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ANXIETY, DEPRESSION, AND ANGER IN THE BORDERLAND OF CHRONIC PAIN

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Dedicated to Matias and Aapo

CONTENTS

ABSTRACT

Chronic pain has been strongly associated with such symptoms as anxiety, depression, and anger, which are known to complicate pain treatment and outcome. In acute pain, emotional reactions, e.g. fear and avoidance, function as a beneficial warning signal. In chronic pain, the emotional components lose their usefulness and tend to maintain the disability. Despite the co-occurrence of chronic pain symptoms, possible causality and linking mechanisms remain unclear. In addition, due to the overlap between chronic pain symptoms and psychiatric symptoms, the psychiatric assessment is demanding.

The aim of this cross-sectional study was to assess the prevalence of depression and anxiety in chronic pain, to examine the associations between chronic pain and depression, anxiety, and anger, and to assess possible mechanisms explaining these associations.

Study participants comprised 100 consecutive chronic pain patients referred to the Meilahti Pain Clinic of Helsinki University Hospital. The study utilized both the psychiatric diagnostic approach (SCID-I interview for DSM-IV) and several self-administered questionnaires, i.e. Beck Depression Inventory (BDI), Pain Anxiety Symptom Scale-20 (PASS-20), State Trait Anger Expression Inventory-2 (STAXI-2), and Harm Avoidance scale of Temperament and Character Inventory (TCI). Concerning the BDI, a two-factor model with specific somatic and cognitive-emotional subscales was utilized. Current pain intensity was measured with Visual Analog Scale (VAS).

The majority (75%) of the patients had at least one lifetime Axis I DSM-IV disorder. The most common disorders were mood and anxiety disorders. The prevalence of major depressive disorder (MDD) was 37% and of a specific anxiety disorder 25% over the past 12 months. All of the specific anxiety disorder categories of DSM-IV were represented among the patients. The majority (77%) of the lifetime anxiety disorders preceded the onset of pain. The temporal relationship concerning mood disorders was different, as only 37% preceded pain onset. The Harm Avoidance dimension of the TCI was associated with pain-related anxiety (PASS-20). The experienced pain intensity influenced the strength of the association between the Harm Avoidance HA4 subscale and PASS-20. The association was stronger in patients who experienced a higher pain level than in those with a low level of pain. A similar pain intensity-dependent effect was detected concerning the association between inhibited anger and the somatic symptoms of depression. Patients who fulfilled the diagnostic criteria of MDD scored higher in both the somatic and cognitive-emotional subscales of the BDI compared with those without

MDD. However, the somatic-physical-related items were more strongly associated with the diagnosis of MDD.

The prevalence of psychiatric disorders was high in chronic pain patients. Due to the unclear boundaries between pain and psychiatric disorders, the assessment can be demanding. Interpreting strictly the somatic criteria in the psychiatric diagnostic assessment reduces the sensitivity and may result in treatment failures due to missed diagnoses.

The mechanisms linking chronic pain to depression and anxiety are complex. Analyzing the temporal relationship between the constructs can shed some light on the causality directions. Anger and aggression are seldom routinely assessed in pain patients. Inhibited anger is easily overlooked in clinical practice and would require more active screening. In addition, personality factors may influence how patients adjust to chronic pain. Understanding the personality profile is useful in more individualized and efficient treatment planning.

In conclusion, the psychiatric diagnostic approach provides clinically important information on chronic pain patients. Assessing psychiatric comorbidity enables efficient and individualized treatment planning in chronic pain.

TIIVISTELMÄ

Psyykkiset liitännäisoireet ovat yleisiä kroonisessa kivussa, ja ne voivat vaikuttaa laaja-alaisesti kivun kokemiseen. Akuuttiin kipuun liittyvä välttämiskäyttäytyminen voi toimia suojaavana tekijänä edesauttaen paranemista. Sen sijaan kroonisessa kivussa nämä pelko ja välttämisreaktiot toimivat usein päinvastoin ylläpitäen kipuun liittyvää toiminnanvajausta. Krooniseen kipuun yleisesti liittyviä oireita ovat ahdistuneisuus, masentuneisuus, sekä aggression ja suuttumuksen tunteet. Psyykkisten liitännäisoireiden on todettu vaikeuttavan potilaiden hoitoa ja huonontavan hoidon ennustetta. Kroonisen kivun ja psyykkisten liitännäisoireiden välillä vaikuttavat mekanismit ovat huonosti tunnettuja. Lisäksi arviointia vaikeuttaa psyykkisten oireiden päällekkäisyys kipuoireiston kanssa.

Tutkimuksessa pyrittiin selvittämään masentuneisuuden, ahdistuneisuuden sekä vihantunteiden esiintymistä kroonisilla kipupotilailla. Lisäksi tutkimuksessa arvioitiin miten koettu kivun voimakkuus heijastuu psyykkisiin oireisiin sekä niiden välisiin suhteisiin.

Tutkimukseen osallistui 100 kroonista kipupotilasta Meilahden Kipuklinikalla. Menetelminä käytettiin DSM-IV luokitukseen perustuvaa diagnostista SCID-I haastattelua sekä Beckin Depressioasteikkoa (BDI), ahdistuneisuutta mittaavaa Pain Anxiety Symptom Scale-20 (PASS-20) -asteikkoa, suuttumuksen ilmaisua mittaavaa State Trait Anger Expression Inventory-2 (STAXI-2) -asteikkoa sekä Cloningerin Temperamenttimalliin liittyvää Harm Avoidance (vaikeuksien välttäminen) -asteikkoa. Kivun voimakkuutta arvioitiin Visual Analog Scale (VAS) -mittarilla. Beckin depressioasteikosta muodostettiin kahden faktorin malli, joka sisälsi erilliset asteikot masennuksen kognitiivis-emotionaalisille ja somaattisille oireille.

Suurimmalla osalla (75 %) potilaista oli jokin elinaikainen mielenterveyden häiriö. Yleisimpiä olivat mieliala- ja ahdistuneisuushäiriöt. Kuluneen 12 kuukauden aikana vakavaa masennuksen esiintyi 37 %:lla ja ahdistuneisuushäiriöitä 25 %:lla potilaista. Verrattaessa elinaikaisten mieliala- ja ahdistuneisuushäiriöiden alkamista suhteessa kivun alkamiseen, 77 % ahdistuneisuushäiriöistä oli alkanut ennen kipua, kun taas masennuksen osalta tilanne oli erilainen, 37 % mielialahäiriöistä edelsi kipua. Temperamenttipiirre Harm Avoidance korreloi positiivisesti kipuun liittyvän ahdistuneisuusoireen kanssa. Potilailla, joilla kipu oli voimakkaampaa, myös Harm Avoidance yhdistyi voimakkaammin ahdistuneisuuden tasoon, verrattuna niihin, joilla kipu oli lievempää. Vastaava kivun voimakkuudesta riippuva yhteys esiintyi myös vihan tunteen tukahduttamistaipumuksen (Anger-In) sekä depression somaattisten oireiden välillä. Kun verrattiin Beckin depressionasteikon faktorimallin mukaisia asteikkoja vakavasti masentuneiden ja ei-masentuneiden

kipupotilaiden välillä, sekä kognitiivis-emotionaaliset että somaattiset oirepisteet olivat korkeammat vakavasti masentuneilla. Kuitenkin somaattisten oireiden yhteys masennusdiagnoosiin oli selvempi kuin kognitiivis-emotionaalisten oireiden.

Kroonisilla kipupotilailla esiintyy runsaasti mielenterveyden häiriöitä, jotka tulee ottaa huomioon hoidossa. Arviointia vaikeuttavat kroonisen kivun ja psyykkisten oireiden päällekkäisyys. Psyykkisiin häiriöihin, kuten masennukseen liittyy usein fyysisiä oireita, jotka tulee huomioida diagnostiikassa. Mikäli diagnostisia kriteereitä tiukennetaan liikaa, osa potilaista jää vailla tarvitsemaansa hoitoa. Kroonisen kivun, masennuksen ja ahdistuneisuuden yhteydet ovat monimuotoisia. Oireistojen ajallisten suhteiden selventäminen voi tuoda lisävalaistusta syy- ja seuraussuhteiden arvioinnissa. Krooniseen kipuun liittyvät vihantunteet voivat jäädä havaitsematta erityisesti mikäli ne suuntautuvat sisäänpäin. Myös persoonatekijät voivat osaltaan vaikuttaa siihen miten potilaat sopeutuvat krooniseen kipuun ja siihen miten hoitoa tulisi yksilöllisesti suunnitella.

Psykiatrisen diagnostiikan hyödyntäminen on tärkeä osa kipupotilaiden arviointia. Psykiatrisella arvioinnilla saadaan kattava kokonaiskuva potilaan psyykkisistä oheisoireista sekä niiden kliinisestä merkityksestä ajatellen kroonisen kipupotilaan yksilöllistä ja kokonaisvaltaista hoitoa.

LIST OF ORIGINAL PUBLICATIONS

This thesis is based on the following original publications, referred to in the text by their Roman numerals:

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II. Knaster, P., Estlander, A.M., Karlsson, H., Kaprio, J., Kalso, E. (2012). Temperament traits and chronic pain: the association Harm Avoidance and pain-related anxiety. PLoS One, vol. 7, no.10, pp.Article Number: e45672.

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IV. Knaster, P., Estlander, A.M., Karlsson, H., Kaprio, J., Kalso, E. (2014). Diagnosing depression in chronic pain patients: DSM-IV major depressive disorder vs. Beck Depression Inventory (BDI). (Submitted to PLoS One).

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ABBREVIATIONS

AMOS	Analysis of Moment Structures
BAI	Beck Anxiety Inventory
BDI	Beck Depression Inventory
BDIneg	Beck Depression Inventory, Negative View of Self subscale
BDIphys	Beck Depression Inventory, Physical and Somatic subscale
C	Cooperativeness
CFA	Confirmatory Factory Analysis
CI	Confidence Interval
COMT	Catechol-O-methyltransferase
CPAIN	Current Pain
CRPS	Complex Regional Pain Syndrome
DSM-III	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders, 3rd edition, revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th edition
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th edition, text revision
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, 5th edition
FABQ	Fear-Avoidance Beliefs Questionnaire
FPQ	Fear of Pain Questionnaire
GAD	Generalized Anxiety Disorder
HA	Harm Avoidance
IASP	International Association for the Study of Pain
ICD	International Classification of Disease
ICD-10	International Classification of Disease, 10th edition
MDD	Major Depressive Disorder
MINI	Mini International Neuropsychiatric Interview
MMPI	Minnesota Multiphasic Personality Inventory
MPQ	McGill Pain Questionnaire
NS	Novelty Seeking
OCD	Obsessive Compulsive Disorder
OR	Odds ratio
P	Persistence

PASS-20	Pain Anxiety Symptom Scale-20
PASW	Predictive Analytics Software
PTSD	Posttraumatic Stress Disorder
RD	Reward Dependence
RMSEA	Root Mean Square Error of Approximation
SCID-I	Structured Clinical Interview for DSM-IV Axis 1 Disorders
SCID-I/P	Structured Clinical Interview for DSM-IV Axis 1 Disorders, Patient Edition
sd	Standard Deviation
SD	Self-Directedness
SNRI	Serotonin and Norepinephrine Reuptake Inhibitor
SPSS	Statistical Package for Social Sciences for Windows
SSRI	Serotonin Selective Reuptake Inhibitor
ST	Self-Transcendence
STAXI-2	State Trait Anger Expression Inventory-2
TCI	Temperament and Character Inventory
TSK	Tampa Scale for Kinesiophobia
VAS	Visual Analog Scale

1. INTRODUCTION

The biopsychosocial model of chronic pain (Turk et al., 2002) has been one of the key approaches in pain medicine during the past decades. According to the model, pain is more than a perception or a simple sensory process. The biopsychosocial model of pain emphasizes that the psychological and social factors interact with the biological and physiological factors, modulating the pain experience and disability. The biopsychosocial model reflects the idea of the integration of mind and body, as opposed to pain being purely physical or psychological.

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" (Merskey et al., 1994). The definition emphasizes the role of emotion in pain. The affective components of pain have a predominantly negative valence. Depression, anxiety, and fear have been the most often described emotions in chronic pain patients. Emotions are part of the pain experience, being more than just a consequence or reaction to it. Acute pain causes avoidance and behavioral reactions that protect the body from harm and further injuries. Unlike acute pain, chronic pain has no protective or other useful functions. Instead, chronic pain is strongly associated with emotional burden and physical incapacity.

The pain experience is formed by a multitude of interacting factors. The complexity is further increased by variability between individuals. As pain becomes more chronic, the psychological and social factors play an even bigger role in the maintenance of dysfunction and suffering (Gatchel, 2004). The factors behind the transition process from acute to chronic pain are not well understood. Mechanisms related to the alteration and sensitization of the peripheral and central nervous system have been among the central targets in pain research. Psychosocial factors have emerged as an important factor in these processes. Considering the complexity of these factors, it is understandable that clear boundaries between chronic pain and emotions are difficult to define. Previous studies have revealed a close association between pain and depression, however, the mechanisms underlying the association remain largely unclear. Anxiety as a symptom has been suggested to contribute to the chronification of pain. Far less is known about anxiety disorders and anger in chronic pain patients.

2. REVIEW OF THE LITERATURE

2.1. CHRONIC PAIN

2.1.1. DEFINITIONS OF CHRONIC PAIN

Chronic pain is defined in various ways. The core of the definition is that the pain lasts longer than expected based on the tissue healing process (Turk et al., 2010). Because of difficulties in defining the length of the normal healing process, the definition of chronic pain relies on time markers from the onset of pain. The time frame for chronicity may vary, typically being three or six months (Turk et al., 2010). Regarding chronic pain, factors other than the original tissue pathology are thought to explain the presence and maintenance of pain. Chronic pain results from sensitization of the neural system after input from tissue damage has diminished (Bonica, 1990).

The frequency of chronic pain may also vary. It can be continuous or episodic. Chronic pain can be classified according to site of pain, such as head, lower back, abdomen, etc., or organ system, such as gastrointestinal pain. Chronic pain is often classified also according to the pathophysiological mechanism. Neuropathic pain is derived and maintained by pathological changes in the nervous system. Nociceptive pain is associated with tissue damage, representing a normal reaction to mechanical or thermal stimuli. Visceral pain refers to pain in inner organs. Idiopathic pain refers to pain with unknown or poorly understood etiology. Idiopathic pain includes disorders such as temporomandibular joint disorder, fibromyalgia, irritable bowel syndrome, interstitial cystitis, and pelvic pain (Merskey et al., 1994). The underlying mechanisms of idiopathic pain are poorly understood, but they are supposed to be related to complex interactions of several factors, including genetic vulnerabilities and environmental factors (Diatchenko et al., 2006b). The term psychogenic pain has been strongly rejected in the biopsychosocial approach to pain due to its dualistic view of psychological and medical factors (Sullivan 2000).

