

From the DEPARTMENT OF CLINICAL NEUROSCIENCE

Karolinska Institutet, Stockholm, Sweden

# **GETTING CLOSE WITH DISCOMFORT - EXPOSURE THERAPY FOR FIBROMYALGIA**

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**Karolinska  
Institutet**

Stockholm 2019

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Printed by Eprint AB 2019

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ISBN 978-91-7831-635-9

# GETTING CLOSE WITH DISCOMFORT

## Exposure therapy for fibromyalgia

### THESIS FOR DOCTORAL DEGREE (Ph.D.)

To be defended in public at the Samuelsson Lecture Hall, Karolinska Institutet, Stockholm, Sweden

Friday 6<sup>th</sup> of December, 2019 at 1 pm

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*To Edda, Lovis and Erik. You make life wonderful.*



## ABSTRACT

**Background:** Fibromyalgia (FM) is a common and debilitating disorder for which there are currently no treatments available that are satisfyingly effective. Cognitive behavior therapy (CBT) might be a promising treatment option, but most CBT studies—evaluating various multi-component protocols—have rendered mixed results. Exposure therapy has shown some promise in treating other chronic pain conditions, but has not been evaluated specifically for patients with FM. The general aim of this PhD project was to develop and evaluate an exposure therapy protocol for FM. More specifically, the aims were to investigate:

- The acceptability and efficacy of internet-delivered exposure therapy for FM (Study I and II).
- The cost-effectiveness of the treatment (Study III).
- Potential mediators of treatment effect (Study IV).

**Methods:** Acceptability, preliminary efficacy and health economic effects of the treatment was investigated in an open pilot study (Study I). The efficacy of the treatment was evaluated in a randomized controlled trial, where participants were randomized to either internet-delivered exposure therapy (iExp) or a waitlist control (WLC) (Study II). Participants were individuals 18-65 who had received a FM diagnosis from a physician and who self-referred to participate in the studies. Primary outcome was FM symptoms, and secondary outcomes included fatigue, disability, quality of life, anxiety, depression, insomnia and psychological inflexibility. The treatment consisted of 10 weeks of therapist-supported exposure therapy delivered on an online platform. The cost-effectiveness of the treatment was investigated from both a societal perspective and a healthcare unit perspective using data from the randomized trial (Study III). To investigate potential mediators of treatment effect, a mediational analysis was conducted using data from the randomized trial with weekly measurements of three potential mediators (FM-related avoidance behavior, mindful non-reactivity and FM-related worry) and treatment outcome (FM symptoms) (Study IV).

**Results:** Therapist-supported exposure therapy rendered acceptable adherence and treatment completion, with over 70% of participants initiating work with exposure in both Study I and II. Participants receiving iExp had significantly lower FM symptoms at post-treatment, compared to pre-treatment (Study I) and compared to the WLC (Study II), respectively. Moderate within-group (Study I) to large between-group (Study II) effect sizes favoring iExp was observed on the primary outcome, and significant improvements were also observed on all secondary outcomes (Study I-II). All improvements were maintained at the 6- (Study I-II) and 12- (Study II) month follow-up. iExp was highly cost-effective compared to no treatment, with each

successful treatment incurring a large societal cost saving (Study III). A reduction in avoidance behavior mediated a reduction in FM symptoms for participants receiving iExp compared to participants in the waitlist group (Study IV).

**Conclusion:** Overall, the studies in this PhD project point to that iExp is an acceptable, effective and cost-effective treatment for FM compared to waitlist control, and that targeting avoidance behavior may be important in exposure therapy for FM. Future studies are needed that compares iExp against an active treatment control, and will benefit if including competing mediators of a different treatment paradigm.



## LIST OF SCIENTIFIC PAPERS

- I. Ljótsson B, Atterlöf E, Hedman-Lagerlöf M, Andersson E, Jernelöv S, Hedman E, Kemani M, Wicksell RK. (2014). Internet-Delivered Acceptance and Values-Based Exposure Treatment for Fibromyalgia: A Pilot Study. *Cogn Behav Ther* 43:93-104.
- II. Hedman-Lagerlöf M, Hedman-Lagerlöf E, Axelsson E, Ljótsson B, Engelbrektsson J, Hultkrantz S, Lundbäck K, Björkander D, Wicksell RK, Flink I, Andersson E. (2018). Internet-based Exposure Therapy for Fibromyalgia: A Randomized Controlled Trial. *Clin J Pain* 34:532-42.
- III. Hedman-Lagerlöf M, Hedman-Lagerlöf E, Ljótsson B, Wicksell RK, Flink I, Andersson E. (2019). Cost-Effectiveness and Cost-Utility of Internet-Delivered Exposure Therapy for Fibromyalgia: Results From a Randomized, Controlled Trial. *J Pain* 20(1):47-59.
- IV. Hedman-Lagerlöf M, Andersson E, Hedman-Lagerlöf E, Wicksell RK, Flink I, Ljótsson B. (2019). Approach as a key for success: Reduced avoidance behaviour mediates the effect of exposure therapy for fibromyalgia. *Behav Res Ther* 122, 103478.

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## LIST OF ABBREVIATIONS

ACR	American College of Rheumatology
ACT	Acceptance and commitment therapy
AE	Adverse event
CAM	Complementary/alternative medicine
CBT	Cognitive behavior therapy
CI	Confidence interval
CNS	Central nervous system
CR	Conditioned response
FA model	Fear and avoidance model
FIQ	Fibromyalgia Impact Questionnaire
FM	Fibromyalgia
IASP	International Association for the Study of Pain
IBS	Irritable bowel syndrome
ICER	Incremental cost-effectiveness ratio
Internet-CBT	Internet-delivered cognitive behavior therapy
iExp	Internet-delivered exposure therapy
MADRS-S	Montgomery Åsberg Depression Rating Scale-Self rated
NS	Neutral stimulus
QALY	Quality-adjusted life years
PASS	Pain Anxiety Symptoms Scale
PRS	Pain Reactivity Scale
PVAQ	Pain Vigilance and Awareness Questionnaire
SSS	Symptom Severity Scale
TENS	Transcutaneous electrical nerve stimulation
UR	Unconditioned response
US	Unconditioned stimulus
WLC	Waitlist control
WPI	Widespread Pain Index
WTP	Willingness-to-pay

# 1 INTRODUCTION

Imagine having long-lasting pain in multiple parts of your body and feeling almost constantly fatigued. The pain might move around from day to day and will often intensify with cold weather, but is always present one way or another. Often of a grinding, dull nature, sometimes sharp and burning. After a day filled with more activity than usual you might need to stay in bed for a whole day to recover. Imagine being overly sensitive to certain fabrics, smells, and sounds, and not having slept well for years. You have problems with concentration, finding words and holding a conversation. Imagine that normal touch—like someone placing their hand on your arm, or your child giving you a hug—being so painful you have to bite your lip.

This is reality for many individuals living with fibromyalgia. In Sweden, around 200 000 individuals have this condition, the vast majority of which are women. Many of them describe feeling poorly understood by their environment and healthcare personnel. Due to the absence of objective signs of the disorder, many patients feel their complaints either are not taken seriously, or their symptoms not being recognized as fibromyalgia. One may go for years before receiving a correct diagnosis. And when you do, there are no really effective treatments available.

My interest in fibromyalgia began during the latter part of the psychology program. I learned about an exposure-based therapy that had shown effective in irritable bowel syndrome, and I got curious whether the treatment could be effective for also patients with fibromyalgia, this puzzling and many-faceted condition. Together with a fantastic team of researchers me and a fellow student were able to explore this as part of our master's thesis. That was the start of the present doctoral project, and the studies presented within this thesis show where we have come this far. The results are limited by design and method but do point us in in new and exciting directions. I hope this thesis can inspire future research endeavors.

*Stockholm, November 2019*



## 2 BACKGROUND

### 2.1 FIBROMYALGIA

#### 2.1.1 Clinical characteristics

Fibromyalgia (FM) is a condition marked by chronic pain and multiple symptoms of both somatic and psychological nature. The predominant feature is widespread pain, tenderness and stiffness in the muscles, tendons and ligaments, without any demonstrated tissue abnormality. More specifically patients with FM have a decreased pain threshold, which means that they display heightened pain responses to normally nonpainful stimuli (also known as *allodynia*) and heightened pain responses to normally painful stimuli (also known as *hyperalgesia*).<sup>1</sup> FM pain may occur body wide, migrate over the body, or in pre-specified points on the body particularly sensitive to pressure (so-called tender points). The pain often varies from day to day and many patients report the pain aggravating by certain weather conditions.<sup>2-5</sup> Other common features of the disorder include fatigue, sleep disturbances, subjective swelling, paresthesias, cognitive dysfunction, headaches and irritable bowel syndrome (IBS), depression and anxiety.<sup>6</sup> These symptoms can often be as disabling as the pain itself, and altogether FM constitutes a plethora of medically unexplained symptoms, not only causing disability, but often also symptom-related distress and avoidance of daily activities.<sup>7,8</sup> Not surprisingly, FM is associated with a lower health-related quality of life, and the experience of illness seems to be worse compared to many other disorders.<sup>1</sup>

#### 2.1.2 Diagnostic criteria

There are no confirmatory biomarkers or histological analysis available for FM, and diagnosis is therefore based on the presence of FM-like symptoms\*. The first diagnostic criteria for classification of FM were published in 1990 by the American College of Rheumatology (ACR),<sup>10</sup> and depended primarily on the physical examination of tender points. However, the tender point criteria were problematic since the examination turned out to be unreliable, with many physicians either not performing it or doing it incorrectly. Situations arose where patients who had once fulfilled the criteria but—due to fluctuation in tender points or measurement error—failed to satisfy the criteria during a later examination. Also, in the 1990 version there were no criteria for other symptoms most commonly associated with FM such as sleep disturbances, fatigue or cognitive dysfunction.

