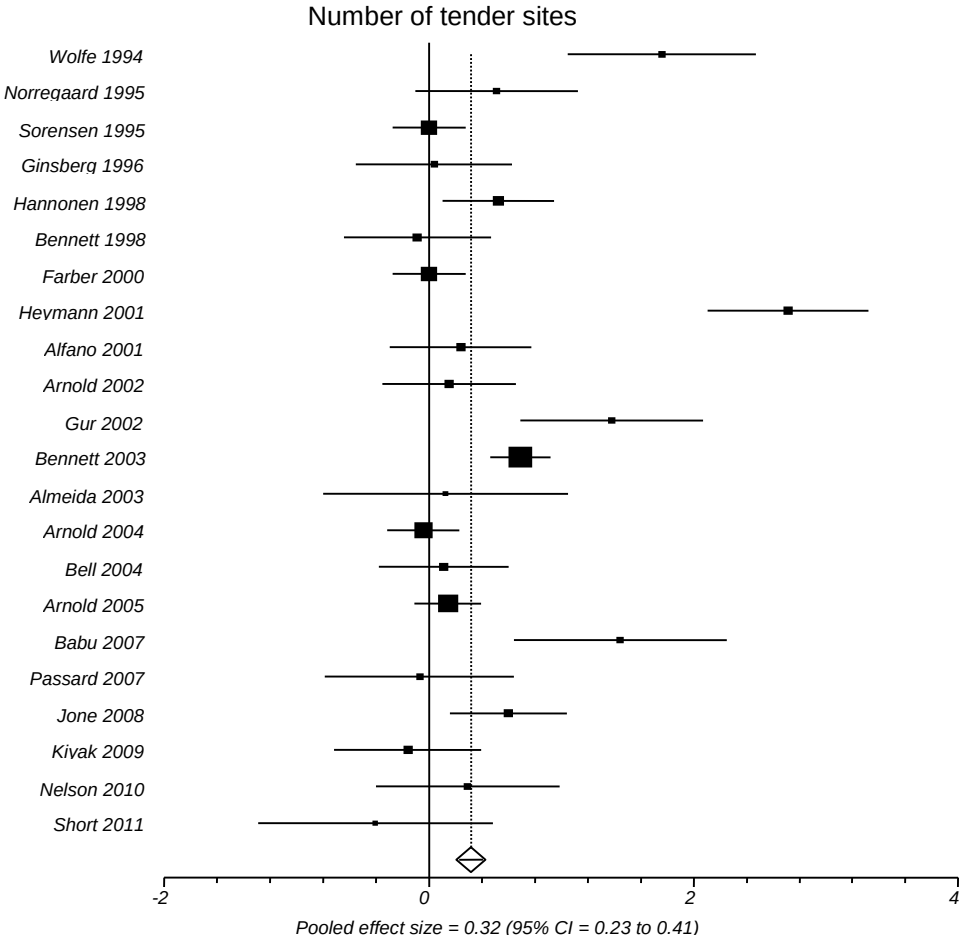


Figure 4-9 Forest plot: pooled effect size of placebo in reducing the number of hyperalgesic tender sites

In contrast, the number of hyperalgesic tender sites did not change from baseline to endpoint in the untreated groups. The pooled mean effect size was 0.06 (95% CI -0.07 to 0.19), which was significantly smaller than that in the placebo groups.

4.4 Brief summary

Of the 107 trials included in this project, one had directly compared placebo group with untreated group and 44 had compared active with untreated groups. The results showed that placebo was significantly better than untreated group for all seven outcomes, suggesting that placebo is effective per se for FM. The effect size is clinically significant according to Cohen's definition (ES=0.5) (Cohen, 1988) for pain and overall FM impact score, and statistically significant for others (Table 4-10). The clinical benefits obtained from placebo cannot be ignored.

In this study, I've collected sufficient number of studies to investigate the placebo effect in the treatment of FM. These studies included both pharmacological trials and non-pharmacological trials. The participants that involved in the trials were mostly women and middle aged.

The placebo effect in the treatment of FM has been proved by both direct and indirect comparison. Evidence shows that placebo is

effective and it's not due to natural history of the disease or regression to the mean.

Seven outcomes were measured in the included trials. Effect size was calculated as the mean change from baseline to endpoint. Each outcome measurement was pooled to produce an overall effect size of placebo (Table 4-10). Pain reduction was the most widely measured outcome with the largest number of trials and largest number of participants. The placebo effect on pain reduction was also the largest. Six outcomes were measured with participants' self-report and 1 was measured by physician. The effect size of placebo in all 7 outcomes was significantly greater than that observed in the untreated groups. This demonstrates that placebo is effective in FM. Some signals have also been picked up in the analysis. Firstly, later studies were more likely to produce positive results on the placebo effect than earlier ones. Secondly, studies with larger sample size are more likely to show placebo effect.

Table 4-10 Summary of placebo effect

Outcome	No. of trials	No. of participants	Poole effect size (95%CI)	Publication Bias (Egger)	Heterogeneity (I^2)
Pain reduction	47	4472	0.53 (0.49, 0.58)	-0.94, p=0.09	73%, p<0.0001
Fatigue	30	3465	0.31 (0.26, 0.36)	-0.30, p=0.45	25%, P=0.1078
Physical function	14	2435	0.27 (0.22, 0.33)	-1.47, p=0.05	46.7%, p=0.0276
Sleep quality	18	1048	0.41 (0.32, 0.49)	-0.90, p=0.07	0%, p=0.5195
FIQ total score	33	3897	0.47 (0.43, 0.52)	0.19, p=0.76	64.3%, p<0.0001
BDI total score	9	1504	0.21 (0.14, 0.29)	0.06, p=0.95	51.7%, p=0.0351
No. of hyperalgesic tender sites	23	1120	0.30 (0.21, 0.38)	1.58, p=0.24	84.4%, p<0.001

Chapter 5 Determinants of placebo effect

5.1 Introduction to this chapter

In this chapter, possible determinants of the placebo effect will be explored through subgroup analysis. Demographic characteristics such as age and gender will be considered first. Characteristics of the disease such as baseline severity and disease duration will also be examined. Other factors such as study settings, effect size of the active treatment etc will be discussed after. Meta-regression will be used in this chapter to confirm the result from subgroup analysis.

5.2 Age and gender

Participants' mean age and percentage of women in each trial were extracted for this analysis. The mean ages were categorised into 3 groups: <40 years (5 trials with 115 participants in the placebo groups), 40-50 years (29 trials with 3,474 participants), >50 years (9 trials with 711 participants). Due to the range and distribution of participants' mean age at study level, this was the best way to break down age groups in order to keep each group sufficient number of trials. The youngest groups had the smallest placebo effect size, (ES 0.42, 95%CI 0.16 to 0.68) followed by the middle group (ES 0.51,

95%CI 0.47 to 0.56), and then the oldest groups (ES 0.68, 95%CI 0.57 to 0.79).

The percentage of women in each trial also affected the placebo effect. In general, with the increase of the percentage of women, the placebo effect in pain reduction decreased. Trials with less than 80% women participants had the largest placebo effect size (ES 0.65, 95%CI 0.32 to 0.98) whereas trials with 100% women participants had the smallest placebo effect size (ES 0.21, 95%CI 0.02 to 0.39) (Table 5-1).

Table 5-1 Subgroups analysis by age and gender

	No. of trials	No. of patients	ES (95%CI)	Heterogeneity (I^2)	P Publication bias
Age (years)					
<=40	5	115	0.42 (0.16, 0.68)	66.1%, p=0.02	0.60
>40, <=50	29	3474	0.51 (0.47, 0.56)	64%, p<0.01	0.81
>50	9	711	0.68 (0.57, 0.79)	86.6%, p<0.01	0.03
Women%					
<80%	4	77	0.65 (0.32, 0.98)	52.6%, p=0.09	0.86
>80%, <90%	7	500	0.48 (0.35, 0.61)	64%, p=0.01	0.50
>90%,<100%	19	3342	0.57 (0.53, 0.62)	82.4%, p<0.01	0.78
100%	9	277	0.21 (0.02, 0.39)	42.2%, p=0.09	0.60

5.3 Duration of disease

Duration of disease is defined as the length of time since the participant's first diagnosis of FM until they entered the trial (years). Mean duration of disease varied from 3.3 years to 17.5 years. Subgroup analysis was undertaken by every 5 year interval (**Table 5-2**).

From the table, it can be seen that the placebo effect in pain reduction decreased with increase in disease duration, Participants with the shortest duration of FM had the largest placebo effect (0.59, 95%CI 0.51 to 0.76). Participants who had FM over 13 years had the smallest placebo effect (0.26, 95%CI -0.09 to 0.60).

5.4 Baseline pain severity

Baseline pain severity was calculated as

Baseline severity = baseline score/ full score on the measure×100%

Regardless of what scale was used to measure pain in each trial, the baseline pain severity was taken as the percentage of the full score on that scale. The lower the percentage is, the less severe the pain is. All trials were grouped by the baseline severity of pain in the

placebo groups. The group that had the lowest baseline pain severity (<60%) had the smallest placebo effect (ES 0.22, 95%CI 0.06 to 0.42). There was a tendency for increasing placebo effect with increase of baseline severity of pain (Table 5-3).

Table 5-2 Subgroup analysis by duration of disease

	No. of trials	No. of participants	ES (95%CI)	Heterogeneity	$P_{\text{publication bias}}$
3-7 years	13	1237	0.59 (0.51, 0.67)	76.3%, p<0.01	0.30
8-12 years	8	1208	0.56 (0.49, 0.65)	89.5%, p<0.01	0.44
13- years	2	65	0.26 (-0.09, 0.60)	N/A*	N/A*

*not applicable as only 2 trials in this group

Table 5-3 Subgroup analysis by baseline pain severity

Baseline%*	No. of trials	No. of participants	ES (95%CI)	Heterogeneity	$P_{\text{publication bias}}$
<60	8	195	0.22 (0.06, 0.42)	32.26, p=0.17	0.98
60-70	23	3,025	0.54 (0.49, 0.59)	75.3, p<0.01	0.43
>70	15	1,147	0.56 (0.48, 0.65)	79.9%, p<0.01	0.40

*Percentage of baseline pain value in the full score on the scale

5.5 Chance of getting placebo

Chance of getting placebo in an RCT depends on the number of interventions included. This is because that patients involved in the RCT have to be told the interventions included in the trial. Although they do not know which treatment (active or placebo) they will receive, they do know the likelihood of getting placebo according to the number of groups. Some trials had one experimental group and placebo group while others had more. Therefore, the chance of getting placebo for the participants varied across the trials. Subgroup analysis was performed to find out whether the chance of getting placebo had any impact on participants' expectation and the placebo effect.

Of 45 trials, 32 trials had two groups (i.e., 50% chance of getting placebo), 7 trials had three groups (i.e., 33% chance) and 6 trials had 4 groups (i.e., 25% chance). The placebo effect on pain reduction was 0.45 (95%CI 0.40 to 0.51), 0.76 (95%CI 0.68 to 0.84) and 0.45 (95%CI 0.34 to 0.55) respectively. It is reasonable to say the chance of getting placebo had little influence on placebo effect in this case (Figure 5-1).

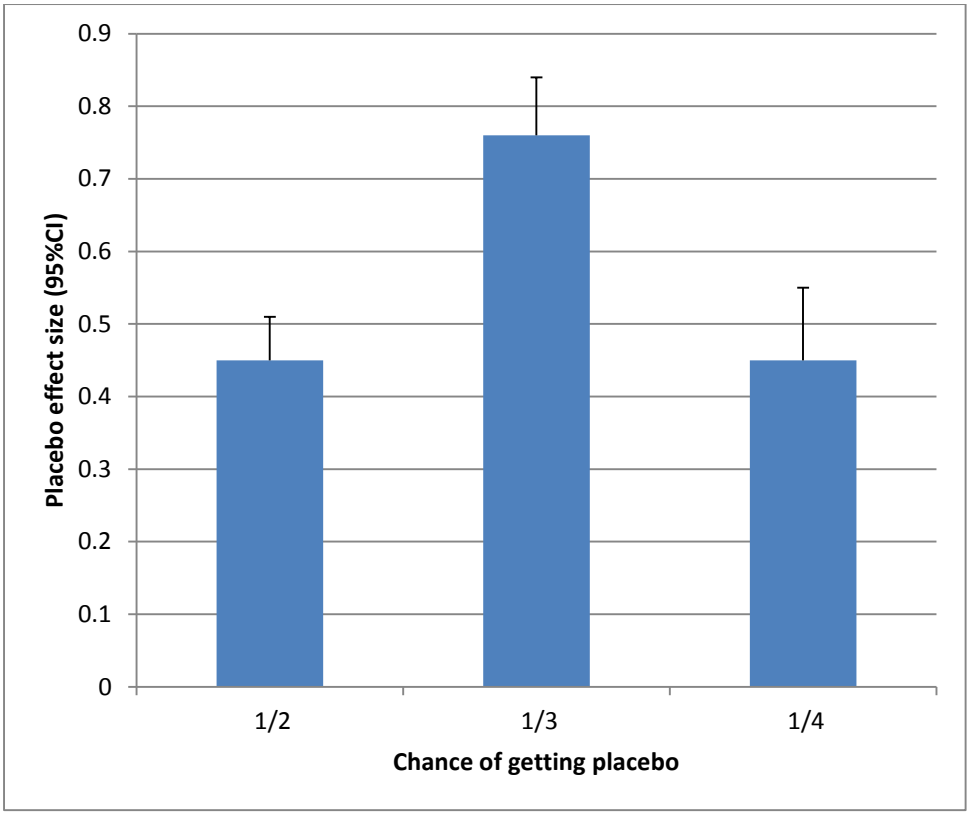
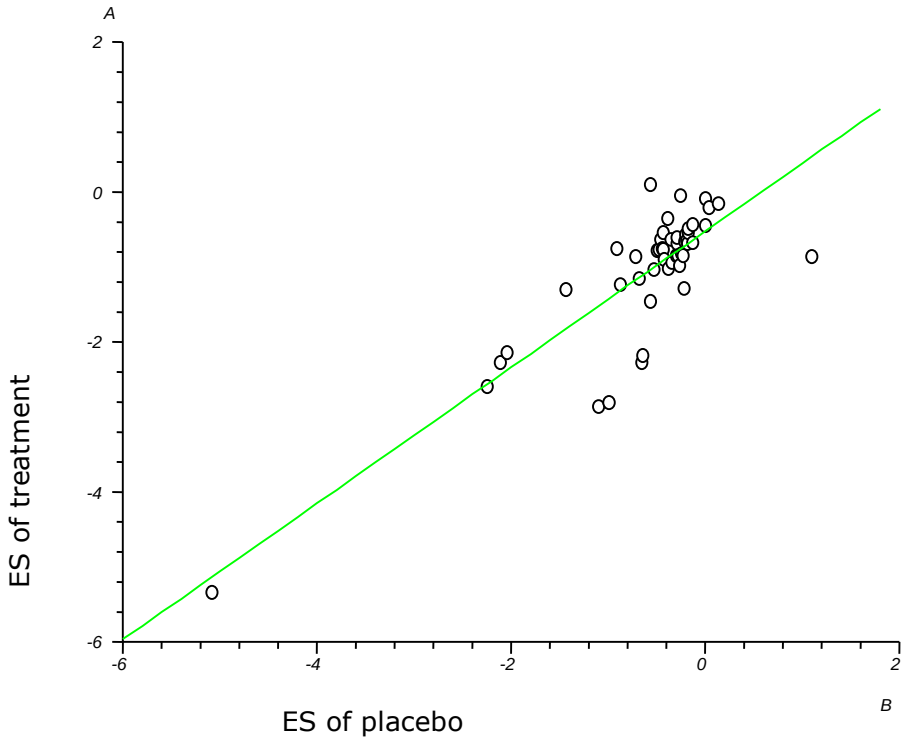


Figure 5-1 Subgroup analysis by chance of getting placebo

5.6 Effect size of active intervention

Irrespective of the size of the trials, the ES of placebo increased with the ES of active treatment (**Figure 5-2**).