2.1.2. CHRONIC PAIN AND THE PSYCHIATRIC DIAGNOSTIC APPROACH

The psychiatric approach of assessing chronic pain is based on the psychiatric symptom criteria of a disorder according to the Diagnostic and Statistical Manual of Mental Disorders (DSM) (American Psychiatric Association, 2013) or the

International Classification of Disease (ICD) (World Health Organization, 1994). The terms "pain" or "chronic pain", are mentioned only occasionally in these classifications. The psychiatric approach to chronic pain relies much on the diagnosis of Pain Disorder, the diagnostic criteria of which have changed in the most recent version of the DSM, the DSM-5 (American Psychiatric Association, 2013). The former editions, the DSM-IV and the text revision DSM-IV-TR, as well as ICD-10, defined Pain Disorder as a part of the somatoform disorders. The main criteria of Pain Disorder include duration of pain at least 6 months, pain without clear organic pathology, and distress because of pain. Pain also interferes with important areas of functioning. Psychological factors are supposed to have an important role in the onset, severity, and maintenance of pain, however, medical background factors can also exist (American Psychiatric Association, 1994). In the recent DSM-5 (American Psychiatric Association, 2013), the criterion concerning the psychological etiology of the unexplained somatic symptoms has been abolished. The new category Somatic Symptom Disorder emphasizes the excessive distress, disability, and anxiety related to pain. Pain Disorder is combined with other former somatoform disorders without a separate classification (American Psychiatric Association, 2013).

Despite the strong clinical impression about the linkage between pain and depression or anxiety, pain is not among the diagnostic criteria of any of the depression or anxiety disorders in the DSM. However, the description part of the DSM related to the diagnostic manual states that pain and aches can be present in depression (American Psychiatric Association, 1994).

2.1.3.   PREVALENCE AND OUTCOME OF CHRONIC PAIN

Chronic pain is common in the general population. In a large cross-sectional study conducted in 15 European countries in 2004, 19% of the respondents had chronic pain, the prevalence ranging from 12% to 30%. In Finland, the prevalence was 19% in adult subjects. In that study, chronic pain was defined as having a duration of at least 6 months, being present during the last month at least twice a week, and having an intensity of 5 or higher on a 10-point scale (Breivik et al., 2006). In another study in Finland with 6500 individuals, the prevalence of daily chronic pain was 14.3% and that of any chronic pain 35.1% (Mantyselka et al., 2003). Chronic pain is associated with other chronic conditions. Among American adults with chronic back pain, the significantly associated other physical diseases included stroke, high blood pressure, asthma, digestive disease, HIV, epilepsy, and impaired vision. The odds ratio for having any comorbid chronic physical disorder was 2.0 (95% CI 1.7-2.4) (Von Korff et al., 2005). A general view has been that females present more chronic pain than males (Rustoen et al., 2004, Wijnhoven et al., 2006, Tsang et al., 2008).

A potential explanation is that females more easily report pain than males or that females are more vulnerable to pain (Wijnhoven et al., 2006). Another common reporting has been the increase in prevalence with age (Tsang et al., 2008). Having chronic pain has also been associated with low education and a low socioeconomic status (Eriksen et al., 2003, Rustoen et al., 2004, Saastamoinen et al., 2005). The discrepant findings of epidemiological studies may arise from differences in the definitions of chronic pain related to duration, frequency, and intensity. Commonly utilized assessment methods include telephone interviews, postal surveys, and personal interviews (Verhaak et al., 1998).

Chronic pain is a long-lasting disorder. In a European population study, 60% of subjects had had chronic pain for 2-15 years. The duration of pain in 21% of subjects exceeded 20 years (Breivik et al., 2006). In a 7-year population-based follow-up study conducted as a postal survey, one-third of patients originally with pain still had pain after 7 years. Chronic pain was as prevalent at the beginning as at the end of the study (11% vs. 10%) (Papageorgiou et al., 2002). Among 973 acute non-radicular back pain patients in primary care, 41% had full recovery within 12 months. Risk factors for non-recovery were higher initial pain intensity, previous sick leaves due to back pain, lower education, and emotional distress (Menezes Costa et al., 2009). Several studies have emphasized the role of social support in chronic pain outcome. Adequate social support and social relations have been associated with better pain adjustment and treatment outcome (Raichle et al., 2007, Miró et al., 2009, Jensen et al., 2011). On the other hand, excessive sympathy and worry of family members may have the opposite outcome, decreasing the adjustment to chronic pain (Boothby et al., 2004, Cano et al., 2004, Jensen et al., 2011).

Chronic pain is strongly connected to poor self-rated health appraisals and functional disability (Mantyselka et al., 2003). In the Finnish population, the number of lost working days during the last 6 months was 19.8 days, which is among the highest in European countries (Breivik et al., 2006). Population studies have revealed chronic pain to be a common, long-lasting, and debilitating disorder that causes marked functional disability. Chronic pain is considered to be one of the most costly medical conditions in society today (Maniadakis et al., 2000).

2.2. THE BIOPSYCHOSOCIAL MODEL OF CHRONIC PAIN

2.2.1. BACKGROUND OF THE BIOPSYCHOSOCIAL MODEL OF PAIN

The gate control theory of pain by Melzack and Wall was one of the first pain theories describing the connection between psychosocial factors and pain perception. The theory maintained that pain is more than a simple sensory process. Instead, pain perception is based on a modulation by a complex feedback network comprising both

the peripheral and the central nervous systems (Melzack and Wall, 1965, Melzack, 1993). The model of Loeser presented the following four different domains in pain: 1) nociception, referring to the nerve function carrying information about tissue damage to the central nervous system, 2) pain, referring to the subjective experience, 3) suffering, referring to emotional negative responses to pain, and 4) pain behavior, referring to expressions of pain (Loeser, 2000).

The definition of pain by IASP contains the emotional factor of unpleasantness (Merskey et al., 1994). Pain is aversive because of its original functioning as a warning signal. The quality of the emotional components of pain is negative. The general finding is that the negative emotional components in one way or another complicate pain management. The core of the biopsychosocial model of pain is that the psychological and social factors interact with the biological and physiological aspects of pain, modulating the pain experience and disability. The model opposes the division of pain being purely either physiological or psychogenic. As pain becomes more chronic, the psychological and social factors play an even bigger role in the maintenance of dysfunction and suffering (Gatchel, 2004)

The vulnerability-diathesis-stress model (Ingram et al., 2005) describes the action between the individual biologic and genetic factors (diathesis) and the environmental stress factors. The result is formed by an interaction between the stress effect and the individual vulnerability. A high level of vulnerability is associated with a lower tolerance for environmental stress factors, resulting in a predisposition for problems in mental health. Low vulnerability is protective against stress. In addition to the genetic factors, vulnerability may involve factors such as personality, cognitions, and neurologic and medical conditions. Concerning mental health, the model was originally presented in relation to schizophrenia (Norman et al., 1993). Banks and Kerns postulated that pain has a specific and unique character as a stressor related to its aversive and fear-evoking nature. The diathesis involves various personal and cognitive characteristics that exist before the onset of pain and are activated by pain, resulting in emotional disability (Banks and Kerns, 1996). While current psychological research strongly opposes the concept of a "pain-prone personality", other theories have presented the role of personality as a possible vulnerability factor for chronic pain and pain-related disability (Ramirez-Maestre et al., 2004).

Studies on depression and anxiety have dominated the biopsychosocial research on pain. The majority of the studies have been psychological, where the term depression may refer to a symptom, mood, or disorder (Banks and Kerns, 1996). Anxiety-related studies have rarely used structured diagnostic methods. Studies on personality and pain are few. In clinical practice, the biopsychosocial view of pain has become the most relevant and largely accepted approach also in "response to medicine's inability to treat chronic, intractable pain and to control pain-related disability" (Duncan, 2000).

2.2.2. BRAIN STRUCTURES IN CHRONIC PAIN

The term pain matrix refers to the brain areas associated with pain perception and processing. The pain matrix is not a distinct restricted unity, but shows remarkable variability between individuals and different pain conditions. The pain experience is formed by an interplay of several brain areas rather than a specific pain center. The areas active in pain are activated by other type of stimuli as well (Apkarian et al., 2011). Despite the association between pain and activity in certain brain areas, the causality of the findings is difficult to prove.

The spinothalamic tract is the main carrier of nociceptive information from the periphery to the central nervous system between the spinal cord and the thalamus. Connections to the brainstem area link nociception with the autonomic nervous system and homeostatic processes (Tracey and Mantyh, 2007). The descending pain modulatory system (Fields, 2000), a structural neural network connecting the brainstem with the spinal cord, can either inhibit or facilitate pain transmission. The descending modulatory system is highly regulated by the biogenic amines serotonin and norepinephrine (Delgado, 2004). Several brain regions, such as the anterior cingulate cortex, insula, amygdala, and prefrontal cortex, have connections to the descending modulatory system. These connections could partly explain the interactions between anxiety, depression, and pain perception (Tracey and Mantyh, 2007). The role of the descending pain modulatory system is further elucidated by the studies on placebo analgesia in humans. Anticipating pain relief has activated the descending inhibitory system, particularly the pathways connecting the frontal areas, the anterior cingular cortex (ACC), and the periaqueductal gray (PAG). The activation of the pain network induced by placebo resembles the activation seen in opioid analgesia (Petrovic et al., 2002).

One of the main findings of the recent brain imaging studies has been the structural anatomical changes of the brain in chronic pain patients. A well-described finding has been the reorganization of the somatosensory cortex in complex regional pain syndrome (CRPS) (Maihöfner et al., 2003). Recent studies have shown the change in the distribution or loss of the gray matter in the areas associated with nociception, particularly in the prefrontal areas (Apkarian et al., 2004, Apkarian et al., 2011). Reversibility of gray matter changes has been reported after successful pain treatment (Rodriguez-Raecke et al., 2009).

Recent findings have suggested that the active brain regions in chronic pain differ from the regions in acute pain. The brain activity in chronic pain shifts from the sensory areas to the emotional and motivational areas of the brain, including the medial prefrontal cortex, amygdala, and basal ganglia (Apkarian et al., 2011). The areas commonly involved in pain perception, such as the insula and the cingular cortex, are considered to be related to the emotional aspects of pain (Apkarian et al., 2011, Bushnell et al., 2013). A recent longitudinal study comparing

chronic pain patients with patients who had had pain, but had improved, reported functional changes in the connections between the nucleus accumbens and the reward-motivational areas. The finding was linked to the pain chronification process (Baliki et al., 2012). Recent theories have suggested that chronic pain is associated with functional changes concerning the pathways related to learning, memory, and reward in the prefrontal-mesolimbic areas (Mansour et al., 2014).
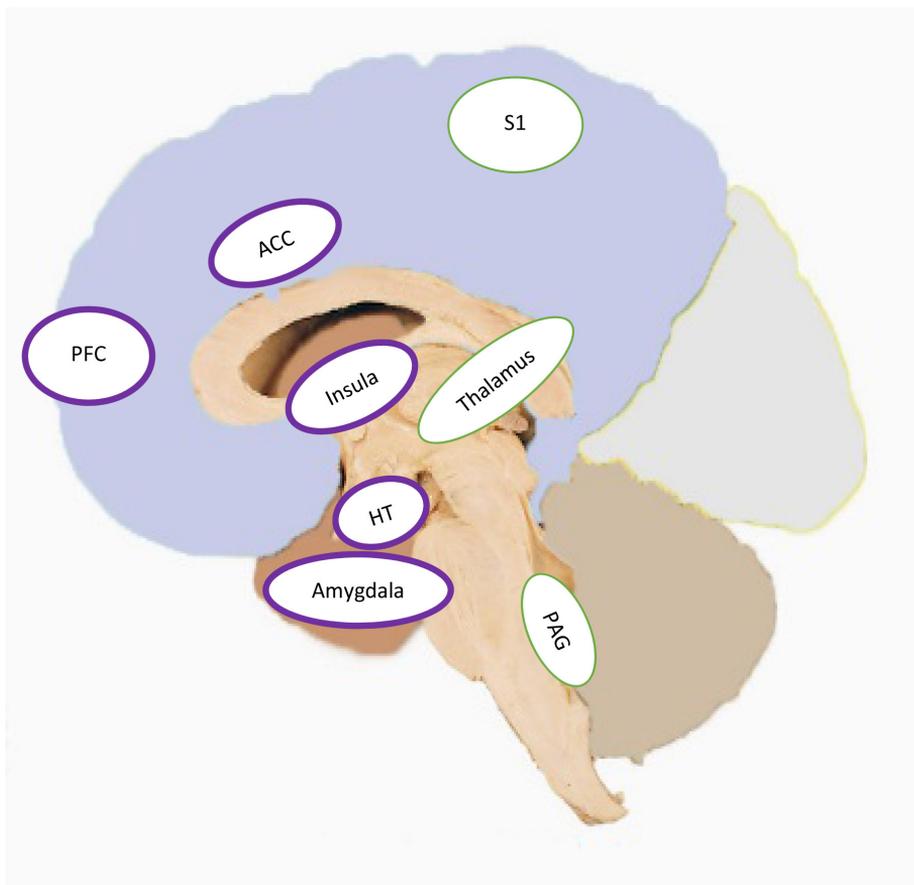
Figure 1. Pain matrix of the brain. (PFC; Prefrontal cortex, ACC; Anterior cingulate cortex, HT; Hypothalamus, PAG; Periaqueductal gray, S1; Primary somatosensory cortex). Bolded ovals represent the areas related to the emotional pain network with connections to the descending pain modulatory system and PAG (Denk et al. 2014).

2.2.3.   GENETIC FACTORS

Recent studies have indicated the importance of genetic factors in chronic pain. According to the results of twin studies, the heritability can range between 13% and 60% depending on the population and pain characteristics (Denk et al., 2014).