Due to the problems stated above, updated criteria were published in 2010/2011 where the tender point examination was omitted, and a further revision published in

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\*Of note, skeptical voices have also been raised regarding the diagnostic label of FM and the very existence of the disorder.<sup>1,9</sup>

2016<sup>11</sup> added a generalized pain criterion. Diagnostic criteria for FM now incorporate key symptoms of the disorder besides widespread pain, provide severity scales for widespread pain and somatic symptoms, and excludes other somatic conditions that sufficiently explain the symptoms<sup>†</sup>. However, the 2016 criteria have not gained full impact in either clinical practice or within the research field. In Sweden the majority of patients are still diagnosed according to the ACR 1990 criteria within the healthcare system. To summarize, there is still no internationally accepted definition of FM.

### **2.1.3 Prevalence, comorbidity and health economic aspects**

Most prevalence studies estimate the prevalence of FM to between 2% and 4%.<sup>12</sup> However, the majority of prevalence studies are based on the ACR 1990 criteria which have shown to yield lower prevalence rates than the modified 2010 criteria,<sup>13,14</sup> indicating that FM might be more common than previously thought. Women seems to be more afflicted than men, although when using the later version of the criteria (i.e., without tender point examination) the sex ratio seems to be more equal,<sup>1</sup> however still with a predominance in women. Although being most common in patients over 50 years of age,<sup>12</sup> FM also occurs in children and adolescents.<sup>15</sup>

FM has a high degree of comorbidity. Common co-occurring conditions are found within the cardiovascular and respiratory diseases and other pain-related conditions,<sup>16</sup> and FM patients also display a high rate of anxiety and depressive disorders.<sup>17</sup> Several of these disorders (e.g., chronic fatigue syndrome, temporomandibular disorder, IBS, migraine) have overlapping symptoms such as generalized pain sensitivity, and no consistent demonstrated tissue abnormality. Observations from genetic research demonstrating that these syndromes run in families suggest that they share heritable pathophysiologic features.<sup>18,19</sup>

FM is also a costly disorder. Patients with FM on average have a mean healthcare cost that is almost three times higher than comparison patients.<sup>16</sup> Being the chronic pain condition with the highest rates of sick-leave, unemployment, claims for incapacity benefits and work absenteeism, FM incurs high costs also on a societal level.<sup>20,21</sup>

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<sup>†</sup>Diagnostic criteria according to the 2016 revisions to the 2010/2011 criteria.<sup>11</sup>

- (1) Generalized pain, defined as pain in at least 4 of 5 regions, is present.
- (2) Symptoms have been present at a similar level for at least 3 months.
- (3) Widespread Pain Index (WPI)  $\geq 7$  and Symptom Severity Scale (SSS) score  $\geq 5$  OR WPI of 4–6 and SSS score  $\geq 9$ .
- (4) A diagnosis of fibromyalgia is valid irrespective of other diagnoses. A diagnosis of fibromyalgia does not exclude the presence of other clinically important illnesses.



## **2.2 ETIOLOGY AND CONTRIBUTING FACTORS**

Available evidence suggests that FM does not have a clear etiology but may be caused by multiple interacting factors, including neurotransmitter- and cytokine imbalances in the central nervous system (CNS),<sup>22</sup> disturbances in the hypothalamic–pituitary–adrenal axis,<sup>23</sup> genetic factors<sup>24</sup> and psychiatric comorbid conditions.<sup>23</sup> Thus, there seems to be many roads that can lead to the development of FM. As for the question regarding what FM actually ‘is’, the leading pathophysiological hypothesis is that FM is a disorder within the CNS related to pain transmission and pain processing<sup>1</sup> and that the CNS has a leading role in the augmentation and amplification of pain in FM.

The International Association for the Study of Pain (IASP) defines pain as “an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage”.<sup>25</sup> This definition highlights the inherent subjective nature of pain and fits well with the medically unexplained pain that is the core feature of FM. It is also well known that the experience of pain is a complex interaction of biological, psychological and social factors.<sup>26</sup> This is further highlighted below.

### **2.2.1 Pain physiology in FM**

When pain occurs as a consequence of clear tissue damage or inflammation, signals from nociceptors (pain neurons) are transported via nerve cells to the dorsal horn in the spinal cord, from which the information are further transferred to the brain. Interestingly, the brain can also receive pain signals with only little or even without nociceptive information, meaning that the patient experiences pain without tissue damage or inflammatory processes.<sup>27</sup> This is the case in FM and other functional pain disorders such as IBS, functional abdominal pain or chronic cardiac chest pain. The incoming pain signal may be amplified or inhibited, resulting in an augmented or attenuated pain perception.<sup>1</sup> In FM, it seems that the CNS itself contributes to an active amplification of sensory stimuli,<sup>28,29</sup> leading to an enhanced response to noxious stimuli as well as an intensified excitability of the neurons in the spinal cord transmitting nociceptive information to the brain.<sup>30</sup> Also, blunting of the descending inhibitory pathways in FM attenuates the capacity for the CNS to achieve brain-regulated inhibition of pain signals.<sup>31-34</sup>

Various psychological factors are also involved in the process of pain amplification. For instance, depressive mood and anxiety are factors that have been shown to amplify the nociceptive signals in experimental pain.<sup>35</sup> Also, avoidance behaviors and hypervigilance are two factors that are relevant in the understanding of FM (further elaborated below).

## 2.2.2 Two psychological factors relevant for FM

### 2.2.2.1 Avoidance behaviors

From an evolutionary perspective, avoidance is a logical response to pain. With pain being an important warning signal about potential tissue damage, avoidance behaviors such as avoiding stimulation or physical activity will promote the early healing process in acute pain.<sup>36</sup> However, when pain has become chronic, although avoidance behaviors might involve a short-term decrease in symptoms or symptom-related distress, they do not lead to long-term improvement and may therefore be viewed as a maladaptive response.<sup>37</sup> The involvement of intermittent short-term reduction of symptoms and/or distress promotes the maintenance of avoidant behavior, and may explain why it is a common feature in the symptomatology of chronic pain conditions.<sup>37-39</sup> Importantly, several studies point to avoidance behaviors as a maintaining and even exacerbating factor of pain intensity, hypervigilance towards bodily symptoms, disability and psychological distress, as well as pain catastrophizing (i.e., the tendency to interpret pain as highly threatening) in patients with chronic pain conditions.<sup>40-44</sup>

Avoidance behaviors in chronic pain have a diverse topography. The most obvious are overt (i.e., visible to others) behaviors serving to relieve, control or avoid pain and other aversive symptoms, such as using short-term analgesics, daytime resting or avoiding certain pain-eliciting situations. However, avoidance behaviors can also be of subtle nature, such as doing certain activities in a different manner or with an aid, over-activity (i.e., “biting the bullet”), pacing activity or mental strategies (e.g., distraction‡, worry/rumination or thought suppression) to reduce pain or pain-related distress.<sup>40,43,44,46-48</sup> Notably, with FM comprising a wide range of debilitating symptoms, not only pain is a possible focus of avoidance. The studies in the present thesis therefore define avoidance behavior as any overt or covert behavior that serves the primary function to relieve or avoid FM symptoms or acute distress associated with FM.

### 2.2.2.2 Hypervigilance

Like avoidance behaviors, attention to pain is a normal and evolutionary valuable process in cases of acute pain (i.e., it is functional to attend to potential threats in the environment). One of the first discussions of excessive attention to pain<sup>49</sup> defined hypervigilance as a perceptual habit of scanning the body for somatic sensations, brought on by a tendency to appraise bodily sensations as threatening.