$r^2 = 0.703821$, $P < 0.0001$

Figure 5-2 Correlation between effect size of active treatment and placebo

Treatment effect size and placebo effect size were correlated in a linear regression test. The result shows a significant correlation between the effect size of active intervention and placebo.

5.7 Type of active treatment

Subgroup analysis was undertaken to examine whether types of active treatment affected the placebo effect. The results showed that placebo for pharmacological treatments have a larger effect size than the placebo/ sham treatment for non-pharmacological treatments (Table 5-4).

Table 5-4 Subgroup analysis by active treatments

Type of treatment	No. of trials	No. of participants	ES of placebo (95%CI)	Heterogeneity	P publication bias
Acupuncture	3	80	0.28 (-0.04, 0.59)	0%, P=0.71	N/A
Analgesics	2	341	0.37 (0.19. 0.50)	N/A	N/A
Antidepressants	21	3085	0.57 (0.52, 0.63)	79%, p<0.01	0.27
Muscle relaxant	2	41	0.55 (0.12, 1.00)	N/A	N/A
Hypnotics	2	371	0.51 (0.37, 0.66)	N/A	N/A
Magnetic field	4	487	0.30 (-0.02, 0.62)	0%, p=0.94	0.01

5.8 Route of delivery

The most commonly used route of delivery was oral administration. 30 trials used oral medication which included 3,878 participants in their placebo control groups. Two types of needling were used in the trials, namely, intravenous injection (2 trials with 30 participants in control group) and acupuncture (3 trials with 80 participants in control group). Intravenous injection associated with a larger placebo effect than acupuncture. Physical touch was also commonly used as a route of treatment delivery. Within this group, 4 trials used sham magnetic field as placebo and 2 trials used sham electrotherapy as placebo. Subgroup analyses were undertaken by different types of delivery route. The results showed that apart from oral placebo, none of the other placebos had significant pain reduction effects demonstrated with much broader 95%CIs which included zero (Table 5-5). This could be due to the small number of trials and small numbers of participants in each of these trials.

5.9 Length of treatment period

Length of treatment period was recorded by weeks in most of the included trials. If not, it was rounded up to the closest number of weeks. Subgroup analysis was done by every four weeks interval. The placebo effects varied but there was no clear trend that the placebo effect was dependent on the length of treatment (Table 5-6).

Table 5-5 Subgroup analysis by route of delivery

Route of delivery	No. of trials	No. of participants	ES (95%CI)	Heterogeneity(I^2)	$P_{publication\ bias}$
Needling					
Intravenous Injection	2	30	0.47 (-0.05, 0.98)	N/A	N/A
Acupuncture	3	80	0.28 (-0.04, 0.59)	0%, p=0.71	N/A
Oral	30	3,878	0.55 (0.51, 0.60)	81.4%, p<0.01	0.07
Physical touch					
Magnetic field	4	487	0.30 (-0.02, 0.62)	0%, p=0.94	0.01
Electro stimulation	2	47	0.18 (-0.22, 0.58)	N/A	N/A

Table 5-6 Subgroup analysis by length of treatment period

Treatment period	No. of trials	No. of participants	ES (95%CI)	Heterogeneity	$P_{publication\ bias}$
≤4 weeks	11	259	0.59 (0.41, 0.76)	49.3%, p=0.03	0.04
5-8 weeks	7	266	0.35 (0.17, 0.52)	74%, p<0.01	0.48
9-12 weeks	16	1821	0.42 (0.35, 0.48)	61.8%, p<0.01	0.83
13-16 weeks	7	1573	0.65 (0.57, 0.72)	86.4%, p<0.01	0.41
17- weeks	5	501	0.66 (0.53, 0.78)	78.2%, p<0.01	0.27

5.10 Age of the treatment

The age of treatment was defined as the number of years between the year when a drug was first developed or approved and the year when the trial was published. Since treatments like acupuncture and magnetic field can trace back to hundreds of years ago, subgroup analysis by treatment age mainly focused on pharmacological treatments. The hypothesis is that people have higher expectation on new drugs. It might enhance the placebo response. Therefore, the placebo effect in newer drugs might be higher. The age of the treatment was categorised by every 10 years. However, the youngest two groups had larger placebo effect than the two older groups, but the oldest drug groups had larger placebo effect again. No certain tendency was found in this subgroup analysis. The age of treatment did not have a clear influence on the placebo effect (**Figure 5-3**).

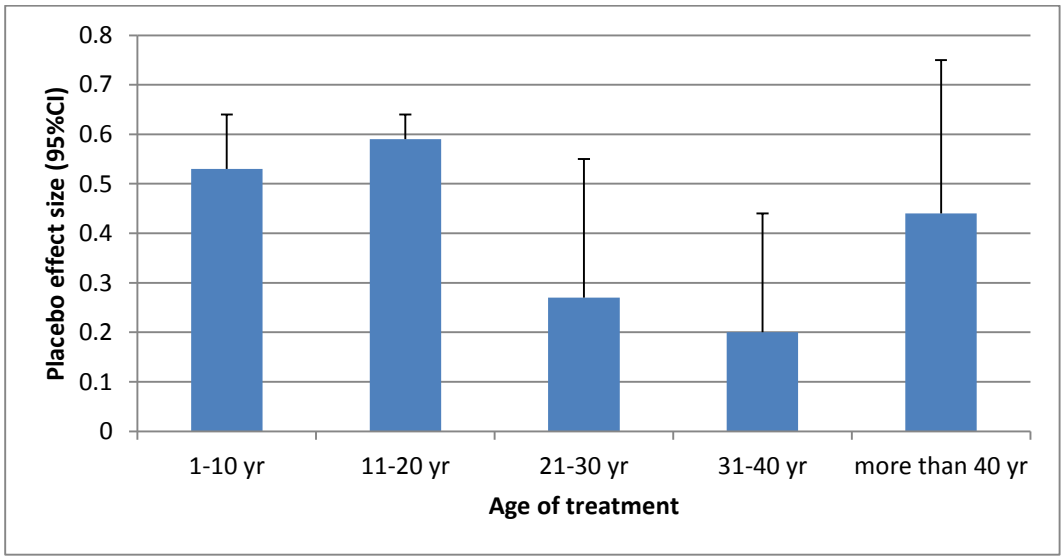


Figure 5-3 Subgroup analysis by age of treatment

5.11 Funding body

Twenty-four trials had industrial funding (fully or partially) and contained 3,629 participants in the placebo controlled groups. Only 5 trials did not get any industrial funding. In these non-industry funded trials, 151 participants were randomised into the placebo groups. Subgroups analysis showed placebo effect size in industry funded trials was 0.54 (95%CI 0.50 to 0.59), and that of non-industry funded trials was 0.41 (95%CI 0.17 to 0.64) (Table 5-7).

5.12 Study Setting

Two aspects of the study setting were considered in subgroup analysis, namely, the number of study centres and the method used to recruit participants.

More trials were conducted in multi centres (26 trials, 3,932 patients) than single centres (16 trials, 326 patients). The ESs of placebo on pain reduction were 0.55 (95%CI 0.5 to 0.59) and 0.41 (95%CI 0.26 to 0.57) respectively. There is no statistically significant difference between the two groups.

Table 5-7 Subgroup analysis by funding body

Funding body	No. of trials	No. of patients	ES (95%CI)	Heterogeneity (I^2)	$P_{publication\ bias}$
Industry	24	3629	0.54 (0.50, 0.59)	80.3%, p<0.01	0.05
Non-industry	5	151	0.41 (0.17, 0.64)	84.2%, p<0.01	0.36

Table 5-8 Subgroup analysis by study setting

	No. of trials	**No. of patients**	**ES (95%CI)**	**Heterogeneity (I^2)**	**$P_{publication\ bias}$**
No. of centres					
Single	16	326	0.41 (0.26, 0.57)	45.5%, p=0.02	0.74
Multiple	26	3932	0.55 (0.50, 0.59)	78.8%, p<0.01	0.28
Participant recruit					
Advertisement*	5	102	0.10 (-0.18, 0.37)	0%, p=0.67	0.86
Referral**	33	3730	0.56 (0.51, 0.61)	76.8%, p<0.01	0.54

*participants were recruited via advertisement in community or patient association
**participants were recruited via doctors' referral

Participants in all trials were recruited either through the community or by doctor's referrals. In total 33 trials used physician referral for recruitment and recruited 3730 participants. 5 trials used advertisement in the community or FM patient associations and invited people to refer themselves to participate in the studies. 102 participants were recruited in this way. Participants who were referred by their doctors had a significantly larger placebo effect for pain reduction, (ES, 0.56, 95%CI 0.51 to 0.61) than community recruited participants who only showed slight improvement from placebo (ES, 0.10, 95%CI -0.18 to 0.37) (Table 5-8).

5.13 Blinding

Whether participants are blinded to the treatment could greatly impact on the placebo effect. However, all included trials claimed they blinded the participants from the treatment they were given. After reading the trials carefully, only one trial was considered inadequately blinded to participants (Gur, 2002). The effect size of placebo was greater in trials in which patients were apparently fully blinded (**Table 5-9**).

Care providers also play an important role in keeping participants blinded in a trial, and assessors need to be blinded to treatment to minimise measurement bias. In the included trials, most care providers and assessors appeared to be adequately blinded. There was no apparent difference in placebo effect according to blinding of the care provider, but there was a larger placebo effect in studies where the assessor was not fully blinded.

Table 5-9 Subgroup analysis by blinding

	No. of trials	No. of participants	ES (95%C)	Heterogeneity	P publication bias
Care providers					
Yes	33	3,903	0.54 (0.49, 0.59)	78.4%, p<0.01	0.22
No	8	289	0.58 (0.40, 0.75)	65.6%, p=0.01	0.23
Assessors					
Yes	35	3,115	0.55 (0.50, 0.60)	76.7, p<0.01	0.02
No	3	158	0.71 (0.47, 0.96)	80.2%, p=0.01	N/A
Participants					
Yes	43	4,220	0.53 (0.49, 0.57)	75.6%, p<0.01	0.07
No	1	25	1.10 (0.76, 1.42)	N/A	N/A

5.14 Meta-regression

A meta-regression was performed to adjust for covariates. Variables that showed a clear tendency in previous subgroup analysis (e.g. the proportion of women was negatively associated with the magnitude of the placebo effect) were chosen for the model. The Log value of placebo effect size was used as the dependent variable and the effect size of active treatments, baseline severity, proportion of female participants and mean age of participants were used as independent variables in this analysis. According to the empirical evidence of 10 studies for each variable, 4 variables were predefined to ensure better power. The random-effects model was used to adjust for variance between studies. The analysis was undertaken using STATA 11.0.

The effect size of treatment had a positive relationship with the placebo effect, which means the larger the effect size of the treatment is, the larger effect size of the placebo to this treatment is. Proportion of women participants had a negative relationship with the placebo effect. It indicates that female gender might be less responsive to placebo. However, due to the power of the analysis, no statistically significant result was found in this meta-regression (Table 5-10).

Table 5-10 Meta-regression

ES.placebo	Coef.	Std. Err.	t	P>|t|	[95% Conf.	Interval]
ES.treatment	0.15	0.09	1.78	0.09	-0.02	0.33
BaselineSeverity	-1.31	0.85	-1.54	0.13	-3.04	0.42
WomenProportion	-0.01	0.01	-0.93	0.36	-0.02	0.01
MeanAge	-0.001	0.02	-0.09	0.93	-0.03	0.03
Conbined	1.94	1.27	1.53	0.14	-0.64	4.52

5.15 Brief summary

Different variables have been considered as possible determinants of the placebo effect. Age, baseline severity and effect size of the treatment were found to have positive association with the placebo effect. Female gender and disease duration were found to have negative association with the placebo effect. Other factors were considered too but no clear pattern was observed.

Chapter 6 Nocebo Effect in Fibromyalgia

6.1 Introduction to this chapter

Nocebo effect refers to the worsening of symptoms or increase in adverse events (AEs) that patients experience after taking a placebo. Nocebo includes both expected adverse effects and non-specific effects that cannot be related to the pharmacological action of the treatment. The word “nocebo” meaning “I shall harm” was first introduced by Kennedy in the early 1960s (Colloca and Benedetti, 2007). The nocebo effect is the opposite of the placebo effect and has received wider attention from basic scientist and clinicians only recently (Hauser et al., 2012a).

The nocebo effect shares some common features with the placebo effect. Expectation plays an important role on how both nocebo and placebo work (Kool et al., 2009). A class experiment that looked at the impact of people negative thoughts on their symptoms was done by Pfingsten and colleagues. They divided 50 people with chronic pain back randomly into two groups and asked them take a leg flexion test. They told one group that the test could increase their pain slightly but told the other group that the test had no impact on the pain level. The result showed that patient who had the negative information reported s tronger pain (Pfingsten et al., 2001). The negative psychological context surrounding the treatment and its impact on the

patient's brain and body has been investigated in a few studies (Bootzin and Bailey, 2005). Several neurotransmission systems may be involved in the production of the nocebo effect, such as dopamine, opioids, beta-endorphins, and cholecystokinin within brain regions associated with pain and learning processes, such as the prefrontal cortex and hippocampus (Flaten et al., 2006).

