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PAIN AND PSYCHOPATHOLOGY

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CONTENTS

CHAPTER 1

GENERAL INTRODUCTION

“From such a gentle thing, from such a fountain of all delight, my every pain is born”

Michelangelo di Lodovico Buonarroti Simoni

(1475-1564)

GENERAL INTRODUCTION

This dissertation concerns pain, its severity and impact on daily activities, and its association with mental disorders such as depressive, anxiety, and substance use disorders. The economic and societal burden of pain and these common mental disorders is high and imposes a relevant public health problem. Therefore, the aim of this study is to evaluate epidemiological characteristics and treatment of pain and mental health problems.

CASE DESCRIPTION

During my work as a psychologist the clinical centre of excellence for Body, Mind, and Health, specialized in diagnosing and treating patients with comorbid somatic and psychiatric problems, I have seen many patients who suffer from mental problems as well as physical symptoms. Whether their physical condition was explained or unexplained, one of the most prominent symptoms mentioned is pain. These pain symptoms were severe and disabling, clearly reducing one's quality of life. Most people had problems with work, social functioning, and self-esteem. In combination with a mental disorder, these patients lost all hope of recovery. This introduction will start with a brief description of two patients, which exemplifies the burden of pain, especially when psychiatric problems are comorbid.

The first patient, a 42-year old man, was involved in a car accident. Right after the accident the pain symptoms started, especially on the right side of his body. His hand and leg would start to shake during tasks that needed any physical effort and, consequently, he avoided tasks for which physical effort was needed. He used medication for his pain symptoms but thought this was not effective, and he was afraid he would become addicted. Before the accident, he was a very active and positive person, working hard for his own company, but due to the pain he was unable to work and became depressed. He had trouble accepting that he was unable to do the things the way he had always done. He tried starting to work again, multiple times, but without success. This made him more depressed. He talked to nobody about this, locked himself in his house and

lay on his bed most of the day. He worried constantly, asking himself if things would become better and how things would be in the future. Since the accident, he had a markedly diminished interest and pleasure in all activities. He also reported trouble sleeping, with three to four hours of sleep every night. Due to the pain and his worries about his future, he was unable to concentrate on other things and his energy level dropped to a minimum. He did not report any suicidal behaviour. This all happened in the two years before he came to seek help.

The second patient, a 58-year old woman, reported being ill most of her life. From the age of 3, she received a variety of medical examinations due to pain in the gastrointestinal area and fatigue. All examinations were inconclusive. In the last twenty years, the pain had become worse. She experienced pain all over her body, day and night, making it unbearable to live. Furthermore, she had a total loss of energy. Sixteen years ago, she was diagnosed with fibromyalgia syndrome and chronic fatigue syndrome. Despite the pain, she kept on working (in her youth, she indicated that her father forced her to work, and when she was married at age 19 her husband also forced her to work and to do all the housekeeping). In the last year before the interview, these symptoms started to become worse with an increased speed, with no apparent reason. She experienced pain in her ear, throat, teeth, tongue, neck, shoulders, back, knees, cramps in hands and legs, and neuropathic pain in her legs. Small actions that for most people would be effortless, increased her pain and drained her energy. Consequently, she was bedridden for most of the day and had to sit in a chair for the remainder. She walked very slowly and carefully and was forced to use a wheelchair for longer distances. Her house had been adjusted to her situation, such as a stair lift and a large bathroom. Washing and dressing were still possible, although the more specific actions (e.g. zipper of pants/jacket) were problematic, and her partner needed to help her with this. Eating was necessary, not something she enjoyed. She still enjoyed being in nature, however, using her wheelchair (and her partner for pushing) for longer trips. Pain medication has had no effect, just as psychotherapy and rehabilitation were unsuccessful. She described her situation as being trapped in her body, with her body having an abundance of painful physical symptoms, but her mind being healthy. Her only wish, which was supported by her husband and child, was to end her suffering, in a humane way.

These two patients exemplify what pain can do to a person or the other way around. It made me realize that pain is not just a physical condition, but that it can also have a tremendous effect on our mental wellbeing. It might be a separate dimension of mental ill health. Depressive symptoms were almost always present, such as loss of interest, fatigue, hopelessness, cognitive problems, and problems with sleeping. Anxiety was also often present, mainly anxious worries of what the future would bring. Most alarming for me, however, was that pain can be so severe and detrimental, that life is not worth living anymore. Although pain, mental disorders, and even suicidal behaviour, are common in patients I worked with, it was unclear for me whether this was also common outside my work in a specialised mental health centre, and this left me with several questions. Are pain and mental disorders strongly associated in the literature? Is pain a crucial factor for developing mental disorders? If so, does this only apply to people who receive care (the so-called clinical samples), or is everybody (the so-called general population) at risk? And what about suicidal behaviour: Can someone really experience so much interference due to pain, that they perceive death as the only option to escape their suffering? If this is all true, what can be done to forestall all this? In this thesis, I hope to answer these questions and to contribute to the detection, treatment, and further research of the dreadful consequences of pain.

PAIN

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’ [1]. This definition of pain was first published in 1979, but our understanding of pain has been substantially advanced since then. A revised definition of pain that possibly better captures the essence of what we currently understand to be pain was therefore proposed, including a biopsychosocial perspective: ‘Pain is a distressing experience associated with actual or potential tissue damage with a sensory, emotional, cognitive and social component’ [2]. Whatever definition of pain is used, most important is the subjective experience of the person reporting pain, which is arduous to measure objectively. Nonetheless, an estimated 20% of the adult worldwide population suffers from moderate to severe pain [3-5].

Although pain is a subjective experience, it can be explained neurobiologically. In general, most pain originates from an outside stimulus (e.g. heat), or from injury to sensory fibres or the central nervous system. From this point, it follows an ascending pathway to the brain via the peripheral nervous system and the dorsal horn in the spinal cord, ultimately leading to the perception of pain [6-9]. This experience of pain can then be classified in many ways, such as by physiology, severity, duration, or syndromes. Physiological pain can roughly be divided into nociceptive and neuropathic pain: nociceptive pain is defined as the normal response to injury of tissues such as the skin, muscles, or joints, whereas neuropathic pain is defined as pain that occurs without a damaging stimulus of outside, but is the result of nerve damage [9,10]. Severity of pain is often measured on a Likert or numeric scale ranging from 'not severe at all/no pain' to 'worst pain imaginable', and can also include the amount of interference of pain with daily activities, both crucial in the development of clinically significant pain in the future [11]. Duration of pain is often divided in acute pain and chronic pain: acute pain is characterised as pain of less than three to six months' duration, whereas chronic pain lasts for more than three to six months, or persists beyond the course of an acute disease or after tissue healing is complete [12]. Pain syndromes are somatic diseases in which pain is one of the main symptoms, such as in fibromyalgia [13]. In this thesis, all these classifications of pain are discussed.

Nevertheless, pain has a substantial impact on quality of life and mental health [3-5], which not only applies for adults [3,5], but also for children and adolescents [14] and the elderly [5,15,16]. People with pain are less able, or even unable, in performing all kinds of daily activities, such as sleeping, walking, and household chores [3]. Moreover, pain interferes with the ability to work, and can even lead to the loss of a job [3], resulting in increased direct and indirect costs due to loss of work productivity, increased visits to health professionals and use of medication [3,17,18]. Pain can even be so severe, that those who believe that treatment is not effective anymore might choose to end the suffering by committing suicide [19]. In a report of the World Health Organisation (WHO) pain is indicated as an important risk factor for suicidal behaviour [20], consisting of suicidal ideation, plans and attempts [21-23]. However, this conclusion is based on a review, conducted in 2006, with mostly clinical, retrospective and cross-sectional studies [24]. Fortunately, two longitudinal population-based studies more recently examined the impact of

headache on suicidal behaviour and found that those with a severe headache are 1.5 to four times more likely to exhibit suicidal behaviour compared to those with no or a mild headache, controlled for depression and anxiety [25,26].

The staggering prevalence and the societal and economic burden of pain provide ample justification for regarding pain as a relevant public health problem. With pain being the main topic of this thesis, we hope to contribute to a better understanding of pain as a health problem, ultimately helping people with pain and health professionals in developing and re-evaluating pain management programs and interventions for pain.

MENTAL DISORDER

For mental disorder, the WHO uses the following description: “Mental disorders comprise a broad range of problems, with different symptoms. However, they are generally characterised by some combination of abnormal thoughts, emotions, behaviour and relationships with others” [27]. However, the most widely used manual for diagnosing a mental disorder is the Diagnostic and Statistical Manual of Mental Disorders (DSM), currently in its fifth edition. The DSM defines a mental disorder roughly as follows: a behavioural or psychological syndrome or pattern that occurs in an individual that reflects an underlying psychobiological dysfunction, the consequences of which are distress or disability, but which not merely is an expectable response to common stressors and losses or solely a result of social deviance or conflicts with society. Using the DSM’s definition of a mental disorder, the lifetime prevalence of any mental disorder is around 40% in several countries around the world, including the Netherlands, Germany and Brazil [28-30]. The three most prevalent categories of mental disorders are mood, anxiety and substance use disorders, all with a lifetime prevalence of around 20% [28-30]. However, when considering 12-month prevalence of these mental disorders, anxiety disorders are by far the most prevalent, ranging from 10.1% to 14%, compared to the 12-month prevalence of mood disorders which ranges from 6.1% to 7.8% [28,29]. Many previous studies have focussed on mood disorders, particularly a depressive disorder, but with anxiety disorders also being highly

prevalent, this thesis will focus mainly on these two disorders, and in a smaller part also on substance use disorders.

And what 'defines' these disorders, then? Well, the DSM characterises a depressive disorder as a depressed mood or irritable and loss of interest or pleasure in most activities, next to symptoms such as weight loss, sleep disturbance, loss of energy, and feelings of worthlessness. Anxiety disorders are characterised by excessive fear and anxiety and related behavioural disturbances. Lastly, the DSM defines a substance use disorder as "a maladaptive pattern of substance use leading to clinically significant impairment or distress", and it consists of substance abuse and substance dependence. Characteristic of substance abuse is the recurrent substance use resulting in social or interpersonal problems. Substance dependence is characterised, among others, by a tolerance of the substance, withdrawal symptoms and a persistent desire for the substance. A mental disorder has a negative impact on one's quality of life and imposes a huge societal and economic burden [29,31-33], and might lead to suicidal behaviour [20]. According to the WHO, in 90% of the suicides in high-income countries a mental disorder was present, the most prominent being mood and substance use disorders [20].

The aetiology of a mental disorder is complex and can vary greatly between disorders and individuals. Nonetheless, several models exist which can be used in explaining mental disorders, with the biopsychosocial model, or diathesis-stress model, being the most used currently. This model assumes that mental disorders are the consequence of an interplay of a certain disposition or vulnerability (biological and psychological factors; diathesis) with social factors or stressors. Much research exists that examine a wide variety of stressors that might increase the risk of developing a mental disorder. Stressors with a significant association with mental disorders range from psychosocial factors (e.g. being lower educated, a parent with a psychiatric history, childhood trauma, having symptoms of a mental disorder) to physical factors (e.g. somatic illness) [34-37]. Of the physical factors, pain is one of the most frequently mentioned symptoms, be it a specific pain location (head, neck, back, joints), severity of the pain, or interference with normal activities due to pain [38-41].

COMORBIDITY

Exhaustive research exists indicating a significant association between pain and mental disorders. Moreover, pain itself can be a mental disorder of its own, such as in a somatic symptom disorder [42], but treating pain as a mental disorder might lead to 'overpsychologizing' or mislabelling pain, missing possible explanations of the cause of pain [43]. Therefore, in this thesis, we will not make statements whether pain is 'all in your head' or not, but just focus on how a person experiences pain in general. Pain and mental disorders are relevant public health concerns on their own, but when they are comorbid, the severity of both conditions increases and reduces health-related quality of life [44]. Therefore, this thesis focusses on both conditions.

The prevalence of any common mental disorder (mood, anxiety, and substance use disorders) in the general adult population reaches 35% in individuals with pain, and those with pain have a twofold increased risk of such a mental disorder [45]. The association between pain and mental disorders seems to be the strongest for mood disorders: in clinical settings (e.g. pain or psychiatric clinics) the prevalence of depression in individuals with pain reaches a staggering 85% [46], and considering the general population, two large-scale studies found prevalence rates of 15.7% [47] and 17.5% [45]. Both studies also show a more than twofold increased risk for depression in individuals with pain compared to those without pain. Prevalence rates for the pain-anxiety comorbidity are also high, even higher than for the pain-depression comorbidity in the general population: up to 26.5% [45]. Here too, individuals with pain are more likely (more than two-fold increased risk) to have an anxiety disorder than those without pain [45,47]. Last, but not least, substance use disorders. This mental disorder is less common in individuals with pain: two large-scale studies found prevalence rates not exceeding 4.8% [45] and 5.1% [47], but both studies showed that individuals with pain have an approximately two-fold increased risk of having this disorder compared to those without pain. Thus, pain and common mental disorders are strongly associated.

Knowledge of the longitudinal association between pain and mental disorders in the general population is still scarce. Most research has been conducted in clinical samples. For example, two studies examined the association of pain with depressive and anxiety disorders four years later,

using data from a large longitudinal cohort study in the Netherlands, one focusing on new onset of depressive and anxiety disorders [39], and the other focusing on the recurrence of these disorders [40]. In both studies, more severe pain was associated with a 1.5-fold increased risk for a new onset and recurrence of a depressive and anxiety disorder four years later, compared to individuals reporting no pain [39,40]. The exact pain location might not be of importance, as individuals reporting pain of any location (i.e. neck, back, head, orofacial area, abdomen, or joints) were up to four times more likely to develop a new onset depressive or anxiety disorder, compared to those without pain [39]. The same can be said for the recurrence of depressive and anxiety disorders: several pain locations (i.e. neck, head, chest, abdominal) were significantly associated with an increased risk for the recurrence of a depressive and anxiety disorder four years later [40]. Moreover, pain is often not limited to one location but occurs in multiple locations and might, therefore, be clustered. The most prominent clusters of pain are musculoskeletal, gastrointestinal, and cardiorespiratory, all having a significant association with depressive and anxiety symptoms [48-50]. Another clinical study, among users of stimulant drugs (cocaine and methamphetamine), individuals with more interference with work and social activities due to pain in the past 30 days, were two to three times more likely to develop a substance use disorder compared to individuals without pain in the past 30 days [51]. The severity of pain and interference with daily activities due to pain thus seem to be crucial factors in the development of common mental disorders. As already mentioned, these studies used clinical samples to examine the longitudinal pain-mental disorder association, and are therefore not representative of the general population.

The longitudinal association between pain and mental disorders has been examined in a few population-based studies. One of these studies, among an elderly population, showed that non-depressed and non-anxious individuals with moderate to severe interference with normal activities due to pain were more than 2-times more likely to develop a possible or probable depressive and anxiety disorder 3 years later, compared to those without pain [52]. In another population-based study, also among an elderly population, more severe pain significantly increased the risk of a new onset depression [53]. These population-based studies also exhibit some limitations, however: these studies were conducted among individuals of 50 years and

older, making it difficult to make inferences of this association in other populations, such as adults (18 years and older). Furthermore, self-report questionnaires were used to measure symptoms of mental health in the past week, rather than a diagnostic interview to assess an actual mental disorder. A need for longitudinal research examining the pain-mental disorder association in the general population, using a comprehensive diagnostic instrument to assess mental disorders, exists.

TREATMENT

A wide variety of interventions exist that either focus on painful physical symptoms or on mental disorders. However, when both are present, response to treatment is poorer and leads to more treatment resistance when only the mental symptoms are treated [54-58]. Therefore, treatment should focus on both, and this multifaceted comorbidity might need a multifaceted intervention [59], such as collaborative care. In a collaborative care approach, progress is actively monitored and adherence to psychological and pharmacological treatment is assessed, with multiple professionals working collaboratively and integrating primary, secondary and, when necessary, tertiary care [60,61]. Excessive research exists reporting on the effectiveness and cost-effectiveness of collaborative care for mental disorders [61-65]. Most studies focus on collaborative care in the treatment of depression and show positive results for the effectiveness and cost-effectiveness of collaborative care [61-64], even reducing suicidal ideation [66,67]. Collaborative care also increased disease control of medical chronic illnesses (diabetes and coronary heart disease) [68] and reduced pain-related disability and pain severity [69], next to depressive symptoms. However, the contents of collaborative care can involve a variety of different interventions [61-63,65]. An effective behavioural and pharmacological combination for pain and depression might be problem-solving treatment (PST) and an antidepressant [70]. Duloxetine is a good option to act as an antidepressant in a collaborative care model, as this medication is effective in reducing depressive as well as pain symptoms [71-76], and has proved to be more effective than SSRI's and placebo [73,77,78].

This thesis builds on the assumption that collaborative care is effective in the treatment of a depressive disorder and pain symptoms, and provides an extension to this model by adding analgesics to improve the effect on pain symptoms [79]. The pharmaceutical treatment of chronic pain mainly consists of a three-stepped method, based on the WHO's pain ladder [80]. However, this method has an emphasis on opiates, which have been a major factor in the opioid addiction epidemic, with associated drug-overdose deaths, in the United States [81]. Not surprisingly, the management of chronic pain with opioids have been subject to debate [82-87]. Therefore, the development of other algorithms is encouraged [88]. In this thesis, we present a new pain medication algorithm as an attractive alternative to the WHO pain ladder for patients with pain symptoms and depression. This new algorithm lays an emphasis on differentiating pain into nociceptive and neuropathic pain, and avoiding opiates as much as possible, embedded in a collaborative care approach. Collaborative care, including an antidepressant and pain medication, may be effective in treating depression with comorbid pain, but so far, this has not yet been evaluated as such.

TOPICS OF THIS DISSERTATION

It may now be clear that pain and concomitant mental disorders impose a public health problem, on a clinical level as well as for the general population. Several questions regarding pain and mental disorders remain, however.

In view of the foregoing, we know that more severe pain, more disabling pain, and a wide variety of pain locations are associated with mental disorders, especially depression and anxiety [39,40,48-50]. However, it is unknown whether more severe and more disabling pain show a stronger association with comorbid depression and anxiety than with one of these disorders alone, be it current or in remission. Whether clustered pain locations (i.e. musculoskeletal, gastrointestinal, cardiorespiratory) are associated with these mental disorders, current and in remission, has also not been investigated yet. Moreover, because pain is often present in multiple locations – also known as widespread pain, as seen in patients with fibromyalgia [13] – other pain-related factors than a specific location might also be imperative in the development of

depression and anxiety. Pain and mental disorders are also common in the general elderly population: more severe pain and more interference with daily activities due to pain increased the risk of developing a mental disorder significantly, even when other mental disorders were controlled for [52,53]. However, whether this increased risk also holds for the general adult population is unknown. Individuals with pain, particularly headache, are at increased risk for developing suicidal behaviour, which is not all accountable to concomitant common mental disorders [25,26]. The association of pain other than headache, for example, pain in general – i.e. severity of pain and interference with daily activities due to pain, independently of a specific location or origin – with subsequent suicidal behaviour is still unknown. In this thesis, we, therefore, also examine whether pain might be a unique risk factor, independently of the presence of mental disorders, in the general population. Knowing the interplay between pain and mental disorders also raises the question what can be done to benefit individuals with this comorbidity. Countless interventions exist for pain symptoms, mental disorders, and the co-occurrence of both. A promising approach in the treatment of concomitant pain and depression is collaborative care, which has proven to be an effective multifaceted model [61-65]. However, a collaborative care model including problem-solving treatment (PST), active monitoring of the use and prescription of pain medication, differentiated for nociceptive and neuropathic pain, and an antidepressant, using newly developed algorithms, has not been evaluated as such. This thesis aims to address these gaps.

AIMS AND OUTLINE OF THIS THESIS

The main objectives of this thesis are:

1. To examine the association between pain and mental disorders (*Chapter 2*)
2. To enhance our understanding of the longitudinal association between pain and mental disorders in subjects with widespread pain (Chapter 3) and in the general population (Chapter 4), and its effect on suicidal behaviour (Chapter 5)
3. To examine the effectiveness of a multifaceted treatment model for depression and pain (*Chapter 6, Chapter 7, and Chapter 8*)

The following hypotheses are discussed in this thesis:

a. Pain will have a significant association with both depressive and anxiety disorders
b. Pain will be most strongly associated with comorbid depressive and anxiety disorders, compared to the association with these disorders separately
c. The association of pain with depressive or anxiety disorders in remission will not differ significantly from the association of pain with no history of these disorders
d. More severe pain, a passive pain-related coping style, and poor illness perceptions are significant risk factors in the development of depressive and anxious symptomatology
e. More severe and more interfering pain are significant risk factors in the development of common mental disorders
f. More severe and more interfering pain are significant risk factors in the development of suicidal behaviour, independent of common mental disorders
g. A multifaceted treatment model, including pain management, will be more effective for the treatment of pain and depression than medication only

The findings reported in this thesis may contribute to a better understanding of the contribution of pain and pain-related factors in mental disorders, and how they are intertwined longitudinally. These insights might be instrumental for pain management programs and in identifying better strategies for prevention and early interventions for mental disorders.

Part one, 'Association between pain and mental disorders', focuses on the cross-sectional association between pain and depression and anxiety:

In *Chapter 2*, the cross-sectional association of the two most common mental disorders - depression and anxiety - with pain, in a large cohort study is examined. We investigate the association of current and remitted depressive, anxiety and co-morbid depressive and anxiety disorders with pain severity as well as with pain location.

Part two, 'Psychological outcomes of pain', discusses the longitudinal psychological consequences of pain and pain-related factors. We explore whether individuals with pain are at increased risk of developing a common mental disorder and whether they tend to show more suicidal behaviour:

Chapter 3 reports on the impact of pain-related factors in the development of depression and anxiety, in patients with widespread pain. Pain, pain-related coping, and illness perceptions are investigated as possible predictors for depressive and anxious symptomatology.

In *Chapter 4*, the main topic is the longitudinal association of pain with mental disorders, in a large population-based study. The impact of pain severity and interference with daily activities due to pain on the development of the most common mental disorders is investigated.

In *Chapter 5*, the longitudinal association of pain with suicidal behaviour, in the same population-based study used in *Chapter 4*, is examined. We investigate the impact of pain severity and interference with daily activities due to pain on the development of suicidal behaviour: ideation, plans, and attempts.

In **part three**, '**Treatment',** we focus on the design and effectiveness of a multifaceted treatment model for depression and pain:

Chapter 6 gives a description of the methods and design of a randomized controlled trial that evaluates the effectiveness of collaborative care with pain medication and duloxetine, and collaborative care with pain medication and a placebo, against duloxetine only. In this chapter, a new algorithm for pain medication is introduced.

Chapter 7 reports on the factors hampering the study described in *Chapter 7*, which led to the premature termination of this study.

In *Chapter 8*, the results of the randomized controlled trial described in *Chapter 7* are reported. With the limited data available, explorative results are shown of the effectiveness of collaborative care with pain medication and duloxetine, and collaborative care with pain medication and placebo, compared to duloxetine alone, on depressive and pain outcomes.

Finally, in **part four, epilogue,** we will give an overview of the main findings of this thesis, which will be discussed considering the most recent developments in the field of pain and mental disorders:

In *Chapter 9*, the main findings, methodological aspects and clinical implications of the studies included in this thesis are discussed, and suggestions for future research are presented.

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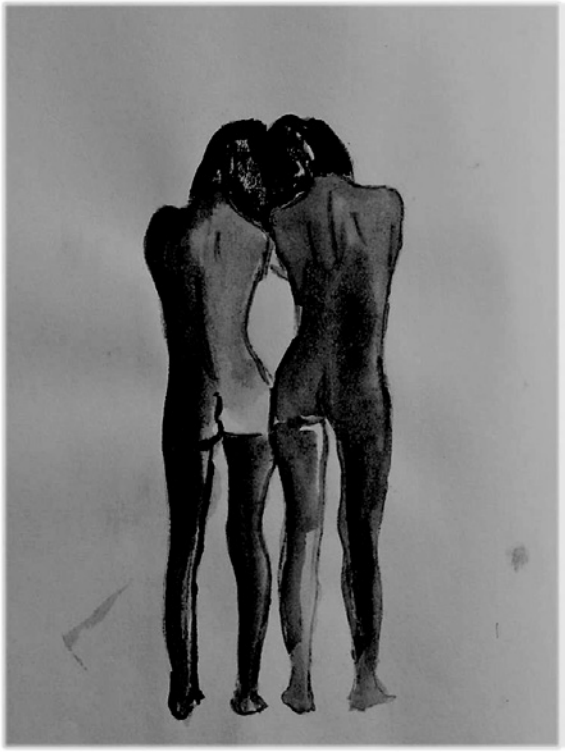
PART I

PAIN AND MENTAL DISORDERS: ARE THEY ASSOCIATED?



CHAPTER 2

THE ASSOCIATION OF PAIN WITH DEPRESSION AND ANXIETY

"One thing you can't hide - is when you're crippled inside"

John Lennon

(1940-1980)

This chapter is based on:

Heer EW de, Gerrits MMJG, Beekman ATF, Dekker J, Marwijk HWJ van, Waal MWM de, Spinhoven P, Penninx BWJH, Feltz-Cornelis CM van der. The association of depression and anxiety with pain: a study from NESDA. PLoS ONE 2014; 9(10): e106907.

ABSTRACT

Background: Chronic pain is commonly co-morbid with a depressive or anxiety disorder. The objective of this study was to examine the influence of depression, along with anxiety, on pain-related disability, pain intensity, and pain location in a large sample of adults with and without a depressive and/or anxiety disorder.

Materials and methods: The study population consisted of 2981 participants with a depressive, anxiety, co-morbid depressive and anxiety disorder, remitted disorder or no current disorder (controls). Severity of depressive and anxiety symptoms was also assessed. In separate multinomial regression analyses, the association of presence of depressive or anxiety disorders and symptom severity with the Chronic Pain Grade and location of pain was explored.

Results: Presence of a depressive (OR = 6.67; 95% CI = 2.81-15.88; p <.001), anxiety (OR = 4.84; 95% CI = 2.22-10.57; p < .001), or co-morbid depressive and anxiety disorder (OR = 30.26; 95% CI = 12.68-72.23; p < .001) was associated with the Chronic Pain Grade. Moreover, symptom severity was associated with more disabling and severely limiting pain. Also, a remitted depressive or anxiety disorder showed more disabling and severely limiting pain (OR = 3.53; 95% CI = 1.67-7.43; p < .001) as compared to controls. A current anxiety disorder (OR = 2.96; 95% CI = 2.16-4.04; p < .001) and a co-morbid depressive and anxiety disorder (OR = 5.15; 95% CI = 3.80-6.98; p < .001) were more strongly associated with cardio-respiratory pain, than gastro-intestinal or musculoskeletal pain. These findings remain after adjustment for chronic cardio respiratory illness.

Conclusions: Patients with a current and remitted depressive and/or anxiety disorder and those with more severe symptoms have more disabling pain and more pain of cardio-respiratory nature, than persons without depressive or anxiety disorder. This warrants further research.

INTRODUCTION

Chronic pain is common in up to 70% of patients with depressive and anxiety disorders [1-9]. Chronic pain and depression most likely have a bidirectional association: depression is a predictor of persistent pain and pain is a predictor of the persistence of depression [1,3,10]. A possible explanation is that impaired functioning caused by pain can lead to social isolation, which in turn can lead to a negative effect on depressive symptoms, and vice versa [11,12]. Furthermore, different brain areas, such as the amygdala and hypothalamus, play a role in both depression and pain [13,14]. Also, when depression and chronic pain are co-morbid, recognition and treatment of depression are less effective, as patients mostly only present their physical complaints and receive treatment accordingly [1].

Most studies up to now have only considered the relationship of pain with depression, whereas its association with anxiety disorders has been less examined. It is likely that the association of pain and anxiety is equally important, as depression and anxiety commonly appear together. Pain may cause feelings of anxiety, which in turn can make one more sensitive to pain, with persistence of the pain experience as a consequence [15]. Furthermore, anxiety disorders and chronic pain share underlying cognitive and behavioural processes, such as increased attention towards threat and anxious avoidance of physical exertion [16,17]. Fear avoidance can play a role in chronic pain, with the (acute) pain experience leading to pain catastrophising and pain-related fear which in turn will lead to greater disability and persistent pain experience [15]. Therefore, we need more comprehensive insight by studying both depression and anxiety in concert (separately and as co-morbid problems) with pain [18–20]. Another reason to study the cross-sectional relationship between depressive and anxiety disorders and pain is that pain also has a negative impact on the prognosis of psychopathology and psychiatric treatment outcome, with pain leading to more treatment resistance [2,21–23]. Pain may be a marker of a more difficult-to-treat disorder, and lead to a longer time before remission [24].

Pain is a common presenting symptom in depression and anxiety and several studies have explored this association for specific pain symptoms, such as back pain [25–27] or neck pain [27,28]. However, pain symptoms often occur in more than one location and thus may be clustered; clustering of (medically unexplained) physical symptoms was examined by Wessely et al. [29], Nimnuan et al. [30], and Fink et al. [31]. These studies found different clusters of pain symptoms, the most prominent being musculoskeletal, gastro-intestinal, and cardio-respiratory pain. Associations were found between depressive, but mostly anxiety symptoms and cardio-respiratory pain, musculoskeletal pain and gastro-intestinal pain. However, the strength of these associations and the correlation with pain-related disability has not yet been explored [32–34]. Therefore, this study will explore the association of clustered locations of pain (musculoskeletal, gastro-intestinal, and cardio-respiratory) with depression and anxiety, while taking severity of pain and pain-related disability into account.

We aim to examine and compare the impact of current and remitted depressive, anxiety and co-morbid disorders on different pain-variables in a large sample of individuals with depressive and/or anxiety disorders versus normal controls. We will explore if severity of depressive or anxiety symptoms is associated with severity of pain and pain-related disability, and whether these associations are stronger for certain clustered pain locations. We expect that not only a depressive disorder will have a strong association with abovementioned pain-variables, but that an anxiety disorder will show a comparably strong association, with comorbid depression and anxiety showing the strongest association.

MATERIALS AND METHODS

SAMPLE

The present study used data from the Netherlands Study of Depression and Anxiety (NESDA): an ongoing longitudinal cohort study in which 2981 participants, recruited from the community, general practice and secondary mental health care, are monitored to investigate the long-term course and consequences of depressive and anxiety disorders. Penninx et al. [35] provide a detailed description of the NESDA study design and sampling procedures. NESDA was designed to include patients with depressive and anxiety disorders at different stages of development of their disorder. In order to achieve this, participants were recruited from the community, in primary care and in specialised mental health care [35]. At baseline, healthy controls, persons with a prior history, and persons with a current depressive and/or anxiety disorder, between 18 and 65 years old, were included. The sample was stratified for setting (community, primary care, and specialised mental health). Furthermore, the sample includes a range of psychopathology: from those without a depressive or anxiety disorder (controls) to those with a current, first or recurrent (in the past 6 months) depressive or anxiety disorder and those with a remitted disorder (at baseline, a depressive and/or anxiety disorder was diagnosed in the past, but no diagnoses were present at 6 months before baseline). The disorders included dysthymia, major depressive disorder, general anxiety disorder, panic disorder, social phobia, and agoraphobia. Exclusion criteria were not being fluent in Dutch and a primary diagnosis of psychotic, obsessive compulsive, bipolar or severe addiction disorder. The research protocol was approved by the Ethical Committee of participating universities and written informed consent was obtained from all participants. Interviews were conducted by specially trained research staff.

The sample consists of 2329 persons with a current diagnosis of depression (n = 396) or anxiety disorder (n = 543), a remitted disorder (n = 628) and 652 persons without a history of depressive and/or anxiety disorder and no current diagnosis of depression or anxiety disorder. All 2981 participants were interviewed, by specially trained clinical research staff, for depression and/or anxiety in the baseline interview using the DSM IV based Composite International Diagnostic

Interview (CIDI, version 2.1), a reliable and valid instrument for assessing depressive and anxiety disorders [36].

The baseline measurement of NESDA, collected between September 2004 and February 2007, was used for this study. Next to the structured interview to assess mental health, self-report questionnaires were used to assess physical health (such as chronic disease, pain, and severity of mental health).

MEASURES

PAIN ASSESSMENT

Pain was assessed using the 7-item Chronic Pain Grade (CPG) Scale by von Korff [37]. The CPG is a reliable and valid instrument for chronic pain populations and the general population [37,38]. The CPG is a good instrument for measuring pain-related variables and for making a hierarchical classification of pain intensity and pain-related disability. It has good internal consistency (with a Cronbach's alpha of 0.91) and the item-total correlations are all high, ranging from .69 to .83.

The CPG grades (chronic) pain using pain intensity and pain-related disability. Pain intensity is based on the mean of the average, worst, and present pain on a scale of 0–100. Pain–related disability is based on the mean of interference with usual activities, work/household activities, and family/social activities on a scale of 0–100, and the number of days (0–180) one is unable to carry out usual activities due to pain in the previous 6 months. To create 5 grades for chronic pain, the following calculations were used: pain intensity was divided into low intensity (score <50) and high intensity (score ≥ 50). To calculate the score of pain-related disability, an overall score of 0–6 was created by assigning 0–3 points for disability score (0–29 = 0; 30–49 = 1; 50–69 = 2; 70–100 = 3) and adding 0–3 points for number of disability days (0–6 days = 0; 7–14 days = 1; 15–30 days = 2; >30 days = 3).

With these scores, 5 grades of chronic pain can be calculated:

1. grade 0: no pain symptoms
2. grade 1: low pain intensity (<50) – low disability (<3 points)
3. grade 2: high intensity (≥50) – low disability (<3 points)
4. grade 3: high disability – moderately limiting (3-4 disability points, regardless of intensity)
5. grade 4: high disability – severely limiting (5-6 disability points, regardless of intensity)

Along with the CPG, we also assessed the specific pain location. To locate the specific pain location, an inventory was made, with a self-report questionnaire, of pain symptoms in the back, neck, head, stomach, joints, chest, and face. Participants could report one or more of these pain locations, and were asked which of these pain locations bothered them the most in the last six months. We then categorised these pain locations as musculoskeletal (back, neck, head, joints, face), gastro-intestinal (stomach), and cardio respiratory (chest) pain symptoms. Participants could report multiple pain symptoms across the categories.

DEPRESSION AND ANXIETY

The presence of a depressive or anxiety disorder was established using the CIDI. In this study, psychopathology profiles were made for each participant. A participant either had no psychopathology (n = 652), a remitted disorder (depression and/or anxiety) (n = 628), a current depressive disorder (n = 396), a current anxiety disorder (n = 543) or a current co-morbid depressive and anxiety disorder (n = 762) (in the past 6 months).

In addition to this categorical approach of disorders (yes/no), we also assessed severity of depressive and anxiety symptoms. Severity of depressive symptoms was assessed with the Quick Inventory of Depressive Symptomatology-Self-Report (QIDS-SR) [39], in which no pain items are included. The QIDS-SR is the shortened version of the self-rated Inventory of Depressive Symptomatology (IDS-SR) [40] and is a 16-item questionnaire with a range of 0 to 27 with high internal consistency (Cronbach's $\alpha = 0.86$). A score of 0–5 refers to none to mild depressive symptoms, a score of 6–10 refers to mild severity, a score of 11–15 refers to moderate severity,

and a score of 16 or higher refers to (very) severe depressive symptoms. Severity of anxiety symptoms was assessed with the Beck Anxiety Inventory (BAI) [41], which also does not include any pain items. The BAI is a 27-item questionnaire ranging from 0 to 63 also with high internal consistency (Cronbach's $\alpha = 0.92$). A score of 0–9 refers to normal severity, whereas a score of 10–18 refers to mild severity, a score of 18–29 refers to moderate severity, and a score higher than 29 refers to severe anxiety symptoms [42].

COVARIATES

Covariates were selected a priori based on previous research on the association of depression and anxiety with pain. Socio-demographic factors included gender, age, level of education, and partner status. Furthermore, the presence of chronic diseases was taken into account as a covariate. Based on self-report during the initial interview, the presence of a chronic disease was assessed. These chronic diseases were then categorised, by a physician, into cardio respiratory disease (coronary heart disease, angina pectoris, heart failure, chronic nonspecific lung disease, stroke, hypertension), gastro-intestinal disease (diabetes, (gastro-intestinal) ulcer, ulcerative colitis or Crohn's disease, liver cirrhosis, hepatitis) and musculoskeletal disease (arthritis, osteoarthritis, rheumatism). Because medication can have an analgesic influence on pain, the use of antidepressants and other psychotropic drugs were also selected as covariates. Also, the number of depressive episodes was taken into account as a covariate.

STATISTICAL ANALYSES

All statistical analyses were performed in SPSS 19 for Windows. Descriptive analyses were used to assess baseline characteristics across the total sample. To assess the associations of type of disorder with the CPG, we used multinomial logistic regression analyses. For the pain outcome variable (the CPG) we used the group with no pain (CPG0) as a reference category. For type of disorder, the healthy control group without depression or anxiety was selected as a reference category. In this analysis, we controlled for all the covariates.

We used adjusted multinomial analyses to assess the association of severity of depressive and anxiety symptoms with the outcome variable CPG, with the lowest severity category as the reference category.

Furthermore, we used four separate logistic regression analyses to examine the association of depression and/or anxiety with the outcome variable of location of pain (1. no pain, 2. musculoskeletal pain (controlling for the presence of musculoskeletal disease), 3. gastro-intestinal pain (controlling for the presence of gastro-intestinal disease), and 4. cardio respiratory pain (controlling for the presence of cardio respiratory disease)). Here also, having no depressive or anxiety disorder was used as a reference category.

RESULTS

Table 1 presents the baseline characteristics of the total population. Of the total sample, 652 participants reported no psychopathology, and slightly less participants (628) reported a remitted depressive and/or anxiety disorder (with a mean of 1.73 depressive episodes). The least participants had a current depressive disorder (with a mean of 10.29 depressive episodes), followed by a current anxiety disorder. Most participants reported a current comorbid depressive and anxiety disorder, with a mean of almost 10 depressive episodes. 26.4% of the total sample used antidepressant medication. Of the 2981 participants, 170 (5.7%) reported no pain symptoms. Most participants (92.4%) reported having musculoskeletal pain, followed by gastro-intestinal pain (1432 participants), and cardio respiratory pain (764 participants).