Self-reported high attention to pain has been associated with higher pain intensity, emotional distress and psychosocial disability, and to be a significant predictor of disability, distress and healthcare utilization regardless of pain intensity.<sup>46</sup> Moreover,

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‡Distraction has also been assumed to lessen pain,<sup>45</sup> which may explain why some CBT protocols for FM promote distraction as a pain coping strategy.

hypervigilance as a maintaining factor in chronic pain has been subject to empirical investigation,<sup>50,51</sup> and patients with FM have been shown to display higher vigilance to pain<sup>52,53</sup> and other noxious stimuli<sup>53</sup> than other chronic pain patients. One hypothesis is that FM would involve a generalized pattern of hyper-responsiveness to internal and external discomfort,<sup>54,55</sup> that is, not only pain but other noxious stimuli as well. Others claim<sup>52</sup> that hypervigilance neither is an abnormal individual characteristic, nor unique for FM, but highly depending on the threat value of pain. Support for this notion is the finding that hypervigilance was mediated by pain intensity and catastrophic thinking about pain, in both FM patients and patients with low back pain.<sup>52</sup>

### **2.3 PSYCHOLOGICAL THEORIES OF PAIN AND FM**

Interactions between pain perception and -processing, avoidance behaviors and hypervigilance to bodily symptoms can be understood within psychological theoretical theories. With learning theory as a base, the fear and avoidance model (FA model) and acceptance and commitment therapy (ACT) are described below. The theories are overlapping and may all contribute to the understanding of partial maintenance of symptoms and severity in FM.

Learning theory stipulates that behaviors are learned via respondent and operant conditioning and social learning. In respondent conditioning, a neutral stimulus (NS) is paired with an unconditioned stimulus (US), where the US naturally and automatically elicits an unconditioned response (UR). After the NS has been associated with US it becomes a conditioned stimulus (CS), that alone elicits the now conditioned response (CR).<sup>56</sup> In chronic pain, the CR is often distress, annoyance or fear. Operant learning prescribes that reinforcement of a behavior increases its future probability, and punishment decreases it.<sup>57</sup> In chronic pain, avoidance behaviors in chronic pain are hypothesized to be maintained by (negative) reinforcement, while non-pain behaviors are extinguished by nonreinforcement (e.g., the pleasure of the behavior outweighed by its cost in terms of increased symptoms) or punishment (e.g., increased pain). A potent reinforcer of avoidance behaviors is short-term symptom reduction (i.e., pain, fatigue, stiffness), as well as reduction of the conditioned response (e.g., distress, annoyance and fear). From a learning theory perspective, hypervigilance lowers the threshold for detecting aversive symptoms, which may further amplify this learning process.<sup>46</sup>

One psychological model that has applied learning theory to chronic pain and extended with cognitive theory is the *fear and avoidance model* (FA model).<sup>39</sup> According to the FA model, pain experience after an injury can be interpreted as either dangerous or harmless. When pain is perceived as non-threatening, rapid confrontation with daily activities is likely to occur, leading to recovery. In catastrophizing patients, pain-related fear activates avoidance behavior and hypervigilance, leading to functional disability,

disuse and depression. The latter will in its turn maintain the pain experience, further fueling a vicious cycle of fear and avoidance. A revised version of the FA model<sup>58</sup> also acknowledges the importance of valued goals in relation to pain-related avoidance.

Originally developed for low-back pain the FA model stipulates that, for fearful patients, pain-related fear cognitions are the maintaining factor of chronic pain. Indeed, there are studies showing that catastrophizing is associated with increased disability, pain intensity and decreased pain threshold.<sup>59-61</sup> However, the FA model was never intended to explain all cases of chronic pain,<sup>62</sup> and may not be as applicable to generalized pain disorders such as FM.<sup>58</sup> Firstly, avoidance may also be elicited without the conscious feeling of fear, for instance as a habitual response.<sup>63,64</sup> Secondly, chronic pain can elicit a multitude of negative emotions besides fear (e.g., annoyance, frustration and sadness), all of which can become conditioned and trigger avoidance behaviors. Thirdly, not all patients with chronic pain display overt pain-related avoidance, but respond to pain with excessive activity<sup>65-67</sup> (so-called pain-persistence patterns or endurance-related responses<sup>68,69</sup>). Prospective studies show that endurance behavior is a significant predictor of pain intensity.<sup>70,71</sup> Thus, although the FA model is relevant for many patients with pain and FM, complementary approaches are also needed.

Another development within learning theory of chronic pain is *acceptance and commitment therapy* (ACT). According to ACT theory, human suffering can be explained by the human unwillingness to experience negative thoughts, emotions and bodily sensations (e.g., pain). This so-called *experiential avoidance* leads to a narrow and inflexible behavioral repertoire and the individual becoming increasingly separated from important life values, aggravating disability and impairing quality of life.<sup>72</sup> *Psychological flexibility* is a construct that can be viewed as the opposite to experiential avoidance, and may be defined as actively embracing aversive inner experiences when they occur as ongoing inner experiences, and to engage in activities guided by one's goals, while in the presence of those inner experiences. One aspect of psychological flexibility is acceptance—that is, to allow unwanted private experiences to come and go without trying to alter them. Pain acceptance have been shown to be associated with less pain, pain-related anxiety and avoidance, distress and disability<sup>73,74</sup> and greater psychological well-being<sup>75</sup> in chronic pain patients. In FM, pain acceptance has been shown to be associated with less FM severity, anxiety and depression, as well as better general health and functioning.<sup>76</sup>

## **2.4 TREATMENT OF FM**

### **2.4.1 Non-psychological treatments**

The pharmacological agents most thoroughly evaluated for treating FM include antidepressants such as amitriptyline, duloxetine and milnacipran, and the antiepileptic

agent pregabalin/gabapentin.<sup>77</sup> These drugs have shown to have positive effects not only on pain but also on secondary symptom domains in FM.<sup>78</sup> However, the observed effect sizes of these drug treatments are mostly modest and tolerability is often limited by side effects. Overall, the benefits of pharmacotherapy in FM have been argued to be of limited clinical relevance.<sup>77,79</sup>

Also, a broad range of other non-pharmacological treatments have been evaluated for FM. Examples include (but are not restricted to) physical exercise, balneotherapy, body awareness therapy, biofeedback, complementary/alternative medicine (CAM) treatments (e.g., acupuncture, chiropractic therapy, homeopathy, massage therapy, meditative moment therapies or mind/body-therapies), trans-magnetic stimulation and trans-direct current stimulation.<sup>80</sup> A recent meta-analysis<sup>80</sup> concluded that exercise and meditative moment therapies may be beneficial for FM patients. However, studies are generally too small and of insufficient quality, why no definitive conclusions regarding the benefits of these treatments can be made.<sup>79,80</sup>

## **2.4.2 Psychological treatments**

The majority of psychological treatments evaluated for FM have been varieties of cognitive behavior therapy (CBT), described below. Additional psychological interventions evaluated for FM include mindfulness-based interventions,<sup>81,82</sup> short-term psychodynamic therapy<sup>83</sup> and hypnosis.<sup>84</sup> Apart for a few exceptions (e.g., attention modification training<sup>85</sup>) most of these studies have had null findings or modest effects.

## **2.4.3 Cognitive behavior therapies**

CBT is the most evaluated psychological treatment for FM,<sup>86</sup> with over 40 randomized clinical trials. Apart from a few studies (e.g.,<sup>87-90</sup>), results between trials have been mixed with mostly small to moderate effects. The varying results could possibly be due to methodological issues such as differences in sample size and type of intervention(-s). For instance, the majority of these studies have evaluated multi-component protocols consisting of a combination of CBT interventions, such as cognitive restructuring, problem-solving techniques, relaxation, patient education, stress- and self-management.<sup>91</sup> Despite the many evaluations of CBT for FM, only two trials have investigated what actually drives the treatment effects (i.e., mediators).<sup>92,93</sup> Additionally, there is little evidence regarding the cost-effectiveness of CBT for FM.<sup>94-97</sup>

### *2.4.3.1 Exposure therapy*

Being one of the central interventions in CBT, exposure constitute the main component in CBT protocols for various anxiety disorders<sup>98-104</sup> and have also been successfully evaluated for some somatic conditions.<sup>105-107</sup> In essence, exposure therapy involves repeated and sustained contact with stimuli that elicit symptom-related distress. This can be done by systematic exercises in which the patient provokes aversive and/or

feared bodily symptoms (interoceptive exposure), approach avoided situations (in-vivo exposure) or imagine fearful or painful memories, feelings or thoughts (imaginative exposure). Exposure also involves refraining from so-called safety behavior to reduce anxiety or distress (i.e., a subtle form of avoidance behavior). The central process of improvement in exposure is not established, but hypotheses include an increased tolerance for fear and distress, as well as the patient gaining new information on being able to cope with the stimuli, situations and symptoms.<sup>108</sup>

With avoidance behaviors and hypervigilance acknowledged as contributing factors in chronic pain, exposure has been proposed as a reasonable intervention<sup>38,39</sup>. Indeed, exposure *in vivo* have been evaluated in a few clinical trials,<sup>109-112</sup> and two trials have investigated ACT (which also has a major focus on exposure) for FM.<sup>89,93</sup> Although some of these exposure *in vivo* trials have also included FM patients, none has investigated exposure therapy specifically on an FM population. Findings pertaining to other chronic pain conditions (e.g., low back pain) cannot necessarily be generalized to FM, since patients with FM differs from the larger chronic pain population, not least by displaying a multitude of other symptoms.

