From the Department of Clinical Neuroscience
Karolinska Institutet, Stockholm, Sweden

MORE THAN PAIN - ASSESSMENT AND TREATMENT OF PAIN-RELATED DYSFUNCTION IN PEDIATRIC CHRONIC PAIN

Marie Kanstrup

Stockholm 2017

Published by Karolinska Institutet.
Printed by E-Print AB 2017

ISBN 978-91-7676-756-6

More than pain - Assessment and treatment of pain-related dysfunction in pediatric chronic pain
THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

Marie Kanstrup

Principal Supervisor:
PhD, associate professor
Rikard Wicksell
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

Co-supervisor(s):
PhD
Linda Holmström
Karolinska Institutet
Department of Women's and Children's Health
Division of Pediatric Neurology

Professor
Mats Lekander
Karolinska Institutet
Department of Clinical Neuroscience
Osher Center for Integrative Medicine
and
Stockholm University
Stress Research Institute

Opponent:
Professor
Lance McCracken
Department of Psychology
Institute of Psychiatry, Psychology & Neuroscience
King's College London

Examination Board:
Professor
Yvonne Brandberg
Karolinska Institutet
Department of Oncology Pathology

PhD, associate professor
Pia Enebrink
Karolinska Institutet
Department of Clinical Neuroscience
Division of Psychology

MD, PhD, associate professor
Gustaf Ljungman
Uppsala University
Department of Women's and Children's Health
Pediatric Oncology

“Is anybody listening, tell me can you see

This darkness surrounding me

Now it's getting colder, heavy on my shoulder

And it's getting hard to breathe

Vision’s getting blurry, I'm getting worried

Cause it's getting hard to see

When you're living in the house of pain”

Living in pain: Notorious B.I.G feat. 2Pac, Mary J Blige & Nas

ABSTRACT

Background: Pediatric chronic pain is prevalent, affecting between 11-38% of children and adolescents, with a subset of individuals suffering from substantial pain-related disability. Dysfunction in emotional, social and physical domains, as well as parental distress, commonly co-occurs with pediatric chronic pain. The effectiveness of behavior oriented treatments for child pain intensity and disability is today well known, but there is still a need for further development of such treatments, including evaluations of different treatment formats and parent support programs. There is also a need to further develop and evaluate instruments to assess pain-related dysfunction in pediatric chronic pain.

Purpose and aims: The purpose of this doctoral project was to develop effective ways to assess and treat dysfunction in pediatric chronic pain. The aims were to 1) evaluate the psychometric properties of the Insomnia Severity Index (ISI) for youths (study I) and the psychometric properties of the Pain Interference Index (PII) (study II), 2) investigate the prevalence of insomnia and the relationships between sleep and functioning (emotional and physical) (study I), 3) identify and evaluate existing research on intensive interdisciplinary treatment (IIPT) for pediatric chronic pain (study III), 4) investigate the effects of Acceptance and Commitment Therapy (ACT) on functioning in a clinical pilot study of individual and group treatment for adolescents with chronic pain (study IV) and 5) investigate the effects of parental support based on ACT on functioning in a clinical pilot study of individual and group treatment for parents of adolescents with chronic pain (study IV).

Methods: Psychometric properties of the ISI and the PII were evaluated using cross-sectional data from pediatric participants with chronic debilitating pain. Evaluations included principal component analysis, correlational and regression analyses, and analysis of internal consistency. The importance of insomnia for the relationships between pain intensity, depression and functional disability were assessed by examining the indirect effects of insomnia in the relationship between pain and depression, and between pain and functional disability. To evaluate the current evidence for IIPT for pediatric chronic pain, a systematic review and meta-analysis was conducted. Finally, to investigate the effects of individual and group ACT treatment for adolescents with chronic pain and their parents, non-parametric analyses of differences between groups and over time were conducted, as well as analyses of clinically significant changes for adolescent and parent outcomes.

Results: Results from the psychometric evaluations in study I and II supported the concurrent criteria validity and reliability for the ISI and the PII in this sample. The principal component analysis supported a 1-factor solution for PII. More than half of the sample reported clinically relevant scores of insomnia, and indirect effects of insomnia were found for the relationships between pain and depression, and between pain and functional disability. In study III, the systematic searches resulted in 10 studies matching criteria for inclusion (1 randomized controlled trial and 9 non randomized studies), and the meta-analysis yielded preliminary evidence for positive treatment effects of IIPT, but findings showed substantial heterogeneity. In study IV, adolescents reported significant improvements in functioning outcomes (i.e. pain interference, pain reactivity, depression, and psychological flexibility). Parents reported improvements in parental pain reactivity and psychological flexibility. There were no differences between group and individual treatment, and the pattern of results illustrated significant changes during the second half of treatment. Clinically significant changes were reported to a large extent in adolescent (21-63%) and parent (54-76%) variables.

Conclusions and further directions: The PII and ISI are reliable and valid instruments that can be used to assess pain interference and insomnia in children and adolescents presenting with chronic pain. IIPT holds promise as a treatment format for addressing pain and pain-related dysfunction, but due to a small number of studies and methodological weaknesses, more research in this field is needed. The treatment evaluation of ACT for adolescents with chronic pain supported the promising findings from previous studies, illustrating improvements in adolescent functioning after treatment. Also, results indicate the utility of the ACT based parent support. Particularly, larger clinical trials with rigorous methodology are needed to evaluate the relative utility of individual and group treatment formats, mechanisms of change and the effects of parental support programs.

POPULÄRVETENSKAPLIG SAMMANFATTNING

Långvarig smärta är vanligt hos barn och ungdomar, och drabbar mellan 11-38%. En del av dem som drabbas upplever också omfattande smärtrelaterade svårigheter, till exempel depression, fysisk funktionsnedsättning, och problem i kamratrelationer. Det är även vanligt att föräldrar till barn med långvarig smärta mår dåligt.

Behandlingar som är inriktade på beteendeförändring har visat sig fungera för att minska smärta och öka funktionsförmåga, men många frågor kvarstår, till exempel rörande det vetenskapliga stödet för effekter av intensiva teambaserade behandlingsprogram för inneliggande patienter, eller skillnader mellan individuella och gruppbaserade insatser i öppenvård. Det behövs också mer kunskap om hur vi på ett effektivt sätt kan behandla depression hos barnet, och hjälpa föräldrar att må bättre och hantera sina barns svårigheter på ett mer funktionellt sätt. Vidare behövs fler frågeformulär för att utvärdera olika smärtrelaterade svårigheter, som är specifikt utvecklade för barn och ungdomar med långvarig smärtproblematik.

I detta doktorandprojekt utvärderas två olika frågeformulär. Det ena, Insomnia Severity Index (ISI) (studie I) syftar till att mäta sömnproblem såsom svårigheter att somna, nattliga uppvaknanden, och påverkan av sömnproblem dagtid. ISI är ett välanvänt formulär världen över men har inte tidigare utvärderats i svensk översättning för just barn och ungdomar med långvarig smärta. Det andra formuläret, Pain Interference Index (PII) (studie II) är ett nyskapat formulär som syftar till att mäta hur mycket smärtan påverkar ens beteenden i vardagen. Vidare har vi undersökt det vetenskapliga stödet för ett särskilt behandlingsformat, intensiv interdisciplinär smärtbehandling (IIPT) för barn och ungdomar med långvarig smärta (studie III). Dessutom utvärderas effekterna av Acceptance and Commitment Therapy (ACT) för ungdomar med långvarig smärta och deras föräldrar, genomförd i grupp eller individuellt (studie IV).

Som underlag för analyserna användes frågeformulär från barn och ungdomar med långvarig smärta och deras föräldrar (studie I, II och IV), samt ett antal vetenskapliga artiklar som lokaliserats genom sökande i digitala databaser på ett systematiskt sätt och därefter sammanställts för analys (studie III).

Resultaten visar att de båda frågeformulären PII och ISI som utvärderades i studie I och II på ett tillförlitligt sätt mäter det kliniska problem de är tänkta att mäta, och vi såg även att påtagliga sömnproblem rapporterades av mer än hälften av de barn och ungdomar som ingick i studien. Analyserna pekar också på att sömnproblem spelar en viktig roll i sambandet mellan smärtintensitet och depression, och mellan smärtintensitet och smärtrelaterade begränsningar (pain interference).

När det gäller det vetenskapliga stödet för IIPT så kunde vi se preliminära positiva effekter från de 10 studier som ingick i vår sammanställning (studie III). Dock var resultaten ojämna, och det skulle behövas fler studier med andra typer av upplägg (till exempel där effekterna av IIPT-behandlingen jämförs med effekterna av en annan behandling, eller av att vara placerad på väntelista, och där deltagarna lottas till de olika grupperna) för att man ska kunna dra säkra slutsatser.

I behandlingsutvärderingen av ACT (studie IV) så rapporterade både ungdomar och föräldrar förbättringar inom ett flertal områden efter genomgången behandling, till exempel minskad påverkan av smärta på beteenden, minskad depression samt minskad känslomässig reaktivitet (oro, ilska, med mera) i relation till barnets smärta.. Det framkom inga skillnader mellan de som hade lottats till individuell behandling jämfört med dem som hade lottats till gruppbehandling. Dock behövs studier med fler deltagare, för att säkerställa dessa preliminära resultat.

Denna doktorsavhandling bidrar med ökad kunskap om effekter av olika behandlingsinterventioner och format, och kan ligga till grund för fortsatta studier inom området långvarig smärta hos barn och ungdomar, samt vidareutveckling av effektiva behandlingsinsatser för smärtrelaterad funktionsnedsättning. Vidare innebär resultaten från utvärderingarna av PII och ISI att de kan rekommenderas för användning i kliniska sammanhang för att mäta förekomst av sömnproblem och smärtpåverkan på beteenden i samband med bedömning och behandling. De kan även rekommenderas för användning i fortsatt forskning om sömnproblem och smärtans påverkan på beteenden, och de samband som finns mellan dessa problem och andra relaterade svårigheter, hos barn och ungdomar med långvarig smärta. Behovet av mer kunskap är fortsatt stort, och andra metoder för datainsamling och analys, såsom kvalitativa intervjustudier, eller många upprepade mätningar över tid med hjälp av digitala verktyg, kan ge viktig information i framtida studier. Likaså behövs utvecklingsinsatser för att säkerställa att de behandlingsinterventioner som visat sig vara effektiva för långvarig smärtproblematik når ut till de barn och föräldrar som är i behov av hjälp.

LIST OF SCIENTIFIC PAPERS

I. Insomnia in paediatric chronic pain and its impact on depression and functional disability

II. Evaluating the Statistical Properties of the Pain Interference Index in Children and Adolescents with Chronic Pain

III. Systematic Review on Intensive Interdisciplinary Pain Treatment of Children With Chronic Pain.

IV. A Clinical Pilot Study of Individual and Group Treatment for Adolescents with Chronic Pain and Their Parents: Effects of Acceptance and Commitment Therapy on Functioning

CONTENTS

LIST OF ABBREVIATIONS

ACT	Acceptance and Commitment Therapy
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
CBS	Contextual Behavioral Science
CBT	Cognitive Behavior Therapy
CES-DC	Center for Epidemiological Studies Depression Scale Children
CTT	Classical Test Theory
FDI/-P	Functional Disability Inventory/Parent version
GRADE	Grading of Recommendations Assessment, Development and Evaluation framework for assessing quality of evidence
HADS	Hospital Anxiety and Depression Scale
IASP	International Association for the Study of Pain
IIPT	Intensive Interdisciplinary Pain Treatment
IRT	Item Response Theory
ISI	Insomnia Severity Index
MA	Meta-Analysis
MDT	Multi-Disciplinary Treatment
NRS	Numerical Rating Scale
PCA	Principal Component Analysis
PII	Pain Interference Index
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses check-list
PIPS	Psychological Inflexibility in Pain Scale
PPFQ	Parent Psychological Flexibility Questionnaire

PRO/Ms	Patient Reported Outcome/Measures
PROMIS-PI	Patient Reported Outcomes Measurement Information System Pain
PRS/-P	Pain Reactivity Scale/Parent version
RCT	Randomized Controlled Trial
RFT	Relational Frame Theory
SR	Systematic Review

1 INTRODUCTION

Pediatric chronic pain is common and often related to dysfunction. The complexity of the problem implies the need for further investigation of how pain-related dysfunction can be addressed in treatment. There is also a need to develop and implement valid and reliable assessments for outcomes of treatments aimed at increasing functioning in pediatric chronic pain.

1.1 Pediatric chronic pain – definitions and diagnoses

The International Association for the Study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage". In this definition IASP stresses, regardless of type, that the pain experience is psychological (1), lacking objective measurement. Pain is always complex (2) and subjective (3). Pain and pain syndromes are defined and classified according to a set of principles (1). In children and adolescents, i.e. pediatric populations, 3 months is generally considered the cut-off for when pain is referred to as chronic, for both clinical and research purposes, but 2 months is also a common cut-off, used for functional gastrointestinal disorders in particular (1, 4, 5). Though chronic pain syndromes can result from tissue damage (e.g. inflammation) or nerve damage (e.g. from amputation), pediatric chronic pain often lacks a primary or clear etiological cause (6). Such pain has been referred to as idiopathic pain, functional pain and, more recently, primary pain disorder (6-9). In the definition of this last term, it is highlighted that the pain is often related to other problems, such as sleep difficulties and impaired emotional functioning which in turn hampers the return to normal functioning (7).

1.2 Prevalence and risk factors

Chronic pain is highly prevalent in pediatric populations, affecting between 11% to 38% as shown in a systematic review from 2011 (10). In a Norwegian community sample of adolescents (n=7373), up to 44% reported pain at least once a week over the past 3 months (11). Prevalence rates vary depending on age and gender, pain location, and how pain has been defined and reported (10, 12). More girls than boys report chronic pain, and the prevalence of pain, and multiple pains, increases with age (10-13). Pediatric chronic pain has been shown to persist into adulthood (14-16), which indicates the need for early interventions. In order to understand who is at risk for developing chronic and debilitating pain, a large number of factors have been investigated and shown to be of importance. As

described in a recent review of by McKillop and Banez (17), these include intra-individual differences in for example temperament, perceived stress, adverse life events, mental health and coping, demographic factors such as age and sex, and inter-individual aspects in social relations, parenting, and presence of psychopathology and chronic pain in the parent (17). However, more knowledge is needed regarding how developmental aspects and co-existing intra- and interpersonal risk- and protective factors, are related over time. The need for more and better-conducted studies is also put forth in a recent review of risk and prognostic factors for pediatric musculoskeletal pain (18). Using the Grading of Recommendations Assessment, Development and Evaluation framework for assessing quality of evidence (GRADE), the authors found high quality evidence only for lower socio-economic status. Because many children and adolescents with chronic pain also report dysfunction, using functional ability as an outcome measure is an important addition in studies of risk and prognostic factors of future health (17). Further, more research is needed regarding gender differences in pediatric chronic pain, to improve our understanding of pain related disabilities, and identify predictors for future functioning (19).

1.3 Pain and dysfunction

Chronic pain in youth is commonly associated with physical, emotional and social dysfunction. Although some report minor influence of pain in everyday life, a subset of young individuals suffering from chronic pain report substantial impairment (11). In a study by Huguet and Miró (13), about 5% of the 37% who had chronic pain reported moderate or severe pain-related disability. Associations between chronic pain and disability has been shown in most life domains for children, from broad categories of physical, emotional and social functioning to more specific areas such as sleep and school attendance (20-22). Concurrent self-report, parent report, and objective assessment of physical activity (actigraphy) have altogether shown adolescents with chronic pain to be less physically active than healthy controls (23). In the Norwegian study (n=7373), multisite pain and pain that occurred more frequently were both associated with more disability, as compared to pain in one location and pain that occurs more seldom (11) and in this study, depending on pain type and number of locations, between 30-64% of adolescents with chronic pain reported that this pain caused difficulties sitting during school lessons. When compared to adolescents without chronic pain, and adolescents with pain related to Juvenile Idiopathic Arthritis, youths who had a primary pain condition were found to have worse school functioning, missed school days to a much larger extent, and visited the school nurse more often (24).

1.3.1 Mental health co-morbidity

A growing body of research supports the presence of co-morbid mental health conditions in pediatric chronic pain, and the reciprocal relationship between chronic pain and mental health symptomatology (25). In a large retrospective investigation of children admitted to hospital because of chronic pain (n=3752) (26), 44% were diagnosed with co-morbid psychiatric disorders. Hoftun and colleagues (27) also found strong associations between pain, anxiety and depression in their large community sample (n=7373), and where the associations influenced the relationship between pain and lifestyle factors such as sedentary behavior. In this study, 81% of girls scoring above the cut-off for symptoms of anxiety and depression also had chronic non-specific pain. In a longitudinal study of adolescents with chronic pain, and adolescents with depression, reciprocal associations were seen between pain and depression, with the strongest influence being that of changes in pain on subsequent depression (28). Furthermore, the presence of depression and anxiety is linked to functional disability in clinical samples of pediatric chronic pain patients (29, 30). Pain-related anxiety has been put forth as owning specific relevance for impairment in functioning. For example, Caes, Fisher, Clinch, Tobias, and Eccleston (31) found in a large sample of adolescents reporting recurrent pain (n=856) that pain-related anxiety was associated with pain-related interference in daily activities, and for girls specifically, pain related-anxiety was related to social impairment. Khan and colleagues (32) examined anxiety and school functioning (attendance, concentration, and keeping up with schoolwork) using child, parent and clinician reports, and by use of structural equation modeling. Anxiety was found to directly influence all three domains of school functioning, when controlling for pain, and the authors stress the importance to focus on anxiety rather than pain when targeting school impairment in youths with chronic pain.

In addition to the emotional distress related to having chronic pain conditions in adolescence, having a chronic pain condition in youth is also associated with increased lifetime risk for mental health problems (33-35), and mental health problems are related to more dysfunction when present together with chronic pain. For example, in adults with chronic pain, recent data from a tertiary sample show a high prevalence of co-morbid depression, which was related to higher health care costs, and to several other pain-related aspects of dysfunction (e.g. work absence and interference with functioning) (36).

Thus, the common presence of mental health co-morbidity in pediatric chronic pain as well as the increased risk of anxiety and depression in adulthood, and related health care costs,

illustrates the complexity of the condition and the need to address emotional dysfunction as part of treatment.

1.3.2 Sleep problems

Sleep problems in adolescence include for example delayed sleep onset time, daytime sleepiness and insomnia, and sleep problems are commonly related to distress or impaired functioning in general adolescent populations (37). Research based on different methodological approaches support that sleep problems are related to negative effects on cognition and behavior, and likely to cause both inattention and sleepiness, which altogether can affect the development of a young individual over time (38). Findings from a systematic review of 141 studies showed that shorter sleep duration is related to poorer mental and physical health in youths (39). Another example of the negative effects of sleep problems is the result from a meta-analysis of 21 longitudinal studies of insomnia and depression (three of the studies were conducted with children and adolescents), where insomnia consistently predicted depression (40). In an early study of Archbold and colleagues (41), insomnia appeared as the most common sleep disorder among patients at two pediatric clinics. The co-morbidity of insomnia or short sleep duration and obesity and metabolic syndrome, as well as other medical conditions and their relationship to various sleep disturbances in pediatric populations, has also been acknowledged (42). Despite the potentially detrimental effects of sleep problems on the development of children and adolescents, there is often a lack of proper screening and management of insomnia and other sleep problems in pediatric clinical samples (43, 44).

Concerning pain and sleep, a bi-directional association is assumed, as studies have shown both that pain affects sleep, and that sleep affects pain (45-48). Findings from a systematic review of 56 studies conducted with pediatric patients with chronic pain conditions (49) support the link between sleep problems and chronic pain, as shown with both objective and subjective sleep measures, and also indicates the importance of sleep problems for functioning in the context of chronic pain. Focusing on results from single studies, the high prevalence of significant sleep problems can be exemplified by the findings from Long and colleagues (50) where 53% of pediatric chronic pain patients scored above cut-off for clinically significant sleep disturbances, and Shurman and colleagues (51), where nearly half the sample of children with chronic abdominal pain categorized as functional gastrointestinal disorders reported clinically significant sleep problems. Palermo and colleagues (52) compared healthy youths from the community with youths who had chronic pain recruited from a pain clinic, and found that the risk for insomnia was significantly higher in the group

with chronic pain as compared to healthy youths. In the chronic pain group, 54% reported either difficulties falling asleep or staying asleep, versus 20% in the control group.