TABLE 1. BASELINE CHARACTERISTICS OF TOTAL NESDA SAMPLE (N=2981)

Characteristics		
Demographics		
Female gender, N (%)	1979	(66.4)
Age in years, Mean (SD)	41.9	(13.1)
Level of education, N (%)		
Basic	199	(6.7)
Intermediate	1736	(58.2)
High	1046	(35.1)
Partner or married, N (%)	2066	(69.3)
Psychopathology characteristics		
No Psychopathology, N (%)	652	(21.9)
Remitted disorder, N (%)	628	(21.0)
# of depressive episodes, Mean (SD)	1.73	(5.91)
Current depressive disorder, N (%)	396	(13.3)
# of depressive episodes, Mean (SD)	10.29	(71.26)
Current anxiety disorder, N (%)	543	(18.2)
Current depressive and anxiety disorder, N (%)	762	(25.6)
# of depressive episodes, Mean (SD)	9.88	(72.60)
Severity of depression (QIDS)*, N (%)		
None	1121	(37.6)
Mild	820	(27.5)
Moderate	627	(21.0)
(Very) Severe	374	(12.5)
Severity of anxiety (BAI)**, N (%)		
Normal	1477	(49.5)
Mild	758	(25.4)
Moderate	493	(16.5)
Severe	218	(7.3)
Other characteristics		
Musculoskeletal chronic disease, N (%)	648	(21.7)
Gastro-intestinal chronic disease, N (%)	335	(11.2)
Cardio-respiratory chronic disease, N (%)	775	(26.0)
Antidepressant use, N (%)	785	(26.4)
Use of other psychotropic drugs, N (%)	700	(23.5)

Abbreviations: SD = standard deviation; QIDS = Quick Inventory of Depressive Symptoms; BAI = Beck Anxiety Inventory

*39 missing; **35 missing

Table 2 shows the pain characteristics, separated in no psychopathology, remitted disorder, current depressive disorder, current anxiety disorder, and current depressive and anxiety disorder. Of the total sample and of each of the abovementioned groups, most participants had low intensity and low pain-related disability (CPG1), and pain of musculoskeletal origin. Especially when a depressive disorder is comorbid with an anxiety disorder, more participants report highly disabling and severely limiting pain (CPG4).

TABLE 2. BASELINE PAIN CHARACTERISTICS DIVIDED BY PSYCHOPATHOLOGY

			Psychopathology									
	Total		None		In remission		Depression		Anxiety		Depression and anxiety	
	N=2981		N=652		N=628		N=396		N=543		N=762	
Chronic Pain Grade*	N	%	N	%	N	%	N	%	N	%	N	%
Grade 0	170	(5.7)	82	(12.6)	33	(5.3)	19	(4.8)	23	(4.2)	13	(1.7)
Grade 1	1635	(54.8)	441	(67.6)	379	(60.4)	194	(49)	315	(58)	306	(40.2)
Grade 2	605	(20.3)	81	(12.4)	134	(21.4)	86	(21.7)	118	(21.7)	186	(24.4)
Grade 3	311	(10.4)	29	(4.4)	48	(7.7)	60	(15.2)	52	(9.6)	122	(16)
Grade 4	259	(8.7)	19	(2.9)	33	(5.3)	37	(9.3)	35	(6.4)	135	(17.7)
Pain location												
No pain	170	(5.7)	82	(12.6)	33	(5.3)	19	(4.8)	23	(4.2)	13	(1.7)
Musculoskeletal	2753	(92.4)	552	(84.7)	586	(93.3)	374	(94.4)	507	(93.4)	734	(96.3)
Gastro-intestinal	1432	(48.0)	207	(31.7)	250	(39.8)	216	(54.5)	278	(51.2)	481	(63.1)
Cardio respiratory	764	(25.6)	77	(11.8)	117	(18.6)	101	(25.5)	156	(28.7)	313	(41.1)

*1 missing

ASSOCIATION OF DEPRESSION AND/OR ANXIETY WITH THE CPG

Table 3 shows results from the adjusted multinomial logistic regression analysis assessing the association of depression and/or anxiety with the CPG. The results show a significant association and the odds ratios (ORs) rise per CPG level. For all CPG levels, the ORs were significantly elevated compared to the reference group. Having a co-morbid depressive and anxiety disorder, as compared to having no disorder, showed the strongest association (OR = 30.26; 95% CI = 12.68–72.23). Also, when compared to having no depression or anxiety, there is still a high odd of having

disabling pain symptoms when the depressive or anxiety disorder is remitted (CPG1: OR = 1.87; 95% CI = 1.17–2.97; CPG4: OR = 3.53; 95% CI = 1.67–7.43).

TABLE 3. ASSOCIATIONS OF DEPRESSIVE AND ANXIETY DISORDERS WITH THE CHRONIC PAIN GRADE, WITH NO DEPRESSION AND/OR ANXIETY DISORDER AS A REFERENCE CATEGORY

	CPG1[a, b]	**CPG2**[a, b]	**CPG3**[a, b]	**CPG4**[a, b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
No depression/anxiety	reference	reference	reference	reference
Depression/anxiety in remmission	1.87* (1.17-2.97)	3.45** (2.02-5.87)	3.49** (1.81-6.73)	3.53* (1.67-7.43)
Depressive disorder	1.35 (0.72-2.55)	3.53** (1.76-7.08)	7.14** (3.28-15.54)	6.67** (2.81-15.88)
Anxiety disorder	2.10* (1.25-3.54)	4.06** (2.26-7.30)	5.15** (2.57-10.31)	4.84** (2.22-10.57)
Co-morbid depressive and anxiety disorder	3.13* (1.56-6.25)	10.18** (4.87-21.26)	19.72** (8.77-44.35)	30.26** (12.68-72.23)

Abbreviations: CPG = Chronic Pain Grade; OR = odds ratio; CI = confidence interval
* p <.05; ** p < .001
a: Reference category is no pain (CPG0)
b: Adjusted for age, gender, level of education, partner status, antidepressant use, use of other psychotropic drugs, chronic diseases, and number of depressive episodes

However, the confidence intervals do overlap. Therefore, four sensitivity analyses were performed, each with another psychopathology group (remitted disorder, current depressive disorder, current anxiety disorder, comorbid depression and anxiety) as a reference category, to examine the possible differences in associations between pain and various depressive and anxiety disorder categories (Tables 4-7).

With a current depressive disorder or anxiety disorder as the reference category, the results show no significant differences between these disorders on the CPG. A current anxiety disorder and a current depressive disorder also show no significant difference with a remitted disorder. Only a co-morbid depressive and anxiety disorder had a significantly higher association with the CPG compared to a remitted, current depressive, and current anxiety disorder. These findings were similar to those in the analysis with the reference group of healthy controls. The unadjusted results did not differ from the adjusted results.

TABLE 4. ASSOCIATIONS OF DEPRESSIVE AND ANXIETY DISORDERS WITH THE CHRONIC PAIN GRADE, WITH REMITTED DISORDER AS A REFERENCE CATEGORY

	CPG1[a, b]	**CPG2**[a, b]	**CPG3**[a, b]	**CPG4**[a, b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Depression/anxiety in remission	reference	reference	reference	reference
No depression/anxiety	.54* (.34-.85)	.29** (.17-.50)	.29** (.15-.55)	.28* (.14-.60)
Depressive disorder	.72 (.39-1.36)	1.03 (.52-2.01)	2.04 (.98-4.25)	1.89 (.85-4.20)
Anxiety disorder	1.13 (.64-2.00)	1.18 (.64-2.18)	1.47 (.74-2.94)	1.37 (.65-2.91)
Co-morbid depressive and anxiety disorder	1.68 (.84-3.36)	2.95* (1.43-6.09)	5.65** (2.61-12.22)	8.58** (3.84-19.21)

Abbreviations: CPG = Chronic Pain Grade; OR = odds ratio; CI = confidence interval
* p <.05; ** p < .001
a: Reference category is no pain (CPG0)
b: Adjusted for age, gender, level of education, partner status, antidepressant use, use of other psychotropic drugs, chronic diseases, and number of depressive episodes

TABLE 5. ASSOCIATIONS OF DEPRESSIVE AND ANXIETY DISORDERS WITH THE CHRONIC PAIN GRADE, WITH CURRENT DEPRESSIVE DISORDER AS A REFERENCE CATEGORY

	CPG1[a, b]	**CPG2**[a, b]	**CPG3**[a, b]	**CPG4**[a, b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Depressive disorder	reference	reference	reference	reference
No depression/anxiety	.74 (.39-1.40)	.28** (.14-.57)	.14** (.06-.31)	.15** (.06-.36)
Depression/anxiety in remission	1.38 (.74-2.59)	.98 (.50-1.91)	.49 (.24-1.02)	.53 (.24-1.17)
Anxiety disorder	1.56 (.79-3.05)	1.15 (.56-2.35)	.72 (.34-1.54)	.73 (.32-1.65)
Co-morbid depressive and anxiety disorder	2.31* (1.10-4.85)	2.88* (1.34-6.21)	2.76* (1.25-6.09)	4.53** (2.00-10.30)

Abbreviations: CPG = Chronic Pain Grade; OR = odds ratio; CI = confidence interval
* p <.05; ** p < .001
a: Reference category is no pain (CPG0)
b: Adjusted for age, gender, level of education, partner status, antidepressant use, use of other psychotropic drugs, chronic diseases, and number of depressive episodes

TABLE 6. ASSOCIATIONS OF DEPRESSIVE AND ANXIETY DISORDERS WITH THE CHRONIC PAIN GRADE, WITH CURRENT ANXIETY DISORDER AS A REFERENCE CATEGORY

	CPG1[a, b]	**CPG2**[a, b]	**CPG3**[a, b]	**CPG4**[a, b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Anxiety disorder	reference	reference	reference	reference
No depression/anxiety	.48* (.28-.80)	.25** (.14-.44)	.19** (.10-.39)	.21** (.10-.45)
Depression/anxiety in remission	.89 (.450-1.57)	.85 (.46-1.57)	.68 (.34-1.35)	.73 (.34-1.54)
Depressive disorder	.64 (.33-1.26)	.87 (.43-1.78)	1.39 (.65-2.97)	1.38 (.61-3.13)
Co-morbid depressive and anxiety disorder	1.49 (.72-3.06)	2.51* (1.18-5.30)	3.83* (1.74-8.42)	6.25** (2.76-14.15)

Abbreviations: CPG = Chronic Pain Grade; OR = odds ratio; CI = confidence interval
* p <.05; ** p < .001
a: Reference category is no pain (CPG0)
b: Adjusted for age, gender, level of education, partner status, antidepressant use, use of other psychotropic drugs, chronic diseases, and number of depressive episodes

TABLE 7. ASSOCIATIONS OF DEPRESSIVE AND ANXIETY DISORDERS WITH THE CHRONIC PAIN GRADE, WITH COMORBID DEPRESSIVE AND ANXIETY DISORDER AS A REFERENCE CATEGORY

	CPG1[a, b]	**CPG2**[a, b]	**CPG3**[a, b]	**CPG4**[a, b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
Co-morbid depressive and anxiety disorder	reference	reference	reference	reference
No depression/anxiety	.32* (.16-.64)	.10** (.05-.21)	.05** (.02-.11)	.03** (.01-.08)
Depression/anxiety in remission	.60 (.30-1.20)	.34* (.16-.70)	.18** (.08-.38)	.12** (.05-.26)
Depressive disorder	.43* (.21-.91)	.35* (.16-.75)	.36* (.16-.80)	.22** (.10-.50)
Anxiety disorder	.67 (.33-1.39)	.40* (.19-.85)	.26* (.12-.57)	.16** (.07-.36)

Abbreviations: CPG = Chronic Pain Grade; OR = odds ratio; CI = confidence interval
* p <.05; ** p < .001
a: Reference category is no pain (CPG0)
b: Adjusted for age, gender, level of education, partner status, antidepressant use, use of other psychotropic drugs, chronic diseases, and number of depressive episodes

Because the reference group for pain (CPG0) was small (N = 170), another sensitivity analysis was conducted where CPG0 and CPG1 were combined to form the reference category (Table 8). This analysis showed that the association between type of disorder and CPG mostly remains: as can be seen in table 8, all associations became less strong after combining CPG0 and CPG1 as a reference category, but remained significant.

TABLE 8. SENSITIVITY ANALYSIS, WITH CPG0 AND CPG1 COMBINED: ASSOCIATIONS OF DEPRESSIVE AND ANXIETY DISORDERS WITH THE CHRONIC PAIN GRADE, WITH NO DEPRESSION AND/OR ANXIETY DISORDER AS A REFERENCE CATEGORY

	CPG2[a, b]	**CPG3**[a, b]	**CPG4**[a, b]
	OR (95% CI)	OR (95% CI)	OR (95% CI)
No depression/anxiety	reference	reference	reference
Depression/anxiety in remission	1.99** (1.45-2.73)	2.01* (1.22-3.30)	2.03* (1.10-3.73)
Depressive disorder	2.78** (1.93-4.01)	5.61** (3.39-9.29)	5.23** (2.77-9.85)
Anxiety disorder	2.09** (1.50-2.92)	2.65** (1.61-4.35)	2.48* (1.34-4.59)
Co-morbid depressive and anxiety disorder	3.63** (2.61-5.04)	7.01** (4.38-11.23)	10.72** (6.07-18.96)

Abbreviations: CPG = Chronic Pain Grade; OR = odds ratio; CI = confidence interval
* p <.05; ** p < .001
a: Reference category is CPG0 combined with CPG1
b: Adjusted for age, gender, level of education, partner status, antidepressant use, use of other psychotropic drugs, chronic diseases, and number of depressive episodes

ASSOCIATION OF SEVERITY OF DEPRESSIVE AND ANXIETY SYMPTOMS WITH THE CPG

Table 9 shows the association of the severity of depressive symptoms (as measured with the QIDS) and anxiety symptoms (as measured with the BAI) with the CPG. Similar to the main finding, as the severity of the depressive symptoms increases, the odds of having highly disabling and severely limiting pain increases as well. The same accounts for the association between severity of anxiety symptoms and the CPG. The unadjusted results did not differ from the adjusted results.

TABLE 9. ASSOCIATION OF SEVERITY OF DEPRESSIVE SYMPTOMS AND ANXIETY SYMPTOMS WITH THE CHRONIC PAIN GRADE

	CPG1[a]	**CPG2[a]**	**CPG3[a]**	**CPG4[a]**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
QIDS[b]				
None	reference	reference	reference	reference
Mild	2.59** (1.55-4.34)	3.72** (2.13-6.49)	3.99** (2.13-7.49)	4.05** (1.99-8.23)
Moderate	1.10 (0.59-2.02)	1.56 (.91-3.40)	3.32* (1.62-6.80)	2.91* (1.31-6.48)
(Very) Severe	1.11 (.43-2.87)	2.18 (.81-5.87)	4.66* (1.65-13.16)	7.93** (2.70-23.35)
BAI[c]				
Normal	reference	reference	reference	reference
Mild	1.76 (.59-12.51)	2.41* (1.36-4.29)	2.66* (1.42-4.97)	3.07* (1.54-6.12)
Moderate	2.23 (.99-5.03)	4.22* (1.82-9.79)	3.89* (1.60-9.45)	6.69** (2.66-16.84)
Severe	2.73* (1.02-3.02)	6.70* (1.44-31.20)	8.29* (1.73-39.59)	13.32* (2.73-64.97)

Abbreviations: CPG = Chronic Pain Grade; OR = odds ratio; CI = confidence interval; ; QIDS = Quick Inventory of Depressive Symptoms; BAI = Beck Anxiety Inventory
* p <.05; ** p < .001
a: Reference category is no pain
b: Adjusted for age, gender, level of education, partner status, chronic diseases, antidepressant use, use of other psychotropic drugs, number of depressive episodes, and severity of anxiety symptoms
c: Adjusted for age, gender, level of education, partner status, chronic diseases, antidepressant use, use of other psychotropic drugs, number of depressive episodes, and severity of depressive symptoms

Because the reference group for pain (CPG0) was small (N = 170), a sensitivity analysis was conducted where CPG0 and CPG1 were combined to form the reference category (Table 10). This analysis showed that the association found between severity of depressive and anxiety symptoms and CPG mostly remains, with more severe depressive or anxiety symptoms being more strongly associated with more disabling and limiting pain, when CPG0 and CPG1 were combined to have a larger reference group. However, the associations are less strong compared to the associations as seen in Table 9.

TABLE 10. SENSITIVITY ANALYSIS, WITH CPG0 AND CPG1 COMBINED: ASSOCIATION OF SEVERITY OF DEPRESSIVE SYMPTOMS AND ANXIETY SYMPTOMS WITH THE CHRONIC PAIN GRADE

	CPG2[a]	**CPG3[a]**	**CPG4[a]**
	OR (95% CI)	OR (95% CI)	OR (95% CI)
QIDS[b]			
None	reference	reference	reference
Mild	1.55* (1.18-2.02)	1.65* (1.11-2.46)	1.67* (1.00-2.80)
Moderate	1.67* (1.21-2.33)	3.14** (2.04-4.83)	2.75** (1.58-4.78)
(Very) Severe	2.05* (1.36-3.09)	4.37** (2.61-7.33)	7.42** (4.08-13.649)
BAI[c]			
Normal	reference	reference	reference
Mild	1.42* (1.09-1.85)	1.57* (1.09-2.24)	1.81* (1.14-2.87)
Moderate	1.99** (1.44-2.75)	1.83* (1.19-2.81)	3.15** (1.91-5.19)
Severe	2.59** (1.63-4.13)	3.12** (1.86-5.53)	5.16** (2.83-9.41)

Abbreviations: CPG = Chronic Pain Grade; OR = odds ratio; CI = confidence interval; ; QIDS = Quick Inventory of Depressive Symptoms; BAI = Beck Anxiety Inventory

* p <.05; ** p < .001

a: Reference category is no pain

b: Adjusted for age, gender, level of education, partner status, chronic diseases, antidepressant use, use of other psychotropic drugs, number of depressive episodes, and severity of anxiety symptoms

c: Adjusted for age, gender, level of education, partner status, chronic diseases, antidepressant use, use of other psychotropic drugs, number of depressive episodes, and severity of depressive symptoms

ASSOCIATION OF DEPRESSION AND/OR ANXIETY WITH MUSCULOSKELETAL, GASTRO-INTESTINAL, AND CARDIO RESPIRATORY PAIN SYMPTOMS

Table 11 shows the multinomial logistic regression analyses assessing the association of depression and/or anxiety with three clustered pain locations. For those with pain, the highest ORs are seen in co-morbid depression and anxiety. The ORs for musculoskeletal pain range from 2.28 (95% CI = 1.53–3.42) for a depressive or anxiety disorder in remission to 3.88 (95% CI = 2.33–6.47) for a co-morbid depressive and anxiety disorder. For gastro-intestinal pain, the ORs range from 1.40 (95% CI = 1.10–1.78) for a depressive or anxiety disorder in remission to 3.31 (95% CI = 2.57–4.27) for a co-morbid depressive and anxiety disorder. Cardio respiratory pain shows a range in ORs from 1.74 (95% CI = 1.27–2.40) for a depressive or anxiety disorder in remission to 5.15 (95% CI = 3.80–6.98) for co-morbid depressive and anxiety disorder. The unadjusted results did not differ from the adjusted results.

TABLE 11. ASSOCIATIONS OF DEPRESSIVE AND ANXIETY DISORDERS WITH PAIN LOCATION, WITH NO DEPRESSION AND/OR ANXIETY AS REFERENCE CATEGORY

	No pain[a]	**Musculoskeletal[a]**	**Gastro-intestinal[a]**	**Cardio respiratory[a]**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
No depression/anxiety	reference	reference	reference	reference
Depression/anxiety in remmission	.47* (.30-.75)	2.28** (1.53-3.42)	1.40* (1.10-1.78)	1.74* (1.27-2.40)
Depressive disorder	.52* (.28-.97)	2.64** (1.53-4.56)	2.43** (1.84-3.22)	2.63** (1.86-3.70)
Anxiety disorder	.39** (.24-.66)	2.29** (1.49-3.51)	2.08** (1.61-2.68)	2.96** (2.16-4.04)
Co-morbid depressive and anxiety disorder	.19** (.10-.38)	3.88** (2.33-6.47)	3.31** (2.57-4.27)	5.15** (3.80-6.98)

Abbreviations: OR = odds ratio; CI = confidence interval
* p <.05; ** p < .001
a = adjusted for age, gender, level of education, partner status, antidepressant use, use of other psychotropic drugs, number of depressive episodes, and chronic disease

DISCUSSION

The high proportion of participants with anxiety and depressive disorders in this study reflects the sampling strategy for including sufficient numbers of respondents to examine individuals at different stages of development and severity of depression and anxiety. This study demonstrates considerable associations between presence of depressive and anxiety disorders (current and remitted) and symptom severity with different pain dimensions, namely pain-related disability, pain intensity, and the location of pain symptoms (musculoskeletal, gastro-intestinal, and cardio respiratory).

PRESENCE AND SEVERITY OF DEPRESSIVE OR ANXIETY DISORDER

Our results show that having a depressive or anxiety disorder increases the odds of highly disabling and severely limiting pain. Also, the severity of the depressive and anxiety symptoms are significantly associated with pain-related disability and limiting pain, with more severe symptoms having higher odds for highly disabling and severely limiting pain.

Depressive and anxiety disorders may add to pain as they increase the likelihood of social isolation, increased attention towards threat and avoidance of physical exertion [11,12,16,17]. Depression and anxiety disorders also share the same pathophysiological pathways as pain [43–45]. They facilitate the central modulation of the pain response, in the periaqueductal gray, amygdala, and hypothalamus [1,13,14], and when deficits occur in these areas, modulation of signals from the body are disturbed, leading to a more severe experience of pain. Although these brain areas all play a role in depression, anxiety, and pain, not every individual responds the same to pain stimuli [46–48]. Some individuals are more sensitive to pain than others. The use of EEG may help in identifying neuronal markers for sensitivity to pain [46], and whether there are differences between depressive and anxious individuals. Furthermore, depression and anxiety induce stress and increases the production of pro-inflammatory cytokines [49–51], which may increase pain [52,53]. The finding showing higher pain-related disability in co-morbid depression and anxiety in our study is similar to findings from the STAR*D studies [54–56].

DEPRESSIVE OR ANXIETY DISORDER IN REMISSION

Regarding the association of a remitted disorder and pain, we expected persons with remitted depression or anxiety to have similar pain symptoms as controls without depression or anxiety. However, this is not the case. Persons with a remitted depressive or anxiety disorder still showed high odds on the pain outcomes when compared to those that have no such disorder. This is remarkable, because this means that having a remitted disorder is not the same as having no disorder with regards to pain. This raises several questions.

First, pain symptoms may be residual symptoms in depressive and anxiety disorder. This finding may suggest that pain in patients with remitted depressive or anxiety disorder might be indicative of a risk for recurrence, as disability in life (e.g. disability to fulfil his or her role at home) is an important risk factor for the recurrence of anxiety disorders [57], and our results show that those with a remitted diagnosis still have high odds of having pain symptoms and pain-related disability.

Another explanation for the high odds of pain symptoms in remitted depression or anxiety might be that treatment, if it was provided, for the depressive or anxiety disorder is not effective for pain symptoms, or treatment should be different when pain is co-morbid with the depressive or anxiety disorder. For example, it has been suggested that patients with depression and pain are a distinctively other group of patients than those with depression without pain, with the former having a focus on health and the latter having a focus on a negative view of the self [58,59]. If that is the case, the treatment should be different for depressive disorder with pain and depressive disorder without pain. The same could possibly apply to patients with an anxiety disorder with or without pain. This finding warrants further research, to examine if having a depressive or anxiety disorder in remission may be a possible risk factor for subsequent long lasting chronic pain.

PAIN LOCATION

Of the total sample, 92.4% reported pain symptoms of musculoskeletal nature, followed by 48% reporting gastro-intestinal pain and 25.6% of cardio respiratory pain. Because musculoskeletal pain has by far the highest prevalence in this study, we expected that this pain location would have the highest association with depression and anxiety. However, this expectation was not confirmed. Our findings show that those with a depressive or anxiety disorder (be it current, comorbid or in remission) have high odds for having musculoskeletal pain, but the odds for having pain of cardio respiratory origin are also large when compared to those not having a depressive or anxiety disorder. Furthermore, persons having a current anxiety or co-morbid depressive and anxiety disorder show high odds for having cardio respiratory pain. These findings remain after adjustment for chronic cardio respiratory illness.

In a review by Celano & Huffman [60], a depressive disorder was associated with cardiac disease, such as coronary artery disease. This also applies to anxiety which appears to be a risk factor for coronary heart disease and cardiac mortality [61]. The finding that anxiety shows such high odds for cardio respiratory pain symptoms, even when we controlled for cardio respiratory disease, could be due to the fact that anxious patients with chest pain are more sensitive to bodily sensations [62]; in that case, the experience of pain would be centrally modulated in such a way as to elevate the odds for experiencing pain. However, another explanation might be possible as well; stress induced anxiety has an elevating effect on cytokines [49], and elevated cytokines lead to pain symptoms. This might explain our findings.

In the STAR*D study, depressed patients (with less sleep quality and sympathetic arousal) showed an association with higher cardiac risk, which may be similar to our findings [63] whereby having a depressive disorder had higher odds for having cardio respiratory pain when compared to having no depressive or anxiety disorder. Even when we controlled for having a chronic disease of cardio respiratory origin, the association remained strong and significant. Previous research showed that having a mental illness is a possible risk factor for cardiovascular disease [64,65]. Our finding that a depression/anxiety, whether or not in remission, shows a strong association with cardiac pain is worth exploring in further longitudinal research to explore a possible causal

relation of depression and/or anxiety (current or in remission) with cardiac disease, of which cardio respiratory pain might be an early indicator.

STRENGTHS AND LIMITATIONS

A strength of this study is the large sample size. Also, because patients with a depressive or anxiety disorder often report pain in multiple locations, the categorisation of pain locations makes these results clinically relevant and widely applicable. Moreover, this study not only examines the association of pain with depressive or anxiety disorder, but also with co-morbid depression and anxiety, as well as with remitted disorders. Additionally, in the analyses of the pain symptoms, the no pain group was the reference category which is new compared to earlier studies that compared low pain with high pain – which is subject to interpretation bias as pain is a subjective experience. In our study, we had a healthy control group with no pain in which better contrasts could be made with those who had pain.

This study also has some limitations. First, it is not possible to make inferences about causality because this was a cross-sectional observational study. Second, some of the subgroups of our sample were smaller than the other groups, such as those with no pain symptoms (CPG0, N = 170). However, a sensitivity analysis revealed that the association between severity of depressive and anxiety symptoms and CPG mostly remains, with more severe depressive or anxiety symptoms being more strongly associated with more disabling and limiting pain when CPG0 and CPG1 were combined to have a larger reference group. Therefore, these associations can be considered valid and of clinical relevance as they indicate a clear difference in association with depression or anxiety between patients with and without pain. Another possible limitation is the self-reporting of physical illness, which might lead to overreporting or underreporting of chronic physical illness; however, a study by Kriegsman et al. [66] shows that patients report their physical illness fairly accurately when compared to the reports of their general practitioner, even when taking depressive symptomatology into account. Furthermore, no information was available whether a physical illness was organic or functional, which may have its effect on pain. For example, individuals with an organic disease describe their pain as consistent, whereas those

without an organic disease describe their pain as variable and diffuse [67]. Also, PTSD has been linked to increased risk for pain [68,69]. Therefore, future research that examines the association of anxiety disorders with pain should also include PTSD.

CONCLUSIONS

This study shows that depressive and anxiety disorders have a similar and very strong association with the CPG (which includes pain-related disability and pain intensity) and musculoskeletal pain, cardio respiratory pain, and gastro-intestinal pain compared to a control group without depressive or anxiety disorder. Depression and anxiety share the same pathophysiological pathways as pain and can have a reciprocal effect on each other, which could explain these associations. Moreover, even a remitted disorder has a strong association with pain. This might mean that patients with depression or anxiety and pain are a different group and need different treatment than patients that do not have pain accompanying their depression or anxiety. Depression and anxiety also have a strong association with cardio respiratory pain, and this association remained after correction for cardiovascular or respiratory illness. This strong association between depression/anxiety (current or in remission) with cardio respiratory pain is an interesting finding, which warrants further longitudinal research to examine a possible causal relation of cardiac pain and a mental disorder (current or in remission) with cardiac disease.

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PART II

THE MENTAL RISKS OF HAVING PAIN

CHAPTER 3

PAIN, PAIN-RELATED COPING, AND ILLNESS PERCEPTIONS IN RELATION TO DEPRESSION AND ANXIETY IN FIBROMYALGIA SYNDROME

"Everything hurts"

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(1475-1564)

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ABSTRACT

Background: Patients with widespread pain, such as in fibromyalgia, are vulnerable for depression and anxiety, which composes a relevant public health problem. Identifying risk factors for the onset of depression and anxiety is therefore warranted. Objective of this study was to determine whether severe pain, maladaptive coping, and poor illness perceptions are associated with depressive and anxious symptomatology in fibromyalgia.

Material and methods: Consecutive patients referred to an outpatient clinic completed sets of physical and psychological questionnaires at baseline and at 18-month follow-up. A total of 452 patients with fibromyalgia syndrome (FMS) were eligible for inclusion, and subsequently, 280 patients returned the baseline questionnaire. Depressive and anxious symptomatology was measured with the Hospital Anxiety and Depression Scale. To measure pain severity, coping style, and illness perceptions, the Fibromyalgia Impact Questionnaire, Pain Coping Inventory, and the Illness Perception Questionnaire-Revised (IPQ-R) were used, respectively. Multivariable logistic regression analyses, bootstrapping and calibration, were performed to examine the association of pain severity, pain coping, and illness perception with depressive and anxiety symptoms at follow-up, adjusted for sociodemographic variables. Initial level of depressive and anxiety symptoms was selected as covariates.

Results: Mean age was 42.6 years and 95.4% were female. At 18-month follow-up, 68 (of the 195) patients were depressed and 80 (of the 197) were anxious. Only the IPQ-R subscale "emotional representations" showed a significant positive association with depressive symptoms at follow-up (OR = 1.10; 95% CI = 1.01-1.19; p = .03), next to the initial level of depressive symptoms (OR = 1.30; 95% CI = 1.17-1.45; p = < .001). In case of anxiety, only the IPQ-R subscale "treatment control" showed a significant negative association with anxiety symptoms at follow-up (OR = 0.87; 95% CI = .77-.99; p = .04), next to the initial level of anxiety symptoms (OR = 1.45; 95% CI = 1.29-1.63; p < .001).

Conclusions: Our data suggest that not pain severity or maladaptive coping, but poor illness perceptions are important in elevated depressive and anxious symptomatology. Patients with fibromyalgia who think their illness negatively affects their mental well-being are at increased risk for more depressive symptoms, and those who think treatment of their illness will not be effective are at increased risk for more anxiety symptoms. Strengthening illness beliefs and reducing catastrophic thinking, therefore, seem crucial factors in the treatment of patients with FMS.

INTRODUCTION

Fibromyalgia syndrome (FMS) is a medical diagnosis of unknown aetiology mainly characterized by chronic and widespread pain [1]. Other symptoms include fatigue, gastrointestinal symptoms, and joint stiffness [1–3]. Furthermore, a growing body of evidence shows a comorbidity of FMS with psychological symptoms, particularly with depression and anxiety [2–9]: lifetime prevalence of depression and anxiety in patients with FMS go up to 70 and 60%, respectively [8]. Widespread pain and mental disorders compose a relevant public health problem due to the high economic and societal burden [10–13]. A better understanding of risk factors for the onset of depressive and anxious symptomatology in FMS might, therefore, be instrumental in identifying strategies for prevention and early interventions, such as those recommended by the European League Against Rheumatism (EULAR) [14, 15]. Risk factors for the onset of depression and anxiety have been studied longitudinally, and include pain, a negative perception of health, dysfunctional coping strategies, personality traits (e.g., neuroticism), female gender, and lower education [10, 16]. This study will focus on those factors that have shown to be associated with an increased risk of depression and anxiety in chronic pain patients, and that might be easily modifiable in treatment: severity of pain [10, 17–20], coping strategy [21–23], and illness perceptions [24–26]. To date, longitudinal studies exploring the contribution of all these risk factors in subsequent depressive and anxious symptomatology in patients with FMS in one study are lacking.

Widespread pain is characteristic for FMS [1] and thorough research exists exploring the association of widespread pain and severity of pain with depressive and anxiety disorders [10, 17–20]. In several cross-sectional studies, among which a review and a large survey among 17 countries, multiple pain locations were more strongly associated with depression and anxiety when compared with one pain location and no pain [10, 17, 18]. In two longitudinal studies, every additional pain location increased the risk of a new onset and recurrence of a depressive and/or anxiety disorder with 29 and 7%, respectively [19, 20]. Moreover, for every increase in the severity of pain the risk increased with 57% for new onset and 11% for recurrence of depression and/or anxiety [19, 20].

Another risk factor associated with depression and anxiety is coping style. Patients with FMS tend to cope passively, such as catastrophizing [27, 28]. In patients with FMS, pain is indirectly associated with depression through its relationship with a passive coping style [21]. A passive coping style, in turn, is significantly associated with depression [27]. Furthermore, in studies among patients with other rheumatic diseases, passive coping strategies, including withdrawal and worrying or catastrophizing, were also associated with psychological distress [22, 23].

A maladaptive coping style is associated with poor illness perceptions [29], that in turn are associated with depressive and anxiety symptoms [24–26, 29, 30]. In patients with chronic widespread pain, negative beliefs about their illness, such as that the illness would affect their emotional well-being, were found to be associated with an increase of depressive and anxious symptomatology [24, 25]. Also, patients with rheumatoid arthritis who had negative beliefs about the consequences of their illness were more depressed over time [26].

Patients with FMS are characterized by pain in multiple locations, or widespread pain. This makes them vulnerable for depression and anxiety. However, it is unknown whether other characteristics are associated with the onset of depression and anxiety. Cross-sectional studies suggest that more severe pain, a maladaptive (passive) coping style, and negative illness perceptions are related to depression and anxiety in patients with (chronic) pain and in patients with rheumatic diseases [17, 18, 21–25]. FMS is a rheumatic disease, characterized by chronic pain, which makes it likely that these factors would also play a role in the onset and persistence of depressive and anxious symptomatology in this population. However, these factors have not been studied in concert and longitudinally in FMS before. Therefore, a study exploring this association in a longitudinal design in FMS is warranted. The aim of this study is to examine pain, pain-related coping, and illness perception as possible risk factors for depressive and anxious symptomatology in patients with FMS. We hypothesize that more pain, passive pain-related coping and poor illness perceptions at baseline are associated with more depressive and anxiety symptoms in FMS.

MATERIALS AND METHODS

STUDY DESIGN

This study used data from an observational, prospective cohort study, with follow-up every 6 months for up to 18 months. Not all questionnaires of interest were used at every follow-up measurement, and, therefore, the baseline and 18-month data were used for this study.

SETTING

Data were collected of newly referred consecutive patients to the Sint Maartenskliniek rheumatology outpatient clinic, location Nijmegen and Woerden, the Netherlands, between December 2011 and November 2014.

ETHICS STATEMENT

This study was carried out in accordance with the recommendations of the local medical ethical board with written informed consent from all subjects. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The Institutional Review Board of the University Medical Centre, Nijmegen, approved the study (protocol number: 2011/271).

PARTICIPANTS

Patients were included in the cohort after being classified as having FMS by certified rheumatologists, who followed the ACR guidelines [31, 32] as a diagnostic aid. Other inclusion criteria were being 18 years or older and to be able to read and write in the Dutch language. There were no exclusion criteria next to these inclusion criteria. A total of 452 patients with FMS were eligible for inclusion, 311 gave informed consent (68.8%), and subsequently, 280 patients returned the baseline questionnaire (90.0%). Most frequent dropout reasons were lack of energy

or concentration, and lack of time. Several patients did not specify a reason. For this study, all 280 participants were included. See Figure 1 for a flowchart.

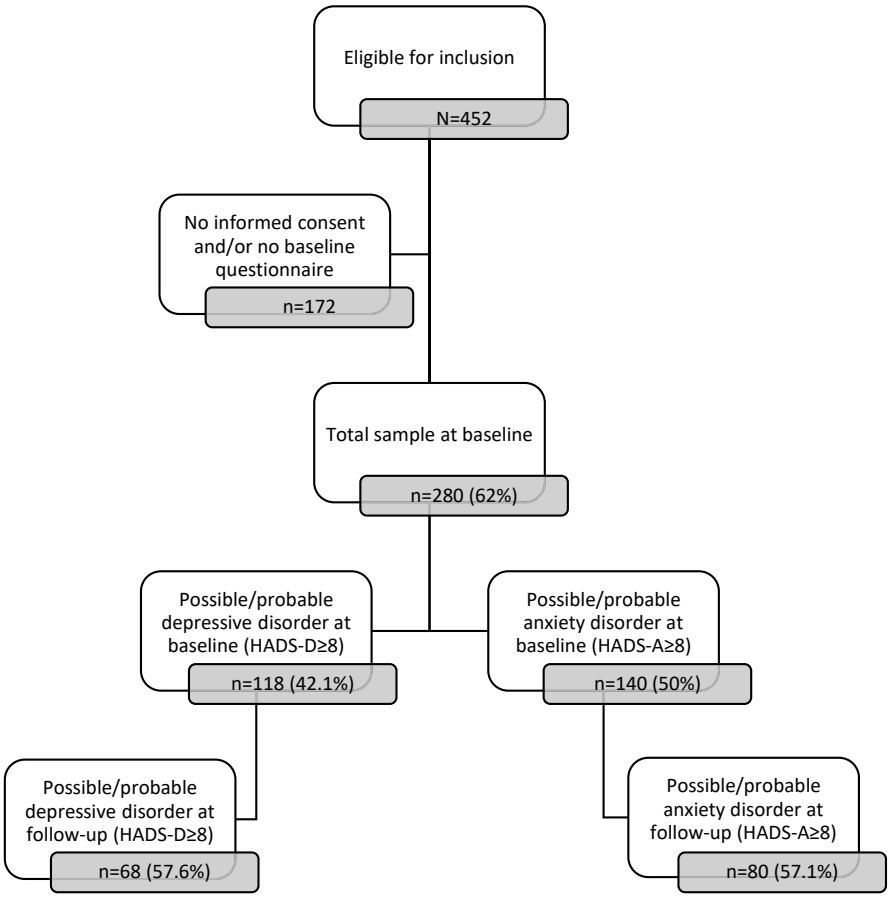

FIGURE 1. FLOWCHART OF THE INCLUSION PROCEDURE

MEASURES

ANXIETY AND DEPRESSIVE SYMPTOMS

The primary outcomes were the presence of depressive symptoms (yes/no) and the presence of anxiety symptoms (yes/no). Anxiety and depressive symptomology were assessed using the self-rated, 14-item Hospital Anxiety and Depression Scale (HADS) [33], which scores the severity of depressive (HADS-D) and anxiety (HADS-A) symptoms, both subscales ranging from 0 to 21. This measure was developed specifically for medically ill populations and excludes bodily symptoms such as sleep disturbance, fatigue, and pain that may be directly attributable to the physical illness [33]. The HADS has been widely used in people with medical illnesses, and its factor structure has been confirmed [34–36]. The presence of depressive and anxiety symptoms was defined using the cut-off scores of ≥8 for "possible/probable" depressive or anxiety disorder [33]. The cut-off score of 8 or more for both subscales has shown good predictive value for depressive and anxiety disorders, in somatic, psychiatric, and primary care patients, as well as in the general population [37]. Both subscales of the HADS have a good internal consistency (Cronbach's alpha for HADS-D ranges from 0.67 to 0.90; Cronbach's alpha for HADS-A ranges from 0.68 to 0.93) [37].