Previously, a systematic review was conducted to look at the nocebo effect evident in RCTs examining drug treatments for FM, (Hauser et al., 2012b). In this chapter, we have extended the assessment of nocebo effects in both pharmacological and non-pharmacological trials.

6.2 Methods

From the included studies (204 RCTs that met inclusion/exclusion criteria), the ones that reported any incidence of side effect were selected for analysis of nocebo effects. Data included information on the article identification and year of publication, country or countries where the study was performed, sample size, age and percentage of female participants, drug treatments, treatment duration, study design (parallel or crossover), number of patients treated with placebo, number of patients treated with placebo and experiencing any AE, and patients treated with placebo and withdrawn because of an AE.

To estimate the frequency of nocebo in these trials, we calculated the ratio of patients treated with placebo who reported at least one AE versus all placebo-treated patients. The frequency of nocebo dropouts was estimated as the ratio of patients treated with placebo who then discontinued the treatment because of intolerance versus all placebo-treated patients. Relative risks were calculated to find out whether placebo is safer than active treatments. Linear regression and subgroup analysis were used to determine the possible factors that might influence the nocebo response.

6.3 Results

Twenty-nine placebo controlled trials were included in the nocebo effect analysis (Table 6-1). Both pharmacological trials and non-pharmacological trials were included, and all trials used placebo as control. In most studies gastrointestinal side effects (e.g. constipation, diarrhoea, and nausea), dizziness, dry mouth, and headache were the most commonly reported AEs.

18 trials reported the number of participants who withdrew from the study due to intolerance of adverse effects. Meta-analysis showed 9.0% participants in placebo controlled groups discontinued their treatments because of side effects (95%CI 8.0 to 10.0, I^2=54%, p<0.05, Egger=1.82, p=0.1025) (**Figure 6-1**).

Table 6-1 Characteristics of 29 RCTs reporting nocebo effects

Features	No.
No. of Participants in all trials	8019
No. of placebo treated participants	4090
Mean age, range (yr) in placebo group	49.2 (39.3, 52.9)
Women% in placebo group	93 (83.9, 96.7)
Countries where the trials were carried out	
Brazil	1
Canada	2
France	1
Germany	2
USA	17
Multi-nation	7
Mean Jadad score	4.7
Drugs studied (No. of trials)	
Amitriptyline	1
Citalopram	1
Cyclobenzaprine	1
Dolasetron	1
Duloxetine	4
Esreboxetine	2
Farabloc	1
Fluoxetine	1
Gabapentin	1
Milnacipran	5
Nabilone	1
Paroxetine	1
Pregabalin	5
Sodium oxybate	1
Terguride	1
Tramadol/Acetaminophen	1
Tropisetron	1

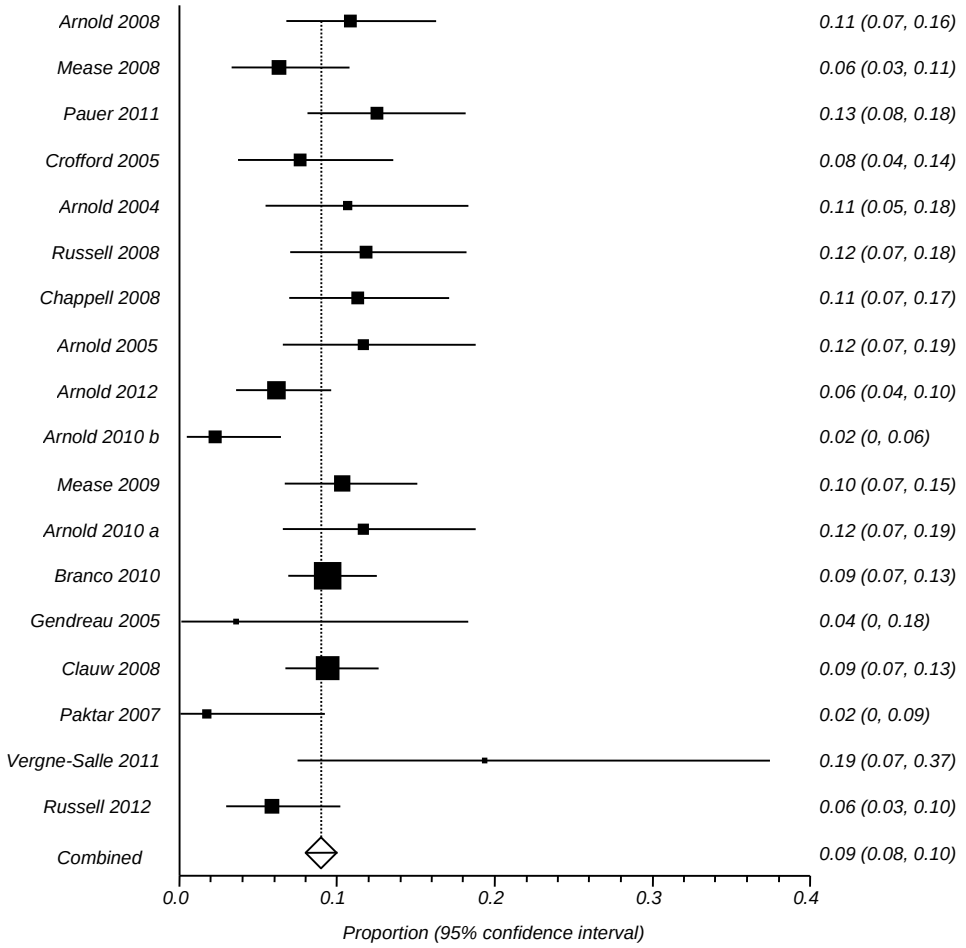


Figure 6-1 Proportion of participants who withdrew due to adverse effect in placebo groups

The incidences of common adverse effects were pooled from all trials. In the placebo groups, the incidences of different adverse effects varied (Figure 6-2). Ideally, the incidence of the same set of AEs should have been pooled from no treatment groups to see if these AEs were caused by the placebo. However, none of the trials that had no treatment controlled groups reported such data.

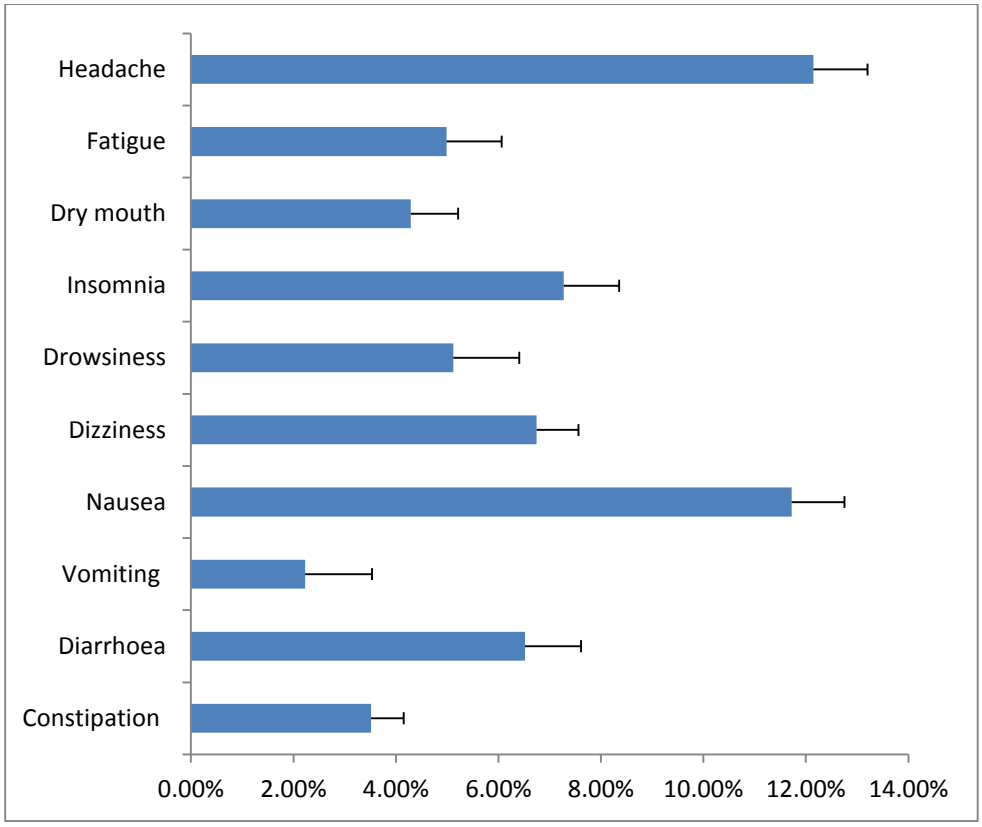


Figure 6-2 Frequency of different adverse effect in placebo groups

Relative risk was calculated to find out how safe is placebo compared with the treatment. For example, compared with the treatment group, participants in placebo controlled groups were less likely to drop out from the study due to adverse effects (relative risk, 0.53, 95%IC 0.47 to 0.60) (Figure 6-3).

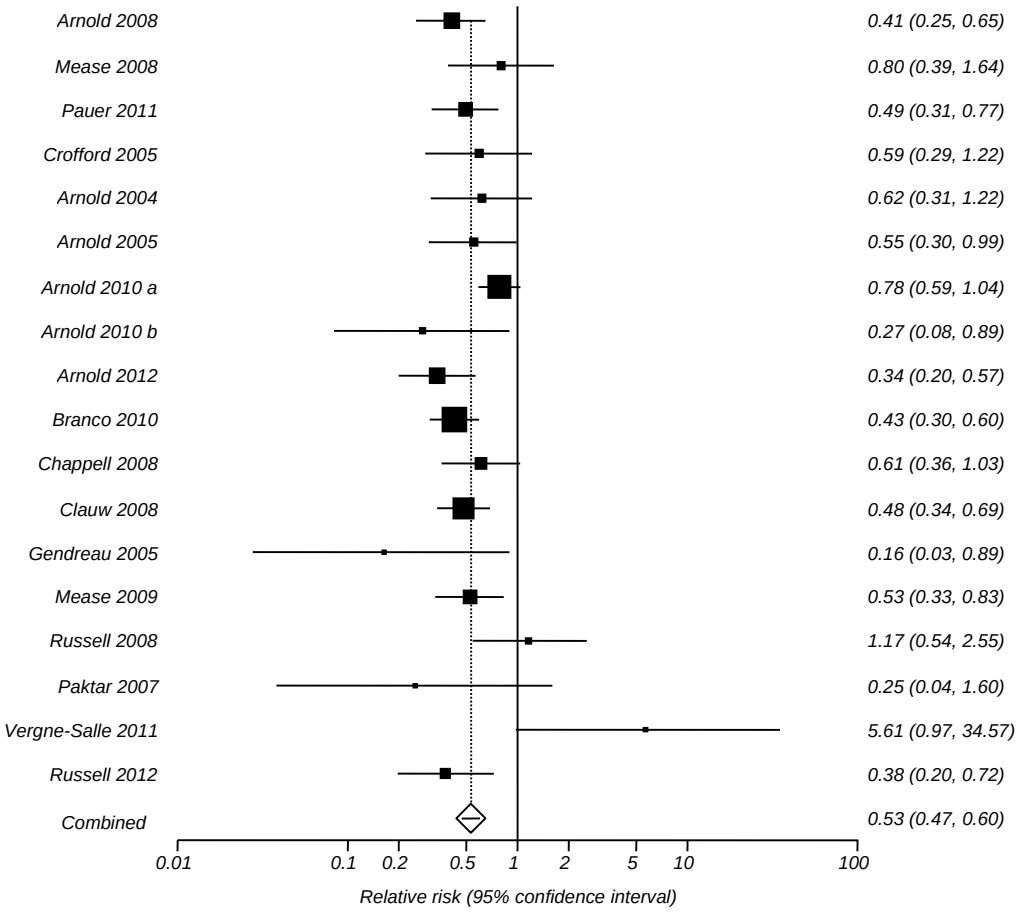


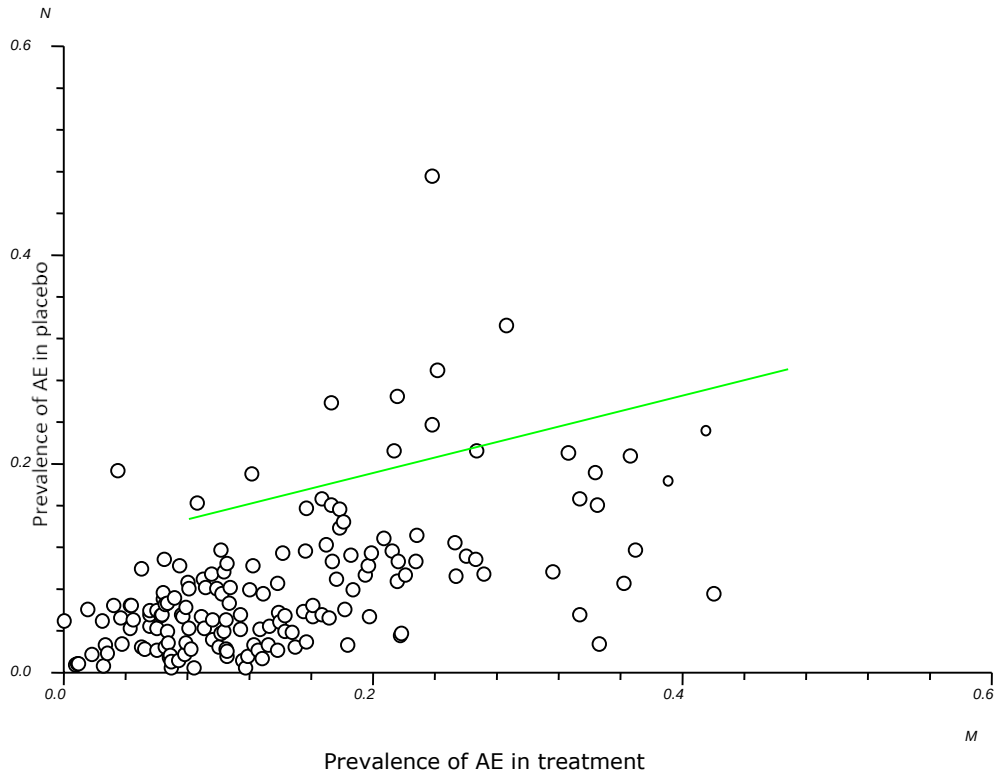
Figure 6-3 Relative risk of dropouts due to adverse effect in placebo group versus treatment group

The similar result was also found in all commonly reported adverse effects (Table 6-2).