In addition to the bi-directional associations between pain and sleep, it has been suggested on basis of studies including pediatric populations (53) that sleep may influence chronic pain more than pain influences sleep, and that targeting sleep thus may be a way forward in both prevention and treatment of chronic pain. For young adults from the general population, Bonvanie and colleagues (54) found that sleep problems were associated with chronic pain and pain severity, and predicted chronic pain and exacerbation of pain severity over time. How the relationship between sleep and pain is affected by mood or emotions should be subject for further exploration (53). Though relationships between depression, functional disability and sleep in pediatric chronic pain have been reported in several articles (see e.g. (21, 50, 55)), specifically how these factors interrelate need more investigation. In the study by Palermo and colleagues (52), cognitive arousal such as worry and anxiety was related to increased risk for insomnia, and in a prospective study with adolescents with chronic pain, pain, depressive symptoms and sleep hygiene were risk factors for later symptoms of insomnia (56). In a recent cross-sectional study of 213 pediatric participants with chronic pain (57), 74% reported sleep problems, which were associated with increased pain and functional disability. In this study, negative affect was found to mediate the relationship between poor sleep and increased pain, and the relationship between sleep and functional disability was mediated by both positive and negative affect.

Taken together, the prevalence and importance of sleep problems in pediatric populations and in the context of pain highlight a need for studies further exploring the complex relationships between pain, sleep and other factors, e.g. evaluating the importance of insomnia in mediating the relationship between symptoms and functioning.

1.3.3 Pain interference

As described above, chronic pain in youth is commonly associated with dysfunction in physical, as well as emotional and social aspects of life. The impact of pain, or *pain interference*, in all these aspects is important both as a clinical outcome and in communicating with and understanding the patient (58, 59). Pain interference addresses an overall reactive dimension of having pain, such as the impact of pain on an individual's sense of engagement, rather than, say, the perceived ability to carry out physical activities (60). To meet the need for a measure of pain interference that is appropriate for different ages and developmental stages, and at the same time useful for both clinicians and researchers in the

pediatric chronic pain context, two initiatives have been taken. First, a co-operative network of researchers created a pain interference scale for the Patient Reported Outcomes Measurement Information System (PROMIS-PI) (61, 62). In a parallel process, our research group created the Pain Interference Index (PII). The PII was created on basis items included in the West Haven-Yale Multidimensional Pain Inventory (MPI) (63) and the Brief Pain Inventory (BPI) (64) but items were re-formulated with the attempt to create an age-appropriate measure. (The methodology and results from the development of PII is presented in 2.2 and onwards.) Pain interference as defined in the process of creating the PII concerns *the influence of pain on behaviors*, that is, to what extent pain impacts everyday functioning. Both PII and PROMIS-PI cover pain interference in relation to schoolwork, leisure activities, friends, mood, physical activities and sleep, and as such they might offer a way to assess several domains of pain-related dysfunction without having to administer several different questionnaires. In an adult sample, higher pain interference was correlated to lower physical functioning, but these constructs were not as strongly correlated when measured over time (60). Thus, it seems important to clarify the construct of pain interference and the use of the term in research (65) i.e. that pain interference concerns the overall impact of pain on everyday functioning - it is not just a proxy measure of physical functioning/disability. Notably, in pediatric chronic pain, the PROMIS-PI scale has recently been evaluated using longitudinal data (66). Results from this study support both the validity and the responsiveness to change for the interference scale, in a sample of pediatric patients with chronic pain attending a multi-disciplinary chronic pain clinic.

Further research in pediatric samples is needed to evaluate pain interference in relation to specific physical and emotional disability, and the utility of pain interference as a key outcome after behavioral treatment interventions.

1.3.4 Parent and family aspects

Pain in children and adolescents has a negative impact on the whole family, and is associated with e.g. parental depression, anxiety, stress and economic burden (67-71). In a qualitative study from 2007 (72), parent's reported a difficult struggle dealing with their adolescent's pain and experienced a major impact on both parenting strategies and life as a whole, e.g. managing siblings and maintaining a normal personal life. These difficulties in parenting a child with chronic pain were expressed in a second qualitative study, focusing specifically on fathers, where feelings of helplessness was one of the major themes in interviews (73). In a systematic review from 2010 (69) covering 16 cross-sectional studies, a general pattern emerged where poorer family functioning was reported in families where the child suffered

from chronic pain as compared to healthy controls, and that pain disability posed more of a problem than pain intensity, in relation to family functioning. Thus, it seems child dysfunction in relation to pain rather than the actual level of pain, is what matters for family functioning. Furthermore, Chow and colleagues (74) reported that parent distress (fear of pain and catastrophizing) and behavior (avoidance of activities and protective behavior) was not just associated with child functioning at baseline, but also that parent behaviors significantly predicted child depression and school functioning at four months post the intervention (described as a combination of medical, physical and psychological interventions). On basis of these findings, parent factors are stressed as important treatment targets in future intervention studies for children with pediatric chronic pain (74).

In addition to emotional, physical and social family functioning, impact on the socio-economical status is also commonly seen in relation to pediatric chronic pain. Researchers have highlighted significant health care and societal costs for pediatric chronic pain patients and their families (75, 76). In a study by Groenewald and colleagues (75), both direct medical costs and productivity losses were examined in a sample of 149 adolescents with chronic pain, and the mean and median cost for a 12 months period was estimated to $11,787 and $6,770, respectively. This illustrates the importance of effectively addressing pediatric chronic pain, in order both to improve the socio-economic status for suffering families and to lessen the strain on the health care system.

Parents of children with chronic pain commonly report own chronic pain (77), i.e. there is an increased risk for pain and related problems in children of parents with chronic pain. In addition, adult chronic pain, akin to pediatric chronic pain, is also related to poor emotional, physical and social functioning, which may have detrimental effects on the family environment (78). In systematic reviews, a range of adverse outcomes has been identified in children where parental chronic pain is present (79, 80). Findings from a large population based sample of adolescents in Norway (n=3227) showed that presence of maternal and paternal chronic pain more than doubled the risk for depression and anxiety in both girls and boys, and maternal chronic pain showed to be a significant risk factor for conduct problems in girls (81). The prevalence of maternal and paternal chronic pain in this study was high (27% and 24%, respectively, which can be compared to the prevalence of chronic pain in adults in general, e.g. about 19% of the population in USA. (82)).

Thus, given the importance of parental factors in pediatric chronic pain, there is a critical need to develop evidence based parental support for parents of children with chronic pain.

1.4 Psychological treatment approaches

For most chronic pain conditions in both adult and pediatric populations, the use of traditional pharmacological and surgical interventions does not lead to desired outcomes in terms of sufficient levels of pain reduction and/or improvements in functioning (6, 83). Nevertheless, findings from a retrospective study of highly impaired pediatric pain patients (n=2249), illustrated that indication for pharmacological treatment was lacking for 43% of the patients that were taking analgesic medication (33% of the total sample) (84). This further illustrates the need for other treatment approaches for these patients, such as behavior oriented rehabilitation programs, which are widely considered a more effective alternative to medical interventions for chronic pain (83). Below, two such behavioral approaches are described, as well as one distinct format of delivery of behavioral interventions.

1.4.1 Cognitive behavior therapy (CBT)

Cognitive Behavior Therapy (CBT) as we know it today has its origins in learning theory and experimental research, including the early work conducted by Pavlov more than a hundred years ago on classical (also known as associative or respondent) learning, and subsequently by Skinner on operant learning, where the consequences following a behavior affects the likelihood for, i.e. reinforces, particular future behaviors (85). Behavior therapy showed to be successful in a number of areas previously considered unmanageable, including but not limited to many anxiety disorders. CBT then evolved during the 1960's and 1970's to include interventions based on cognitive processes. In more recent years, the continuous development of CBT has resulted in advances in learning theory as illustrated by e.g. Relational Frame Theory, and the incorporation of mindfulness and acceptance techniques, as seen in Acceptance and Commitment Therapy (described in more detail in 1.4.2) (85).

CBT includes many psychological interventions in child and adolescent populations, and there is robust evidence for CBT to manage pain and procedural distress (86). CBT is focused on the experiences and behaviors of an individual in given situations, and CBT-programs are normally aimed at improving symptoms and functioning. Pain-related feelings, thoughts and overt behaviors, such as avoidance of activities or situations assumed to increase pain, are assessed as part of treatment, and interventions are tailored and carried out in order to help the patient adapt and adjust according to specified goals (87-89).

A Cochrane systematic review and meta-analysis from 2014 evaluated the evidence for psychological interventions (primarily CBT, and only delivered face-to-face), for chronic and recurrent pediatric pain (88). In this review, findings from 37 randomized controlled trials

(RCTs) included beneficial effects from psychological treatments for children suffering from headache in regard to pain intensity, disability and anxiety but not depression post treatment, with support for maintenance of effects over time for the change in pain and disability but not anxiety. For children with non-headache conditions, beneficial effects were found post treatment for pain and disability, but no evidence was found for maintenance of effects at follow-up. Further, effects for depression or anxiety were not found in this group at post or at follow-up (88).

Notably, of the 37 RCTs included in the Cochrane review, only 6 studies could be included in analyses of effects on depression. A similar pattern was found in an unpublished systematic review of depression outcomes in psychological treatment evaluations for pediatric chronic pain, including both RCTs and non-randomized treatment evaluations (90). Out of 91 eligible studies, only 24 of these examined depression as an outcome (i.e. not just descriptively), and 17 of these studies described significant effects on depression, either pre to post, or pre to follow-up.

Given what we know about the complexity of pediatric chronic pain and mental health co-morbidity, the fact that few studies exist where depression and anxiety have been included as outcomes and even fewer that report lasting improvements in these domains, highlight the need for future intervention studies to address more than pain, i.e. emotional adjustment and sleep difficulties, and to evaluate these outcomes with valid and reliable assessments.

1.4.2 Acceptance and commitment therapy (ACT)

Acceptance and Commitment Therapy (ACT) constitutes a development within CBT, and is theoretically founded in contextual behavioral science (CBS) (91) and based on Relational Frame Theory (RFT), a novel theory of human language and cognition with a growing evidence base (92, 93). RFT originated in the question of how verbal rules guide human behavior (94). In ACT, a core feature is the focus on changing the context around our thoughts, emotions and experiences, i.e. our relationship to them, rather than the content or intensity of them, thereby changing the impact that they have on our behavior. ACT serves to increase psychological flexibility, defined as *"the ability to contact the present moment more fully as a conscious human being, and to change or persist in behavior when doing so serves valued ends"* (p. 7 in (95)). In ACT, several processes are suggested as important for increased psychological flexibility: *Acceptance* of psychological experiences (thoughts, feelings, sensations), *cognitive defusion*, *flexible present-focus attention, and self-as-context/observer,* i.e. awareness and perspective taking on psychological experiences rather

than being caught up in them or trying to disconnect or distract from them and from the present, and awareness of being distinct from on-going thought and emotional processes, and *values-based action and committed action*, i.e. active focus on what is important in life and how to achieve that, instead of focusing on reducing symptoms and distress (96, 97). Exposure to previously avoided situations is considered central to achieving behavior change, and acceptance of persisting symptoms is thus promoted as an alternative to avoidance. Though still a novel approach for the pediatric population, ACT akin to CBT has already been used to treat a variety of conditions, most commonly pain, as seen in a systematic review from 2015 (98). Studies that have been conducted provide support for the effectiveness of ACT for pediatric populations with pain and other physical concerns, but this support is compromised by the preliminary nature of the evidence as existing studies vary greatly in methodological quality, with small sample sizes being a prominent limitation (98, 99). When Pielech, Vowles and Wicksell summarized the theory and application of ACT for pediatric chronic pain, they also suggested the need for studies with larger samples and controlled study designs, as well as the need for continued focus on mechanisms of change, and the inclusion and assessment of parents in treatment (100).

The primary aim in ACT for chronic pain conditions is to increase functioning. Instead of focusing on symptom reduction, the ability to engage in valued activities despite the presence of potentially disturbing and distressing experiences and symptoms such as pain, is the focus of the treatment (i.e. psychological flexibility) (95, 101). There is a growing evidence base suggesting the effectiveness of ACT for adults with chronic pain, in improving physical and emotional functioning in particular (see e.g. (102)), and ACT is now considered a treatment with strong research support for chronic or persistent pain by the Society of Clinical Psychology, American Psychological Association (103).

Our research group in Stockholm has evaluated an ACT-based outpatient intervention in a series of studies including pediatric participants with chronic pain. In the first study, a case study from 2005 (104), increased values-oriented activities, increased functioning, and decreases in pain and disability was reported by the participant during and after treatment. The second study was a pilot study of the individually delivered ACT-intervention (n=14) (105). Here, a similar pattern of increased functioning, including increased school attendance and clinically important changes in pain and pain interference was seen for a majority of participants. In the third study, a RCT (106), the ACT-intervention was compared to a multi-disciplinary approach (MDT) including amitriptyline (total n=32). Treatment in the control group continued after post-assessments, which complicated comparisons between the groups.

Both groups improved significantly over time on most outcomes, with the ACT-group having statistically better results as compared to MDT in 3 of 11 outcomes when including follow-up measures (pain impairment beliefs, pain intensity, pain discomfort), and 6 out of 11 outcomes when compared post treatment (pain impairment beliefs, pain interference, the mental health scale for Short Form Health Survey, fear of movement, pain related discomfort and pain intensity). In the Cochrane-review (88), this RCT was one of few studies reporting depression as an outcome, with a medium effect size for the ACT-condition and a small effect size for the MDT over time, including follow-up assessments. When compared at post-treatment, the difference in improvements in depression between MDT and ACT was near statistical significance in favor of ACT (p=.055, medium effect size).

The utility of specifically targeting ACT-based processes of change, i.e. psychological flexibility, to improve functioning was analyzed using data from the RCT (107). Here, analyses of mediators of change were conducted with depression and pain interference as outcomes. Six variables, which represented treatment targets of importance for ACT and CBT respectively, were tested as mediators. Results suggested that changes in pain impairment beliefs and pain reactivity, which are consistent with ACT-theory, mediated outcomes, but self-efficacy, catastrophizing, fear of movement, and pain intensity, targets more common in traditional CBT-interventions, did not. In the ACT-condition, pain impairment beliefs and pain reactivity also predicted depression and pain interference at follow-up, with control for previous effects (107).

Another ACT-based program for adolescents, in the UK, with residential patients, has also been shown to improve functioning in severely disabled adolescents with chronic pain (n=98) (108). Following the 3-week program, adolescents improved in self-reported functioning across a number of variables, and in objectively measured physical performance. Significant effects were seen both post-treatment and at 3-months follow-up. Notably, no significant changes were reported for pain intensity. Acceptance during treatment was correlated with sustained changes in outcome measures at follow-up, which adds further promise to ACT-processes as treatment targets that might serve to improve functioning outcomes (108).

In addition to these programs, a few more studies on ACT-interventions for pediatric chronic pain exist, conducted in for example Iran (109) and USA (110). However, ACT is still a novel approach when used with pediatric patients who suffer from chronic pain. The current evidence is promising, as improvements in functioning have been consistently reported, and further developments are thus warranted.

1.5 Formats of treatment delivery

Psychological treatment approaches for pediatric chronic pain can be delivered in various formats, such as individual face-to face therapy, group-delivered interventions for patients with similar pain characteristics, and multi-disciplinary approaches of different intensity, from outpatient interventions to residential (87, 88, 111). Further, a separate Cochrane review has evaluated the current evidence for remotely delivered psychological therapies for pediatric chronic pain (112). Regarding ACT specifically, existing studies have examined both individual interdisciplinary outpatient treatment (for example (106) and group-delivered interdisciplinary residential treatment (108), although no head-to head comparisons between treatment formats (i.e. with the same treatment content) have yet been made. Thus, this should be investigated in future studies. Furthermore, no study had prior to the present doctoral project systematically synthesized the outcomes from intensive interdisciplinary treatments for pediatric chronic pain.

1.5.1 Intensive interdisciplinary pain treatment (IIPT)

For patients with severely debilitating pain, it is commonly proposed that an intensive and interdisciplinary setting is required to facilitate improvement. As described by Odell and Logan (111), intensive interdisciplinary pain treatment (IIPT) programs are characterized on the one hand, by the multi-modal treatment team, which can include physicians, psychologists and physiotherapists, as well as for example nurses, occupational therapists or counselors, all specialized in the assessment and management of pain, and on the other hand, by the intensity of treatment delivery, which has either an inpatient or a day hospital setup (as opposed to outpatient treatment). In IIPTs, there is a strong focus on physical rehabilitation, and on the psychological management of pain, by means of behavior/CBT/ACT-interventions (111). Parents are also commonly included in treatment. Positive outcomes for children have been reported from a number of treatment centers, including greater improvements for IIPT in comparison both to outpatient treatment (113, 114), and to waiting-list control (115). There is also support for statistically and clinically significant long-term effects after IIPT (116), as well as cost-effectiveness (117). However, though specialized rehabilitation programs around the world for children and adolescents with debilitating chronic pain are similar in many aspects (e.g. admission criteria, structure, components, and interdisciplinary approach (as described recently in (118)), there is variation in treatment setting, dose and treatment components, along with routines for evaluation and follow-up. Thus, more research is needed regarding the current empirical support for IIPTs, to facilitate further development and implementation.

1.6 Parental interventions

As discussed in 1.3.4, it is common for parents of children with chronic pain to experience distress that affects their ability to effectively support their child in doing what is required to retain or improve functioning (119-121). Parents are therefore often included in the treatment of children with chronic pain.

1.6.1 CBT-interventions for parents

In CBT-interventions for parents, focus has commonly been on targeting parent behaviors that might have an effect on child functioning, for example by teaching parents operant techniques for behavior modification (120). An early non-controlled evaluation of an interdisciplinary CBT-program for adolescents with chronic pain and their parents included parent stress and parent anxiety and depression as outcomes (n=57 adolescent-parent dyads) (67). In this study, which included interventions based on operant learning and CBT-principles, improvements were seen in parent anxiety, depression and parent stress, and continued to improve at 3-months follow-up. Focusing specifically on the CBT-intervention problem solving skills for parents of pediatric chronic pain sufferers has also shown promising results, for example near significant reductions in parent depression as compared with the treatment as usual-control group, with a medium effect size (p= .06, d= -0.68) (122).