PAIN

Pain was assessed using the pain severity subscale of the Dutch translation of the Fibromyalgia Impact Questionnaire (FIQ) [38, 39], ranging from 0 (no pain) to 10 (severe pain). Reliability and validity of the FIQ are good [38].

PAIN COPING

Pain coping was measured using the Pain Coping Inventory (PCI) [40]. The PCI consists of six scales (33 items) measuring cognitive and behavioural pain-coping strategies that represent two higher order, active, and passive pain-coping dimensions. Items are rated according to a 4-point Likert scale ranging from 1 (hardly ever) to 4 (very often) in terms of frequency with which strategies are applied when dealing with pain. Active pain-coping strategies reflect three cognitive-behavioural strategies, measuring patient's efforts to distract themselves from pain (distraction, five items), to reinterpret and transform the pain (pain transformation, four items), and to function despite pain (reducing demands, three items). Passive pain coping reflects three cognitive-behavioural strategies, assessing behavioural tendencies to restrict functioning (resting, five items), to avoid environmental stimuli (retreating, seven items), and catastrophic cognitions about the pain (worrying, nine items). A composite score of the active and passive coping dimensions can be calculated by taking the mean of the three active and passive coping strategies. Confirmatory construct and criterion validity of the scales and the second-order structure with respect to active and passive pain-coping strategies were supported [40, 41].

ILLNESS PERCEPTIONS

Participants completed the Revised version of the Illness Perception Questionnaire (IPQ-R) [42], which assesses patients' perception of their illness. The following seven dimensions of the IPQ-R were included: Timeline (e.g., "My illness will last a short time"), Timeline cyclical (e.g., "My symptoms come and go in cycles"), Consequences (e.g., "My illness is a serious condition"), Personal control (e.g., "Nothing I do will affect my illness"), Treatment control (e.g., "My treatment will be effective in curing my illness"), Illness coherence (e.g., "I do not understand my illness"), and Emotional representations (e.g., "My illness makes me feel angry"). The IPQ-R is a reliable and well-validated self-report questionnaire [42–44].

COVARIATES

Initial levels of depressive and anxiety symptoms play an important role in subsequent depressive and anxious symptomatology [20, 45]. Therefore, baseline HADS-D score (initial level of depressive symptoms) and baseline HADS-A score (initial level of anxiety symptoms) were inserted in the statistical models as covariates.

SOCIODEMOGRAPHIC VARIABLES

Assessed sociodemographic variables were as follows: sex, age, partner status, and education level (primary/lower secondary and higher secondary/professional).

STATISTICAL METHODS

Descriptive statistics were performed to describe the sample at baseline, regarding sociodemographic variables, pain severity, pain coping, illness perceptions, and depressive and anxiety symptoms. To examine which variables predicted depressive (n = 68) and anxiety symptoms (n = 80) at 18-month follow-up, the following steps were performed: (1) selection of potential variables: univariate logistic regression analyses were performed, with $p < 0.05$ as a selection criterion for potential predictive variables; (2) multivariable logistic regression analyses using backward selection (stopping rule $p < 0.2$); (3) internal validation with a bootstrap procedure (500 samples) to estimate the amount of over-fit; and (4) through calibration, the slope value was calculated and used to correct and shrink the regression coefficients, the percentage of explained variance (R2), and the c-index. Initial level of depressive symptoms and initial level of anxiety symptoms were inserted in the models as covariates, and their association with the outcome variables was shown when significant. The models' performance was assessed by the percentage of variance; the agreement between the predicted probabilities of the outcome and the observed probabilities in the original data ($p > 0.05$; i.e., Hosmer–Lemeshow

test); and by the models' discriminative ability [as reflected by the c-index that equals the area under the receiver operating characteristic curve (AUC)].

RESULTS

DESCRIPTIVE DATA

Table 1 shows the baseline characteristics of the 280 persons in this cohort. Mean age of the study sample was 42.6 years, and 95.4% were female. Mean pain severity was 6.75 on a 10-point Likert scale. Of the participants, 118 (42.1%) had a possible or probable depressive disorder, and 140 (50%) had a possible or probable anxiety disorder at baseline.

POSSIBLE/PROBABLE DEPRESSIVE DISORDER

Table 2 shows the univariate associations of all predictor variables and the covariates with depressive symptomatology at 18-month follow-up (n = 68). Regarding the depression outcome, a passive coping style (OR = 2.92), and the IPQ subscales "timeline" (OR = 1.09), "consequences" (OR = 1.22), "personal control" (OR = 0.89), and "emotional representations" (OR = 1.19) had a significant univariate association with a possible/probable depressive disorder at 18-month follow-up. The covariates' initial level of depressive symptoms and initial level of anxiety symptoms also had a significant univariate association with a possible/probable depressive disorder at 18-month follow-up (OR = 1.37 and OR = 1.21, respectively). After logistic regression with backward selection (Table 3), the IPQ subscale "emotional representations" (OR = 1.10) was significantly associated with possible/probable depressive disorder at 18-month follow-up, next to initial level of depressive symptoms (OR = 1.30). Thus, subjects who respond emotionally regarding their illness and have more initial depressive symptoms at baseline are at increased risk for a possible or probable depressive disorder at follow-up. Together, these variables in the

regression model accounted for 30% of the variance of the depression score at follow-up. The overall fit of the derived model was good ($\chi 2 = 13.85$, $p = 0.09$).

TABLE 1. SOCIODEMOGRAPHIC VARIABLES, PAIN CHARACTERISTICS AND DEPRESSIVE AND ANXIOUS SYMPTOMATOLOGY OF THE FIBROMYALGIA COHORT AT BASELINE (N=280)

Characteristics		
Demographics		
Female gender, N (%)	267	(95.4)
Age in years, Mean (SD)	42.61	(11.1)
Level of education, N (%)		
Low	122	(44)
Middle	95	(34)
High	55	(20)
Partner or married, N (%)	218	(77.9)
Pain characteristics		
Pain severity, Mean (SD)	6.75	(2.09)
Pain Coping strategies, Mean (SD)		
Passive	43.83	(7.97)
Active	29.16	(4.93)
Illness Perceptions, Mean (SD)		
Timeline	23.71	(4.26)
Consequences	19.86	(4.26)
Personal control	20.34	(3.66)
Treatment control	17.00	(2.88)
Illness coherence	15.00	(4.09)
Timeline cyclical	14.69	(3.27)
Emotional representations	15.76	(4.74)
Depressive/anxious symptomatology		
HADS Depression, N (%)		
Normal	162	(57.9)
Possible/probable depression	118	(42.1)
HADS Anxiety, N (%)		
Normal	139	(50.0)
Possible/probable anxiety	140	(50.0)

Abbreviations: SD = standard deviation; HADS = Hospital Anxiety and Depression Scale

TABLE 2. UNIVARIATE LOGISTIC REGRESSION ANALYSES OF SOCIODEMOGRAPHICS, PAIN SEVERITY, COPING STRATEGIES AND ILLNESS PERCEPTIONS, FOR DEPRESSIVE AND ANXIETY SYMPTOMS

Characteristics	**HADS depression (n=68)**		**HADS anxiety (n=80)**	
	OR	95% CI	OR	95% CI
Demographics				
Sex	1.06	(.26-4.36)	1.39	(.34-5.74)
Age	1.00	(.98-1.03)	.98	(.96-1.01)
Higher educational level	.61	(.30-1.24)	.61	(.30-1.24)
Partner or married	.84	(.41-1.70)	.75	(.38-1.49)
Pain characteristics				
Pain severity	1.15	(.99-1.33)	1.13	(.98-1.30)
Pain Coping strategies				
Passive	2.92*	(1.27-6.73)	2.80*	(1.23-6.35)
Active	.54	(.26-1.13)	.60	(.30-1.20)
Illness Perceptions				
Timeline	1.09*	(1.01-1.17)	1.06	(.99-1.14)
Consequences	1.22*	(1.12-1.33)	1.17*	(1.08-1.26)
Personal control	.89*	(.81-.97)	.94	(.86-1.02)
Treatment control	.91	(.81-1.01)	.90*	(.81-.99)
Illness coherence	.96	(.89-1.03)	.95	(.89-1.02)
Timeline cyclical	.93	(.85-1.02)	1.03	(.94-1.12)
Emotional representations	1.19*	(1.10-1.28)	1.19*	(1.10-1.28)
Covariates				
HADS baseline depression score	1.37*	(1.24-1.52)	1.21*	(1.11-1.32)
HADS baseline anxiety score	1.21*	(1.12-1.32)	1.44*	(1.30-1.61)

Abbreviations: HADS = Hospital Anxiety and Depression Scale; OR = odds ratio; CI = confidence interval
* p <.05

POSSIBLE/PROBABLE ANXIETY DISORDER

Table 2 shows the univariate associations of all predictor variables and the covariates with anxious symptomatology at 18-month follow-up (n = 80). Regarding the anxiety outcome, a passive coping style (OR = 2.80), and the IPQ subscales "consequences" (OR = 1.17), "treatment control" (OR = 0.90), and "emotional representations" (OR = 1.19) had a significant univariate association with a possible/probable anxiety disorder at 18-month follow-up. The covariates' initial level of depressive symptoms and initial level of anxiety symptoms also had a significant univariate association with a possible/probable anxiety disorder at 18-month follow-up (OR = 1.21 and OR = 1.44, respectively). After logistic regression with backward selection, treatment control (OR = 0.87) was significantly associated with possible/probable anxiety disorder at 18-month follow-up, next to initial level of anxiety symptoms (OR = 1.45) (Table 3). Thus, subjects who think that their treatment is not effective regarding their illness and have more anxiety symptoms at baseline are at increased risk for a possible or probable anxiety disorder. Together, these variables in the regression model accounted for 40% of the variance of the anxiety score at follow-up. The overall fit of the derived model was good ($\chi 2 = 13.05$, $p = 0.11$).

TABLE 3. MULTIVARIABLE LOGISTIC MODEL PREDICTING DEPRESSIVE AND ANXIETY SYMPTOMS AT 18-MONTH FOLLOW-UP

	HADS depression (n=68)			**HADS anxiety (n=80)**		
	OR	95% CI	p-value	OR	95% CI	p-value
HADS baseline depression score	1.30	(1.17-1.45)	<.0001			
HADS baseline anxiety score				1.45	(1.29-1.63)	<.0001
Treatment control				.87	(.77-.99)	.04
Emotional representations	1.10	(1.01-1.19)	.03			
Model performance	*Model*	*Corrected*		*Model*	*Corrected*	
Explained variance (Nagelkerke R^2)	.35	.30		.44	.40	
C-index	.82	.80		.85	.83	
Calibration						
Hosmer and Lemeshow	X^2=13.85			X^2=13.05		
Slope value	.89			.90		

Abbreviations: HADS = Hospital Anxiety and Depression Scale; OR = odds ratio

DISCUSSION

To the authors' knowledge, this is the first study to document on pain, illness perception, and coping style as risk factors for depressive and anxious symptomatology in patients with FMS. The results here indicate that patients with FMS who believe their illness will have a negative effect on their mental well-being, who also have elevated levels of depressive symptoms, are more likely to be depressed on subsequent occasions. Furthermore, patients with FMS who think that treatment of their illness will not be effective and who also have elevated levels of anxiety symptoms are more likely to be anxious on subsequent occasions. Our hypothesis that poor illness perceptions are a risk factor for depressive and anxious symptomatology is therefore confirmed.

Only illness perceptions and initial level of affective symptoms were found to play a significant role in depressive and anxious symptomatology, suggesting that these factors are possibly more important than other well-known risk factors, such as pain, which is contrary to what we expected. These findings are consistent with previous research in similar populations. For example, patients with chronic (widespread) pain who had a strong belief that their illness would affect their mental well-being were more likely to report depressive and anxiety symptoms [24, 25], whereas pain intensity did not show such an association [24]. In patients with rheumatoid arthritis, the patients' beliefs and emotional responses to their illness were key factors explaining the association between pain and depression [46]. Furthermore, in two large longitudinal studies, the association between pain and new onset and recurrence of depression and anxiety were mediated by (subthreshold) depressive symptoms [19, 20]. This could explain our finding that not pain severity, but negative cognitions about the illness and the initial level of affective symptoms are more important as risk factors in the development of subsequent depressive and anxious symptomatology. Neurobiological abnormalities might also play a role, which persists in patients who have experienced strong negative emotions, possibly through negative biases in the processing of emotional information [47]. On the other hand, pain and emotion share neuronal networks, and pain, one of the main characteristics of FMS, might cause a dysregulation in the

neuronal network associated with emotion [48]. Thus, patients with FMS who experience negative affective symptoms and negative perceptions regarding their illness might, therefore, have developed neurobiological abnormalities, making them vulnerable for subsequent depressive and anxious symptomatology.

Contrary to what we expected, a passive coping style was not a significant risk factor for depressive and anxiety symptoms, in contrast to a previous study in patients with FMS [21]. However, they used another construct of passive coping, emphasizing on emotion-focused strategies, whereas passive coping in this study was mostly characterized by avoidant strategies. In a study in patients with systemic sclerosis, a rheumatic disease, emotion-focused coping had a strong association with depressive symptoms, whereas avoidant focused coping did not [22]. Furthermore, in patients with chronic heart failure, an avoidant coping style was indirectly associated with depression and anxiety through poor illness perceptions [29], which might explain our findings. This might suggest that emotional components of coping with an illness are more important than other maladaptive forms of coping. In our study, passive coping consisted of three cognitive-behavioural strategies, one of them being catastrophizing or worrying, which is an emotional component also. Therefore, future studies should explore the subcategories of passive coping to explore whether the emotional components of coping are indeed more important than other components.

STRENGTHS AND LIMITATIONS

Strengths of this study are the longitudinal design and the large sample size. However, several limitations need to be addressed. The sample of this study consisted of patients with FMS, which limits the generalizability to other populations. However, comparable results were found in other rheumatologic populations [22, 24, 25, 46]. This might suggest that our results are generalizable to populations characterized by a chronic disease. In this study, the HADS, which was developed specifically for medically ill populations, was used to measure depressive and anxious symptomatology. Although this instrument has good internal consistency and can be used as case

finding for depressive and anxiety disorders [37], and is widely used in rheumatologic populations, no inferences could be made whether patients met criteria for a depressive or anxiety disorder. For such purposes, diagnostic (semi)structured interviews need to be used, such as the Mini-International Neuropsychiatric Interview [49] or Composite International Diagnostic Interview [50]. In addition, we used a single self-reported questionnaire (FIQ) to measure pain severity, which prevents us to make inferences of other aspects of functioning and well-being, such as quality of life. Besides, it is possible that factors not studied here might play a crucial role in depressive and anxious symptomatology in patients with FMS. Received treatment, whether it is physical [51–54], psychological, or pharmacological [55], can influence both depressive as anxiety symptoms. Patients in this study received advice for treatment, based on the recommendations of the EULAR [14, 15], after the baseline measurement. Treatment advice could be referral (back) to the general practitioner, physiotherapist, psychologist, or a multimodal rehabilitation program. Unfortunately, no information was available whether this advice was followed, or if another treatment was received other than advised. We were, therefore, unable to make any inferences on the effect of treatment on depression and anxiety. Other factors that might influence depressive and anxious symptomatology are medication use, comorbidity with other chronic diseases [56], and perceived social support [57]. Unfortunately, due to the limited sample size at follow-up (68 patients for depressive symptoms and 80 for anxiety symptoms), it was not possible to include more factors in the statistical models. Future research with larger sample sizes is needed. A larger sample size is also necessary to examine the incidence of depressive and anxious symptomatology, by excluding those patients with depressive and anxiety symptoms at baseline. The sample size of this study was too small, unfortunately.

CONCLUSION

Our study highlights the importance of illness perceptions in the development of depressive and anxious symptomatology in patients with FMS. Developing treatment interventions aimed at modification of poor illness perceptions is therefore of interest. It has been shown that interventions focusing on illness perceptions, such as cognitive treatment and illness perception focused intervention, is effective in improving maladaptive perceptions in patients with chronic low back pain [58], and even has a positive effect on depressive and anxious symptomatology [59]. In addition, cognitive behaviour therapy focusing on catastrophizing has shown to be effective at increasing acceptance of the illness and global functioning in patients with FMS [60]. Our findings corroborate the recommendations of the EULAR for psychological treatment, such as cognitive behaviour therapy, in case of depressed mood [15]. Thus, strengthening illness beliefs and reducing catastrophic thinking seem to be important factors in the treatment of patients with FMS, allowing them to improve their health. Future research should further explore the effects of such interventions.

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CHAPTER 4

PAIN AS A RISK FACTOR FOR COMMON MENTAL DISORDERS

"Behind every beautiful thing, there's some kind of pain"

Bob Dylan

This chapter is based on:

Heer EW de, Have M ten, Marwijk HWJ van, Dekker J, Graaf R de, Beekman ATF, Feltz-Cornelis CM van der. Pain as a risk factor for common mental disorders. Results from the Netherlands Mental Health Survey and Incidence Study-2: a longitudinal, population-based study. PAIN 2017; doi: 10.1097/j.pain.0000000000001133. [Epub ahead of print]

ABSTRACT

Background: Pain might be an important risk factor for common mental disorders. Insight into the longitudinal association between pain and common mental disorders in the general adult population could help improve prevention and treatment strategies.

Materials and methods: Data were used from the first two waves of the Netherlands Mental Health Survey and Incidence Study-2, a psychiatric epidemiological cohort study among the Dutch general population aged 18-64 years at baseline (N=5,303). Persons without a mental disorder 12 months prior to baseline were selected as the at-risk group (n=4,974 for any mood disorder; n=4,979 for any anxiety disorder; n=5,073 for any substance use disorder). Pain severity and interference due to pain in the past month were measured at baseline using the Short Form Health Survey. DSM-IV mental disorders were assessed at both waves using the Composite International Diagnostic Interview version 3.0.

Results: Moderate to very severe pain was associated with a higher risk for mood (OR=2.10; 95%CI=1.33-3.29; $p < .01$) or anxiety disorders (OR=2.12; 95%CI=1.27-3.55; $p < .01$). Moderate to very severe interference due to pain was also associated with a higher risk for mood (OR=2.14; 95%CI=1.30-3.54; $p < .01$) or anxiety disorders (OR=1.92; 95%CI=1.05-3.52; $p < .05$). Pain was not significantly associated with substance use disorders. No interaction effects were found between pain severity or interference due to pain and a previous history of mental disorders.

Conclusions: Moderate to severe pain and interference due to pain are strong risk factors for first-incident or recurrent mood and anxiety disorders, independent of other mental disorders. Pain management programs could therefore possibly also serve as a preventative program for mental disorders.

INTRODUCTION

According to the International Association for the Study of Pain (IASP), pain is 'an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage' [1]. 19% of the adult European population suffers from moderate to severe pain [2]. Pain has substantial impact on quality of life and mental health. Thorough research exists examining the prevalence and cross-sectional association between pain and common mental disorders in population based [e.g. 3,4] and clinical studies [e.g. 5-9]. The economic and societal burden of pain and common mental disorders is high [5,7,10,11], and therefore composes a relevant public health problem. A better understanding of the prospective contribution of pain in mental disorders might be instrumental in identifying better strategies for prevention and early interventions of mental disorders, particularly because pain is modifiable. However, results of longitudinal studies, assessing the effect of pain on first-incident and recurrent mental disorders, are scarce.

In studies from clinical settings [12-14] a longitudinal association between pain and mental disorders was found. Among at-risk stimulant (cocaine and methamphetamine) users, subjects with a higher number of days with pain (which interfered with work and social activities) were more likely to develop alcohol and opioid abuse/dependence compared to subjects without pain [12]. In two studies from the Netherlands Study of Depression and Anxiety (NESDA) - one among subjects with no previous history of and no current depressive or anxiety disorder [13], and one among subjects with a remitted depressive or anxiety disorder [14] - a higher number of pain locations and more severe pain were associated with the onset of a depressive and anxiety disorder, and with the recurrence of a depressive disorder. However, the extent to which results from these clinical studies can be generalized to the general population is unknown, and these results therefore need to be replicated and validated in population-based studies.

Several population-based studies have investigated such a longitudinal association between pain and symptoms of depression [15-17] and of anxiety [15,16]. In non-depressed subjects, those with moderate to severe interference due to pain [15], more severe pain [17], and chronic low

back pain [16] were more likely to report depressive symptoms at follow-up, compared to those without pain. In non-anxious subjects, the same results were found for moderate to severe interference due to pain [15] and chronic low back pain [16]. After adjusting for affective disorder at baseline, the strength of the pain-affect associations was weakened [15], suggesting they modify each other's association with pain. However, the results of these studies are limited as they focus on an elderly population [15,17], and relied on self-report questionnaires to measure symptoms of mental health problems in the last week [15-17] rather than on standardized diagnostic interviews to assess current and history of mental disorders. Furthermore, these studies focus either on depression and anxiety or on substance use disorders only, but as these are among the most common mental disorders in adults [11], they should be studied in concert. This study aims to address these gaps.

MATERIALS AND METHODS

SETTING AND PARTICIPANTS

In short, the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2) has a longitudinal epidemiological cohort design. This study was conducted among the Dutch general population aged 18–64 years. It is based on a multistage, stratified random sampling of households, with one respondent randomly selected in each household. In the first wave (T0), performed from November 2007 to July 2009, a total of 6,646 persons were interviewed (response rate 65.1%; average interview duration 95 min). This sample was nationally representative, although younger subjects were somewhat under-represented [18]. All T0 respondents were approached for follow-up (T1) three years after T0, from November 2010 to June 2012. Of this group, 5,303 persons were re-interviewed (response rate 80.4%, excluding those deceased; average interview duration 84 min). Attrition rate was not significantly associated with all main categories of mental disorders (i.e. mood, anxiety, and substance use) and all individual 12-month mental disorders at baseline, after controlling for sociodemographic characteristics [19]. Comprehensive data on attrition in NEMESIS-2 can be found elsewhere [19].

More severe pain was, however, significantly associated with less attrition (OR=.91; p=.01), after adjustment for sociodemographic characteristics. The interviews were laptop computer assisted and almost all were held at the respondent's home. The mean period between both interviews was three years and seven days. The Medical Ethics Committee for Institutions on Mental Health Care (METIGG) approved the study. After having been informed about the study objective, respondents provided written informed consent. A more comprehensive description of the design is provided elsewhere [20].

For this study, three different at-risk groups were selected: 1) subjects without any 12-month mood disorder at baseline (n=4,974); 2) subjects without any 12-month anxiety disorder at baseline (n=4,979); and 3) subjects without any 12-month substance use disorder at baseline (n=5,073). For subjects in each of these at-risk groups it was possible to have another mental disorder at baseline. For example, those at-risk for incident or recurrent mood disorders at follow-up, thus those not having a mood disorder 12 months prior to baseline, could have an anxiety or substance use disorder 12 months prior to baseline. As a mental disorder before 12-months prior to baseline was not an exclusion criterion, a disorder at follow-up could be. either a first incident case or a recurrent case. Data were used from the first two waves of NEMESIS-2.

MEASURES

MENTAL DISORDERS

Mental disorders were assessed using the Composite International Diagnostic Interview (CIDI) version 3.0, a fully structured lay-administered diagnostic interview of mental disorders [21]. The CIDI was developed and adapted for use in the World Mental Health Survey Initiative. In the Netherlands, the CIDI 3.0 was first used in ESEMeD, which is part of this initiative [22]. The CIDI 3.0 version used in NEMESIS-2 was an improvement of the one used in the Dutch ESEMeD study (some small improvements were administered, such as reformulation of questions to better match the English version). The mental disorders considered in this paper include: any mood disorder (major depression, dysthymia, bipolar disorder), any anxiety disorder (panic disorder,

agoraphobia, social anxiety disorder, generalised anxiety disorder) and any substance use disorder (alcohol/drug abuse and dependence). Research has demonstrated acceptable reliability and validity for assessing these common mental disorders [23]. The appearance of any common mental disorder (i.e. any mood, anxiety or substance use disorder) between baseline and follow-up was the outcome variable of this study.

At baseline, respondents were asked whether a mental disorder lifetime occurred to them and, if so, if this happened in the past 12 months. At T1, respondents were asked the same questions about mental disorders, but then the time period referred to mental disorders they had experienced since the baseline interview.

PAIN ASSESSMENTS

At baseline, pain severity was assessed using a question from the SF-36-item Short Form Health Survey [24]: “How much pain did you experience in the past four weeks?” Respondents could choose between “no pain”, “very little pain”, “little pain”, “moderate pain”, “severe pain” and “very severe pain”. These answers were categorised into: 0 = no pain, 1 = very little pain, 2 = little pain, 3 = moderate to very severe pain.

Interference due to pain was measured with the SF-36 question: “How much interference did you experience with normal activities (including work outside household, and domestic work) in the past four weeks as a consequence of pain?”. Respondents could choose between “no interference”, “little interference”, “moderate interference”, “much interference” and “very much interference”. These answers were categorised into: 0 = no interference, 1 = little interference, 2 = moderate to very much interference. The pain scale of the SF-36, consisting of pain severity and interference due to pain, has a high reliability [25].

COVARIATES

The demographics at baseline were as follows: age in categories (18–24, 25–34, 35–44, 45–54, 55+), gender, education (primary, lower secondary, higher secondary, higher professional/university), living situation (with partner or not) and working situation (having a paid job or not). Furthermore, mental disorders reported at baseline, other than the dependent variable, were selected as covariates. For example, in the analyses for mood disorder, in which subjects with a mood disorder 12 months prior to baseline were excluded, 12-month anxiety disorder and 12-month substance use disorder at baseline were selected as covariates.

STATISTICAL METHODS

First, cross-sectional analyses were performed to examine baseline differences regarding sociodemographic characteristics and mental disorders for pain severity and interference due to pain, for all the 5,303 subjects. Second, logistic regression analyses were performed, for each mental disorder separately, to examine the risks of both pain severity and pain interference on first incidence or recurrence of the mental disorder three years later. In all analyses, we first adjusted for demographics and the time between measurements (model 1) and additionally for other psychopathology at baseline (model 2). For example, in the fully adjusted model to study risk indicators of any incident or recurrent mood disorder (model 2), 12-month anxiety and substance use disorder at baseline were included as covariates. Persons with no pain and persons with no interference due to pain were selected as the reference category. To test for linear trends, potential determinants (i.e. pain severity and interference due to pain) were also modelled separately as continuous variables (p for trend test). Moreover, we studied whether a previous history of a mental disorder modified the association between pain and the risk of a mental disorder at 3-year follow-up. Six interaction-effects were calculated between a previous history of a mental disorder and the two types of pain (severity and interference) on incident or recurrent disorders at follow-up (i.e. mood, anxiety and substance use disorders). Two-tailed testing procedures were used in all analyses with 0.05 alpha levels, except the interaction analyses, where an alpha of 0.001 was used. All statistical analyses were performed with Stata

version 12.1, using weighted data to ensure they were representative of the national population. Robust standard errors were calculated to obtain correct 95% confidence intervals and p values.

RESULTS

DESCRIPTIVE DATA

The baseline characteristics of all 5,303 respondents who participated at the first two waves, tabulated according to the presence of the two pain characteristics (severity and interference) are shown in Table 1 and Table 2.

Being female, less educated, not having a paid job, and presence of any mood, anxiety, and substance use disorder 12 months prior to baseline were significantly associated with a higher score on pain severity. Female gender, older age, lower education, not having a paid job, presence of any mood and anxiety disorder 12 months prior to baseline were significantly associated with a higher score on interference due to pain.

TABLE 1. SOCIODEMOGRAPHICS AND MENTAL DISORDERS ACROSS PAIN SEVERITY, AT BASELINE, OF ALL RESPONDENTS WHO PARTICIPATED AT THE FIRST TWO WAVES (N=5303)

		Pain severity				
	Total	None	Very little	Little	moderate to very severe	
	N=5303 (100%)	n=3100 (59.0%)	n=621 (11.9%)	n=784 (14.0%)	n=797 (15.1%)	
Sociodemographics	*N (%)[a]*	*%[b]*	*%[b]*	*%[b]*	*%[b]*	*P-value*
Female gender	2922 (49.5)	44.2	50.7	57.0	62.6	<.0001
Age						.11
18-24	355 (12.0)	13.0	11.2	10.0	10.7	
25-34	851 (19.8)	20.9	21.0	17.9	16.7	
35-44	1376 (24.5)	25.5	21.6	23.4	23.8	
45-54	1308 (23.4)	22.5	24.0	24.6	25.2	
55+64	1413 (20.2)	18.1	22.2	24.1	23.6	
Education						<.0001
Primary	226 (7.1)	5.6	9.2	5.9	12.4	
Lower secondary	1388 (22.4)	22.0	16.5	23.6	27.6	
Higher secondary	1728 (41.7)	42.1	40.8	41.7	40.4	
Higher professional /university	1961 (28.8)	30.3	33.4	28.8	19.5	
Living without partner	1641 (32.6)	32.1	34.5	31.3	34.0	.66
Not employed	1286 (23.5)	20.4	22.4	24.6	35.3	<.0001
Mental disorders						
Any 12-month mood disorder	329 (6.3)	4.7	5.5	8.4	11.5	<.0001
Any 12-month anxiety disorder	324 (6.5)	5.6	5.6	7.8	11.8	<.0001
Any 12-month substance use disorder	230 (5.5)	4.4	6.8	7.3	7.3	.04

a. Data are in unweighted numbers and weighted column percentages
b. Data are in weighted column percentages

TABLE 2. SOCIODEMOGRAPHICS AND MENTAL DISORDERS ACROSS PAIN INTERFERENCE, AT BASELINE, OF ALL RESPONDENTS WHO PARTICIPATED AT THE FIRST TWO WAVES (N=5303)

		Pain interference			
	Total	None	Little	moderate to very severe	
	N=5303 (100%)	n=4043 (77.3%)	n=806 (14.4%)	n=451 (8.3%)	
Sociodemographics	*N (%)[a]*	*%[b]*	*%[b]*	*%[b]*	*P-value*
Female gender	2922 (49.5)	45.6	63.0	63.2	<.0001
Age					.02
18-24	355 (12.0)	12.6	11.6	8.1	
25-34	851 (19.8)	20.4	20.8	13.5	
35-44	1376 (24.5)	24.8	20.1	28.7	
45-54	1308 (23.4)	22.9	24.9	25.9	
55+64	1413 (20.2)	19.3	22.5	23.9	
Education					<.0001
Primary	226 (7.1)	6.1	8.9	13.7	
Lower secondary	1388 (22.4)	21.5	24.1	28.2	
Higher secondary	1728 (41.7)	42.0	39.0	41.8	
Higher professional /university	1961 (28.8)	30.4	28.0	16.3	
Living without partner	1641 (32.6)	32.2	32.6	37.1	.26
Not employed	1286 (23.5)	20.2	28.0	44.7	<.0001
Mental disorders					
Any 12-month mood disorder	329 (6.3)	4.8	10.1	14.2	<.0001
Any 12-month anxiety disorder	324 (6.5)	5.1	11.0	12.2	<.0001
Any 12-month substance use disorder	230 (5.5)	5.0	7.3	6.8	.04

a. Data are in unweighted numbers and weighted column percentages
b. Data are in weighted column percentages

OUTCOME DATA AND MAIN RESULTS

MOOD DISORDERS

Of the 4974 persons at risk for a mood disorder, 304 developed a mood disorder (185 a first-incident disorder and 119 a recurrent disorder) over the next three years. Table 3 displays the associations between pain at baseline and first-incidence or recurrence of any mood disorder at 3-year follow-up.

Respondents with moderate to very severe pain at baseline (n=797, 15.1%) had two times higher odds of developing any mood disorder (OR=2.10; 95%CI=1.33-3.29) at three-year follow-up, compared to those without pain. Compared to model 1, adjusting for other psychopathology at baseline (model 2) slightly reduced the effect of baseline severity of pain.

Respondents with little interference due to pain at baseline (n=806, 14.4%) had approximately two times higher odds of developing any mood disorder (OR=1.73; 95%CI=1.19-2.53) at three-year follow-up, compared to those without pain. Respondents with moderate to very severe interference due to pain at baseline (n=451, 8.3%) also had approximately two times higher odds of developing any mood disorder (OR=2.14; 95%CI=1.30-3.54) three years later, compared to those without interference due to pain. Compared to model 1, adjusting for other psychopathology at baseline (model 2) slightly reduced the effect of baseline interference due to pain.

The p for trend analyses showed that with higher pain severity and with more interference due to pain, the risk of any incident or recurrent mood disorder increased (all models: $p<.01$).

TABLE 3. PAIN CHARACTERISTICS AT BASELINE AS RISK INDICATORS OF ANY FIRST-INCIDENT (N=185) OR RECURRENT (119) MOOD DISORDER THREE YEARS LATER

	Any first-incident or recurrent mood disorder at 3-year follow-up (n=304)				
		Model 1[a]		Model 2[b]	
	n (%)	OR	95% CI	OR	95% CI
Pain severity					
None	150 (5.5)	reference		reference	
Very little	28 (4.8)	.87	(.51-1.49)	.85	(.50-1.46)
Little	49 (8.3)	1.55*	(1.00-2.41)	1.47	(.93-2.31)
Moderate to very severe	77 (12.4)	2.24***	(1.44-3.47)	2.10**	(1.33-3.29)
p for trend		*p*<.001***		*p*=.001**	
Pain interference					
None	195 (5.5)	reference		reference	
Little	58 (10.4)	1.85**	(1.26-2.71)	1.73**	(1.19-2.53)
Moderate to very severe	50 (12.7)	2.27**	(1.41-3.67)	2.14**	(1.30-3.54)
p for trend		*p*<.001***		*p*<.001***	

Abbreviations: OR = odds ratio; CI = confidence interval
a. Controlled for demographics (gender, age, education, living situation, working situation) and time between measurements (T0–T1)
b. Controlled for demographics (gender, age, education, living situation, working situation), any anxiety disorder, any substance use disorder, and time between measurements (T0–T1)
* p < .05; ** p < .01; *** p<.001

ANXIETY DISORDERS

Of the 4979 persons at risk for an anxiety disorder, 179 developed an anxiety disorder (131 a first-incident disorder and 48 a recurrent disorder) over the next three years. Table 4 displays the associations between pain at baseline and first-incidence or recurrence of any anxiety disorder at 3-year follow-up.

Respondents with little pain severity at baseline (n=784, 14.0%) had more than two times higher odds of developing any anxiety disorder three years later (OR=2.33; 95%CI=1.41-3.85), compared to those without pain. Respondents with moderate to very severe pain at baseline (n=797, 15.1%) had two times higher odds of developing any anxiety disorder (OR=2.12; 95%CI=1.27-3.55) at three-year follow-up, compared to those without pain. Compared to model 1, adjusting for other psychopathology at baseline (model 2) slightly reduced the effect of baseline severity of pain.

Respondents with little interference due to pain at baseline (n=806, 14.4%) had approximately two times higher odds of developing any anxiety disorder (OR=1.90; 95%CI=1.21-2.99) at three-year follow-up, compared to those without pain. Respondents with moderate to very severe interference due to pain at baseline (n=451, 8.3%) also had approximately two times higher odds of developing any anxiety disorder (OR=1.92; 95%CI=1.05-3.52) three years later, compared to those without interference due to pain. Compared to model 1, adjusting for other psychopathology at baseline (model 2) slightly reduced the effect of baseline interference due to pain.

The p for trend analyses showed that with higher pain severity and with more interference due to pain, the risk of any incident or recurrent anxiety disorder increased (all models: p<.01).

TABLE 4. PAIN CHARACTERISTICS AT BASELINE AS RISK INDICATORS OF ANY FIRST-INCIDENT (N=131) OR RECURRENT (N=48) ANXIETY DISORDER THREE YEARS LATER

	Any first-incident or recurrent anxiety disorder at 3-year follow-up (n=179)				
		Model 1[a]		Model 2[b]	
	n (%)	OR	95% CI	OR	95% CI
Pain severity					
None	79 (2.8)	reference		reference	
Very little	19 (3.7)	1.39	(.68-2.83)	1.27	(.63-2.57)
Little	42 (6.5)	2.52***	(1.53-4.13)	2.33**	(1.41-3.85)
Moderate to very severe	39 (6.8)	2.24**	(1.34-3.74)	2.12**	(1.27-3.55)
p for trend		*p*<.001***		*p*<.001***	
Pain interference					
None	108 (3.2)	reference		reference	
Little	43 (6.6)	1.95**	(1.22-3.10)	1.90**	(1.21-2.99)
Moderate to very severe	28 (7.4)	2.06*	(1.14-3.71)	1.92*	(1.05-3.52)
p for trend		*p*=.001**		*p*=.003**	

Abbreviations: OR = odds ratio; CI = confidence interval

a. Controlled for demographics (gender, age, education, living situation, working situation) and time between measurements (T0–T1)

b. Controlled for demographics (gender, age, education, living situation, working situation), any mood disorder, any substance use disorder, and time between measurements (T0–T1)

* p < .05; ** p < .01; *** p<.001

SUBSTANCE USE DISORDERS

Of the 5073 persons at risk for a substance use disorder, 160 developed a substance use disorder (100 a first-incident disorder and 60 a recurrent disorder) over the next three years. Thus, most cases developed a first-incident disorder. Table 5 displays the associations between pain at baseline and first-incidence or recurrence of any substance use disorder at 3-year follow-up.

Both pain characteristics (severity and interference) at baseline were not significantly associated with any incident or recurrent substance use disorder at follow-up.

TABLE 5. PAIN CHARACTERISTICS AT BASELINE AS RISK INDICATORS OF ANY FIRST-INCIDENT (N=100) OR RECURRENT (N=60) SUBSTANCE USE DISORDER THREE YEARS LATER

	Any first-incident or recurrent substance use disorder at 3-year follow-up (n=160)				
		Model 1[a]		Model 2[b]	
	n (%)	OR	95% CI	OR	95% CI
Pain severity					
None	95 (4.3)	reference		reference	
Very little	19 (4.4)	1.18	(.58-2.43)	1.20	(.59-2.46)
Little	20 (3.2)	1.03	(.63-1.70)	1.02	(.62-1.69)
Moderate to very severe	26 (3.9)	1.15	(.65-2.04)	1.14	(.65-2.02)
p for trend		*p*=.60		*p*=.63	
Pain interference					
None	118 (4.1)	reference		reference	
Little	21 (3.3)	1.08	(.54-2.17)	1.07	(.53-2.16)
Moderate to very severe	20 (5.1)	1.55	(.78-3.07)	1.51	(.77-2.97)
p for trend		*p*=.25		*p*=.28	

Abbreviations: OR = odds ratio; CI = confidence interval

a. Controlled for demographics (gender, age, education, living situation, working situation) and time between measurements (T0–T1)

b. Controlled for demographics (gender, age, education, living situation, working situation), any mood disorder, any anxiety disorder, and time between measurements (T0–T1)

* p < .05; ** p < .01; *** p<.001

INTERACTION EFFECTS

No interaction effects were found for a previous history of a mood disorder with pain on the risk of developing a mood disorder at 3-year follow-up, a previous history of an anxiety disorder with pain on the risk of developing an anxiety disorder at 3-year follow-up, and a previous history of a substance use disorder with pain on the risk of developing a substance use disorder at 3-year follow-up. These effects applied for both pain severity and interference due to pain. This implies that the association between pain and mental disorders did not significantly differ between subjects with a first onset and subjects with a recurrent mental disorder.