The treatment manual<sup>113</sup> in previous trials evaluating exposure *in vivo* all build on the FA model. The main component is exposure *in vivo* exercises, mainly targeting overt avoidance behaviors derived from the patient's ratings on a questionnaire<sup>114</sup> assessing the threat value of various physical movements from daily life. In contrast, a treatment that comprise also interoceptive exposure (i.e., actively provoking FM symptoms) could possibly be more effective in reducing symptom-related distress. Also, a functional view on avoidance (capturing also covert avoidance, as well as avoidant behavior related to other FM symptoms than pain only) should theoretically be able to target an increased number of relevant avoidance behaviors.

#### 2.4.3.2 Internet-delivered CBT

Internet-delivered CBT (internet-CBT) is an online-based treatment, designed and structured to promote the same behavioral changes as in traditional face-to-face CBT. The patient takes part of self-help material and works with CBT exercises and strategies, guided by an identified therapist who gives feedback and answers questions.<sup>115</sup> Internet-CBT has been shown to be as effective as traditional face-to-face-therapy for a number of somatic and psychiatric conditions.<sup>116</sup>

Internet as treatment modality may be beneficial for several reasons when evaluating a novel treatment protocol. First, as internet-CBT demands less time per patient from the therapist, it is possible to conduct a relatively large-scale clinical trial with little resources, increasing statistical power to detect meaningful differences. Also, with the patient not being tied to attend scheduled meetings at a clinic national recruitment is possible, generating a larger population to the sample and thereby increasing the

generalizability of any potential findings. Second, the treatment content is highly structured, which minimizes the risk of treatment contamination due to non-adherence from the therapist. In other words, internet-CBT allows the treatment content to be more to-the-point by eliminating non-specific treatment factors, which enables the isolation and investigation of potentially effective treatment components.<sup>117</sup>

Internet-CBT could also be a suitable treatment modality for the FM population, as treatment participation does not require scheduled meetings at a clinic which, due to symptom fluctuation, could be a problem in FM. Instead, the patient works with the treatment in her own pace, repeating the treatment content whenever necessary. With the access to CBT treatment being generally low,<sup>118</sup> internet-CBT may also enhance the access to a potentially effective treatment. Internet-CBT for FM with therapist support has previously been investigated in two trials,<sup>119,120</sup> both using traditional CBT protocols, with mixed results. Hence there is a gap of knowledge regarding the acceptability and efficacy of exposure therapy for FM in internet format.

## **2.5 SUMMARY OF THE BACKGROUND OF THE THESIS**

FM is a prevalent and disabling condition. It is associated with low quality of life and high comorbidity with other conditions, and is also a costly disorder for both healthcare providers and society. Most likely the etiology of FM is multifactorial, i.e., many roads can lead to the development of FM. Avoidance behaviors and hypervigilance are probably important and interacting psychological mechanisms in the maintenance of chronic widespread pain, the main feature of FM.

Altogether the available evidence suggests that CBT might have the potential to alleviate FM symptoms. However, the overall between-group effect sizes are low and the health economic aspects of this treatment is still unclear. Additionally, we still do not know what drives the treatment effect in the different CBT protocols. Thus, there is still a need for large-scale clinical trials designed to take the first steps in investigating mechanisms and mediators of treatment outcome in CBT for FM. Internet-CBT could increase outreach to patients with FM but the evidence of this treatment format is still limited.

Exposure is a potentially promising treatment strategy, but a new approach compared to previous trials might yield better results. A functional view on avoidance, acknowledging that additional symptoms besides pain can elicit symptom-related avoidance, and targeting also covert avoidance; open up for identifying more relevant avoidance behaviors to target in treatment.

### **3 AIMS**

The overall aim of the thesis was to develop and evaluate an internet-delivered exposure-based treatment for FM. The premise was to explore whether exposure to stimuli associated with FM-related distress as well as avoided situations and activities would be beneficial for patients with FM. Specific aims and hypotheses for each study are presented below:

#### **3.1 STUDY I**

The aim of the first study was to develop a first version of the treatment protocol and to evaluate the acceptability, efficacy and health economic effects of an internet-delivered exposure- and acceptance-based treatment for FM.

#### **3.2 STUDY II**

This study aimed to revise the treatment protocol and evaluate the efficacy of internet-delivered exposure therapy (iExp) compared to a waitlist control group within a randomized controlled trial. Based on the results from Study I, we hypothesized that the treatment would be more effective than the control group.

#### **3.3 STUDY III**

Study III used data from Study II, and aimed to evaluate the treatment's cost-effectiveness and cost-utility. We hypothesized that iExp would be cost-effective compared to a waitlist control.

#### **3.4 STUDY IV**

Study IV used data from Study II, and sought to investigate possible mediators of treatment outcome. We hypothesized that FM-related avoidance behaviors, FM-related worry and/or mindful non-reactivity would mediate a change in FM symptoms for participants receiving iExp compared to participants in the waitlist control group.



## 4 EMPIRICAL STUDIES

### 4.1 DESIGNS, ASSESSMENTS, ANALYSES

**Study I** was an open pilot study where 41 participants received internet-delivered exposure- and acceptance-based CBT. Main outcome was severity and impact of FM symptoms, measured by The Fibromyalgia Impact Questionnaire (FIQ),<sup>121</sup> and secondary outcomes included fatigue, anxiety, depression, insomnia, psychological inflexibility, pain disability, and health-related quality of life. Treatment acceptability was operationalized as having completed all introductory parts of the treatment and initiated work with exposure. Assessments were made online at pre-treatment, weekly during treatment, post-treatment and at 6-months follow-up. Within-group effects were tested with paired *t*-tests to estimate whether changes from pre- to post-treatment and from pre-treatment to 6-months follow-up were statistically significant. Effect sizes were calculated using Cohen's *d*<sup>122</sup> (i.e., the standardized mean difference between two values), where meaningful differences have been suggested to be *d*=0.2 (small), *d*=0.5 (moderate) and *d*=0.8 (large).

**Study II** was a randomized controlled trial using waitlist as control, where 140 participants were randomized on a 1:1 ratio to either internet-delivered exposure therapy (iExp) or to a waitlist control group (WLC). The primary outcome was identical to Study I, and secondary outcomes included fatigue, anxiety, depression, insomnia, disability, quality of life and psychological inflexibility. Assessments were made online at pre-treatment, weekly during treatment, post-treatment, and for the treatment group also at 6- and 12-months follow-up. Participants on WLC were offered treatment after post-treatment assessment was completed. Efficacy was analyzed on an intention-to-treat basis using mixed effects modelling to estimate if there was a significant time\*group interaction effect on change from pre- to post-treatment. Effect sizes were calculated using Cohen's *d*<sup>122</sup>.

**Study III** was a health-economic evaluation of the iExp treatment and used data from Study II. Data was collected at pre- and post-treatment and at 12-month follow-up (treatment group only, as the waitlist group were crossed over to treatment after 10 weeks). Costs for healthcare consumption and productivity loss was collected using a cost diary,<sup>123</sup> and analyzed in relation to outcome (i.e., treatment responder defined as reliable change on FIQ, and also quality-adjusted life years (QALYs) using EQ-5D.<sup>124</sup> We used national tariffs to estimate costs for health care visits, and productivity losses were estimated using gross earnings data from each participant. Cost-effectiveness comparisons were analyzed using incremental cost-effectiveness ratios (ICERs), defining the cost for one additional treatment responder when offered iExp instead of WLC, as well as the net benefit approach with different willingness-to-pay (WTP) scenarios. We analyzed cost-effectiveness both from a societal perspective (including all direct and indirect costs) as well a healthcare unit perspective (which included

only direct treatment costs). All analyses were made according to the intention-to-treat principle.

**Study IV** was a mediation analysis using data from Study II. Proposed mediators were FM-related avoidance behaviors,<sup>125</sup> mindful non-reactivity<sup>126</sup> and FM-related worry,<sup>127</sup> and outcome was FM symptoms.<sup>121</sup> Assessments were made online at pre-treatment, post-treatment and weekly during treatment on both mediators and outcome. Univariate and multivariate models were used to estimate the direct effect of the treatment, as well as the indirect effects of the proposed mediators; on the outcome. A time-lagged analysis was made to confirm unidirectionality, that is, that a change in the mediator predicted a change in the outcome and not vice versa.

## **4.2 PARTICIPANTS**

All participants in Study I-IV were 18-65 years old, self-referred, had daily access to internet and confirmed having received a FM diagnosis from a physician. In Study I, advertisements were posted on a FM patient association website, an online discussion forum for CBT therapists and a website containing information on internet interventions. In Study II, information was also spread through social media and advertising in a national newspaper. All studies included participants from all of Sweden, of which almost all were women (100% vs. 98%). The mean age ranged between 50.3 to 52 years and the majority (63% vs. 66%) had commenced college or university education. Participants had on average had their FM diagnosis for between 9 to 10 years when entering the study, although the mean duration of FM symptoms was considerably longer (15—17.5 years).