The variation of certain genes impacts both pain processing and the psychological vulnerability characteristics, e.g. personality traits (Diatchenko et al., 2006b). The genes related particularly to the serotonergic and noradrenergic pathways have been investigated as possible mediators between pain and emotional processes. Among the most studied genes has been the catechol-O-methyltransferase (COMT) gene, which catabolizes catecholamines such as dopamine, norepinephrine, and epinephrine. The haplotypes of the gene have been related to the variation in pain sensitivity (Diatchenko et al., 2006a). In addition, pain sensitivity has been dependent on the interaction of the haplotype with the level of tendency to catastrophize in patients with shoulder pain. Patients with low COMT activity and high tendency to catastrophize had the highest pain ratings (George et al., 2008). Caspi and colleagues reported the moderating effect of the serotonin transporter gene polymorphism between stressful life events and depression (Caspi et al., 2003). Despite the fact that several other studies failed to replicate the results, the current opinion supports the view that the serotonin transporter polymorphism affects the relationship between stress and depression (Karg et al., 2011). A gender-dependent mediating role of serotonin genes between pain and depression has been reported recently in patients after lumbar disc operation (Lebe et al., 2013). The serotonin transporter gene polymorphism has been associated also with the risk of fibromyalgia (Cohen et al., 2002). However, in the most recent meta-analysis no association was found between either the COMT polymorphism or the serotonin transporter polymorphism and susceptibility to fibromyalgia (Lee et al., 2012).

2.3. PSYCHIATRIC COMORBIDITIES AND THE BIOPSYCHOSOCIAL MODEL OF CHRONIC PAIN

2.3.1. ANXIETY IN CHRONIC PAIN
2.3.1.1. *Anxiety symptoms and pain*

Acute pain may trigger fear and anxiety. The survival function of pain relies on the fear and avoidance it causes in order to protect individuals from further damage. Generally, fear can be understood as a behavioral and physiological reaction to immediate threat, while anxiety is related to the anticipation or expectancy of a potential threat. Anxiety is characterized by cognitive and attentional biases for potential cues of danger or negative and threatening interpretations of neutral stimuli (Bishop, 2007). In chronic pain, fear and anxiety have lost their beneficial function. When fear and anxiety continue, they eventually become part of the psychopathology of chronic pain.

In chronic pain literature, one of the most important models has been the Fear-

Avoidance Model of Pain (Lethem et al., 1983, Vlaeyen et al., 2000). According to this model, catastrophic interpretations of pain gradually lead to the avoidance of physical activity, which in turn is followed by degeneration of the muscular system, muscle coordination, and strength. This vicious cycle predisposes to exacerbation and maintenance of chronic pain (Leeuw et al., 2007).

Similar to depression, anxiety has been associated with poorer pain treatment outcome and ability to return to work after rehabilitation (Burton, 1997, Dersh et al., 2007a). Patients with high level of fear and anxiety report more severe pain and disability and have more exaggerated pain behavior (Vlaeyen et al., 1995, Crombez et al., 1999). Reduction of anxiety level after multidisciplinary treatment is often accompanied by improvement in pain intensity, disability, and general activity. Pain-related anxiety has been presented to be one of the key factors for maintaining functional disability (McCracken and Gross, 1998). Pain-related fear may in fact be more disabling than the pain itself (Crombez et al., 1999). Having both anxiety and depression with chronic pain is associated with enhanced pain severity and disability compared with having only one of these disorders (Bair et al., 2008).

2.3.1.2. *Anxiety disorders in chronic pain patients*

Anxiety disorders are common in the general population. In a Finnish population study, the prevalence of anxiety disorder was 4.1%, females having a higher prevalence (4.8%), mostly due to the higher prevalence of panic disorder in women (Pirkola et al., 2005). Anxiety disorders often go undiagnosed, untreated, or the treatment is not consistent with guideline recommendations (Sihvo et al., 2006).

Compared with depression, the prevalence of anxiety disorders has been less studied in chronic pain (Dersh et al., 2002). In population studies, anxiety disorders have been as common in chronic pain patients as depression (McWilliams et al., 2003, Von Korff et al., 2005). In a study across 17 countries, individuals with chronic back and neck pain were two to three times more likely than healthy persons to have panic disorder, social anxiety disorder, generalized anxiety disorder (GAD), or posttraumatic stress disorder (PTSD) during the past 12 months (Demyttenaere et al., 2007).

In clinical pain subjects, the rates of anxiety disorders have varied largely depending on the study population (Table 1). A prevalence as high as 60% has been recorded in patients with fibromyalgia (Arnold et al., 2006) and headache (Verri et al., 1998). Comorbidity with mood disorders is also common (Dersh et al., 2002).

Concerning the specific anxiety disorders in chronic pain, the most studied disorders have been panic disorder, GAD, and PTSD (Dersh et al., 2002). Particularly high prevalences (80%) of PTSD have been reported in selected patient groups, e.g.

combat veterans (Beckham et al., 1997) and torture survivors (Williams et al., 2010).

Asmundson and colleagues presented possible linking mechanisms to explain the co-occurrence of pain and anxiety. They may reciprocally induce and maintain each other through common mechanisms such as physiological arousal or avoidance. Common vulnerability factors, such as trait anxiety, may also explain the co-occurrence (Asmundson and Katz, 2009). Anxiety-sensitivity (AS), defined as a trait-like fear of bodily sensations (Reiss, 1997), has been presented as one mediating mechanism between pain and anxiety. Individuals with a high level of AS have a hypervigilant tendency to monitor bodily symptoms and react with elevated anxiety and fear, resulting in exaggerated pain experience (Esteve and Camacho, 2008). In the classical study of Gatchel and colleagues, the anxiety disorders were more common in the early phases of pain. Their conclusion was that anxiety reflects acute pain, while chronic pain is more characterized by depression (Gatchel et al., 1996).

Table 1. Distributions of axis I psychiatric diagnoses in chronic pain patients.

Reference study	Year	Clinical population	Country	Diagnostic criteria (method)	Mood disorder	Anxiety disorder	Other disorder
Reich et al.	1983	43 pain clinic patients, 15M 28F	USA	DSM-III (semi-structured interview)	Current MDD 23% Dysthymia 7%	Current Anxiety disorder 7%	Current Adjustment disorder 14% Substance use disorder 28% Somatoform disorder 53%
Large	1986	50 pain clinic patients	New Zealand	DSM-III (semi-structured interview)	Current MDD 8% Dysthymia 28%	Current Anxiety disorder 8% Panic disorder 2% PTSD 2% GAD 4%	Current Somatoform disorder 16%
Fishbain et al.	1986	283 pain clinic patients, 156M 127F	USA	DSM-III (semi-structured interview)	Current MDD 5% Dysthymia 23% MDD+Dysthymia 28%	Current Any anxiety disorder including adjustment disorder 63% GAD 15%	Current Adjustment disorder with mood symptoms 28% Conversion 38% Substance dependence 15% Somatization 4% Conversion 38% Psychogenic pain 0.3%
Polatin et al.	1993	200 patients with chronic back pain	USA	DSM-III-R (SCID-I)	Current MDD 45% Lifetime MDD 64% Lifetime bipolar 2% Lifetime dysthymia 2%	Lifetime Anxiety disorders 19% Panic disorder 3% Phobic disorders 11% OCD 2% PTSD 1% GAD 2%	Lifetime Substance abuse disorder 36% Somatoform disorder 97%
Verri et al.	1998	88 chronic headache patients, 18M 70F	Italy	DSM-III-R (SCID-I/P)	Current MDD 25% Lifetime MDD 39% Dysthymia 17%	Current Panic disorder 5% Social phobia 13% Simple phobia 24% GAD 70%	Current Somatoform disorder 6%
Arnold et al.	2006	78 fibromyalgia patients	USA	DSM-IV (SCID-I/P)	Lifetime MDD 62% Bipolar disorder 13% Dysthymia 1%	Lifetime Any anxiety disorder 60% Panic disorder 28% Agoraphobia 1% Social phobia 21% Specific phobia 22% OCD 6% PTSD 23% GAD 5%	Lifetime Substance use disorder 26% Eating disorder 9% Somatoform disorder 1%

Study	Year	Sample	Country	Instrument	Mood disorders	Anxiety disorders	Other disorders
Castro et al.	2009	400 pain clinic patients, 69M 331F	Argentina	DSM-IV (MINI)	Current MDD 42% Past MDD 58% Dysthymia 54 %	Current Panic disorder 7% Agoraphobia 9% Social phobia 37% Specific phobia 4% OCD 3% PTSD 2% GAD 5%	Hypochondria 11% Substance use disorder 4% Eating disorder 2%
Gerhardt et al.	2011	110 population-based patients with chronic pain, 47M 63F	Germany	DSM-IV (SCID-I)	Current MDD 7% Mood disorders 13% Dysthymia 3%	Current Anxiety disorder 21% Panic disorder 6% Agoraphobia 4% Social phobia 5% Specific phobia 6%	Current Adjustment disorder 3% Substance use disorder 7% Eating disorder 6%
Reme et al.	2011	565 low back pain sick list patients, 273M 279F	Norway	DSM-IV (MINI)	Current MDD 3% Past MDD 8% Current dysthymia 1% Past manic episode 1%	Current anxiety disorder 12% Lifetime anxiety disorder 39% Current panic disorder 1% Lifetime panic disorder 5% Current agoraphobia 4% Lifetime agoraphobia 5% Current social phobia 5% Current OCD 1% Current PTSD 1% Current GAD 4%	Current and past alcohol use disorder 2.2% Current somatoform disorder 18%
Radat et al.	2013	182 neuropathic pain patients, 87M 95F, in neurologic and pain units	France	DSM-IV (MINI)	Current MDD 17% Lifetime MDD 40% Current dysthymia 1% Current bipolar 1% Lifetime bipolar 7%	Current anxiety disorder 20% Lifetime anxiety disorder 39% Current panic disorder/ agoraphobia 14% Lifetime panic disorder/ agoraphobia 28% Current social phobia 2% Lifetime social phobia 6% Current OCD 2% Lifetime OCD 2% Current PTSD 3% Lifetime PTSD 7% Current GAD 12% Lifetime GAD 23%	

2.3.1.3. *Trait anxiety and pain*

The inter-individual variation in the pain experience has evoked interest in examining whether personality-related factors can influence the pain experience. Based on the psychoanalytic theories, Engel introduced the term "pain-prone personality". According to his model, individuals with certain personality characteristics are more susceptible to pain. Chronic pain is suggested to be a reflection of unresolved inner psychological traumas converted into somatic symptoms. Among affected individuals, chronic pain functions as a variant of or a substitute for depression, aggression, or guilty feelings (Engel, 1959). Engel's model has subsequently been criticized for lacking empirical evidence and for supporting the dualistic mind-body distinction (Sullivan et al., 2001).

The Minnesota Multiphasic Personality Inventory (MMPI) (Butcher et al., 1989), a trait-dimensional personality inventory, has been commonly used in pain research. The MMPI was thought to be capable of distinguishing patients with organic pain from patients with psychogenic or functional pain (Hanvik, 1951). According to MMPI studies, chronic pain patients were characterized by high scores on the hypochondriasis, hysteria, and depression subscales of the MMPI (Strassberg et al., 1981, Love et al., 1987). However, both earlier and recent studies have shown the state dependence of several MMPI scales. MMPI scores have changed or improved after pain treatment (Hagedorn et al., 1985, Love et al., 1987, Fishbain et al., 2006). The final conclusion has been that the studies using MMPI could not indicate any specific personality profile for chronic pain patients (Prokop et al., 1980, Love et al., 1987, Wade et al., 1992).

Neuroticism, included in most of the major personality trait models (Eysenck, 1947, McCrae and Costa, 1987, Costa and McCrae, 1992, Zuckerman et al., 1993), is characterized by a tendency to experience negative emotions such as anxiety, worry, irritability, instability, and anger. Neuroticism has been associated with enhanced somatic complaints and experience of bodily sensations (Watson et al., 1989). It has been associated also with discrepancies between subjective and objective health perceptions (Costa and McCrae, 1987). Regarding pain, neuroticism has been associated with elevated reported pain intensity (Ramirez-Maestre et al., 2004). In some studies, neuroticism has been associated with the perceived distress of pain, but not with the experienced pain level itself (Wade et al., 1992, Schmidt et al., 2011). A high level of neuroticism predicted ineffective strategies to solve pain-related problems, which in turn were linked to greater pain intensity (Ramirez-Maestre et al., 2004).

Harm avoidance (HA), one of the temperament traits in the psychobiological personality model of Robert Cloninger, is characterized by a tendency to react intensively to aversive stimuli with fear, withdrawal, or behavioral inhibition. Temperament is related to the automatic emotional reactions to an experience and environmental events (Cloninger et al., 1993). Elevated levels of HA have been

robustly associated with anxiety and depression (Miettunen et al., 2012) and are likely to be both state- and trait-related (Abrams et al., 2004). Studies utilizing the Temperament and Character Inventory (TCI) (Cloninger et al., 1994) have reported an elevated level of HA in chronic pain patients compared with healthy controls (Table 2). The second most constant finding has been low self-directedness associated with chronic pain (Conrad et al., 2013). An elevated score of HA has been measured particularly in migraine (Di Piero et al., 2001, Mongini et al., 2005, Abbate-Daga et al., 2007, Sánchez-Román et al., 2007), musculoskeletal (Boz et al., 2004, Malmgren-Olsson et al., 2006), and fibromyalgia patients (Mazza et al., 2009, Lundberg et al., 2009, Glazer et al., 2010). As anxiety and depression are common in chronic pain, their state effect may partly explain the elevated level of HA (Mongini et al., 2005). In other studies, high HA has persisted despite controlling for the possible state effect of anxiety and depression (Anderberg et al., 1999, Mazza et al., 2009).

Table 2. Temperament and Character Inventory (TCI) findings in chronic pain patients.