DISCUSSION

This is one of the first large scale studies assessing pain as a risk factor for the prospective development of first or recurrent episodes of common mental disorders in the adult general population. Prevalence of moderate to very severe pain was 15.1% and for moderate to very severe interference due to pain 8.3%. These subjects had a more that twofold increased risk for developing a first-incident or recurrent mood and anxiety disorder three years later. Adjusting for mental disorder at baseline, other than the one as the dependent variable, only slightly attenuated the strength of the pain-mental disorder associations. Moreover, the effect of pain on mental disorders did not differ between subjects who developed a first-incident mental disorder and subjects who developed a recurrent mental disorder. Our findings, therefore, show that pain is a common, strong and unique risk factor for mood and anxiety disorders.

Our findings are consistent with and extend previous longitudinal findings between pain and mood and anxiety [13-15,17]. The strength of the association between pain severity and interference due to pain with mood and anxiety disorders is higher in the current study compared to previous longitudinal studies: In clinical studies more severe pain increased the risk for onset of a depressive and anxiety disorder between a one- to twofold factor [13] and for recurrence of depression by a 1.2-fold factor [14]; in population studies, among elderly, more severe pain

increased the risk for depressive symptoms by a 1.1-fold factor [17], and more interference due to pain increased the risk for depressive and anxiety symptoms by almost a twofold factor [15]. In the present study, a more than 2-fold increased risk was found for both pain severity and interference due to pain in developing a mood and anxiety disorder. This may be attributed to methodological differences in study sample, study size and outcome measures. For example, although the population studies [15,17] used non-depressed and non-anxious subjects, depression and anxiety were measured with a self-report questionnaire regarding symptoms in the last week. A major contribution of the present study is the use of a standardized diagnostic interview to assess mental disorders in the last 12-months and lifetime history of mental disorders. This enabled us to 1) assess clinical and chronic symptoms of common mental disorders, 2) assess the risk of pain in subjects without a mental disorder in the last 12 months, and 3) evaluate whether the risk of pain differs in subjects with a recurrent mental disorder and subjects with a first-onset mental disorder. Our findings therefore extend previous literature by showing that when pain becomes more severe or interferes with normal activities, the risk of full-blown first-incident or recurrent mood and anxiety disorders increases substantially in the general adult population.

Regarding first-incident and recurrence of substance use disorder, we found no association with pain severity or with interference due to pain at baseline. In a study among at-risk stimulant users, more days of pain (which interfered with work and social activities) was associated with a two- to threefold increase of developing a substance use disorder [12]. It could therefore be expected that, in the present study, interference due to pain would also be associated with substance use disorder. A possible explanation for this discrepancy might be attributed to several methodological differences. Edlund et al. (2013) [12] used a sample of at-risk stimulant users, which might not be comparable to the general adult population. Furthermore, they used a non-validated measure for pain and adjusted their results only for severity of depression, based on a short self-report questionnaire. However, it could also indicate that pain is a risk factor for developing a substance use disorder in an at-risk sample, but not in the general adult population. Nevertheless, Volkow et al. (2016) [26] warn for the possible abuse hazards of opioid use by chronic pain patients, as opioid analgesics are the most commonly prescribed class of

medications for pain, with an elevated risk of abuse and addiction. In our study, we were unable to distinguish between specific substance use disorders, such as opioid use, due to a small number of subjects in this category. Therefore, in future studies, the specific association between pain, mental disorders and opioid use should be taken into account.

STRENGTHS AND LIMITATIONS

This study had the advantage of a large population sample, which was followed-up for three years, the use of a standardized instrument to assess common mental disorders and the possibility to adjust for a wide variety of confounders in investigating the relationship between pain characteristics at baseline and mental disorders at follow-up. However, some limitations should be mentioned.

The outcome of the main analysis was aggregated as we have pooled both first-incident and recurrent mental disorders. However, we did examine whether results would differ for subjects with a recurrent mental disorder from those with a first-incident mental disorder, and found no significant difference. This might be explained due to the relatively small number of subjects with a recurrent or first-incident mental disorder at follow-up, especially for anxiety (48 subjects with a recurrent disorder and 131 subjects with a first-onset disorder) and substance use disorders (60 subjects with a recurrent disorder and 100 subjects with a first-onset disorder). Studies with larger sample sizes of incident and recurrent mental disorders are needed to study this more accurately. Mental disorders were also aggregated by pooling several specific mood, anxiety and substance use disorders due to the small numbers reporting a specific mental disorder. Consequently, no inferences can be made whether pain is a risk factor in developing one of these specific disorders and in developing another mental disorder not considered in our study. Additionally, the use of the SF36 to measure pain severity and interference due to pain is limited. This questionnaire only asks for pain in the last four weeks, so no inferences could be made on chronic pain. However, in two large clinical studies, chronic pain (pain with a duration of at least 90 days) was not associated more strongly with the onset and recurrence of a depressive and anxiety disorder when compared to less chronic pain [13,14], indicating that current severe pain

might be a more important risk factor when considering mental disorders. Despite a follow-up period of three years in this study, we cannot make any inferences about a causal pathway of pain towards a mental disorder. Besides, it is possible that factors not studied here might play a mediating role in the link between pain and mental disorders. For example, sleep problems can play a mediating role in the link between persistent pain and depression and anxiety [27,28]. Dysfunctional cognitive pain responses, such as catastrophizing or hopelessness, also seem to mediate the association between pain and depression [29]. In future research and interventions of pain, problems with sleep and dysfunctional cognitive responses should therefore also be considered. Sleep problems and dysfunctional cognitions are modifiable factors, and when these factors mediate the association between pain and mental disorders, interventions targeted at sleep and cognitions might also be effective in reducing both pain and the risk of mental disorders.

CONCLUSIONS

Our finding that pain has a significant impact in the development of a mental disorder in the adult general population is important for health professionals, who would do well by monitoring and detecting possible symptoms of a mental disorder when pain symptoms are present. Pain management programs could then possibly also serve as a preventative program for mental disorders in subjects with pain; reducing pain symptoms might lead to a reduced risk for developing a mental disorder. However, more longitudinally research is needed exploring causality and other mediating factors in the association between pain and mental disorders.

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CHAPTER 5

PAIN AS A RISK FACTOR FOR SUICIDAL BEHAVIOUR

"People fear death even more than pain. It's strange that they fear death. Life hurts a lot more than death. At the point of death, the pain is over"

Jim Morrison

(1943-1971)

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ABSTRACT

Background: Pain might be an important risk factor for suicidal behaviour. However, the association between pain characteristics and the incidence of suicidal behaviour in the general adult population, taking mental disorders into account, is still unknown. This study aims to explore this.

Materials and methods: Data were used from two waves (collected between 2007 and 2012) of the Netherlands Mental Health Survey and Incidence Study-2, a nationally representative survey among the general population. Persons without prior 12-month suicidal behaviour at baseline were included in this study (N=5,242). Pain severity and interference due to pain in the past month were measured at baseline using the 36-item Short Form Health Survey. Suicidal behaviour and DSM-IV mental disorders were assessed at both waves using the Composite International Diagnostic Interview version 3.0.

Results: Moderate to very severe pain (OR=3.39; 95% CI = 1.74-6.61; $p < .001$) and moderate to very severe interference due to pain (OR=2.35; 95% CI = 1.22-4.53; $p = .01$) were associated with a higher risk for incident suicidal behaviour at follow-up after adjustment for baseline sociodemographics and 12-month prevalence of mental disorders, compared to persons reporting no pain. No interaction effects were found between pain severity or interference due to pain and mental disorders.

Conclusions: In conclusion, moderate to severe pain and interference due to pain are risk factors for suicidal behaviour independently of possible concomitant mental disorders. We suggest taking assessment and management of suicidal behaviour in patients with pain into account both in clinical treatment as well as in suicide prevention action plans.

INTRODUCTION

Suicidal behaviour is defined as suicidal ideation, plans, and attempts [1-3]. Although chronic pain is mentioned as an important risk factor for suicidal behaviour in a WHO report [4], many European countries have developed suicide prevention plans that only take mental disorders into account [1], and not pain. Pain occurs in 19% of the adult European population [5]. In severe cases [6-9], if treatment is no longer effective, one of the choices to end pain might be to commit suicide [10]. Hence, the association of pain with suicidal behaviour might be a relevant public health problem. However, the current evidence on the size of this association is limited. Two reviews found mostly clinical, retrospective or cross-sectional studies, and, importantly, they did not control for concomitant mental disorders, that have a known association with suicidal behaviour [6,9]. An association between pain and suicidal behaviour was found in cross-sectional studies while controlling for the presence of common mental disorders [e.g. 11-13], and pain was a risk factor for suicidal behaviour, over and above mental disorders in two longitudinal, population-based studies [14,15]. Adolescents with headaches had a 1.5-fold increased risk of subsequent suicidal behaviour, after adjustment for depression [15]. Subjects with severe (migraine and non-migraine) headaches had a more than a four-fold increased risk of suicide attempt, compared to subjects with mild headaches, after adjustment for depressive and anxiety disorders [14]. As both studies focused only on headaches or migraines, the association of pain in general with subsequent suicidal behaviour in the general adult population, over and above common mental disorders, still needs further exploration. To gain insight into the interplay of physical pain and suicidal behaviour we need longitudinal population-based research, exploring the role of pain in the incidence of suicidal behaviour, taking mental disorders into account that have a known association with suicidal behaviour. Our study aims to do so.

We will explore the influence of pain characteristics in general (pain severity and interference with normal activities due to pain) on subsequent suicidal behaviour in the adult general population, using data of the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). We hypothesise that subjects with more severe pain and subjects with more interference due to pain are at increased risk for suicidal behaviour compared to subjects without

pain, in an adult general population sample. Furthermore, we hypothesise that this association will be stronger in subjects with a mental disorder compared to subjects without a mental disorder.

MATERIALS AND METHODS

STUDY DESIGN AND PARTICIPANTS

Data were used from the first two waves of NEMESIS-2, a psychiatric epidemiological cohort study among the Dutch general population aged 18–64 years at baseline [16]. Design and methods of the NEMESIS-2 study are described elsewhere [16], but a brief summary is given here. The NEMESIS-2 study is based on a multistage, stratified random sampling of households, with one respondent randomly selected in each household. The sample was nationally representative, although younger subjects were somewhat under-represented. The Medical Ethics Committee for Institutions on Mental Health Care (METIGG) approved the study. After having been informed about the study objective, respondents provided written informed consent.

See figure 1 for a flowchart of the inclusion procedure. In the first wave (T0), performed from November 2007 to July 2009, a total of 6,646 persons were interviewed (response rate 65.1%; average interview duration 95 min). The interviews were laptop computer assisted and almost all were held at the respondent's home. All T0 respondents were approached for follow-up (T1) three years after T0, from November 2010 to June 2012. Of this group, 5,303 persons were re-interviewed (response rate 80.4%, excluding those deceased; average interview duration 84 min). The mean period between both interviews was three years and seven days. Baseline psychopathology was not significantly associated with attrition at follow-up, after controlling for sociodemographics [17], compared to other studies that did find such an association [18-20]. Furthermore, in the cohort used for this study (i.e. those without 12-month suicidal behaviour at baseline), pain characteristics at baseline were not significantly associated with attrition at follow-up, after controlling for demographics.

For this study, those persons without 12-month suicidal behaviour at T0 were selected (N=5,242). Lifetime previous suicidal behaviour was not an exclusion criterion if in the last 12 months at baseline no suicidal behaviour was reported.

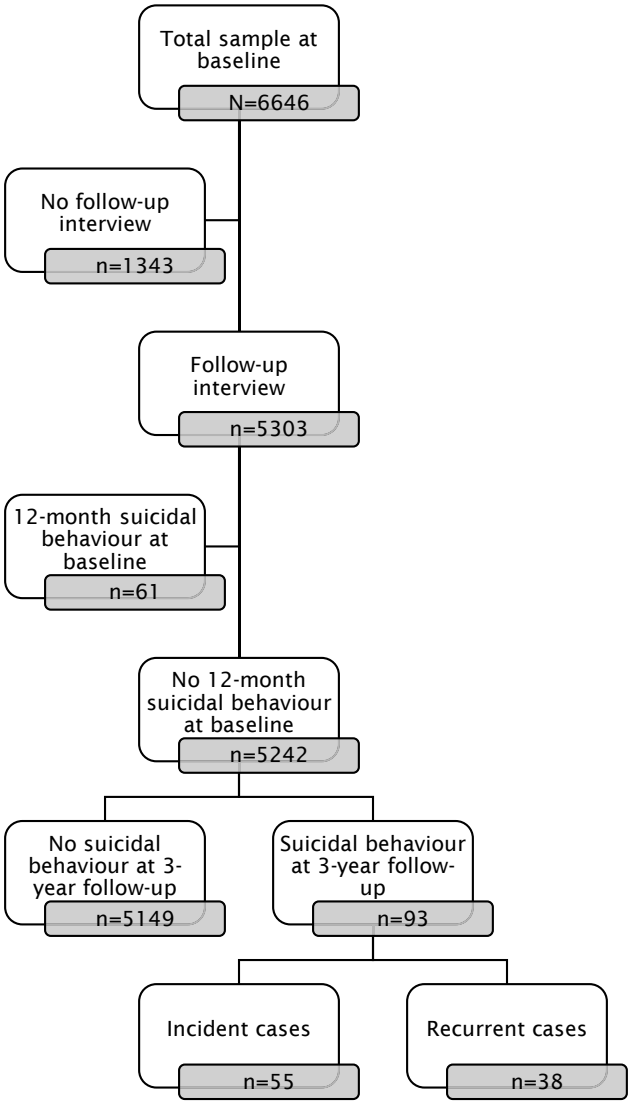

FIGURE 1. FLOWCHART OF THE INCLUSION PROCEDURE

MEASURES

SUICIDAL BEHAVIOUR

Suicidal behaviour, defined as ideation, plans and/or attempts (yes/no), was assessed using the Suicidality Module of the Composite International Diagnostic Interview (CIDI) version 3.0, a fully structured lay-administered diagnostic interview of mental disorders and suicidality [21]. The CIDI was developed and adapted for use in the World Mental Health Survey Initiative. In the Netherlands, the CIDI 3.0 was first used in ESEMeD [22], which is part of this initiative. The CIDI 3.0 version used in NEMESIS-2 was an improvement of the one used in the Dutch ESEMeD study. At baseline, respondents were asked about previous experiences of suicidal ideation ("Have you ever seriously thought about committing suicide?"), suicide plans ("Have you ever made a plan for committing suicide?") and suicide attempts ("Have you ever attempted suicide?"). To increase reporting, the experiences were not mentioned but listed in a booklet and referred to by number (Events A, B, and C). Respondents were asked whether each experience lifetime occurred to them and, if so, if this happened in the past 12 months. At T1, respondents were asked the same questions about suicidal behaviour, but then the time period referred to suicidal behaviour they had experienced since the baseline interview. At T1, subjects were selected who did not report any suicidal behaviour in the last 12 months at baseline.

PAIN ASSESSMENTS

At baseline, pain severity was assessed using a question from the SF-36-item Short Form Health Survey [23,24]: "How much pain did you experience in the past four weeks?" Respondents could choose between "no pain", "very little pain", "little pain", "moderate pain", "severe pain" and "very severe pain". Due to the small number of subjects in the moderate, severe, and very severe pain categories, grouping these categories together into one answer category was needed to create more equal groups. Therefore, the categories used in this study were: 0 = no pain, 1 = very little pain, 2 = little pain, 3 = moderate to very severe pain.

Interference due to pain was measured with the SF-36 question: "How much interference did you experience with normal activities (including work outside household, and domestic work) in the past four weeks as a consequence of pain?". Respondents could choose between "no interference", "little interference", "moderate interference", "much interference" and "very much interference". Due to the small number of subjects in the moderate, much, and very much interference categories, we grouped these categories into one answer category to create more equal groups. Therefore, the categories used in this study were: 0 = no interference, 1 = little interference, 2 = moderate to very much interference.

COVARIATES

The demographics at baseline were as follows: age in categories (18–24, 25–34, 35–44, 45–54, 55–64), gender, education (primary, lower secondary, higher secondary, higher professional/university), living situation (with partner or not) and working situation (having a paid job or not). Twelve-month prevalence of mental disorders at baseline, as measured with the CIDI version 3.0 [21], included: any mood disorder (major depression, dysthymia, bipolar disorder), any anxiety disorder (panic disorder, agoraphobia, social anxiety disorder, generalised anxiety disorder, specific disorder) and any substance use disorder (alcohol/drug abuse and dependence). Research has demonstrated acceptable reliability and validity for assessing these common mental disorders [25].

STATISTICAL METHODS

First, univariate analyses were performed to describe the sample at baseline, regarding sociodemographics, mental disorders, pain severity and interference due to pain. Second, logistic regression analyses were performed with two models to examine both the risks of pain severity and pain interference on suicidal behaviour at follow-up. In model 1, the odds ratios (OR) were adjusted for demographics. In model 2, they were also adjusted for any 12-month mood disorder, any 12-month anxiety disorder and any 12-month substance use disorder at baseline. In both models, persons with no pain and persons with no interference due to pain were selected as the reference category. To test for linear trends, potential determinants (i.e. pain severity and interference due to pain) were also modelled separately as continuous variables in both models (p for trend test). To study whether the three main groupings of mental disorders (mood/anxiety/substance use) increase the risk of suicidal behaviour in persons with pain, separate interactions between these three main groupings of mental disorders and pain (severity and interference) were tested. Two-tailed testing procedures were used in all analyses with 0.05 alpha levels, except the interaction analyses, where an alpha of 0.001 was used. All statistical analyses were performed with Stata version 12.1, using weighted data to ensure they were representative of the national population. Robust standard errors were calculated to obtain correct 95% confidence intervals and p values [26].

RESULTS

DESCRIPTIVE DATA

Table 1 describes the baseline characteristics of the 5,242 persons in this cohort. In all, 50.6% were men and most of the participants were 35 years of age or older. Of the total participant group, 68% had a partner and 76.9% had a job. Most subjects (41.8%) attended higher secondary school, whereas 7.1% of the subjects had only attended primary school. Most subjects (83.1%) did not have any 12-month mood, anxiety or substance use disorders, whereas 5.5% reported any mood disorder, 10.0% any anxiety disorder and 5.3% any substance use disorder in the past 12 months. Of the cohort, 14.8% experienced moderate to very severe pain, 26.0% reported (very) little pain and 59.2% reported having no pain in the past month. Regarding interference due to pain in the month before baseline, 8.3% had moderate to very severe interference, 15.2% reported (very) little interference and 76.5% reported no interference.

At follow up, 93 subjects (1.8%) reported suicidal behaviour of which 55 were an incident case and 38 were a recurrent (lifetime) case. Of these 93 subjects, 17 made a suicide plan and 9 made a suicide attempt.

OUTCOME DATA AND MAIN RESULTS

PAIN SEVERITY AND SUICIDAL BEHAVIOUR

Table 2 shows the odds ratios (OR) of pain severity at baseline with suicidal behaviour three years later. In both models of pain severity, only the category of moderate to very severe pain was significantly associated with incident suicidal behaviour three years later. When controlling for demographics (model 1), those with moderate to very severe pain had four times higher OR for suicidal behaviour than did those who did not report pain. When also controlling for mental disorders (model 2), the OR was still more than three times higher. The p for trend showed that with higher pain severity, the risk of suicidal behaviour significantly increased (both models: $p < .001$).

TABLE 1. BASELINE CHARACTERISTICS (SOCIODEMOGRAPHICS, PAIN, MENTAL DISORDERS) OF THE TOTAL SAMPLE, AND OF THOSE WITH AND WITHOUT SUICIDAL BEHAVIOUR AT 3-YEAR FOLLOW-UP

	Total sample		**No suicidal behaviour at 3-year follow-up**	**Suicidal behaviour at 3-year follow-up**
	N=5242		n=5149	n=93
Sociodemographics	*N*[a]	*%*[b]	*%*[b]	*%*[b]
Female gender	2891	(49.4)	49.4	51.5
Age				
18-24	349	(11.9)	11.9	13.5
25-34	843	(20.0)	19.9	21.4
35-44	1361	(24.5)	24.7	18.5
45-54	1290	(23.3)	23.1	31.6
55+64	1399	(20.3)	20.4	15.1
Education				
Primary	222	(7.1)	6.8	19.5
Lower secondary	1370	(22.3)	22.2	26.9
Higher secondary	1707	(41.8)	42.0	30.4
Higher professional /university	1943	(28.9)	29.0	23.2
Living without partner	1595	(32.0)	31.8	39.7
Not employed	1257	(23.1)	22.7	42.3
Pain characteristics				
Pain severity*				
None	3071	(59.2)	59.7	35.0
Very little	618	(12.0)	12.0	11.8
Little	777	(14.0)	14.0	13.9
Moderate to very severe	775	(14.8)	14.3	39.2
Pain interference**				
None	4010	(77.7)	78.1	55.6
Little	794	(14.2)	14.1	23.6
Moderate to very severe	436	(8.1)	7.8	20.8
Mental disorders				
Any 12-month disorder	834	(16.8)	16.1	52.6
Any 12-month mood disorder	288	(5.5)	5.0	30.6
Any 12-month anxiety disorder	511	(10.0)	9.5	36.5
Any 12-month substance use disorder	281	(5.3)	5.2	8.3

* 1 missing; ** 2 missings

a. Data are presented in unweighted numbers

b. Data are presented in weighted percentages

TABLE 2. PAIN SEVERITY AS RISK FACTOR OF INCIDENT OR RECURRENT SUICIDAL BEHAVIOUR THREE YEARS LATER (FIRST ONSET: N=55; RECURRENT: N=38)

	Model 1			**Model 2**		
	OR	95% CI	p-value	OR	95% CI	p-value
Pain severity						
None	reference			reference		
Very little	1.68	.70-3.99	.24	1.69	.72-4.00	.23
Little	1.73	.91-3.31	.10	1.43	.74-2.79	.29
Moderate to very severe	4.00	2.08-7.70	<.001	3.39	1.74-6.61	<.001
p for trend			<.001			<.001
Covariates						
Female gender (vs male)	.76	.36-1.61	.47	.59	.26-1.33	.20
Age (vs 18-24)						
25-34	1.77	.46-6.87	.40	1.71	.42-6.90	.45
35-44	2.66	1.03-6.83	.04	2.34	.86-6.37	.09
45-54	1.77	.82-3.79	.14	1.47	.65-3.35	.35
55+64	2.69	1.15-6.31	.02	2.25	.92-5.47	.07
Education (vs primary)						
Lower secondary	2.38	.77-7.34	.13	2.65	.89-7.88	.08
Higher secondary	1.21	.50-2.90	.67	1.08	.45-2.62	.86
Higher professional /university	.80	.38-1.68	.56	.75	.35-1.60	.45
Living without partner (vs with partner)	1.21	.74-1.98	.44	.91	.53-1.58	.75
Not employed (vs employed)	2.27	1.13-4.57	.02	1.84	.86-3.95	.12
Mental disorders						
Any 12-month mood disorder (vs no mood disorder)				4.78	2.17-10.52	<.001
Any 12-month anxiety disorder (vs no anxiety disorder)				3.08	1.29-7.35	.01
Any 12-month substance use disorder (vs no substance use disorder)				.58	.18-1.84	.35

Abbreviations: OR = odds ratio; CI = confidence interval
Data are presented in adjusted odds ratios with 95% confidence intervals
Model 1: controlled for demographics (gender, age, education, living situation, working situation) and time between measurements (T0–T1)
Model 2: controlled for demographics (gender, age, education, living situation, working situation), time between measurements (T0–T1), and any mood disorder, any anxiety disorder, and any substance use disorder

PAIN INTERFERENCE AND SUICIDAL BEHAVIOUR

Table 3 shows the odds ratios (OR) of interference due to pain at baseline with suicidal behaviour three years later. Little interference due to pain was significantly associated with suicidal behaviour compared to the reference category when adjusted for demographics only (model 1), with two times higher OR, but when adjusted for mental disorders (model 2), the association became non-significant. The category of moderate to very severe interference due to pain was significantly associated in both models, with those with moderate to very severe interference having almost three (model 1) and more than two (model 2) times higher OR for suicidal behaviour when compared to the reference category. With more interference due to pain, the risk of suicidal behaviour significantly increased (p for trend in model 1: <.001; in model 2: .01).

INTERACTION EFFECTS

No interaction effects were found for any mood disorder with pain, any anxiety disorder with pain, and any substance use disorder with pain on the risk of suicidal behaviour. These effects applied for both pain severity and interference due to pain. This implies that the association between pain and suicidal behaviour did not significantly differ between subjects with and subjects without a mental disorder.

TABLE 3. PAIN INTERFERENCE AS RISK FACTOR OF INCIDENT OR RECURRENT SUICIDAL BEHAVIOUR THREE YEARS LATER (FIRST ONSET: N=55; RECURRENT: N=38)

	Model 1			**Model 2**		
	OR	95% CI	p-value	OR	95% CI	p-value
Pain interference						
None	reference			reference		
Little	2.22	1.14-4.34	.02	1.74	.81-3.74	.15
Moderate to very severe	2.87	1.64-5.02	<.001	2.35	1.22-4.53	.01
p for trend			<.001			.01
Covariates						
Female gender (vs male)	.78	.38-1.58	.49	.62	.28-1.35	.23
Age (vs 18-24)						
25-34	1.75	.44-6.98	.42	1.62	.39-6.71	.51
35-44	2.66	1.03-6.86	.04	2.33	.84-6.50	.11
45-54	1.76	.82-3.77	.15	1.45	.64-3.31	.37
55+64	2.70	1.16-6.30	.02	2.24	.91-5.50	.08
Education (vs primary)						
Lower secondary	2.54	.88-7.34	.08	2.76	.95-8.00	.06
Higher secondary	1.26	.56-2.86	.58	1.12	.48-2.62	.79
Higher professional /university	.81	.40-1.66	.57	.77	.37-1.61	.49
Living without partner (vs with partner)	1.19	.73-1.95	.48	.89	.51-1.57	.69
Not employed (vs employed)	2.29	1.18-4.44	.02	1.87	.90-3.88	.09
Mental disorders						
Any 12-month mood disorder (vs no mood disorder)				4.54	2.10-9.80	<.001
Any 12-month anxiety disorder (vs no anxiety disorder)				3.17	1.26-7.95	.01
Any 12-month substance use disorder (vs no substance use disorder)				.63	.22-1.83	.40

Abbreviations: OR = odds ratio; CI = confidence interval
Data are presented in adjusted odds ratios with 95% confidence intervals
Model 1: controlled for demographics (gender, age, education, living situation, working situation) and time between measurements (T0–T1)
Model 2: controlled for demographics (gender, age, education, living situation, working situation), any mood disorder, any anxiety disorder, any substance use disorder, and time between measurements (T0–T1)

DISCUSSION

The aim of this study was to explore the longitudinal influence of pain severity and interference due to pain occurring in the last month on subsequent suicidal behaviour in the general adult population. We found that the risk of incident suicidal behaviour was significantly higher for persons with more severe pain and for those who experience more interference due to pain, which confirm our first hypothesis. These results did not change when adjusting for demographics and, more importantly, for concurrent mental disorders. In accordance with previous studies [14,15], adjusting for mental disorders did not significantly attenuate the observed risk of suicidal behaviour.

Our second hypothesis, that the association between pain and suicidal behaviour would be stronger in subjects with a mental disorder, was not confirmed. The effect of pain on suicidal behaviour did not differ between subjects with a mental disorder and subjects without a mental disorder. Our findings, therefore, show that pain is an important and unique risk factor for suicidal behaviour, independent of mental disorders, and extend previous research by showing that more severe pain and more interference due to pain are risk factors for suicidal behaviour at three-year follow-up in the general population, even when mental disorders are taken into account. Pain and suicidal behaviour may share similar biological pathways that can explain our results. For example, a dysfunction in serotonin transmission, also implicated in pain, might ultimately lead to suicidal behaviour [27,28]. More research on shared biological pathways between pain and mental disorder is needed to shed light on this issue.

Our study found a higher OR than Calati et al. in their meta-analysis [6]; this may be related to the fact that the current study used a large nationally representative sample and had a longitudinal design, whereas Calati et al. [6] also included cross-sectional studies. This allows us to look at the incident suicidal behaviour in persons with and without pain over time. Although we used a representative sample of the adult population, no information was available on fatal suicide attempts, so no inferences could be made whether pain also plays an important role in fatal attempts. However, Stenager et al. [29] found that painful somatic diseases were a risk

factor for suicide. Furthermore, Fishbain [30] also demonstrated that fatal suicide attempts are more present in patients with chronic pain, and indicate that further research is required assessing pain as a risk factor for fatal suicide attempts.

STRENGTHS AND LIMITATIONS

Major strengths of this study are the longitudinal design and the large representative sample of the general population. Moreover, this is the first study to examine pain severity and interference due to pain as a risk factor for suicidal behaviour in a large sample of the general population. This sample is representative of the general adult population (age 18-64 year), but might not be generalizable to other age categories, although comparable results were found in adolescents [15]. However, several limitations need to be noted as well. This study was based on self-reports, and suicidal behaviours might therefore have been underreported. Furthermore, we grouped suicidal ideation, plans, and attempts in suicidal behaviour, which makes it not possible to distinguish between these behaviours. We also did not distinguish between a new onset and recurrent (lifetime) case regarding suicidal behaviour due to the small sample reporting suicidal behaviour at T1: 55 subjects reported new onset suicidal behaviour and 38 subjects reported recurrent (lifetime) suicidal behaviour. Whether pain might play a more important role in new onset or in recurrent suicidal behaviour remains unknown. Future longitudinal research should take this into account, but this requires much larger samples with subjects reporting (new onset and recurrent) suicidal behaviour. Regarding pain, we measured this with two items from the pain subscale of the SF36. A more comprehensive measurement of pain is preferred, in which more aspects of pain are distinguished, such as frequency/chronicity and cause or origin of pain. Regarding frequency/chronicity, the subjects in this study were asked to report pain severity and interference due to pain in the month before baseline, and although our results show a significant association of these pain variables with suicidal behaviour in the following three years, a measurement of a longer duration of pain (e.g. chronic pain vs. acute pain) might result in stronger association with suicidal behaviour [9,31]. Moreover, pain is not time independent and severity can change over time, affecting our results. For example, previous literature suggests

that a change in severity of pain is associated with the course and severity of mental disorders [32,33], and it is therefore not unlikely that a change in pain severity could lead to a change in the risk of suicidal behaviour (e.g. less severe pain over time might decrease the risk of suicidal behaviour). However, in the present study, measurement of pain referred to pain in the four weeks prior to baseline. As the course of pain was not assessed in detail in NEMESIS-2 in the period between baseline and first follow-up, no inferences could, therefore, be made whether changes in the course of pain affected suicidal behaviour. To differentiate pain trajectories, associated with suicidal behaviour, we need to measure pain more comprehensively in future studies.

The effect of this limitation is that we probably underestimate associations between pain and suicidality. It is conceivable that if we had restricted ourselves to a longer duration of pain at baseline or a measurement of increasing pain over time, we would have found even stronger associations with suicidal behaviour at follow-up [9,31]. Regarding the cause or the origin of the pain, pain itself, of course, can be the trigger for a mental disorder, such as in a somatic symptom disorder [34]. However, there is a recent debate on whether this new DSM-5 diagnosis might lead to overpsychologising and mislabelling pain [35]. Therefore, instead of making statements whether the experienced pain is part of a mental disorder, this study only focused on how severe the individual experienced the pain and how much interference due to pain there was. The experienced pain might also be explained as part of a more 'somatic' disease, such as cancer [36], cardiovascular disease [37], and rheumatoid arthritis [38]. It is often clinically difficult to tease out primary and secondary factors. In the present study, however, we did not know whether the experienced pain originated from a somatic disease. Furthermore, pain is highly associated with a variety of somatic diseases, and controlling for somatic diseases would then lead to overcorrection of the statistical model. An area of further study would be to consider to what extent pain is 'mentally' or 'somatically' attributable, and if so, to examine whether the risk of suicidal behaviour differs from non-attributable pain. Other factors, such as social support and poor pain-related coping (e.g. catastrophising), might also play a mediating role in the link between pain and suicidal behaviour, [39,40], but these were not studied here. In a study among 360 patients with rheumatic disease, less social support was associated with an increased risk for

suicidal behaviour [40], and in a sample of 1512 pain patients, catastrophising was an important predictor of both the presence and severity of suicidal ideation, even after controlling for measures of affective function (e.g. depression, anxiety) [39]. In future research and treatment of pain, social support and catastrophising as pain-related coping should be considered, as this may explain why pain predicts suicidality and can help designing strategies to prevent suicidal behaviour. Furthermore, the course of mental disorders is diverse [41-43], where one could differentiate between an incident, remitted, and chronic course. Literature shows that these different courses are associated with different courses of the severity of pain [32,33], and although we studied the effect of pain on suicidal behaviour in a sample without mental disorders at baseline, it is of interest to study how different trajectories of mental disorders, next to different trajectories of pain, are associated with subsequent suicidal behaviour.

CONCLUSIONS

Our finding that pain has a significant impact on suicidal behaviour may be important for developing and customising suicide prevention plans for patients suffering from pain [44]. To date, such plans mainly focus on mental disorders [1]. Furthermore, two longitudinal studies [14,15] reported the increased risk of headaches and migraines on suicidal behaviour versus controls. Our findings broaden this finding by including pain of any form – if is severe or significant interference is experienced due to pain – as a risk factor for suicidal behaviour. Therefore, the risk of suicidal behaviour may need further discussion, even in the absence of common mental disorders when persons present themselves with severe pain or significant interference due to pain. More longitudinal research is needed that focuses on the role of pain in suicidal behaviour, in which pain is measured more comprehensively, including pain location, origin of pain, and pain-related coping.

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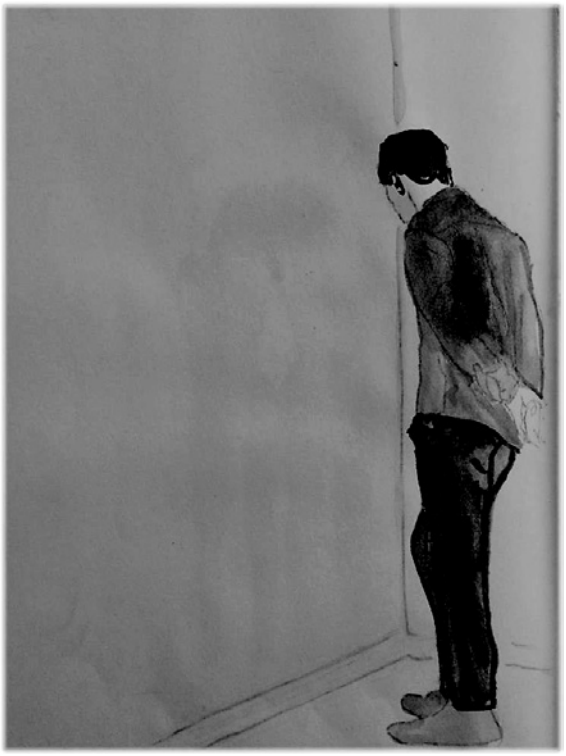
PART III

TREATMENT



CHAPTER 6

EFFECTIVENESS AND COST-EFFECTIVENESS OF TRANSMURAL COLLABORATIVE CARE FOR DEPRESSIVE DISORDER AND PAIN: DESIGN OF A RANDOMIZED, PLACEBO-CONTROLLED MULTICENTRE TRIAL (CC:PAINDIP)

"Mental pain is less dramatic than physical pain, but it is more common and also more hard to bear. The frequent attempt to conceal mental pain increases the burden: it is easier to say, "My tooth is aching" than to say "My heart is broken.""

C.S. Lewis

(1898-1963)

This chapter is based on:

Heer EW de, Dekker J, Eck van der Sluijs JF van, Beekman ATF, Marwijk HWJ van, Holwerda TJ, Bet PM, Roth J, Hakkaart-Van Roijen L, Ringoir L, Kat F, Feltz-Cornelis CM van der. Effectiveness and cost-effectiveness of transmural collaborative care with consultation letter and duloxetine for major depressive disorder and (sub)chronic pain: design of a randomized placebo-controlled multi-centre trial: CC:PAINDIP. BMC Psychiatry 2013; 13:147.

ABSTRACT

Background: The comorbidity of pain and depression is associated with high disease burden for patients in terms of disability, wellbeing, and use of medical care. Patients with major and minor depression often present themselves with pain to a general practitioner and recognition of depression in such cases is low, but evolving. Also, physical symptoms, including pain, in major depressive disorder, predict a poorer response to treatment. A multi-faceted, patient-tailored treatment program, like collaborative care, is promising. However, treatment of chronic pain conditions in depressive patients has, so far, received limited attention in research. Cost effectiveness of an integrated approach of pain in depressed patients has not been studied. This article describes the aims and design of a study to evaluate effects and costs of collaborative care with the antidepressant duloxetine for patients with pain symptoms and a depressive disorder, compared to collaborative care with placebo and compared to duloxetine alone.

Materials and methods: This study is a placebo controlled double blind, three-armed randomized multi-centre trial. Patients with (sub)chronic pain and a depressive disorder are randomized to either: (a) collaborative care with duloxetine; (b) collaborative care with placebo; or (c) duloxetine alone. 189 completers are needed to attain sufficient power to show a clinically significant effect of 0.6 SD on the primary outcome measures (PHQ-9 score). Data on depression, anxiety, mental and physical health, medication adherence, medication tolerability, quality of life, patient-doctor relationship, coping, health resource use and productivity will be collected at baseline and after three, six, nine and twelve months. In the collaborative care conditions (a) and (b), a care-manager provides problem-solving treatment and integrated symptom management guidance with a self-help manual, monitors depressive and pain symptoms, and refers patients to a physiotherapist for treatment according to a 'Graded Activity' protocol. A psychiatrist provides duloxetine or placebo and pain medication according to algorithms, and monitors pain and depressive symptoms. In condition c), the psychiatrist prescribes duloxetine without collaborative care. After 12 weeks, the patient is referred back to the general practitioner with a consultation letter, with information for further treatment of the patient.