## **4.3 THE INTERVENTION**

### **4.3.1 Study I**

The intervention in the pilot study was based on an internet-CBT manual for IBS<sup>128</sup> and an ACT manual for face-to-face group treatment for FM.<sup>93</sup> The treatment was delivered via a secure internet platform, with self-help texts, images, and worksheets. The 10-week treatment consisted of five consecutive modules to which the participant got gradual access by completing homework assignments. The main intervention was exposure to stimuli associated with FM-related distress, such as FM symptoms and avoided situations and activities. Exposure exercises were based on the participant's FM-related avoidance behaviors as well as their identified life values. These were both mapped by the participant in the first treatment module, setting the stage for behavioral change, and participants were encouraged to try and carry out both types of exposure during treatment. Exposure exercises involved provoking FM symptoms, approach

avoided situations and activities, and refraining from avoidance behaviors. A lot of emphasis was put on explaining the treatment rationale, in which the role of avoidance behavior in maintaining and exacerbating FM symptoms was stressed (see Figure 1, the maintenance model).

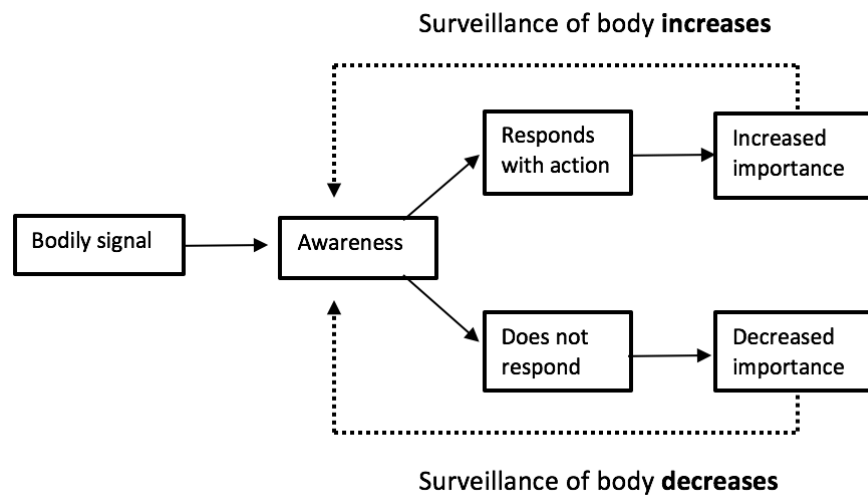


Figure 1. Screenshot of the maintenance model.

To increase the ability to stay present in exposure exercises with one's full attention (i.e., to refrain from covert avoidance behaviors such as distraction), participants were encouraged to practice neutral labelling of symptoms. Participants were taught a 10-minute self-observation exercise to practice once daily, involving observing and labelling the breath, interoceptive sensations and thoughts, and the external environment. Moreover, participants were taught a shorter version where instructions were to pause the current activity for a short while, then observe their bodily sensations for a short while, then continue as before. An additional short exercise was also presented, tailored to be used in situations when experiencing distressful symptoms. Participants were also introduced to exercises in how to loosen entanglement from negative thoughts (also known as decentering or cognitive defusion).

Each participant was assigned a therapist whose main function was to encourage any progress made in the treatment, support the participant in finding individual exposure exercises, answer questions and help problem-solve when needed. Therapist contact consisted of written messages within the treatment platform, and additional telephone calls were used if the participant needed further support. Any participants who lagged behind were reminded by their therapist through platform-delivered mobile text messages and phone calls. The web platform also contained a closed discussion forum where participants could discuss their treatment with each other.

### **4.3.2 Lessons learned from Study I**

The starting point of this PhD project was to investigate whether patients with FM could benefit from a treatment focusing on decreasing symptom-specific avoidance behaviors and hypervigilance through systematic exposure. We originated from a manual that has shown effective in IBS,<sup>105,106,128-130</sup> a condition highly comorbid with FM. Early on we decided to incorporate elements from ACT as we hypothesized that certain ACT interventions (e.g., focusing on life values) would increase motivation to engage in behavior change.

The lessons drawn from Study I was that many participants were in fact positive to behavior change using a more traditional rationale for exposure (i.e., using a maintenance model similar to the one used in the manual for IBS). Also, a challenge emerged in delivering the rationale for values-based action. Several participants experienced problems in identifying important life values and deriving valued activities that were independent of their FM. One possible explanation could be that the introduction to and exercise in identifying and mapping life values were in the first module of treatment, i.e., at a time when they were just getting acquainted with the treatment context and format, and with a dense amount of other concurrent psychoeducational material. It is probably a fair estimate that this intervention, when not delivered within a full ACT context (i.e., with complementing facilitating interventions) might not have achieved its full potential.

Moreover, the therapists in Study I found a challenge in motivating the participants to conduct exposure using two partly differing rationales. In values-based exposure, participants were first encouraged to join in values-based behavioral activation, and later on to engage in values-based exposure exercises. In contrast, when conducting exposure as prescribed originally in the IBS-manual, exercises were derived from the participants' symptom-specific avoidance behavior. Consequently, exercises were not necessarily associated with life values (although, of course, they could be), but rather with the emphasis to try to challenge as many avoidance behaviors as possible. Although the purpose was to provide a broader perspective on behavioral change by offering two related yet complementary approaches to exposure, the impression from the therapists was that most participants found this confusing.

### **4.3.3 Study II**

In Study II the number of modules were extended to eight, with three modules assigned to different aspects of exposure. Exposure exercises were derived only from FM-related avoidance behaviors, i.e., overt and covert avoidance behaviors with the function to relieve FM symptoms and FM-related distress. These were mapped by the participant in a behavior diary in the first three modules of the treatment. Participants were encouraged to go full throttle in their exposure, albeit concurrently emphasizing autonomy and control. In essence, our message to the participant was: *We suggest you*

*go all in on these exposure exercises and challenge yourself 'to the max'. However, it is you who are in the driving seat here and you can do it any way you want. Only you can adapt these principles to your own life.*

In contrast to Study I, the concept of life values was not introduced until the end of treatment, as part of the relapse prevention and maintenance of gains. The rationale of the self-observation exercise was somewhat extended in that it was presented as an extra suitable exercise for participants who identified that they tended to respond to pain with pain-persistent behaviors. Homework reports, worksheets and images were also revised. There was no discussion forum in Study II.

**My exposure**

Name of exercise:

**1. Preparations**

What is the source of discomfort (what do I need to expose myself to)?

What is it I plan to do? Where? When?

What symptoms do expect as an outcome of the exposure?  
 What will be the consequences of doing this?  
 What are my expectations?  
 What would be the worst possible outcome?

Which, if any, fibromyalgia/safety behaviors do I risk engaging in during the exposure?

How *discomfortable* do I predict this will be (0-100)?

How *difficult* do I predict this will be (0-100)?

**2. Outcome and experiences**

Date for the exposure exercise:

What was the outcome of doing the exposure? What happened?

How high was the *discomfort*? (0-100)?

How *difficult* was it (0-100)?

Did I manage to refrain from the safety behaviors that I decided not to engage in?

Did I stay in the situation as long as I intended to? (yes/no)

What are my thoughts about this now? What are my experiences from doing this exercise?

**3. If I were to do the same exercise again / for next time:**

Predicted degree of *discomfort* (0-100)

Predicted degree of *difficulty* (0-100)

How can I vary the exposure?  
 (E.g another environment, time of day, context, in company with someone/by my own)

Figure 2. Exposure worksheet in Study II.

#### 4.4 SAFETY PARAMETERS

Severe psychiatric conditions requiring immediate intervention were ruled out before inclusion, via an online screening procedure as well as a clinical intake interview with a psychology graduate student under supervision or a clinical psychologist. Participants that were excluded due to severe depression or suicidal ideation were recommended to seek regular psychiatric services.

In both Study I and II, all participants were assessed weekly regarding suicidal ideation. Any participant scoring  $\geq 4$  on the suicide item on the Montgomery-Åsberg Depression Rating Scale-self report (MADRS-S)<sup>131</sup> were phoned by their therapist, who conducted a comprehensive assessment of immediate suicide risk. If deemed necessary, a crisis plan was established together with the participant.

Adverse Events (AE) were collected in Study I and II. Questions regarding AEs were collected at post-treatment, 6- and 12-months follow-up (the latter with Study II only), with detailed follow-up questions on any possible event. All AEs were assessed by a clinical psychologist, and if needed followed-up with a telephone interview.

#### **4.5 ETHICAL CONSIDERATIONS**

The majority of patients with FM are treated with pharmacological agents, although often with insufficient effects and with more or less severe side effects. Finding new treatments is therefore of great importance. Comorbidity is high, both regarding somatic and psychiatric conditions, thus this is a vulnerable patient group with an overall broad and pronounced suffering. This presents the research group with a variety of ethical aspects on patient safety when conducting studies investigating novel treatments. Several ethical considerations have been taken into account in this PhD-project.