However, when synthesized, the existing evidence for benefits for parents after receiving parental interventions in the context of pediatric chronic pain is still limited, as seen in a Cochrane systematic review from 2015 (121). Here, the effectiveness of psychological therapies for parents of children with chronic illnesses was examined. A total of 47 RCTs were included, and 14 of these concerned children with painful conditions. The interventions, primarily CBT-based, included a varying proportion of parent sessions, from parent sessions only, to majority of treatment sessions aimed at the child. For painful conditions, analyses showed that parent interventions were useful in reducing child pain related symptoms post-treatment (based on 9 studies), with a small effect, but this was not maintained at follow-up (based on 6 studies). Based on 2 studies, no effect was found for improvements in parent adaptive behaviors post-treatment. Analyses of child outcomes post treatment (7 studies) and at follow up (3 studies), showed no beneficial effects for reducing child disability, or for child mental health improvements post treatment (4 studies) or at follow up (2 studies). No study evaluated parent mental health outcomes (121). Based on these findings, the authors suggested improvements in trial design, as well as regarding measurement and evaluation of outcomes. Furthermore, the authors specifically suggested future research on the relation between changes in parent outcomes and child outcomes, and that detailed descriptions of

how interventions to both child and parent were delivered should be provided, in order to enable an evaluation of the separate treatment components (121). Thus, the value of adding parental interventions for improving children's functional outcomes is unclear, and more knowledge is needed regarding the relationships between child and parent factors in the pediatric chronic pain context. The parental processes central to the promotion of specific child outcomes, and the most effective implementation of parental interventions to this end, have yet to be investigated. A notable recent example of improved study design and reporting of parent outcomes is a multi-center RCT by Palermo and colleagues (123), comparing internet-delivered CBT (n=138) with internet-delivered education (n=135), where internet-delivered CBT for adolescent with chronic pain was found to improve not only adolescent functioning but also decreased parent miscarried helping, parent anxiety, depression and self-blame, and improved parent behavioral responses to pain. Parent modules included education about chronic pain and recognizing stress and negative emotions, education about and training in use of operant strategies and modeling, sleep and lifestyle, communication strategies, and relapse prevention (123). In a secondary longitudinal evaluation of this study (124), associations between child and parent functioning over the course of one year was examined. Parent distress (including depression, anxiety and catastrophizing regarding child pain) was found to predict child disability over time, indicating that parents who are highly distressed are also less effective in helping their child adapt to and implement behavioral pain management strategies. The authors stress the need for more research concerning interventions that ameliorate parent emotional functioning, and also improves pain outcomes for the child (124).

1.6.2 ACT-interventions for parents

In cross-sectional studies, parental ACT-processes have been put forth as potentially important treatment targets to improve child outcomes (125, 126). It is hypothesized that parents of children with chronic pain struggle with their own distress of seeing their child in pain and with worry about their pain condition, which prevents them from coaching their child flexibly and effectively towards long-term goals and values (125). Thus, parents also need to practice e.g. acceptance and perspective taking on thoughts and emotions, to increase their own psychological flexibility. ACT-specific pediatric chronic pain treatment programs like the one in the UK (108) and ours in Stockholm (see e.g. (106)) involve parents in conjunction with child treatment to a varying degree. ACT-processes are targeted with children and parents in a similar fashion in both these programs.

In a pilot study with pediatric patients with neurofibromatosis type 1 and chronic pain, the parents were also taught ACT-strategies, but though promising results were reported by the youth, for example reduced pain interference, findings for parent variables did not reach statistical significance (127). In a recent pilot trial investigating a group-based ACT-intervention for parents of adolescents with chronic pain (n=6 parent-adolescent dyads at completion) (128), the intervention was found to be feasible and parents reported increased psychological flexibility at post and follow-up, and decreased parent protective responses and adolescent pain interference was seen at follow-up.

Preliminary results from a manuscript in preparation (129), in which child and parent outcomes from the UK residential program have been evaluated (n=165 adolescents and parent dyads), show improvements in both adolescent functioning and parent outcomes. Improvements were reported in parent depression, parent acceptance, and parent psychological flexibility. Further, adolescents improved in functioning outcomes as well as pain acceptance. The changes in parent psychological flexibility were significantly related to changes in adolescent pain acceptance, while controlling for changes in functioning outcomes.

Thus, the specific utility of training parents to deal with their own distress related to their child's pain in an ACT-consistent manner may hold promise, and more research is needed to evaluate if ACT-treatment results in improved outcomes for parents.

1.7 Assessment of pain-related dysfunction

Patient reported outcomes (PROs) and related measures (PROMs) are important in the clinical as well as the research setting (130). The patient possesses exclusive knowledge that can shed light on outcomes that are crucial in many clinical domains (131). Pain disorders are illustrative of the importance of patient reported outcomes, with the full pain experience only truly known to the sufferer, as pain and pain-related dysfunction can only to some extent be estimated and reported by proxy.

Almost ten years ago, a network of researchers, the Pediatric Initiative on Methods, Measurement and Pain Assessment in Clinical Trials, (PedIMMPACT) (132) recommended that several areas should be taken into account in interventions for pediatric chronic or recurrent pain, there among physical, emotional and role functioning domains. The authors stressed the need for further evaluation of available instruments as well as the development of new instruments to fill the gaps identified, for example regarding co-morbid sleep difficulties. Notably, the PedIMMPACT refrained from recommending a particular assessment for sleep,

as there were no validated standard instruments for assessing insomnia/sleep problems in pediatric chronic pain patients. Similarly, Lewandowski and colleagues (133) stated on basis of a systematic review of sleep measures for the pediatric population that developing assessments of insomnia for the pediatric population should hold priority. Further, sleep outcomes were not presented in the Cochrane-review from 2014 (88), as only one study assessed sleep (134), and in a recent review of outcomes of specialized rehabilitation programs for children and adolescents with severe disabling chronic pain (118), only three studies reported sleep outcomes.

Eccleston and colleagues (135) also noted a relative absence of valid and reliable assessments for many domains in pediatric chronic pain after conducting a review of previously used instruments in this population. Similarly, for parents of children with chronic pain (136), a systematic review of parental functioning measures showed both diversity and lack of consistency, as well as a need for more reporting of clinically relevant psychometric data for the available instruments.

The transit towards functioning as the primary outcome in treatment for pediatric chronic pain is reliant on the development of valid and reliable instruments (137), both in clinical and research contexts. Thus, the development and psychometric evaluation of assessments particularly created for children and adolescents with chronic pain should be a priority for future investigations. Furthermore, consensus around functioning outcome domains and their assessments facilitate evaluations of existing empirical support, i.e. systematic reviews and meta-analyses.

1.7.1 Development and psychometric evaluation of assessments

In classical test theory (CTT), the approach to test development and evaluation is based on total scores, i.e. summaries of the scores for a set of items, where every observation represents the true score for an individual (i.e. the hypothetical score that would be the mean of observed scores from an unlimited number of test occasions) and measurement error (the random error part of the score we observe). Information about tests from the CTT-approach concerns psychometric properties of total tests and is specific to the sample in question (138-140).

1.7.2 Evaluating the reliability of assessments

In the Standards for Educational and Psychological Testing (141) p. 25, reliability is defined as *"the consistency of [such]measures when repeated on a population of individuals or groups*. Reliability thus represents the dependability of results, and determining the reliability

of a scale is a part of the process whereby evidence for validity is gathered (142). The main goals in reliability analyses are to identify sources of random measurement error and their sizes, and the stability over time for a test (141, 143). Estimations of reliability can be carried out through analyses of internal consistency of a scale, through analyses of relationships between repeated measures (test-retest/stability), analyses of measurement errors (stemming from sources within as well as external to the individual), and analyses of similarities between raters/observers for non-self report assessments (141, 142). Based on CTT-assumptions, information about reliability is sample-specific.

1.7.3 Evaluating the validity of assessments

Validity is defined as *"the degree to which evidence and theory support the interpretations of test scores entailed by proposed use of tests"* (p. 9, (141)). Validity is not a property of the test with distinct and fixed types – instead it is a process by which we continuously gather evidence for different aspects of validity (141). Validity refers to how well we measure what we intend to measure, in the specific setting and with the participants in question, and is therefore directly related to the strength of the conclusions of a study (142). For example, the interpretation of an assessment can differ between populations and study settings for many reasons (language comprehension, relevance of the construct, developmental aspects et cetera) (141), hence the evidence for validity of an assessment must always be reflected upon in order to determine if the conclusions from a particular study are valid (for example, if the results of a treatment evaluation can be attributed to an intervention, rather than other influences (internal validity), and if the results can be generalized to other settings or populations (external validity) (143). Empirical evidence for validity can be gathered through examinations of relationships between test content and the construct it aims to measure, through examinations of response processes, through examination of the internal structure of a scale (e.g. factor analysis to establish uni- or multidimensionality), and through examination of the test's relationship to other variables, that is, with the underlying interpretation of constructs which can be predictive or concurrent in its nature, and the consequences of the testing (141, 142). Though there is *"remarkable unreliability in use of the terms reliability and validity"* (p. 358 in (143)), and some overlap between terms, a few specific definitions are worth noting: *Construct validity*, which refers to how well the assessment reflects the domain of interest; *content validity*, which concerns how the items relate to the concept behind the measure; *criterion validity*, which encompasses the correlation (concurrent or predictive) between the assessment and other relevant criteria; *convergent and discriminant validity*, which refers to how well the assessment is related to or different from other

assessments concerning similar or dissimilar constructs, and finally; *face validity*, which is not a formal type of validity but still important, as it refers to the experience of how well an assessments appears to measure what we are interested in (143) and thus might also be important in relation to the perceived relevance of an assessment for the participants. All these ways of gathering evidence for validity illustrate the iterative nature of the process. When using a test in a novel population; there is again a need for these reflections, analyses and investigations. Thus, without support for the validity of an assessment, we cannot be confident in our interpretation of data.

1.8 Evaluating the state of evidence by conducting a systematic review and meta-analysis

A systematic review (SR) aims to synthesize and evaluate empirical evidence for a particular research question, according to pre-determined criteria for inclusion, and can include evaluations of the validity of the studies included in the SR (144). A meta-analysis (MA) is often included in a SR, and refers to the statistical methods used to sum up the results from all the studies included in a SR (144, 145), i.e. that investigates the same phenomenon, to estimate the mean and variance of underlying population effects (146, 147). The quality of reporting in a SR is increased if the SR includes for example detailed reporting on protocol and registration, criteria for inclusion and exclusion of studies, a detailed description of the search strategy, selection and data collection, a clear synthesis, assessments of risks of bias both for individual studies and across studies, and more (148) - all of which serves to enhance replicability of the SR and evaluation of the validity of the findings. The Preferred Reporting Items for Systematic reviews and Meta-Analyses Check-lists (PRISMA), which includes a flowchart for the documentation of study identification, screening, assessment of eligibility and final number of studies included in the search and inclusion process, is an important guideline commonly adhered to by researchers conducting SRs (148). Quality ratings of included studies can be conducted using checklists like the Cochrane Collaboration Risk of Bias Tool for RCTs (144, 149) and the Quality Appraisal tool for non-randomized studies (150, 151). The methodological quality of the SR itself and thus the confidence in conclusions from the SR and MA can be evaluated by checklists such as the A MeaSurement Tool to Assess systematic Reviews (AMSTAR) (152, 153). The quality of evidence and strength of recommendations can be classified according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system, which states how certain the estimate of effects found in an SR and MA is or, in other words, to which degree further research is likely to change the confidence in the estimate of effect (see e.g. (154)). Cochrane reviews, for instance, use GRADE to specify the level of quality for evidence from

randomized trials in their SRs and MAs (144). Studies are thereby examined in regard to methodological quality (design and risk of bias in the individual studies), if the evidence is direct or indirect (involving for example the generalizability of findings), the homogeneity or heterogeneity in results, if results are precise or imprecise (e.g. how wide the confidence intervals are) and finally, taking into account the risk of publication and selective reporting bias (144). The level of quality in the body of evidence is then rated as high, moderate, low or very low.

In sum, SR and MA are used to synthesize current evidence and estimate population effects, and can help both health care professionals and patients to make informed decisions about health care. In pediatric chronic pain, the need for further development of effective interventions that address more than pain is evident. Findings from SR and MA are important tools for future research in this regard.

2 AIMS

The purpose of this doctoral project was to develop effective ways to assess and treat dysfunction in pediatric chronic pain. The overall aims were to evaluate instruments assessing pain interference and insomnia, as well as the state of evidence for Intensive Interdisciplinary Pain Treatment, (IIPT), and the effects of Acceptance and Commitment Therapy (ACT) for this population. The specific aims in the respective studies are described below.

2.1 Study I

The study aims were: 1) To conduct a psychometric evaluation of a Swedish translation of the Insomnia Severity Index (ISI) in a sample of pediatric participants with chronic pain, 2) to assess the frequency and severity of insomnia in this sample, 3) examine the relationships between pain, insomnia, depression and functional disability and 4) explore the functional importance of insomnia in the relationship between pain and depression, and pain and disability.

2.2 Study II

The aim of study II was to evaluate the statistical properties of the Pain Interference Index (PII) in pediatric patients with chronic pain, including examinations of the factor structure of PII, concurrent criteria validity by examining the relationships between PII and pain intensity, depression and functional disability, and examinations of reliability by analyzing the internal consistency.

2.3 Study III

In study III, a systematic review and meta-analysis, the aims were to: 1) Describe the nature of IIPTs for pediatric chronic pain related to significant distress and disability, and to provide details on components in such treatments, and 2) to evaluate the effectiveness of IIPT post-treatment and at follow-up by conducting a meta-analysis of 5 outcome domains: Pain intensity, disability, school functioning, anxiety, and depressive symptoms.

2.4 Study IV

The aims of study IV were to preliminarily evaluate: 1) The effects of an ACT-based intervention for adolescents with disabling chronic pain conditions on functioning (i.e. pain interference, pain reactivity, depressive symptoms and functional disability) pain intensity and psychological flexibility, 2) the effects of an ACT-based parental support program on

parent emotional functioning, pain reactivity and psychological flexibility, 3) differences between group and individual treatment formats, 4) temporal change patterns and 5) clinically significant changes.

3 METHODS

The doctoral project includes several methodological approaches. Table 1 gives an overview of study design, data collection, participants, statistical analyses, and assessments used in each study respectively.

3.1 Designs and settings

As presented in Table 1, study I and II had a cross-sectional design, and psychometric evaluations were included in both these studies. Study III was a systematic review and meta-analysis and study IV was a randomized non-controlled pilot trial.

Study I, II and IV were conducted within a specialist pain treatment setting, the Functional Unit for Behavior Medicine Pain Treatment Services, Functional Area Medical Psychology, at Karolinska University Hospital in Stockholm, Sweden. All pediatric participants had been referred to the service due to chronic pain. Study III, a systematic review and meta-analysis, was an international collaboration with pediatric chronic pain researchers.

3.2 Assessments for children and adolescents

Assessments included in study I, II and IV are described below. See Table 1 for an overview of assessments in study I, II and IV respectively.

3.2.1 Pain Intensity

Current pain intensity was assessed by a numerical rating scale (NRS) (155) in two versions. In study I and II, pain was rated on a scale from 0 to 10, with 0 representing *no pain* and 10 *worst imaginable pain*. The scale was administered at the time of first visit to the clinic, by a physician specialized in pediatric pain. In study IV, pain was assessed via self-report in conjunction with other questionnaires at all time points, on a scale from 0 to 6, with 0 representing *no pain*, and 6 *extreme pain*. Though using 0-10 is recommended and most often used, the interval 0-6 is also common (156). Examination of the validity of NRS, by comparing the NRS with Visual Analogue Scales and Faces Pain Scale Revised support its use with children and adolescents (157) and there is also support for the convergent and discriminant validity of the NRS when used with children and adolescents who suffer from chronic pain (158).

3.2.2 Insomnia

Insomnia in children and adolescents was assessed with the Swedish translation of Insomnia Severity Index (ISI), adapted for youths (159). There is evidence for validity and reliability

for the ISI from many populations in different settings and languages translations (160-167). The ISI has shown sensitivity to change over time after treatment (159, 168) and can also be used for the purpose of screening insomnia problems (159, 168). ISI consists of 7 items relating to sleep problems experienced during the two weeks prior to assessment, including difficulty falling asleep, remaining asleep, and interference of sleep problem in daytime activities. The items are rated from 0 (not at all) to 4 (very much), and the maximum score is 28. Before this doctoral project, only one study examining the validity and reliability of ISI in the pediatric population existed to our knowledge (161). In this Chinese version, ISI was found to correspond with other measures of insomnia, indicating concurrent validity, and criterion validity for the ISI was supported correlations between total scores and DSM-IV-TR diagnosis of clinical insomnia. Further, ISI showed an adequate internal consistency of Cronbach's alpha=0.83 which supports the reliability of the ISI. A cut-off for clinically significant insomnia was set at 9 in that study (161).

3.2.3 Depression

Depression was assessed with the Center for Epidemiological Studies Depression Scale Children (CES-DC), in which the experiences, over the previous week, of 20 symptoms of depression are rated on a scale from 0 (not at all) to 3 (often) (169, 170). The maximum score is 60, and for adolescents, a cut-off score at 16 and above was suggested for discriminating major depressive disorder (171). In a Swedish study, examining the validity of the Swedish translation for adolescents, the cut-off was proposed to be 24 (172). In this study, the Cronbach's alpha reliability coefficient was .91, and the validity of the CES-DC was supported by its correlation with another measure of depression, the Beck Depressive Inventory (172). CES-DC has also been used previously with pediatric participants with chronic pain (e.g. (52)), showing adequate internal consistency.

3.2.4 Functional Disability

Functional Disability in children and adolescents was assessed with the Functional Disability Inventory Parent version (FDI-P), where parents rate their child's functional disability (173). In the FDI, daily activities such as walking, school attendance and peer activities are assessed on a scale from 0 (no problems) to 4 (impossible), and the maximum score is 60. It was originally developed to measure functioning in a broad spectrum of pediatric conditions, but has been used extensively with pediatric chronic pain populations and has shown evidence of reliability and validity as well as sensitivity to change after treatment (174). Its use has been extended to include Swedish adolescents as well (175), and the parent-version has shown good correspondence with child ratings (173, 176).

3.2.5 Psychological Inflexibility

Psychological inflexibility in pain (i.e. the inability to behave in line with a valued life when pain, unpleasant thoughts or emotions are present) was assessed with the Psychological Inflexibility in Pain Scale (PIPS) (177, 178). PIPS include 12 items, which are rated on a scale from 1 (never true) to 7 (always true), and the maximum score is 84. Items concern the extent to which pain controls the participant's life and valued activities, which often become limited through attempts to avoid pain and pain-related experiences. Research with adult chronic pain patients support the psychometric properties of the instrument as seen in for example adequate internal consistencies supporting its reliability, and strong relations with variables such a disability, and with other measures of acceptance and avoidance which supports the criterion and construct validity of the PIPS (178). Furthermore, PIPS has shown sensitivity to change after ACT-intervention (179). Preliminary analyses from the same sample as in study I and II has indicated the adequacy of PIPS for pediatric chronic pain, with results showing that PIPS explained a significant amount of variance in pain interference and depression, when controlling for pain intensity (180). PIPS has also shown excellent internal consistency, high correlations with the Chronic Pain Acceptance Questionnaire (CPAQ) which is a validated measure of acceptance (see e.g. (181)) and moderate correlations with depression as measured by the CES-DC. In addition, a preliminary Rasch-analysis with a subset of the sample in these preliminary analyses (n=75) indicated support for unidimensionality, precision and sensitivity, i.e. reliability of the PIPS (182).

3.2.6 Pain Interference

Pain Interference was assessed using the Swedish version of the Pain Interference Index (PII), also described in 1.3.2. Prior to this doctoral project, no thorough investigation of the psychometric properties in the Swedish version of PII had been conducted with pediatric participants. PII has shown sensitivity to change after treatment in pediatric participants with chronic pain (106). PII consists of six items, rated on a scale from 0 (not at all), to 6 (completely), with a maximum score of 36. PII assesses the extent of pain impact on everyday functioning, including difficulties with school, leisure activities, spending time with peers, as well as effect on mood, physical activities, and sleep. In an English version of PII, Martin and colleagues (183) found evidence for concurrent criterion and construct validity, reliability and feasibility for both PII child report and parent-report, when used with youths suffering from medical conditions and co-morbid chronic pain (183). There is also support for the reliability and concurrent criterion validity of PII when used with adult patients with chronic pain (184).

3.2.7 Pain Reactivity

Pain reactivity was assessed using the Pain Reactivity Scale (PRS) for children. The PRS measures worry and general emotional reactivity to pain (e.g. anger, sadness) (106), and includes five items rated on a scale from 0 (never/not at all), to 6 (always/very much). The maximum score is 30. Preliminary regression analyses (180) indicated that the PRS is important for explaining variance in pain interference and depression, when controlling for pain intensity. Also, PRS has shown sensitivity to change after treatment, and mediating effects on functional outcomes (106, 107).

3.3 Assessments for parents

3.3.1 Parent Pain Reactivity

Pain reactivity was assessed by the Pain Reactivity Scale for parents (PRS-P) where parents rate their own reactivity to their child's pain. See 3.2.7 for details.