Table 6-2 Relative risk of adverse effects in placebo groups compared with treatment groups

Adverse effect	No. of trials	Relative risk (95%CI)	Heterogeneity	P Publication bias
Constipation	16	0.25 (0.20, 0.30)	21.1%	0.46
Dizziness	20	0.46 (0.34, 0.63)	72.5%	0.64
Dry mouth	16	0.40 (0.26, 0.64)	65.5%	0.18
Fatigue	8	0.72 (0.54, 0.94)	0%	0.52
Headache	20	0.85 (0.76, 0.95)	53.9%	0.62
Hot flush	4	0.24 (0.10, 0.59)	70.2%	0.01
Nausea	22	0.58 (0.48, 0.69)	53.6%	0.41
Palpitation	5	0.45 (0.30, 0.66)	0%	<0.05

Linear regression shows that frequency of adverse effects in the placebo groups is higher when that in the treatment groups is higher (**Figure 6-4**).



r2=0.24, P < 0.01

Figure 6-4 Linear regression of adverse events in treatment and placebo groups

When recruiting participants into their trials, the researchers need to explain all the possible adverse effects that the participants may experience from the treatment under study. Therefore, the participants might have had some expectation for certain types of adverse effects, even if they are randomised to placebo.

To further confirm whether nocebo effect goes with active treatment adverse effect, the British National Formulary (2010) was used to check for the common adverse effects of the included treatments. Four drugs (Cyclobenzaprine, Milnacipran, Tropisetron, and Tramadol) could not be found in the book and therefore, the US Food and Drug Administration official website was used to find relevant information (Appendix 5 Common adverse effects by treatment).

All included trials were then re-grouped according to treatment side effect profile of the study medication. Group A comprised the trials that used treatments which share a similar type of AE and group B comprised trials that used treatments which do not have this type of AE. The subgroup analysis was done to compare the AE incidence between these two groups (Table 6-3). According the guidance for patient information sheet & consent form, for any new drug or procedure that is to be studied in a clinical trial, researchers should explain to the patients the possible AEs and report them if the patients suffer any of these AEs or any other symptoms. The known AEs should be explained in terms that the patients will clearly understand. If the drug is relatively new, the researchers should inform the patients that there may be unknown AEs (Burns et al., 2005). Therefore, the hypothesis of this sub-group analysis is that the patients' consent form informed all participants of the possible AEs they might have from the study treatment and built up expectation of such AEs from the participants. Consequently, the frequency of such AEs would be higher than that in the trials which used treatment without such AEs.

Except for nausea, Group A had no more expected nocebo effects than group B. Therefore, no clear conclusion can be draw based on the subgroup analysis.

Table 6-3 Subgroup analysis by type of adverse effect

	No. of trials	Proportion (95%CI)	Heterogeneity	$P_{publication}$
Constipation				
Group A*	9	3.9%, (3.0-5.0)	56%, p<0.05	0.07
Group B**	7	3.2%, (2.5-4.1)	32.5%, p>0.05	0.28
Diarrhoea				
Group A	2	6.9%, (4.1-10.4)	N/A***	N/A
Group B	8	6.5%, (5.4-7.6)	4.1%, p>0.05	<0.05
Nausea				
Group A	16	13.3%, (12.2-14.5)	88%, p<0.05	0.02
Group B	7	5.5%, (3.9-7.3)	52.3%, p>0.05	0.06
Dizziness				
Group A	10	6.7%, (5.6-7.8)	51.5%, p<0.05	0.50
Group B	10	6.8%, (5.7-8.1)	79.8%, p<0.05	<0.05
Drowsiness				
Group A	4	4.7%, (3.1-6.7)	75.8%, p<0.05	0.12
Group B	6	5.4%, (3.8-7.2)	0%, p>0.05	0.28

Insomnia				
Group A	5	7.6%, (6.4-8.9)	54%, p>0.05	0.78
Group B	7	6.5%, (4.8-8.6)	45.2%, p>0.05	0.05
Dry mouth				
Group A	12	4.0%, (3.1-5.2)	79.7%, p<0.05	<0.05
Group B	4	4.8%, (3.3-6.6)	88.3%, p <0.05	0.32
Headache				
Group A	9	12.8%, (11.5-14.2)	58.3%, p<0.05	0.83
Group B	12	11.2%, (9.6-12.8)	89.3%, p<0.05	<0.05

*Group A, trials that used the treatments which are likely to give patients the adverse effect as expected according to British National Formulary or FDA
**Group B, trials that used the treatments which are not likely to give patients the adverse effect as expected according to British National Formulary or FDA
***not applicable

6.4 Discussion

In brief, in all the 29 included trials, AEs were observed in both treatment groups and placebo groups. As there was no untreated control group, the nocebo effect cannot be confirmed. The types of AEs that were reported included both expected adverse effects and non-specific effects cannot be directly related to the use of placebo, some of which may be part of the symptoms of FM. Overall, about 9% of participants dropped out in the placebo groups. Whether this is due to the use of placebo remains unknown. However, compared with the active treatment, the placebo was 2-times safer (e.g., only 50% drop-out rate of the treatment). The magnitude of the nocebo effect in FM was influenced by the active treatment. When the active treatment was more likely to cause AEs, the frequency of AEs in the placebo group was higher.

Similar results were found in FM drug trials by Häuser and Mitsikostas (Hauser et al., 2012b, Mitsikostas et al., 2012). However, only frequency of AEs was measured for the placebo group only. Whether these AEs are due to placebo remains to be confirmed. In this study, discontinuation due to the given placebo was observed. According to Myers et al, communicating the possible AEs of a given treatment could lead to participants' withdrawal from the trial (Myers et al., 1987).

6.5 Caveats and future work

Some signals of the nocebo effect have been observed in the trials. However, caveats in this study are obvious. Firstly, to fully establish the nocebo effect in FM, it requires an untreated control group, or knowledge of the background incidence of each AE in the disease population. The true nocebo effect can only be quantified as all the negative effects in the placebo group minus non-specific factors such as symptoms from the disease or comorbid conditions and AEs from accompanying medications (Colloca et al., 2008).

Secondly, in a clinical trial, the methods used for recording AEs could have an impact on the type and the frequency of AEs reported. According to Rief, patients report more AEs when given a standard list of symptoms than when they report them spontaneously (Rief et al., 2009a). Therefore, the incidence of AEs reported might have been slightly different from the reality.

Thirdly, in the attempt to make a sub-group analysis, the patient's information sheet and consent forms that were used in the trials were not available. Therefore, we can't exclude the possibility that some AEs were not mentioned to the participants and consequently altered the expectation of certain AEs. It would also be very helpful to know the participant information sheet in each trial to examine the specific information that participants receive with respect to possible side-

effects. The result from this analysis was not significantly different between two groups and was not the most robust way of doing so. However, as in a systematic review, that was the best we could do.

Chapter 7 Cross Disease Comparison

7.1 Introduction to this chapter

Many rheumatologic conditions are associated with chronic pain. Some conditions are non-inflammatory, e.g. fibromyalgia (FM) and some are systemic inflammatory, e.g. rheumatoid arthritis (RA) (Lee et al., 2011). The pain mechanisms in different conditions vary, depending on the condition as well as individual factors. There are two main pain mechanisms of chronic pain, namely, peripheral mechanisms and central mechanisms (Schaible, 2007) .

Peripheral pain mechanisms play important roles in both osteoarthritis (OA) and RA. This type of pain mechanisms stem from abnormalities in the peripheral nerves. Enhanced pain sensitivity in local areas is often the result of peripheral pain mechanisms (Schaible et al., 2011). In contrast, central pain mechanisms work on the level of the central nerves system, leading to enhanced widespread pain sensitivity. It augments the central pain processing so patients would feel increased pain in response to normally painful stimuli (hyperalgesia) or non-painful stimuli (allodynia). The typical chronic pain condition is FM (Millan, 2002).

The placebo effect has been confirmed in many conditions, such as headache (Harden et al., 1996), Parkinson's disease (Lidstone et al.,

2010), and depression (Brown, 1994)etc. A recent systematic review and meta-analysis that included both placebo and untreated control groups confirmed the existence of the placebo effect in the treatment of OA (Zhang et al., 2008). In this review, the placebo effect was examined in RCTs that studied a wide range of both pharmacological and non-pharmacological interventions. Overall, the effect size of placebo analgesia in OA was 0.51 (95%CI, 0.46, 0.55). That is significantly higher than the untreated group (0.03, 95%CI, -0.13, 0.18). In the direct comparison among trials with placebo and untreated groups, the difference between placebo (0.77, 95%CI, 0.65, 0.89) and untreated groups (-0.08, 95%CI, -0.65, 0.48) was significant. This review also found some potential determinants of the placebo response in OA. The higher the ES of treatment is the great the placebo response is. Higher baseline pain produced higher placebo effect. The more invasive the treatment is administrated, the larger placebo response it can induce (Zhang, et al., 2008).

In this present review of placebo effect in FM, similar results were found. Both direct and indirect comparison between placebo and untreated groups confirmed that placebo response occurred in FM. The ES of treatment and baseline pain severity were also shown as potential determinants of the placebo effect. However, whether placebo works differently for different types of pain such as FM, OA and OA remains unknown. It is well known that pain FM is largely driven by central pain mechanism, whereas pain in RA is largely

driven by inflammation. Pain in OA, however, is driven by both peripheral and central mechanisms. These three types of pain provide an excellent opportunity to examine the mechanism of the placebo analgesia.

7.2 Methods

In order to make comparisons of the placebo effect in FM, OA and RA, three investigators created databases of each disease separately (Xi Chen, FM; Kun Zou, OA; Natasya Abdullah, RA) Treatments that have been studied in RCTs in two or all three of these conditions were then selected. The effect size of placebo was then compared between the 3 conditions for each treatment. Four types of treatments (magnetic treatment, homeopathy, NSAIDs, and acupuncture) were found in common among the three diseases. I chose magnetic treatment and homeopathy in my study.

7.3 Magnetic field placebo in FM, OA and RA

Magnetic field was one of the treatments that have been studied in placebo-controlled RCTs in FM, OA and RA. There were 4 placebo-controlled trials of magnetic field in FM, 15 trials in OA and 2 trials in RA. Study characteristics are in Table 7-1. Pain reduction was measure in the RCTs in all three conditions (Table 7-2).

Table 7-1 Study characteristics

Features	FM	OA	RA
No. of total participants	156	659	134
No. of placebo treatment participants	77	310	96
Mean age, yr in placebo group	46.7	50.2	61.7
Women% in placebo group	91.3%	89.7%	78.1%

Table 7-2 Pain reduction by placebo in three diseases

Disease	No. of trials	ES (95%CI)	Heterogeneity	P publication bias
FM	4	0.30 (-0.02, 0.62)	0%, p=0.94	0.01
OA	15	0.71 (0.31, 1.11)	85.4%, p<0.05	0.29
RA	2	0.39 (0.10, 0.68)	N/A	N/A

Meta-analysis has shown that sham magnetic field device (placebo) was effective for OA and RA, but not for FM. The placebo effect in these trials was greatest in OA, with a mean effect size that was more than twice that in the other 2 conditions. The placebo response in RA was next in magnitude, and the lowest effect size was in FM (Figure 7-1).

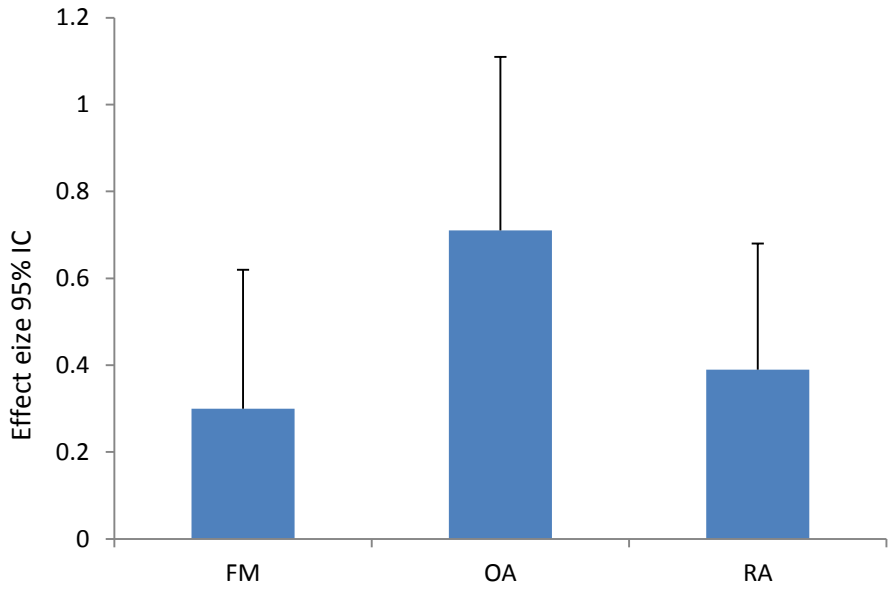


Figure 7-1 Cross disease comparison (magnetic field)

7.2 Homeopathy in FM and RA

Homeopathy is a system of alternative medicine, based on the doctrine of “like cures like”, according to which a substance that causes the symptoms of a disease in a healthy person will cure similar symptoms in a sick person (Evans et al., 2013). However, one major difference with homeopathic medicines is that substances are used in ultra high dilutions, which makes them non-toxic. It is widely held, however, that there is little if any scientific support for this hypothesis (Belfer et al., 2013). As yet, science has not been able to explain the mechanism of action of ultra high dilutions in the body, but laboratory experiments have repeatedly demonstrated that homoeopathically prepared substances cause biological effects.

Based on the fact that the highly diluted homeopathy remedies barely contain any “real medicine”, the therapeutic effect is largely contributed by the contextual factors, which are not the result of the active components of the treatment but are inherent within the treatment “package” (Steinsbekk et al., 2007). Therefore, homeopathy is in fact a placebo on its own with large contextual factors in delivery. In this review, only trials with homeopathy consultation were included to understand how the context of “treatment package” influences chronic pain conditions. Data were taken from the homeopathy treatment groups.