Reference study	Clinical population	TCI scores in chronic pain patients
Abbate-Daga et al., 2007	Migraine (n=105); healthy controls (n=79)	HA↑, P↑, SD ↓
Anderberg et al., 1999	Fibromyalgia (n=38); controls (n=38)	HA↑
Boz et al., 2004	Migraine patients (n=51); tension-type headache patients (n=81); healthy controls (n=82);	HA ↑ in tension-type headache patients
Boz et al., 2007	Tension headache (n=45) healthy controls (n=50)	HA ↑, SD ↓
Conrad et al., 2007	Chronic pain mixed (n=207) healthy controls (n=105)	HA ↑, SD ↓, C ↓
Di Piero et al., 2001	Migraine patients (n=121) tension-type headache patients (n=42)	Both groups HA ↑, patients with migraine NS ↓, P ↑
Gencay-Can et al., 2012	Fibromyalgia (n=42); healthy controls (n=48)	HA ↑, ST ↑, SD ↓
Glazer 2010	Fibromyalgia (n=129); first-degree relatives (n=27); healthy controls (n=30)	HA ↑ in patients and first-degree relatives
Lundberg et al., 2009	Fibromyalgia (n=191); healthy controls (n=652)	HA ↑, P ↑, SD ↓
Lundqvist et al., 2005	Vestibulodynia (n=28); controls (n=28)	HA ↑
Malmgren-Olsson et al., 2006	Musculoskeletal pain (n=78); healthy controls (n=118)	HA ↑, SD ↓
Mazza et al., 2009	Fibromyalgia (n=60); healthy controls (n=80)	HA ↑, SD ↓
Mongini et al., 2005	Migraine (n=49); healthy controls (n=47)	HA ↑, P ↑, SD ↓
Sánchez-Román et al., 2007	Migraine (n=142); healthy controls (n=108+269); non-migraine pain patients (n=30)	Migraine patients HA ↑, non-migraine pain patients HA ↑, NS ↓, SD ↓, C ↓

Harm Avoidance (HA); Self-Transcendence (ST); Self-Directedness (SD); Persistence (P); Novelty seeking (NS); Cooperativeness (C)

2.3.1.4.   *Assessing anxiety in chronic pain*

Several instruments and approaches have been used in the assessment of anxiety in chronic pain. Anxiety as a symptom is multifaceted, having cognitive, emotional, and physiological characteristics. The questionnaires vary according to the extent to which they emphasize certain symptoms over others. Scales such as the Hospital Anxiety and Depression Scale (HADS) (Zigmond et al., 1983) or the State-Trait Anxiety Inventory (STAI) (Spielberger et al., 1983) have been used in chronic pain studies. These measures can be seen as general measures of anxiety, which is why their validity in pain-related anxiety or special patient groups has been criticized (Julian, 2011). Other pain-specific anxiety scales include the Pain Anxiety Symptoms Scale (PASS) (McCracken et al., 1992), a 40-item self-report assessing cognitive anxiety, fearful appraisals, escape and avoidance of pain, and physiological symptoms, and its shortened version, Pain Anxiety Symptom Scale-20 (PASS-20) (McCracken and Dhingra, 2002). The Fear-Avoidance Beliefs Questionnaire (FABQ) (Waddell et al., 1993) emphasizes more how pain-related anxiety is linked to the restriction in work and physical activity and the avoidance of pain. The McGill Pain Questionnaire (MPQ) (Melzack, 1975) is a word list questionnaire with adjectives describing the pain sensation and experience. Other fear-avoidance-related measures are questionnaires such as the Tampa Scale for Kinesiophobia (TSK) (Kori et al., 1990), addressing fear in movement and pain catastrophizing, and the Fear of Pain Questionnaire (FPQ) (McNeil et al., 1998).

The symptom-overlapping phenomenon, similar to that seen in pain-depression assessment studies, may have an impact on pain-anxiety studies as well. The anxiety score may rely strongly on the level of pain severity (McCracken et al., 1996).

In conclusion, anxiety and anxiety disorders are common in chronic pain and have been connected to enhanced disability in chronic pain patients. The fear-avoidance model of chronic pain has been one of the major models presenting how the pain chronification process results from fear-related avoidance behavior. The mechanisms underlying the co-occurrence between pain and anxiety are poorly understood. Personality-related factors may predispose pain patients to higher distress and ineffective coping. Several studies have shown the positive correlation between the temperament trait Harm Avoidance and chronic pain. However, due to the cross-sectional design of the studies, no causality can be assigned.

2.3.2.   DEPRESSION IN CHRONIC PAIN

2.3.2.1.   *Prevalence of depression in chronic pain*

Depression is the most widely reported and studied mental disorder in chronic pain. The prevalence of depression in chronic pain patients appears to be markedly higher than in the normal population (Dersh et al., 2002). The prevalence of depression in

this patient group varies considerably depending on the study population, ranging between 1.5% and 100% (Bair et al., 2003). The studies vary in their definition and measurement of chronic pain and depression. The word depression may refer to mood, symptom, or disorder (Banks and Kerns, 1996). The majority of the psychology-based studies assess depression by self-report questionnaires instead of structured diagnostic interviews. The heterogeneity of the studies causes major difficulties when comparing results (Dersh et al., 2002).

In a population study covering 17 countries worldwide, the prevalence of major depression in patients with chronic back or neck pain varied between 2.5% and 15.7%. The odds ratio against not having chronic pain was 2.3 for depression (Demyttenaere et al., 2007). The National Comorbidity Survey Replication study with 9282 adult Americans reported a 19% prevalence of chronic spinal pain during the past 12 months among the respondents. Of the individuals with chronic pain, 12.6% had major depression, 4.4% bipolar I or II disorder, and 17.5% any mood disorder (Von Korff et al., 2005).

The prevalence of depression can be very high in clinical patient populations and in pain clinic samples, up to 100% (Romano and Turner, 1985). Studies based on DSM criteria generally report a prevalence of current MDD from 30% to 45%, while the lifetime prevalence may reach 60% (Table 1).

2.3.2.2. Association between chronic pain and depression

Despite the high co-occurrence of chronic pain and depression, the causality of the association is unclear. The causality, the "hen and egg dilemma", has been one of the key questions in pain-depression studies. Depression severity has been positively related to pain severity, frequency of pain, and number of pain sites. Also the duration of pain has been associated with depression (Fishbain et al., 1997). Depression increased the perception of pain and lowered pain tolerance (Banks and Kerns, 1996). In follow-up studies, depression has predicted onset of chronic pain, and also chronic pain at baseline has predicted onset of depression (Gureje et al., 2001, Chou, 2007, Meyer et al., 2007). One may conclude that there is evidence for a reciprocal pattern. Chronic pain may function as a risk factor for depression (Fishbain et al., 1997), but also the opposite direction, i.e. depression being a risk factor for pain, may exist (Chou, 2007, Meyer et al., 2007). In the review of Fishbain et al. (1997), the majority of the studies supported that depression temporally followed pain, instead of being antecedent to pain. On the other hand, Polatin reported that 54% of pain patients with depression had experienced the symptoms before the onset of pain (Polatin et al., 1993).

2.3.2.3. Assessing depression in chronic pain

Considering the high psychiatric comorbidities, one potential explanation offered has been the symptom overlap phenomenon. Chronic pain and psychiatric disorders, such as depression and anxiety, share a number of common symptoms. Insomnia, fatigue, restlessness, and difficulties in concentrating and thinking can be attributed directly to the effect of pain or they can be signs of a psychiatric disorder. According to the DSM-IV, the symptom criteria that are fully attributed to the somatic condition should not be included in the psychiatric diagnosis (Diagnostic and Statistical Manual of Mental Disorders, 4th edition, 1994). However, there is no general opinion concerning the assessment procedure of these items in the context of various medical conditions. The judgment concerning the etiology of a specific symptom is demanding and leaves room for interpretation (Kathol et al., 1990, Koenig et al., 1997, Akechi et al., 2003, Wilhelm et al., 2004, Mitchell et al., 2012). Thus, the high prevalence of psychiatric disorders in chronic pain can be an overestimation because of the overlapping of somatic symptoms.

Wilson and colleagues (2001) used three different approaches for diagnosing depression in 129 chronic pain patients: the inclusive method (standard DSM-IV criteria for major depression), the etiologic method (excluding symptoms from the diagnosis if they could be attributed to pain), and the substitutive method (somatic symptom criteria of depression were replaced by cognitive-behavioral symptoms commonly related to depression). The prevalences of depression were 35.7% (inclusive), 30.3% (substitutive), and 19.4% (etiologic). In addition, patients were asked about their opinion regarding the origin of their somatic depression symptoms. Most of the patients linked the symptoms directly to pain, after which 45% of the patients who originally met the inclusive criteria no longer met the criteria of depression. However, the group scored equally high in the Beck Depression Inventory compared with those with major depression. The authors of the study cautioned clinicians against causality analysis of the symptoms in the diagnosis of depression in chronic pain (Wilson et al., 2001). The inclusive method has also shown better sensitivity and reliability compared with the other methods (Koenig et al., 1997).

The most widely used assessment tool in pain-depression studies, the Beck Depression Inventory (BDI), was originally developed to assess the severity of depression in psychiatric patients and to follow their response to therapy (Beck et al., 1961). The BDI possesses similar kinds of problems concerning symptom overlap, and its ability to assess depression in medical illnesses has been questioned (Cavanaugh et al., 1983, Kathol et al., 1990, Wesley et al., 1991, Aikens et al., 1999, Forkmann et al., 2009). Similar concerns have been addressed regarding other scales, e.g. the Middlesex Hospital Questionnaire Depression scale (MHQ-D) (Love, 1987) or the Hospital Anxiety and Depression Scale (HADS) (Zigmond et al., 1983).

Some authors have suggested that the symptom profile of depression in chronic pain differs from psychiatric depression. Symptoms related to negative cognitions of self have been less common than somatic-behavioral symptoms of depression (Morley et al., 2002, Poole et al., 2006). The somatic subscales of depression may be strongly correlated with pain intensity (Wesley et al., 1991). In their study, Morley and colleagues analyzed 1947 chronic pain patients using BDI. The factor model from this data included two specific factors, the Negative View of Self and the Somatic and Physical Function factors. Several of the depression-related emotional items, such as sadness, pessimism, or suicidal ideas, were not included in the factor model. Their conclusion was that depression in chronic pain is different from the psychiatric model of depression, and that BDI is likely to measure general distress rather than depression in chronic pain (Morley et al., 2002).

To sum up, depression has been the most studied psychiatric disorder in chronic pain. The prevalence of depression is generally high, however, large variability exists between studies. Depression has shown positive correlations with pain-related variables such as pain severity, duration of pain, or number of pain sites. Longitudinal studies suggest a reciprocal risk pattern, with individuals who have either pain or depression being at risk for developing the other. Diagnosing depression in chronic pain entails difficulties due to the symptom overlap phenomenon. Understanding and formulating the construct of depression in chronic pain have been goals in psychological studies on chronic pain.

2.3.3. ANGER IN CHRONIC PAIN

Feelings of anger have been reported to be common in chronic pain patients (Okifuji et al., 1999, Greenwood et al., 2003, Fishbain et al., 2011). In the psychoanalysis-based theories of Engel (1959), chronic pain was a substitute for anger and depression, particularly in patients unable to express their emotions. Definitions of anger vary in the different theories. Most commonly, anger is defined as a normal emotion with a variable range of intensity, from mild irritation to rage. It is a reaction to a perceived threat or injustice to oneself or persons near oneself (Smith, 1994). Anger includes cognitive elements and a tendency for action. Aggression refers to behavioral reactions that follow anger. The aim of aggression is to cause destruction and damage to persons or objects (Spielberger, 1988).

Pain-related anger is far less studied than anxiety and depression. In pain patients, the target of the angry feelings can be the pain itself, the healthcare system, the employer, insurance companies, family members, etc. However, among 96 chronic pain patients the most common target of anger was oneself (Okifuji et al., 1999). The majority of the anger and pain studies have utilized Spielberger`s

State Trait Anger Expression Inventory (STAXI) (Spielberger, 1988), a self-report questionnaire comprising six scales: State Anger, Trait Anger, Anger Expression-Out, Anger Expression-In, Anger Control-Out, and Anger Control-In. A revised shortened version, STAXI-2, has also been developed and translated into Finnish. Some authors have raised questions concerning the validity of the anger expression scales. For example, the anger-in subscales may cover only deliberate anger inhibition, excluding the more unconscious parts of the constructs (Burns et al., 2008). In addition, the model of Spielberger has been criticized for being too narrow and simplified (Linden et al., 2003).

Anger management style refers to the way in which individuals handle their anger. Anger can be expressed outward (anger-out), with angry feelings expressed by shouting, arguing, throwing objects, etc. The opposite style, anger-in, involves suppressing and inhibiting the anger. Anger control refers to the ability to control angry feelings regardless of the direction of expression (Spielberger et al., 1988)

Cross-sectional studies have reported an association between anger-out and elevated pain responsiveness and pain ratings (Bruehl et al., 2007, Burns et al., 2007). Anger-out has been associated with greater pain intensity in migraine (Materazzo et al., 2000), fibromyalgia (Sayar et al., 2004), and chronic low back pain (Lombardo et al., 2005). In addition, it has been associated with a decreased level of functioning (Duckro et al., 1995, Burns et al., 1998). The opposite management style, suppressing anger, has also been associated with higher pain intensity and pain ratings (Arena et al., 1997, Materazzo et al., 2000, Nicholson et al., 2003, Sayar et al., 2004). Some studies have also reported observations concerning the linkage between suppressed anger and depression (Tschannen et al., 1992, Duckro et al., 1995, Materazzo et al., 2000, Bruehl et al., 2002, Nicholson et al., 2003, Sayar et al., 2004). One explanation has been that the possible linking mechanisms are more related to a general negative affect rather than specifically anger suppression (Burns et al., 2008). Individuals with high negative affectivity have a tendency to experience marked distress and report high levels of symptoms (Watson et al., 1989).

Compared with healthy controls, chronic pain patients with high inhibited anger showed increased muscle tension reactivity in an EMG recording after anger induction, suggesting that muscle reactivity could explain partly the association between anger and pain (Burns et al., 2006). Another model associated the endogenous opioid system with anger. Impaired opioid function was associated with high anger expression in a finger pressure task (Bruehl et al., 2007). Neuroimaging studies may provide a linkage between anger and pain. Several interconnected brain regions, such as the amygdala, anterior cingular cortex, prefrontal and orbitofrontal cortex, and insula, are involved in the regulation of both conditions (Davidson et al., 2000).

Anger is common in chronic pain, however, the number of current studies is limited. Cross-sectional studies have shown an association between anger management and the pain experience. Both anger inhibition and anger expression outward have been associated with elevated pain intensity. In addition, anger inhibition has been related to depressed mood in chronic pain patients.

3. AIMS OF THE STUDY

The aims of this study were to examine the psychiatric comorbidity related to chronic pain using both the diagnostic and dimensional approaches and to assess relations and mechanisms between the psychiatric disorders and the pain experience.

Specific aims were as follows:

1) To investigate the prevalence of mental disorders among chronic pain patients and the temporal relationship between the lifetime disorders and the onset of pain.