3.3.2 Parent Anxiety and Depression

Parent anxiety and depression was assessed with the Hospital Anxiety and Depression Scale (HADS) (185). HADS consists of 14 items divided into two equal subscales, HADS-depression and HADS-anxiety. Items are rated on a scale from 0 (most of the time) to 3 (not at al), and concern anxious and depressive symptoms. The maximum score is 42 (21, respectively, for the subscales). HADS is a well-established measure, which has been used in a wide variety of settings and populations, as shown in for example the literature review by Bjelland and colleagues (186). In this review, based on 747 studies using HADS, 71 papers including one conducted in a Swedish sample (187) were used for extracting information about the factor structure, internal consistency, relationship to other variables, and information about HADS as a case finder. Findings support the internal consistency, concurrent validity, and use of HADS both for assessing symptom severity and identifying cases from non-cases. Concerning cases, a cut-off of >8 on each subscale respectively, defines caseness (186). HADS has also been used previously with parents of adolescents with chronic pain. In the findings of Eccleston and colleagues (67), for example, HADS showed sensitivity to change after treatment.

3.3.3 Parent Psychological Flexibility

Parent psychological flexibility was assessed with the Parent Psychological Flexibility Questionnaire (PPFQ) (125). Support was found for both reliability and construct validity of this original scale, and results indicated its usefulness and importance for gaining information

about parental responses in relation to adolescent functioning. The original scale consisted of 31 items, and further development of the instrument resulted in a 17-item version with support for reliability and criterion-related validity (188). In this doctoral project, a 10-item version of the PPFQ translated into Swedish was used, on the basis of a psychometric evaluation including factor analysis (n=263 parents of children and adolescents with chronic pain) (189). The maximum score of this version is 60, and items are rated on a scale from 0 *never true* to 6 *always true*. Items include ratings of the degree to which, for example, valued activities are carried out despite the presence of child pain. The psychometric evaluation of the Swedish version indicated good internal consistency with alpha .86, a three-factor solution, and support for the concurrent criteria validity of the instrument (189).

3.4 Statistical analyses

An overview of statistical analyses included in each study is found in Table 1.

Table 1. Design, data collection, participants, statistical analyses and assessments for included studies.

	Study I	Study II	Study III	Study IV
n	154	163		48
Study design				
Cross-sectional design	•	•		
Randomized non-controlled pilot trial				•
Systematic review and meta-analysis			•	
Data collection				
Pre-treatment assessments	•	•		
Semi-structured clinical interview	•	•		•
Self-report questionnaires (pen and paper)	•	•		•
Repeated assessments (pre, mid and post treatment)				•
Systematic searches and data extraction			•	
Participants				
Pediatric patients with chronic pain	•	•		•
Parents of pediatric patients with chronic pain	•	•		•
Studies evaluating the effects of IIPTs			•	
Statistical analyses				
Correlational analyses	•	•		
Regression analyses	•	•		
Factor analysis (principal component analysis (PCA))		•		
Analyses of internal consistency (Cronbach's alpha)	•	•		•
Analyses of indirect effects/mediation	•			
Analyses of differences between groups: Student's t test	•	•		
Analyses of differences between groups: Mann Whitney U-test				•
Analyses of change over time: Wilcoxon signed rank's test				•
Effect size calculations			•	•
Analyses of clinically significant changes: Jacobson Truax method for reliable change				•
Meta-analysis			•	
Assessments				
Current pain intensity: NRS 0-10	•	•		
Current pain intensity: NRS 0-6				•
Insomnia Severity Index (ISI)	•			•
Center for Epidemiological Studies Depression Scale Children (CES-DC)	•	•		•
Functional Disability Inventory (FDI-P)	•	•		•
Pain Interference Index (PII)		•		•
Psychological Inflexiblity in Pain Scale (PIPS)				•
Pain Reactivity Scale (PRS)				•
Pain Reactivity Scale Parent (PRS-P)				•
Hospital Anxiety and Depression Scale (HADS)				•
Parent Psychological Flexibility Questionnaire (PPFQ)				•

3.4.1 Correlation and regression analyses

Correlational analyses were used to characterize the relationship between variables, for example by use of bivariate correlation analyses (Pearson's correlation coefficient, or *r*) to assess the relationship between variables for examination of concurrent criteria-related validity (study I and II). Hierarchical regression analyses were used in study I and II, to predict values of the dependent variable (DV) on basis of one or more independent variables (IVs), thereby assessing how much each predictor variable contributes to predicting the outcome, or the amount of variance explained by predictor variables in the outcome variable (for example, in study I, the relevance of insomnia and pain intensity (IVs) for depression and functional disability (DVs)). Data was checked for assumptions before regression analyses were conducted, including degree of variance, multi-collinearity and correlations with variables not included in the analyses and sample size (190, 191).

3.4.2 Factor analysis

Factor analysis was used to determine whether the items in the assessment questionnaire PII reflected the same underlying variable, i.e. pain interference. Principal Component Analysis (PCA) is a standard procedure for evaluating the factor structure and can be used for reducing the number of items or variables to a smaller number (190, 191). PCA informs the researcher about patterns in the data, and combines variables into factors if they are correlated with each other but not with other subsets of variables (190, 191). When conducting a PCA, it is important to consider that it is sensitive to, among other things, the sizes of the correlations included, the sample size, missing data, and assumptions for normality and linearity (191).

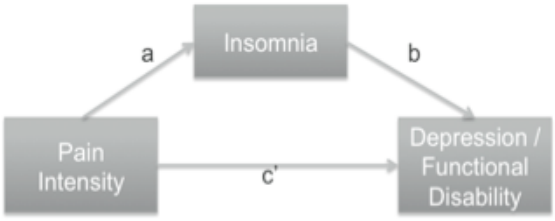
3.4.3 Analyses of internal consistency

Analyses of internal consistency by use of Cronbach's alpha were conducted to evaluate the reliability of assessments in study I, I and IV. Cronbach's alpha takes into account both the variance within each item and the co-variance between every item in relation to all other items included in the assessment (190). It concerns interrelationships between items, and on the basis of this, indicates whether all items can be assumed to measure the same construct. High consistency indicates reliability of a measure (192). However, alpha is affected by the number of items in an assessment, with fewer items reducing alpha, and a large number of items increasing alpha (190, 192). Alpha is sample-specific, and therefore it is important to identify alpha for the scale for the specific sample in question in order to interpret data (192).

3.4.4 Analyses of indirect effects/mediation

Analyses of mediation/indirect effects can be used for better understanding of how the effect from one variable on another operates (193). In study I, analyses of indirect effects were conducted to evaluate the mediating function of insomnia on the relationship between pain intensity and depression, as well as between pain intensity and disability. The model for these indirect/mediation effects (Figure 1) was based on previous longitudinal research suggesting sleep problems to be key for subsequent depression (40). Due to data being cross-sectional, many aspects of mediation are unavailable, such as evidence for temporal precedence (194). Significant indirect effects based on cross-sectional data are therefore insufficient to evaluate mediation, as time is a requirement for mediation to happen (195). To establish mediation according to Kazdin (196), a pattern of consistency should be seen, over a number of studies in which requirements such as strong associations, specificity, consistency, experimental manipulation, timeline, gradient and plausibility are addressed. Establishing indirect effects in cross-sectional data can provide a part of the argument for a possible mediator (193) and are thus informative e.g. to form hypotheses to be tested in longitudinal or experimental designs. In study I, the indirect effects were evaluated by means of the cross-product of coefficients (194) and the importance of the mediator (insomnia) was evaluated using both the Sobel test and a non-parametric bootstrapping method (197).

Figure 1. The influence of insomnia on the relationship between pain intensity and depression, and pain intensity and functional disability.



3.4.5 Tests of within and between group differences

To evaluate differences within and between groups, both parametric and non-parametric analyses were performed: The Student's t test, a parametric test of differences based on the normal distribution comparing means from two independent groups, and the Mann-Whitney U-test, a non-parametric test used to compare two independent conditions (190). Mann-Whitney U-test was chosen for study IV because of non-normal distributions in several variables. Non-parametric tests such as the Mann-Whitney U-test make fewer assumptions

about the data, and the test is based on a ranking-principle in which ranks are assigned to scores, with low ranks assigned to low scores and vice versa. In non-parametric tests, the median and range is used instead of the mean and standard deviation in the parametric counterparts (190). Mann-Whitney U tests were used for comparisons between group and individual treatment conditions, and between completers and non-completers in study IV, and t-tests were used for analyzing sex differences in study I and II.

For non-parametric analyses of change between two related conditions in non-normal distributions, i.e. repeated measures data, the Wilcoxon signed rank's test was chosen. In this test, differences are calculated, and then ranked as described above, but with the sign of difference assigned to the rank, i.e. the direction of the change (190). The Wilcoxon signed rank's test was used in study IV for assessing when changes occurred, e.g. pre to post comparisons.

3.4.6 Effect size calculations

An effect size is useful for evaluating the importance of the findings in a study as it enhances interpretability and adds information beyond p-values, which can have limited practical meaning e.g. due to their sensitivity to sample size (198, 199). There are many different effect size statistics, but they all share the advantage of allowing comparisons between studies as they are independent of sample size (198). In study IV, effect sizes for non-parametric data were calculated from z scores and the number of total observations by use of *r*, which is a measure of the strength of an association (190, 198). Effects were considered small if above 0.10, medium if above 0.30, and large if above 0.50, as proposed by Cohen (200). In study III, effect sizes were calculated by use of Cohen's *d*, which is one approach for describing the standardized difference between means (190, 198). Importantly, effect sizes should be interpreted in the actual context (198), both with consideration of the design and procedure, such as the use of reliable measures, and the implications of the findings, such as costs for delivery, comparison with similar interventions, and sustained effects (198, 201).

3.4.7 Analyses of clinically significant changes

According to Kazdin (p. 332, in (202)) *"clinical significance refers to the practical or applied value or importance of the effect of an intervention—that is, whether the intervention makes a real (e.g. genuine, palpable, practical, noticeable) difference in everyday life to the clients or to others with whom the clients interact"*. There are many different approaches available for attempting to evaluate clinical significance, for example the proportion of participants who return to normal functioning (203). However, when criteria for determining

normal functioning are lacking, one alternative is to evaluate if the level of functioning after therapy falls outside the range of the dysfunctional population. In study IV, we calculated clinically significant changes using mean-based statistics, by the 1991 Jacobson and Truax approach (204), in which a change of two standard deviations (SD) from the mean of the population under investigation in the direction of better functioning is defined as a clinically significant change. Calculations of deterioration, with a change of two standard deviations in the direction of decreased functioning defined as clinically significant, were also conducted.

3.4.8 Systematic review and meta-analysis

The search strategy for the systematic review was developed in collaboration with an experienced librarian, and the search was based on the main terms Pain or Chronic pain, combined with terms that indicated interdisciplinary or multidisciplinary teams, in the context of children and adolescents. Search terms were grouped into three categories: intervention, target population and clinical condition. Six databases were searched electronically (Cochrane, Medline/PubMed, Psychinfo, Pubmed, PubPsych, and Web of Science), and databases were searched from inception to the 17th of February 2014.

Two independent researchers screened abstracts for eligibility, and discrepancies were resolved through discussion with two additional independent researchers. Treatment evaluations with a RCT or non-randomized design were considered eligible. Studies were included if 1) the intervention coordinated by three or more different health professionals 2) treatment took place in an inpatient or day hospital setting 3) participants were aged <22 years 4) participants had severe or disabling chronic pain 5) the study was published in English and 6) the study had ≥10 participants post-treatment. Included articles were read in full-text by three independent researchers, and evaluated by three additional independent researchers, with discrepancies again resolved through discussion.

Meta-analysis, i.e. a statistical combination of results from included studies, was performed in study III to estimate the effect size at immediate post-treatment and short-term follow-up for all 5 outcomes: Pain intensity, disability, school functioning, anxiety and depression. Cohen´s d was computed for the changes between baseline and post-treatment, and baseline and short-term follow-up, with effect sizes of 0.2 defined as small, 0.5 defined as medium and 0.8 defined as large (200). Due to heterogeneity in the meta-analyses (144, 205), a random effects model was chosen on the basis of the assumption that the studies estimate different but still related effects from the intervention (144). The choice of a random effects model is also generally preferred in social sciences, on the basis of both the assumptions

about the population (variability in population parameters assumed) and the type of inferences the researcher wants to make (most commonly generalizations of findings beyond the studies included) (147).

3.5 Description of the ACT-intervention

At the tertiary pain clinic where study I, II and IV was conducted, the standard treatment was an ACT-based outpatient treatment, focusing on functional restoration, behavioral activation, and a functional approach to longstanding pain and symptoms. The clinic used an interdisciplinary approach involving psychologists, pain physicians and physiotherapists. Prior studies have evaluated this approach for both pediatric and adult patients (see e.g. (106, 179, 206)). In study IV, some additions were made to the protocol compared with the protocol for the previous RCT with pediatric patients, such as the addition of a physiotherapist, additional involvement of the pain physician, and additional psychologist sessions for both parents and adolescents. This resulted in a total of 18 sessions, with one session conducted with both adolescent and parent present (continued pain education). Psychologists conducted a majority of the sessions. Four phases comprise the treatment, with slightly different objectives: 1) Preparing for behavior change (including educational components about longstanding pain, and about behavior analysis of antecedents, behaviors and short- and long term consequences), 2) Shifting perspective (from reduction of pain and related symptoms, to a valued life as defined by the patient), 3) Acceptance (that is, practice the willingness to experience pain, symptoms and related experiences without attempting to change them) and cognitive defusion (that is, noticing private events such as thoughts, feelings and bodily sensations and practicing perspective taking in relation to these events, thereby facilitating behaviors in favor of long term values and goals), and 4) Values oriented behavior activation (behavior change in service of a valued life). Consistent throughout all treatment phases is the emphasis on the function of behaviors, i.e. does the behavior serve avoidance of symptoms/aversive control or exposure to symptoms in the service of moving towards what is important in the long run/appetitive control. It is worth noting that, though acceptance and defusion were explicitly practiced in one of the phases, the emphasis on these alternate processes is interweaved throughout all phases of treatment. As this intervention was the standard treatment at the clinic, pediatric patients referred to the clinic but not involved in the study also received the same treatment, with minor individual adaptations. Details regarding the inclusion and exclusion criteria for study IV are given in 3.6 below. Participants were randomized to receive either individual or group treatment (for both adolescents and parents), with the same content in both contingencies, but with group

sessions being 2 hours instead of 45 minutes to allow for participation from all group members. Care was taken to ensure the age-appropriateness of metaphors and exercises. An overview of the intervention can be found in study IV (Table 1), and for a description in Swedish of this ACT-approach to chronic pain, see Wicksell (207).

3.6 Participant-related ethical considerations

Participants in the included studies were invited at the time of their first visit to the clinic (study I and II) or when meeting the team to decide about treatment (study IV). The local ethics committee had approved the studies (see below), and data collection primarily consisted of self-report questionnaires, with an additional and limited amount of information gathered as part of clinical interviews (e.g. pain characteristics). All participants and their accompanying parent received oral and written age-adapted information about the respective cross-sectional study (study I and II) or treatment evaluation (study IV), and both child and parent provided signed informed consent. Participants were informed that participation in the study was voluntary, and that refraining from participation or dropout would not affect their care at the clinic in any way, in line with the Declaration of Helsinki Ethical Principles (208). In study IV, standard treatment was offered if suitable to those participants who were not eligible, who declined participation, or who dropped out.

3.6.1 Inclusion and exclusion criteria

Participants eligible for inclusion in study I and II were consecutive patients, referred due to longstanding and/or recurrent pain, with a pain duration of at least 3 months). Inclusion criteria were a participant age of between 10 and 18 years for study I and between 7 and 18 years for study II. Both study I and II required participants to have adequate Swedish language skills. In study IV, inclusion criteria were a participant age between 14-18 years (initially 12-18 years which was altered due to low inflow of younger patients), >6 months pain duration, little or no effect from previous pain treatments, and substantial pain disability detected in the assessment procedure. Exclusion criteria were 1) expected improvement without treatment (e.g. improvement between referral and assessment), 2) psychiatric co-morbidity that was considered the main reason for disability, required immediate treatment or was assumed to interfere with treatment, 3) substantial risk for suicide, 4) substantial cognitive impairment or reduced proficiency in Swedish, 5) other on-going or planned treatments within the following 6 months, 6) pain was recurrent rather than continuous (defined as ≥4 pain free days per week), 7) pain fully explained by a pathological process e.g. cancer.

3.6.2 Risks and adverse events

When planning the studies, we considered respondent burden, i.e. time and effort needed for participation (209), and questionnaire burden. All included assessments were considered relevant for participants, which is suggested to be a more relevant factor than the time it takes to complete them (210). In case distress would arise from items in the questionnaires, this could be addressed as part of subsequent clinical interviews, if needed.

As described by Duggan and colleagues (211), adverse events from psychological interventions treatment are seldom reported, despite the risks that interventions can be associated with issues such as increases in symptoms or sustained deterioration. It is often difficult to establish how such harm has occurred – whether from the treatment, the application of the treatment, or factors that are related to the patient. The intervention in study IV involved exposure to previously avoided and possibly pain-provoking situations, in the presence of symptoms. Participants were therefore thoroughly informed about the treatment objective – living a valued life – and that this is can involve increased pain and associated distress. To evaluate possible adverse events from the intervention in study IV, clinically significant deterioration was therefore analyzed and reported.

3.7 Research-related ethical considerations

A number of steps can be taken to ensure both the quality of a study and research ethics throughout the process of planning of a study, conducting the analyses and report the outcomes (212). By using the Cochrane Collaboration Risk of Bias Tool (144, 149), possible sources of bias identified for study IV was the lack of blinding (in this case that the researchers were also involved in data collection, delivering the intervention, and analyzing the results), and the lack of pre-registration of the study (meaning that external examiners can not know if selective reporting has occurred). Steps taken to counteract bias was the use of a randomized sequence generation and allocation concealment, detailed reporting of reasons for attrition and exclusion after the start of the study, and the reporting of a broad range of outcomes, including non-significant findings. Another common problem in psychological intervention studies is power, with many studies being underpowered and thus more susceptible for bias (212). In study IV, a formal power analysis was conducted prior to the start of the study, based on the RCT (106), though this was only reported in the ethics approval and not in the article. Attrition subsequently led to the study being under-powered for the comparison between groups (individual and group treatment). In the article, this issue was clearly stated in relation to results. Furthermore, a conservative p value was chosen ($p <$

.01), and both effect sizes and analyzes of clinical significance were presented as the p-value in itself is not sufficient for justifying a scientific conclusion (213).

For study III, a systematic review and meta-analysis, guidelines were followed to ensure study quality, including for example pre-registration of the study in PROSPERO, an international prospective register of systematic reviews with the aim of avoiding duplication and facilitate comparisons of the a completed review to its initial plan and thus reduce possible biases (214).

3.8 Ethical permits

For study I and II, ethical permits are 2009/470-31/3, and amendment: 2011/1734-32, and for study IV, the ethical permit is 2009/815-31/4. The PROSPERO-number for study III is CRD42014010719.

4 RESULTS

4.1 Study I: Insomnia in pediatric chronic pain

Participants in the study (n= 154) had a mean age of 14.6 years, and 75.3% were girls. There was a high prevalence of continuous or weekly pain (85.3%), and multiple pain locations were reported by a majority of the participants (75.8%). Furthermore, a majority also reported school absence due to pain (31% once a week or absent from PE, and 44% extensive or total absence, e.g. missing parts of school every day, or never attending school).

ISI showed satisfactory psychometric properties in this sample, including support for reliability with an internal consistency of alpha 0.88, and item-total correlations between 0.41 and 0.83, which corresponded to the original article by Bastien and colleagues (159). Support for concurrent criteria validity was gathered from significant bivariate correlations between ISI and CES-DC (depression) and FDI-P (functional disability) (r=0.32 – 0.50, p< .001).