Two homeopathy trials were found in FM and another two trials were found in RA. Study characteristics are in Table 7-3. Homeopathy (placebo) was neither effective in FM, nor in RA for pain outcome (Figure 7-2).

Table 7-3 Homeopathy study characteristics

Features	**FM**	**RA**
No. of total participants	109	142
No. of placebo treated participants	53	128
Mean age, yr in placebo group	46.5	63.4
Women% in placebo group	96.4%	77.7%

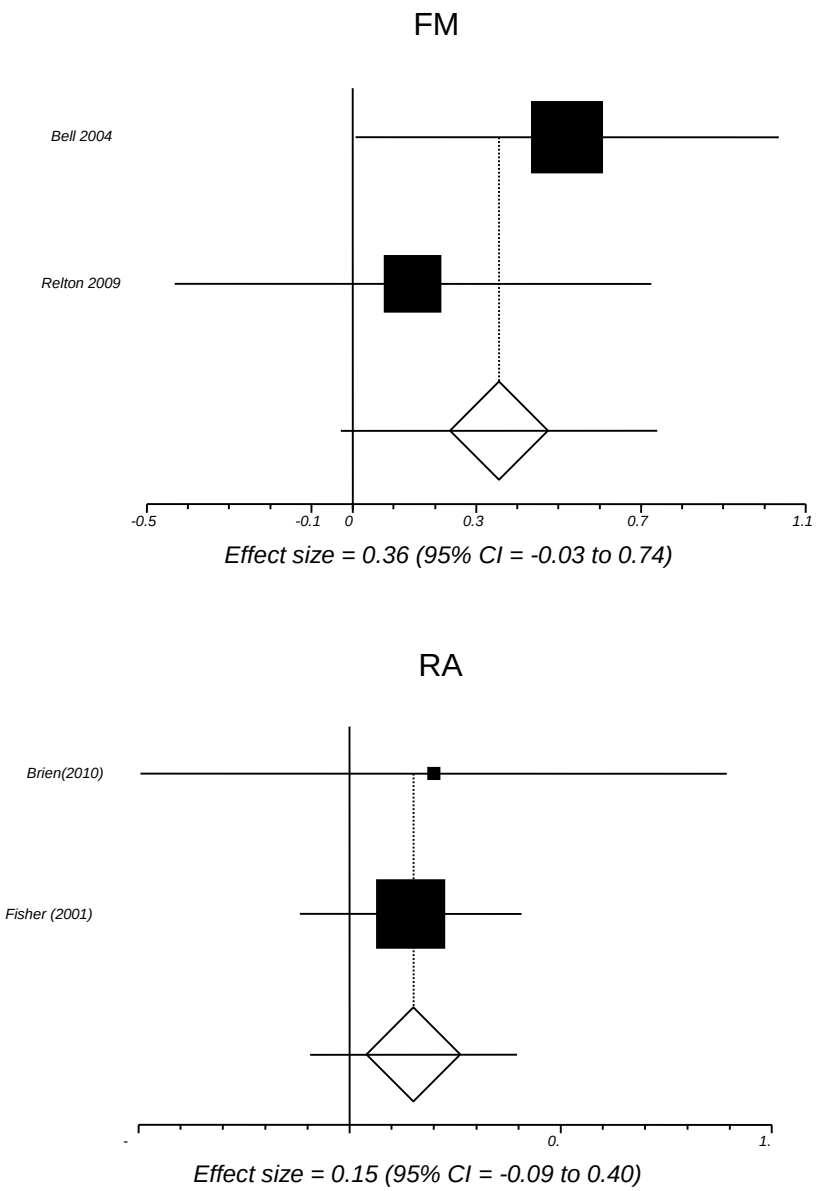


Figure 7-2 Placebo effect for pain due to FM and RA in homeopathy trials

7.4 Discussion

The placebo effect in the three conditions varied, depending on the type of placebos. For example, magnetic field placebo works for OA and RA but not FM, suggesting that placebo may only work for mildly/partially central-sensitised pain.

The three selected pain conditions are all common rheumatoid diseases. Chronic pain is a feature of all three, but with different mechanisms.

FM is the prototypical non-inflammatory chronic pain syndrome. Abnormalities in pain perception have been identified by quantitative sensory testing methods. Compared to healthy controls, FM patients have notably lower pressure pain thresholds (Hudson et al., 2003). Partly due to specific defects such as loss of descending analgesic activity and central sensitization, the diffuse hyperalgesic state of central augmentation of pain processing has been often identified (Gracely et al., 2002).

In contrast to FM, RA is a typical systemic inflammatory disease. The inflammation contributes to the chronic pain in RA. However, inflammation may not be the only pain-causing factor. Some patients do not get improvement in pain reduction despite treatment with anti-inflammatory drugs (Rupp et al., 2006). The central pain-processing mechanisms have also been examined. Studies that utilized dolermetry to assess pain thresholds suggest that RA patients have higher pain sensitivity than healthy control at both joint and non-joint sites (Rupp et al., 2006, Wolfe and Michaud, 2007).

OA is a common degenerative joint disease. Damage to cartilage and bone is the main character of this condition. Because of the chronic pain, many individuals with OA suffer from significant disability and health care costs (Lawrence et al., 2008). There is a lot of debate on the pain mechanism of OA. The association between pain intensity and peripheral joint damage is poor at a population level (Bedson and Croft, 2008) but strong within individuals (Neogi et al., 2009). Studies have shown that, OA pain which is considered peripheral driven, historically, may also be modulated via widespread mechanism controlled by the central nervous system. A recent systematic review has demonstrated that people with OA have lower pressure pain threshold than non-OA controls at the disease joint site, distal and remote areas (Suokas et al., 2012).

Many epidemiological studies also observe that people with OA are more likely to develop pain elsewhere at the late stage of the disease (Ingham et al., 2011), and about 12.1% people still suffer from chronic pain after the total joint replacement (Nikolajsen et al., 2006). These suggest that pain in OA also has some central components, although it may not similar as pain in FM.

It has been stated that the placebo analgesia is predominantly mediated by enhancement of descending inhibitory systems. Three principal pharmacologic mediators have been suggested, namely, high levels of endogenous opioids, dopamine release, and low levels

of cholecystokinin (Abhishek and Doherty, 2013). The role of endogenous opioids in placebo analgesia has been proved in a few studies. According to Lipman, the cerebrospinal fluid concentration of endogenous opioids is higher in chronic pain patients who responded to the placebo administration than the ones that didn't respond (Lipman et al., 1990). The fact that the placebo response induced by verbal suggestion could be blocked by naloxone (an opiate antagonist) also confirms the role of opioids in mediating placebo analgesia (Amanzio and Benedetti, 1999).

The opioid receptors are widely and differentially expressed in central nervous systems (Abbadie et al., 2000, Mansour et al., 1995). The μ-opioid receptors, in particular are widely distributed throughout the forebrain, midbrain, and hindbrain. Its distribution corresponds with its role in pain perception and sensorimotor integration (Mansour et al., 1988). Conversely, moderate amounts of K-opioid receptors have been found in many brain areas (Mansour et al., 1988). In the peripheral nervous systems, the opioid receptor expression was also found (Bagnol et al., 1997, Gray et al., 2005, Holzer, 2004). Peripheral opioid receptor-mediated analgesia has also been well studied in clinical trials. According to Tegeder, administration of the peripherally restricted opioid agonists (M6G) could reduce hyperalgesia induced by peripheral actions (Tegeder et al., 2003). Topical administration of opioid also achieved effective pain reduction in the treatment of painful skin ulcers (Twillman et al., 1999). The

expression of opioid receptors in both central and peripheral nervous systems potentially explained how placebo-induced endogenous opioids achieve analgesia in both central and peripheral driven painful conditions.

7.5 Caveats and future work

This is an attempt to understand the impact of pain mechanism on the placebo response. Three pain models were used to compare the placebo effect in this study. However, the study carried a few caveats. First of all, the small number of available studies for the comparison is the biggest caveat. The evidence has shown that different pain mechanisms may have an impact on the magnitude of the placebo effect. But the result is not consistent. The small number of available trials may be the main reason for the inconsistent results. Also because of the small trial number, it was impossible to do subgroup analysis. Secondly, the magnetic and homeopathy treatments chosen for this comparison did not have classic placebo. Both treatments were complementary and alternative medicine and the design of placebo was not easy. Thirdly, comparison was only done on pain reduction due to available data. Pain was a shared outcome by all the three conditions. However, it is the only shared outcome that has been reported in the included trials. Quality of life and overall improvement were also considered as shared outcomes for comparison, but no data were extracted from the available trials.

Future research needs to include more trials from each of the three conditions by increasing the type of treatment. Association of the placebo effect with certain type pain mechanism needs to be further clarified.

7.6 Brief summary

Attempt was made to compare the placebo effect in three diseases, OA, RA and FM. Two commonly used treatments among the three diseases magnetic therapy and homeopathy were chosen to make the comparison. The result was tentative which may be due to small sample size and practicalities of using placebo in these trials.

Chapter 8 General Discussion

8.1 Summary of study findings

FM is a common condition in the general population that causes multiple regional pain, fatigue and chronic disability. The mechanism of pain is predominantly central and strongly associates with non-restorative sleep and lack of delta sleep. Many studies have investigated different treatments for FM, which provides an opportunity to systematically review the placebo effect in RCTs undertaken in FM. Over two hundred placebo-controlled trials were found in the literature search. A wide range of different treatments were studied in these trials, including drugs, physical interventions such as exercise and balneotherapy, psychological treatments such as CBT, and complementary therapies such as homeopathy and acupuncture. Some trials used placebo as their study control while others used an untreated group as control. This permits an investigation of the placebo effect and its determinants in FM. This study has yielded three key findings. Firstly, participants treated by placebo obtain significant improvements in all the main outcome measures such as pain, fatigue, sleeping quality, functionality and overall wellbeing. Secondly, these effects are superior to any changes observed in untreated control groups. Thirdly, the main determinants that increase the magnitude of this placebo effect in FM are: a higher effect size of the active treatment, greater symptom

severity at baseline, being male, older age, and having a shorter duration of FM.

8.2 Placebo effect in FM

The first objective of the study is to determine whether placebo is effective in FM. Since the power of the placebo response was first highlighted by Beecher, (Beecher, 1955), the debate as to whether the placebo effect exists never stopped. Many studies suggest that the observed beneficial effects from placebo could be explained by factors such as the natural remission of disease and regression to the mean. However, the comparison between the placebo group and untreated control and waiting list control in the present review strongly supports the existence of the placebo effect in FM. A similar finding was also observed by Zhang, et al, (2008) in OA, where a true positive placebo effect (ES, 0.51, 95% CI 0.46 to 0.55) was found, compared to untreated group. Overall, the pain reduction caused by placebo in OA is greater than that observed in FM, which suggests that different mechanisms of pain may be amenable to placebo.

There are several possible explanations of why placebo could benefit FM patients. Firstly, the patients' expectation of clinical benefits may play a critical role in the placebo effect (Benedetti, 2008). Different studies have shown that the administration of placebo could modulate patients' pain perception and the placebo response was dependent

on expectation (Price et al., 1999, Benedetti et al., 2003). In Benedetti's experiment, two groups of participants were administrated a pharmacological preconditioning with ketorolac for two days. In the third day, ketorolac was replaced by placebo for both groups but one group received verbal suggestion of analgesia and the other group received verbal suggestion of hyperalgesia. The positive verbal instructions induced strong placebo analgesia but the negative verbal instructions produced hyperalgesia. It demonstrated that placebo analgesia depends on patients' expectation of pain reduction (Benedetti et al., 2003). In the clinical trial setting, FM patients were expecting to be treated. Although they had been informed of the chance of getting placebo before getting into the trials, the expectation of getting the real treatment and improvement of the symptoms might still trigger the placebo response.

Secondly, the contextual meaning of the treatment could be a factor to produce the placebo response. When patients were enrolled in a trial, they were assessed by doctors and they were fully aware of the whole treatment process. Nelson found that any medical treatment has two components, the specific effects of the treatment and the knowledge that the treatment is being performed. In his study, patients who were administrated with analgesics openly had larger improvement than patients who had hidden administration of the drugs (Nelson et al., 2010). It proves that patients' knowledge that the therapy was being performed can bring clinical benefits.

Thirdly, certain brain areas and specific neural systems might have been involved in the placebo effect. Neuroimaging has provided evidence that the endogenous opioid system is central to mediating placebo effects on pain, and placebo analgesia is associated with a number of brain regions, including prefrontal, limbic, and brainstem regions (Bennett et al., 2003, Patkar et al., 2007). FM pain is a result of augmentation of sensory input that is mediated by the central nervous system and also peripheral sensitisation with reduced efficiency of descending inhibitory systems (Nielsen and Henriksson, 2007). The placebo might have improved FM symptoms by mediating the activity of brain and neural systems.

8.3 Determinants of the placebo effect

The second objective of the study is to find possible determinants of the placebo effect in FM. Several factors have been investigated, among which patients' gender and age, treatment effect size, baseline severity and duration of disease were found to have potential influences on the magnitude of placebo effect.

8.3.1 Effect size of treatment

The effect size of the placebo increased in line with the effect size of the active treatment. This supports the theory that the magnitude of the placebo effect is largely determined by the expectation of the patients. Vase also agreed on this finding in their “placebo analgesia” study. In this study, the placebo for drugs had larger effect size than that for the non-drug treatments (Vase, 2002). In the present study, the placebo effect size for analgesics was 0.37 (95%CI 0.19 to 0.50), antidepressants, 0.57 (95%CI 0.52 to 0.63), muscle relaxant, 0.55 (95%CI 0.12 to 1.00), and hypnotics, 0.51 (95%CI 0.37 to 0.66). While, the placebo effect size for acupuncture was 0.28 (95%CI -0.04 to 0.59) and that for electromagnetic therapy was 0.30 (95%CI -0.02 to 0.62). It indicates that the patient expectation for non-pharmacological treatments and alternative medicines may be less than that for pharmacological treatments in FM. When patients know that they have been involved in a trial with stronger treatment, their expectation is enhanced. Consequently, the placebo response in such trials becomes higher. The result was also proven in a coffee study. Participants were all given decaffeinated coffee but the ones who were told that they would all receive regular coffee had a greater increase in alertness and heart-rate than the ones who were told that they would receive either regular or decaffeinated coffee (Kirsch and Weixel, 1988).