First, the fact that many patients with FM have cognitive difficulties (e.g., concentration problems, memory deficits and difficulty carry on conversations—often by patients themselves referred to as ‘fibro-fog’), had bearings on several areas in the studies. One such area is assessment of the competence of understanding patient information and giving informed consent. To ensure that the participants voluntarily agreed to participate in the research, the assessing psychologist (or psychology graduate student) in Studies I and II informed the participants what they may expect if they choose to participate in the study and of their right to discontinue treatment at any time. This information was provided in both verbal and written form and contact information was given in case of questions or uncertainties. Participants who expressed difficulties reading or understanding the self-help texts were offered extra support by their therapist via telephone. Another related issue is the weekly assessments, implying an extra burden for participants suffering from heavy fatigue and cognitive deficits. To address this issue, we put a lot of effort in selecting short questionnaires, to keep the total number of items relatively low while at the same time maximizing patient safety and the quality of the data. All measures were collected using an assessment tool that securely stores sensitive data in accordance with applicable rules and regulations.

Second, online-delivered treatment can theoretically pose a challenge in how to detect any sudden deterioration in mental health since there is no face-to-face contact.

However, the possibility of having online contact several times per week, and the weekly assessment of symptoms (including suicidal ideation) provides the participant and therapist an opportunity to detect deterioration in physical or mental health that is not possible in usual healthcare, where the patient usually meets with the therapist only once a week without any contact in-between sessions.

Third, to ensure the integrity of the participants the treatment was provided on an encrypted web platform, accessed by participants and therapists via a two-factor authentication. Personalized passwords were confirmed via text messages to the participant's and therapist's mobile phones.

Finally, all studies were reviewed and approved by the Regional Ethics Review Board in Stockholm, Sweden, and the clinical Studies I and II were also registered in the ClinicalTrials.gov trial registry.

To summarize; when weighing the need of developing more effective treatments for FM with the need of safety and integrity of the individual, we were able to include participants that have few other effective treatment options, regardless of where they live in Sweden and with the opportunity to intense therapist contact. The study design with a large sample that enables high power and a highly structured treatment, enabled good conditions for answering the research questions.

## 5 RESULTS

### 5.1 STUDY I

#### **Internet-Delivered Acceptance and Values-Based Exposure Treatment for Fibromyalgia: A Pilot Study.**

Post-treatment assessments were completed by 40 out of 41 participants (98%). Significant improvements were seen at all outcomes from pre- to post-treatment (all  $ps < .001$ ), and from pre-treatment to follow-up (all  $ps < .001$ ). A moderate within-group effect size was observed on the primary outcome ( $d=0.71$ ; 95% CI 0.46 to 0.91) at post-treatment, and looking from pre-treatment to follow-up the effect size was large ( $d=0.96$ ; 95% CI 0.66 to 1.27). Thirty out of 41 participants commenced work with exposure, indicating that the treatment was acceptable. There were significant cost reductions both at post-treatment ( $p=.002$ ) and at follow-up ( $p=.04$ ) compared to pre-treatment.

### 5.2 STUDY II

#### **Internet-based Exposure Therapy for Fibromyalgia: A Randomized Controlled Trial.**

All participants completed the primary outcome at pre- and post-treatment assessments. On the primary outcome there was a significant interaction effect of group and time with a large between-group effect size ( $d=0.90$ ; 95% CI 0.55 to 1.24), favoring the treatment group. In the iExp group, 44% of the participants achieved a reliable improvement on the primary outcome. Significant improvements were also seen on all secondary outcomes, the majority with moderate to large effect sizes ( $d=0.44$  to 1.24). All effects were stable at 6- and 12-month follow-up. Treatment adherence was high, with 74% of the participants initiating work with exposure.

### 5.3 STUDY III

#### **Cost-Effectiveness and Cost-Utility of Internet-Delivered Exposure Therapy for Fibromyalgia: Results From a Randomized, Controlled Trial.**

iExp was found to be highly cost-effective compared to WLC, as shown by a greater total cost reduction at post-treatment (-5,097; 95% [CI -9,337 to -857];  $p=.018$ ). Cost differences between iExp and WLC were primarily driven by a lower cost of work cutback in the iExp group. From a societal perspective the ICER was estimated to -5,025/.33=-\$15,295, meaning there was a cost reduction of -US\$15,295 for each additional responder to iExp treatment. From a healthcare unit perspective, the corresponding figure was 726/.33=\$2,211. Two sensitivity analyses showed that iExp would remain cost-effective also when assuming markedly higher intervention costs.



The cost-effectiveness of iExp seemed to be driven partly by decreases in direct medical and indirect non-medical costs in the iExp group, but also by an increase in direct non-medical costs in the waitlist group. Analyses of dose-response relationships revealed that participants who made a reliable improvement (i.e., a reliable decrease on FIQ) from pre- to post-treatment had significantly lower costs post-treatment and correspondingly, participants who made a reliable deterioration (i.e., a reliable increase on FIQ) had higher costs post-treatment. Analyzing the iExp group from post- to follow-up showed that a clinical deterioration was associated with significantly higher costs of sick-leave at follow-up.

#### **5.4 STUDY IV**

##### **Approach As a Key for Success: Reduced Avoidance Behaviour Mediates the Effect of Exposure Therapy for Fibromyalgia**

iExp significantly predicted decrease in FM symptoms, consistent with the results in Study II. In the multivariate model, all proposed mediators were significant mediators of exposure therapy on FM symptoms. In the multiple mediation model, the mediators together explained 60% of the treatment effect, of which FM-related worry emerged as the strongest mediator. However, in the time-lagged analyses, only FM-related avoidance behavior displayed a unidirectional relationship over time with FM severity, whereas for mindful non-reactivity and FM-related worry the relationship was bidirectional.

## 6 DISCUSSION

Our findings suggest that internet-delivered exposure therapy is an acceptable treatment for patients with FM that is significantly better than no treatment in reducing FM symptoms as well as all secondary outcomes. The treatment also seems to be highly cost-effective, with each successfully treated participant resulting in a large societal cost reduction, and appears to achieve its effect by a reduction in FM-related avoidance behaviors. The findings are discussed below.

### 6.1 IS INTERNET-DELIVERED EXPOSURE THERAPY ACCEPTABLE AND EFFECTIVE FOR PATIENTS WITH FM?

To answer this question two studies were conducted. Study I involved the development of the treatment manual and evaluation of its acceptability and preliminary efficacy. Study II began with an in-depth inventory of experiences from therapists and participants from Study I, which lay the foundation for an extensive revision of the treatment manual. The updated version, which focused solely on exposure based on FM-related avoidance behaviors, was evaluated regarding efficacy and long-term effects in a randomized controlled trial.

In both Studies I-II, 73—74% of participants initiated work with exposure, indicating that they found the treatment acceptable. Also, data attrition was low in both studies, implying that participants in general were not too burdened by the weekly online assessments.

Comparing results from Study I and II to earlier trials on CBT for FM, the within-group effects seen in Study I were higher than those reported in a review on psychological treatments for FM.<sup>132</sup> Moreover, the between-group effect sizes on pain intensity ( $d=0.86$ ), fatigue ( $d=0.88$ ) and disability ( $d=0.91$ ) in Study II is higher than the corresponding mean between-group effect sizes reported in a meta-analysis on CBT trials for FM (pain intensity  $d=0.29$ , fatigue  $d=0.27$ , disability  $d=0.43$ ),<sup>91</sup> but with a therapist time of only 175 minutes for a whole treatment. However, the studies included in this meta-analysis<sup>91</sup> used various control conditions (of which treatment-as-usual was the dominant one), thus, comparisons should be made bearing this in mind. Results from Study II was also slightly higher than the between-group effect sizes reported by other studies on fatigue, sleep problems and the risk difference (RD) in attaining  $\geq 50\%$  pain relief (RD 0.27) and a  $\geq 20\%$  improvement of health-related quality of life (RD 0.31) in a recent review and meta-analysis on internet-delivered psychological therapies for FM ( $\geq 50\%$  pain relief RD 0.10;  $\geq 20\%$  improvement of health-related quality of life RD 0.22).<sup>133</sup>

With the exception of a recent Dutch study,<sup>109</sup> results from Study II are also comparable to previous randomized controlled trials of exposure therapy for other chronic pain

conditions (although it should be noted that the primary outcome in Study II differs from previous trials, i.e., by also covering FM symptoms other than pain and pain-related disability). As described previously though, the iExp treatment manual differ from existing exposure protocols for chronic pain. Whereas in previous trials exposure is aimed to target pain-related fear, exposure according to iExp primarily targets the individual's symptom-specific avoidance behaviors, and also acknowledges and emphasizes the role of covert avoidance behaviors. The regular structured training in observing and labelling aversive bodily sensations might have helped the participants to identify and prevent subtle or covert avoidance behaviors, thereby facilitating the effects of exposure. In addition, the fact that iExp exercises also comprised interoceptive exposure (i.e., actively provoking aversive bodily symptoms) might have helped to decrease symptom-related distress.