More than 50% of participants scored above 9 on the ISI, which has been suggested as cut-off for insomnia (161) and high ratings of depression were seen (CES-DC M=24).

Hierarchical regression analyses showed that insomnia explained a significant amount of variance in depression: r^2 change=18%, F change=33.67 (1,131), p< .001 and functional disability (r^2 change=14%, F change=21.64, (1,125), p< .001) when controlling for demographic characteristics (age, sex, pain duration).

Indirect effects of insomnia were found for both the relationship between pain and depression, and between pain and functional disability, with both the Sobel test and the bootstrap method being significant at $p \leq .01$.

4.2 Study II: Pain interference in pediatric chronic pain

Participants in study I and II were drawn from the same sample. In study II (n=163), the participants had a mean age of 14.1 years and 74.2% were girls. Continuous pain was reported by 55.8%, and daily episodes of pain by 22.7%, and the median pain duration was 36 months.

The psychometric evaluation of PII included item analysis, where response rates were excellent, and levels of skewness and kurtosis were satisfactory. The items also had adequate inter-correlations ranging between 0.32 and 0.69. Results from the PCA illustrated a 1-factor solution to be adequate for this instrument (eigenvalue >1), which accounts for 58.7% of the variance in this set of items.

Support for the reliability of PII in this sample was found in analyses of internal consistency, with Cronbach's alpha=0.86. Concurrent criteria validity was supported by moderate correlations between PII and pain intensity, functional disability (FDI-P) and depression (CES-DC) (r=.381 – 0.691, p< .001).

Hierarchical regression analyses illustrated the importance of PII in predicting levels of both FDI-P and CES-DC (p< .001) when controlling for age, and results were similar when controlling for pain intensity as well.

4.3 Study III: IIPT for pediatric chronic pain

The systematic searches resulted in 2577 abstracts, from which 65 articles met initial inclusion criteria and after reading of these, the final number of included studies were 10, with 1 RCT that compared IIPT to wait-list control group, and 9 uncontrolled prospective studies/non-randomized studies. The total number of participants was 1020, where the majority were girls, the mean age was 13.9 years, and mean duration of pain was 2.95 years. Characteristics for the IIPTs programs included a mean treatment duration of 16 days, psychological and physical interventions were reported in all 10 studies, and medical interventions in 9 studies. Parents were reported to be included in 8 studies. There was a range of treatment components included in the IIPTs. Only 3 studies reported details on pain medication during treatment for the participants.

Quality ratings using the Cochrane Collaboration Risk of Bias Tool for the RCT (149) and the Quality Appraisal Tool for the non-randomized studies (150, 151) showed that all 10 studies described the intervention and participant characteristics in a detailed manner. Consistent methodological limitations were observed, with the most protruding one being that only 1 study was an RCT.

The meta-analysis provided preliminary evidence for positive treatment effects. Pooled estimates from the 9 non-randomized studies were presented separately from the results of the RCT. Effect sizes for the RCT were based on the intervention-group only, thus within-group analyses were conducted for both the RCT and the non-randomized studies. Large improvements at immediate post-treatment were observed for disability (large effect in the RCT, d= -0.80 in favor of IIPT) and across 6 non-randomized studies (d=-1.09), small improvements were observed for pain intensity (RCT significant effect d=-0.38, 4 non-randomized studies small non-significant d= -0.32, and no or small effects for depression (RCT no effect, d= -0.22, 5 non-randomized studies small beneficial effect d= -0.37. The positive effects were maintained (disability) or further improved (pain intensity, depression)

at short-term follow-up. Due to substantial heterogeneity in measurements of anxiety and school functioning, effect sizes were calculated only, and not pooled. For anxiety, no effect was reported at post-treatment in the RCT, but for 4 non-randomized studies, effect sizes were large and ranged from -0.82 to -1.14. The positive effects remained at follow-up, and for the RCT, there was a positive large effect at follow-up (d= -1.02). For school functioning, the RCT and one non-randomized study had large effects post-treatment. At follow-up, the RCT and 4 non-randomized studies had moderate to large effect sizes (d=0.53 to -1.0).

4.4 Study IV: ACT for adolescents with chronic pain and their parents

A total of 48 adolescents were included in the study, and 30 completed post-assessments (24 girls). There were no significant differences between completers and non-completers/exclusions at pre for any of the variables included in further analyses, hence, analyses reported here are based on the final sample of completers (n=30 adolescents and n=28 parents). The mean age of participants was 16 years, and they reported a mean pain duration of more than 4 years. The majority reported continuous pain and multiple pain locations. Parents consisted of 28 parents (24 mothers), with a mean age of 47 years. Notably, 57% of the parents reported a pain duration of 1 year or more.

No significant differences were found between the individual treatment condition and the group treatment condition. Analyses illustrated significant (p< .01) improvements (medium to large effects) in pain interference, depression, pain reactivity and psychological flexibility post-treatment. Parent ratings of adolescent functional disability did not improve significantly p= .032). No significant changes were seen in adolescent pain intensity at any of the time points. Additionally, analyses showed significant (p< .01) improvements (large effects) in parent pain reactivity and psychological flexibility post-treatment. There were no significant changes reported in parent anxiety or depression. The pattern of results illustrated more significant changes from mid- to post, than from pre- to mid treatment.

On all significant outcomes, clinically significant changes in the direction of functionality were observed for 21%–63% of the adolescents across the different outcome measures and in 54%–76% of the parents. Deterioration was reported by 7% of participants regarding pain reactivity, and depression. In parent rated functional disability, 11% reported deterioration, and 4% reported deterioration in pain intensity. Of the 30 participants, deterioration in one or more of the variables above was reported by 5 participants in total.

In addition to the results in the article, a complimentary analysis of the effects of treatment on sleep was conducted. Sleep was assessed in study IV as a secondary outcome variable. In the

sample, median scores were above the suggested cut-off on ISI for clinically significant sleep problems (9, as found in (161)) at pre, and no significant changes were seen at either mid or post treatment (median pre=10.50, range 1-27, median mid=11.00, range 0-28, and median post=11.00, range 0-28, (*p* between .109 to .731).

5 DISCUSSION

5.1 Assessment of pain-related dysfunction: Insomnia and pain interference

This doctoral thesis contains two studies aimed at the development of reliable and valid measures of pain-related dysfunction, specifically insomnia and pain interference.

The findings from study I include support for the internal consistency and concurrent criteria validity of the Swedish translation of the ISI used in a sample of pediatric patients with chronic pain. The ISI is already a well-know measure of insomnia in adults, used world wide (152-159), including a recent study evaluating the psychometric properties of the ISI in a sample of Swedish adults with chronic pain (166). Our findings suggest that insomnia can also be adequately assessed in the pediatric chronic pain population, for which measures of insomnia have been lacking. A systematic review from 2011 (133), found no measure of insomnia that had been evaluated for adolescents and, to our knowledge, the only study that existed in this regard prior to this doctoral project was the Chinese evaluation of ISI for adolescents (161). Thus, the results from our study are relevant for a range of pediatric health care services where insomnia should be assessed and treated, in line with recent suggestions (43, 44).

Our findings replicate and extend prior studies showing insomnia to be prevalent in pediatric chronic pain. In a cross-sectional study by Palermo and colleagues (52), where insomnia symptoms were assessed using only 2 questions (difficulties falling asleep and staying asleep), 54% of youths with chronic pain reported one of these difficulties as compared to 20% in the comparison group. In our study, using the ISI, 52% of the participants scored above the cut-off for insomnia suggested in previous research with adolescents (161). We found insomnia to be highly important in explaining depression and functional disability in pediatric chronic pain, more so than pain intensity. This is also in line with the findings in the study by Palermo and colleagues (52), who noted that presence of chronic pain rather than levels of pain intensity, was more important in regression analyses with insomnia symptoms as the outcome. Similar findings were seen in a longitudinal study by Palermo and colleagues (56), with behavioral factors rather than pain intensity predicting insomnia over time, and presence of insomnia being related to lower health related quality of life and higher use of medical services. Further, our results suggest that insomnia strongly influences the relationship between pain and functioning. Thus, targeting insomnia directly in treatment appears to be important. Insomnia of pain related origin might spiral into a primary problem of its own (as discussed by Palermo and colleagues). Given the prevalence of sleep problems

in adolescent populations (37), insomnia might also have been present before the onset of pain, and serve as an exacerbating factor. Regardless of direction, insomnia appears highly relevant for functional outcomes and as seen in the longitudinal study by Palermo and colleagues (56), insomnia symptoms persisted over time for both the chronic pain group and the healthy control group. This indicates the need to address insomnia in adolescents both with and without co-morbid medical conditions. More research is needed to confirm whether insomnia is a *"candidate mediator"* (p. 17 in (196)) which mediates functional outcomes in pediatric chronic pain, for example RCTs in which a sleep intervention targeting insomnia or other sleep problems is given as an add-on to one of two treatment groups receiving a behavioral pain management intervention like the one in study IV or those described in study III, and where insomnia symptoms are assessed parallel to other potential mediators, in both groups repeatedly during treatment.

The findings from study II include support for the factor structure, internal consistency and concurrent criteria validity of this Swedish version of the PII when used in a pediatric chronic pain sample. Items in PII are likely to reflect the same underlying dimension of pain interference, as indicated by factor analysis. Our results point to the utility of the construct of pain interference for pediatric chronic pain, and for using the PII when assessing pain interference in this population. Importantly, PII has also been evaluated in an English version with pediatric participants suffering from chronic illness and pain, and support was found for the reliability and validity of both child and parent-report (183). Further, both the child version and the parent version of PII have shown sensitivity to change after ACT-based behavioral treatment interventions (106, 127, 215). These findings, together with the brevity of the instrument and the ease with which instructions and items can be understood, support further use of PII both for repeated assessments during treatment, and as a measure of treatment outcome.

A moderate correlation between PII and the FDI-P indicates concurrent criteria validity. The fact that the association appears to be moderate, and not strong, indicates the difference between pain interference and the physical functioning domain, in turn highlighting the importance that both factors are addressed in treatment. This has also been put forth in a study of adult pain interference and physical functioning (60). Our research group has examined the indirect effects of pain interference as measured by PII on the relationship between pain intensity and physical and emotional functioning (assessed with the FDI-P and CES-DC) in the same sample as study I and II (216). Results showed significant effects of pain interference on both these outcomes, and directionality was indicated by the absence of

effects when depression and functional disability were tested as mediators for the relationship between pain intensity and pain interference.

The other available instrument for assessing pain interference in children and adolescents with chronic pain, PROMIS-PI (62), which has been developed using Item Response Theory (IRT) has recently been evaluated in a clinical sample with results indicating validity and responsiveness. The PROMIS is a large-scale initiative aimed at developing PROs for chronic disease in general. Through IRT-analyses, item banks are created for different disorders, and computerized adaptive tests can then be used which selects items based on an individuals response to previous items (62, 66). Implementation of the PROMIS system would be an important addition for pediatric chronic pain research as well as for clinical purposes in Sweden, and PII could serve as a useful legacy scale for evaluation and subsequent implementation of the PROMIS-PI, which has not yet been evaluated in Swedish.

A final important note concerning PII and ISI is that there is now support for their validity and reliability in both pediatric and adult samples that suffer from chronic pain. The need for studies with a developmental focus that follow late adolescents with chronic pain into young adulthood, has been put forth (217), and by using the PII and the ISI, it is possible to investigate insomnia and pain interference longitudinally in this important period of life.

5.2 Effects of IIPT and ACT outpatient treatment

Two different studies were conducted to examine the utility of behavior-oriented treatments for pediatric chronic pain.

The systematic review included 10 studies evaluating IIPTs for pediatric chronic pain associated with severe distress and disability. Characteristics of included studies showed similarities regarding participants and treatment programs, but less consistency regarding assessments of relevant outcome domains, and lack of details around the dose of different interventions included in the programs.

The meta-analysis provided preliminary evidence for positive treatment effects of IIPT. Large effect sizes were seen for important outcomes, for example disability, and beneficial effects were maintained or further improved at short-term follow up. Notably, only one study was a RCT. This lack of rigorous methodology in the vast majority of included studies prevents causal conclusions, as findings can be attributed to other factors than the treatment per se (e.g. consumer satisfaction, or factors unrelated to treatment). There is a great need for more studies investigating the effects of IIPT by RCT design.

There was substantial heterogeneity in outcomes included in the meta-analysis. Heterogeneity in studies can result from clinical diversity such as differences in the participants or outcomes examined, from statistical heterogeneity caused by methodological diversity, or both, but it is commonly difficult to establish to which degree heterogeneity results from one, the other or both sources (144). Different strategies can be used to deal with heterogeneity. One option is a random effects model for analyses, as used in this study. Alternative strategies include refraining from meta-analysis, exploring subgroups of studies, or changing the effect measure (144). The small number of studies prevented options that use sub-group analyses to explore heterogeneity. Further, for the outcomes for anxiety and school functioning, the measures used were too dissimilar, and meta-analysis was not conducted.

In addition to conducting studies with higher methodological quality, there is a need to conduct studies that promote further developments of IIPTs, for example providing detailed descriptions of treatment content and dose of components/interventions delivered by the respective disciplines included in the IIPT, and using randomization of included components to examine their effects. Further, intensive data collections with multiple assessment points, for example using real time data collections (218) could be used to examine in more detail at what point changes occur, and in relation to which interventions and contextual factors. Finally, coherence in outcome measures for physical, social and emotional domains, and the inclusion of assessments of pain medication and health-care costs to a larger extent in future evaluations of IIPTs would provide important information for professionals and patients alike.

The pilot trial of ACT supports previous findings, as increased functional outcomes were seen post treatment, which provides further promise for the utility of ACT in this population. Despite the brevity of the protocol, and the severity of pain-related dysfunction in the sample, statistically as well as clinically significant improvements were seen in a range of adolescent outcomes. The study also provided novel findings concerning outcomes for parents after participating in a parent support program in conjunction with their child's treatment. Parent psychological flexibility has been put forth as a potentially important treatment target in interventions for pediatric chronic pain (125, 188) and this issue was explicitly targeted in parent sessions. Although the parent support program only consisted of 4 sessions in total, significant reductions in parent pain reactivity and improvements in parent psychological flexibility were reported post-treatment. This promising result paves the way for further research into parent support based on ACT.

Preliminary comparisons of group and individual treatment formats were conducted, and similar results were found for both formats. Thus, from a resource allocation perspective the study provides preliminary support for utilizing a group format if no clinical factor clearly calls for individual treatment. A future methodologically rigor noninferiority trial including a larger sample and a pre-specified noninferiority margin for the primary outcomes (219) could provide further information regarding our preliminary finding indicating that group interventions may be as effective as individual interventions.

The results from our preliminary evaluation of temporal change patterns suggest that effects may occur in the later phase, indicating the need for studies examining treatment components, and studies that explore trajectories of change, in line with the study by Palermo and colleagues (220), where some patients reported improvements, and others reported worsening or minimal improvements in pain and function during the 8-10 week treatment period. Our preliminary findings could imply that some individuals that do not respond quickly may yet be benefitting from the treatment. This could also imply the relevance of further exploring the temporal dimension, since a subgroup of patients may illustrate continuous improvements over time and benefit from a more extensive treatment program. However, there is a need for more information regarding predictors and moderators of change, and how treatment can be adapted on the basis of such findings. Some examples of factors that have been suggested to be of importance for treatment outcomes include anxiety, willingness to self-manage pain, parent distress and behaviors, and acceptance and psychological flexibility. Cunningham and colleagues compared children with chronic pain who had clinical versus subclinical levels of anxiety, and found clinical levels of anxiety to be associated with poorer treatment response in pain intensity and functional disability after CBT-treatment (221). Logan and colleagues found that willingness to self-manage pain increased during interdisciplinary treatment, for both children and parents, and that child willingness was associated with outcomes such as depression and functional disability, indicating that readiness to change is a potential mechanism of change in treatment and predictor of treatment response (222). Findings from two studies on longitudinal associations between child and parent functioning have been discussed in 1.3.4 and 1.6.1, with one study showing parent avoidance and protective behaviors to predict child depression and school functioning post treatment (74), and the other study showing that higher parent distress predicted less improvement in child disability over one year (124). Further, as noted in 1.6.2, changes in parent psychological flexibility was significantly related to changes in adolescent pain acceptance (129). Finally, as discussed in 1.4.2, the association between child acceptance and sustained changes in outcome (108), as well as the mediating role of psychological flexibility for treatment outcomes has been shown

(106). Thus, building on promising initial findings such as these, future studies examining predictors, moderators and mechanisms of change can be conducted to increase our knowledge on how to improve child and parent outcomes.

In study IV, clinically significant improvements were seen to a large extent for both adolescent and parent outcomes, indicating that the treatment had a multi-dimensional practical impact for many participants. However, some participants did not report such changes, and a small subset of adolescents even reported clinically significant deterioration. This finding serves as a further reminder of the importance to investigate predictors and moderators of treatment outcome, as well as ways in which to tailor treatment for particular subgroups of patients. In addition, what constitutes a clinically significant change in functioning outcomes for pediatric chronic pain patients should be investigated further, and with other approaches. As described by Kazdin (202), several considerations should be taken into account when evaluating clinically significant changes, from the meaning and interpretation of the measure, to how the assessment relates to the goal of the therapy, and the constructs reflected. For pain intensity, analyses have been made to assess minimally clinically significant differences for pain intensity (see e.g. (223)), and for the FDI, clinical reference points have been suggested for what constitutes different degrees of disability (174), which enhances both the clinical and the research utility for the FDI as an outcome measure. Similar steps should be taken for assessments concerning other important treatment outcomes, such as the PII and the PROMIS pain interference scale (66).

As seen in Table 2, findings from the systematic review on IIPT and from the pilot study of ACT show both similarities and differences. The IIPT has a greater focus on physical rehabilitation, which is also reflected in physical functioning outcomes. This indicates that this particular treatment format may be important for participants with severe physical dysfunction. Both IIPT and outpatient ACT resulted in preliminary positive treatment effects for depression. The co-morbidity of chronic pain and mental health problems is well known, and emotional outcomes constitute important treatment targets (25). Adolescents in study IV as well as in the bigger sample in study I and II presented with high scores of depression, indicating the presence of severe emotional dysfunction in this sample (median score for CES-DC at pre in study IV was 28, and in study I the mean was 24.20, as compared to the mean score of 13.2 for CES-DC in a Swedish general adolescent population (172), and to a clinical sample of adolescents with chronic pain where the mean for CES-DC was 14.22 (52). When analyzing ratings of depression in study IV, we found a medium effect size for the improvements pre- to post, and clinically significant improvements in 39% of participants.

Similarly, the effects from IIPT showed a small beneficial effect on depression at post and follow-up for the non-randomized studies, and a moderate effect for the RCT at follow up. These are particularly relevant findings, as reports of improvements in depression after CBT for pediatric chronic pain have been lacking (88).

Table 2. Overview of effect sizes for children from study III and IV, and similarities and differences between IIPT-studies included in study III and the ACT-treatment delivered in study IV.