8.3.2 Baseline severity and duration of disease

Baseline pain severity has been considered as a predictor for placebo response. A positive association between baseline pain and the placebo effect was found in OA (Zhang, et al, 2008). According to Goetz, Parkinson's disease patients with higher baseline function were more likely to have higher placebo effect (Goetz et al., 2008). In this study, we also found positive association between the two. However, the duration of FM was found to have a negative association with the placebo effect. Patients who suffered from FM for longer period of time had smaller placebo effect. In fact, it has been studied that early intervention to FM could promise a higher chance of good prognosis (Goetz et al., 2008), which means the longer the patients live with FM, the harder it becomes to treat the disease, including by placebo. Also patients with longer experience of FM have better understanding that treatments may have limited effect on the disease. Therefore, their expectation becomes lower.

8.3.3 Gender

Gender is a proven determinant of the placebo response (Hauser et al., 2012a). The male gender has been suggested to be better placebo responder in a few studies. In a placebo analgesia study, male participants responded to the manipulation of the expectancies through pain information during ischemic pain, but the female

participants did not (Flaten et al., 2006). In a conditioning study that employed a motion-sickness paradigm, men showed a greater reduction in rotation tolerance and responded more strongly to rotation and to suggestions than women (Enck et al., 2008). Different results were also found in the literature. According to Averbuch and Katzper, no gender difference was found in response to placebo (De Craen et al., 1999a). The present study used subgroup analysis and found that the placebo effect decreased in women. In other words, men are more likely to respond to placebo. This finding is consistent with the fact that women are more likely to have FM and other chronic pain than men. Women also reported longer duration of symptoms than men (Munguia-Izquierdo and Legaz-Arrese, 2008, Tomas-Carus et al., 2007a). The management of these types of pain is more challenging in women.

One possible explanation is that women perceive disease differently from men. Women have significantly greater self-reported symptom awareness than men (Vlahiotis et al., 2010). Because of greater selective attention to their bodies and an increased attribution of bodily sensations to physical illness, women perceive an excess of symptoms compared with men (Da Costa et al., 2005).

Another reason why men are more likely to respond to placebo is that men are better responders to treatments in general, considering the placebo was administrated to FM patients as a treatment in the trials.

According to Mathai, the likelihood of response to tadalafil in pulmonary arterial hypertension patients is higher in men than women (Ang et al., 2010). In Achilles tendinopathy patients, eccentric training, an exercise that has been proven to be very effective in treating pain in the middle of the Achilles tendon, resulted in significantly larger pain reduction in men than women (Van Koulil et al., 2010). The same result is also found in a growth hormone treatment study. In the study, boys with growth hormone deficiency, or multiple pituitary hormone deficiency had significantly better response to growth hormone treatment (Edinger et al., 2005b).

The role of personality trait in placebo response has been studied. High dispositional optimism and low state anxiety were found to be significant predictors of placebo response (Carleton et al., 2011). According to Parmelee (2009), female gender is associated with greater psychological distress and that makes women less likely to respond to placebo. Novelty seeking personality trait is another predictor of placebo response (Carleton et al., 2011), and it is more prevalent in men (Ali et al., 2009). The association between gender and personality traits also partially explains why men are better placebo responders.

8.3.4 Age

The present study found that the placebo effect increased with age. A few other studies also found that the elderly people had a significant response to placebo. For example, according to Alexopoulos, more than half of elderly depression patients showed at least 25% improvement by taking placebo (Alexopoulos et al., 2007). In Parkinson's disease studies, older individuals also showed a significant response to placebo (Goetz et al., 2008). This could be explained by the fact that people of different ages have difference perception of disease. Although prevalence of FM goes up with age, older people report less severe symptoms. They are more likely to regard pain as part of the aging process and cope with it, (Cronan et al., 2002). Another possible explanation is that the older patients had higher treatment expectation. As Lewin has argued, higher treatment expectation is linked to better treatment response, (Kiyak, 2009). Best of our knowledge, there is no other study that has confirmed either positive or negative relationship between patient's age and the placebo effect in FM. Whether this age-related placebo effect in FM is related to the experience, social ability and other contextual factors deserves further investigation.

8.3.5 Other factors

Industry funded trials had larger placebo effect (ES, 0.54, 95%CI 0.50 to 0.59) than non-industry funded trials (ES, 0.41, 95%CI 0.17 to 0.64). In general, industry-funded trials tend to have more funding, and they often come with a new drug or new therapy. Drugs that tested in industry funded trials tend to have larger effect size than the same drugs in non-industrial funded trials (Finckh et al., 2005). This might enhance the contextual effect in the trial setting and bring up the placebo effect.

Noticeably, the trials that recruited the participants via doctor's referral (ES, 0.56, 95%CI 0.51 to 0.61) had larger placebo effect than the ones that recruited the participants via advertisements (ES, 0.10, 95%CI -0.18 to 0.37). As suggested by Kaptchuk, a warm consultation by a physician results in a larger placebo response (Kaptchuk et al., 2008b). In his IBS study, higher percent of patients who received sham acupuncture treatment with good patient-practitioner interaction (62%) reported more pain relief than patients who also received sham acupuncture but with limited interaction with the practitioners (44%) (Kaptchuk et al., 2008b). It indicates that doctors' involvement had more weight to the effect size of the placebo. Studies have shown that the doctors' confidence, willingness to monitor the progress, the certainty of the diagnosis, and good outlook of the treatment results are all proven to be positive elements of how

doctors' evolvement can enhance the placebo response (Thomas, 1987, Thomas, 1994, Gracely et al., 1985).

Other factors have also been analysed as potential determinants of the placebo effect, such as blinding, route of delivery, length of treatment period, age of the treatment since it was first developed (based on the first publication), and the change of getting placebo. Blinding and concealment has been proven to have an impact on the treatment response, as in a post-operative analgesia study, hidden administration of parenteral morphine induced lower onset of pain relief than open administration of the same drug (Colloca et al., 2004). In general, more invasive way of drug delivery and higher frequency of drug administration are associated with higher placebo response (Zhang, et al., 2008). However, in this review, no clear tendency was found. It might be that the placebo effect in FM is not influenced by these factors or the available data are not sufficient to detect any tendency.

Study quality was initially considered as a possible determinant of placebo effect. However, most placebo controlled trials had very good mark in the Jadad score. This made the subgroup analyses according to different quality scores difficult. Further study using another quality indicator is warranted.

8.4 Is CAM just placebo？

In this review, a few types of complementary and alternative medicines (CAM) were included. There are a lot of debates on whether CAM is just placebo. In fact, the answer depends on the specific type of CAM. Acupuncture is a typical CAM that has been used to treat FM. The results showed that acupuncture was effective in pain reduction and other FM symptoms management, and so was the sham acupuncture. According to Vickers, the therapeutic effect of acupuncture is not just placebo effect. In his systematic review of acupuncture for chronic pain, he found that acupuncture was an effective treatment for chronic pain and he also found significant difference between true and sham acupuncture. However, the difference was relatively modest. It suggested that acupuncture was more than a placebo but carried a large proportion of placebo effect (Vickers et al., 2012). Homeopathy was another type of CAM in this review. The mechanism of the action of the ultra-high dilutions has not been scientifically explained. Based on the fact that homeopathy remedies barely contain any “real medicine” and the therapeutic effect is largely contributed by the contextual factor, it was regarded as placebo.

8.5 Applications of study findings

The confirmation of placebo effect in this study can shed some light on clinical practise. Although the use of placebo as a treatment should be avoided (Wang et al., 2010a), good physicians should harness the placebo effect to maximise the benefits to their patients (Wigers et al., 1996). Because the placebo effect consists of contextual effect which is largely derived from the physician-patient interaction (Alfano et al., 2001), physicians should always maximise this interaction to enhance the treatment benefits.

The study finding can also inform the future clinical trial design. Since the double-blind, randomised controlled trial has become the “gold standard” of clinical research, many researchers presuppose that effectiveness can only be granted if a treatment demonstrates an additional/specific effect over placebo (Kravitz et al., 2006). As being proved that the all treatments to FM carry certain proportion of placebo effect, it’s no longer a valid presupposition that only a specific effect over placebo effect are worth looking for. In order to be aware of this placebo trap, future clinical trials should diversify research strategies to use multiple methods, such as randomised comparison against waiting list or usual care. This type of comparison enables the researchers to quantify the overall benefit from the treatment.

8.6 Study caveats

This study has a number of caveats. Firstly, the included trials may not cover all eligible trials in FM, especially those unpublished. Unlike the systematic review of placebo in OA, the number of FM RCTs was relatively small. Furthermore, many included trials did not present their result in numerical data and could not be used for meta-analysis. Although language was not restricted in the literature search, only a few non-English publications were found and none of these were included in meta-analysis because of the lack of numerical data. Like many other meta-analysis, we had to analyse the data at study-level, many determinants at individual patient level could not be characterised.

Secondly, inclusion of many disparate treatments and their placebo in this review resulted in high heterogeneity for the placebo effect. Although we carefully considered the reasons for marked heterogeneity and undertook a number of subgroup analyses to identify the reasons for the heterogeneity, we still failed to identify the reasons of heterogeneity for some subgroups and a random effects model had therefore to be used to give an overall estimate.

Thirdly, in order to prove the placebo effect in FM, it would be ideal to directly compare changes in a placebo treated group and an untreated control group within the same study. The placebo effect

was mainly determined as the difference between baseline and endpoint, rather than the difference in benefit between placebo and untreated groups. Only one trial with a three arm study design provided this comparison and unfortunately it had a small sample size and a limited number of outcome measures.

Fourthly, the influence of gender on the magnitude of the placebo effect would best be studied by comparison between separate large groups of men and women who receive placebo. However, no trials separately reported outcomes according to gender. Instead, the percentage of women in the trials was used as an indirect way of determining a gender difference in placebo response.

Furthermore, there was no untreated control group in the analysis for the nocebo effects. The risk of the unwanted effects from the placebo group cannot therefore be separated from those from the FM symptoms or the effects caused by the factors other than placebo.

8.7 Future work

In future research, studies should focus on three aspects of the placebo effect in FM to further extend the knowledge from this systematic review. Firstly, determinants of the placebo effects should be investigated further at the patient level. Secondly, proportion of the placebo effect within each treatment need to be calculated. Being

able to understand the certain proportion of placebo effect that one treatment carries can provide better guidance to the design of new trials on the treatment. Thirdly, nocebo effect requires more research in the context of the comparison with the background risk of the unwanted events in the population, or an untreated control in trials.

8.8 Overall conclusion of the study

In conclusion, the placebo has been proven to be effective in FM. It reduces pain, fatigue and depression, improves non-restorative sleep and overall quality of life. The effect size of placebo is significantly influence by the effect size of the treatment. Men are more responsive to placebo, so does older age. In contrast, the longer duration of disease is, the more difficult to demonstrate the placebo effect. Not only can placebo be effective as a treatment in FM but it may also cause some side effects, though less than those from the active study medication. The placebo effect in FM may be smaller than that in OA or RA.

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Appendix 1 Searching strategy

Medline OVID 1948-present

1. exp Meta-Analysis/
2. systematic review.mp.
3. quantitative review.mp.
4. quantitative overview.mp.
5. statistical pool.mp.
6. 1 or 2 or 3 or 4 or 5
7. exp Randomized Controlled Trial/
8. exp Clinical Trial/
9. exp Double-Blind Method/
10. exp Single-Blind Method/
11. Comparative Study/
12. 7 or 8 or 9 or 10 or 11
13. exp Fibromyalgia/
14. fibromyalgia syndrome.mp.
15. Chronic widespread pain.mp.
16. Fibrositis.mp. or Fibromyalgia/
17. 13 or 14 or 15 or 16
18. 12 and 17
19. 6 and 17
20. 18 or 19

Appendix 2 Data extraction form

Randomised controlled trial

General

Trial ID	Category
Author(s)	
Disease	
Year of publication	Country
Setting Community ☐ GP ☐ Hospital ☐	Study design parallel ☐ cross-over ☐
Source	
Funding body Industry (fully ☐ partially ☐ unclear ☐) Non-industry ☐ Unknown ☐	

Quality of trial (Jadad's checklist) Total score:

Question	Yes	No	Unknown/NA
6. Was the study described as randomised (This includes the use of words such as randomly, random, and randomisation)?	☐1	☐ 0	
7. Was the method of random allocation appropriate (eg, table of random numbers, computer generated, etc)?	☐1	☐ -1	☐0
8. Was the study described as double blind?	☐1	☐ 0	

9. Was the method of double blind appropriate (eg, identical placebo, active placebo, dummy, etc)?	☐1	☐ -1	☐0
10. Was there a description of withdrawal and drop-outs?	☐1	☐ 0	

Further quality assessment

	Random number	Allocation concealment	Blind care provider	Blind patient	Blind assessor	Intention to treat analysis
Yes	☐	☐	☐	☐	☐	☐
No	☐	☐	☐	☐	☐	☐
Unknown	☐	☐	☐	☐	☐	☐

Details about the trial

Diagnostic criteria:	Existing therapy Continued ☐ Stopped ☐ Unknown ☐
Proportion/eligible	Primary outcome

Demographic info

Intervention (route, dosage and treatment period)	Number of patients	Number of withdrawals	Age (mean±SD)	Female%

Observational period:

Outcome Pain

Group (intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

Outcome Fatigue

Group (intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

Outcome Function

Group (intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

Outcome Sleep

Group (intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

Outcome Quality of Life (QoL)

Group (intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

Outcome other 1:

Group (intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

Outcome other 2:

Group (intervention)	Baseline		Endpoint		Change	
	Mean	SD	Mean	SD	Mean	SD

Adverse event (s)

Side-effect	a/n1	b/n2

Comments: _____

Appendix 3 Full report of study characteristics

Category	Trial	Country	Funding body	Jadad score	Treatment	Control	Age (E)	Age (C)
Self-management	1. (Cedraschi et al., 2004)	Switzerland	Non-industry	3	Self-management	Waiting list	48.9	49.8
Self-management	2. (Hsu et al., 2010)	USA	Non-industry	3	Self-management	Waiting list	Not reported	Not reported
Self-management	3. (Williams et al., 2010)	USA	Non-industry	3	Self-management	Usual care	50.17	50.75
Patient education	4. (Sukenik et al., 1999a)	Spain	Unknown	3	Patient education	Usual care	39.2	42.3
Patient education	5. (Stuifbergen et al., 2010)	USA	Non-industry	3	Patient education	Usual care	Not reported	Not reported
Exercise	6. (Mccarney et al., 2007)	USA	Non-industry	3	Qigong	Usual care	Not reported	Not reported
Exercise	7. (Verhagen et al., 2007)	Spain	Non-industry	3	Multidisciplinary rehabilitation	Usual care	50	51.4
Exercise	8. (Carson et al., 2010)	USA	Unknown	3	Exercise	Waiting list	51.4	55.8