Discussion: This study enables us to show the value of a closely monitored integrated treatment model above usual pharmacological treatment. Furthermore, a comparison with a placebo arm enables us to evaluate effectiveness of duloxetine in this population in a real-life setting. Also, this study will provide evidence-based treatments and tools for their implementation in practice. This will facilitate generalization and implementation of results of this study. Moreover, patients included in this study are screened for pain symptoms, differentiating between nociceptive and neuropathic pain. Therefore, pain relief can be thoroughly evaluated.

Trial registration: NTR1089

INTRODUCTION

Patients with major depressive disorder (MDD) and co-morbid chronic pain now have an elevated risk of not receiving optimal care [1-4]. The burden of co-morbid pain to depression is high for patients in terms of disability, wellbeing, and use of medical care [5]. Complex, integrated collaborative care including active pain management is perhaps better for this population than antidepressants alone, but there is limited evidence. Once such integrated care is available and effective, the added value of an antidepressant over placebo is also under debate. In this trial, we aim to evaluate to what extent depressive symptoms improve in patients with MDD with concomitant pain symptoms of both 6–12 weeks and ≥ 12 weeks duration [6]: a) with collaborative care versus an antidepressant alone, and b) with an antidepressant versus placebo within the collaborative care condition.

There is a strong correlation between pain and psychiatric distress reporting [7-11]. Physical symptoms, including several pain symptoms, increase the likelihood of a depressive disorder [12]. Also, many patients with pain symptoms experience a depression [5,13,14], and when the number of pain symptoms increases, the prevalence of depression increases as well [15,16]. Vice versa, when the severity of depression increases, so does the severity of pain complaints [10]. Furthermore, several studies indicate that pain symptoms are common in patients with MDD: the ARTIST trial reports a 69% rate of pain symptoms in primary care patients with depression [17]; in psychiatric clinics in Spain, almost 60% of patients with depression had pain complaints [18]; an international telephone survey in 18,980 patients with MDD showed that 43.4% presented themselves with chronic painful physical conditions [19], with headache, back pain, and limb pain being the most prevalent; the mean prevalence of pain was 65% in a meta-analysis of 14 studies [5], and a US telephone survey reported a 65.6% prevalence of chronic pain in depressed persons (N = 5808) [20]. Although a strong correlation has been found between depression and pain, it is not clear if depression causes pain [8], but it is suggested that pain could be a symptom of depression [5,9,21].

Moreover, depression and painful physical symptoms increase costs by increased utilization of healthcare services [5,22-24]. A 2.8 and 4-fold expenditure elevation is reported in depressed patients with back pain and migraine, respectively [25]. These costs are the so-called direct medical costs. But most costs of mental disorders in general, and depression specifically, are indirect costs, because of productivity loss and absenteeism: More than 70% of the total costs of depression consists of these indirect costs [26].

Therefore, good detection and diagnosis of comorbid conditions is necessary in the first place to be able to treat those conditions adequately [9,27]. In patients for whom psychiatric consultation was asked by a General Practitioner because of Medically Unexplained Symptoms including pain, up to 86% unrecognized depressive and anxiety disorders were found by the consulting psychiatrist [28,29]. Depression is high on the list of possible diagnoses if a patient presents with multiple unexplained physical symptoms including general aches and pains [5,30]. However, even in case of recognition, simple treatment of the depression is not sufficient. Physical symptoms including pain in MDD are associated with treatment resistance and predict a poorer response to treatment [1-4,31]. Greater risk of relapse, suicide, and substance abuse have been reported [32,33]. Residual symptoms in MDD predict relapse; patients with residual symptoms relapsed 3 times as fast compared to those who were asymptomatic at remission [34]. Among patients with residual symptoms, > 90% had mild-to-moderate physical symptoms including pain [32]. Improvement in painful physical symptoms is associated with higher remission rates in MDD [35]. In a study in newly referred neurologic outpatients, pain occurred in 10-55% of several diagnostic groups; and comorbid MDD occurred in 10-30%. Pain as well as MDD symptoms persisted over a period of 12 months, and the authors stated that for remission of both, interventions were needed specifically addressing pain symptoms as well as depressive symptoms [36].

Treatment of chronic pain in depressed patients has been addressed [33], with a focus on pain treatment. Particularly for patients with both depression and pain, flexible, integrated, multi-faceted [37], patient-tailored methods of treatment are needed, in combination with improvement of adherence, i.e. disease-management programs such as collaborative care (CC) [38-40]. Two recent meta-analyses have indeed shown the effectiveness of such collaborative

care approaches in primary care [41,42]. Little is also known about the added effect of an antidepressant such as duloxetine over placebo when collaborative care is available.

Collaborative care is successful in the treatment of depression, can vary in content and intensity [42] and combines various interventions for the treatment of disorders and includes active monitoring of symptoms, using questionnaires at each session with a professional. The contents of collaborative care consist of a diagnostic assessment of complaints, and contracting, to improve adherence. Also, a self-help manual, guided by a care-manager, can be part of collaborative care. This manual contains information about different symptoms and how to cope with them; the coping can be addressed in terms of emotional coping, cognitive coping and behavioural coping (e.g. tips for a healthy lifestyle which can decrease physical complaints; information on pleasurable activities which can be done with complaints) [43-46]. Next to this manual, a psychotherapy is offered in CC. Mostly, this is cognitive behavioural therapy or problem-solving treatment (PST), both effective in the treatment of depression [47]. Next to psychotherapy, medication can be an element of a collaborative care approach, guided by a psychiatrist. Several studies indicate that tricyclic antidepressants (TCAs) are effective in the treatment if pain and depression coexist, as well as selective serotonin and noradrenalin reuptake inhibitors (SNRIs) such as duloxetine [48] and venlafaxine, that have been shown to alleviate pain and depressive symptoms [49-52]. However, in a meta-analysis of Spielmans (2008) the analgesic effect of Duloxetine has been questioned [53], which calls for establishing the effect size for concomitant pain in depressed patients by duloxetine. In case of comorbid physical complaints, a physiotherapist can also be part of a collaborative care approach. Because treatment in CC is dependent on the process of symptom reduction, systematic monitoring of the complaints is an important part of CC. Furthermore, as a systematic review showed that psychiatric consultation to primary care with a consultation letter is effective for somatoform disorders [54], adding the use of such a consultation letter to CC can be useful. General practitioners (GP's) see treatment of complex comorbid conditions such as the comorbid condition under study as challenging and tend to refer these patients to either mental health care or pain specialists. Because GP's in general find treatment of this patient group difficult, the

benefits of a collaborative care approach may be substantial and a transmural collaborative care approach may be useful [38-42].

Recently, a trial explored efficacy of collaborative care for MDD and musculoskeletal pain [55] and another trial explored efficacy of collaborative care for chronic pain in the primary care setting [23], both with positive results, but in one study the collaborative intervention was more expensive than care as usual [56]. However, treatment of other chronic pain conditions in depressive patients has, so far, not received much attention. Also, cost effectiveness of an integrated approach of pain in depressed patients has not been studied yet.

DEFINITION OF (SUB)CHRONIC PAIN IN THIS TRIAL, AND THE WAY ITS TREATMENT IS ADDRESSED IN THE COLLABORATIVE CARE ARM

According to the international Association for the study of Pain (IASP), pain is an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage [57].

Most pain originate from an outside stimulus (heat or a sting), but may also result from injury to sensory fibres (or even from damage to the central nervous system itself), and follows an ascending pathway to the brain [58, 59]. Through nociceptors, a signal is transmitted via the peripheral nervous system to the dorsal horn in the spinal cord, and from there to the brain, where the perception of pain is constructed. The dorsal horn acts as a pathway for transmission of nociceptive information [58-60]. In the brain, the descending control systems are activated (possibly through the spinomesencephalic tract). Serotonin (5-HT) appears to play a significant role in the descending pathway of pain [60].

Serotonin, norepinephrine, substance p, glutamate, NMDA and gamma-aminobutyric acid (GABA) play a role in pain processing in rats and mice [61-65] and in humans [46,66]. Increasing the availability of norepinephrine and 5-HT may promote pain inhibition centrally [62]. At the central level, pain can be modulated by attention [67] and by mood [68]. In chronic pain the

relationship between trigger and pain is not clear anymore (or detected tissue damage cannot fully account for pain intensity) and the pain persists past the normal time of healing. Also, in chronic pain, gray matter degeneration occurs in the anterior cingulated cortex and prefrontal cortex as well as in the left parahippocampal cortex [69], brain areas that are also implicated in depressive disorder and that may diminish the ability of patients to learn [70,71], and thus to follow treatment properly. Furthermore, chronic pain is associated with sleep disturbances [72] and chronic stress causes dendritic regression and loss of dendritic spines in hippocampal neurons that is accompanied by deficits in synaptic plasticity and memory [73].

In this study, in the collaborative care treatment, specific attention is paid to the management of pain by proper pain medication and adherence to pain medication. For this purpose, the pain is classified as nociceptive pain or neuropathic pain by a questionnaire, the PAINDETECT [74] and treatment of pain will be applied based on which of these two sorts of pain a patient has. Nociception leads to pain, but the amount of pain experienced depends on integration in the cerebral rostral centers, the dorsal horn, and in the peripheral input. Neuropathic pain occurs without a damaging stimulus of outside and is associated with increased excitation and decreased inhibition of ascending pain pathways. Nociceptive pain may have a protective nature, at least in its acute form, but neuropathic pain is the result of nervous damage [75]. However, in case of chronic pain, fibre loss occurs in the spinal cord and in the peripheral nerve, due to chronic central inhibition [63,76-78]. In some cases, the pain can be mixed. An algorithm is used for administration of pain medication according to the classification.

Confusion exists in terminology in describing physical symptoms and pain associated with depression: They may be somatised symptoms of MDD, or so-called associated symptoms; Medically Unexplained Symptoms, that frequently occur together with MDD; Chronic painful physical conditions that are symptoms of a chronic illness, such as diabetic neuropathy; or chronic painful conditions resulting from centralisation of a formerly peripheral pain symptom.

In this trial, we aim to improve depressive symptoms of patients with MDD with concomitant sub-chronic or chronic pain symptoms of nociceptive, neuropathic, mixed or functional nature.

As discerning nociceptive pain from neuropathic pain may have therapeutic consequences in the treatment of (sub)chronic pain [74], we address both these issues in this RCT. We define sub-chronic pain as pain with 6–12 weeks duration, and chronic pain as pain of ≥ 12 weeks duration.

This Randomized Controlled Trial aims to evaluate effectiveness and cost effectiveness of this transmural collaborative care model with Consultation Letter (TCCCL) in patients with MDD and concomitant (sub)chronic pain.

MATERIALS AND METHODS

OBJECTIVES

The primary objective of this randomized placebo-controlled trial is to establish effectiveness on severity of depression (measured by Patient Health Questionnaire (PHQ-9)) of a closely monitored integrated intervention (TCCCL + duloxetine) for concomitant depression and (sub)chronic pain compared to either TCCCL + placebo and compared to Duloxetine alone.

Secondary objectives of this trial are to establish cost effectiveness in terms of Quality of Adjusted Life Years (QALY) as measured by EuroQol-5 and SF-36 and costs measured by TIC-P; and to establish improvement on pain in terms of Brief Pain inventory (BPI).

The study will evaluate the following hypothesis: Combined treatment (TCCCL + Duloxetine) is more effective than mono-treatment (either TCCCL + placebo or Duloxetine alone) in depressive symptom reduction on the PHQ-9 as main outcome for patients with MDD and (sub) chronic pain.

STUDY DESIGN

This study is a three-armed randomized multi-centre trial led by GGz Breburg, with three collaborating mental health institutions: GGz Breburg, Arkin, and GGz inGeest, who will all include 73 patients in order to have 3 × 63 completers for the study.

PARTICIPATING MENTAL HEALTH INSTITUTIONS

Three mental health institutions participate in this study. Patients will be treated at these institutions according to protocol. The participating mental health institutions are: GGz Breburg in Tilburg, GGZ inGeest in Amsterdam and Arkin/PuntP, also in Amsterdam.

RECRUITMENT OF CARE-MANAGERS AND PSYCHIATRISTS IN THE MENTAL HEALTH INSTITUTIONS

Care-managers and psychiatrists will be recruited at the three participating mental health institutions (GGz Breburg, Arkin, GGz inGeest) and form treatment teams for the trial. The care-managers are psychiatric nurses or psychologists who receive training in care management (including PST) to provide in the collaborative care interventions. The psychiatrists are trained in prescribing duloxetine and placebo medications as well as the pain medication according to the algorithm and in writing a consultation letter for the general practitioner and patient. Psychiatrists are blinded for the antidepressant medication (duloxetine/placebo), but not for the pain medication. Pain medication management will be provided by the psychiatrists in the duloxetine and placebo arm with collaborative care, but not in the treatment arm with duloxetine alone. In this study, care-managers and psychiatrists work according to a 'Case Registration Form' (CRF). In this CRF all the steps are described that a care-manager/psychiatrist has to do during an appointment with a patient.

RECRUITMENT OF PATIENTS

All the patients that are referred to the participating mental health institutions are screened for depressive symptoms and pain complaints. This study will focus on patients with a depressive disorder and (sub)chronic pain complaints. Sub chronic pain is defined as pain of ≥ 6 weeks and chronic pain is defined as pain with a duration of at least 12 weeks. Consecutive patients that present themselves at the special mental health outpatient clinic will be screened for MDD and concomitant pain of ≥ 6 weeks duration with a questionnaire.

This questionnaire will consist of the PHQ-9 [13] and the item on 'average pain' from the BPI [79], that will be used as a screener for respectively depressive disorder and (sub)chronic pain symptoms. Also, the patient will receive an informed consent form with information about the study. Patients are eligible for the study if they have a score of 10 or more on the PHQ-9 and a score of 3 or more on the 'average pain' item of the BPI. When a patient screens positive on the questionnaires mentioned above, the patient will receive a telephonic interview in which a MINI interview will be administered in order to clinically confirm the diagnosis MDD and to confirm that the patient suffers from (sub)chronic pain. In that case, he or she will receive additional information about the treatment part of the study and will be asked if he or she is willing to participate. When the patient is willing to participate, the patient is included in the study. A baseline questionnaire with second informed consent form, for the treatment part of the study, will be sent to the patient’s home address or made available on a secured website. After completion of the baseline questionnaire, the patient will be randomized in one of the three interventions.

TREATMENT ALLOCATION AND BLINDING

This is a placebo controlled double blind study for the medication part of the study, which means that the allocation of duloxetine/placebo in the collaborative care arm is blinded.

Patients visiting the three participating Mental Health Institutions will be randomly assigned to one of the three treatment groups. Collaborative care and Duloxetine alone will be administered in a non-blind fashion. Administration of medication within the collaborative care conditions will be double blind and placebo controlled. Outcome assessments will be performed by a blinded research assistant.

DEBLINDING

After 12 weeks, the placebo-controlled part of the study will end and the patient and physician will be deblinded for this part of the intervention. This deblinding procedure is described more detailed in the intervention.

EMERGENCY DEBLINDING

Emergency deblinding of the medication condition is performed by telephone to a research associate who is not involved in treatment procedures. This happens in case of serious adverse medical events. Subjects, who are deblinded before the end of the treatment procedures, will not be incorporated in the final analysis. In case of emergency deblinding or non-compliance, the code of medication (duloxetine or placebo) in the collaborative care groups will be broken. In case of duloxetine, the medication will be reduced and stopped according to protocol. All the remaining medication of this patient will be asked back and stored in a closed cabinet, separately from the rest of the study medication. In case of non-compliance, the patient will be excluded from this study and the final analysis.

PATIENT EXCLUSION CRITERIA

Patients with pain for which by diagnostic medical assessment a structural and continuing physical cause has been found in terms of tissue damage, illness or otherwise, that requires treatment, such as pain due to cancer or recent post traumatic pain, are excluded from the study and advised to seek such treatment. Other exclusion criteria are:

a. A PHQ-9 < 10 or a BPI score < 3
b. Alcohol use >3 units (1 unit = 1 glass of ≥0.25 l) a day or drug abuse or dependence in the last 6 months, defined as current use of any hard drugs (defined by Dutch law, e.g. XTC, cocaine, heroin, magic mushrooms) or cannabis, as evident from history or, in case of suspicion during clinical interview, from laboratory findings
c. Psychotic symptoms or use of antipsychotic medication that may influence perception of pain
d. Use of St John's wort (Hypericum Perforatum)
e. Pregnancy and breastfeeding
f. Inability to participate in case of too severe language barrier
g. Dementia
h. History of renal and liver dysfunction for which treatment is needed
i. Uncontrolled hypertension despite treatment for hypertension
j. Lastly, suicidal ideation is an exclusion criterion if this constitutes immediate danger and the need for crisis management according to the consulted psychiatrist. This will be measured with the suicidal ideation item of the PHQ-9. For this purpose, a suicide protocol is used in the study, defining degrees of suicide risk and prescribing necessary steps to be taken to advert such risk

EXCLUSION OF THE STUDY DURING THE INTERVENTION PHASE

Non-compliance is defined as not having used at least 80% of the prescribed medication (duloxetine/placebo) or no show on more than 20% of the appointments made with the psychiatrist or care-manager. The psychiatrist uses pill counts at every session to check if at least 80% of the pills have been used.

INTERVENTION

FIRST AND SECOND DESIGN ARM: DULOXETINE/PLACEBO PLUS COLLABORATIVE CARE

This intervention contains collaborative care, duloxetine or placebo, and pain medication according to an algorithm. Collaborative care will be provided within a multidisciplinary team comprising of a care-manager, psychiatrist and a physiotherapist. They all will apply treatment simultaneously according to protocol. Only patients in the collaborative care arms will receive treatment of all three specialists. The patients in the Duloxetine alone arm will only receive treatment of the psychiatrist.

The GP of the patient will be informed of the participating of the patient. Also, GP's in the same areas as the mental health institutions will receive information about the study and are asked to refer patients if they have the complaints under study. The interventions will be monitored every two weeks and when needed, the doses of medication can be raised according to the algorithm shown in Figures 1 and 2. The minimum duration of the interventions will be 12 weeks. The medication blinding code will be broken after 12 weeks. A maximum of 2 sessions will follow to end the treatment. After this, medication and follow up treatment will be handed over to the GP. In case of treatment response (50% reduction on the initial score), but non-remission, as indicated by a score of > 5 on the PHQ-9 after 12 weeks, the patient will be referred to the GP with subsequent antidepressant treatment and pain medication advice.

The detailed content of the collaborative care intervention is described below:

1. Diagnostic assessment of the nature of pain symptoms

The nature and the extent of the pain symptoms will be explored by the psychiatrist with the BPI and the painDETECT [74]. The 'average pain' item from the BPI will be used to assess the severity of the pain symptoms. To identify the pain symptoms as nociceptive and/or neuropathic, the painDETECT will be used. Because a patient can have both neuropathic pain and nociceptive pain at the same time, our pain medication protocol has been edited accordingly. Chronic pain may be a function of a chronic underlying pathology that appears within 4 to 6 weeks of an initial trauma; however, in accordance with the use of the terms chronic and sub-chronic pain in musculoskeletal pain or back pain, we apply the terms chronic and sub-chronic as follows: we define sub-chronic pain as pain with at least 6 weeks and less than 12 weeks duration, and chronic pain as pain of ≥ 12 weeks duration [6].

2. Contracting

During the initial visit, the care-manager informs the patient about the depressive disorder and pain symptoms, and their association. The treatment plan is then jointly formulated by the psychiatrist, the care-manager and the patient.

3. Pain medication protocol

In this study, pain is divided in nociceptive pain and neuropathic pain and treatment of pain will be applied based on which of these two sorts of pain a patient has. Classification as nociceptive pain, neuropathic pain or mixed pain will be done with the PainDETECT questionnaire that was specifically validated for this purpose [74].

In all instances, patients are urged to take the medication at pre-set intervals, to medicate properly so as to prevent serious pain. In all instances, duloxetine (or placebo) is prescribed as adjuvant.

The psychiatrist will use the painDETECT questionnaire to identify the pain as nociceptive or neuropathic. When it is not clear in which of these two categories the pain belongs, both the algorithms for nociceptive and for neuropathic pain are followed. The algorithm for nociceptive pain, is adapted and changed from the WHO pain ladder [80]. It is updated for the use of selective Coxinhibitors, the role of so-called adjuvants is more prominent here; the role of opioids is much less prominent, but the principle of adding medication that is common in the WHO pain ladder, is maintained. This algorithm has been developed by the research group and was tested for feasibility in patients with mental disorder in a pilot of this trial. Figure 1 shows a graphical version of above mentioned algorithm.

When, after 12 weeks, the patient is referred to the GP, the GP is advised, through a Consultation Letter, to continue the medication for a duration of 6 months, as is advised in the 'NHG standard – depression' [81], a guideline for general practitioners. The GP will monitor pain symptoms with the BPI during a consult, every 6 weeks.

4. Manual guided self-help for behavioural techniques aimed at improving coping with pain

During the treatment, the patient works through a self-help manual, guided by the care-manager. The manual is based on several existing self-help books [43-46]. This self-help book contains information about depression and pain symptoms and their interaction, antidepressant medication, relaxation techniques and a diary for pain complaints. Every chapter contains exercises for the patients to perform. The care-manager informs the patient about the content of the manual, reinforces achievements and motivates the patient to continue. In the present study, the self-help manual is part of a complete intervention package and is therefore meant as additional to the other components of the intervention.

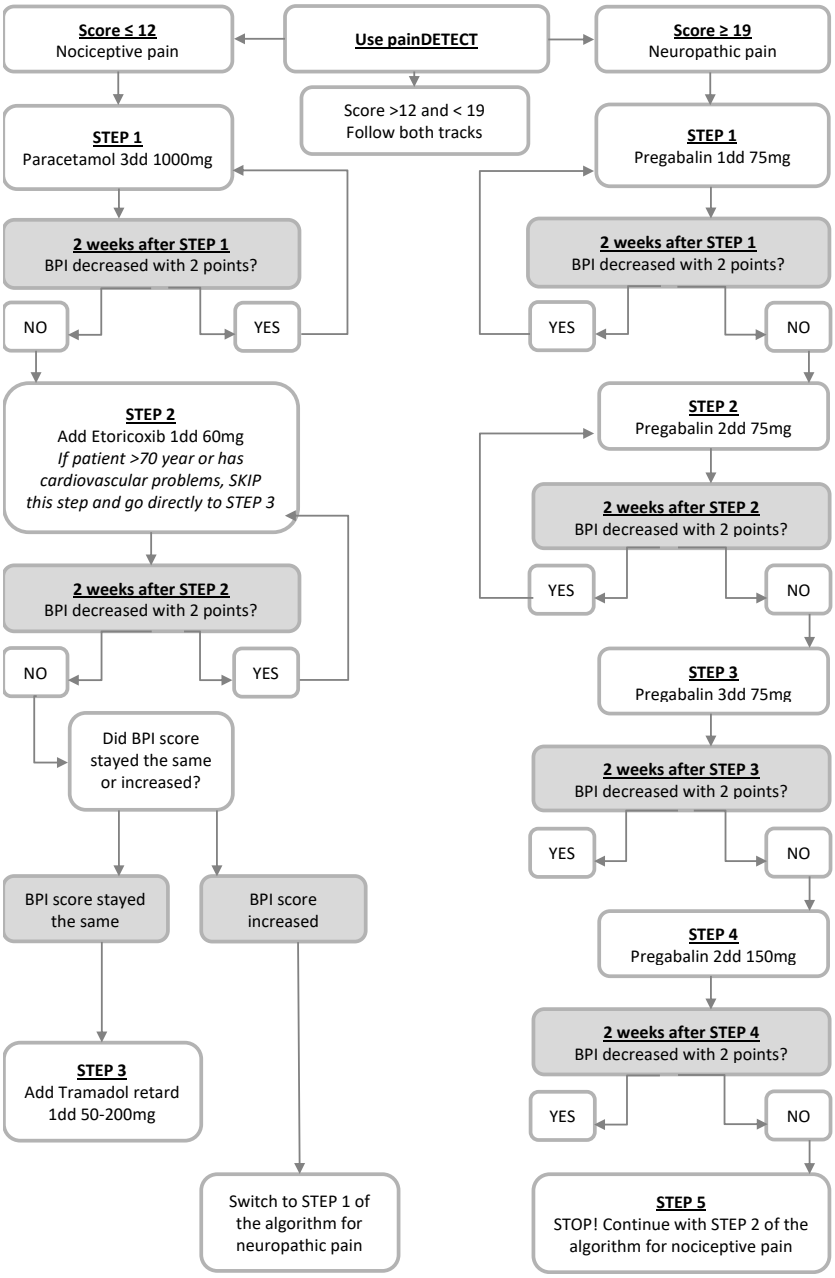


FIGURE 1. PAIN MEDICATION ALGORITHM FOR NOCICEPTIVE PAIN (LEFT TRACK), NEUROPATHIC PAIN (RIGHT TRACK) AND MIXED PAIN (BOTH TRACKS)

5. Problem Solving Treatment

Problem Solving Treatment (PST) is a brief, structured psychological intervention, guided by the care-manager, that has been shown to be effective in the management of depressive disorders and stress related disorders [82]. The problem-solving approach consists of 7 stages and is based on the common observation that emotional symptoms are often associated with problems in daily life and it encourages patients to formulate practical ways of dealing with such problems. The goal of PST is to teach patients to use their own skills and resources to function better [82,83], thus improving coping skills.

6. Antidepressant medication

In the two collaborative care conditions, patients will either receive duloxetine or placebo in a double-blind fashion. The psychiatrist will monitor medication use according to protocol. In case of any adverse effects, an adverse effects protocol is followed. The pharmacists check for possible interactions of the antidepressant medication with other medication use of the patient and instructs the doctors providing treatment accordingly.

Patients will start with a dose of 30 mg once daily in the first two weeks and 60 mg once daily from the third week. From this point the PHQ-9 will be used to measure the severity of depressive symptoms. Based on the score on the PHQ-9, the dose will be raised (when the score did not decrease; with a maximum of 90 mg) or stay the same (when the score on the PHQ-9 has decreased with 5 or more points or the score on the PHQ-9 is 5 or lower). This use of the PHQ9 for monitoring was used as well in other collaborative care studies in the Netherlands, with a focus on depression [84-87]. By using the PHQ9, comparisons can also be made with these studies. After 12 weeks, the randomization code will be broken and medication will be prescribed if necessary in a standard continuation phase of at least six months. Pharmacotherapy will be gradually discontinued according to protocol and/or clinicians' judgment. When the patient is referred to the GP, the GP is advised, through a Consultation Letter, to continue duloxetine for the duration of 6 months. After this period, if possible, the GP reduces and stops the use of duloxetine in a period of 4 weeks. In case of placebo, the GP is advised to only prescribe

medication when the patient still has depressive symptoms. Figure 2 shows the graphical version of the abovementioned algorithm.

7. Monitoring treatment outcome and motivational techniques aimed at improving adherence

Patient adherence will be improved by contracting and psycho-education and by frequent follow-up appointments in which both adherence and progress will be evaluated. Provider adherence will be improved by instructions from the researchers. Treatment outcome is monitored with a variety of questionnaires (see section 'Outcome parameters').

8. Referral to the physiotherapist by the care-manager according to a protocol

Next to manual guided self-help, Problem Solving Treatment and medication, patients receive physiotherapy. The physiotherapist will treat patients according to the protocol of 'graded activity'. This treatment consists of information of physical and psychological processes and how these can be intertwined. The next step is to formulate reasonable goals on what to achieve with this therapy. According to these goals, intermediate steps are formulated that have to take into account the amount of time that is predetermined. The physiotherapist stimulates the patients with positive feedback. Also, the therapist works on a structured time schedule to optimize the course towards the determined goals. Next to the exercises, the therapist pays attention to the progress of the patients. This will be illustrated by graphs and when positive, these serve as a possible positive reinforcer and can motivate the patient. The patients also conduct the exercises at home, so these exercises generalize to situations the patients live in. In this, the patients are stimulated by their physiotherapist.

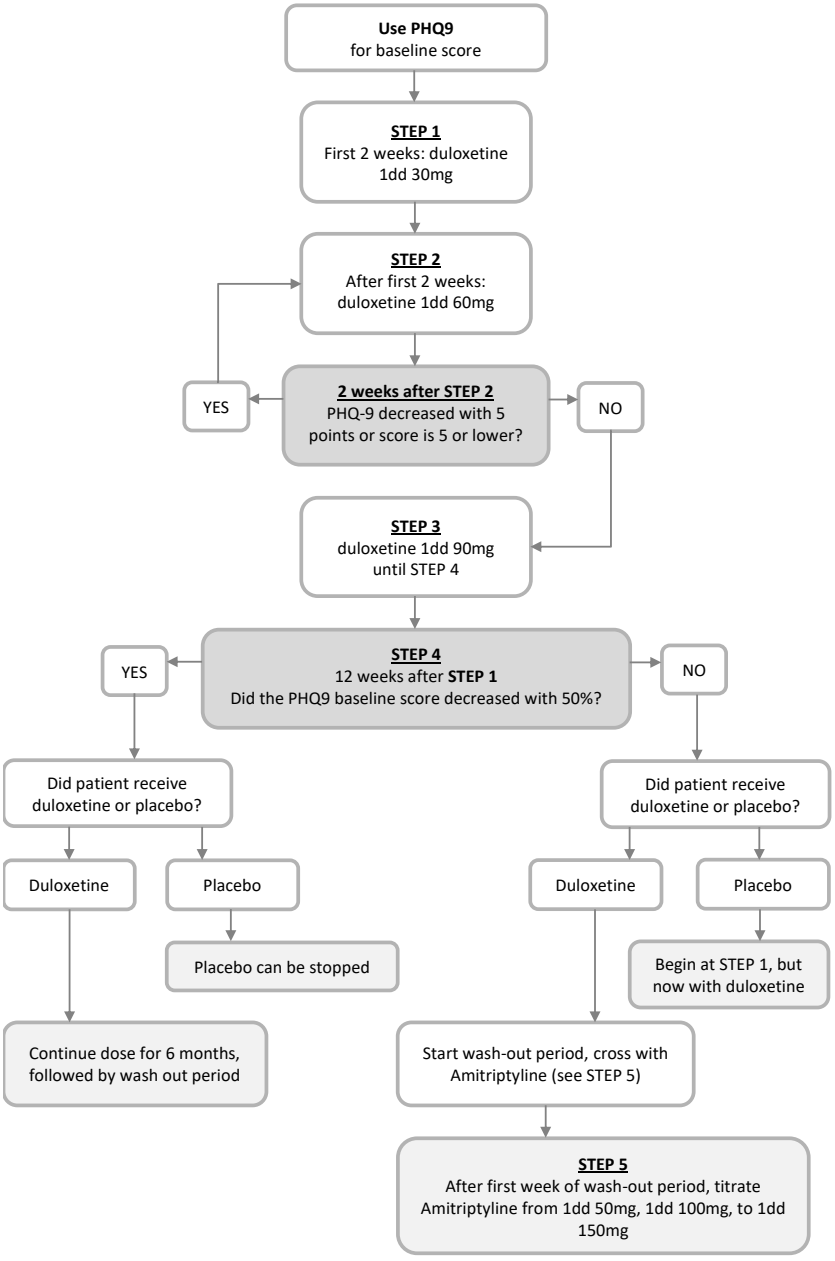


FIGURE 2. ALGORITHM FOR DULOXETINE

9. Consultation Letter

The consultation letter is written by the psychiatrist and is meant for the GP and the patient. In this letter, the symptoms of the patient are described (somatic and psychological). This letter will also contain the treatment the patient has received in this study, as well as if the patient improved or not. The expected course of the complaints will be described, and with this an advice is given how to continue treatment of the patient by the GP. An advice is given for continuing medication (antidepressants and pain medication), the number of regularly scheduled consults with the patient every 6 weeks as check-up, to perform only physical examination if the patient presents the same symptoms again, and refrain from repeated lab or diagnostic procedures as well as to avoid hospitalization, as long as the patient does not deteriorate or presents with new symptoms. Also, the GP can consult the psychiatrist if needed. This consultation letter is sent 3 months after start of treatment, when the patient is referred to the GP.

THIRD DESIGN ARM: DULOXETINE ALONE

In the Duloxetine alone condition, patients will receive duloxetine according to the algorithm as described in Figure 2. No other components, i.e. PST, manual guided self-help, pain medication, physiotherapy, and a consultation letter, of collaborative care will be given here. Patients in this condition will oly be prescribed Duloxetine by a psychiatrist.

MEASURES

Measurement will take place at baseline (T0), and three, six, nine and twelve months after baseline, respectively T1, T2, T3 and T4.

DEPRESSIVE SYMPTOMS

Primary parameter used to substantiate the study hypothesis will be severity of depression (PHQ-9) [13]. The severity of depressive symptoms is measured with the Patient Health Questionnaire depression sub-scale [13], a brief but validated instrument that scores each of the DSM-IV criteria for major depressive disorder. Response is defined as a 50% reduction in symptoms [13, 39, 88]. Remission is defined as < 5 points on the PHQ-9 [88].

PAIN SYMPTOMS

Secondary parameter will be the severity of pain symptoms as measured with the total BPI. The BPI has been validated for chronic non-malignant pain [79]. The localization of pain and pain being nociceptive, neuropathic or mixed of nature is assessed at the beginning of the treatment by use of the PAINDETECT questionnaire [74].

COST-EFFECTIVENESS

In addition to the improvement in the severity of symptoms, the cost utility of the three conditions will be compared to each other. To evaluate the cost utility of each condition, the difference in direct medical costs per patient receiving collaborative care and duloxetine, collaborative care and placebo, or Duloxetine alone is related to the difference in terms of Quality Adjusted Life Years (QALY) gained. This will yield a cost per QALY estimate. These data will be collected with the Trimbos/iMTA questionnaire for Costs associated with Psychiatric Illness (TiC-P), a measure commonly applied in economic evaluations of treatment in mental care [89,90].

The TiC-P measures direct costs of medical treatment such as the number of contacts with the general practitioner and multiple other care providers (e.g. paramedics and medical specialists) during the last three months. Medication use is measured during the last four weeks. Also, the TiC-P includes a short form of the Health and Labor questionnaire (HLQ) for collecting data on productivity losses [91], the SF-HLQ. It measures productivity loss by collecting data on absence from work, reduced efficiency at work and difficulties with job performance [92].

The EuroQoL (EQ-5D) [93] and the Short Form-36 (SF-36) [94] will be used to assess quality of life. Both are validated instruments for the measurement of general health-related quality of life. The EQ-5D measures quality of life on five dimensions, namely mobility, self-care, usual activities, pain/discomfort and anxiety depression.

ADDITIONAL MEASURES

Confusion exists in terminology in describing physical symptoms and pain associated with depression [5,95]: They may be somatised symptoms of MDD, or so-called associated symptoms [96]; Medically Unexplained Symptoms, that frequently occur together with MDD [97]; chronic painful physical conditions that are symptoms of a chronic illness, such as diabetic neuropathy; or chronic painful conditions resulting from centralisation of a formerly peripheral pain symptom [63]. In this study, we use the psychiatrist's professional view on whether what kind of physical symptoms a patient has. Comorbid mental disorders will be assessed with the PHQ and GAD7 [98]. Hypochondriac tendencies will be measured using the Whitely Index [99]. The Patient-Doctor Relationship Questionnaire (PDRQ-9) [100] will be used to measure the patient doctor relationship from the perspective of the patient. Physical symptoms are measured by the Physical Symptoms Questionnaire (LKV: Lichamelijke Klachten Vragenlijst) [101]. The Morisky Medication Adherence Scale (MMAS) [102] will be used to measure pain medication adherence. The questionnaire TiC-P (‘vragenlijst voor zorggebruik en productieverliezen bij psychische aandoeningen') [89] will be used to assess provided health care. To measure coping in stressful situations, the 'Coping Inventory for Stressful Situations (CISS) [103], Dutch version, will be used.

To measure the tendency to overload, the 'Tendency to Overload Questionnaire' (TOQ) short form will be used [in press].

CONTROLLING VARIABLES

The following demographic variables are measured at baseline and will be taken into account as possible effect modifiers: age, gender, nationality and ethnicity, marital status, living conditions, education and work status. Also, pain classification (neuropathic, nociceptive, subchronic, chronic) will be taken as effect modifier. Moreover, existing somatic comorbidity will be taken as effect modifier. Co-morbid chronic medical illness will be measured with the Dutch Central Bureau for Statistics list (CBS list). The list contains 28 chronic conditions (e.g. diabetes and MS).

SAMPLE SIZE

In a former RCT on collaborative care performed in the primary care setting, the effect size of a collaborative care intervention versus no such intervention as measured by PHQ-9 was 4.64/7.6 = 0.6 (the SD on the endpoint PHQ-9 varied between 7.0 and 8.3) [104]. In this study, we compare collaborative care plus duloxetine and collaborative care plus placebo versus the monotherapy duloxetine alone, and we compare collaborative care plus duloxetine versus collaborative care plus placebo. To have a minimum power of 80% to detect a standardized difference of 0.5 a minimum of 63 patients per arm is needed, that is 189 completers. In order to anticipate for possible loss to follow up of 20%, 3 × 79 (237) patients will be included [105].

ANALYSES

Apart from patients that will have to be excluded because of noncompliance as described above, or patients who had to undergo emergency deblinding due to serious medical adverse events, intention to treat analysis will be performed. Multi-Level Analysis will be performed which will allow us to correct for variance associated with the different sites in this Multisite RCT. Effect sizes will be estimated in terms of Cohen's d and regression analysis will be performed. Possible confounders such as age, gender, immigrant status, level of education, history of treatment and life events will be included as covariates in the analysis. An independent Helmert analysis will be performed with the following contrasts: Duloxetine alone versus TCCCL + duloxetine and TCCCL + placebo; and then TCCCL + duloxetine versus TCCCL plus placebo.

To assess the cost effectiveness, we will apply a cost-utility analysis. The results will be expressed as cost per QALY. The economic evaluation will be undertaken from a societal perspective. Hence, all relevant effects and costs due to resource utilisation within the healthcare (direct medical costs) and costs due to production losses (productivity costs) will be included.

CONTROLLING VARIABLES IN ANALYSES

As possible effect modifiers, co morbid mental health disorders as measured with the PHQ (e.g. anxiety) will be taken into account. Another parameter will be the severity of hypochondriac tendencies (WI) as a possible effect modifier [99]. The CBS list 'chronic diseases', developed by the Dutch Central Bureau of Statistics, will be used to evaluate physical co morbidity that may cause pain (e.g. Diabetes, Multiple Sclerosis). Process measures will be compliance and adherence to treatment, measured by the self-report questionnaire Morisky Medication Adherence Scale (MMAS) [102] and the patient-doctor relationship as measured by the PDRQ-9 [100], as well as assessment of the care provided in both conditions [89]; this includes care the patients have received up to a year before they fill in the baseline questionnaire.