2) To investigate the relationship of the trait-anxiety construct Harm Avoidance with pain-related anxiety.

3) To investigate how anger management of chronic pain is related to depression.

4) To assess the dimensional and categorical approaches of depression in chronic pain and the differences between the somatic-physical and cognitive-emotional symptoms of depression.

4. SUBJECTS AND METHODS

4.1. STUDY DESIGN AND PARTICIPANTS

The subjects of this cross-sectional study comprised 100 clinical patients remitted for treatment and assessment to the Helsinki University Central Hospital Pain Clinic. The clinic is a specialized pain clinic receiving patients from other clinics and hospitals in the greater Helsinki area.

The inclusion criteria were chronic pain for at least one year, age 30-60 years, fluency in the Finnish language, and willingness to participate in the study. Exclusion criteria were malignant pain syndromes, strong opioid medication, psychosis, and active drug or alcohol abuse. The recruitment was continued until 100 patients had been enrolled. Participation was suggested to a total of 121 consecutive patients during a scheduled visit in the clinic. The study session was held within 1-3 weeks from the visit. Before the session, patients signed an informed consent. Patients filled in the questionnaires and were interviewed face-to-face by the researcher psychiatrist (PK). The interviews were performed between March 2005 and July 2006.

Among the 21 patients not included in the final sample were patients who had initially shown willingness but who did not show up, patients who declined participation prior to the study session, one patient who interrupted, and two patients with a large amount of missing data.

The study protocol was approved by the Ethics Committee of the Department of Surgery, Helsinki University Central Hospital, Finland.

4.2. DATA COLLECTION

4.2.1. PAIN-RELATED ASSESSMENT

The pain-related measures were assessed using the Pain Questionnaire ("Kipukysely", www.suomenkivuntutkimusyhdistys.fi), a self-administered questionnaire used routinely in the Pain Clinic. It contains questions related to treatment of pain, onset of pain, localization and duration of pain, demographic data, family and work situation, etc.

The questionnaire includes the visual analog scale (VAS) consisting of a horizontal line, with one end (0) indicating no pain and the other end (10) indicating maximal pain. Patients were asked to mark the point on the continuum that represents their current level of pain.

Pain-related functional disability was measure by a scale comprising 18 items describing the pain interference with daily activities such as, lying, sitting, cleaning, sexual activities, etc. Each item has three response options; 1 "not at all", 2 "somewhat", and 3 "much". A sum score (range 18-54) is calculated, with a higher score indicating more severe disability.

The pain diagnosis and classifications were performed by the pain clinicians as part of the treatment program. Pain diagnoses were classified into four etiological groups: neuropathic, nociceptive, visceral, or idiopathic pain. In case there were several pain conditions, the main presenting pain was chosen as the primary pain.

4.2.2.   SELF-REPORT QUESTIONNAIRES

The Beck Depression Inventory (BDI) is a self-administered 21-item scale used to assess the current severity of depression. Several versions of BDI exist; the one most commonly used is the BDI-IA (Beck et al., 1996a). Each item is rated on four-point scale (0 to 3), with possible total score ranging from 0 to 63. The traditional cut-off scores are 0–9: indicating minimal depression, 10–18: indicating mild depression, 19–29: indicating moderate depression, and 30–63: indicating severe depression (Beck et al., 1961).

A number of studies support the validity and other psychometric properties of the BDI (Kearns et al., 1982, Beck and Steer, 1984, Varjonen et al., 1997, Steer et al., 1999).

The questionnaire included several items related to somatic symptoms of depression. Morley et al. (2002) presented a two-factor model of the BDI based on a confirmatory factor analysis performed on a large sample of chronic pain patients. This model includes two subscales.

The first subscale "Negative View of Self" (6 items, range 0–18) includes the items of failure, guilt, self-blame, self-dislike, punishment, and body image change.

The second subscale "Somatic and Physical Function" (7 items, range 0–21) includes the items of work difficulty, loss of appetite, loss of libido, fatigability, insomnia, somatic preoccupation, and social withdrawal.

The remaining items (sadness, pessimism, dissatisfaction, suicidal ideas, crying, irritability, indecisiveness, and weight loss) did not form a coherent factor. The two-factor model showed stability and fitted the data better than the other tested models (Morley et al., 2002).

Regarding the data of the present study, a confirmatory factor analysis (CFA) was performed to determine whether the data fitted the factor model.

The State Trait Anger Expression Inventory, revised version (STAXI-2) (Spielberger, 1999) is a questionnaire measuring the experience, expression, and control of anger. It comprises six scales: State Anger, Trait Anger, Anger Expression-Out, Anger Expression-In, Anger Control-Out, and Anger Control-In, as well as five subscales. An additional Anger Expression Index measures the total anger expression derived from anger control and expression scales. The Inventory has been translated into Finnish. The psychometric properties of STAXI have shown relatively high validity and reliability (Spielberger, 1999, Gollwitzer et al., 2005).

In this study, two scales were used to describe the anger management style: Anger Expression-In (Anger Inhibition), which describes the suppression of angry feelings (8 items, range 8-32), and Anger Expression-Out (8 items, range 8-32), which describes the extent to which a person expresses angry feelings outwards. The psychometric properties have been estimated in several samples (Spielberger et al., 1988, Spielberger, 1999, Borteyrou et al., 2008).

The Harm Avoidance (HA) scale is one of the four temperament scales of the Temperament and Character Inventory (TCI) (Cloninger et al. 1994), a self-administered questionnaire based on the temperament model of Robert Cloninger (Cloninger et al. 1993). The Finnish translation of the version with 240 true/false questions was used. The factor structure, internal validity, and test-retest reliability of the TCI have been previously demonstrated in both general and psychiatric populations (Brandstrom et al., 1998, Pelissolo and Lepine, 2000, Miettunen et al., 2004). The psychometric properties of the Finnish version indicated good functioning of the model (Miettunen et al., 2004).

The HA scale comprises four subscales describing different aspects of the anxiety trait:

HA1 Anticipatory Worry (11 items, e.g. "Usually I am more worried than most people that something might go wrong in the future."),
HA2 Fear of Uncertainty (7 items, e.g. "I often feel tense and worried in unfamiliar situations, even when others feel there is little to worry about."),
HA3 Shyness with Strangers (8 items, e.g. "I often avoid meeting strangers because I lack confidence with people I do not know."),
HA4 Fatigability (9 items, e.g. "I have less energy and get tired more quickly than most people.").

The Pain Anxiety Symptom Scale-20 (PASS-20) (McCracken and Dhingra, 2002) is a shortened version of the original PASS (McCracken et al., 1992). It measures fear, anxiety, and worries specific to pain. It is a self-report instrument consisting of 20 questions and a six-point Likert-scale reflecting four facets of pain-related anxiety.

The Fearfulness subscale describes fearful appraisals and interpretations about pain (e.g. "When I feel pain, I think I might be seriously ill.").

The Cognitive subscale describes cognitive anxiety and difficulties in concentrating (e.g." I can't think straight when in pain.").

The Escape/Avoidance subscale describes avoidant behavior and reactions as a response to pain (e.g. "I go immediately to bed when I feel severe pain.").

The Physiological anxiety subscale describes physiological symptoms of anxiety (e.g. "Pain seems to cause my heart to pound and race.").

The PASS-20 scales have strong positive correlations with the scales of the original PASS and have shown stability concerning the four-factor model. The psychometric properties of the questionnaire, its validity, internal consistency, and reliability have been found to be good to excellent (McCracken and Dhingra, 2002, Coons et al., 2004). The Finnish version of PASS-20 was used in the study. In the text, the term PASS denotes PASS-20 if not otherwise specified.

4.2.3. PSYCHIATRIC INTERVIEW

The clinician version of the Structured Clinical Interview for DSM-IV (SCID-CV) was used to diagnose Axis 1 disorders (First et al., 1996). The Axis 1 mental diagnoses were assessed over the lifetime, the past month, and the past 12 months. Because the clinician version has a summarized form for the anxiety disorders, this section was modified to be equivalent to the diagnostic criteria of the research version. Somatization disorder, undifferentiated somatoform disorder, and hypochondriasis were omitted due to validity and reliability issues. The onset of the disorders was assessed according to the recollection of the patient. The temporal association between the onset of pain and the onset of the psychiatric disorders was assessed on the basis of the Pain Questionnaire. The researcher psychiatrist (PK) had participated in a SCID training workshop organized by the Department of Psychiatry, Helsinki University Central Hospital.

4.3. STATISTICAL ANALYSES

The data were analyzed using SPSS, PASW, and AMOS (Arbuckle and Wothke, 1999) software.

The parametric and non-parametric statistical methods were used when appropriate. Univariate analyses included Student's t-test, Mann-Whitney test, Kruskal-Wallis test, and Pearson's correlation coefficient. Cronbach's alpha was applied to assess internal consistency. Missing values were replaced with the mean score of the variable. The proportion of the missing values concerning the self-report questionnaire variables was low, varying between 1% and 3%.

In the statistical analyses concerning multiple comparisons, the p-value correction was performed either using the Bonferroni correction or in the case of multiple correlated variables according to the recommendations by Li and Ji (Nyholt, 2004, Li and Ji, 2005). Linear and logistic regression models were used to examine the relationships between variables.

The effect of pain severity on the regression analyses was taken into account by using the approach recommended by Aiken and West (1991). Interaction variables were created based on significant predictor variables and pain severity. The influence of pain was tested by forming two groups based on the median split of the pain intensity VAS. The results were illustrated by plotting the regression curves at +1SD, mean, and -1SD values of the pain intensity variable. This approach was used when assessing the effect of the anger management style on depression and the connection between Harm Avoidance and pain-related anxiety.

A confirmatory factor analysis using the AMOS program (Arbuckle and Wothke, 1999) was used to assess whether the present BDI data fitted the BDI model by Morley, which was used in the study. The methods of estimation were the Chi-square test and the root mean square error of approximation (RMSEA).

4.4. ETHICAL ASPECTS

The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Helsinki University Central Hospital. Before entering the study, all subjects gave their written informed consent.

5. RESULTS

5.1. CHARACTERISTICS OF PATIENTS

5.1.1. SOCIODEMOGRAPHIC CHARACTERISTICS

Females comprised 62% of the patients. The mean age of patients was 47.9 years (SD 7.3, range 30–60). The mean age of females was 47.0 years (SD 7.5) and of males 49.4 years (SD 6.8). Of all patients, 60% were married or living with a partner and 16% lived alone. Regarding education, 21% of patients had a university level education, 54% had a vocational education, and 25% had no professional education. Altogether, 39% were on sick leave, 39% were employed or studying, 12% were pensioners, and 4% were unemployed.

5.1.2. PAIN CHARACTERISTICS

The median duration of chronic pain was 4 years (range 1-44). Sixteen percent of patients reported that they had had pain for more than 10 years. The majority (61%) had pain duration between one and five years. The mean current pain score using the Visual Analog Scale (VAS) was 6.0 (SD 2.1), ranging from 0 to 10.0 cm. Compared with women, men reported a higher level of current pain (6.6 (SD 1.8) vs. 5.6 (SD 2.2), t (98) = 2.47, p= 0.015).

Neuropathic pain was the most common (49%) pain category. The most common neuropathic disorders were peripheral neuropathies, spinal cord-related pain disorders, and pain related to central nervous system conditions such as multiple sclerosis or stroke. Of patients, 21% had nociceptive pain, the majority of which was related to osteoarthritic or other connective tissue pain conditions. A further 5% had visceral pain originating from internal organs such as the pancreas, bladder, uterus, or bowels. Idiopathic pain accounted for 25% of pain. This group included such pain conditions as fibromyalgia, temporomandibular disorder, vulvodynia, and pain of unknown etiology. All of the patients had at least one regular medication for chronic pain. Tricyclic antidepressants were used by 48% of patients. Other antidepressants (mainly SSRIs or SNRIs) were used by 56%. Only 17% of patients were without any antidepressants.

5.1.3.   CHARACTERISTICS OF DIMENSIONAL VARIABLES

Descriptive statistics of the psychological variables are presented in Table 3. The internal consistencies of the dimensional variables were acceptable. Some of the lower Cronbach alpha levels may be related to the low numbers of items in the variable.

Table 3. Descriptive statistics for the dimensional variables of the study.

	Minimum	Maximum	Mean	SD	Cronbach alpha
BDI sum score, range 0–63 (21 items)	1.0	46.0	17.4	10.3	0.90
BDI, Negative View of Self, range 0–18 (6 items)	0.0	18.0	3.9	4.0	0.84
BDI, Somatic and Physical Function, range 0–21 (7 items)	1.0	20.0	7.2	3.5	0.73
Anger Expression-In, range 8–32 (8 items)	8.0	30.0	20.0	4.3	0.69
Anger Expression-Out, range 8–32 (8 items)	8.0	31.0	17.6	4.3	0.81
Harm Avoidance, range 0–35 (35 items)	2.0	34.0	17.0	6.9	0.88
HA1 Anticipatory Worry, range 0–11 (11 items)	1.0	11.0	4.8	2.5	0.73
HA2 Fear of Uncertainty, range 0–7 (7 items)	0.0	7.0	3.7	1.9	0.66
HA3 Shyness with Strangers, range 0–8 (8 items)	0.0	8.0	2.9	2.2	0.75
HA4 Fatigability, range 0–9 (9 items)	0.0	9.0	5.7	2.2.	0.72
PASS-20 total, range 0–100	8.0	95.0	47.4	17.9	0.91
PASS Fearfulness, range 0–25 (5 items)	0.0	22.0	10.2	5.3	0.77
PASS Escape-avoidance, range 0–25 (5 items)	2.0	24.0	12.5	5.2	0.76
PASS Cognitive Anxiety, range 0–25 (5 items)	4.0	25.0	15.5.	5.1	0.82
PASS Physiological Anxiety, range 0–25 (5 items)	0.0	25.0	9.2	5.3	0.72
Pain Disability score, range 18–54 (18 items)	22.0	54.0	40.1	7.1	0.87
Current pain score, Visual Analog Scale (0–10.0)	6.0	10.0	9.9	2.1	-

PASS= Pain Anxiety Symptom Scale, BDI=Beck Depression Inventory,
Missing data: Harm Avoidance 1/100, HA2 1/100, PASS 1/100, PASS subscales 1/100, Pain disability 3/100

The zero-order correlations of the main dimensional variables are presented in Table 4. Current pain intensity did not correlate with any of the variables, except for the BDI physical and somatic function scale. Harm Avoidance had a positive correlation with the scales related to negative emotions such as pain-related anxiety, inhibition of anger, and the BDI scales.