IIPT		
Outcome	Effect size post treatment	
	RCT	Non-randomized
Pain intensity	*d* = -0.38 (CI -0.67 to -0.10)	*d* = -0.32 (CI -0.70 to 0.06), 4 studies ns
Disability	*d* = -0.80 (-1.13 to -0.47)	*d* = -1.09 (CI -1.71 to -0.48), 6 studies
Depression	*d* = -0.22 (CI -0.64 to 0.11) ns	*d* = -0.37 (CI -0.64 to -0.11), 5 studies
Anxiety*	*d* = 0.00 (CI -0.28 to 0.28) ns	*d* = between -0.06 to -1.14, 6 studies
School functioning*	*d* = -0.88 (CI -1.21 to -0.54)	*d* = -0.94 (CI -1.28 to -0.61), 1 study
*= Estimates not pooled		
Duration	Approximately 128 h Mean number of days=16	
Characteristics of delivery	Inpatient setting Intensive treatment delivery Interdisciplinary: 7 studies included 5 disciplines Treatments included medical (9 studies), psychological (10 studies), and physical interventions (10 studies). Parental interventions in program reported in 8 studies	
Characteristics of content	Pain intensity a primary outcome in most studies Focus on functional restoration and psychological pain management Content included CBT-interventions	
ACT		
Outcome	Effect size post-treatment	
Pain intensity	*r* = -0.13	
Functional disability	*r* = -0.35	
Depression	*r* = -0.37	
Pain reactivity	*r* = -0.49	
Pain interference	*r* = -0.51	
Psychological flexibility	*r* = 0.59	
Duration	18 sessions Duration of sessions in individual condition: 1h Duration of session in group condition: 2h	
Characteristics of delivery	Outpatient setting Weekly sessions Interdisciplinary with 3 disciplines (medical, psychological, physiological). Majority of sessions delivered by psychologist Parent support program part of treatment: 4 sessions	
Characteristics of content	Pain intensity not a primary outcome Focus on psychological processes for pain management Content for all sessions based on ACT	

[a] For *d*, effect sizes of above 0.2, 0.5 and 0.8 are considered small, medium and large; [b] For *r*, effect sizes of above 0.10, 0.30 and 0.50 are considered small, medium and large

5.3 Clinical implications

Almost 10 years has passed since the PEDIMPPACT recommendations were issued (132), stating the need for development of reliable and valid assessment of pain-related dysfunction, such as functional impairment and sleep outcomes, specifically for pediatric patients with chronic pain. In this statement, authors encouraged both the evaluation of adaptations of existing well-known existing measures to the pediatric chronic pain population, as well as the development of new measures particularly for this group. The studies included in this thesis provide support for two instruments of relevance for the assessment of pain-related dysfunction. Both the PII and the ISI are brief instruments that are easy to administer and complete, which also makes them good candidates for repeated assessments and for use with digital tools. They have a clear clinical utility as they assess domains that can be targeted in treatment.

Behavior-oriented multidisciplinary treatment programs based on CBT and ACT, delivered in intensive residential or day hospital settings or as outpatient interventions in group or individual format are promising for improving a range of functional outcomes in pediatric patients with chronic pain. To confirm and extend these findings, there is a need for studies with a more rigorous design, control-conditions, and with larger samples, as well as investigations of mechanisms of change and their relation to the theoretical foundations of the treatments. Such information is crucial in order to establish which type of treatment program and/or format, which is best suited for particular patient profiles.

The high prevalence of insomnia indicates the need to address sleep difficulties as part of treatment. Similar to our findings from the additional analyses of insomnia in study IV, other treatment evaluations have also reported an absence of changes in sleep outcomes after CBT-treatment for pediatric chronic pain (134, 224). However, in an intensive interdisciplinary treatment evaluation by Logan and colleagues, sleep habits improved, and were of importance for post-treatment reductions in pain intensity for adolescents with chronic pain (225). It has been hypothesized that sleep problems in pediatric chronic pain might have other explanations than pain in itself and that an increased focus on assessing and treating specific sleep problems such as insomnia, but also sleep times, sleep quality and quantity, in pediatric chronic pain as well as pediatric primary care in general, is needed (43, 224).

The preliminary findings from the evaluation of parent outcomes after the brief ACT-based parental support program are promising. Parents of children with pediatric chronic pain often struggle with their own distress related to their child's condition, and commonly also report own chronic pain (119, 120). Thus, parental distress as well as parent mental health need to

be addressed in order to facilitate effective parent behaviors. The findings from study IV together with similar findings from recent studies indicate that parent psychological flexibility can be targeted successfully in treatment (128, 129).

5.4 Limitations

In the psychometric evaluation of ISI and PII, limitations include the lack of child reported functional disability as only the FDI-parent version was used. Similarly, an additional measure of sleep, either a validated self-report questionnaire or actigraphic assessment would have been beneficial for additional information regarding validity in the psychometric evaluation of the ISI.

The non-randomized study design of 9 of the 10 studies included in study III limits our confidence in the conclusions from the meta-analysis. When studies included in a MA have a non-experimental study design, this prevents causal conclusions (146) and highlights the need for future RCTs.

A potential limitation concerning the search strategy in study III is that searches were conducted exclusively in databases, which is related to a risk for file-drawer effects/publication bias (147). However, unpublished material can lack detailed reporting, which limits possibilities for quality assessment, and the process of finding unpublished material can be difficult to replicate (226).

Similar limitations as identified for studies concerning ACT-interventions in pediatric populations (98, 99) also hold true for study IV. There was no control group for adolescents or parents, which limits the certainty about main treatment effects. Improvement might thus be a result of unspecific factors, not related to treatment. Further, the sample is relatively small, and the design did not allow for examination of change processes. As follow-up assessments were not included, analyses of the stability of treatment effects were prevented. This lack of follow-up assessments also prevented further analyses of deterioration over time. Concerning the comparison between treatment formats, there were some unexpected difficulties as a few participants declined participation after being randomized to group treatment. Logistical reasons including inflow of participants and changes in staff brought the study to an end before the desired number of participants was achieved. Finally, information regarding medication for the sample would have provided important information. As many children with chronic pain are medicated despite lack of indication for pharmacological treatment (84), and few studies have properly addressed and evaluated the incremental utility

of medications in treatment programs for pediatric chronic pain (as noted in study III), this is an important addition for future studies.

5.5 Future research

Current prevalence rates and availability of evidence-based treatments clearly suggest the need to increase access to effective therapies for pediatric patients with chronic pain. New technology is already in place using internet-based solutions (123, 227), which reduces geographical barriers to care, and facilitates multi-center studies/studies with a national or international uptake and thus a large sample size. Such initiatives could be used for large-scale analyses of predictors and moderators of treatment effects, and identification of sub-groups of patients, for example those who have the highest co-morbidity or most severe dysfunction, or the group associated with the most extensive health care costs (as seen in the study by Groenewald and colleagues (75)), and provide more information about health service and medication use (76) in relation to treatment outcomes. Further, the utilization of more intensive data-collections through computerized measures enables thorough analyses of change processes.

Consensus around process and outcome measures is needed in order to pool data. Recent advances in assessment development suggest it might be time for updated PedIMMPACT recommendations.

Qualitative investigations of patient experiences related to both successful and unsuccessful treatment outcomes can shed light on mechanisms of change and if theoretical assumptions supported from adult research also holds true in pediatric populations. Qualitative methodology will also be important in future development of assessments, and in evaluations of what constitutes clinically significant changes for a developing individual (202, 217). By focusing on engaging the patient in both the health care service and the research agenda, i.e. patient-public-involvement (PPI), the unique experience of the child and adolescent should be taken into account (228). This could advance clinical routines and research questions, and information could be gained about possible improvements to interventions for particular subgroups of patients, patient satisfaction, and adverse treatment events, which have been called for in treatment of pediatric chronic pain (118, 229).

Finally, given the high prevalence of chronic pain in pediatric populations and the co-morbidity with mental health disorders and family disturbances, preventative efforts are needed on a large scale for young people and families, promoting healthy emotional, social and physical functioning from an early age and beyond.

6 CONCLUSIONS

Pain interference and insomnia are important factors for pain-related dysfunction in pediatric chronic pain and can be adequately assessed using the PII and the ISI. In the treatment of pediatric pain-related dysfunction, IIPT is promising although more and larger well-designed studies are needed. Also, a relatively brief outpatient ACT program may be used to improve functioning in pediatric chronic pain, delivered as individual or group treatment. Furthermore, results indicate preliminary evidence for the utility of ACT based parent support, in improving parent emotional reactivity and psychological flexibility, in the context of pediatric chronic pain. The results from the studies included in the present thesis can contribute to improved assessment and treatment of this complex condition, and warrant more research on how to improve child and parent outcomes. Future studies should utilize both rigorous methodology and frequent data collections to increase our knowledge about outcomes as well as change processes, and advance our understanding of how to help those who experience pain-related dysfunction in the presence of pediatric chronic pain.

7 ACKNOWLEDGEMENTS

Many people have contributed significantly to this publication in different ways, before and during my doctoral studies. I want to give thanks to some of you in print but in my heart, the list is longer.

Rikard Wicksell, my principal supervisor. I remember when I first contacted you many years ago, and presented my hopes about conducting scientist-practitioner psychology research within the pediatric somatic context. Ever since that very moment, you've provided knowledge, help and support, opportunities for participation, and challenges to learn from and grow with, among these are trans-Atlantic conference symposium adventures and advice around dealing with reviewers, research questions, patients, parents, and more. I am deeply grateful to you for believing in me right from the start. We've had fun, and we've worked hard. Your vision about changing the world is an inspiration to us all - let's keep to our valued directions, and keep moving, to do just that. Thank you, for everything.

Linda Holmström, co-supervisor. You have been instrumental in my progress every step of the way, from preparing for admission to this very day when my thesis defense is approaching. No doctoral student should ever be admitted without a supervisor like you assigned to the team. Thank you, dear Linda, for sharing your time, wisdom and warm heart.

Mats Lekander, co-supervisor. Thank you for your kind words, your rapid responses and your appreciative style, and for providing me with wise advice based on your experience of the doctoral process and academia.

Gunnar Olsson, your hard work and soft heart have changed the lives of countless people, young and old, with and without pain, and you deserve countless songs and limericks. You have been a true pioneer in pediatric chronic pain treatment, and many have since followed your lead, in the service of those who suffer. Thank you, for your kindness, your positive spirit, and for always taking the time to discuss patient-related concerns with me.

Thank you to the **research community**, for sharing your findings, time, critical comments, encouragement and expertise. Thank you in particular, reviewers of the included articles, for your time and your valuable comments, questions and suggestions. Thank you all **children and parents** involved in my research, for generously dedicating time and energy to answering questionnaires in order to help us move our understanding of pediatric chronic pain and related dysfunction a little further.

I first became aware of the research process during my time at Uppsala University. Thank you to the Developmental psychology group at that time, **Gunilla Bohlin, Lilianne Nyberg, et al**, for inviting me to this part of the world. Thank you **Linda Forssman,** my intelligent, creative mentor but first and foremost friend – from the day we met, in a tiny office with a low ceiling, until this day, where life and space has expanded. Thank you for phone calls when they were needed the most, for sincere and spot-on advice, for knowing how to listen, for artistic collaborations, for all the fun we've had!

Thank you **Mike Kemani,** extraordinary psychologist, researcher and colleague, and much-appreciated friend, for all your help and kindness, for thinking things through that extra bit, for sincere and successful attempts to understand things big and small, and for sharing your knowledge. **Camilla Wiwe-Lipsker,** remarkable psychologist and researcher, intelligent and kind colleague – thank you for helping out, listening in, and cheering me on. Thank you to both Camilla and Mike for taking the time to improve my thesis. **Our team** has grown exponentially over the years. I am forever grateful to have been part of the team vision and everyday work. Thank you current and former co-workers, in and around the team: **Maria Elb, Birgitta Hellgren, Catrine Mitander, Ingrid Olsson, Milka Dinevik, Agneta Julinder, Peter Eriksson, Björn Liliequist, Martin Jonsjö, Jenny Rickardsson, Jenny Åström, and many, many more**, for everything from encouraging words, warm smiles, and interesting lunch discussions, to practical help, clever questions, insightful answers, and general support.

In the spring of 2008, thanks to the combined effort of **Anna Söderström, Terry Jones and Bill Yule**, I did my clinical placement abroad and met a role model for life when it comes to real world research – the amazing researcher, clinician and friend, **Gillian Colville**. Thank you, Gillian, for everything you have done for me. I would not have pursued the research path had it not been for you. Thank you also to **Rachel Harman** and the whole Pediatric Psychology team at St Georges Hospital, London, for supporting my professional and personal growth spurt.

This thesis exists because of the **Doctoral School for Health Care Science (NFV).** Thank you to everyone involved, **Lena Von Koch, Inger Tjergefors, Lena Wettergren, et al**, for funding the project and for all your support throughout the years in relation to the doctoral process and parallel life activities. **Everyone in HK-12** – what a marvelous group of people, who have generated not only a monumental heap of high-quality research but also lots of positive feelings in relation to the doctoral education process, from start to finish! In particular: **Håkan Nero** – I'm so delighted I got the chance to get to know you. You are a

friend who makes both statistics challenges and non-research conversations a true joy! Thank you for encouraging me in these last months of thesis writing! **Lie Åslund**– thank you for friendship, enjoyable teamwork, and reflective discussions around the doctoral process and family life, from admission and onwards!

Aila Collins, Sara Widén & Anna Warensjö – thank you for engaging collaborations around teaching at KI. Thank you to the admin staff at CNS, **Bob Harris, Eva Holmgaard, Renny Lidström, et al**, for all your swift and friendly help.

Thank you **Chris Eccleston and the whole team at the University of Bath, Centre for Pain Research, and the Pain Services at the Royal National Hospital for Rheumatic Diseases,** for welcoming me as a visitor in October 2016. Thank you in particular to the amazing **Abbie Jordan** and **Jeremy Gauntlett-Gilbert** for inspiring discussions about research, exciting on-going collaborations and intriguing future plans. Your kind and encouraging words, sharing of knowledge and provision of support mean the world to me. Thank you, brilliant **Emily Holmes,** for your energy, inspiration and kindness, which lifted my research spirit when it was low. Similarly, **Bianka Karshikoff** –thank you for kind, clever and honest advice, and hugs. **Julie Lasselin** – thank you for your advice and support, and for being an inspiration when it comes to finding one's direction in the professional dimension. Thank you, kind and intelligent **Rebecca Grudin,** for friendship and support in context. Your being there for me in this last phase of my doctoral studies meant a lot. Thank you, awesome researchers **Tanja Hechler, Amy Lewandowski Holley, Laura Simons, Gerrit Hirschfeld and Boris Zernikow,** international co-authors in the systematic review, for letting me take part in the project, which was such a valuable experience in countless aspects. Thank you **Rebecka Ringström** for our friendship over the years, QoL-coffee, and your contribution to study I. **Susanne Gustafsson**, thank you for help with the search strategies in study III and for pointing me in the direction of the Cochrane Collaboration. Thank you everyone involved in the establishment of the **Cochrane Associated Centre Sweden** – you are such an inspiring network. Thank you, **Matteo Bruschettini** and **Carl Gornitzki** for supportive feedback and great teamwork. Thank you **Minna Johansson** for encouragement and support. Thank you **Gustav Nilsonne** for sharing your thoughts around post-doc life and learning.

Nanna Svartz, and newfound friends in the network – thank you for letting me in and for sharing. The heads and hearts of the women involved will change the world. In particular, **Johanna Enö-Persson** - thank you for honest, important and inspiring discussions around present and future work and life contexts. **Maria Bragesjö** – thank you for support and inspiring discussions about future projects. **Journal Club Somatic symptoms** – thanks for

stimulating discussions and inspiring outlooks on theoretical models and research challenges. **The ACBS-community, internationally and nationally**, thank you for providing a space to gather efforts aimed at behavior change in the service of a better world.

Friends – I want to mention some of you here, who have been of particular importance not just as friends, but also for my work. Thank you **Anna Söderström** - since we were seven, you have been my beloved sister-"bästis". Thank you for knowing me and supporting me, sometimes more than I know and support myself. I'm lucky to have you in my life. Also, thanks to you, I now know the difference between last and latter! Thank you **Johnny Pellas**, for each and every laugh we share, and for your advice around all things important, including how to recognize and deal with a tired hippocampus. Thank you also to your lovely family - spending time with the **Pellas-quartet** is always a source of comfort and kindness. Thank you **Anna Stolt** for being a wise friend who provides objective outlooks on complicated issues, and for your whole-hearted happiness and pride when things work out for me. Thank you **Sandra Lindblad** for shining light on rainy days, your incredible pep-talking skills and inspiring ability to seize the moment. **Anna Edman, Henrik Johansson and Tekla** – thank you for understanding what it means to struggle with a thesis, and for friendship, through many phases of life, and more to come.
Family, in blood and extended –for there are many of you. Thank you, my loving and lovely **mom Elisabeth and dad Stefan**, for being proud of me, for your kindness, and all the help you provide. Thank you, **my brother Mathias and family, my uncle Lars Eric, Ann-Sofie and my family members from the Holm-Sandin family, my family from the Kanstrup side - Mita and Jörgen, Ulrika and family,** and many more extraordinary persons around us, for words of encouragement, food, and never-ending support in various, equally important ways.

MOSES, ILIAN, MATHIAS

Everything that matters, **love and life extra large.**

I know you would have preferred I'd spent more time with you rather than in front of my computer. Therefore, this thesis is not dedicated to you.

But you know that my life is.

Jag älskar er!

8 REFERENCES

1. Merskey H, Bogduk N, International Association for the Study of Pain. Task Force on Taxonomy. Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms. 2. ed. Seattle: IASP Press; 1994. xvi, 222 s. p.

2. Zouikr I, Karshikoff B. Lifetime Modulation of the Pain System via Neuroimmune and Neuroendocrine Interactions. Frontiers in Immunology. 2017;8:276.

3. Ebert MH. Behavioral and Psychopharmacologic Pain Management. Kerns RD, editor: Cambridge: Cambridge University Press; 2010.

4. Hyams JS, Di Lorenzo C, Saps M, Shulman RJ, Staiano A, van Tilburg M. Functional Disorders: Children and Adolescents. Gastroenterology. 2016.

5. Friedrichsdorf SJ, Giordano J, Desai Dakoji K, Warmuth A, Daughtry C, Schulz CA. Chronic Pain in Children and Adolescents: Diagnosis and Treatment of Primary Pain Disorders in Head, Abdomen, Muscles and Joints. Children. 2016;3(4):42.

6. Sen D, Christie D. Chronic idiopathic pain syndromes. Best practice & research Clinical rheumatology. 2006;20(2):369-86.

7. Schechter NL. Functional pain: time for a new name. JAMA Pediatr. 2014;168(8):693-4.

8. Basch MC, Chow ET, Logan DE, Schechter NL, Simons LE. Perspectives on the clinical significance of functional pain syndromes in children. Journal of pain research. 2015;8:675-86.

9. Treede R-D, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. A classification of chronic pain for ICD-11. Pain. 2015;156(6):1003.

10. King S, Chambers CT, Huguet A, MacNevin RC, McGrath PJ, Parker L, et al. The epidemiology of chronic pain in children and adolescents revisited: a systematic review. Pain. 2011;152.

11. Hoftun GB, Romundstad PR, Zwart J-A, Rygg M. Chronic idiopathic pain in adolescence – high prevalence and disability: The young HUNT study 2008. Pain. 2011;152(10):2259-66.

12. Swain MS, Henschke N, Kamper SJ, Gobina I, Ottová-Jordan V, Maher CG. An international survey of pain in adolescents. BMC Public Health. 2014;14(1):1-7.

13. Huguet A, Miró J. The Severity of Chronic Pediatric Pain: An Epidemiological Study. The Journal of Pain. 2008;9(3):226-36.

14. Brattberg G. Do pain problems in young school children persist into early adulthood? A 13-year follow-up. Eur J Pain. 2004;8(3):187-99.

15. Hassett AL, Hilliard PE, Goesling J, Clauw DJ, Harte SE, Brummett CM. Reports of chronic pain in childhood and adolescence among patients at a tertiary care pain clinic. J Pain. 2013;14(11):1390-7.

16. Kashikar-Zuck S, Cunningham N, Sil S, Bromberg MH, Lynch-Jordan AM, Strotman D, et al. Long-term outcomes of adolescents with juvenile-onset fibromyalgia in early adulthood. Pediatrics. 2014;133(3):e592-600.

17. McKillop H, Banez G. A Broad Consideration of Risk Factors in Pediatric Chronic Pain: Where to Go from Here? Children. 2016;3(4):38.

18. Huguet A, Tougas ME, Hayden J, McGrath PJ, Stinson JN, Chambers CT. A Systematic Review with Meta-analysis of Childhood and Adolescent Risk and Prognostic Factors for Musculoskeletal Pain. Pain. 2016;157(12):2640-2656.