TIMEFRAME OF THE STUDY

The goal is to enrol 219 patients to obtain 189 patients that will complete the study. The preparatory period is approximately 6 months. Care-managers will be recruited subsequent to the approval of the Medical Ethical Board and the care-managers will be trained. The inclusion and intervention period will be 24 months. The follow-up phase will last 12 months. Data analysis will take 6 months. The entire study period is 4 years.

ETHICAL PRINCIPLES

This study will be conducted in accordance with the code of ethics that has been established by the declaration of Helsinki (1964) and amended in Edinburgh (2000). Subjects will be informed of all procedures and asked for written informed consent. The patients will be informed that they can withdraw their consent to participate at any time without specification of reasons and without negative consequences regarding future medical treatment. A medical adverse events protocol is established. Every session with the psychiatrist side-effects, that may have occurred since the last session, will be measured with the Dutch translation of the Antidepressant Side-Effects Checklist (ASEC-21) [106]. When the patient has a serious side-effect not mentioned on the ASEC-21, an adverse medical events protocol will be followed, involving emergency deblinding.

The study has been approved by the Medical Ethics Committee of the VU Medical Centre (reference number: 08072).

DISSEMINATION OF RESULTS

This study will establish cost effectiveness of TCCCL and then make the following products available for long term implementation:

a. Training module of psychiatrists and psychiatric nurses working in a specialty mental health outpatient clinic to perform TCCCL integrated depression and pain treatment, and to refer the patient back to the GP with a CL letter within 3 months
b. Format of a Consultation Letter to the GP
c. Algorithm for psychiatrists about how to monitor and improve the pain medication of the patient according to a protocol
d. A self-management manual for patients including activation and relaxation techniques
e. A practical protocol for duloxetine use in patients with depression and pain

CONCLUSIONS

This paper describes the study protocol of a multi-center randomized controlled trial evaluating collaborative care, antidepressant medication and pain medication in the treatment of depressive disorders with (sub)chronic pain. The aim of this study is to compare three treatments in terms of (cost)effectiveness.

STRENGTHS AND LIMITATIONS

A strength of this study is that the three-arm design enables us to show the value of a closely monitored integrated treatment model above usual pharmacological treatment. Another strength of the study is that the comparison with a placebo arm enables us to evaluate effectiveness of duloxetine in this population in a real-life setting. Also, a strong aspect of this design is that this will provide evidence-based treatments and tools for their implementation in practice. This will facilitate generalization and implementation of results of this study.

Furthermore, patients included in this study are screened for pain symptoms, differentiating between nociceptive and neuropathic pain, unlike the studies of Goldstein et al. [107]. Therefore, pain relief can be thoroughly evaluated. Another strength of the study is the structured implementation of a transmural model, aimed at better collaboration between GP and specialty mental health clinic in complex patients with depression and concomitant (sub)chronic pain.

A limitation of the study is that, with this study design, we will not be able to make inferences about the effectiveness of the respective ingredients of the collaborative care model (such as PST or the self-help manual).

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CHAPTER 7

REPORT OF THE PREMATURELY TERMINATED CC:PAINDIP STUDY

"We don't even ask happiness, just a little less pain"

Charles Bukowski

(1920-1994)

This chapter is based on:

Heer EW de, Dekker J, Beekman ATF, Marwijk HWJ van, Holwerda TJ, Bet PM, Roth J, Feltz-Cornelis CM van der. Report for Medical committee Eli Lilly, date: November 2015.

OVERVIEW OF STUDY METHODOLOGY

STUDY DESIGN

This study was a three-armed randomized Multi Centre trial, with three collaborating mental health institutions: GGz Breburg, Arkin, and GGz inGeest. The design is described extensively elsewhere, and is summarized here.

TREATMENT ALLOCATION AND BLINDING

This was a placebo controlled double blind study for the medication part of the study, which means that the allocation of duloxetine/placebo in the collaborative care arm was blinded. Patients visiting the three participating Mental Health Institutions were randomly assigned to one of the three treatment groups. Collaborative care and Duloxetine alone were administered in a non-blind fashion. Administration of medication within the collaborative care conditions was double blind and placebo controlled. Outcome assessments were performed by a blinded research assistant.

DEBLINDING

After 12 weeks, the placebo-controlled part of the study was ended and the patient and physician were deblinded for this part of the intervention. This deblinding procedure is described more detailed in the 'intervention' section.

INTERVENTION

FIRST AND SECOND DESIGN ARM: DULOXETINE/PLACEBO PLUS COLLABORATIVE CARE

This intervention contained collaborative care, duloxetine or placebo, and pain medication according to an algorithm. Collaborative care was provided within a multidisciplinary team comprising of a care-manager, psychiatrist and a physiotherapist. They all applied treatment simultaneously according to protocol. Only patients in the collaborative care arms received treatment of all three specialists. The GP of the patient was informed of the participating of the patient. Also, GP's in the same areas as the mental health institutions received information about the study and were asked to refer patients if they had the symptoms under study. The interventions were monitored every two weeks and when needed, the dose of medication was raised according to an algorithm. The minimum duration of the interventions was 12 weeks. The medication blinding code was broken after 12 weeks. After this, medication and follow up treatment were handed over to the GP. In case of treatment response (50% reduction on the initial score), but non-remission, as indicated by a score of > 5 on the PHQ-9 after 12 weeks, the patient was referred to the GP with subsequent antidepressant treatment and pain medication advice. If after 12 weeks (when the medication code was broken) no treatment response had occurred on severity of depressive symptoms, as indicated as less improvement than 50% on the initial PHQ-9 score, the patient would not be referred to the GP, but would be referred to further specialized mental health care.

THIRD DESIGN ARM: DULOXETINE ALONE

In the Duloxetine alone condition, patients received duloxetine according to an algorithm. No other components, i.e. PST, manual guided self-help, pain medication, and physiotherapy of collaborative care were given here. Patients in this condition were only prescribed Duloxetine by a psychiatrist.

DATA COLLECTION

Measurement took place at baseline (T0), and three, six, nine and twelve months after baseline, respectively T1, T2, T3 and T4

MEASURES

DEPRESSIVE SYMPTOMS

Primary parameter, used to substantiate the study hypothesis, was severity of depression as assessed by the Patient Health Questionnaire depression scale (PHQ9), a brief but validated instrument that scores each of the DSM-IV criteria for major depressive disorder. Response was defined as a 50% reduction in symptom. Remission was defined as < 5 points on the PHQ-9.

PAIN SYMPTOMS

Secondary parameter was the severity of pain symptoms as measured with the total Brief Pain Inventory (BPI). The BPI has been validated for chronic non-malignant pain.

REASONS OF THE PREMATURELY TERMINATED STUDY

The study was well performed and well documented. There were no serious adverse events. In the first stage of the study, enrolment went well and interventions were delivered appropriately. However, from 2012, due to several developments, the enrolment was severely hampered. The main reason why this study is prematurely terminated is therefore the disappointing enrolment. In a 2-year period, only 60 patients were included in the study. The objective of this study was to enrol at least 189 patients. With 30 enrolments a year, this would take another 4-5 years to reach the objective. This was not deemed feasible.

FACTORS HAMPERING THIS STUDY

There are several causes for the disappointing enrolment. In the first stage of the study, enrolment of patients went well and providing the interventions proved feasible. However, surrounding the start of the study, in the Netherlands a series of unprecedented changes in the organization and financial reimbursement of mental health care were introduced.

First, recent budget cuts of the government and health insurance companies on mental health care caused reorganizations at two of the three sites that made further inclusion of patients impossible.

Second, health insurance companies no longer reimbursed treatment automatically, but started restrictive and complex reimbursement policies, aimed at reducing costs and length of care. This caused the reorganizations of two of the three sites, which did lead to inclusion stops at those two sites. Multiple attempts to include more sites for this study failed, as those possible sites too were confronted with the cuts of the government and health insurance companies.

Third, the transition to 'Basic mental health care' and 'Specialized mental health care' did lead to less referrals of eligible patients through the sites. GP's were incentivized to change their referral policies, further reducing the patients in specialized mental health care.

Fourth, in 2012, health insurance companies started a new policy in which patients, who received care in a mental health institution, had to pay an extra contribution on top of the 'normal' costs of the insurance. Consequently, less patients wanted to receive care in mental health, and, therefore, less patients could be selected for possible inclusion in this study. Later, this became a general measure for all health care.

Fifth, the health insurance companies would not compensate for physical therapy anymore, which made referrals to a physical therapist more difficult for patients who did not have a supplementary insurance that covers this kind of care.

Sixth, reimbursement of travel costs was stopped by the insurance companies, thus making it hard for patients with low incomes to visit the institution for treatment.

All the above-mentioned developments in mental health care made it difficult for this study to complete enrolments as envisioned.

OVERVIEW OF STUDY POPULATION

Figure 1 shows the number of included and excluded patients, with reasons of exclusion and reasons why patients did not continue treatment

As can be seen in Figure 1, the randomization was equally divided among the three research conditions. The Collaborative Care + duloxetine condition includes the most patients that prematurely stopped the intervention (76% of the total patients in this condition), followed by Collaborative Care + placebo (55%) and Duloxetine alone (42%). To be accounted for as a completed intervention, a T1 measurement needed to be completed. The duloxetine alone condition is the only condition in which more patients completed the intervention than patients that prematurely stopped the intervention. Those who completed the intervention could, however, have missed three or more sessions, which would make them non-compliant. A total of 10 patients (17%) had not completed any PHQ9 or BPI questionnaire during the treatment sessions. Reasons why patients prematurely stopped the intervention are also shown in Figure 1.

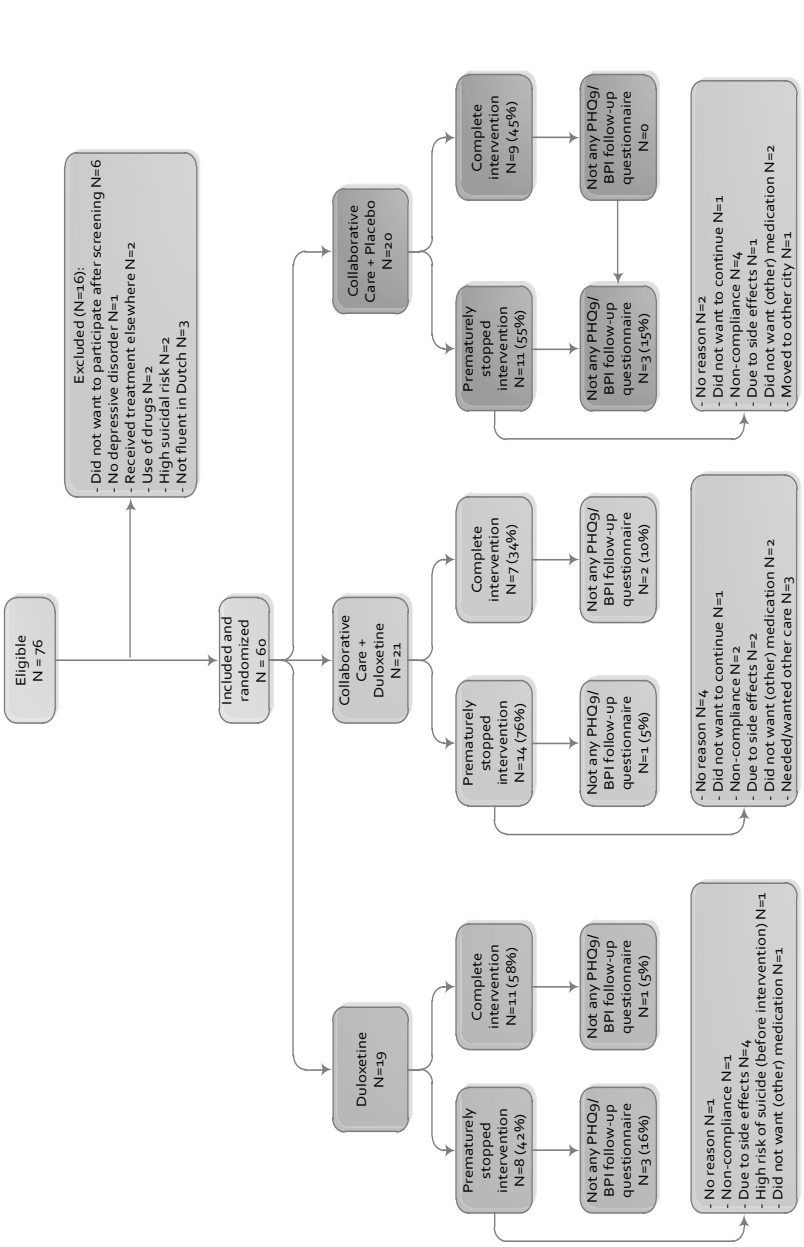

FIGURE 1. OVERVIEW OF INCLUSIONS, PREMATURELY STOPPED, AND COMPLETE INTERVENTION, DIVIDED IN THREE RESEARCH CONDITIONS

Table 1 shows the baseline characteristics of the PAINDIP patients. The PAINDIP cohort consisted of more women than men (57% over 43%), with a mean age of just over 42. Most patients had an intermediate level of education and were employed. The mean score on the PHQ-9 was 17.95 (moderately severe symptoms), with a range of 10-27. The mean score on the BPI was 6.75, with a range of 4-10. This indicates that the patients that were enrolled did indeed suffer from the symptomatology as intended in the design of the study.

TABLE 1. BASELINE CHARACTERISTICS

Characteristics		
Demographics		
Female gender, N (%)	36	(60)
Age in years, Mean (SD)	43,2	(12.4)
Level of education, N (%)		
Basic	17	(28,3)
Intermediate	26	(43,4)
High	17	(28,3)
Dutch nationality, N (%)	53	(88,3)
Work status, N (%)		
Employed	19	(31,7)
Housewife	3	(5,0)
Pension	3	(5,0)
Sick leave	16	(26,7)
Unemployed	17	(28,3)
Other	2	(3,3)
Symptoms		
Depression (PHQ-9 (range 0-27)), Mean (SD)	17,5	4,3
Pain (BPI average pain (range 0-10)), Mean (SD)	6,9	1,7

Abbreviations: SD = standard deviation; PHQ = Patient Health Questionnaire; BPI = Brief Pain Inventory

SAFETY INFORMATION

No (serious) adverse events were reported. Adverse effects of the medication did occur however, but these were expected side effects, such as headache, dry mouth, etc. These are shown in Table 2. The ASEC-21, a self-report questionnaire, was used to check which side effects patients experienced, due to the use of an antidepressant. This questionnaire specifically asks for the presence of patient-perceived side effects. These side effects are all known side effects of duloxetine, as mentioned by the European Medicines Agency (EMA). This indicates that safety was not an issue in the trial.

TABLE 2. NUMBER OF PATIENTS WHO REPORTED SIDE EFFECTS MEASURED WITH THE ASEC-21

Symptom	**Total sample (n=60)**		**Duloxetine (n=19)**		**CC+duloxetine (n=21)**		**CC+placebo (n=20)**	
	N	%	N	%	N	%	N	%
Drowsiness	28	(47%)	9	(47%)	11	(52%)	8	(40%)
Dry mouth	27	(45%)	8	(42%)	12	(57%)	7	(35%)
Nausea or vomiting	27	(45%)	9	(47%)	13	(62%)	5	(25%)
Feeling light-headed on standing	27	(45%)	6	(32%)	13	(62%)	8	(40%)
Insomnia	26	(43%)	6	(32%)	11	(52%)	9	(45%)
Headache	25	(42%)	10	(53%)	9	(43%)	6	(30%)
Sweating	23	(38%)	9	(47%)	7	(33%)	7	(35%)
Yawning	18	(30%)	7	(37%)	8	(38%)	3	(15%)
Decreased appetite	17	(28%)	5	(26%)	7	(33%)	5	(25%)
Tremor	15	(25%)	3	(16%)	7	(33%)	5	(25%)
Blurred vision	14	(23%)	3	(16%)	7	(33%)	4	(20%)
Feeling like the room is spinning	13	(22%)	1	(5%)	8	(38%)	4	(20%)
Weight gain	13	(22%)	3	(16%)	7	(33%)	3	(15%)
Constipation	12	(20%)	5	(26%)	5	(24%)	2	(10%)
Problems with sexual function	10	(17%)	4	(21%)	6	(29%)	0	(0%)
Diarrhoea	9	(15%)	1	(5%)	3	(14%)	5	(25%)
Increased appetite	9	(15%)	3	(16%)	5	(24%)	1	(5%)
Palpitations	9	(15%)	2	(11%)	6	(29%)	1	(5%)
Disorientation	8	(13%)	2	(11%)	5	(24%)	1	(5%)
Problems with urination	7	(12%)	3	(16%)	3	(14%)	1	(5%)
Increased body temperature	3	(5%)	0	(0%)	0	(0%)	3	(15%)
Average number of persons reporting side effects	16		6		7		4	

Abbreviations: CC = Collaborative Care

CONCLUSION

This study was a three-armed randomized Multi Centre trial, with three collaborating mental health institutions: GGz Breburg, Arkin, and GGz inGeest. The study was well performed and well documented. There were no serious adverse events. The main reason why this study is prematurely terminated is the disappointing enrollment, mostly due to changes in regulation and reimbursement policy of health insurance companies and government. This made it hard for patients to visit the Specialty Mental Health Institutions and follow the treatment as envisioned.

In all research conditions, the number of patients that prematurely stopped the intervention was high (42%-76%). However, total loss to follow-up on primary outcome (not any PHQ9 and/or BPI follow-up questionnaire) was only 17%. The Collaborative Care conditions showed the highest number of patients that prematurely stopped the intervention.

CHAPTER 8

TREATMENT OF DEPRESSIVE DISORDER AND PAIN: RESULTS OF THE CC:PAINDIP STUDY

"There is no coming to consciousness without pain"

C.G. Jung

(1875-1961)

This chapter is based on:

Heer EW de, Dekker J, Beekman ATF, Marwijk HWJ van, Holwerda TJ, Bet PM, Roth J, Timmermans L, Feltz-Cornelis CM van der. Comparative effect of collaborative care, pain medication, and duloxetine in the treatment of Major Depressive Disorder (MDD) and comorbid (sub)chronic pain: results of a randomized, placebo-controlled, multicenter trial (CC:PAINDIP). Accepted for publication in 'Frontiers in Psychiatry'

ABSTRACT

Background: Evidence exists for efficacy of collaborative care (CC) for major depression (MDD), for efficacy of consequent use of pain medication against pain, and for efficacy of duloxetine against both MDD and neuropathic pain. Their relative effectiveness in comorbid MDD and pain has never been established so far. This study evaluates the effectiveness of CC with pain medication and duloxetine, and CC with pain medication and placebo, compared to duloxetine alone, on depressive and pain symptoms.

Materials and Methods: Three-armed, randomized, multicentre, placebo-controlled trials in consecutive patients were presented at three specialized mental health outpatient clinics with patients who screened positive for MDD. Interventions lasted 12 weeks. Pain medication was administered according to an algorithm that avoids opiate prescription as much as possible, where paracetamol, COX inhibitors, and pregabalin are offered as steps before opiates are considered. Patients who did not show up for three or more sessions were registered as non-compliant. Explorative, intention-to-treat and per protocol, multilevel regression analyses were performed. The trial is listed in the trial registration.

Results: This study was prematurely terminated because of massive reorganizations and reimbursement changes in mental health care in the Netherlands during the study period. Nevertheless, 60 patients completed the study. Patients in all treatment groups reported significantly less depressive and pain symptoms after 12 weeks. CC with placebo condition showed the fastest decrease in depressive symptoms compared to the duloxetine alone group (b = -.78; 95% CI = -1.33--.22; *p* = .01). Non-compliant patients did not improve over the 12-week period. Pain outcomes did not differ between the three groups.

Conclusions: In MDD and pain, patient's compliance and placebo effects are more important in attaining effect than choice of one of the three treatments. Active pain management in CC with COX inhibitors and Pregabalin as alternatives to Tramadol or other opiates might provide an attractive alternative to the current WHO pain ladder as it avoids opiate prescription as much as

possible. The study was sufficiently powered to show an exploratory result, but the generalizability is limited due to the small sample size. Larger studies are needed.

INTRODUCTION

Pain is common among depressive patients [1-4], with comorbidity rates amounting to two thirds (5). A depressive disorder is a risk factor for developing low back pain [6,7], neck pain [6] and joint pain [8]. The burden of depression with comorbid pain increases the likelihood of disability to work and unemployment, decreases wellbeing [9,10] and doubles health care costs compared to patients with pain without depression [10]. This comorbidity is associated with treatment resistance and poor response to treatment when only the depressive symptoms are treated [11-13]. Therefore, it is evident that treatment needs to address both depression and pain.

One option for a dual and integrated treatment approach that addresses both depression and pain is collaborative care, which is effective in the treatment of depression [14-17] and pain [18]. Collaborative care is a framework for multifaceted care, including psychological as well as pharmacological interventions and interdisciplinary collaboration of health professionals, and is applicable in primary, secondary and tertiary care settings [19]. In a large randomized controlled trial, antidepressant treatment in combination with a behavioural intervention, such as Problem-Solving Treatment (PST), was more effective in reducing depressive and pain symptoms in primary care patients [20]. Antidepressants such as duloxetine are reported to be effective for depressive and pain symptoms [21-26], and appear to be more effective than SSRIs and placebos [23,27,28]. However, to co-manage pain, the use of analgesics might improve the effect on pain symptoms in patients with depression [20].

In general, the World Health Organization pain ladder is used in pain treatment, which suggests three steps, the second and third steps of which involve opiates, and antidepressants; pregabalin and mood stabilizers have been suggested as adjuvant medication [29]. However, this emphasis on opiates in the WHO pain ladder has been a major factor in the development of an opioid addiction epidemic in the United States, and opioid analgesics are now the most commonly prescribed class of medications in the United States and are associated with drug-overdose deaths [30]. Hence, the prescribing practices for opioids, particularly as they relate to the management of chronic pain, have been subject to debate [31-36]. It is advised to use non-opioid

medications in the treatment of pain in patients with depression [33]. This new development makes the outcomes of the present study highly relevant, as we developed a new algorithm that might be an attractive alternative to the WHO pain ladder, specifically for the comorbid condition of depressive disorder and pain. This algorithm lays an emphasis on avoiding opiates as much as possible, differentiating between nociceptive pain and neuropathic pain, and prescription of so-called adjuvant medication (i.e. antidepressants and Pregabalin) from the start instead of later or only optional in the WHO pain ladder. Furthermore, this new algorithm is embedded in a collaborative care approach involving active monitoring of medication use and its effects. The algorithm is shown in Figure 1.

Pain is common in patients with Major Depressive Disorders (MDD) and has a negative influence on treatment outcome; hence treatment should address both. Evidence exists for the efficacy of collaborative care against MDD, for the efficacy of consequent use of pain medication against pain, and for the efficacy of duloxetine against both MDD and neuropathic pain. However, their relative effectiveness has not yet been established. Also, in view of miscellaneous results on the effectiveness of duloxetine for pain, a placebo condition in this specific patient group with comorbidity was needed. Hence the aim of this study was to evaluate the effectiveness of collaborative care with Problem Solving Treatment (PST), pain medication and duloxetine, and collaborative care with PST, pain medication and placebo, compared to duloxetine alone, on depressive and pain outcomes. We aim to report on the factors that hampered the inclusion of participant in this study as well.

MATERIALS AND METHODS

STUDY DESIGN

The design of the study has been described in more detail elsewhere [37] but is summarized here. This study was a three-armed, randomized, multicenter, placebo-controlled trial. The three treatment groups of this study consisted of:

1. Collaborative care including pain medication treatment, combined with duloxetine;
2. Collaborative care, including pain medication treatment, combined with a placebo;
3. Duloxetine only.

The allocation of duloxetine/placebo in the collaborative care groups was double-blind and the duloxetine only group was open label.

SETTING

This study was led by the Clinical Centre for Body, Mind, and Health, and performed within this center and two other mental health institutions in the Netherlands: Arkin, and GGZ inGeest. Inclusion took place between December 2011 and May 2014.

ETHICAL STATEMENT

This study was carried out in accordance with the recommendations of the scientific committees of the three participating institutions with written informed consent from all subjects in accordance with the Declaration of Helsinki. All subjects gave written informed consent in accordance with the Declaration of Helsinki. The protocol was approved by the respective scientific committees of the three participating institutions, the medical ethical committee, and by the Central Commission for Human Bound Research (CCMO, dossier number: NL30081.029.10). The trial is listed in the trial registration: www.trialregister.nl; NTR number: NTR1089.

PARTICIPANTS

Consecutive patients presented at three specialized mental health outpatient clinics. All patients screened positive for MDD (Patient Health Questionnaire depression sub-scale (PHQ9) [38] score 10 or more, and MDD classification by MINI interview) and pain (Brief Pain Inventory (BPI) [39] score 3 or more); they were asked informed consent and randomly assigned to one of the three treatment groups.

RANDOMIZATION

Each participating patient received a unique identification number. This number was inserted into a specially designed program for randomization. The randomization number (1 for CC+duloxetine, 2 for CC+placebo, and 3 for duloxetine) was digitally sent to the pharmacist of the VU medical center. The pharmacist changed the labels of medication so no information was provided whether the pills were duloxetine or a placebo. The pharmacist could identify the medication by a unique number. After receiving a randomization number, the pharmacist would send four unique medication numbers to the contact of the mental health center where the patient was registered. The contact would ensure the psychiatrist received the correct medication for the included patient. Two people controlled the unique medication numbers assigned to a patient. Study investigators, research coordinators, attending care teams and the patients were blinded to treatment allocation when randomized into one of the collaborative care groups. Medication in the duloxetine alone group was open label.

MEASURES

DEPRESSIVE SYMPTOMS

The severity of depressive symptoms was measured with the Patient Health Questionnaire depression sub-scale (PHQ9), a brief but validated instrument that scores each of the DSM-IV criteria for major depressive disorder [38]. Each item is scored from 0 (not at all) to 3 (nearly every day). The total score thus varies from 0 to 27; higher scores indicate higher levels of depressive symptoms. A cut-off score of 10 or higher is recommended to indicate moderate levels of depression [40].

PAIN SYMPTOMS

To measure pain symptoms the BPI [39] was used, measuring average pain severity on a scale of a 10-point scale (0 = no pain; 10 = the most severe pain). The BPI was completed at every session (seven in total) with the psychiatrist (every other week), who used the BPI score to adjust the medication. Including the score used to screen for eligible patients and the baseline BPI score, a total of nine BPI measures were obtained.

Classification of nociceptive pain, neuropathic pain or mixed pain was done using the painDETECT questionnaire that was specifically validated for this purpose [41]. The painDETECT was used in the first therapy session in the collaborative care treatment groups and was used to determine the choice of pain medication according to the pain algorithm.

ASSESSMENTS

Before treatment started, all participants completed a baseline questionnaire. During treatment, patients completed the BPI, PHQ9 and the Antidepressant Side-Effects Checklist (ASEC-21) [42] every other week, according to a Case Registration Form (CRF). The ASEC-21 is a checklist to measure the number of side effects due to the use of an antidepressant. The CRF assessments were used for analyses.

INTERVENTION

A comprehensive description of the intervention can be found elsewhere [37]. Here we will provide a summary of the intervention.

In all three treatment groups, the intervention lasted 12 weeks. All participants completed the painDETECT questionnaire (to assess nociceptive and neuropathic pain), the PHQ9 and the BPI at baseline. During treatment, assessments of PHQ9 and BPI were performed every other week. Patients who did not show up for three or more sessions were registered as non-compliant.

Every week, each patient had a session with a psychologist, and every other week a session with a psychiatrist. In case of treatment response (50% reduction of the initial score), but non-remission, as indicated by a score of > 5 on the PHQ9 after 12 weeks of treatment, the patient was referred to the general practitioner (GP) with subsequent antidepressant treatment and pain medication advice. If after 12 weeks (after de-blinding the medication code) no treatment response had occurred on severity of depressive symptoms, as indicated as less improvement than 50% on the initial PHQ9 score, the patient was not referred to the GP but referred instead for further specialized mental health care. In all treatment groups, a CRF was used to monitor treatment and guide the therapist to carry out treatment per protocol. The psychologist and psychiatrist both had a CRF made for a specific patient and for their specific treatment. Both the CRF of the psychiatrist and of the psychologist were divided into sections, with each section representing a session. Each session started with the steps that had to be followed for that specific session. The CRF for the psychiatrist was as follows: each session started by asking about the presence and severity of 21 common antidepressant side effects using the ASEC-21. When an adverse event not mentioned on the ASEC-21 was attributed to the antidepressant therapy, the therapist could write this down. Subsequently, the depressive and pain symptoms were monitored using the PHQ9 and the BPI. The scores on these questionnaires were used to determine the next step in the medication algorithms, which could also be found in the current section of the CRF. The algorithm for pain medication is shown in Figure 1. The CRF for the psychologist was as follows: each session consisted of PST, and every session one problem was addressed that bothered the patient the most. These sessions took place every week.

COLLABORATIVE CARE

In the collaborative care groups, duloxetine or placebo was prescribed, and pain medication was administered according to an algorithm specifically designed for this study. This algorithm avoids opiate prescription as much as possible, which is considered as an alternative to the current WHO pain ladder, with paracetamol, COX inhibitors and pregabalin as steps before opiates are started.

In the collaborative care groups, duloxetine (or placebo) and pain medication were administered by a psychiatrist, using algorithms that are shown in Figure 1 and Figure 2.

Collaborative care was simultaneously provided by a team of a care-manager (psychologist) and a psychiatrist. Only patients in the collaborative care groups were treated by all specialists. The care-manager was responsible for "Problem Solving Treatment" (PST), a brief, structured psychological intervention.

DULOXETINE ONLY

The patients in the duloxetine only group received treatment of the psychiatrist who used a CRF and the duloxetine algorithm in prescribing duloxetine.

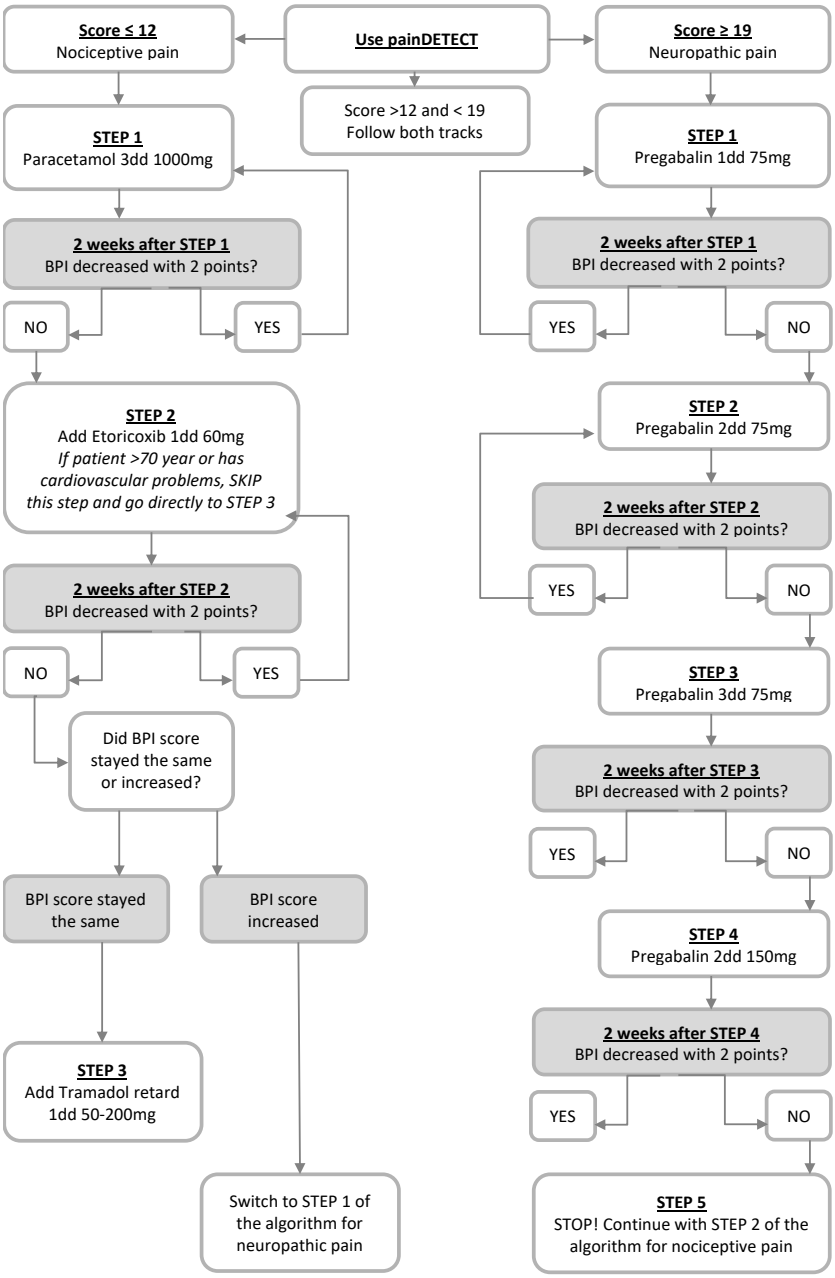

FIGURE 1. PAIN MEDICATION ALGORITHM FOR NOCICEPTIVE PAIN (LEFT TRACK), NEUROPATHIC PAIN (RIGHT TRACK) AND MIXED PAIN (BOTH TRACKS)

STATISTICAL METHODS

The 12 weeks CRF assessments were available only for limited analyses. Although the sample size was smaller than intended, explorative, intention-to-treat and per protocol, multilevel regression analyses were performed.

Descriptive analyses were performed to describe the sample at baseline, regarding gender, age, compliance, severity of depressive symptoms and pain severity. Differences between treatment groups and between compliant and non-compliant patients were analysed regarding baseline characteristics. All linear variables were normally distributed (normality was tested with the Shapiro-Wilk test). Although the required sample sizes were not reached, we performed explorative, intention-to-treat, multilevel regression analyses (MLAs). We evaluated the effect of time for the whole sample, the effect of the treatment group, and the effect of the treatment group over time in terms of depressive symptoms and in terms of pain symptoms over a 16-week period (from moment of screening to the end of the therapy sessions). Quadratic functions of time were included to examine whether there was an initial increase in outcomes followed by a decrease (negative quadratic function), or the other way around (positive quadratic function). Third, explorative, per protocol MLAs were used to evaluate the effect in case of compliance. The duloxetine only group was used as the reference group in all analyses because we expected the collaborative care groups to be the most effective compared to the duloxetine only group. The number of patients who reported side effects on the ASEC-21 is presented for the total sample and for all the treatment groups.

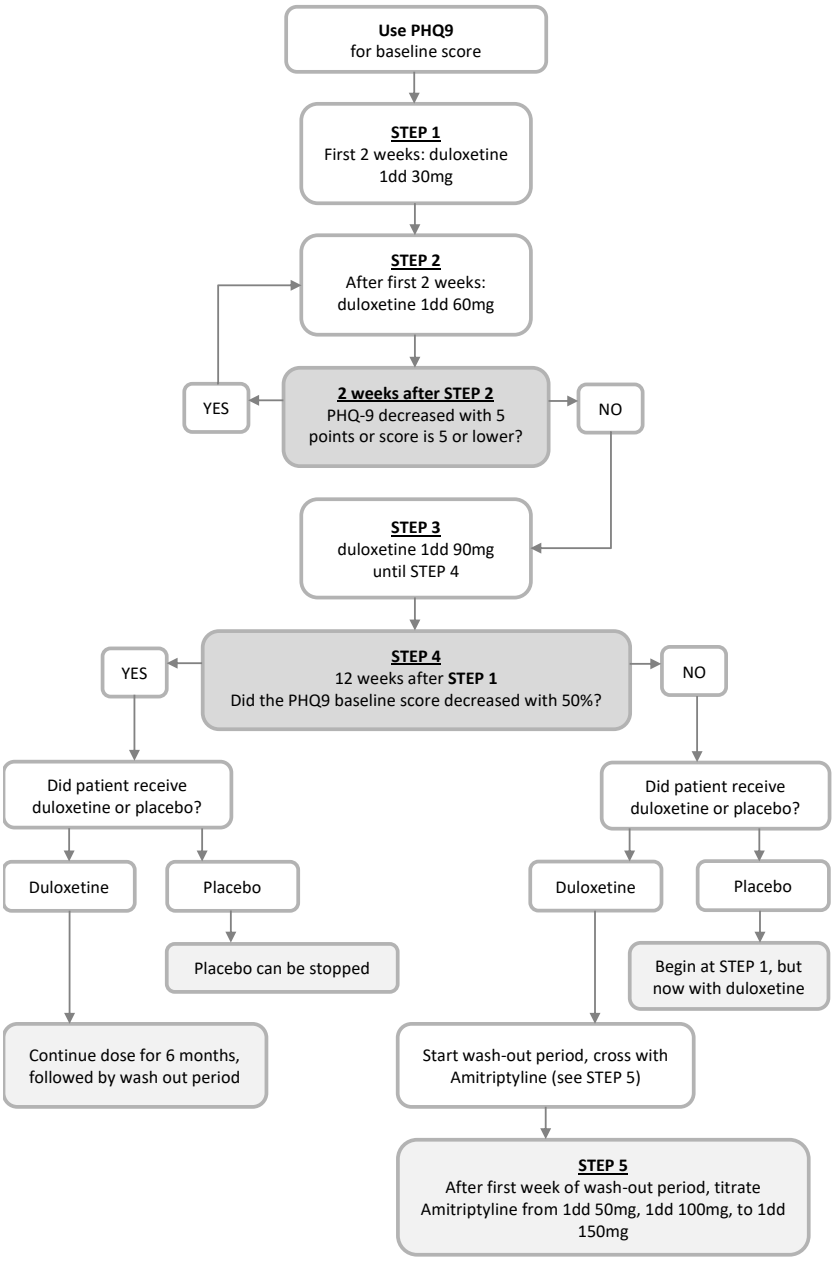

FIGURE 2. ALGORITHM FOR DULOXETINE

RESULTS

PARTICIPANT FLOW

Of the 76 eligible patients, 16 were excluded for several reasons, including having an elevated risk of suicide or not being fluent in Dutch. Twenty-one patients (35%) were randomly assigned to the collaborative care with duloxetine condition, 20 patients (33.3%) to the collaborative care with placebo condition and 19 patients (31.7%) to the duloxetine alone condition. Of the total sample, 29 patients (48.3%) were compliant, whereas 31 patients (51.7%) were non-compliant for several reasons: a) side effects; b) did not want the medication; c) did not want to continue in the study; d) moved to another city; e) needed/wanted other care. Of all included patients, follow up measurements were attained during the intervention period, hence no loss of follow up occurred in this time frame.