Exercise	9.	(Stigler, 1997)	Spain	Unknown	3	Exercise	Usual care	54.07	55.06
Exercise	10.	(Da Costa et al., 2005)	Canada	Unknown	3	Exercise	Usual care	49.2	52.3
Exercise	11.	(Fontaine et al., 2010)	USA	Non-industry	2	Exercise	Usual care	48.5	47.8
Exercise	12.	Garbonell-Baeza 2010	Spain	Unknown	1	Dance	Waiting list	54.2	51.4
Exercise	13.	(Gowans et al., 2001)	Canada	Unknown	3	Exercise	Usual care	Not reported	Not reported
Exercise	14.	(Gusi et al., 2006)	Spain	Non-industry	3	Exercise	Usual care	51	51
Exercise	15.	(Haak and Scott, 2008)	Sweden	Unknown	3	Qigong	Waiting list	54	53.4
Exercise	16.	Hammond 2005,	UK	Unknown	3	Exercise	Usual care	48.36	48.73
Exercise	17.	(King et al., 2002)	Canada	Non-industry	3	Exercise	Waiting list	45.2	47.3
Exercise	18.	(Kingsley et al., 2005)	USA	Non-industry	3	Exercise	Waiting list	45	47
Exercise	19.	(Lemstra and Olszynski, 2005)	Canada	Unknown	3	Multidisciplinary rehabilitation	Usual care	49.7	49.11
Exercise	20.	(Martin et al., 1996)	Canada	Non-industry	3	Exercise	Usual care	43.9	45.7

Exercise	21. (Munguia-Izquierdo and Legaz-Arrese, 2008)	Spain	Unknown	3	Exercise	Usual care	50	46
Exercise	22. (White et al., 1999a)	Spain	Unknown	3	Titling whole body vabration	Usual care	52.4	53
Exercise	23. (Sanudo et al., 2011)	Spain	Non-industry	3	Exercise	Usual care	55.48	56.15
Exercise	24. (Tomas-Carus et al., 2007b)	Finland	Unknown	3	Exercise	Usual care	51	51
Exercise	25. (Tomas-Carus et al., 2007a)	Portugal	Unknown	2	Exercise	Usual care	51	51
Exercise	26. (Tomas-Carus et al., 2008)	Spain	Unknown	3	Exercise	Usual care	50.7	50.9
Exercise	27. (Tomas-Carus et al., 2009)	Spain	Unknown	3	Exercise	Usual care	50.7	50.9
Exercise	28. (Valkeinen et al., 2008)	Finland	Non-industry	3	Exercise	Usual care	59	58
Exercise	29. (Van Santen et al., 2002)	Netherland	Non-industry	3	Exercise	Usual care	46.2	42.8
Exercise	30. (Wang et al., 2010a)	USA	Unknown	3	Tai Chi	Usual care	49.7	50.5

Exercise	31. (Wigers et al., 1996)	Norway	Non-industry	3	Exercise	Usual care	43	46
Physical treatment	32. (Alfano et al., 2001)	USA	Unknown	4	Magnetic field	Sham treatment	44	44.8
Physical treatment	33. (Almeida et al., 2003)	Brazil	Unknown	4	Ultrasound and current	Sham treatment	56	57
Physical treatment	34. (Babu et al., 2007)	India	Unknown	5	EMG	Sham treatment	43.2	35.3
Physical treatment	35. (Bach and Clement, 2007)	Germany	Unknown	3	Farabloc	Sham treatment	49.02	48.08
Physical treatment	36. (Colbert et al., 1999)	USA	Partially industry	5	Magnetic field	Sham treatment	51.15	48.17
Physical treatment	37. (Enck et al., 2008)	Turkey	Unknown	2	Laser	Sham treatment	Not reported	Not reported
Physical treatment	38. (Hauser et al., 2012a)	USA	Non-industry	5	Electrostimulation	Sham treatment	51.3	54
Physical treatment	39. (Kravitz et al., 2006)	USA	Non-industry	5	Neurofeedback	Sham treatment	45.9	48.1
Physical treatment	40. (Nelson et al., 2010)	USA	Non-industry	5	Neurofeedback	Sham treatment	51.6	52
Physical treatment	41. (Passard et al., 2007b)	France	Unknown	5	Magnetic field	Sham treatment	52.6	55.3

Physical treatment	42. (Roizenblatt et al., 2007)	Brazil	Non-industry	4	Current stimulation	Sham treatment	54.2	50.8
Physical treatment	43. (Alghalyini, 2008)	USA	Unknown	4	Magnetic field	Sham treatment	54.2	51.67
Physical treatment	44. (Sutbeyaz et al., 2009b)	Turkey	Unknown	5	Magnetic field	Sham treatment	42.96	40.89
CBT	45. (Goetz et al., 2008)	Spain	Unknown	3	CBT	Usual care	46.35	47.04
CBT	46. (Ang et al., 2010)	USA	Unknown	3	CBT	Usual care	Not reported	Not reported
CBT	47. (Edinger et al., 2005b)	USA	Unknown	3	CBT	Usual care	50.1	48.3
CBT	48. (Sephton et al., 2007)	USA	Non-industry	3	Mindfulness-based stress reduction	Waiting list	48.4	47.6
CBT	49. (Van Koulil et al., 2010)	Netherland	Non-industry	3	Pain-persistence CBT	Waiting list	41.1	40.9
CBT	50. (Carleton et al., 2011)	Canada	Unknown	5	Attention modification	Sham treatment	Not reported	Not reported
CBT	51. (Kool et al., 2009)	Germany	Unknown	3	CBT	Waiting list	53.4	52.3
Acupuncture	52. (Deluze et al., 1992)	Switzerland	Unknown	5	Acupuncture	Sham treatment	46.8	49

Acupuncture	53. (Pfingsten et al., 2001)	USA	Unknown	3	Acupuncture	Sham treatment	46.1	48.1
Acupuncture	54. (Martin et al., 2006a)	UK	Unknown	3	Acupuncture	Sham treatment	51.7	47.9
Balneotherapy	55. (Ardic et al., 2007)	Turkey	Unknown	3	Thermal bathing	Waiting list	43.5	48.8
Balneotherapy	56. (Evcik et al., 2002)	Turkey	Unknown	2	Thermal bathing	Usual care	42	41.5
Balneotherapy	57. (Fioravanti et al., 2007)	Italy	Unknown	2	Mud pack+ bath	Usual care	46.2	48.6
Balneotherapy	58. (Fioravanti et al., 2009)	Italy	Unknown	2	Phytothermotheray	Usual care	53.2	48.62
Balneotherapy	59. (Camerlain and Myhal, 2009)	Netherland	Unknown	3	SPA	Usual care	48	47
CAM	60. (Ali et al., 2009)	USA	Non-industry	5	Intravenous micronutrient therapy	Placebo	51.7	50.7
CAM	61. (Kiyak, 2009)	Turkey	Unknown	5	Wool	Sham treatment	37.4	37.4
CAM	62. (Menzies et al., 2006)	USA	Non-industry	2	Guided imagery	Usual care	Not reported	Not reported
Analgesics	63. (Arnold et al., 2007)	USA	Partially industry	5	Gabapentin	Placebo	49.2	47.3

Analgesics	64. (Mease et al., 2008)	USA	Unknown	5	Pregabalin	Placebo	50.9	49
Analgesics	65. (Bennett et al., 2003)	USA	Fully industry	5	Tramadol/Acetaminophen	Placebo	49	51
Analgesics	66. (Crofford et al., 2005)	USA	Unknown	5	Pregabalin	Placebo	48	49.7
Analgesics	67. (Mease et al., 2008)	USA	Unknown	5	Pregabalin	Placebo	50.1	48.6
Analgesics	68. (Berger et al., 2007)	Multi-national	Fully industry	5	Pregabalin	Placebo	49.6	48.1
Analgesics	69. (Skrabek et al., 2008) 2008	Canada	Non-industry	5	Nabilone	Placebo	Not reported	Not reported
Analgesics	70. (Vaeroy et al., 1989)	Norway	Unknown	5	Carisoprodol, paracetamol & caffeine	Placebo	46	48.3
Antidepressant	71. (Arnold et al., 2002)	USA	Fully industry	3	Fluoxetine	Placebo	46	46
Antidepressant	72. (Arnold et al., 2004)	USA	Fully industry	5	Duloxetine	Placebo	49.9	48.3
Antidepressant	73. (Arnold et al., 2005)	USA	Fully industry	5	Duloxetine	Placebo	Not reported	Not reported
Antidepressant	74. (Arnold et al., 2010b)	USA	Fully industry	5	Duloxetine	Placebo	50.7	49.6

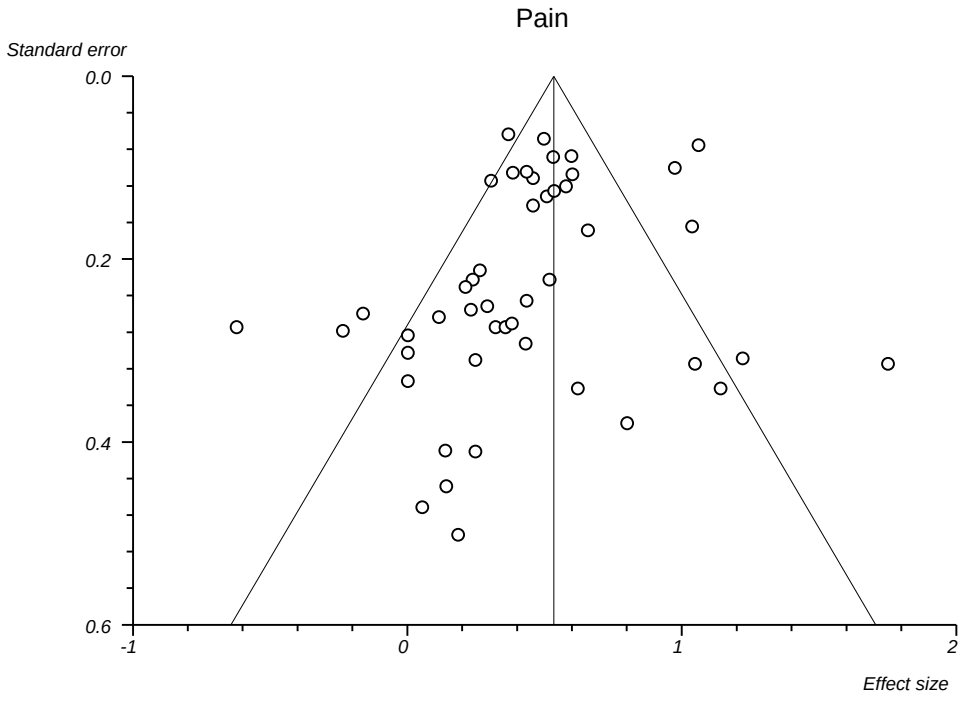
Antidepressant	75. (Mccarney et al., 2007)	USA	Fully industry	5	Milnacipran	Placebo	49.1	48.7
Antidepressant	76. (Arnold et al., 2010a)	USA	Fully industry	5	Esreboxetine	Placebo	49.2	50.1
Antidepressant	77. (Arnold et al., 2012)	USA & Canada	Fully industry	5	Esreboxetine	Placebo	50.6	49.9
Antidepressant	78. (Sukenik et al., 1999b)	Multi-national	Fully industry	5	Milnacipran	Placebo	48.3	49.2
Antidepressant	79. (Carette et al., 1986)	Canada	Unknown	2	Amitriptyline	Placebo	41.8	40.1
Antidepressant	80. (Hadler, 2003)	Canada	Partially industry	5	Amitriptyline	Placebo	44.1	47.1
Antidepressant	81. (Russell et al., 2008)	Multi-national	Fully industry	3	Duloxetine	Placebo	50.75	50.23
Antidepressant	82. (Clauw et al., 2008)	USA	Fully industry	5	Milnacpran	Placebo	49.5	50.7
Antidepressant	83. (Last and Adelaide, 2013)	Switzerland, Czech Republic, Germany	Fully industry	2	Terguride	Placebo	48.5	49
Antidepressant	84. (Farber et al., 2000)	Germany	Fully industry	5	Tropisetron	Placebo	50	48.5
Antidepressant	85. (Benedetti et al., 2007)	USA	Fully industry	5	Milnacipran	Placebo	47.4	48

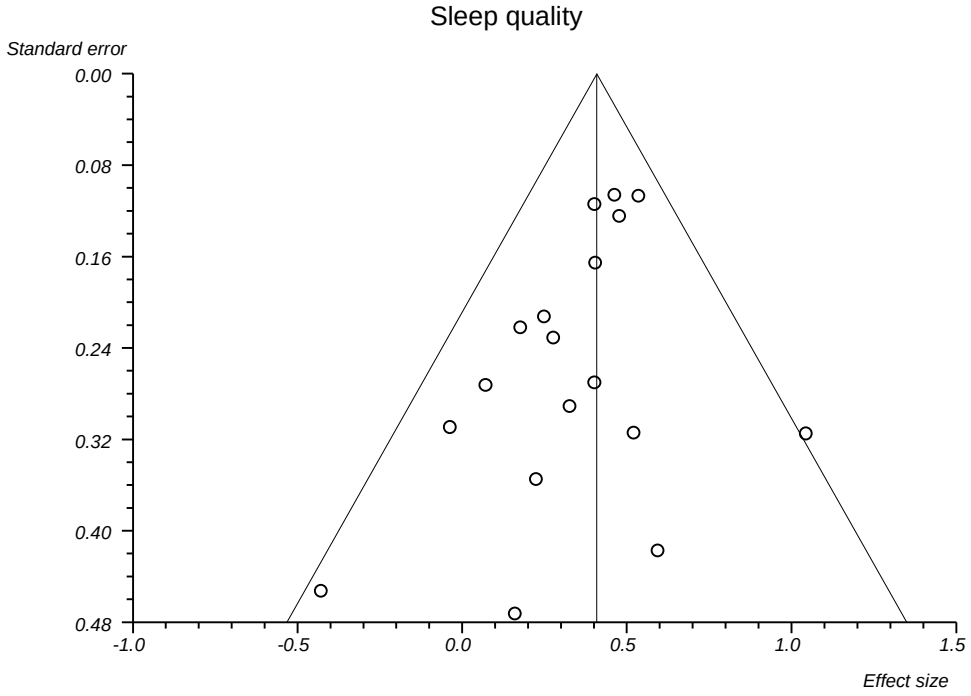
Antidepressant	86. (Burns et al., 2005)	Belgium	Fully industry	5	Amitriptyline	Placebo	46	46
Antidepressant	87. (Enck et al., 2008)	Turkey	Unknown	2	Amitriptyline	Placebo	30.36	28.52
Antidepressant	88. (Hannonen et al., 1998)	Finland	Unknown	5	Moclobemide	Placebo	47.6	48.9
Antidepressant	89. (Heymann et al., 2001)	Brazil	Unknown	5	Amitriptyline	Placebo	53.4	49.4
Antidepressant	90. (Mease et al., 2009)	USA	Fully industry	5	Milnacipran	Placebo	49.9	49.4
Antidepressant	91. (Norregaard et al., 1995)	Denmark	Fully industry	3	Citalopram	Placebo	48	50
Antidepressant	92. (Patkar et al., 2007)	USA	Fully industry	5	Paroxetine	Placebo	47.9	49.1
Antidepressant	93. (Russell et al., 2008)	US & Puerto Rico	Fully industry	3	Duloxetine	Placebo	50.9	50.3
Antidepressant	94. (Sorensen et al., 1995)	Germany	Fully industry	4	Tropisetron	Placebo	50	48.5
Antidepressant	95. (Spath et al., 2004)	Germany	Fully industry	4	Tropisetron	Placebo	51.2	48.5
Antidepressant	96. (Vergne-Salle et al., 2011)	France	Unknown	3	Dolasetron	Placebo	49.1	51.3