19. Boerner KE, Schinkel M, Chambers CT. It is not as simple as boys versus girls: the role of sex differences in pain across the lifespan. Pain management. 2015;5(1):1-4.

20. Konijnenberg AY, Uiterwaal CS, Kimpen JL, van der Hoeven J, Buitelaar JK, de Graeff-Meeder ER. Children with unexplained chronic pain: substantial impairment in everyday life. Archives of disease in childhood. 2005;90(7):680-6.

21. Palermo TM, Fonareva I, Janosy NR. Sleep quality and efficiency in adolescents with chronic pain: relationship with activity limitations and health-related quality of life. Behavioral sleep medicine. 2008;6(4):234-50.

22. Petersen S, Hagglof BL, Bergstrom EI. Impaired health-related quality of life in children with recurrent pain. Pediatrics. 2009;124(4):e759-67.

23. Wilson AC, Palermo TM. Physical activity and function in adolescents with chronic pain: a controlled study using actigraphy. The journal of pain: official journal of the American Pain Society. 2012;13(2):121-30.

24. Agoston A, Gray L, Logan D. Pain in School: Patterns of Pain-Related School Impairment among Adolescents with Primary Pain Conditions, Juvenile Idiopathic Arthritis Pain, and Pain-Free Peers. Children. 2016;3(4):39.

25. Vinall J, Pavlova M, Asmundson GJ, Rasic N, Noel M. Mental Health Comorbidities in Pediatric Chronic Pain: A Narrative Review of Epidemiology, Models, Neurobiological Mechanisms and Treatment. Children. 2016;3(4).

26. Coffelt TA, Bauer BD, Carroll AE. Inpatient characteristics of the child admitted with chronic pain. Pediatrics. 2013;132(2):e422-9.

27. Hoftun GB, Romundstad PR, Rygg M. Factors associated with adolescent chronic non-specific pain, chronic multisite pain, and chronic pain with high disability: the Young-HUNT Study 2008. The journal of pain : official journal of the American Pain Society. 2012;13(9):874-83.

28. Lewandowski Holley A, Law EF, Zhou C, Murphy L, Clarke G, Palermo TM. Reciprocal longitudinal associations between pain and depressive symptoms in adolescents. Eur J Pain. 2013;17(7):1058-67.

29. Kashikar-Zuck S, Goldschneider KR, Powers SW, Vaught MH, Hershey AD. Depression and functional disability in chronic pediatric pain. The Clinical journal of pain. 2001;17(4):341-9.

30. Benore E, D'Auria A, Banez GA, Worley S, Tang A. The influence of anxiety reduction on clinical response to pediatric chronic pain rehabilitation. The Clinical journal of pain. 2015;31(5):375-83.

31. Caes L, Fisher E, Clinch J, Tobias JH, Eccleston C. The role of pain-related anxiety in adolescents' disability and social impairment: ALSPAC data. European Journal of Pain. 2015; 19(6):842-5.

32. Khan KA, Tran ST, Jastrowski Mano KE, Simpson PM, Cao Y, Hainsworth KR. Predicting Multiple Facets of School Functioning in Pediatric Chronic Pain: Examining the Direct Impact of Anxiety. The Clinical journal of pain. 2015; 40(8):744-55.

33. Eckhoff C, Straume B, Kvernmo S. Multisite musculoskeletal pain in adolescence and later mental health disorders: a population-based registry study of Norwegian youth: the NAAHS cohort study. BMJ open. 2017;7(2).

34. Shanahan L, Zucker N, Copeland WE, Bondy CL, Egger HL, Costello EJ. Childhood somatic complaints predict generalized anxiety and depressive disorders during young adulthood in a community sample. Psychological Medicine. 2014;45(8):1721-30.

35. Noel M, Groenewald CB, Beals-Erickson SE, Gebert JT, Palermo TM. Chronic pain in adolescence and internalizing mental health disorders: a nationally representative study. Pain. 2016;157(6):1333-8.

36. Rayner L, Hotopf M, Petkova H, Matcham F, Simpson A, McCracken LM. Depression in patients with chronic pain attending a specialised pain treatment centre: prevalence and impact on health care costs. Pain. 2016;157(7):1472-9.

37. Gradisar M, Gardner G, Dohnt H. Recent worldwide sleep patterns and problems during adolescence: a review and meta-analysis of age, region, and sleep. Sleep medicine. 2011;12(2):110-8.

38. Beebe DW. Cognitive, behavioral, and functional consequences of inadequate sleep in children and adolescents. Pediatr Clin North Am. 2011;58(3):649-65.

39. Chaput JP, Gray CE, Poitras VJ, Carson V, Gruber R, Olds T, et al. Systematic review of the relationships between sleep duration and health indicators in school-aged children and youth. Applied physiology, nutrition, and metabolism = Physiologie appliquee, nutrition et metabolisme. 2016;41(6 Suppl 3):S266-82.

40. Baglioni C, Battagliese G, Feige B, Spiegelhalder K, Nissen C, Voderholzer U, et al. Insomnia as a predictor of depression: a meta-analytic evaluation of longitudinal epidemiological studies. Journal of affective disorders. 2011;135(1-3):10-9.

41. Archbold KH, Pituch KJ, Panahi P, Chervin RD. Symptoms of sleep disturbances among children at two general pediatric clinics. The Journal of pediatrics. 2002;140(1):97-102.

42. Lazaratou H, Soldatou A, Dikeos D. Medical comorbidity of sleep disorders in children and adolescents. Current opinion in psychiatry. 2012;25(5):391-7.

43. Honaker SM, Meltzer LJ. Sleep in pediatric primary care: A review of the literature. Sleep medicine reviews. 2016;25:31-9.

44. Badin E, Haddad C, Shatkin JP. Insomnia: the Sleeping Giant of Pediatric Public Health. Current psychiatry reports. 2016;18(5):47.

45. Hester DJ, Tang NKY. Insomnia Co-Occurring with Chronic Pain: Clinical Features, Interaction, Assessments and Possible Interventions. Reviews in Pain. 2008;2(1):2-7.

46. Koffel E, Kroenke K, Bair MJ, Leverty D, Polusny MA, Krebs EE. The bidirectional relationship between sleep complaints and pain: Analysis of data from a randomized trial. Health psychology: official journal of the Division of Health Psychology, American Psychological Association. 2016;35(1):41-9.

47. Fishbain DA, Cole B, Lewis JE, Gao J. What Is the Evidence for Chronic Pain Being Etiologically Associated with the DSM-IV Category of Sleep Disorder Due to a General Medical Condition? A Structured Evidence-Based Review. Pain Medicine. 2010;11(2):158-79.

48. Smith MT, Perlis ML, Smith MS, Giles DE, Carmody TP. Sleep Quality and Presleep Arousal in Chronic Pain. Journal of behavioral medicine. 2000;23(1):1-13.

49. Valrie CR, Bromberg MH, Palermo T, Schanberg LE. A systematic review of sleep in pediatric pain populations. Journal of developmental and behavioral pediatrics : JDBP. 2013;34(2):120-8.

50. Long AC, Krishnamurthy V, Palermo TM. Sleep disturbances in school-age children with chronic pain. Journal of pediatric psychology. 2008;33(3):258-68.

51. Schurman JV, Friesen CA, Dai H, Danda CE, Hyman PE, Cocjin JT. Sleep problems and functional disability in children with functional gastrointestinal disorders: an examination of the potential mediating effects of physical and emotional symptoms. BMC gastroenterology. 2012;12:142.

52. Palermo TM, Wilson AC, Lewandowski AS, Toliver-Sokol M, Murray CB. Behavioral and psychosocial factors associated with insomnia in adolescents with chronic pain. Pain. 2011;152(1):89-94.

53. Finan PH, Goodin BR, Smith MT. The association of sleep and pain: an update and a path forward. The journal of pain: official journal of the American Pain Society. 2013;14(12):1539-52.

54. Bonvanie IJ, Oldehinkel AJ, Rosmalen JG, Janssens KA. Sleep problems and pain: a longitudinal cohort study in emerging adults. Pain. 2016;157(4):957-63.

55. Palermo TM, Kiska R. Subjective sleep disturbances in adolescents with chronic pain: relationship to daily functioning and quality of life. The journal of pain : official journal of the American Pain Society. 2005;6(3):201-7.

56. Palermo TM, Law E, Churchill SS, Walker A. Longitudinal Course and Impact of Insomnia Symptoms in Adolescents With and Without Chronic Pain. The Journal of Pain. 2012;13(11):1099-106.

57. Evans S, Djilas V, Seidman LC, Zeltzer LK, Tsao JCI. Sleep quality, affect, pain and disability in children with chronic pain: Is affect a mediator or moderator? The journal of pain: official journal of the American Pain Society. 2017.

58. Dworkin RH, Turk DC, Farrar JT, Haythornthwaite JA, Jensen MP, Katz NP, et al. Core outcome measures for chronic pain clinical trials: IMMPACT recommendations. Pain. 2005;113(1–2):9-19.

59. Amtmann D, Cook KF, Jensen MP, Chen WH, Choi S, Revicki D, et al. Development of a PROMIS item bank to measure pain interference. Pain. 2010;150(1):173-82.

60. Karayannis NV, Sturgeon JA, Chih-Kao M, Cooley C, Mackey SC. Pain interference and physical function demonstrate poor longitudinal association in people living with pain: a PROMIS investigation. Pain. 2017; 158(6):1063-1068.

61. Jacobson CJ, Farrell JE, Kashikar-Zuck S, Seid M, Verkamp E, Dewitt EM. Disclosure and self-report of emotional, social, and physical health in children and adolescents with chronic pain--a qualitative study of PROMIS pediatric measures. Journal of pediatric psychology. 2013;38(1):82-93.

62. Varni JW, Stucky BD, Thissen D, Dewitt EM, Irwin DE, Lai JS, et al. PROMIS Pediatric Pain Interference Scale: an item response theory analysis of the pediatric pain item bank. The journal of pain: official journal of the American Pain Society. 2010;11(11):1109-19.

63. Kerns RD, Turk DC, Rudy TE. The West Haven-Yale Multidimensional Pain Inventory (WHYMPI). Pain. 1985;23(4):345-56.

64. Poquet N, Lin C. The Brief Pain Inventory (BPI). Journal of Physiotherapy.62(1):52.

65. Wilson M. Integrating the concept of pain interference into pain management. Pain management nursing: official journal of the American Society of Pain Management Nurses. 2014;15(2):499-505.

66. Kashikar-Zuck S, Carle A, Barnett K, Goldschneider KR, Sherry DD, Mara CA, et al. Longitudinal evaluation of patient-reported outcomes measurement information systems measures in pediatric chronic pain. Pain. 2016;157(2):339-47.

67. Eccleston C, Malleson PN, Clinch J, Connell H, Sourbut C. Chronic pain in adolescents: evaluation of a programme of interdisciplinary cognitive behaviour therapy. Archives of disease in childhood. 2003;88(10):881-5.

68. Eccleston C, Crombez G, Scotford A, Clinch J, Connell H. Adolescent chronic pain: patterns and predictors of emotional distress in adolescents with chronic pain and their parents. Pain. 2004;108(3):221-9.

69. Lewandowski AS, Palermo TM, Stinson J, Handley S, Chambers CT. Systematic review of family functioning in families of children and adolescents with chronic pain. The journal of pain : official journal of the American Pain Society. 2010;11(11):1027-38.

70. Sleed M, Eccleston C, Beecham J, Knapp M, Jordan A. The economic impact of chronic pain in adolescence: methodological considerations and a preliminary costs-of-illness study. Pain. 2005;119(1-3):183-90.

71. Jaaniste T, Jia N, Lang T, Goodison-Farnsworth EM, McCormick M, Anderson D. The relationship between parental attitudes and behaviours in the context of paediatric chronic pain. Child: care, health and development. 2016;42(3):433-8.

72. Jordan AL, Eccleston C, Osborn M. Being a parent of the adolescent with complex chronic pain: an interpretative phenomenological analysis. Eur J Pain. 2007;11(1):49-56.

73. Jordan A, Crabtree A, Eccleston C. 'You have to be a jack of all trades': Fathers parenting their adolescent with chronic pain. Journal of health psychology. 2015;21(11):2466-2476

74. Chow ET, Otis JD, Simons LE. The Longitudinal Impact of Parent Distress and Behavior on Functional Outcomes Among Youth With Chronic Pain. The journal of pain : official journal of the American Pain Society. 2016;17(6):729-38.

75. Groenewald CB, Essner BS, Wright D, Fesinmeyer MD, Palermo TM. The economic costs of chronic pain among a cohort of treatment-seeking adolescents in the United States. The journal of pain : official journal of the American Pain Society. 2014;15(9):925-33.

76. Toliver-Sokol M, Murray CB, Wilson AC, Lewandowski A, Palermo TM. Patterns and Predictors of Health Service Utilization in Adolescents With Pain: Comparison Between a Community and a Clinical Pain Sample. The Journal of Pain. 2011;12(7):747-55.

77. Hoftun GB, Romundstad PR, Rygg M. Association of parental chronic pain with chronic pain in the adolescent and young adult: Family linkage data from the hunt study. JAMA Pediatrics. 2013;167(1):61-9.

78. Dueñas M, Ojeda B, Salazar A, Mico JA, Failde I. A review of chronic pain impact on patients, their social environment and the health care system. Journal of pain research. 2016;9:457-67.

79. Higgins KS, Birnie KA, Chambers CT, Wilson AC, Caes L, Clark AJ, et al. Offspring of parents with chronic pain: a systematic review and meta-analysis of pain, health, psychological, and family outcomes. Pain. 2015;156(11):2256-66.

80. Umberger W. Children of Parents With Chronic Noncancer Pain: A Comprehensive Review of the Literature. Journal of child and adolescent psychiatric nursing : official publication of the Association of Child and Adolescent Psychiatric Nurses, Inc. 2014;27(1):26-34.

81. Kaasboll J, Lydersen S, Indredavik MS. Psychological symptoms in children of parents with chronic pain-the HUNT study. Pain. 2012;153(5):1054-62.

82. Kennedy J, Roll JM, Schraudner T, Murphy S, McPherson S. Prevalence of persistent pain in the U.S. adult population: new data from the 2010 national health interview survey. The journal of pain: official journal of the American Pain Society. 2014;15(10):979-84.

83. Turk DC. Clinical effectiveness and cost-effectiveness of treatments for patients with chronic pain. The Clinical journal of pain. 2002;18(6):355-65.

84. Zernikow B, Wager J, Hechler T, Hasan C, Rohr U, Dobe M, et al. Characteristics of highly impaired children with severe chronic pain: a 5-year retrospective study on 2249 pediatric pain patients. Bmc Pediatrics. 2012;12.

85. O'Donohue WT, Fisher JE, Fisher JE. General Principles and Empirically Supported Techniques of Cognitive Behavior Therapy. Hoboken, UNITED STATES: John Wiley & Sons, Incorporated; 2009.

86. Graham PJ, Reynolds S. Cognitive behaviour therapy for children and families: Cambridge University Press; 2013.

87. Coakley R, Wihak T. Evidence-Based Psychological Interventions for the Management of Pediatric Chronic Pain: New Directions in Research and Clinical Practice. Children. 2017;4(2):9.

88. Eccleston C, Palermo TM, Williams AC, Lewandowski Holley A, Morley S, Fisher E, et al. Psychological therapies for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev. 2014(5):Cd003968.

89. Noel M, Petter M, Parker JA, Chambers CT. Cognitive Behavioral Therapy for Pediatric Chronic Pain: The Problem, Research, and Practice. Journal of Cognitive Psychotherapy. 2012;26(2):143-56.

90. Kanstrup M. Recent assessment and psychological treatment of co-morbid depression in pediatric chronic pain – a systematic review of studies including depression as an outcome. 2017.

91. Hayes SC, Barnes-Holmes D, Wilson KG. Contextual Behavioral Science: Creating a science more adequate to the challenge of the human condition. Journal of Contextual Behavioral Science. 2012;1(1–2):1-16.

92. Hayes SC, Barnes-Holmes D, Roche B, ebrary I. Relational frame theory: a post-Skinnerian account of human language and cognition. Kluwer Academic/Plenum; 2001.

93. O'Connor M, Farrell L, Munnelly A, McHugh L. Citation analysis of relational frame theory: 2009–2016. Journal of Contextual Behavioral Science. 2017;6(2):152-8.

94. Hayes SC, Strosahl, K., &Wilson, K.G. Acceptance and Commitment Therapy- The Process and Practice of Mindful Change: Guilford Publications; 2011.

95. Hayes SC, Luoma JB, Bond FW, Masuda A, Lillis J. Acceptance and Commitment Therapy: Model, processes and outcomes. Behaviour research and therapy. 2006;44(1):1-25.

96. McCracken LM, Morley S. The psychological flexibility model: a basis for integration and progress in psychological approaches to chronic pain management. The journal of pain: official journal of the American Pain Society. 2014;15(3):221-34.

97. Scott W, Hann KE, McCracken LM. A Comprehensive Examination of Changes in Psychological Flexibility Following Acceptance and Commitment Therapy for Chronic Pain. Journal of contemporary psychotherapy. 2016;46:139-48.

98. Swain J, Hancock K, Dixon A, Bowman J. Acceptance and Commitment Therapy for children: A systematic review of intervention studies. Journal of Contextual Behavioral Science. 2015;4(2):73-85.

99. Wicksell RK, Kanstrup M, Kemani MK, Holmström L, Olsson GL. Acceptance and Commitment Therapy for children and adolescents with physical health concerns. Current Opinion in Psychology. 2015;2(0):1-5.

100. Pielech M, Vowles EK, Wicksell R. Acceptance and Commitment Therapy for Pediatric Chronic Pain: Theory and Application. Children. 2017;4(2).

101. Hayes SC, Duckworth MP. Acceptance and Commitment Therapy and Traditional Cognitive Behavior Therapy Approaches to Pain. Cognitive and Behavioral Practice. 2006;13(3):185-7.

102. Hann KEJ, McCracken LM. A systematic review of randomized controlled trials of Acceptance and Commitment Therapy for adults with chronic pain: Outcome domains, design quality, and efficacy. Journal of Contextual Behavioral Science. 2014;3(4):217-27.

103. Society of Clinical Psychology AD. Acceptance and Commitment Therapy for Chronic Pain. Available at: http://wwwdiv12org/psychological-treatments/disorders/chronic-or-persistent-pain/acceptance-and-commitment-therapy-for-chronic-pain/. 2011; Retrieved July 12th, 2016.

104. Wicksell RK, Dahl J, Magnusson B, Olsson GL. Using acceptance and commitment therapy in the rehabilitation of an adolescent female with chronic pain: A case example. Cognitive and Behavioral Practice. 2005;12(4):415-23.

105. Wicksell RK, Melin L, Olsson GL. Exposure and acceptance in the rehabilitation of adolescents with idiopathic chronic pain - a pilot study. Eur J Pain. 2007;11(3):267-74.

106. Wicksell RK, Melin L, Lekander M, Olsson GL. Evaluating the effectiveness of exposure and acceptance strategies to improve functioning and quality of life in longstanding pediatric pain – A randomized controlled trial. Pain. 2009;141(3):248-57.

107. Wicksell RK, Olsson GL, Hayes SC. Mediators of change in Acceptance and Commitment Therapy for pediatric chronic pain. Pain. 2011;152(12):2792-801.

108. Gauntlett-Gilbert J, Connell H, Clinch J, McCracken LM. Acceptance and values-based treatment of adolescents with chronic pain: outcomes and their relationship to acceptance. Journal of pediatric psychology. 2013;38(1):72.

109. Ghomian S SM. The effectiveness of acceptance and commitment therapy for children with chronic pain on the function of 7 to 12 year-old. International Journal of Pediatrics. 2014;2(7).

110. Martin S, Wolters PL, Toledo-Tamula MA, Schmitt SN, Baldwin A, Starosta A, et al. Acceptance and commitment therapy in youth with neurofibromatosis type 1 (NF1) and chronic pain and their parents: A pilot study of feasibility and preliminary efficacy. American journal of medical genetics Part A. 2016;170(6):1462-70.