The objective of this study was to enrol at least 189 patients. In the first stage of the study, enrolment of patients went well and providing the interventions proved feasible. However, due to several developments, the enrolment was severely hampered and eventually, the study was prematurely terminated. Instead of the envisioned 189 patients, we could only include 60 patients during the available inclusion period. Surrounding the start of the study, a series of unprecedented changes in the organization and financial reimbursement of mental health care were introduced in the Netherlands. Patients referred to specialized mental health care were obliged to pay out of pocket extra fees on top of the “normal” costs of the insurance [43]. A second change was that GP’s were incentivized to change their referral policies, further reducing the number of patients in specialized mental health care. These developments in mental health care made it difficult for this study to complete enrolment as envisioned. Consequently, not all data could be used for analyses, and the follow-up period of only 12 weeks could be used instead of the planned 12 months. However, based on several studies that were performed after the initial planning of our study, in which we assumed 189 patients would be needed to enable us to find a result, we recalculated the power [44] of the study to estimate if analysis of the CRF data might be useful. We found three relevant studies. A study reporting treatment response on the PHQ9 comparing duloxetine with placebo [45] found 66% response in duloxetine versus 25% in

placebo; to find a similar effect, assuming alpha 0.05 and power 80%, N should be 24 patients for each treatment arm. Two other trials, one comparing duloxetine to placebo [22], and an RCT comparing collaborative care versus care as usual found [17] similar differences in effect. Hence, as we had 20 patients per arm, we decided to evaluate the efficacy of collaborative care and duloxetine with pain medication as intended previously, with the data from the CRF assessments, as it might be possible to find an effect. Nevertheless, this should be considered exploratory analyses rather than hypothesis testing. A full report on the factors that hampered this study and led to the premature termination of this study can be requested from the corresponding author.

BASELINE CHARACTERISTICS

Table 1 shows the baseline characteristics of the total sample and the three treatment groups. The total sample consisted of more women than men, with a mean age of 43. Mean score of the PHQ-9 was 17.45 and of the BPI 6.92. Most patients reported neuropathic pain (n=20), and only five patients reported pain of both a nociceptive and neuropathic nature. No significant differences were found between the three treatment groups regarding gender, age, compliance, depressive symptoms and pain symptoms. The two collaborative care groups did not differ regarding the nature of pain. Table 2 shows the baseline characteristics of compliant and non-compliant patients. No significant differences were found between compliant versus non-compliant patients regarding gender, age, treatment condition, severity of depressive and pain symptoms, and nature of pain.

TABLE 1. BASELINE CHARACTERISTICS OF THE TOTAL SAMPLE AND THREE TREATMENT CONDITIONS

Sample characterisitics	**Total sample**		**CC+duloxetine**		**CC+placebo**		**Duloxetine**	
	n=60		n=21		n=20		n=19	
Female gender, n (%)	36	(60)	15	(71.4)	10	(50)	11	(57.9)
Age in years, Mean (SD)	43.2	(12.4)	41.9	(12.2)	41	(12.9)	46.9	(11.7)
Compliance, n (%)								
Compliant	29	(48.3)	10	(47.6)	10	(50)	9	(47.4)
Non-compliant	31	(51.7)	11	(52.4)	10	(50)	10	(52.6)
PHQ9, mean (SD)	17.5	(4.3)	17.2	(4.2)	17.5	(5.0)	17.7	(3.7)
BPI, mean (SD)	6.9	(1.7)	6.7	(2.1)	7.1	(1.4)	7.0	(1.5)
Nature of pain, n (%)*								
Nociceptive	14	(23.3)	7	(33.3)	7	(35)		
Neuropathic	20	(33.3)	10	(47.6)	10	(50)		
Mixed	5	(8.3)	3	(14.3)	2	(10)		

Abbreviations: SD = standard deviation; PHQ = Patient Health Questionnaire; BPI = Brief Pain Inventory; CC = Collaborative Care

* patients in the duloxetine alone group (n=19) did not receive pain medication, therefore, no information was obtained on nature of pain for those patients. Of 2 other patients, information regarding nature of pain was missing.

TABLE 2. BASELINE CHARACTERISTICS OF COMPLIANT AND NON-COMPLIANT PATIENTS

Sample characterisitics	**Compliant patients**		**Non-compliant patients**	
	n=29		n=31	
Female gender, n (%)	16	(55.2)	20	(64.5)
Age in years, Mean (SD)	41.9	(11.4)	44.4	(13.4)
Treatment condition, n (%)				
CC+duloxetine	10	(34.5)	11	(35.5)
CC+placebo	10	(34.5)	10	(32.3)
Duloxetine	9	(31.0)	10	(32.3)
PHQ9, mean (SD)	17.0	(4.0)	17.9	(4.6)
BPI, mean (SD)	7.2	(1.6)	6.7	(1.7)
Nature of pain, n (%)*				
Nociceptive	7	(24.1)	7	(22.6)
Neuropathic	10	(34.5)	10	(32.3)
Mixed	3	(10.3)	2	(6.5)

Abbreviations: SD = standard deviation; PHQ = Patient Health Questionnaire; BPI = Brief Pain Inventory; CC = Collaborative Care

* patients in the duloxetine alone group (n=19) did not receive pain medication, therefore, no information was obtained on nature of pain for those patients. Of 2 other patients, information regarding nature of pain was missing

INTENTION-TO-TREAT ANALYSIS

As is shown in Table 3, patients in all treatment groups reported significant lower depressive (b = -.34; p = <.001) and pain (b = -.07; p = .01) symptoms after 12 weeks (Table 3). ITT analysis showed that, for pain, both collaborative care treatment groups did not show significantly better results than the duloxetine alone group. For the outcome of depression, the collaborative care with placebo condition showed the fastest decrease compared to the duloxetine alone group (b = -.78; p = .01), but this effect diminished at the end of treatment (Figure 3). Figures 3 and 4 show the mean PHQ9 and mean BPI scores of the three treatment groups over time, respectively.

TABLE 3. INTENTION-TO-TREAT, MULTILEVEL ANALYSES COMPARING THE THREE TREATMENT GROUPS FOR DEPRESSIVE AND PAIN SYMPTOMS WITH DULOXETINE ALONE AS REFERENCE CATEGORY

	Depression		**Pain**	
	β	(95% CI)	β	(95% CI)
Time	-.34*	(-.47 – -.20)	-.07*	(-.13 – -.02)
Duloxetine only	reference		reference	
CC+duloxetine	-.31	(-3.16 – 2.54)	-.27	(-1.24 – .71)
CC+placebo	-.54	(-3.43 – 2.34)	.26	(-.73 – 1.24)
Duloxetine only*Time	reference		reference	
CC+duloxetine*Time	-.28	(-.83 – .27)	.15	(-.09 – .40)
CC+placebo*Time	-.78*	(-1.33 – -.22)	-.13	(-.39 – .12)
Duloxetine only*Time*Time	reference		reference	
CC+duloxetine*Time*Time	.02	(-.01 – .05)	-.01	(-.02 – .01)
CC+placebo*Time*Time	.04*	(.01 – .07)	.01	(-.01 – .02)

Abbreviations: CI – confidence interval; CC = Collaborative Care; Time = time from screening to end of therapy sessions

* significant at the .05 level

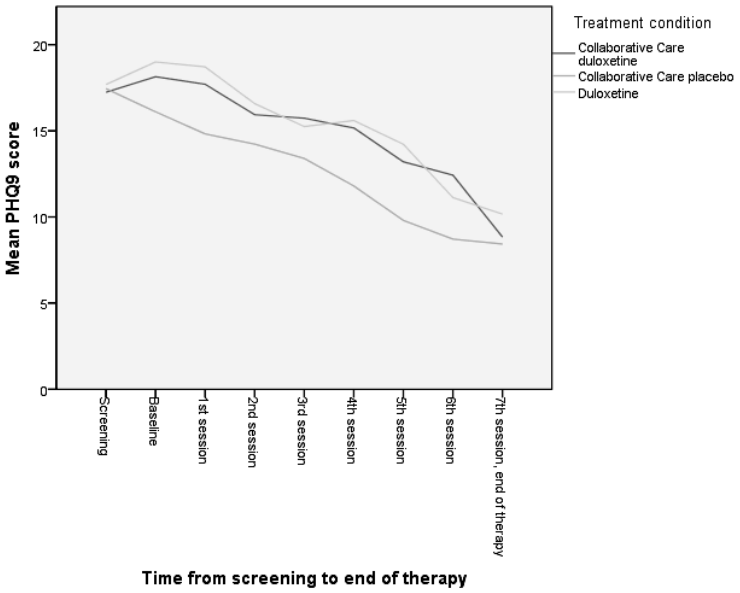

FIGURE 3. MEAN PHQ9 SCORE OF THE THREE TREATMENT GROUPS OVER TIME

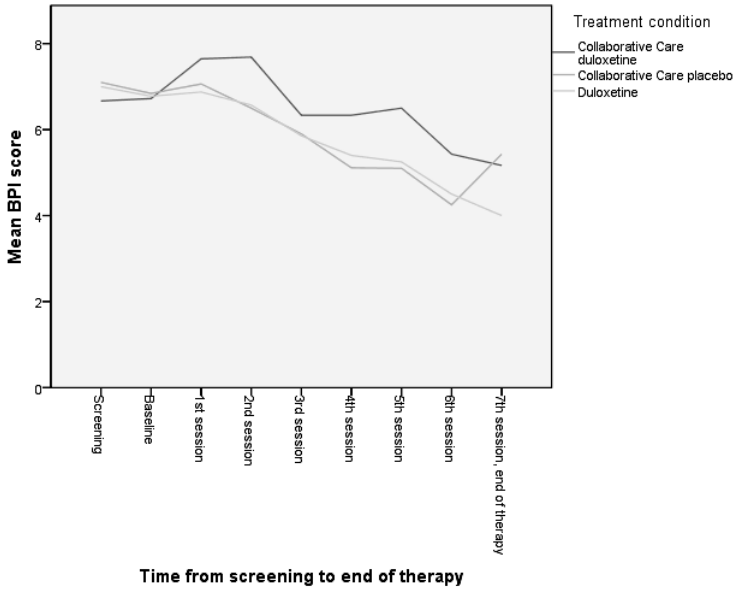

FIGURE 4. MEAN BPI SCORE OF THE THREE TREATMENT GROUPS OVER TIME

PER PROTOCOL ANALYSIS

Per protocol analysis with the compliant patients showed comparable results as the ITT analysis (Table 4). Non-compliant patients did not improve over the 12-week period for depressive or pain symptoms (results not shown).

TABLE 4. EXPLORATIVE, PER PROTOCOL, MULTILEVEL ANALYSES COMPARING THE THREE TREATMENT CONDITIONS FOR DEPRESSIVE AND PAIN SYMPTOMS FOR PATIENTS WHO WERE COMPLIANT, WITH DULOXETINE ALONE CONDITION AS REFERENCE CATEGORY

	Depression		**Pain**	
	β	(95% CI)	β	(95% CI)
Time	-.37*	(-.53 – -.22)	-.13*	(-.20 – -.06)
Duloxetine only	reference		reference	
CC+duloxetine	-.52	(-4.58– 3.54)	-.77	(-2.17 – .64)
CC+placebo	.19	(-3.83– 4.22)	.11	(-1.27 – 1.49)
Duloxetine only*Time	reference		reference	
CC+duloxetine*Time	-.17	(-.86 – .52)	.20	(-.14 – .54)
CC+placebo*Time	-.72*	(-1.40 – -.04)	-.15	(-.48 – .18)
Duloxetine only*Time*Time	reference		reference	
CC+duloxetine*Time*Time	.02	(-.02 – .05)	-.01	(-.02 – .01)
CC+placebo*Time*Time	.04*	(.01 – .07)	.01	(-.01 – .03)

Abbreviations: CI – confidence interval; CC = Collaborative Care; Time = time from screening to end of therapy sessions

* significant at the .05 level

ADVERSE EFFECTS

Table 5 shows the number of patients who reported adverse effects, measured with the ASEC-21. Most patients experienced drowsiness, a dry mouth, nausea, feeling light-headed, insomnia, headache and sweating. In the placebo condition, adverse effects were also experienced. In this treatment condition, most patients experienced insomnia, drowsiness, feeling light-headed, a dry mouth and sweating. In the duloxetine alone condition, headache was the most reported adverse effect.

TABLE 5. NUMBER OF PATIENTS WHO REPORTED SIDE EFFECTS MEASURED WITH THE ASEC-21

Symptom	**Total sample (n=60)**		**Duloxetine (n=19)**		**CC+duloxetine (n=21)**		**CC+placebo (n=20)**	
	N	%	N	%	N	%	N	%
Drowsiness	28	(47%)	9	(47%)	11	(52%)	8	(40%)
Dry mouth	27	(45%)	8	(42%)	12	(57%)	7	(35%)
Nausea or vomiting	27	(45%)	9	(47%)	13	(62%)	5	(25%)
Feeling light-headed on standing	27	(45%)	6	(32%)	13	(62%)	8	(40%)
Insomnia	26	(43%)	6	(32%)	11	(52%)	9	(45%)
Headache	25	(42%)	10	(53%)	9	(43%)	6	(30%)
Sweating	23	(38%)	9	(47%)	7	(33%)	7	(35%)
Yawning	18	(30%)	7	(37%)	8	(38%)	3	(15%)
Decreased appetite	17	(28%)	5	(26%)	7	(33%)	5	(25%)
Tremor	15	(25%)	3	(16%)	7	(33%)	5	(25%)
Blurred vision	14	(23%)	3	(16%)	7	(33%)	4	(20%)
Feeling like the room is spinning	13	(22%)	1	(5%)	8	(38%)	4	(20%)
Weight gain	13	(22%)	3	(16%)	7	(33%)	3	(15%)
Constipation	12	(20%)	5	(26%)	5	(24%)	2	(10%)
Problems with sexual function	10	(17%)	4	(21%)	6	(29%)	0	(0%)
Diarrhoea	9	(15%)	1	(5%)	3	(14%)	5	(25%)
Increased appetite	9	(15%)	3	(16%)	5	(24%)	1	(5%)
Palpitations	9	(15%)	2	(11%)	6	(29%)	1	(5%)
Disorientation	8	(13%)	2	(11%)	5	(24%)	1	(5%)
Problems with urination	7	(12%)	3	(16%)	3	(14%)	1	(5%)
Increased body temperature	3	(5%)	0	(0%)	0	(0%)	3	(15%)
Average number of persons reporting side effects	16		6		7		4	

DISCUSSION

We carried out a randomized controlled trial, testing and comparing the effectiveness of three active treatments among patients with moderately severe MDD and comorbid pain. This is a notoriously hard group of patients to engage and treat, and the prognosis of both dimensions of symptoms, when left untreated, is unlikely to be favorable [11-13]. Our first result is that, at the end of the treatment, patients in all treatment groups had significantly less pain and depressive symptoms. Considering pain, there were no significant differences between the three treatments. However, the depressive symptoms decreased faster among patients in the collaborative care with placebo group than among patients in the duloxetine only group. For patients who were non-compliant, depressive and pain symptoms did not decrease, which indicates that the treatments provided did play a role in the outcomes. Hence, our findings suggest that in comorbid MDD and pain, compliance of the patient and placebo effects are more crucial than choice of one of the three treatments explored in this RCT.

Considering depression, our results are in concordance with a review of 79 studies comparing collaborative care with routine care or alternative treatments and concluded that collaborative care leads to greater improvement in depression outcomes in the short-term as well as the long-term [14]. Furthermore, patients treated with a collaborative care approach also showed improvement in comorbid anxiety outcomes, medication use, mental health quality of life, and patient satisfaction. In our study duloxetine had no surplus value for patients in the collaborative care group, both for depressive symptoms and for pain, which was against our expectations based on studies examining the effect of duloxetine on depression and pain [21,23-28]. Our findings do correspond with a meta-analysis of duloxetine's purported analgesic effects on depressed patients, in which the analgesic effects of duloxetine were not supported [46].

The finding that the collaborative care with placebo condition seems to be the most optimal condition in this study is intriguing. A possible explanation might be the placebo effect, which could increase the effect of collaborative care, at least at the beginning of therapy: a patient who is under study may expect a therapeutic benefit, in our case because of the strict monitoring of

depressive and pain symptoms, monitoring of side effects of duloxetine and placebo, and the special attention by the therapists, which all influence the patients' behavior (also known as the Hawthorne effect) [47]. Thus, expectation of a reward (i.e. expectation of less pain and depressive symptoms) and classical conditioning (i.e. patients most likely had experience with the use of similar medications, and have learned the (positive) effects of these medications, and are therefore more likely to experience a positive effect of the placebo) might contribute to less psychological and physical symptoms [48,49]. Moreover, in patients with irritable bowel syndrome, the patient-practitioner relationship appeared to be the most robust component when considering atypical therapy effects [49], which might also apply to this study. The fast response curve in the placebo group that flattens when the treatment ends, suggests that PST combined with an emphasis on adequate pain management and pain medication is effective, but that there may be another factor that induces the placebo effect. This might be associated with feelings of hope, or with the patient-doctor relationship that develops during the intervention. However, it seems that the placebo effect disappears as soon as the end of the patient-doctor relation is anticipated. We would like to encourage similar studies among larger sample sizes and longer follow-up periods to enhance the generalizability of our results.

STRENGTHS AND LIMITATIONS

This study is a first step to establish an effective treatment for the combination of depression and pain. A major strength of this study is the use of an algorithm for pain medication, which distinguishes nociceptive pain from neuropathic pain. A WHO pain ladder algorithm does exist, but that algorithm focuses mainly on nociceptive pain. An algorithm for neuropathic pain was not yet available. The results indicate that active pain management in collaborative care with COX inhibitors and Pregabalin as alternatives to Tramadol or other opiates might provide an attractive alternative to the current WHO pain ladder as it avoids opiate prescription as much as possible. Recently, it was suggested that adaptations of the original WHO pain ladder are needed (50). For example, opioids should be considered as adjuvant medications instead of the principal medication for the treatment of pain [50], and in other research, it is discussed to select

medication for patients with neuropathic pain with good therapeutic effects and a small likelihood of side effects, such as Pregabalin [51]. Our algorithm is, therefore, a next step in the adaptation of the existing pain ladder. Another strength is the use of a placebo condition in combination with a three-armed design that enabled us to explore the relative effect of CC, pain medication algorithm and Duloxetine alone. Another strength was that the study was sufficiently powered to show an exploratory result.

This study has several limitations that need to be addressed, however. All treatment groups had some form of active treatment, which makes spontaneous recovery or the natural fluctuation of symptoms hard to address. However, in a large observational study, severity of pain did not change over time, and even increased in those persons with depressive symptoms when compared to healthy persons [52], so the decrease in depressive and pain symptoms as found in this study might be accounted for by the treatment offered. Also, the fact that patients in our study who did not comply with the treatment did not improve is an indication that improvement of depressive and pain symptoms was associated with treatment. In this study, we examined the effectiveness of collaborative care, in which we included a new pain management program. We could, however, not assess the impact of this pain management program on treatment effect separately. Therefore, a need exists for future studies also including a treatment group consisting of collaborative care including duloxetine, but no pain management program, to examine whether a pain management program increases treatment effect on top of collaborative care and duloxetine. As mentioned before, the sample size of this study is small due to the reasons described. Although significant results were found, these need to be interpreted with some caution. Research with a larger sample size is needed for generalizability of the results. This study used a follow-up period of 12 weeks, so no inferences could be made regarding the long-term effect of these treatments after end of treatment. However, in a review comparing collaborative care with other treatments, collaborative care had a significant effect on depression outcomes for up to two years after treatment [14], and it is, therefore, plausible that the therapeutic effects found in this study might also last for a longer period than used in this study. To study long-term effects and the cost-effectiveness of these treatments, which was envisioned in the original design, both a larger sample size and longer follow-up period are needed.

CONCLUSION

This study had to be terminated prematurely, and fewer data had to be used to answer our research questions. Therefore, the findings from this study are better thought of as hypothesis forming rather than hypothesis testing, and it would be necessary to see the conclusions replicated in future trials. However, our findings point in the direction that collaborative care with active pain management seems to be a good approach in the treatment of depression when pain is present and provides an attractive alternative to the current WHO pain ladder, as it avoids opiate prescription as much as possible.

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PART IV

EPILOGUE AND SUMMARY

CHAPTER 9

EPILOGUE

“There's always pain around. That's one thing you can guarantee in life - there will always be a surplus of pain”

Nick Cave

EPILOGUE

The main objectives of this thesis were: (1) to examine the association between pain and mental disorders; (2) to enhance our understanding of the longitudinal association between pain and mental disorders in subjects with widespread pain and in the general population, and its effect on suicidal behaviour; and (3) to examine the effectiveness of a multifaceted treatment model for depression and pain. The following questions were addressed:

1. Is pain more strongly associated with depressive and anxiety disorders when pain is more severe and disabling, and when pain locations are clustered?
2. Is pain a predisposing factor in the development of mental disorders and suicidal behaviour?
3. Is a multifaceted treatment model effective in reducing pain and depressive symptoms?

With these research questions in mind, we addressed the following hypotheses:

a. Pain will have a significant association with both depressive and anxiety disorders
b. Pain will be most strongly association with comorbid depressive and anxiety disorders, compared to the association with these disorders separately
c. The association of pain with depressive or anxiety disorders in remission will not differ significantly from the association of pain with no history of these disorders
d. More severe pain, a passive pain-related coping style, and poor illness perceptions are significant risk factors in the development of depressive and anxious symptomatology
e. More severe and more interferent pain are significant risk factors in the development of common mental disorders
f. More severe and more interferent pain are significant risk factors in the development of suicidal behaviour, independent of common mental disorders
g. A multifaceted treatment model, including pain management, will be more effective for the treatment of pain and depression than medication only

PART I: THE ASSOCIATION BETWEEN PAIN AND MENTAL DISORDERS

Part I of this thesis discusses the following hypotheses:

a. Pain will have a significant association with both depressive and anxiety disorders
b. Pain will be most strongly association with comorbid depressive and anxiety disorders, compared to the association with these disorders separately
c. The association of pain with depressive or anxiety disorders in remission will not differ significantly from the association of pain with no history of these disorders

Although extensive research exists examining the association of pain with mental disorders [e.g. 1-7], most studies focused on depression. Knowledge was, therefore, lacking whether the association would be similar for anxiety disorders and for comorbid depressive and anxiety disorders. Moreover, whether individuals with a depressive or anxiety disorder in remission are equal to those with no history of these mental disorders, regarding pain symptoms, was not explored. The first part of this thesis, about the association between pain and mental disorders, contributes to the existing literature by showing that individuals with more severe and disabling pain show a similar risk of also having an anxiety disorder as of having a depressive disorder. Moreover, those with severe and disabling pain are six times more likely to also report a comorbid depressive and anxiety disorder compared to the risk of these disorders separately. Furthermore, our results also show that a depressive or anxiety disorder in remission is not the same as having no history of these mental disorders in terms of pain, as our results show that individuals with pain are more likely to report a disorder that is in remission than to report to have no history of these disorders. Our results also suggest that individuals with musculoskeletal, gastrointestinal, or cardiorespiratory pain are at increased risk for also having a depressive and/or anxiety disorder, be it current or in remission. These results confirm our hypotheses that pain has a significant association with both anxiety and depressive disorders, and that the association is strongest when these mental disorders are comorbid, even more strong than we thought beforehand. However, our hypothesis that individuals with a depressive or anxiety disorder in remission would not differ from individuals with no history of such a disorder

regarding pain was not confirmed. Having severe and disabling pain, or pain of any location, is up to four times stronger associated with having a depressive or anxiety disorder in remission than with having no history of such disorder at all.

This suggests that it may be of benefit to include the assessment of psychological problems in pain management programs and, vice versa, to include pain assessment in psychological treatment, especially when pain is severe and interferes with daily activities. This calls for longitudinal studies examining the effectiveness of such interventions. Future studies are also needed to confirm whether individuals with a history of a mental disorder – preferably differentiating between specific mental disorders – are indeed different than those without such a history when it comes to pain, and if so, whether treatment should be different.

PART II: PSYCHOLOGICAL OUTCOMES OF PAIN

PART II OF THIS THESIS DISCUSSES THE FOLLOWING HYPOTHESES:

a. More severe pain, a passive pain-related coping style, and poor illness perceptions are significant risk factors in the development of depressive and anxious symptomatology
b. More severe and more interferent pain are significant risk factors in the development of common mental disorders
c. More severe and more interferent pain are significant risk factors in the development of suicidal behaviour, independent of common mental disorders

This thesis also expands the existing literature of the longitudinal psychological outcomes of pain. The focus of the existing literature regarding pain and mental disorders was mostly on clinical samples with a mental disorder [e.g. 4,5,8]. Evidence was lacking on the impact of pain severity, coping style, and illness perceptions in the development of psychological symptoms in individuals with a chronic pain condition. There was also a need of longitudinal research examining the psychological outcomes of pain in the general population, especially of the impact of pain in the development of full-blown mental disorders and suicidal behaviour. Previous longitudinal

research in the general population was limited to an elderly population when it comes to mental disorders [e.g. 9,10] or to headache when it comes to suicidal behaviour [e.g. 11,12]. Whether individuals from the general adult population, who report severe and interfering pain, might develop a mental disorder or suicidal behaviour was, thus, unknown. The results in the second part of this thesis, about psychological outcomes of pain, contribute to the existing literature by showing that: (1) poor illness perceptions, in contrast to more severe pain and a passive pain-related coping style, are crucial in developing depressive and anxiety symptoms in individuals with a chronic pain condition; (2) individuals from the general adult population who present with pain, be it severe and interfering, are more likely to develop mood and anxiety disorders, both new onset and recurrent; and (3), severe and interfering pain can progress into suicidal behaviour, even in the absence of a mental disorder. Our hypotheses that more severe and interfering pain are significant risk factors in the development of common mental disorders, especially mood and anxiety, and suicidal behaviour are, therefore, confirmed.

These results suggest that pain is a common, even unique, risk factor regarding mood and anxiety disorders and suicidal behaviour. Targeting pain at an early stage might, therefore, protect in progressing to such detrimental outcomes. Reducing pain symptoms and improving maladaptive illness perceptions might improve the odds of recovering from a mental disorder, or could protect in developing such a disorder or suicidal behaviour whatsoever.

PART III: TREATMENT

Part III of this thesis discusses the following hypothesis:

a. A multifaceted treatment model, including pain management, will be more effective for the treatment of pain and depression than medication only

Countless interventions exist for pain symptoms and for mental disorders. When a mental disorder, such as depression, is comorbid with pain, treatment targeting both conditions might be more effective. Collaborative care has proven to be an effective multifaceted model for these conditions in primary care and in the hospital setting [13-15]. However, collaborative care, including pain management, has not been evaluated yet for use in specialized mental health institutions. Therefore, we designed a randomized controlled trial evaluating whether comprehensively targeting pain symptoms next to the depressive disorder is more effective than only targeting depressive symptoms. To optimize pain management, we designed a new algorithm for the prescription of pain medication, based on the WHO pain ladder. Although this study had to be terminated prematurely, results suggest that individuals with both pain and depression benefit from treatment, whether treatment is multifaceted or not. However, individuals in the multifaceted treatment model, with a placebo instead of an antidepressant, reported the fastest decrease of depressive symptoms. This confirms our hypothesis that a multifaceted treatment model, including pain management, is effective for the treatment of pain and depression, although it was not more effective that treatment with only an antidepressant. Furthermore, treatment was only effective for individuals who were compliant.

Unfortunate, the cost-effectiveness of the multifaceted treatment model in a specialized mental health setting could not be examined, and, thus, remains unknown. However, our results do give some new insights in the treatment of pain and depression. The finding that individuals who received a placebo instead of an antidepressant was surprising. This might be due to placebo effects. For example, expecting an effective treatment (as these individuals received a multifaceted treatment model, consisting of psychological and pharmacological treatment),

combined with a good relationship with the health professional and less to none side effects might give these individuals a head start. Future research should, therefore, also focus on the expectations of participants before and during treatment, and should include measuring the patient-doctor relationship. Additionally, patients' compliance with treatment seems to contribute predominantly to treatment effect. With compliance being a crucial factor for an effective treatment, therapists need to monitor motivation for treatment and focus on keeping patients in treatment. The impact of treatment compliance needs to be examined and replicated in future studies, however. Our results also indicate that active pain management with COX inhibitors and pregabalin as alternatives to opiates might provide an attractive alternative to the current WHO pain ladder as it avoids opiate prescription as much as possible.

METHODOLOGICAL CONSIDERATIONS

Several methodological considerations have already been addressed in the previous chapters. Here, we will discuss the limitations or the studies in general. An important remark is that this thesis is based on different studies with different populations. Furthermore, most of the studies are observational, so statements about causal relationships between pain and psychological distress could not be made. These studies have in common, however, that they all use samples of adults aged 18-65 years. We cannot, therefore, make inferences of populations of other ages.

Another methodological consideration of this thesis, next to that it is based on different studies with different populations, is the assessment of pain and mental disorders. Not all studies in this thesis used the same diagnostic instruments to measure pain symptoms; those used were: (1) the Chronic Pain Grades (CPG), which grades (chronic) pain using questions regarding pain intensity and pain-related disability; (2) one question of the Fibromyalgia Inventory Questionnaire (FIQ), which measures pain severity on a scale of 0 to 10; (3) two questions of the Short Form Health Survey (SF-36), one measuring pain severity and the other measuring interference due to pain mental disorders; and (4) the Brief Pain Inventory (BPI), measuring pain severity on a scale of 0-10. Moreover, these instruments are all self-report questionnaires,

measuring the subjective experience of pain. To date, however, no instruments exists measuring pain purely objective. The diagnostic instruments to measure mental disorders were: (1) the Composite International Diagnostic Interview (CIDI), a fully structured diagnostic interview of mental disorders; (2) the Mini International Neuropsychiatric Interview (MINI), a semi-structured diagnostic interview of mental disorders; and (3) the Hospital Anxiety and Depression Scale (HADS) was used, a self-report questionnaire which assesses the severity of depressive and anxiety symptoms. Although different instruments throughout this thesis were used, all our results show that several pain characteristics – pain severity, interference due to pain, pain location, poor illness perceptions of pain – are strongly associated with (more severe) mental disorders. We feel, therefore, that this thesis provides an in-depth insight into the interplay between pain and mental disorders.

CLINICAL IMPLICATIONS

One of the most important findings of this thesis is that pain is a crucial factor in the association and development of mental disorders and suicidal behaviour. Health professionals, therefore, should do well by identifying possible psychological problems when someone presents with pain. In the Netherlands, an individual with health problems visits a general practitioner (GP), who assesses the problem and advises on the steps that need to be taken. Therefore, the GP should have a crucial role in detecting psychological problems when pain is present. The GP's guideline for depression [16] mentions pain as a risk indicator in the aetiology of depression. However, this guideline advises the GP to screen for depression when he has reason to believe that someone might suffer from depression, based on several symptoms, such as feeling sad, loss of interest, psychomotor agitation, and fatigue. Pain is not mentioned in this list. Moreover, although the guideline mentions pain as a risk factor for depression, it advises to only screen for depression when a patient also mentions psychological problems. Screening for depression is not advised in this case, according to the guideline, because it has not been proven that a patient would benefit from it. Surprisingly, the GP's guideline for anxiety [17] does not mention pain as a risk factor in

the aetiology of anxiety. However, mental disorders are still associated with a high degree of stigma, leaving individuals afraid to seek help for it [18]. They might, therefore, only present their physical symptoms, not asking help for possible psychological problems. Guidelines for mental health practitioners face the same problem as those for the GP. Only the mental health guideline for depressive disorders does mention (chronic) pain as a possible risk factor for a depressive disorder [19], in contrast to the mental health guideline for anxiety disorders [20]. Moreover, the mental health guideline for suicidal behaviour only mentions pain as a risk factor for suicidal behaviour in the elderly population [21]. None of these guidelines, however, mention pain in the treatment of the mental health problem and only focus on reducing the mental health symptoms, such as depressive or anxiety symptoms. This thesis provides evidence that pain is a crucial and possible unique factor in the development of mood and anxiety disorders and suicidal behaviour in an adult population. Therefore, guidelines for both general practitioners and mental health professionals need customizing, by adding that pain is a crucial factor for mental health, and health professionals need to be alert for this. This emphasises the importance to screen for psychological problems at an early stage when pain is present. This could help in the prevention of individuals delaying their help-seeking for mental health problems and could prevent someone from developing a mental disorder or, even worse, suicidal behaviour. Acting on and reducing pain symptoms at an early stage, for example with (psycho)education and medication, might, therefore, lead to a reduced risk of developing a mental disorder and suicidal behaviour. Pain management programs could, thus, possibly serve as a preventative program for mental disorders and suicidal behaviour in subjects with pain. Furthermore, public health strategies, including suicide prevention plans, need to include pain as a more prominent factor and advise to target pain symptoms in treatment to prevent possible detrimental consequences when left untreated. To date, however, suicide prevention plans mainly focus on depression, as a recent review has shown [22]. The GP's guidelines for depressive disorders [16] and anxiety disorders [17] and the mental health guidelines for depression [19], anxiety [20], and suicidal behaviour [21] need to include pain as a crucial target in treatment of those individuals who present with pain symptoms next to a mental disorder. This thesis also provides evidence that pain is indicative of a risk for recurrence of depressive and anxiety disorders. Treatment of individuals with pain

and a mental disorder should, therefore, be different than treatment of individuals with a mental disorder but without pain. For example, treatment of individuals with comorbid pain and a mental disorder should focus more on disability and the negative view of one's own health, whereas treatment of individuals with only a mental disorder should focus more on the specific symptoms of the mental disorder.

FUTURE RESEARCH

This thesis has contributed to the (longitudinal) association between pain and mental health problems. However, more research is needed and directions for future research will be discussed below.

Little research exists examining similar research questions as ours in the populations we used. Besides, our results are based on information of the adult population, aged 18 to 65 years. Therefore, a need exists for studies to substantiate our results in similar populations, but also in populations of other age, such as adolescents and elderly, to improve generalizability. A more comprehensive measurement of pain is preferred in future studies, including chronicity and cause or origin of pain, such as somatic diseases. A need also exists to study pain in other mental disorders (e.g. neurodevelopmental disorders, personality disorders) to broaden our results to these conditions. This thesis mainly focused on mood and anxiety disorders, and in a smaller account to substance use disorders. However, examining mental disorders more specifically (e.g. dysthymia, major depressive disorder, social phobia, generalised anxiety disorder, panic disorder) might yield new insights into the interplay of pain with these specific disorders. Besides, our results are mostly based on DSM-IV diagnoses of mental disorders, whereas the DSM-V is now in use. Sleep problems, medication use, received physical and psychological treatment, and perceived social support are just a few examples of factors affecting mental health outcome [23-26], and might, therefore, affect the pain-mental disorder dyad. Future scientific research would do well by including such factors. Unfortunately, we were unable to evaluate the cost-effectiveness of a multifaceted treatment model for pain and depression. Studies evaluating the

cost-effectiveness of a collaborative care model for depressive and anxiety disorders in primary care show promising results [27,28]. A recent review also shows that collaborative care is cost-effective in the treatment of depressive disorder in older adults [29]. Moreover, a study among individuals with a concomitant chronic physical illness and a depressive disorder recently found collaborative care to be a cost-effective intervention [14]. To date, however, there is a paucity of studies on multifaceted treatment models, such as collaborative care, in other settings than primary care or with a focus on a broader range of mental disorders. We, therefore, encourage further evaluation of such treatment models.

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Everything hurts

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(1475-1564)

SUMMARY

INTRODUCTION

In ***Chapter 1,*** we present the general introduction to the topic of this thesis. Pain and mental disorders are highly comorbid, in clinical populations as well as in the general population. These conditions reduce health-related quality of life significantly and have a negative impact on the economic and societal burden, due to work loss and an increase in health care costs. Moreover, both increase the risk of suicidal behaviour. The comorbidity of pain and mental disorders, therefore, imposes a relevant public health concern. However, evidence whether pain is more strongly associated with comorbid mental disorders and with mental disorders in remission is lacking. Furthermore, knowledge is lacking on the unique role of pain in the development of mental disorders and suicidal behaviour. Treatment of this comorbidity also has not been investigated extensively yet. This thesis focussed on the cross-sectional and longitudinal association of pain characteristics – severity, interference with daily activities, location, pain-related coping, pain-related illness perceptions – with mental disorders and suicidal behaviour, and on the evaluation of a multifaceted treatment model for pain and concomitant depression. First, we examined the association of the two most common mental disorders - depression and anxiety – with pain. Then, we discussed the psychological consequences of pain and pain-related factors in both a clinical sample which is characterized by widespread pain and in the general population. Lastly, we examined a multifaceted treatment model for patients with pain and a concomitant depressive disorder. For all these studies, data were used of different research projects. Results shown in *Chapter 2* are based on data from the Netherlands Study of Depression and Anxiety (NESDA), which recruited 2,981 individuals. The study described in *Chapter 3* is based on data from the Sint Maartenskliniek, where 280 individuals were recruited with a diagnosis of fibromyalgia syndrome. Both *Chapter 4* and *Chapter 5* are based on data from the Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2), in which 6,646 individuals from the general population were interviewed. *Chapter 6*, *Chapter 7*, and *Chapter 8* are based on data collected at three mental health institutions (i.e. GGz Breburg, Arkin, GGZ inGeest), where 60 individuals were recruited.

PART 1: ASSOCIATION BETWEEN PAIN AND MENTAL DISORDERS

In ***Chapter 2*** we examine whether the association between pain and depressive and anxiety disorders would be stronger when depression and anxiety are comorbid. In addition, we examine whether the association with depression and anxiety would differ for certain clustered pain locations – i.e. musculoskeletal, gastrointestinal, cardiorespiratory. The sample consisted of 2,981 individuals, of which 396 had a current depressive disorder, 543 had a current anxiety disorder, 628 had a comorbid depressive and anxiety disorder, 628 had a depressive and/or anxiety disorder in remission, and 652 individuals had no history of depressive and anxiety disorders. The results show that more severe and disabling pain is significantly associated with a depressive disorder as well as with an anxiety disorder. Moreover, this association was the strongest when the depressive and anxiety disorder were comorbid. The same results were also found for all the clustered pain locations. Our findings suggest that individuals with a depressive or anxiety disorder in remission are not the same as individuals without a history of these disorders when it comes to pain. These two groups might need different treatments. Health professionals should be aware that when individuals report severe and disabling pain, or pain of musculoskeletal, gastrointestinal, or cardiorespiratory origin, to inquire after depressive and anxiety symptoms.

PART 2: PSYCHOLOGICAL OUTCOMES IN PAIN

Knowing that pain and mental disorders are often comorbid, we wanted to examine whether pain would also increase the risk of developing a mental disorder. Additionally, we examined the impact of pain on subsequent suicidal behaviour.