Table 4. Intercorrelations of the main dimensional variables.

	Current pain	BDI sum score	BDI Negative view	BDI Somatic and physical function	Harm Avoidance sum score	PASS sum score	Anger inhibition	Anger expression-Out
Current pain	1.00							
BDI sum score	0.16	1.00						
BDI Negative view	0.07	0.84**	1.00					
BDI Somatic and physical function	0.25*	0.87**	0.54**	1.00				
Harm Avoidance sum score	0.19	0.47**	0.45**	0.38**	1.00			
PASS sum score	0.04	0.43**	.29**	0.46**	0.32**	1.00		
Anger inhibition	0.08	0.51**	0.44**	0.39**	0.30**	0.24*	1.00	
Anger expression-Out	0.14	0.15	0.12	0.13	0.14	0.09	0.09	1.00

n=100, PASS= Pain Anxiety Symptom Scale, BDI= Beck Depression Inventory
* correlation significant at p< 0.05 (two-tailed)
** correlation significant at p< 0.01 (two-tailed)

5.2. PSYCHIATRIC DISORDERS IN CHRONIC PAIN PATIENTS (STUDY I)

During the lifetime 75% of subjects had had at least one Axis 1 disorder. The most common disorders were major depressive disorder (MDD) and anxiety disorders. Any 12-month DSM-IV diagnosis was present in 59% of patients. The prevalence of MDD in the preceding 12 months was 37% in the whole sample, with no significant gender difference (females 38.7% vs. males 34.2%). Twenty-five percent of the patients had at least one anxiety disorder (females 29.0% vs. males 18.4%, ns). All of the specific anxiety disorder categories of DSM-IV were represented among the patients, with specific phobias and PTSD being the most common during the lifetime. During the past 12 months the most common psychiatric disorders were generalized anxiety disorder (GAD) and specific phobias. The prevalence of substance use disorders was 17% over the lifetime and 12% over the past 12 months. These rates include both abuse and dependence. The prevalences are high in view of the fact that active abuse problems were among the exclusion criteria of the study. Table 5 presents the prevalences of Axis I disorders in the past 12 months and over the lifetime.

When comparing the time of onset of pain and the psychiatric disorders, the majority (77%) of the anxiety disorders occurred before the onset of pain. This finding was consistent across the various anxiety disorder categories. Concerning depression, MDD followed onset of pain in 65% of cases (Table 5).

In the logistic regression analysis, current pain severity (VAS) was significantly associated with presence of past 12-month mood disorders (OR= 1.29, 95% CI 1.02-1.62), anxiety disorders (OR= 1.46, 95% CI 1.09-1.96), and DSM-IV disorders (OR=1.34, 95% CI 1.06-1.70). Sociodemographic characteristics, education, work, and marital status were not associated with psychiatric disorders in the regression analyses.

The length of the pain symptom was also associated with anxiety (OR=1.07, 95% CI 1.00-1.15) and depression (OR= 1.08, 95% CI 1.01-1.16). In contrast to other pain classes, having neuropathic pain was not associated with psychiatric morbidity, neither was having more than one pain.

The current pain VAS was highest among patients with both mood and anxiety disorders (6.9, SD 2.0, n=16) during the past 12 months. The difference was significant relative to those with neither disorder (5.5, SD 1.8, n=46, p=0.010), but non-significant relative to those with either mood disorder (6.2, SD 2.5, n=29, p=0.31) or anxiety disorder (6.3, SD 2.1, n=9, p= 0.52).

Table 5. Prevalence of past 12-month and lifetime mental disorders and onset of pain in 100 chronic pain patients.

	12-month %	Lifetime %	Lifetime onset before pain n (%)
Any axis I disorder	59	75	-
Two or more axis I disorders	22	39	-
Any mood disorder	45	59	25 (37%)
Major depressive disorder	37	54	19 (35%)
Dysthymic disorder	11	11	4 (36%)
Bipolar disorder	2	2	2 (100%)
Any anxiety disorder	25	39	37 (77%)
Panic disorder	2	6	5 (83%)
Agoraphobia	1	2	1 (50%)
Specific phobia	8	11	9 (82%)
Social phobia	5	7	6 (86%)
Generalized anxiety disorder	8	8	5 (63%)
Obsessive-compulsive disorder	2	2	2 (100%)
Post-traumatic stress disorder	2	12	9 (75%)
Substance use disorder	16	17	nk
Eating disorder	0	2	nk

nk not known

5.3. HARM AVOIDANCE AND PAIN-RELATED ANXIETY (STUDY II)

The HA score correlated positively with the PASS total score (r= 0.32, p< 0.01) (Table 4) and two of its subscales, PASS physiological (r=0. 32) and PASS fearfulness (r=0. 34) (both p< 0.01). With the remaining two subscales, the correlation was not significant. Analyzing separately the subscales of Harm Avoidance, HA4 Fatigability had the strongest association with the PASS scales (correlations ranging between r=0.394, p< 0.001, and r=0.480, p< 0.001). The current pain severity did not correlate significantly with any of the Harm Avoidance or PASS scales (Table 4).

The association between HA and PASS was present also in the multiple regression analyses (Table 6). Adjusted for gender, age, and pain severity, the Harm Avoidance total score was associated with the PASS total score. After adding the BDI sum score to the equations, the association lost its significance. Similar results were detected when using the PASS subscales as dependent variables.

Table 6. Regression analyses with PASS as a dependent variable and pain severity, HA scales, and BDI as independent variables (n=100).

Model 1[a]	β^b	t	p	β^b	t	p
Current pain	-0.016	-0.155	0.877	-0.059	-0.579	0.564
HA	0.328	3.278	0.001	0.163	1.525	0.131
BDI				0.362	3.389	0.001
R^2 adjusted	0.067			0.161		

Model 2[a]						
Current pain	-0.024	- 0.246	0.806	- 0.050	- 0.507	0.614
HA1 Anticipatory Worry	0.231	1.843	0.069	0.153	1.149	0.254
HA2 Fear of Uncertainty	- 0.194	-1.663	0.100	- 0.121	- 0.975	0.332
HA3 Shyness with Strangers	- 0.078	-0.648	0.519	-0.108	-0.901	0.370
HA4 Fatigability	0.465	4.208	<0.001	0.391	3.312	0.001
BDI				0.196	1.650	0.103
R^2 adjusted	0.225			0.239		

PASS= Pain Anxiety Symptom Scale, BDI=Beck Depression Inventory, HA= Harm Avoidance
[a] adjusted for age and gender
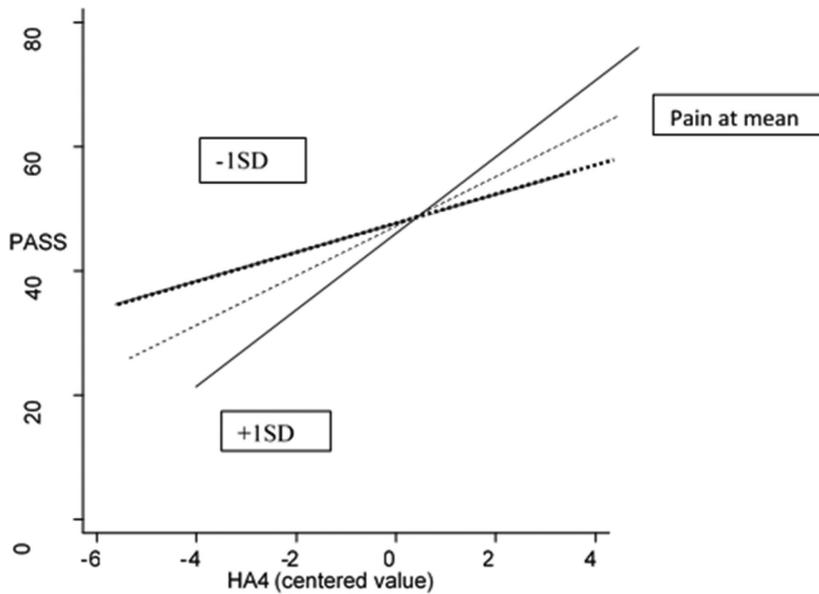[b] standardized coefficient

Figure 2. Influence of pain severity on the relationship between Harm Avoidance subscale HA4 Fatigability and pain-related anxiety (PASS).

Pain at mean – – – – – – – – – – – –
Pain at 1 SD above mean ————————
Pain at 1 SD below mean ·······························

This finding suggests that the association is influenced by the BDI score. The correlation analysis showed that the Harm Avoidance score and the BDI score had a positive correlation (r=0. 47, p< 0.01) (Table 4), indicating a relationship between the constructs. When the analysis was performed using the subscales of HA as independent variables instead of total HA score, the association of HA4 Fatigability remained significant even after adding the BDI score to the equation (Table 6). Similarly, the HA1 Anticipatory Worry subscale remained significant on the PASS-Fearfulness scale (β= 0.285, t= 2.10, p=0.039).

The relation of HA with PASS was further studied by assessing the effect of pain severity on the association. Concerning the HA total score x pain severity, no interaction effect was present. However, an interaction existed between HA4 Fatigability and pain severity (p=0.020). The median split was used to divide patients into low and high pain severity groups. The association between HA4 and PASS was stronger in the high pain severity group than in the low pain severity group. Pain severity acted as a moderator between the variables (Figure 2).

5.4. ANGER MANAGEMENT AND DEPRESSION (STUDY III)

A significant positive correlation existed between Anger Expression-In and the BDI depression scales, the correlations coefficients varying between 0.39 and 0.51. The score for the opposite anger management style, Anger Expression-Out, did not correlate significantly with any of the BDI scores. The current pain severity did not correlate with either of the anger management scales. Anger inhibition had a weak positive correlation also with other scales reflecting negative affectivity, i.e. Harm Avoidance (r= 0.30, p< 0.01) and PASS (pain-related anxiety) (r=0.24, p< 0.05) (Table 4).

The strength of the relationship between Anger Expression-In and the BDI Physical and Somatic scale was dependent on the pain severity. Higher pain severity yielded a stronger association between the variables (interaction term p=0.019) (Figure 3). In other words, pain patients with a tendency to inhibit their angry feelings had more physical symptoms of depression when the pain experience was stronger compared with those who experienced milder pain. Concerning the BDI Negative View of Self scale, no such interaction was present.
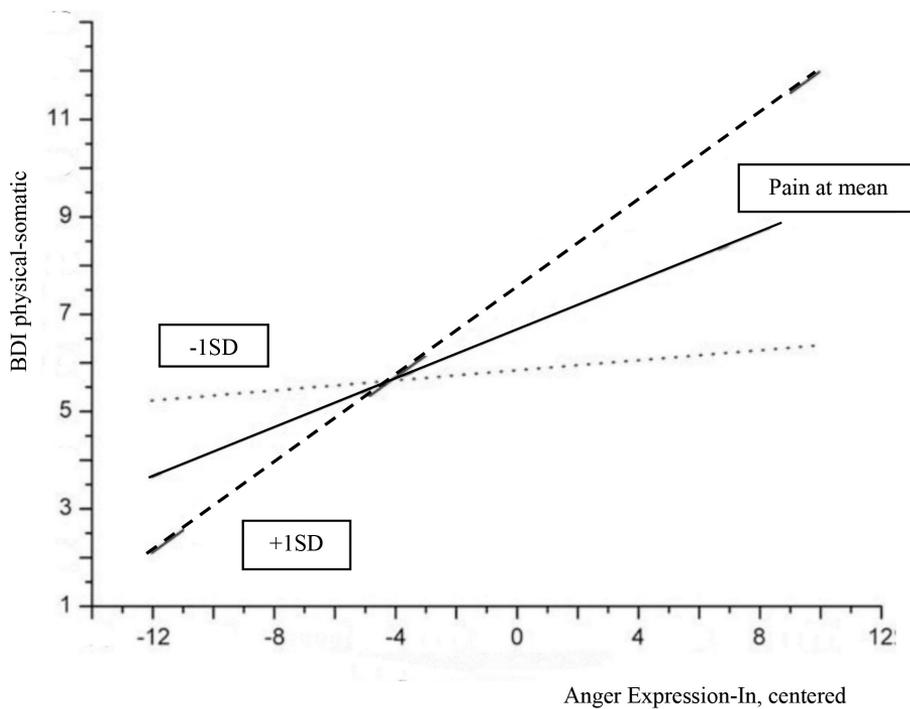

Figure 3. Influence of pain severity on the relationship between the physical and somatic symptoms of depression and inhibited anger management.

Pain at mean ——————
Pain at 1 SD above mean – – – – – – – – – –
Pain at 1 SD below mean ·······························

5.5. SOMATIC AND COGNITIVE-EMOTIONAL ITEMS OF BDI COMPARED WITH DSM-IV MAJOR DEPRESSIVE DISORDER (STUDY IV)

The data of the BDI quesionnaire were analyzed using the confirmatory factor analysis in order to compare it with the two-factor model presented by Morley. The fit of the data to the Morley model was acceptable. The data fit well (Chi-square 74.4, with 64 degrees of freedom provided a non-significant p-value (0.18), and a RMSEA (Root mean square error of approximation measures discrepancy per degree of freedom) of 0.041 (95% CI 0.00-0.075)), when a value of less than 0.05 is taken to indicate a good fit. The result indicated that the model could be utilized in the analysis.

The prevalence of the patients fulfilling the criteria of current MDD (1 month) was 20%. These patients were compared with the 80 patients not fullfilling the current MDD criteria. These groups did not differ regarding age, gender, education, working or social status, or time since pain onset.

Relative to patients without MDD, those with MDD had higher BDI total score 29.0 (SD 9.9) range 10.0-46.0 vs.   14.5 (SD 8.1) range 1-39 , t -6.82, p<0 .001), BDI Negative View of Self score 7.1 (SD 4.9) range 0-18.0 vs. 3.1 (SD 3.4) range 0-13.0 , t -3.51 p=0.002), and BDI Somatic and Physical function score 11.2 (SD 4.0) range 2.0-20.0 vs. 6.2 (SD 2.6) range 1.0 -14.0 , t -6.86, p< 0.001). Patients with MDD also had higher current pain severity VAS 7.1 (SD 1.6) vs. 5.7 (SD 2.1), t -2.82, p< 0.006).   However, the pain disability score did not differ between patients with and without MDD.