Whether the results would be comparable with the treatment delivered in a face-to-face setting remains an empirical question. However, the variability and constant fluctuation of symptoms in FM could pose a risk of cancelled appointments in face-to-face therapy, and the flexibility attained with internet as treatment modality may therefore be beneficial for this patient group. Furthermore, internet-CBT enables patients in rural areas to access treatment, where availability to CBT therapists is mostly scarce.<sup>118</sup> Nonetheless, internet as treatment modality is a restraining factor regarding generalizability, since many patients with FM suffer from cognitive difficulties<sup>134,135</sup> and thus might perceive the amount of reading as too demanding. Internet-delivered therapy is probably suitable for a subgroup of FM patients, while others might benefit more from a face-to-face format. All the while, if some patients with FM can be successfully treated with internet-delivered therapy, this could help relieve the patient burden on the healthcare system and thus facilitate a more efficient use of healthcare resources.

So, yes - internet-delivered exposure therapy is acceptable and effective for a self-referred sample of FM patients when evaluated against a waitlist control, with promising results on several outcomes compared to the majority of CBT protocols previously evaluated for this condition.

## **6.2 IS EXPOSURE THERAPY FOR FM COST-EFFECTIVE?**

We hypothesized that iExp would be cost-effective as we assumed that the effects gained would outweigh the additional costs of a low-resource treatment of internet-CBT. The results indeed supported our hypothesis. iExp was not only cost-effective, but cost saving. For every successful treatment (i.e., a treatment responder) instead of a participant on waitlist, there was a societal cost saving of US\$15,295. iExp had a 100% probability of being cost-effective using a societal perspective, even with a WTP-scenario of \$0.

The results from Study III confirms the cost reductions observed in Study I, and are also in line with other cost-effectiveness analyses from other internet-delivered psychological interventions.<sup>136</sup> The findings from Study III also extend previous findings regarding cost-effectiveness on CBT for FM by including symptom-specific as well as generic outcomes, providing an estimate of the treatment costs also in relation to improvement of FM symptoms in addition to QALYs gained. Dose-response analyses also indicate that clinical gains were associated with decreases in societal costs.

### **6.3 CAN WE IDENTIFY VARIABLES THAT MEDIATE TREATMENT OUTCOME?**

With Study II being the first evaluation of exposure therapy for FM, and with a new treatment manual than in previous trials investigating exposure for other chronic pain conditions, the choice of mediators in Study IV was explorative. Since previous mediation studies from CBT<sup>92</sup> and ACT<sup>93</sup> treatment for FM, as well as exposure therapy for IBS,<sup>137,138</sup> points in a direction where a decrease in avoidance mediates outcome, we aimed to include mediators that functionally capture different aspects of avoidance.

A somewhat unexpected finding was that only FM-related avoidance behavior displayed a unidirectional relationship over time with FM symptoms, whereas the two other proposed mediators seem to be bidirectionally related to treatment outcome. Notably, all three mediators were significant in both the univariate and multivariate mediation analysis, implying that the establishment of temporality is an important feature when investigating treatment mediators.

The results in Study IV are in line with previous findings,<sup>92,93,137,138</sup> and thus add to the growing body of research supporting avoidance behavior as an important treatment target in exposure treatment for chronic pain conditions. The findings are scientifically relevant not only as they provide support for the theoretical underpinnings of exposure (i.e., learning theory), but also since relatively few studies has been dedicated to the nature of avoidance behavior in chronic pain compared to e.g. pain-related fear.<sup>139</sup> From a clinical view, the finding that reducing avoidance behavior are key for a successful treatment outcome in exposure therapy might be informative to clinicians. In addition, the fact that the results favor the utility of exposure as a treatment for FM could be motivating for patients.

## 6.4 GENERAL METHODOLOGICAL ISSUES

### 6.4.1 On pain-related fear

The studies in the present thesis did not have fear of pain or movement as an inclusion criterion, as opposed to previous trials of exposure therapy for chronic pain<sup>109-112</sup> where participants were included based on assessments on fear of pain (as measured by Photograph Series Of Daily Activities, PHODA<sup>114</sup>) or movement (as measured by Tampa Scale for Kinesiophobia<sup>140</sup>). Contrary to these studies, the treatment model used in the present thesis does not stipulate fear *per se* to be the fueling factor in the maintenance process, partly because it is our clinical impression that many patients with FM generally do not identify with being fearful of pain or movement. Furthermore, a post-hoc regression analysis using baseline value of pain-related distress (measured with Pain Reactivity Scale, PRS<sup>127</sup>) and pre-to post change on FIQ showed that pain-related distress at baseline did not predict treatment outcome ( $p=.93$ , unpublished data). Nevertheless, since previous studies show a relationship between pain-related fear and pain outcomes,<sup>59-61</sup> the studies in the present thesis should ideally have included a widely used measure of pain-related fear or pain catastrophizing (e.g., Pain Anxiety Symptoms Scale-short version, PASS-20<sup>141</sup> or Pain Catastrophizing Scale, PCS<sup>142</sup>) to investigate its role in relation to the effects of iExp.

### 6.4.2 iExp vs ACT – the same treatment?

Some might argue that the iExp and ACT share so many characteristics that the similarities overcome the differences. This is a fair question and warrants a discussion.

As previously described, the manual in Study I stemmed partly from an ACT protocol and thus bear several elements of ACT. Although the treatment manual was extensively revised in Study II, iExp and ACT do still share several treatment features. Exposure, self-observation exercises and strategies to promote cognitive entanglement are critical parts in both protocols. Both iExp and ACT acknowledge overt as well as covert avoidance behaviors as important treatment targets. Nonetheless I would argue that the treatments also appear quite distinct from one another, that is, in terms of what is delivered to the patient and how this is framed. One particular aspect that distinguishes the treatments is the rationale for exposure. In ACT, the concept of life values plays an important role and exposure focuses on behavioral change in line with personal life values. Consequently, participants are instructed to derive exposure exercises from one's identified life values. The central message to the patient is that exposure aims to aid the patient into living a life with more purpose and meaning in the presence of pain and suffering. In iExp, the key message to the patient is that structured and repeated exposure teaches the brain to be less hyper-reactive to pain, which thereby might lead to a decrease intensity of symptoms and symptom-related distress. The patients derive suitable exposure exercises from the identified symptom-specific avoidance behaviors. That is, iExp do not emphasize the importance of basing exposure on important life

values, but rather merely 'for the sake of it' to maximize future behavioral flexibility. For the same reason, participants are encouraged to go 'full throttle' in their exposure. The role of life values had a more retracted role in iExp, introduced at the end of treatment as part of maintenance of gains and relapse prevention. The difference in rationales for exposure is closely related to another central distinction between iExp and ACT, namely the desired treatment outcomes. Whereas ACT aims for a valued living via values-driven behavior,<sup>143</sup> iExp aims for reduction of FM symptoms.

Regardless of the various similarities and dissimilarities of iExp and ACT, the active treatment mechanism could potentially still be the same in the two treatments. This warrants more attention in future research.

## **6.5 VALIDITY AND GENERALIZABILITY OF RESULTS**

Undoubtedly the main factor affecting the generalizability of the results from the studies in the present thesis is the use of a waitlist control in Study II. That is, comparisons to other clinical trials should be made bearing in mind that a waitlist control provides an advantageous comparison for the treatment under investigation (i.e., inflating any favorable differences between the treatment group and the control group). Also, without an active treatment control, causal inferences on potential active treatment components should be made with caution.

The use of self-referral in Studies I and II suggest that participants might have been more motivated and open to psychological treatment, or relatively less disabled - or both - than a clinical sample recruited from a tertiary pain clinic. Moreover, the sample in the current study was relatively well educated, with 35% stating  $\geq 3$  years of college or university education. Post-hoc analyses showed that level of education (on a 7-point Likert scale) did not predict treatment outcome (defined as pre- to post change score on FIQ) ( $p=.43$  [regression analysis] vs  $p=.39$  [non-parametric trend test], unpublished data), although it should be noted that this might reflect a low variance in the sample regarding this variable. Nevertheless, the sample in Study II resembled those in previous CBT trials with consecutive clinic patients regarding clinical characteristics and FM symptoms.<sup>91</sup> Thus, we do not believe that the sample constitutes a severe outlier in terms of FM severity.

As there was no formal assessment of FM diagnosis in Studies I-II we cannot be fully sure that all participants had an FM diagnosis. On the other hand, since there is yet no international consensus on diagnostic criteria in the clinical context the sample in Studies I-II probably, at least to some degree, reflect the FM population seen in regular healthcare. The procedure where participants confirm having received a diagnosis from a physician has previously been used successfully in several randomized controlled trials on CBT for adults with IBS.<sup>105,128,129</sup> In the present PhD project, this approach

empowered a large-scale trial with participants from all over Sweden, generating well-powered data for a first evaluation of the treatment's efficacy.