Chapter 3 presents the results of a longitudinal study examining whether more severe pain, pain-related coping, and poor illness perceptions are factors related to a possible or probable depressive and anxiety disorder. A cohort of 280 individuals with widespread pain was followed for 18 months. 68 of the developed a possible or probable depressive disorder and 80 developed a possible or probable anxiety disorder. Our results show that poor illness perceptions are the

most crucial factors studied in elevating depressive and anxiety symptoms. Individuals with widespread pain who think their illness negatively affects their mental wellbeing are at increased risk for elevated depressive symptomatology, and individuals who think the treatment of their illness will not be effective are more likely to show subsequent elevated anxious symptomatology. More severe pain and maladaptive coping did not show such an association. These findings suggest that to prevent individuals from developing depressive and anxiety symptoms, treatment should focus on strengthening poor illness beliefs, especially those mentioned above.

In ***Chapter 4*** results of a longitudinal study assessing pain as a risk factor for the prospective development of common mental disorders in the general population are presented. We examined whether more severe pain and more interference due to pain would put individuals at risk of developing a depressive, anxiety, and substance use disorder over a period of three years. All individuals without a mental disorder 12 months prior to baseline, the so-called at-risk group, participated in this study. Three at-risk groups were created: (1) 4974 individuals at risk of developing a mood disorder; (2) 4979 individuals at risk of developing an anxiety disorder; and (3) 5073 individuals at risk of developing a substance use disorder. More severe pain and more interference due to pain increased the risk of developing a mood disorder substantially in individuals at risk for mood disorders. For individuals at risk for anxiety disorders, these pain characteristics were associated with an increased risk of developing an anxiety disorder three years later. Such results were not found for substance use disorders. Health professionals would, therefore, do well to reduce pain symptoms at an early stage to prevent individuals from developing a mental disorder. Moreover, it is necessary to monitor and detect possible symptoms of a mental disorder when individuals present with pain. A need exists for more longitudinal research exploring causality and possible mediating factors in the association between pain and mental disorders.

The last chapter of part 2, ***Chapter 5***, presents the results of a longitudinal study assessing pain as a risk factor for developing suicidal behaviour. This study was conducted in the same population as in *Chapter 4*. Here, we were interested whether more severe pain and more

interference due to pain would increase the risk for suicidal behaviour three years later, independent of the presence of a mental, disorder. Of the 5,303 individuals who were re-interviewed at follow-up, we selected the 5,242 Individuals who reported no suicidal behaviour 12 months prior to baseline. Our results show that more severe pain and more disabling pain were associated with an increased risk for developing suicidal behaviour three years later, independent of the presence of mental disorders. This finding suggests that assessment and management of suicidal behaviour, when severe and interferent pain is reported by an individual, should be one of the first steps in the treatment of pain. In addition, suicide prevention plans should include severe and interferent pain as a prominent risk factor for suicidal behaviour, and advise in targeting pain symptoms in treatment.

PART 3: TREATMENT

When only depressive symptoms are treated in individuals with a comorbidity of pain and depression, these individuals are more likely to show treatment resistance and a poor response to treatment. Therefore, we wanted to examine the effectiveness of a multifaceted treatment model that addresses both depressive and pain symptoms.

Chapter 6 describes the design of the study (named PAINDIP) in which a multifaceted treatment model is evaluated. This study was a cluster randomized multi-centre trial, consisting of three treatment groups: (1) collaborative care including pain medication treatment, combined with duloxetine; (2) collaborative care, including pain medication treatment, combined with a placebo; and (3) duloxetine only. In the collaborative care groups, the allocation of duloxetine/placebo was double-blind, whereas allocation of duloxetine in the duloxetine only group was open label. For the prescription of pain medication, an algorithm was designed, based on the WHO pain ladder, differentiating between nociceptive and neuropathic pain. For all three groups, a case registration form (CRF) was designed, in which the participating health professionals could read the actions for each session. Medication use, both pain medication as duloxetine/placebo, was actively monitored with the use of the CRF. Participants of the study were referred to a mental health institution and were diagnosed with a major depressive disorder

and concomitant pain. Treatment duration was 12 weeks. The aim of the study was to evaluate effectiveness and cost-effectiveness of the two collaborative care groups, compared to duloxetine alone, on pain and depressive symptoms.

Due to several factors hampering the PAINDIP study, the study had to be terminated prematurely. In ***Chapter 7*** we describe these factors. Although in the first stage of the study enrolment of participants went well, due to the hampering factors we could only include 60 participants instead of the envisioned 189. In the Netherlands, a series of unprecedented changes in the organization and financial reimbursement of mental health care was introduced. Consequently, the insurance fees for patients who were referred to specialized mental health care increased, which the patient had to pay out of pocket. Another change was that general practitioners were incentivized to change their referral policies, to reduce the number of referrals to specialised mental health care. This has led to massive mental health reorganizations, making it difficult to complete enrolment as envisioned.

In ***Chapter 8*** we present the results of the PAINDIP study, comparing the effectiveness of a multifaceted treatment model with a treatment of an antidepressant for pain and depression. Although this study had to be stopped prematurely, sufficient data were gathered for limited analysis. These results, however, should be considered exploratory analysis rather than hypothesis testing. A total of 60 participants were included, 21 participants were randomized into group 1 (collaborative care including pain medication and duloxetine), 20 into group 2 (collaborative care including pain medication and placebo), and 19 into group 3 (duloxetine only). Results show that in all treatment groups the pain and depressive symptoms decreased significantly. Participants in the collaborative care including pain medication and placebo group showed the fastest decrease in depressive symptoms. We found no significant effects for participants who were non-compliant. Patients' compliance, therefore, seems to be more crucial factors for treatment effect than any one of the three treatments provided. However, our findings point in the direction that a multifaceted treatment model, including pain management, might be a good approach in the treatment of pain and depression. The use of our newly designed

pain medication algorithm might provide an attractive alternative to the current WHO ladder. Future trials are needed to see the conclusions replicated.

EPILOGUE

This thesis ends with an epilogue in ***Chapter 9***, in which the findings and implications of *Chapters 2* through *8* are reported. In conclusion, pain has a strong association with depressive and anxiety disorders, especially when depression and anxiety are comorbid and even when these disorders are in remission. Furthermore, poor illness perceptions increase the risk of an elevation of depressive and anxiety symptoms. Moreover, more severe and interferent pain is a crucial risk factor for the development of mental disorders and suicidal behaviour. Health professionals should be alert when individuals present with pain symptoms, to prevent the condition of the individual getting worse. Pain management programs and public health strategies should include the detrimental consequences of pain. When pain and a mental disorder are comorbid, it is important to focus treatment on both symptoms. Multifaceted treatment models, including active pain management, seems to be a good option in treating this comorbidity.

SAMENVATTING

INLEIDING

In ***Hoofdstuk 1*** presenteren we de algemene inleiding met de onderwerpen van dit proefschrift. Pijn en psychische stoornissen komen vaak samen voor, zowel in klinische populaties als in de algemene populatie. Deze comorbiditeit verminderd de kwaliteit van het leven en heeft een negatief effect op de economie en maatschappij, doordat het leidt tot werkverlies en een toename van de kosten voor gezondheidszorg. Bovendien verhoogt dit het risico op suïcidaal gedrag. De comorbiditeit van pijn en psychische stoornissen is daarom een relevant probleem voor de volksgezondheid. Er is echter weinig bewijs of pijn een sterkere associatie met psychische stoornissen heeft als deze stoornissen tegelijkertijd verschijnen en met psychische stoornissen die in remissie zijn. Bovendien ontbreekt kennis over de unieke rol van pijn bij de ontwikkeling van psychische stoornissen en suïcidaal gedrag. De behandeling van pijn met psychische stoornissen is nog niet uitgebreid onderzocht. Dit proefschrift richt zich op de cross-sectionele en longitudinale associatie van pijnkenmerken - ernst, belemmering met dagelijkse activiteiten, locatie, pijn-gerelateerde coping, pijn-gerelateerde ziektepercepties - met psychische stoornissen en suïcidaal gedrag. Daarnaast wordt ook de evaluatie van een behandelmodel voor pijn en depressie belicht. Eerst hebben we de relatie tussen pijn en depressie en angst onderzocht. Vervolgens worden de psychologische gevolgen van pijn en pijn-gerelateerde factoren in zowel een klinische populatie als in de algemene populatie beschreven. Ten slotte beschrijven we het design en de effectiviteit van een behandeling dat zich richt op pijnklachten en depressieve klachten. De resultaten in ***Hoofdstuk 2*** zijn gebaseerd op gegevens van de Nederlandse Studie van Depressie en Angst (NESDA). De studie beschreven in hoofdstuk 3 is gebaseerd op gegevens van de Sint Maartenskliniek. Zowel ***Hoofdstuk 4*** als ***Hoofdstuk 5*** zijn gebaseerd op data van de Netherlands Mental Health Survey and Incidence Study-2 (NEMESIS-2). ***Hoofdstuk 6***, ***Hoofdstuk 7*** en ***Hoofdstuk 8*** zijn gebaseerd op gegevens die zijn verzameld in drie instellingen voor geestelijke gezondheidszorg (GGz Breburg, Arkin, GGZ inGeest).

DEEL 1: RELATIE TUSSEN PIJN EN PSYCHISCHE STOORNISSEN

In ***Hoofdstuk 2*** worden de resultaten gepresenteerd van onderzoek naar het verband tussen pijn, zowel ernst als locatie, en een depressieve- en angststoornis sterker. Van de 2.981 personen hadden er 396 een depressieve stoornis, 543 een angststoornis, 628 een comorbide depressieve en angststoornis, 628 een depressieve- en/of angststoornis in remissie en 652 personen hadden geen geschiedenis van een depressieve- of angststoornis. De resultaten laten zien dat ernstige pijn en pijn die een belemmering vormt voor alledaagse bezigheden sterk samenhangt met zowel een depressieve- als angststoornis, ook als deze in remissie zijn. Bovendien is deze samenhang het sterkst wanneer deze stoornissen comorbide zijn. Dezelfde resultaten werden ook gevonden voor alle geclusterde pijnlocaties. Onze bevindingen suggereren dat personen met een depressieve- of angststoornis in remissie niet hetzelfde zijn als personen zonder een voorgeschiedenis van deze aandoeningen als het gaat om pijn. Dit kan betekenen dat deze twee verschillende groepen ook verschillende behandelingen nodig hebben. Specialisten in de gezondheidszorg moeten zich ervan bewust zijn dat wanneer personen ernstige en belemmerende pijn rapporteren, ongeacht locatie, dat ze dan tevens informeren naar symptomen van depressie en angst.

DEEL 2: PSYCHOLOGISCHE GEVOLGEN VAN PIJN

In deel 2 van dit proefschrift presenteren we de resultaten van onderzoek naar de gevolgen van pijn voor psychische problematiek, waaronder ook suïcidaal gedrag.

Hoofdstuk 3 presenteert de resultaten van een longitudinale studie waarin we de rol van pijn, pijn-gerelateerde coping en ziektepercepties bestuderen in relatie tot het ontwikkelen van depressieve- en angstklachten. Gedurende 18 maanden zijn 280 patiënten, met wijdverspreide pijn, gevolgd met vragenlijsten. Van deze groep rapporteerden er 68 patiënten een dusdanige ernst van depressieve klachten na 18 maanden, dat er mogelijke sprake was van een depressieve stoornis. Tachtig patiënten rapporteerden een dusdanige ernst van angstklachten na 18 maanden dat er mogelijke sprake was van een angststoornis. Onze resultaten tonen aan dat

negatieve ziektepercepties de meest cruciale factoren zijn in het verhogen van depressieve- en angstsymptomen. Patiënten met wijdverspreide pijn die denken dat hun ziekte hun psychisch welzijn negatief beïnvloedt, hebben een verhoogd risico op meer depressieve klachten. Personen die denken dat de behandeling van hun ziekte niet effectief zal zijn, hebben een verhoogde kans op meer angstsymptomen. De ernst van de pijn en coping speelden geen rol in de ontwikkeling van depressieve- en angstklachten. Deze bevindingen suggereren dat de behandeling van patiënten met pijnklachten zich moet richten op het versterken van positieve ziektepercepties om te voorkomen dat individuen mogelijk een depressieve- of angststoornis ontwikkelen.

In ***Hoofdstuk 4*** worden de resultaten gepresenteerd van een longitudinaal onderzoek naar pijn als een risicofactor voor de ontwikkeling van psychische stoornissen in de algemene populatie. Dit onderzoek richtte zich op de vraag of de ernst van en belemmering door pijn een rol speelt bij de ontwikkeling van een stemmingsstoornis, angststoornis en middelenmisbruik. Er werden drie risicogroepen gemaakt: (1) 4974 personen met een risico op het ontwikkelen van een stemmingsstoornis; (2) 4979 personen met een risico op het ontwikkelen van een angststoornis; en (3) 5073 personen met een risico op het ontwikkelen van middelenmisbruik. De resultaten laten zien dat hoe ernstiger de pijn is en hoe meer belemmering met alledaagse activiteiten de pijn veroorzaakt het risico op het ontwikkelen van een stemmingsstoornis en angststoornis aanzienlijk verhoogd. Dergelijke resultaten werden niet gevonden voor stoornissen in het gebruik van middelen. Specialisten in de gezondheidszorg doen er daarom goed aan om pijnklachten in een vroeg stadium te verminderen om te voorkomen dat een psychische stoornis zich ontwikkeld. Bovendien is het noodzakelijk om symptomen van een psychische stoornis te monitoren en te detecteren als mensen pijn rapporteren. Er is behoefte aan meer longitudinaal onderzoek dat de causaliteit en mogelijke mediërende factoren in de relatie tussen pijn en psychische stoornissen bestudeert.

Het laatste hoofdstuk van deel 2, ***Hoofdstuk 5***, presenteert de resultaten van een longitudinaal onderzoek naar pijn als een risicofactor voor het ontwikkelen van suïcidaal gedrag. Deze studie werd uitgevoerd in dezelfde populatie als in Hoofdstuk 4. Dit onderzoek richtte zich op de vraag of de ernst van en belemmering door pijn het risico op suïcidaal gedrag drie jaar later zou

verhogen, onafhankelijk van de aanwezigheid van een psychische stoornis. Onze resultaten tonen aan dat meer ernstige pijn en meer belemmering door pijn gerelateerd zijn aan een verhoogd risico op het ontwikkelen van suïcidaal gedrag, onafhankelijk van de aanwezigheid van psychische stoornissen. Specialisten in de gezondheidszorg doen er daarom goed aan om naar suïcidaal gedrag te vragen als iemand ernstige en belemmerende pijn heeft.

DEEL 3: BEHANDELING

Wanneer alleen depressieve symptomen worden behandeld bij personen met zowel pijn als depressie, is er een grotere kans op een minder succesvolle behandeling. Daarom hebben we de effectiviteit onderzocht van een behandelmodel dat zowel depressieve als pijnklachten aanpakt.

Hoofdstuk 6 beschrijft het design van een studie (PAINDIP) waarin een behandelmodel wordt geëvalueerd. In deze studie vergeleken we drie behandelingen: (1) collaborative care inclusief pijnstillers, gecombineerd met duloxetine; (2) collaborative care, inclusief pijnstillers, gecombineerd met een placebo; en (3) alleen duloxetine. Voor het voorschrijven van pijnmedicatie is een algoritme ontworpen op basis van de WHO-pijnladder, waarin onderscheid wordt gemaakt tussen nociceptieve en neuropathische pijn. In een Case Registration Form (CRF) werden alle stappen van elke sessie bijgehouden. Deelnemers aan dit onderzoek waren doorverwezen naar een instelling voor geestelijke gezondheidszorg en werden gediagnosticeerd met een depressieve stoornis en daarmee gepaard gaande pijn. Behandelingsduur was 12 weken. Het doel van de studie was om de effectiviteit en de kosteneffectiviteit van de twee collaborative care groepen te evalueren, in vergelijking met de duloxetine groep.

Vanwege verschillende factoren die de PAINDIP-studie belemmerden, moest de studie voortijdig worden beëindigd. In ***Hoofdstuk 7*** beschrijven we deze factoren. Hoewel in de eerste fase van de studie goed verliep, konden we vanwege de belemmerende factoren slechts 60 patiënten in de studie includeren, in plaats van de nodige 189. Dit was het gevolg van een reeks ongekende veranderingen in de organisatie en financiële vergoedingen van de geestelijke gezondheidszorg. De verzekeringskosten voor patiënten die verwezen werden naar gespecialiseerde geestelijke

gezondheidszorg namen toe, die de patiënt uit eigen zak moest betalen. Een andere verandering was dat huisartsen werden gestimuleerd om hun verwijzingsbeleid te veranderen, om het aantal verwijzingen naar gespecialiseerde geestelijke gezondheidszorg te verminderen. Dit heeft geleid tot enorme reorganisaties op het gebied van de geestelijke gezondheidszorg, waardoor het moeilijk was om de inclusie zoals gepland af te ronden.

In ***Hoofdstuk 8*** presenteren we de resultaten van de PAINDIP-studie, waarbij de effectiviteit van een behandelmodel wordt vergeleken met een behandeling van een antidepressivum voor pijn en depressie. Hoewel deze studie voortijdig moest worden gestopt, werden voldoende gegevens verzameld voor een beperkte analyse. Deze resultaten moeten echter worden beschouwd als verkennende analyses in plaats van hypothesetoetsend. Een totaal van 60 patiënten werden geïncludeerd: 21 patiënten werden gerandomiseerd in collaborative care inclusief pijnmedicatie en duloxetine, 20 in collaborative care inclusief pijnmedicatie en placebo, en 19 in de groep die alleen duloxetine kreeg. De resultaten tonen aan dat in alle drie de groepen de pijn en depressieve symptomen aanzienlijk afnamen. Patiënten in de groep met collaborative care, inclusief pijnmedicatie en placebo, vertoonden de snelste daling van depressieve symptomen. Patiënten die niet therapietrouw waren lieten geen significante daling van klachten zien. Therapietrouw van patiënten lijkt daarom een belangrijk onderdeel te zijn voor therapiesucces. Onze bevindingen wijzen in de richting dat een behandelingsmodel zoals collaborative care, inclusief pijnmanagement, een goede benadering kan zijn bij de behandeling van pijn en depressie. Het gebruik van ons nieuw ontworpen algoritme voor pijnmedicatie is tevens een goed alternatief voor de huidige WHO-ladder. Toekomstige onderzoeken zijn nodig om onze conclusies te bevestigen.

EPILOOG

Dit proefschrift eindigt met een epiloog in ***Hoofdstuk 9***, waarin de bevindingen en implicaties van Hoofdstukken 2 tot en met 8 worden gepresenteerd. Concluderend kan gesteld worden dat pijn een sterke associatie met depressieve en angststoornissen heeft, vooral wanneer de depressie en angst tegelijkertijd voorkomen en zelfs wanneer deze aandoeningen in remissie zijn. Bovendien verhogen negatieve ziektepercepties het risico op meer depressieve- en angstsymptomen. Ernstige en belemmerende pijn is een cruciale risicofactor in de ontwikkeling van psychische stoornissen en suïcidaal gedrag. Specialisten in de gezondheidszorg moeten alert zijn wanneer personen pijnsymptomen presenteren, om te voorkomen dat de toestand van het individu erger wordt. Programma's voor pijnbestrijding en strategieën voor de verbetering van de volksgezondheid moeten rekening houden met de schadelijke gevolgen van pijn. Wanneer pijn en een psychische stoornis samen voorkomen, is het belangrijk om de behandeling op beide symptomen te concentreren. Veelzijdige behandelingsmodellen, inclusief actieve pijnmanagement, lijken een goede optie bij het behandelen van deze comorbiditeit.

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Na jaren van noeste arbeid is het dan zover: mijn wetenschappelijke apotheose! Gedurende mijn promotietraject dat geleid heeft tot dit proefschrift heb ik veel mensen mogen leren kennen. In dit dankwoord wil ik mij daarom richten tot diegenen die er mede voor hebben gezorgd dat je dit nu leest. Laat ik je daarvoor eerst meenemen terug in de tijd. Om eerlijk te zijn heb ik in mijn hele jeugd niet de droom gehad om onderzoeker te worden, wel vrachtwagenchauffeur trouwens. Nee, het begon eigenlijk pas tijdens de opleiding psychologie (niet in Tilburg, maar in de Domstad, Utereg me stadsie). Ik leerde wat het betekende om wetenschappelijk onderzoek te doen, onder andere door mijn stage bij het Trimbos-instituut. Daar begon vervolgens ook mijn loopbaan als wetenschapper, en de start van mijn promotietraject!

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Een promotie gaat niet zonder promotoren. Prof. dr. Christina van der Feltz-Cornelis, prof. dr. Jack Dekker en prof. dr. Harm van Marwijk hebben mij begeleidt en ervoor gezorgd dat ik met veel plezier heb gewerkt aan dit proefschrift.

Beste Christina, in 2009 begon ik bij jou met mijn onderzoeksstage, en bijna 10 jaar later rond ik mijn promotie bij jou af. Ik ben met je meeverhuisd van het Trimbos-instituut naar GGz Breburg en Tilburg University, waarvoor ik mijn vertrouwde stad Utrecht qua werkplek achter me liet. Ondanks dat je met zoveel dingen bezig was, was je altijd beschikbaar voor overleg of een praatje. Als ik vastliep, wist jij mijn onoverzichtelijkheid weer te structureren en richting te geven, waardoor ik mijn vertrouwen in mijn werk weer herpakte. Je schroomde je er niet voor om mijn werk te voorzien van duidelijke kritiek waar nodig, en ondanks dat dat soms zorgde voor de nodige bloeddrukverhogingen, hartkloppingen en zweetuitbarstingen was het eindresultaat altijd iets om trots op te zijn. Op de universiteit liep je altijd even de kamer van Lars en mij binnen met de vraag: “Alles onder controle?”, om gelijk te peilen hoe de zaken ervoor stonden. Je had

altijd scherp voor ogen wat er moest gebeuren (en als jij een doel voor ogen hebt, hebben anderen het niet altijd even makkelijk om jou van dat doel af te krijgen) en je gaf mij de ruimte om mezelf te ontwikkelen als onderzoeker, en later zelfs ook als psycholoog binnen GGZ Breburg. Ik heb veel van je mogen leren en wil je bedanken voor al die jaren van begeleiding.

Beste Jack, ik heb jou ervaren als een man die vlot knopen kan doorhakken en weer door gaat. Je belde regelmatig om te checken hoe het ervoor stond, of ik nog iets van je nodig had, en hoe het met mij ging. Voor mijn gevoel kon dit soms in enkele seconden allemaal aan bod komen, maar je toonde altijd oprecht interesse en was altijd bereid om mee te denken als ik met mijn handen in het haar zat. Jij stimuleerde mij om goed na te denken over welke boodschap ik wilde overbrengen in een artikel.

Beste Harm, jij was altijd vrolijk gestemd, wat zeer besmettelijk was. Ik heb het als zeer prettig ervaren om met jou te overleggen en om jouw feedback op mijn stukken te lezen. Je deed dit met een kritische blik, en zorgde ervoor dat ik er ook wat van leerde. Naast alleen maar verbetersuggesties stelde je juist veel vragen, wat mij aan het denken zette over hoe ik het verder kon oppakken. In jouw berichten kwamen vrijwel altijd termen als ‘top’, ‘goed werk’ en ‘uitstekend’ voor. Jouw optimisme, scherpe blik en betrokkenheid stimuleerde mij altijd weer om er iets moois van te maken.

Christina, Jack en Harm, ik wil jullie ook expliciet bedanken voor wat voor mij denk ik één van de belangrijkste momenten uit mijn carrière als promovendus is geweest: het moment dat besloten werd om de PAINDIP-studie niet verder door te zetten, eind 2014. Ik zie het nog voor me: een kleine kamer in Amsterdam, Christina, Jack en ik tegenover twee vertegenwoordigers van Eli Lilly. We bespraken de stand van zaken van PAINDIP en de oorzaken van het moeizame verloop, en wat mogelijke consequenties hiervan waren. De vertegenwoordigers pakten hun koffertje weer in en vertrokken. Eigenlijk wist ik het al, zo doorgaan met deze studie zou geen realistische optie zijn, de inclusie liep te veel achter op schema. Daar zat ik dan, met grote ogen en in gedachten verzonken. Zou dit het einde van mijn carrière als promovendus betekenen? Ik werd mij bewust van mijn hartslag, die steeds meer om aandacht leek te schreeuwen. En ik verzonk verder in gedachten. Wat moest ik nu gaan doen? Maar al gauw werd ik weer terug de realiteit van die dag

in getrokken. Ik zat daar natuurlijk nog met twee van mijn promotoren, Christina en Jack. We hebben het toen nog even over deze situatie gehad, wat daarover precies gezegd is weet ik niet meer precies. Waar ik daarna nog regelmatig aan teruggedacht heb, is wat ervoor zorgde dat het vertrouwen in mijn toekomst als onderzoeker in een klap weer terugbracht. Zowel Christina en Jack keken mij aan, en ze zeiden beiden – met volle overtuiging en ik geloofde ze gelijk – dat ze er hoe dan ook voor gingen zorgen dat ik kon promoveren! Ik kon aan ze zien dat ze dit meenden, en ook al was het verder nog helemaal niet concreet, meer had ik niet nodig. Samen met Harm werd er een nieuw plan van aanpak opgesteld en begonnen we al gauw samen te werken met andere organisaties om zo een mooi proefschrift tot stand te brengen. Met succes! Gedurende mijn hele promotietraject hebben jullie mij altijd weten te steunen en heb ik veel van jullie mogen leren.

Daarnaast wil ik mijn PAINDIP-begeleidingscommissie bedanken, dat naast mijn promotoren bestond uit Aartjan Beekman, Tjalling Holwerda, Pierre Bet en Joost Roth. Tijdens de PAINDIP overleggen bespraken we de voortgang en vervolgstappen van het onderzoek. In het begin was ik nog vrij gespannen voor deze overleggen, maar de ontspannen en open sfeer maakte dat ik er steeds meer van kon genieten. De plek van deze overleggen zal ik niet vergeten: de kamer van Aartjan bij GGz inGeest in Amsterdam, achter de VU, met grote, donkergekleurde, eikenhouten meubels (ik heb het nagevraagd bij Aartjan, maar of het echt eikenhout is, is niet geheel zeker, wel heel plausibel). Ik vond het altijd bijzonder om jullie, in mijn ogen zeer ervaren en gespecialiseerde professionals, allemaal bij elkaar te zien, en dat er naast de bespreking van het onderzoek ook veel werd gelachen en nieuwe ideeën werden gecreëerd. Jullie vertrouwen in mij, evenals jullie optimisme en enthousiasme, hebben ervoor gezorgd dat ik telkens weer met volle moed door ging. Aartjan, fijn dat je naast PAINDIP ook bij de meeste van mijn andere projecten in dit proefschrift betrokken was. Je stond altijd klaar voor het geven van goede raad en je noemde jezelf soms de advocaat van de duivel, met als doel om mij aan het denken te zetten over het geschrevene, bijdragend aan mijn ontwikkeling als wetenschapper. De kalmte die jij uitstraalde is regelmatig een goed medicijn geweest tegen de stress die een promovendus, dus ook ik, nogal eens kan ervaren. Tjalling, jij bent altijd zeer enthousiast geweest over de PAINDIP-studie, je wist dit goed en vlot op te zetten binnen PuntP. Als een patiënt een sterke verbetering

liet zien van zijn of haar klachten vertelde je dat vol trots en met overtuiging. Ook toen de PAINDIP-studie voortijdig afgebroken werd bleef je positief, want dit onderzoek heeft binnen PuntP veel meer aandacht gebracht voor pijnstoornissen, wat daarvoor nog een ondergeschoven kindje was. Pierre, wat was ik blij dat ook jij bij de PAINDIP-studie betrokken was. Een studie met medicatie is toch een stuk complexer dan ik had gedacht. Gelukkig konden we van jouw expertise gebruik maken. Jij nam de verantwoordelijkheid omtrent de medicatie op je en zorgde ervoor dat alles qua logistiek en wetgeving goed geregeld was. Joost, als psychiater binnen GGZ inGeest was jij de kartrekker van PAINDIP op jouw afdeling. Ook tijdens de verhuizing van de afdeling naar een ander, geheel nieuw gebouw zorgde jij ervoor dat het onderzoek door kon lopen, ondanks dat de faciliteiten op de nieuwe plek nog niet helemaal optimaal waren (gelukkig kon je dit even ontvluchten tijdens je werkzaamheden op Bonaire).

Graag wil ik ook alle andere betrokkenen van de PAINDIP-studie bedanken: Ellen, Fiona, Astrid, Krista, Irmin, Lotte, Tielke, Margo, Nadine, Jonna, Lisette, Anita, Anneke, Wilma, Inkie, Klaas, Robin. Jullie zorgden ervoor dat de PAINDIP-studie 'op de vloer' goed geregeld was, hartelijk dank daarvoor.

Natuurlijk wil ik ook iedereen bedanken met wie ik aan de andere projecten heb samengewerkt. *NEMESIS-2:* Margreet ten Have en Ron de Graaf, dankzij jullie hebben we mooie artikelen kunnen schrijven met de NEMESIS-II data. Jullie meedenkende houding, uitgebreide kennis, kritische blik en enthousiaste houding maakte het een prettige samenwerking. Margreet, dank voor de vele en uitgebreide analyses en de tekst en uitleg die je bereid was te geven als het mij niet lukte om mijn weg te vinden in het oerwoud van de output. De overleggen op het Trimbos-instituut zorgden er tevens voor dat ik even kon spieken op mijn oude werkplek en met oud-collega's een praatje kon maken. *Sint Maartenskliniek:* Joke Vriezekolk, dankzij jou heeft het fibromyalgie artikel zijn plek in dit proefschrift verworven. Dank voor jouw kennis en kunde bij het opzetten en richting geven van dit project. Ik vond de overleggen erg prettig, met name bij de Sint Maartenskliniek, dat zich in een mooi gedeelte van Nijmegen (eigenlijk in Ubbergen natuurlijk) bevindt. *NESDA:* Brenda Penninx, Marloes Gerrits, Philip Spinhoven, Margot de Waal, samen met jullie, mijn promotoren en Aartjan heb ik een van mijn eerste artikelen van dit proefschrift in een

internationaal wetenschappelijk tijdschrift mogen teruglezen. Dank voor jullie adviezen en ondersteuning hierin, het was leerzaam en inspirerend om met jullie samen te werken.

Een groot deel van mijn leven als promovendus heb ik doorgebracht bij het CLGG, waar ik de psycholoog in mij aan het werk kon zetten. Henk, David, de twee Ellens, de twee Aniques, Lars, Krista, Rens, Floor, Anke, Jonna, Astrid, Eline, Aziza, Remona, Iris, Sandra, zo'n hecht team maak je niet vaak mee. Bij jullie was het nooit een probleem om even binnen te wandelen om te spuien, om lief en leed te delen, maar vooral ook om te lachen. Dat hielp goed als tegenhanger van de soms erg heftige problematiek van patiënten. De ochtend met z'n allen starten met vers gezette koffie (dank je wel Lars, voor het lenen van je koffieapparaat) zorgde ervoor dat de start van de dag goed begon (en hopelijk is in de tussentijd de muur weer geverfd) Ik heb veel met jullie gelachen en ik vind het fijn dat we dit op de vrijmibo's kunnen voortzetten.

Elke woensdag was gereserveerd voor Tranzo. Met Lars en Theo op een kamer geplaatst, alsof ze wisten dat we dezelfde humor hadden (en zo niet, dan zijn ze er gauw genoeg achter gekomen). Jullie nuchterheid en wetenschappelijk enthousiasme, evenals die van de andere Tranzo-collega's die de woensdagdienst draaiden, lieten zien dat wetenschap bedrijven ook echt leuk kan zijn. De heidagen zullen mij zeker bij blijven: twee dagen ergens ver weg van de bewoonde wereld om met z'n allen te dineren, borrelen en dansen. En volgens mij ook iets met wetenschap, maar dat durf ik niet met zekerheid te zeggen.

Jochem, ontzettend bedankt voor het ontwerpen van de omslag. Dat creatieve brein heeft goed zijn best gedaan. Onder het genot van bijzondere Belgische biertjes begonnen we te sparren over hoe de omslag eruit zou moeten zien. Ik was al bekend met je werk, en had er daarom het volle vertrouwen in dat je er iets moois van zou maken. Je stuurde mij regelmatig door wat je had gemaakt, en eigenlijk had ik er niet veel op aan te merken, je wist precies datgene uit te beelden wat ik voor ogen had. Op dit resultaat gaan we uiteraard proosten, met bijzondere Belgische biertjes uiteraard.

Siebe en Christine, ook jullie hebben bijgedragen aan de artistieke uitstraling van dit proefschrift. Dankzij jullie begint elk deel in dit proefschrift mooi beeldend. Bijzonder hoe jullie in een redelijk kort tijdsbestek de inhoud van mijn proefschrift naar beeld wisten te vertalen. De schetsen die

jullie op papier lieten zien toonden al veel diepgang, laat staan het uiteindelijk resultaat. Dank jullie wel!

Lieve familie en vrienden, ook jullie wil ik bedanken. Karin, René, Tim, Rick, Ilse, Ap/Appie, Saskia, Iris, Merel, Cas, Hugo, Lot, Olivia, Zoë, met jullie is het al snel een huis vol, maar des te gezelliger op verjaardagen en feestdagen. Met z'n allen bij pap en mam kerst vieren vergelijk ik altijd toch met een soort Italiaanse familie: veel eten, veel chaos, veel geklets en veel gelach. En ondanks alle volle programma's van iedereen staan jullie altijd gelijk klaar om te helpen als het nodig is. Hans en Tiny, ook jullie wil ik bedanken voor jullie steun, hulp, het heerlijke eten en de lekkere drankjes. Jullie zorgen er altijd voor dat het Maud, Josefien en mij aan niks ontbreekt als we bij jullie zijn. Uiteraard ook bedankt dat ik bij jullie aan de eettafel mocht zitten om die vervolgens om te toveren tot een werkplek. Natuurlijk mogen de bikkels niet ontbreken. Frederik, Jochem, Joris, Jeffrey, Lenno, vanaf de middelbare school bleek dat we allemaal dezelfde voorliefde hadden voor gezelligheid, bier, whisky en Utrecht. De vakanties met elkaar zijn onvergetelijk. Met name die naar Tsjechië, aangezien daar (6 jaar later) een geweldige film van in elkaar is gezet (heeft iemand die nog?). Ook nu we dan toch echt volwassen zijn blijven we genieten van elkaars gezelligheid, een bierproeverijtje hier, een hapje eten daar, en natuurlijk de weekendjes weg om telkens weer een poging te doen om de cultuur van een bepaalde Europese stad op te snuiven (en zolang die cultuur op z'n minst bestaat uit lekker eten en drinken, is dat geen probleem). Eline, jouw man staat naast mij als paranimf, maar dat neemt niet weg dat ik ook jou dankbaar ben. Jij weet hoe je een luisterend oor en troost moet bieden, maar ook om je eigen kwetsbaarheid te laten zien. Ik waardeer jouw oprechtheid en kalmte die je uitstraalt, die hebben op de een of andere manier een besmettelijk effect op je omgeving.

Zoals een promotie niet gaat zonder promotoren, gaat de verdediging van zo'n promotie niet zonder paranimfen. Frederik, het kan ook niet anders dat jij naast mij staat als een van mijn paranimfen. Sinds groep 1 bevriend, en nog steeds zijn de gebruikelijke wandelingen om geluk en leed te delen een traditie die we wat mij betreft nog lang blijven voortzetten. Jouw nuchterheid, optimisme en eerlijkheid hebben mij vaak genoeg doen nadenken over hoe ik situaties anders kan aanpakken als ik ergens in vastliep. En onze gedeelde humor, daar hebben

we menigeen goed mee lastig kunnen vallen, terwijl wij het niet meer hielden van het lachen. Jij bent altijd bereid om te helpen, en ongeacht of je weet wat je kan doen, je zorgt ervoor dat je er bent. En dat is vaak al genoeg. Op de vraag of je 'even' een kleine 300 pagina's wil doornemen om te kijken of je opvallendheden ziet, neem jij dat serieus op en maak je er tijd voor (en haal je hier en daar nog een dubbele spatie of een miniscule typefout eruit, dank daarvoor). En natuurlijk ook bedankt (en Eline uiteraard ook) voor het regelmatig ter beschikking stellen van jullie huis, zodat ik daar in volle concentratie aan dit proefschrift kon werken. Een waardevolle vriendschap!

Lars, wij liepen redelijk gelijk met onze promoties. En doordat we vrijwel altijd wel op dezelfde afdeling, of zelfs in dezelfde kamer, werkten, konden we elkaar goed op de hoogte houden van de voortgang van het onderzoek. De congressen die we bezocht hebben zullen mij ook altijd bijblijven. Zweden natuurlijk, waar we met 2 superluxe Volvo's Lapland doorscheurde. En uiteraard ons laatste congres, in Barcelona, waar we ook van het prachtige weer, de Catalaanse cultuur en de architectuur van Gaudi hebben genoten (en ervaren hoe het is om in een Spaans klein louche appartement te verblijven). Gedurende onze tijd bij het CLGG heeft onze mannenhumor en flauwe grappen furore gemaakt. Mooie momenten om aan terug te denken. En na ons eerst te bekamen in wetenschappelijk onderzoek, zijn we nu ook (wederom tegelijkertijd, hoe houd je het voor mogelijk) begonnen aan de opleiding tot GZ-psycholoog. We blijven dus nog wel even collega's, maar belangrijker is de vriendschap die al vanaf onze Trimbos tijdperk is ontstaan.

Pap, mam, jullie staan altijd voor mij klaar. De deur staat altijd open bij jullie, letterlijk zelfs. In de keuzes die ik heb gemaakt hebben jullie mij altijd gesteund en gerespecteerd (de meeste dan, want ik kan mij wel een aantal keuzes herinneren waar dit niet voor opging) en waar het kon zoveel mogelijk geholpen. Voor het minste of geringste kan ik een beroep doen op jullie. Of het nou voor iets heel praktisch is (meestal iets met gereedschap en/of klussen in huis) of om gewoon even te kletsen, het maakt jullie niks uit, het kan allemaal. Jullie geven mij het gevoel er hoe dan ook voor mij te zijn, en dat is een gevoel dat ik graag ervaar.

Lieve Josefien, kleine druktemaker, ook al heb je geen idee wat promoveren inhoudt, je hebt mij hier enorm mee geholpen. Op momenten dat ik vol met stress zat omdat een deadline mij op de

schouder tikte, of als ik mij zorgen maakte of ik het allemaal wel ging redden, zorgde jij ervoor dat ik het allemaal kon relativeren. Tijd en ruimte lijken niet te bestaan als we samen spelen, genieten en geluk is dan het enige wat telt. En ondanks de bijzondere start die je had (wat er bij sommige mensen gek genoeg toe leidde dat ze je vergeleken met een pak suiker, blijkbaar een goede maatstaf om gewicht in te schatten), vanaf begin af aan heb je je ontzettend krachtig getoond. Tot op de dag van vandaag zit je vol pit en energie, en elke dag weer voel ik mij een trotse en gelukkige papa.

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