The comparisions between pain patients with and without MDD were performed also item by item (21 items) (Table 7). According to the recommendations for correlated variables, the significance level was set to p< 0.0034. Using the Mann-Whitney median rank test in the comparison , 11 of the 21 items were different between the groups. Patients with MDD had higher scores in items representing the somatic/physical function, such as social withdrawal, loss of appetite, and libido, as well as several cognitive-emotional items, which were not included in the factor model, such as irritability, sadness, guilt, or suicidal ideas. The two least differing items between the groups were insomnia and weight loss.

Table 7. Comparing BDI items (according to the two-factor model of BDI) between patients with (n=20) and without (n=80) diagnosis of current MDD.

	Mann-Whitney U-test	Z	p[a]	Factor in BDI model
BDI 5 Guilt	474.00	-3.27	0.001*	BDI Negative view of self
BDI 7 Self-dislike	529.50	-2.78	0.006	BDI Negative view of self
BDI 14 Body image change	515.00	-2.65	0.008	BDI Negative view of self
BDI 6 Punishment	572.50	-2.62	0.009	BDI Negative view of self
BDI 8 Self-accusation	554.00	-2.30	0.022	BDI Negative view of self
BDI 3 Sense of failure	589.50	-2.09	0.037	BDI Negative view of self
BDI 12 Social withdrawal	264.00	-5.06	<0.001*	BDI Somatic/physical function
BDI 18 Loss of appetite	403.50	-4.18	<0.001*	BDI Somatic/physical function
BDI 21 Loss of libido	348.50	-4.07	<0.001*	BDI Somatic/physical function
BDI 17 Fatigability	421.50	-3.64	<0.001*	BDI Somatic/physical function
BDI 15 Work difficulty	524.50	-2.76	0.006	BDI Somatic/physical function
BDI 20 Somatic preoccupation	600.50	-2.09	0.037	BDI Somatic/physical function
BDI 16 Insomnia	631.00	-1.60	0.11	BDI Somatic/physical function
BDI 11 Irritability	349.00	-4.51	<0.001*	Item not in model
BDI 13 Indecisiveness	339.00	-4.25	<0.001*	Item not in model
BDI 9 Suicidal ideas	386.00	-4.11	<0.001*	Item not in model
BDI 4 Dissatisfaction	414.00	-3.63	<0.001*	Item not in model
BDI 2 Pessimism	402.50	-3.61	<0.001*	Item not in model
BDI 1 Sadness	452.00	-3.28	0.001*	Item not in model
BDI 10 Crying	574.00	-2.21	0.027	Item not in model
BDI 19 Weight loss	627.00	-1.77	0.076	Item not in model

[a] Significance level adjusted to p < 0.0034 according to recommendations concerning correlated variables (Li and Ji, 2005; Nyholt, 2004)

In multiple logistic regression analysis after controlling for gender, age, and pain severity, MDD was significantly associated with both the BDI Negative View of Self (OR 1.25, 95% CI 1.09-1.44, p=0.002) and the BDI Somatic/Physical function (OR 1.83, 95% CI 1.33-2.51, p= 0.0002) subscales when only one the subscales was entered into the equation. However, when both subscales were entered together into the same equation (Equation 2), the association was significant only with the BDI Somatic/Physical function scale (OR 1.69, 95% CI 1.23-2.31, p=0.001) (Table 8).

Table 8. Logistic regression analysis with current major depressive disorder as a dependent variable (n=100).

Variable	Equation 1					Equation 2				
	B[a]	S.E.	Wald	p	OR (95%CI)	B[a]	S.E.	Wald	p	OR (95%CI)
Age	0.01	0.04	0.12	0.72	1.01 (0.94-1.10)	0.03	0.05	0.36	0.55	1.03 (0.93-1.14)
Gender	0.75	0.61	1.50	0.22	2.11 (0.64-6.97)	1.60	0.86	3.45	0.063	4.94 (0.92-26.7)
Current pain severity	0.50	0.18	7.76	0.005	1.64 (1.16-2.33)	0.47	0.24	3.93	0.047	1.60 (1.01-2.53)
BDI Negative view of self						0.06	0.09	0.37	0.54	1.06 (0.88-1.27)
BDI Somatic/ physical function						0.52	0.16	10.5	0.001	1.69 (1.23-2.31)
Pain disability						-0.04	0.06	0.36	0.55	0.97 (0.86-1.08)
Pseudo R^2	0.097					0.35				

[a] standardized coefficent, S.E. standard error, OR Odds ratio

References

6. DISCUSSION

6.1. MAIN FINDINGS

In the clinical sample of chronic pain patients, the prevalence of psychiatric comorbidity was high. The majority, 75%, of the patients fulfilled the criteria for at least one lifetime psychiatric disorder. The patients had a wide range of disorders, the most common of which were MDD and anxiety disorders. The majority of the anxiety disorders were present before onset of pain. Thus, the temporal relationship excludes pain having a direct causal effect on anxiety disorders. Concerning depression, the pattern of the temporal relationship was different. In about 60% of patients, depression followed the onset of pain. During the past 12 months the prevalence of MDD was 37% and the prevalence of anxiety disorders 25%. Compared with the prevalences of depression and anxiety in the general adult population in Finland (Pirkola et al. 2005), the prevalences here are six times higher.

The temperament trait Harm Avoidance was associated with pain-related anxiety symptoms. The association weakened after the effect of depression was controlled. In addition, the strength of the association was dependent on pain severity. Patients with higher pain severity had a stronger association between the HA4 Fatigability subscale and pain-related anxiety. In patients with milder pain, the association was weaker. A similar type of pain severity-dependent interaction was detected between anger inhibition and the somatic symptoms of depression. However, no interaction effect existed between anger inhibition and pain concerning the cognitive-emotional symptoms of BDI. The BDI factor model of Morley et al. (2002) was used here in order to differentiate the cognitive-emotional and the somatic-physical items of the questionnaire. When the two factors of Morley's BDI model were compared between patients with and without a DSM-IV-derived diagnosis of MDD, the depressed patients scored higher in both factors. However, the somatic-physiological items were more strongly related to the diagnosis of MDD.

6.2. RESULTS IN RELATION TO PREVIOUS STUDIES

6.2.1. PREVALENCE OF DEPRESSION AND ANXIETY COMPARED WITH OTHER STUDIES USING DSM

The prevalence of depression and anxiety in this study was high, consistent with the findings of several previous studies performed in pain clinic population samples. The tertiary pain clinic patients represent the most complicated portion of chronic pain patients, with enhanced functional disability and past treatment failures, which may explain the reporting of high prevalences of mental comorbidity. The generalizability of the results is thus limited. Compared with more recently published studies (Gerhardt et al., 2011, Reme et al., 2011, Radat et al., 2013), the prevalences of mood and anxiety disorders were markedly higher in this study.

The prevalence of psychiatric disorders may, however, vary considerably between different studies, even if the studies have used structured diagnostic methods based on DSM criteria (Table 1). The large variability is particularly present in the disorder categories of dysthymia, ranging between 1% (Radat et al., 2013) and 23% (Fishbain et al., 1986), and GAD, ranging between 5% (Arnold et al., 2006) and 70% (Verri et al., 1998). In the present study, the prevalences of certain anxiety disorders, such as PTSD, OCD, and social phobia, were generally in line with earlier studies (Table 1). The greater variability concerning the prevalences of GAD and panic disorder may be related to the symptom overlap phenomenon. Despite using structured psychiatric methodologies, defining the boundaries between psychiatric disorders and chronic pain requires subjective interpretation. The interpretation is likely to be more difficult in disorders that have overlapping symptoms with chronic pain, e.g. muscle tension or arousal, typical in GAD and panic disorder. The variations in pain intensity may also affect the diagnostic process. Severe pain causes more arousal, tension, and bodily symptoms.

Another source of the variability is the heterogeneity of pain patients. Some studies may concentrate on specific pain patients such as neuropathic pain patients (Radat et al., 2013) or fibromyalgia patients (Arnold et al. 2006). Neuropathic pain being more localized in nature has been associated with less emotional symptoms than fibromyalgia, which is a more generalized pain (Gormsen et al., 2010). The current study resembled most pain clinic studies by having a heterogeneous patient sample with several types of pain, including idiopathic pain.

The definitions of chronic pain may vary between the studies. According to the most usual definitions, chronic pain lasts longer than three or six months. In the present study, the time inclusion criterion was one year, and the median duration of pain was four years. The psychological symptoms related to pain may vary depending on the duration of pain. Gatchel speculated that a longer duration of pain may be associated with a higher prevalence of depression relative to the

reactive anxiety and fear typical of more acute pain (Gatchel et al., 1996). Considering the long duration of pain in our study, one may expect that the acute anxiety and adjustment reactions have declined.

In addition to depression and anxiety disorders, a structured assessment methodology, such as the SCID interview, may reveal also more rare disorders, e.g. bipolar disorder or obsessive compulsive disorder, which may be clinically important. Bipolar disorder has seldom been explored in related studies in the field (Arnold et al., 2006, Radat et al., 2013). The clinical importance of a psychiatric diagnosis in chronic pain patients is related not only to its impact on the treatment outcome but also to the selection of pharmacological treatment options. Tricyclic antidepressants and other double-acting antidepressants are widely used in chronic pain, also as first-line treatment options, which may complicate the management of bipolar disorder.

6.2.2. ANXIETY, DEPRESSION, AND THE TEMPORAL RELATIONSHIP WITH CHRONIC PAIN

The mechanisms underlying the association between chronic pain and psychiatric comorbidities are unclear. Analyzing the temporal relationship between the conditions can shed some light on the question of causality. The finding that anxiety disorders precede pain onset has been reported in two earlier cross-sectional studies (citations). However, Polatin and colleagues (1993) found the prevalence of anxiety disorders among 200 back pain patients to be relatively low and similar to that in the normal population. In the other study (citation), 87% of 70 PTSD diagnoses preceded pain onset, whereas only 46% of the 50 panic disorder cases preceded pain. Other anxiety disorders were not registered (Dersh et al., 2007b). These results resemble our findings. As the studies are all cross-sectional, with the information on other disorders based on patient recollection, the results must merely be considered as estimates. To date, prospective studies concerning the onset of anxiety disorders related to pain have not been published. Regarding depression, prospective studies have supported a reciprocal pattern considering the risk factor function as well as the temporal relationship, with depression preceding or following chronic pain onset.

6.2.3. ANGER AND PAIN

The number of studies on pain and anger is relatively low compared with anxiety and depression. Regarding the DSM, anger is mentioned only occasionally among the criteria of various disorders. Aggression or irritability belongs to the

symptom criteria of categories such as PTSD, dysthymia, or borderline and antisocial personality disorders (American Psychiatric Association, 1994, American Psychiatric Association, 2013). The DSM category "Intermittent Explosive Disorder" includes verbal and behavioral aggression among the diagnostic criteria, but the diagnosis is seldom used in practice or in research.

The present study confirmed the positive correlation between anger inhibition and depression presented by several previous studies (Tschannen et al., 1992, Duckro et al., 1995, Materazzo et al., 2000). Analyzing separately the two subscales of the BDI showed that anger inhibition correlated with both the cognitive-emotional and somatic-physical symptoms of depression. An interesting finding is the influence of pain severity on the association between anger inhibition and the somatic-physical signs of depression. The finding resembles the earlier-mentioned finding of an association of increased muscle reactivity with pain in patients with a high level of anger-in (Burns et al., 2006). The finding is also associated distantly with the psychodynamic approach-based ideas of Engel that link emotion suppression to bodily symptoms and pain (Engel, 1959). However, the interaction finding may also reflect the dimensional characters of the constructs and their overlapping boundaries. When the symptoms are more intense, they become more fused with each other.

6.2.4. HARM AVOIDANCE AND PAIN-RELATED ANXIETY

To our knowledge, the association between Harm Avoidance (HA) and pain-related anxiety (PASS) has not been previously tested. The positive correlation between the variables is in line with the numerous studies showing a positive association between HA and anxiety disorders in general (Miettunen and Raevuori, 2012). High HA relative to controls has been a constant finding in studies among chronic pain patients (Malmgren-Olsson et al., 2006, Conrad et al., 2007, Mazza et al., 2009). However, lack of healthy controls in our study prevents such an evaluation. Considering the state effect, the association became less significant after the effect of depressive symptoms in the analysis. One possible explanation can be the dimensionality and overlap between the constructs of anxiety and depression (Brown and Barlow, 2009). When the subscales of HA were analyzed separately, the HA4 Fatigability subscale showed the strongest association with pain-related anxiety, even after controlling the state effect of depression. Previous studies in chronic pain patients have shown that the elevation of the HA level has been more clear in the HA4 and HA1 subscales than in the other two subscales (Malmgren-Olsson et al., 2006, Conrad et al., 2007, Lundberg et al., 2009). In a recent brain imaging study, the same HA4 subscale as well as the HA2 subscale were associated

with low opioid receptor availability in the brain areas related to anxiety regulation. The authors suggested that a tendency to negative affectivity could parallel the lower endogenous opioid activity in the affective brain areas (Tuominen et al., 2012). Elevated HA has also been associated with better responsiveness to opioids. A high level of HA in healthy volunteers was associated with higher sensitivity to morphine in the cold pressure test (Pud et al., 2006).

6.2.5. INTERACTION BETWEEN PAIN SEVERITY AND HARM AVOIDANCE

The influence of pain severity on the association between HA and pain-related anxiety resembles the finding concerning anger and depression. Stronger pain is associated with a stronger linkage between the variables. When pain is less severe, the association is weaker. In other words, the level of the anxiety reaction is dependent on the experience of the pain intensity. Temperament may function as a regulatory factor between the external stimulus and its emotional consequence. Because the interaction effect concerned only the HA4 Fatigability subscale instead of total HA, again the state effect of pain on HA4 is possible. However, the HA4 Fatigability scale remained clearly significant. In the model of Cloninger, HA4 Fatigability is related to asthenia and loss of energy. Individuals with high HA4 recover from stress more slowly (Cloninger et al., 1994). One may assume that individuals with a constantly low level of energy are also less able to use effective coping mechanisms, which may predispose to anxiety. HA4 may reflect a specific feature of vulnerability to pain or chronic pain as a stressor might mold the personality structure.

In conclusion, despite the weaknesses of the cross-sectional study design, our results are consistent with those of earlier studies on HA and pain. Considering the lifesaving function of acute pain, fear and avoidance are natural reactions to pain. Thus, it is plausible that Harm Avoidance, in molding the individual reactions to fear-evoking stimuli, is connected to pain perception, pain behavior, and also to the endogenous opioid system.