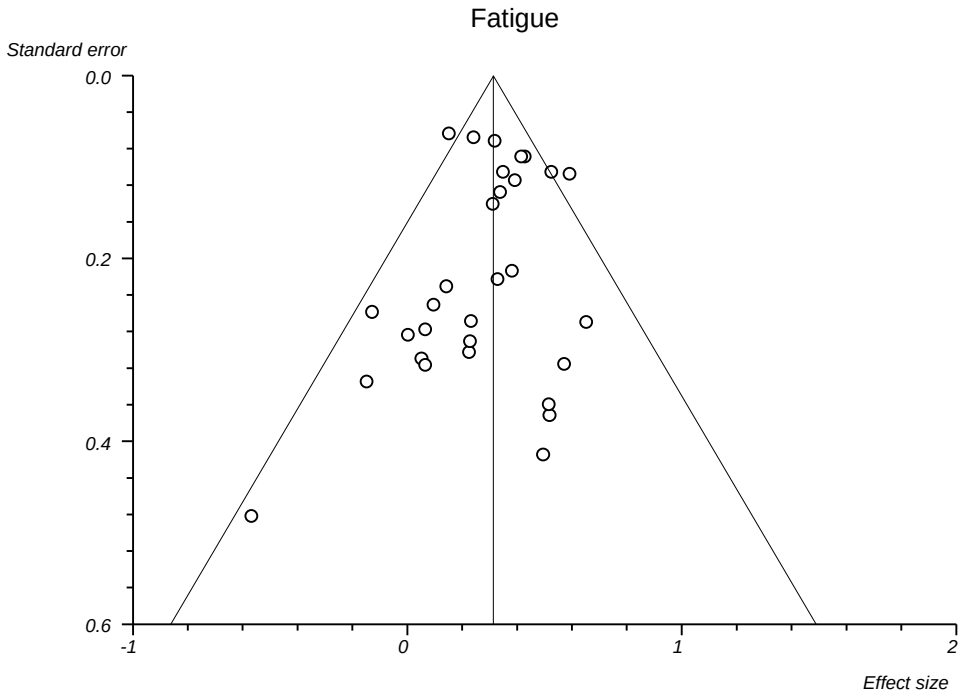
Antidepressant	97. (Hawley and Wolfe, 1994)	USA	Fully industry	5	Fluoxetine	Placebo	48	52.9
Hyponotics	98. (Sicras-Mainar et al., 2009)	USA	Fully industry	5	Sodium oxybate	Placebo	47.4	47.3
Hyponotics	99. (Boonen et al., 2005)	USA	Fully industry	5	Sodium oxybate	Placebo	47	46.5
Hyponotics	100. (Asbring and Narvanen, 2003)	Multi-national	Unknown	5	Sodium oxybate	Placebo	46.4	46.8
Homeopath	101. (Bell et al., 2004)	USA	Unknown	5	Homeopath	Placebo	49.1	47.9
Homeopath	102. (Relton et al., 2009)	UK	Non-industry	3	Homeopath	Usual care	43.9	47.2
Hormone	103. (Bennett et al., 1998)	USA	Fully industry	5	Growth hormone	Placebo	47.9	46.5
Hormone	104. (Finckh et al., 2005)	Swiss	Non-industry	5	Dehydroepiandrosterone	Placebo	59.2	58.7
Alpha1-antitrypsin	105. (Russell et al., 1999)	Spain	Fully industry	5	Alpha1-antitrypsin	Placebo	Not reported	Not reported
Anticholinesterase	106. (Jones et al., 2008)	USA	Non-industry	3	Pyridostigmine	Placebo	49.31	49.78
Muscle relaxant	107. (Briones-Vozmediano et al., 2013)	Canada	Fully industry	5	Cyclobenzaprine	Placebo	45.9	39.3

* Age (E), mean age of the experimental group; Age (C), mean age of the controlled group; CAM, complementary and alternative medicine; CBT, cognitive-behavioural therapy; N/A, not applicable

Appendix 4 Publication bias



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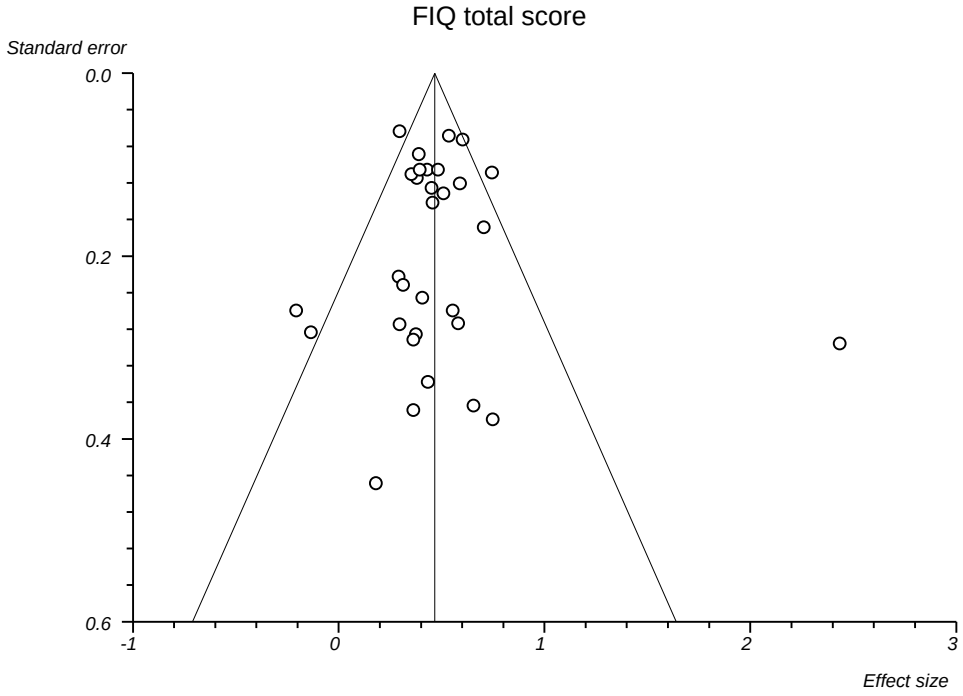
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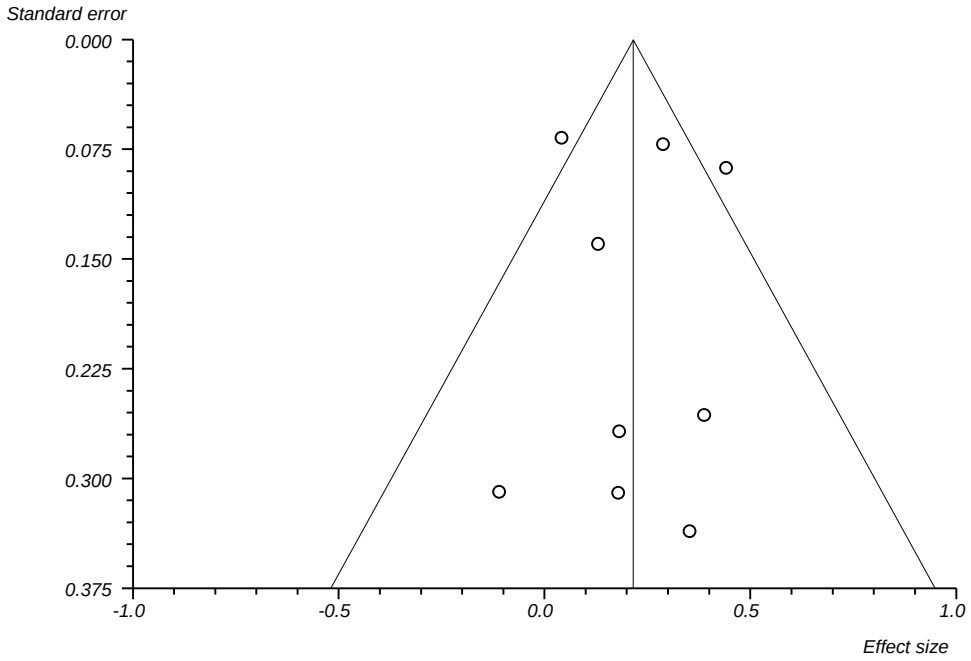
Effect size

Depression



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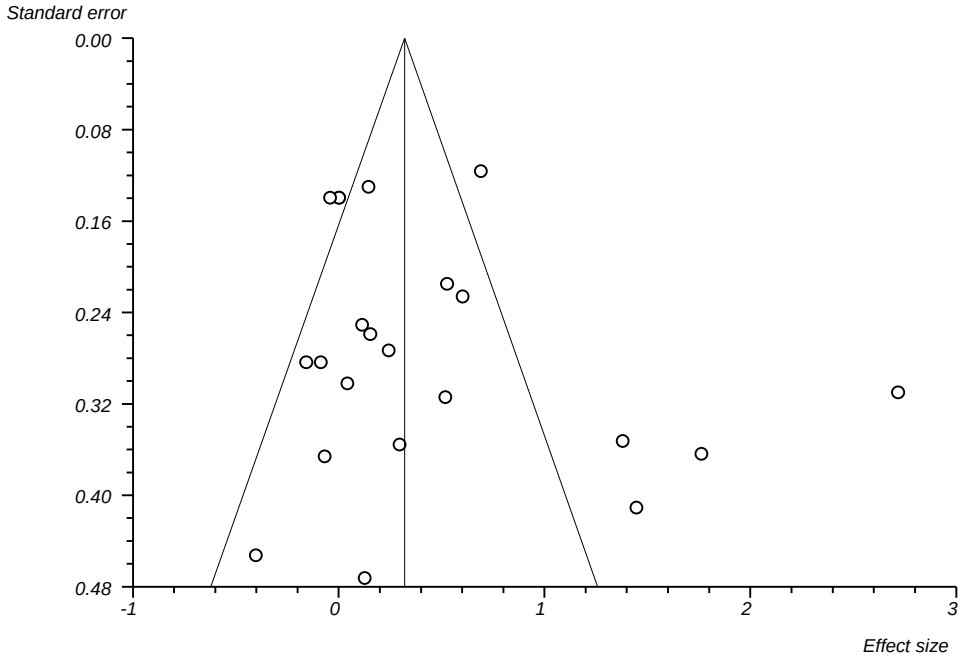

Appendix 5 Common adverse effects by treatment

Treatment	Common AEs	
Nalilone	Drowsiness	Concentration difficulties
	Vertigo	Sleep disturbance
	Euphoria	Dysphoria
	Dry mouth	Hypotention
	Ataxia	Headache
	Visual Disturbance	Nausea
Amitriptyline	Dizziness	Blurred vision
	Sleep disturbance	Constipation
	Drowsiness	Fatigue
	Dry mouth	
Citalopram	Dizziness	Blurred vision
	Sleep disturbance	Constipation
	Drowsiness	Nausea
	Dry mouth	Vomiting
Dolasetron	Diarrhoea	Fatigue
	Constipation	Dizziness
	headache	Drowsiness
Duloxetine	Nausea	Insomnia
	Vomiting	Drowsiness
	Constipation	Headache
	Diarrhoea	Dizziness
	Dry mouth	Fatigue
Fluoxetine	Dizziness	Constipation
	Sleep disturbance	Nausea
	Drowsiness	Vomiting
	Dry mouth	Sleep disturbance
	Blurred vision	Euphoria
Gabapentin	Diarrhoea	Flatulence
	Dry mouth	Appetite changes
	Dyspepsia	Weight gain
	Nausea	Hypertention
	Vomiting	Vasodilation
	Constipation	Oedema
	Abdominal pain	
Paroxetine	Dizziness	Blurred vision
	Sleep disturbance	Constipation
	Drowsiness	Fatigue
	Dry mouth	
Pregabalin	Dry mouth	Drowsiness
	Constipation	Irritability
	Nausea	Euphoria
	Vomiting	Fatigue
	Flatulence	Insomnia
	Oedema	Weigh gain
	Dissiness	
Sodium oxybate	Nausea	Drowsiness
	Vomiting	Dissiness
	Diarrhoea	Headache
	Peripheral oedema	Fatigue
	Sleep disorder	Blured vision
Tramadol	Nausea	Sleep disturbance
	Vomiting	Headache

	Constipation	Euphoria
	Dry mouth	Diarrhoea
	Dissiness	Fatigue
	Drowsiness	
cyclobenzaprine	Dry mouth	Constipation
	Dizziness	Drowsiness
	Fatigue	Nausea
Milnacipran	Blurred vision	Upper respiratory tract
	Nausea	infection
	Constipation	Headache
	Vomiting	Dizziness
	Dry mouth	Insomnia
Tropisetron	Headache	Tiredness
	Constipation	Stomach pain
	Dizziness	Diarrhoea
Tramadol	Dizziness	Vomiting
	Nausea	Insomnia
	Constipation	Dry mouth
	Headache	Diarrhoea
	Drowsiness	