Concerning the generalizability of the results to other chronic pain conditions, there are no obvious reasons to believe that the overall treatment model of iExp would not be efficacious for other populations of chronic pain. Notably, since the iExp manual is written to be tailored to the FM population, self-help texts, case illustrations and worksheet examples are all written to be identifiable from the perspective of an FM patient. Evaluating iExp on a sample of patients with i.e., low back pain, would therefore require an extensive revision of the treatment manual regarding content. Although this remains an empirical question, a potential hypothesis is that the specific focus on the symptomatology and characteristics of FM might have been experienced as positive by the participants, as it might have promoted feelings of identification and validation.

With Study IV being an explorative investigation of mediators of outcome, a potential limitation is that we did not include a measure of hypervigilance to pain as a potential mediator. Since hypervigilance is a common feature in patients with FM it would have served as a natural competitor. A more advanced statistical analysis (i.e., structural equation modelling) could also have provided an investigation of how the process of excessively attending to bodily symptoms relates to avoidance behavior.

## **6.6 FUTURE DIRECTIONS**

The present PhD project has enabled a first evaluation of internet-delivered exposure therapy for FM regarding acceptability, efficacy, cost-effectiveness and mediators of treatment outcome. An obvious question is how the effects stand in comparison to an active control group. A reasonable comparator would be a traditional cognitive-behavioral treatment manual (e.g.,<sup>144</sup>), since traditional CBT is the psychological treatment that has been most extensively investigated within FM. This would also allow for analyses of long-term effects of iExp in relation to an active control condition, including a more in-depth investigation of participants who deteriorate after treatment, and comparing mediators from theoretically divergent perspectives.

One important issue for future studies includes the development of an instrument aimed to capture FM-specific avoidance behavior. A more to-the-point estimate of overt as well as covert avoidant behavior would benefit both clinicians and patients, and could also be of use in future treatment outcome studies and mediation analyses.

Another construct to investigate as a process measure is hypervigilance to bodily symptoms, for instance using the Pain Vigilance and Awareness Questionnaire (PVAQ).<sup>145</sup> Future studies could elucidate whether avoidant behavior and hypervigilance are independent or interdependent processes. For instance, it may be

that hypervigilance is closely correlated to avoidance behavior, and that change in hypervigilance to bodily symptoms due to successful exposure treatment is heavily dependent on change in avoidance behavior. To further advance the field, future mediation studies should ideally use a design that allows for experimental control over the mediators.<sup>146</sup> Here, participants would be randomly assigned to different treatment protocols designed to have a low, medium or high influence on a proposed mediator. This design would allow for a precise manipulation of the mediator and investigation if that manipulation was associated with a subsequent change in FM symptoms. Also, moderated mediation could help elucidate whether the influence of the mediator/-s on treatment outcome are depending on certain variables (e.g., pain-related fear or education level).

Building on knowledge from experimental pain and neuroimaging, future studies could also investigate whether mechanisms of pain processing and pain regulation respond to exposure therapy. A particularly interesting question is whether we can observe any changes in patients' response to noxious stimuli or descending pain inhibitory pathways after having received exposure therapy, as compared to baseline. Using a three-armed design with a WLC as well as a group of healthy participants, specific dimensions on pain regulation could be targeted through validated batteries (e.g., Quantitative Sensory Testing, QST<sup>147</sup>) and assessed through functional magnetic resonance imaging. This type of study could serve as an objective measure of the treatment's effect and also provide an attempt to better understand pathophysiological processes in FM.



## **7 CONCLUSIONS**

Internet-delivered exposure therapy is an acceptable and effective treatment for patients with FM. It has the potential to reach patients nationwide for a condition that has no sufficiently effective treatment available. iExp is also highly cost-effective compared to no treatment, both for healthcare and for society as a whole. Reducing FM-related avoidance behavior mediates a reduction in FM symptoms, and challenging avoidance may therefore be an important target in exposure therapy. Future studies comparing iExp to other treatments are warranted.

## 8 ACKNOWLEDGEMENTS

I am fortunate to have many people that have supported me along this journey. I would like to extend my warmest thanks to the following individuals whom all have made important contributions to the realization of this PhD project.

*Erik Andersson.* We started this project together over a coffee at Hornstull, and I was as nervous as one can be during a first date. Thanks for all the endless support along the way (especially off office hours!), always pushing me one step further. Not only are you a very dedicated supervisor; you are also a true inspiration on my way to independence. I could not have wished for a better main supervisor.

*Brjánn Ljótsson.* You carried a considerable amount of responsibility as co-supervisor even before you were officially appointed as such. You have so many qualities of a good researcher – curious and open to new ideas, always with a sharp mind, and a true team player. Thank you for believing in me and Ehlin and in our idea for a master's thesis. I am so grateful that I got the chance of taking our baby all the way to graduation.

*Ida Flink.* You are so talented it's absurd 😊 A true role model for young female researchers with your scientific soundness, a huge portion of humbleness and integrity, and always widening one's perspectives. Thank you for sharing your valuable competence and knowledge, and for being such a thoughtful and caring person. I look forward to more collaborations ahead, especially within the field of women's health.

*Rikard Wicksell.* You put your faith in Ehlin and me when sharing your treatment manual with us during our masters' thesis. I really appreciate our discussions on psychological theories and general research methodology. You pushed my boundaries by asking sound and relevant questions, and you have really made me a better scientific writer.

*Karolina Lundbäck, Sofia Hultkrantz, Johanna Engelbrektsson, Erland Axelsson and Daniel Björkander.* The therapist superteam. Thank you for being the best therapists I could have ever asked for, and for enduring my detailed supervision.

*Erland Axelsson.* You were not only a most brilliant therapist; you were also my close co-worker in the randomized trial. What should I have done without you? Tirelessly you taught me html programming during late nights at Bondegatan, and were my spare frontal lobe during times of stress. I really look forward to future discussions.

*Maria Lalouni, Marianne Bonnert and Josefin Särnholm.* You always have thoughtful and valuable comments on whatever the subject, and a true heart for research. I am so thankful for having such wise, empathic and cooperative sisters in research.

*Maria Bragesjö.* At last we got to spend more time together! I hope there will be many hours to come. You really have something great going on and I am thrilled and proud to be working in your study.

*Hanna Sahlin and Johan Bjureberg,* fellow members of the Ljótsson research group. Thanks for inspiring meetings and good conversations, and for all the help along the way.

Although not involved in this PhD project but nevertheless an important teacher and supervisor during my doctoral studies have been *Lars-Göran Öst.* You are so generous with sharing your knowledge and competence. The work we did in the systematic review and meta-analysis was indeed rewarding and have contributed into making me a better researcher.

I also want to express my gratitude to *Mats Lekander.* You took the time (and patience!) in explaining the life of cytokines to me when I just could not wrap my head around it. That moment was, in fact, groundbreaking to me. Thank you for believing in me during my graduate studies and spurring my self-confidence. I hope to jam together someday.

*Karin Jensen,* you are truly such an inspiration. One of the relatively few female research group leaders you take such care of the members of your research group; sharing your knowledge and your sharp mind in such a natural way.

*Ehlin Atterlöf,* my very dear friend, co-writer of the master's thesis and fellow queen of the computer room Hanna. I am so proud that we dared to take on the challenge and what we accomplished. Thanks for putting up with me.

This PhD project would not have been realized had it not been for *Kersti Ejeby,* the head of Gustavsberg Primary Care Clinic. You have a true heart for the treatment of mental illness, and have been groundbreaking in realizing evidence-based psychological treatment within primary care. Thank you for letting me pursue my dream.

Important individuals all the way have also been *Kalle Simonsson and Sigrid Salomonsson,* my managers at Gustavsberg Primary Care Clinic. Thank you for being so supportive along the way and for granting me time for research, despite the constantly intense patient flow at the clinic.

Two deeply appreciated individuals that have had an impact on who I am today is *Gitte* and *Mikael Littwold,* my idols and music teachers during elementary- and high school. You gave me (and so many others!) the best introduction possible to the amazing world of music, and a courage to aim for the stars.

*Study participants.* Thank you for investing your time and effort in participating in the studies, for all the questionnaires you so tirelessly completed, and for having the

courage and stamina to pursue challenging work with behavioral change. You are the true heroes of this PhD project.

Two individuals who definitely have played an important role in my pursuit of becoming a researcher are my mother *Inger* and my father *Bengt*. You gave me the gift of curiosity and eagerness to learn, and a grounded sense that I could do anything. Mom, you are the best grandmother Edda and Lovis could ever wish for. Thank you for all your invaluable support. Dad, your combination of humbleness, sense of humor and consideration is the perfect role model for a researcher to be. I am proud to be walking in your footsteps.

Last, but certainly not least, the three individuals constituting the foundation and safe haven in life: *Erik*, the best team member (and dance partner!) one could wish for. Needless to say, you have been an informal supervisor in all this. Always with thoughtful questions to spur my learning, and always open to discuss research. You are the one that initiated this stone into rolling, and for that I am eternally thankful. To many years ahead. *Edda* and *Lovis*, the best thing that ever happened to me was having you. Thank you for sharing your world with me and teaching me how to play. You truly make me a better person and I love you more than words can say.

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