6.2.6. ASSESSING DEPRESSION IN CHRONIC PAIN

In chronic pain patients, the validity of the depression assessment instruments has been criticized due to the symptom overlap problem as well as limitations with self-report. The majority of the psychology-based depression studies in pain patients have used instruments such as the BDI, which was designed to measure the severity of depression in psychiatric patients.

Among the chronic pain patients with MDD, the mean BDI score was close to a

level corresponding to severe depression (MDD 29.0 vs. no MDD 14.5). Regarding the guidelines of the BDI (< 9 no depression, 29+ severe depression), the mean scores are high. Comparing the results of the most recent version of the BDI, the BDI II (Beck et al. 1996b), with SCID-based diagnosis of MDD using receiver operating characteristic (ROC) analysis, Poole and colleagues (2009) suggested a cut-off score of 22+ as being optimal for screening MDD in chronic pain patients. Beck and colleagues (year?) developed a special version of the BDI for medical patients (Steer et al., 1999), however, in chronic pain patients this version is seldom used in research.

Besides Morley, other factor analytic models of depression in pain patients exist (Novy et al., 1995, Poole et al., 2006). The factor solutions may vary between the models, however, the distinction between somatic and emotional symptoms is a characteristic feature. The usual conclusion has been not to rely on somatic items when assessing depression in pain (Morley et al., 2002, Taylor et al., 2005). However, other factor analytic studies have presented conflicting results, supporting the use of the total BDI score, including the somatic items, as part of the depression assessment in chronic pain (Novy et al., 1995, Harris and D'Eon, 2008). Our results support the use of the somatic items as part of the depression assessment process.

Only a limited number of publications assessing the relevance of the MDD criteria in chronic pain patients are available. In evaluation of 129 chronic pain patients, Wilson and colleagues (2001) reported a remarkable decline (from 35.7% to 19.4%) in the prevalence of MDD when using alternative DSM criteria or when the somatic criteria were excluded if somatic symptoms were attributed entirely to pain. However, neither the BDI scores nor the cognitive affective or the somatic subscales differed between the groups. The symptoms that were similar between depressed and non-depressed pain patients were hypersomnia, appetite gain, weight loss or gain, psychomotor retardation, and recent suicidality. The least differing of the BDI items were insomnia, weight loss, and somatic preoccupations.

In the present study, the comparison was made between a categorical method and a dimensional method. The diagnosis of MDD requires at least five symptoms of nine, several of which are somatic in nature. This may explain the association of the physical and somatic function factor with the diagnosis of MDD.

6.3. STUDY LIMITATIONS AND STRENGTHS

6.3.1. PATIENT SAMPLE

One of the major drawbacks of the study is the highly selected patient sample in a tertiary pain clinic, limiting the generalizability of the results. The patients in the clinic represent the most complicated cases of all chronic pain patients. The majority

of the patients have earlier been treated in other clinics with suboptimal treatment outcome. Because psychiatric comorbidity is known to complicate the treatment, one may speculate that this comorbidity is prevalent among these patients. In addition, patients having more psychosocial stress factors may be more willing to participate in the study, causing further bias. Because of the relatively small sample size, the power of the statistical analyses was restricted. The number of males was low (38) relative to females, and the comparisons between genders mostly failed to show any differences. Despite chronic pain, the patients in the study formed a heterogeneous sample concerning type, location, and duration of pain symptom.

Some of the patients had already been treated in our pain clinic for a time and others had started their treatment recently. However, even the latter group of the patients had received treatment for chronic pain in other clinics previously. All of the study patients had been prescribed medication for chronic pain. Common medications used in pain patients include tricyclic antidepressants and SNRIs, affecting pain, anxiety, and depression. Recent changes in the medication or treatment may have occurred prior to the study visit, which may have affected the results of the psychological and pain assessment questionnaires.

6.3.2. STUDY DESIGN

The cross-sectional design of the study is unable to prove any causality. Assessing state effects on trait variables requires a longitudinal study design. In addition, the variation in pain intensity may influence the psychological symptoms and affect the diagnostic process. Using a single moment for pain severity measurement does not yield deeper information concerning the underlying mechanisms between pain and psychological symptoms. Longitudinal studies, on the other hand, are time-consuming and expensive. Participant drop-out is also a problem.

The lack of control patients is another limitation. Determining whether depression and anxiety differ between chronic pain patients and psychiatric patients requires controls. However, considering the multiplicity of the confounding factors, more than one control group would have been necessary; patients with chronic pain without depression or anxiety, patients with depression or anxiety without chronic pain, healthy controls, etc. This would have complicated the structure of the study and restricted the research questions.

6.3.3. SELF-REPORT QUESTIONNAIRES

Data based on self-report questionnaires, such as the STAXI-2, the PASS-20, the TCI, and the BDI, may possess reliability and validity problems. A social desirability bias is possible, particularly in the case of assessing negative emotions such as anger (King and Bruner, 2000). The participants may also understand and interpret the questions differently. Questions regarding the trait-state distinction may require thorough reading and understanding of the wording. The ability to assess oneself and one`s own emotions also varies between individuals. The self-assessment process may also be compromised by several state factors such as the variation in pain severity, medication effects, or acute temporary sleeping problems.

6.3.4. SYMPTOM OVERLAP

Using the SCID interview and DSM to assess mental disorders in chronic pain patients has advantages as well as limitations. Compared with the self-report questionnaires, SCID and DSM have been regarded as the gold standard. Using SCID and DSM allows a broad spectrum assessment that covers a wide range of symptoms as well as comorbidity of the disorders. The symptom overlap problem in chronic pain patients is also present with the DSM. According to the diagnostic guidelines, somatic symptoms should be excluded from the diagnosis if they are "clearly and fully attributable to the somatic condition" (American Psychiatric Association, 1994). However, clear instructions for the assessment are lacking and rely on the subjective interpretation of the examiner. In our study, one examiner with formal training in use of the SCID performed the clinical interviews. Despite the training and clinical experience of the examiner, the subjectivity factor must be taken into account. Subjective interpretation is required also in the DSM sections Somatoform disorders and Pain Disorder, which were omitted from the diagnostic assessment. This decision was based on the known difficulties concerning the reliability and validity of the diagnoses in pain patients. Considering the psychological underpinnings of chronic pain, judgment of when the psychological factors play a significant role in the onset, severity, and maintenance of pain is arbitrary.

6.3.5. RECALL BIAS

The ability of patients to remember the onset of pain and its temporal relationship to the emotional symptoms can be questioned. Determination of pain onset was based on the pain questionnaire. Onset of psychiatric disorders relied on retrospective recall of the time. Different memory probes were used when determining the

time of onset. However, the validity of both lifetime diagnoses and time onset determinations is likely to be lower than that of current diagnoses.

6.3.6. HARM AVOIDANCE

Regarding the personality assessment, only the Harm Avoidance dimension was assessed in detail in this study. Cloninger`s model contains a number of other factors that might have relevance in chronic pain. Harm Avoidance was chosen because it has been the most studied factor in the model. Compared with the other dimensions of the TCI, Harm Avoidance has been the most robust and most consistently associated with various psychiatric disorders (Miettunen and Raevuori, 2012).

7. CLINICAL IMPLICATIONS AND FUTURE PERSPECTIVES

Assessment of symptoms of depression in chronic pain patients is part of the general treatment protocol in pain clinics today. The importance of anxiety in pain-related disability has also been recognized. Among pain studies, the present study represents the minority by using psychiatric diagnostic methodology in the assessment.

Recent psychological research paradigms have involved several cognitive models linked to pain-related anxiety and depression such as the Fear-Avoidance Model of Pain (Lethem et al., 1983, Vlaeyen et al., 1995), the Pain Catastrophizing Model (Sullivan et al., 1995), the Pain Acceptance Model (McCracken and Zhao-O'Brien, 2010), or the Perceived Injustice Model (Sullivan et al., 2012). One of the main differences between the psychological and the psychiatric views has been in a dimensional approach versus a diagnostic approach. The categorical diagnostic approach of DSM has been criticized. Some of the major targets of the criticism have involved its descriptiveness of the diagnoses without underlying empiric models, the general complexity with a multitude of categories, the heterogeneity within a diagnosis, and the comorbidity and overlap between the diagnostic categories (Watson et al., 2006). Another main criticism is the division between cases and non-cases. According to the diagnostic system, one either has a disorder or not. Subthreshold non-cases have symptoms, but not enough to justify the diagnosis and treatment (Goldberg, 2000). However, the categorical and dimensional views are not entirely contradictory, but are partly complementary. The categorical approaches include dimensional measurements of severity, and the dimensional approaches have severity categories and cut-off scores. According to Kraemer et al. (2004), every disorder is both categorical and dimensional, but in order to reach the best clinical or research result one must use a certain approach. One of the major changes in the DSM-5 has been the addition of the dimensional assessment in several disorder categories.

The psychiatric diagnostic approach is needed to make decisions concerning treatment and interventions. The need for the categorical approach is emphasized in clinical work and clinical research (Kraemer et al., 2004). Assessment of past psychopathology and previous episodes of depression or anxiety provides also important background information for the treatment plans. The psychiatric diagnosis may markedly affect the pain treatment procedure by excluding certain treatment options or prioritizing others. Chronic pain patients with a history

of bipolar disorder or substance use disorder may have restrictions concerning pharmacological treatment options. Patients with severe major depressive disorder may need special support because of their functional impairment and cognitive disabilities. Thus, the psychiatric approach can contribute considerably to the multidisciplinary pain management programs. Together with the psychological approach, it can help to develop more individualized and patient-targeted treatment. Psychiatric comorbidity is known to complicate the outcome of pain treatment. One explanation may be that the disorders remain poorly diagnosed and untreated or the treatment is suboptimal.

The relationship between chronic pain and personality has been less investigated in recent years. However, underlying personality structures are known to function as predisposing factors for psychiatric disorders. Even if the pain-prone personality profile was shown to be non-existent, the personality factors have relevance in pain coping and treatment planning.

Our findings highlight the difficulties in defining the borders between pain and psychiatric diagnoses. The essential characteristics of depression and anxiety that constitute chronic pain remain obscure. In this study, the somatic items of BDI were strongly associated with the diagnosis of MDD, whereas Morley hypothesized that depression measured by the BDI is more related to general distress than actual depression because of the lack of the negative self-image typical of depression (Morley et al., 2002). The symptom overlap creates a border area where clear distinctions between pain, anxiety, and depression are difficult or even impossible to make. The result can be either an over-diagnosis or missed diagnoses. Excluding or interpreting strictly the somatic criteria in the diagnostic assessment reduces the sensitivity, which may have such serious consequences as increased suicidality (Tang and Crane, 2006). Determining the core or "real" symptoms of depression and anxiety in chronic pain becomes a challenge also after considering the common neurotransmitter and brain pathway systems. However, due to common background mechanisms, some of the effective treatment options are also common, e.g. SNRIs or cognitive-behavioral therapy.

Despite the cross-sectional study design preventing causality conclusions in our study, some ideas emerge that shed light on underlying mechanisms. As the anxiety disorders preceded pain onset, they cannot be a consequence of pain. One explanation for the temporal finding is that most anxiety disorders develop in early adulthood. This does not, however, explain the high prevalence of anxiety disorders in pain patients compared with the normal population. Some other mechanisms, such as common vulnerability factors, could provide explanations for the co-occurrence. Previous studies have suggested an elevated level of Harm Avoidance in chronic pain patients relative to controls, however, prospective follow-up studies are lacking. In stress-diathesis models in pain, personality has been

presented as a possible vulnerability factor for chronic pain and disability (Banks and Kerns, 1996). According to the Fear-Avoidance model of chronic pain, pain avoidance has been among the main mechanisms leading to pain chronification and disability (Lethem et al., 1983, Vlaeyen et al., 1995). One may assume that individuals with a high level of Harm Avoidance have a tendency to avoid painful situations, which may in turn predispose them to disability.

Harm Avoidance occurs concomitantly with the suppression or inhibition of anger. Anger as a comorbid symptom has evoked little attention in pain research. However, anger and aggressive reactions are apt to cause an immense emotional burden among personnel in pain management units, while anger inhibition may go completely unnoticed.

The stigma concerning psychiatric disorders has evoked criticism and concern. The pain associated with depression has been described using terms such as functional or unexplained, suggesting that the pain is not "real" (Reveler et al., 2006). The fear of stigma may have negative consequences. The fear of being labeled as having a mental disorder may prevent pain patients from seeking help. In the study of Wilson and colleagues (year?), depressed pain patients were inclined to interpret the etiology of their symptoms as pain-related instead of connected to depression. Concern about stigma has centered around the diagnosis of Pain Disorder in the DSM in particular (Young, 2010). The current version, DSM-5, includes major revisions of the section Somatoform Disorders. Pain Disorder is incorporated into the "Somatic Symptom Disorder" section, with a focus on distress and anxiety instead of psychologic etiology or unexplained symptoms (American Psychiatric Association, 2013).

The definition of pain by IASP emphasizes that emotions are an essential part of pain. Pain is a subjective experience. This close relationship has been reflected in several sections of the current study; the pain experience was associated with anxiety and depression despite whether the method of assessment was dimensional or categorical. Pain intensity influenced the associations between other emotional constructs. The findings of the study are in line with the biopsychosocial model of pain. Pain and emotions share similarities and have common underlying mechanisms. The boundaries between pain and its emotional components are blurred. One may think that there is a fuzzy border area that reflects the mind/body entity where making clear distinctions is not possible.

8. CONCLUSIONS

This cross-sectional study showed a high prevalence of psychiatric disorders in 100 chronic pain patients. The prevalence of anxiety and depression was high compared with the general population. The temporal relationship related to pain onset differed between the anxiety disorders and the mood disorders. The temperament trait Harm Avoidance was associated with pain-related anxiety, and the pain intensity influenced the strength of the association. Pain patients with a tendency to inhibit their angry feelings had more somatic and physical symptoms of depression when the pain experience was stronger relative to those who experienced milder pain. Concerning the inhibition of anger and the cognitive-emotional symptoms of depression, the pain experience did not influence the association. Both the cognitive-emotional and somatic-physical symptoms measured by the BDI were associated with the diagnosis of depression. However, the diagnosis of MDD was more strongly related to the somatic-physical symptoms of the questionnaire.

9. ACKNOWLEDGMENTS

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