111. Odell S, Logan DE. Pediatric pain management: the multidisciplinary approach. Journal of pain research. 2013;6:785-90.

112. Fisher E, Law E, Palermo TM, Eccleston C. Psychological therapies (remotely delivered) for the management of chronic and recurrent pain in children and adolescents. Cochrane Database Syst Rev. 2015;3:CD011118.

113. Simons LE, Sieberg CB, Pielech M, Conroy C, Logan DE. What does it take? Comparing intensive rehabilitation to outpatient treatment for children with significant pain-related disability. Journal of pediatric psychology. 2013;38(2):213-23.

114. Hechler T, Wager J, Zernikow B. Chronic pain treatment in children and adolescents: less is good, more is sometimes better. BMC Pediatr. 2014;14:262.

115. Hechler T, Ruhe AK, Schmidt P, Hirsch J, Wager J, Dobe M, et al. Inpatient-based intensive interdisciplinary pain treatment for highly impaired children with severe chronic pain: Randomized controlled trial of efficacy and economic effects. Pain. 2014;155(1):118-28.

116. Zernikow B, Ruhe AK, Stahlschmidt L, Schmidt P, Staratzke T, Frosch M, et al. Clinical and Economic Long-Term Treatment Outcome of Children and Adolescents with Disabling Chronic Pain. Pain Med. 2017.

117. Evans JR, Benore E, Banez GA. The Cost-Effectiveness of Intensive Interdisciplinary Pediatric Chronic Pain Rehabilitation. Journal of pediatric psychology. 2016;41(8):849-56.

118. Stahlschmidt L, Zernikow B, Wager J. Specialized Rehabilitation Programs for Children and Adolescents with Severe Disabling Chronic Pain: Indications, Treatment and Outcomes. Children. 2016;3(4):33.

119. Wilson AC, Fales JL. Parenting in the context of chronic pain: a controlled study of parents with chronic pain. (1536-5409 (Electronic)).

120. Palermo TM, Eccleston C. Parents of children and adolescents with chronic pain. Pain. 2009;146(1-2):15-7.

121. Eccleston C, Fisher E, Law E, Bartlett J, Palermo TM. Psychological interventions for parents of children and adolescents with chronic illness. Cochrane Database Syst Rev. 2015(4):Cd009660.

122. Palermo TM, Law EF, Bromberg M, Fales J, Eccleston C, Wilson AC. Problem-solving skills training for parents of children with chronic pain: a pilot randomized controlled trial. Pain. 2016;157(6):1213-23.

123. Palermo TM, Law EF, Fales J, Bromberg MH, Jessen-Fiddick T, Tai G. Internet-delivered cognitive-behavioral treatment for adolescents with chronic pain and their parents: a randomized controlled multicenter trial. Pain. 2016;157(1):174-85.

124. Law EF, Fisher E, Howard WJ, Levy R, Ritterband L, Palermo TM. Longitudinal change in parent and child functioning after internet-delivered cognitive-behavioral therapy for chronic pain. Pain. 2017.

125. McCracken LM, Gauntlett-Gilbert J. Role of psychological flexibility in parents of adolescents with chronic pain: development of a measure and preliminary correlation analyses. Pain. 2011;152(4):780-5.

126. Smith AM, Sieberg CB, Odell S, Randall E, Simons LE. Living Life with My Child's Pain: The Parent Pain Acceptance Questionnaire (PPAQ). The Clinical journal of pain. 2015;31(7):633-41.

127. Martin S, Wolters PL, Toledo-Tamula MA, Nelson Schmitt S, Baldwin A, Starosta A, et al. Acceptance and commitment therapy in youth with neurofibromatosis type 1 (NF1) and chronic pain and their parents: A pilot study of feasibility and preliminary efficacy. American Journal of Medical Genetics part A. 2016;170(6):1462-70.

128. Wallace DP, Woodford B, Connelly M. Promoting Psychological Flexibility in Parents of Adolescents With Chronic Pain: Pilot Study of an 8-Week Group Intervention. Clinical practice in pediatric psychology. 2016;4(4):405-16.

129. Kemani M, Kanstrup, M, Jordan, A, Caes, L, & Gauntlett-Gilbert, J. Acceptance and Commitment Therapy for Adolescents with Chronic Pain and their Parents: Evaluation of Parent and Adolescent Outcomes and the Relation between Parent Psychological Flexibility and Adolescent Pain Acceptance. 2017.

130. Nelson EC, Eftimovska E, Lind C, Hager A, Wasson JH, Lindblad S. Patient reported outcome measures in practice. BMJ: British Medical Journal. 2015;350.

131. Deshpande PR, Rajan S, Sudeepthi BL, Abdul Nazir CP. Patient-reported outcomes: A new era in clinical research. Perspectives in Clinical Research. 2011;2(4):137-44.

132. McGrath PJ, Walco GA, Turk DC, Dworkin RH, Brown MT, Davidson K, et al. Core outcome domains and measures for pediatric acute and chronic/recurrent pain clinical trials: PedIMMPACT recommendations. The journal of pain: official journal of the American Pain Society. 2008;9(9):771-83.

133. Lewandowski AS, Toliver-Sokol M, Palermo TM. Evidence-based review of subjective pediatric sleep measures. Journal of pediatric psychology. 2011;36(7):780-93.

134. Kashikar-Zuck S, Ting TV, Arnold LM, Bean J, Powers SW, Graham TB, et al. Cognitive behavioral therapy for the treatment of juvenile fibromyalgia: A multisite, single-blind, randomized, controlled clinical trial. Arthritis & Rheumatism. 2012;64(1):297-305.

135. Eccleston C, Jordan AL, Crombez G. The impact of chronic pain on adolescents: a review of previously used measures. Journal of pediatric psychology. 2006;31(7):684-97.

136. Jordan A, Eccleston C, Crombez G. Parental Functioning in the Context of Adolescent Chronic Pain: A Review of Previously used Measures. Journal of pediatric psychology. 2008;33(6):640-59.

137. Palermo TM. Assessment of chronic pain in children: current status and emerging topics. Pain research & management: the journal of the Canadian Pain Society = journal de la societe canadienne pour le traitement de la douleur. 2009;14(1):21-6.

138. Tractenberg RE. Classical and modern measurement theories, patient reports, and clinical outcomes. Contemporary clinical trials. 2010;31(1):1-3.

139. Furr R, & Bacharach, V. P. Psychometrics: An introduction. 2.nd ed. Los Angeles: Sage Publications; 2014.

140. The National Council on Measurement in Education (NCME). Web page glossary. Available from: http://www.ncme.org/ncme/NCME/Resource_Center/Glossary/NCME/Resource_Center/Glossary1.aspx?hkey=4bb87415-44dc-4088-9ed9-e8515326a061 - anchorT.

141. Association. AER. Standards for educational and psychological testing. Washington, DC: American Educational Research Association; 1999.

142. Sullivan GM. A primer on the validity of assessment instruments. J Grad Med Educ. 2011;3(2):119-20.

143. Kazdin AE. Research design in clinical psychology. Boston, MA: Allyn and Bacon; 2003.

144. Higgins JPT, Green S, Cochrane C. Cochrane handbook for systematic reviews of interventions. Chichester, West Sussex. Wiley-Blackwell; 2008.

145. Glass GV. Primary, Secondary, and Meta-Analysis of Research. Educational Researcher. 1976;5(10):3-8.

146. Hesser H, & Andersson, G. Introduktion till metaanalys och systematiska översikter. Lund: Studentlitteratur; 2015.

147. Field AP, Gillett R. How to do a meta-analysis. British Journal of Mathematical and Statistical Psychology. 2010;63(3):665-94.

148. Moher D, Liberati A, Tetzlaff J, Altman DG, The PG. Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLOS Medicine. 2009;6(7):e1000097.

149. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. Bmj. 2011;343:d5928.

150. Moga C GB, Schopflocher D, Harstall C. Development of a quality appraisal tool for case series studies using a modified Delphi technique. 2012. Available from: http://www.ihe.ca./advanced-search/development-of-a-quality-appraisal-tool-for-case-series-studies-using-a-modified-delphi-technique

151. Guo B, Moga C, Harstall C, Schopflocher D. A principal component analysis is conducted for a case series quality appraisal checklist. Journal of clinical epidemiology. 2016;69:199-207.e2.

152. Shea BJ, Grimshaw JM, Wells GA, Boers M, Andersson N, Hamel C, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Medical Research Methodology. 2007;7(1):10.

153. Pollock M, Fernandes RM, Hartling L. Evaluation of AMSTAR to assess the methodological quality of systematic reviews in overviews of reviews of healthcare interventions. BMC Med Res Methodol. 2017;17(1):48.

154. Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. Bmj. 2008;336(7650):924-6.

155. von Baeyer CL. Numerical rating scale for self-report of pain intensity in children and adolescents: Recent progress and further questions. European Journal of Pain. 2009;13(10):1005-7.

156. von Baeyer CL. Support for a common metric for pediatric pain intensity scales. Pain Research and Management. 2000;4(2):157-60.

157. von Baeyer CL, Spagrud LJ, McCormick JC, Choo E, Neville K, Connelly MA. Three new datasets supporting use of the Numerical Rating Scale (NRS-11) for children's self-reports of pain intensity. Pain. 2009;143(3):223-7.

158. Ruskin D, Lalloo C, Amaria K, Stinson JN, Kewley E, Campbell F, et al. Assessing pain intensity in children with chronic pain: Convergent and discriminant validity of the 0 to 10

numerical rating scale in clinical practice. Pain Research & Management : The Journal of the Canadian Pain Society. 2014;19(3):141-8.

159. Bastien CH, Vallieres A, Morin CM. Validation of the Insomnia Severity Index as an outcome measure for insomnia research. Sleep medicine. 2001;2(4):297-307.

160. Yu DSF. Insomnia Severity Index: psychometric properties with Chinese community-dwelling older people. Journal of Advanced Nursing. 2010;66(10):2350-9.

161. Chung KF, Kan KKK, Yeung WF. Assessing insomnia in adolescents: Comparison of Insomnia Severity Index, Athens Insomnia Scale and Sleep Quality Index. Sleep medicine. 2011;12(5):463-70.

162. Lahan V, Gupta R. Translation and validation of the insomnia severity index in hindi language. Indian journal of psychological medicine. 2011;33(2):172-6.

163. Suleiman KH, Yates BC. Translating the Insomnia Severity Index Into Arabic. Journal of Nursing Scholarship. 2011;43(1):49-53.

164. Thorndike FP, Ritterband LM, Saylor DK, Magee JC, Gonder-Frederick LA, Morin CM. Validation of the Insomnia Severity Index as a Web-Based Measure. Behavioral sleep medicine. 2011;9(4):216-23.

165. Fernandez-Mendoza J, Rodriguez-Munoz A, Vela-Bueno A, Olavarrieta-Bernardino S, Calhoun SL, Bixler EO, et al. The Spanish version of the Insomnia Severity Index: A confirmatory factor analysis. Sleep medicine. 2012;13(2):207-10.

166. Dragioti E, Wiklund T, Alföldi P, Gerdle B. The Swedish version of the Insomnia Severity Index: Factor structure analysis and psychometric properties in chronic pain patients. Scandinavian Journal of Pain. 2015;9:22-7.

167. Gagnon C, Belanger L, Ivers H, Morin CM. Validation of the Insomnia Severity Index in primary care. Journal of the American Board of Family Medicine : JABFM. 2013;26(6):701-10.

168. Morin CM, Belleville G, Bélanger L, Ivers H. The Insomnia Severity Index: Psychometric Indicators to Detect Insomnia Cases and Evaluate Treatment Response. Sleep. 2011;34(5):601-8.

169. Radloff LS. The CES-D Scale. Applied Psychological Measurement. 1977;1(3):385-401.

170. Schoenbach VJ, Kaplan BH, Grimson RC, Wagner EH. Use of a symptom scale to study the prevalence of a depressive syndrome in young adolescents. Am J Epidemiol. 1982;116(5):791-800.

171. Fendrich M, Weissman, M. M. & Warner, V. Screening for Depressive Disorder in Children and Adolescents: Validating the Center for Epidemiologic Studies Depression Scale for Children. American Journal of Epidemiology. 1990;131:538-51.

172. Olsson G, von Knorring AL. Depression among Swedish adolescents measured by the self-rating scale Center for Epidemiology Studies-Depression Child (CES-DC). European child & adolescent psychiatry. 1997;6(2):81-7.

173. Walker LS, Greene JW. The functional disability inventory: measuring a neglected dimension of child health status. Journal of pediatric psychology. 1991;16(1):39-58.

174. Kashikar-Zuck S, Flowers SR, Claar RL, Guite JW, Logan DE, Lynch-Jordan AM, et al. Clinical utility and validity of the Functional Disability Inventory among a multicenter sample of youth with chronic pain. Pain. 2011;152(7):1600-7.

175. Fichtel Å, Larsson B. Psychosocial Impact of Headache and Comorbidity with Other Pains among Swedish School Adolescents. Headache: The Journal of Head and Face Pain. 2002;42(8):766-75.

176. Claar RL, Walker LS. Functional assessment of pediatric pain patients: psychometric properties of the functional disability inventory. Pain. 2006;121(1-2):77-84.

177. Wicksell RK, Renofalt J, Olsson GL, Bond FW, Melin L. Avoidance and cognitive fusion - Central components in pain related disability? Development and preliminary validation of the Psychological Inflexibility in Pain Scale (PIPS). European Journal of Pain. 2008;12(4):491-500.

178. Wicksell RK, Lekander M, Sorjonen K, Olsson GL. The Psychological Inflexibility in Pain Scale (PIPS) - Statistical properties and model fit of an instrument to assess change processes in pain related disability. European Journal of Pain. 2010;14(7).

179. Wicksell RK, Ahlqvist J, Bring A, Melin L, Olsson GL. Can exposure and acceptance strategies improve functioning and life satisfaction in people with chronic pain and whiplash-associated disorders (WAD)? A randomized controlled trial. Cognitive behaviour therapy. 2008;37(3):169-82.

180. Klinga M, Olsson, G.L., & and Wicksell, R.K. Pain Related Functioning in Children with Longstanding Pain – Relation to Pain Related Worrying and Psychological Inflexibility. 5th Nordic Congress on Pediatric Pain; Turku, Finland. 2010.

181. McCracken LM, Vowles KE, Eccleston C. Acceptance of chronic pain: component analysis and a revised assessment method. Pain. 2004;107(1-2):159-66.

182. Kanstrup M. Psychological Inflexibility in Pediatric Chronic Pain – a preliminary investigation of the Psychological Inflexibility in Pain Scale (PIPS) for children and adolescents. 2014.

183. Martin S, Nelson Schmitt S, Wolters PL, Abel B, Toledo-Tamula MA, Baldwin A, et al. Development and Validation of the English Pain Interference Index and Pain Interference Index-Parent Report. Pain Med. 2015;16(2):367-73.

184. Kemani MK, Zetterqvist V, Kanstrup M, Holmström L, Wicksell RK. A validation of the pain interference index in adults with long-standing pain. Acta Anaesthesiologica Scandinavica. 2016; 60(2), pp.250-258

185. Snaith RP, Zigmond AS. The hospital anxiety and depression scale. British medical journal (Clinical research ed). 1986;292(6516):344.

186. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: An updated literature review. Journal of psychosomatic research. 2002;52(2):69-77.

187. Lisspers J, Nygren A, Söderman E. Hospital Anxiety and Depression Scale (HAD): some psychometric data for a Swedish sample. Acta psychiatrica Scandinavica. 1997;96(4):281-6.

188. Wallace DP, McCracken LM, Weiss KE, Harbeck-Weber C. The Role of Parent Psychological Flexibility in Relation to Adolescent Chronic Pain: Further Instrument

Development. The journal of pain: official journal of the American Pain Society. 2015; 16(3), pp.235-246.

189. Wiwe Lipsker C, Kanstrup M, Holmström L, Kemani M, Wicksell R. The Parent Psychological Flexibility Questionnaire (PPFQ): Item Reduction and Validation in a Clinical Sample of Swedish Parents of Children with Chronic Pain. Children. 2016;3(4):32.

190. Field A. Discovering Statistics Using SPSS. 3 ed: SAGE publications 2009.

191. Tabachnick BG. Using multivariate statistics. 6th ed. ed. Fidell LS, editor. Boston, Mass. Pearson Education; 2012.

192. Tavakol M, Dennick R. Making sense of Cronbach's alpha. International Journal of Medical Education. 2011;2:53-5.

193. Hayes AF, Rockwood NJ. Regression-based statistical mediation and moderation analysis in clinical research: Observations, recommendations, and implementation. Behaviour research and therapy. 2016.

194. MacKinnon DP, Fairchild AJ, Fritz MS. Mediation analysis. Annual review of psychology. 2007;58:593-614.

195. Preacher KJ. Advances in mediation analysis: a survey and synthesis of new developments. Annual review of psychology. 2015;66:825-52.

196. Kazdin AE. Mediators and mechanisms of change in psychotherapy research. Annual review of clinical psychology. 2007;3:1-27.

197. Preacher K, Hayes A. SPSS and SAS procedures for estimating indirect effects in simple mediation models. Behavior Research Methods, Instruments, & Computers. 2004;36(4):717-31.

198. Fritz CO, Morris PE, Richler JJ. Effect size estimates: current use, calculations, and interpretation. Journal of experimental psychology General. 2012;141(1):2-18.

199. American Psychological A. Publication manual of the American Psychological Association. 6. ed. ed. Washington, D.C.: Washington, D.C. : American Psychological Association; 2010.

200. Cohen J. Statistical power analysis for the behavioral sciences. Hillsdale, N.J.: L. Erlbaum Associates; 1988.

201. Coe R. It's the Effect Size, Stupid - What effect size is and why it is important. Annual Conference of the British Educational Research Association University of Exeter, England, 12-14 September 20022002.

202. Kazdin AE. The Meanings and Measurement of Clinical Significance. Journal of consulting and clinical psychology. 1999;67(3):332-9.

203. Follette WC, Callaghan GM. Clinical Significance. The Encyclopedia of Clinical Psychology: John Wiley & Sons, Inc.; 2014.

204. Jacobson NS, Truax P. Clinical significance: a statistical approach to defining meaningful change in psychotherapy research. Journal of Consulting and Clinical Psychology.1991;59(1):12-9

205. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ: British Medical Journal. 2003;327(7414):557-60.

206. Kemani MK, Olsson GL, Lekander M, Hesser H, Andersson E, Wicksell RK. Efficacy and Cost-effectiveness of Acceptance and Commitment Therapy and Applied Relaxation for Longstanding Pain: A Randomized Controlled Trial. The Clinical journal of pain. 2015;31(11):1004-16.

207. Wicksell R. Att Leva med Smärta - ACT som Livsstrategi. Stockholm: Natur och Kultur 2014.

208. World Medical Association. World medical association declaration of Helsinki: Ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191-4.

209.Lavrakas PJ. Encyclopedia of Survey Research Methods. Lavrakas PJ, editor. Thousand Oaks: Thousand Oaks : SAGE Publications; 2008.

210. Rolstad S, Adler J, Ryden A. Response burden and questionnaire length: is shorter better? A review and meta-analysis. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research. 2011;14(8):1101-8.

211. Duggan C, Parry G, McMurran M, Davidson K, Dennis J. The recording of adverse events from psychological treatments in clinical trials: evidence from a review of NIHR-funded trials. Trials. 2014;15:335.

212. Wicherts JM, Veldkamp CLS, Augusteijn HEM, Bakker M, van Aert RCM, van Assen MALM. Degrees of Freedom in Planning, Running, Analyzing, and Reporting Psychological Studies: A Checklist to Avoid p-Hacking. Frontiers in Psychology. 2016;7:1832.

213. Wasserstein RL, Lazar NA. The ASA's Statement on p-Values: Context, Process, and Purpose. The American Statistician. 2016;70(2):129-33.

214. Hechler T, Kanstrup, M., Lewandowski-Holley, A., Simons, L., Wicksell, R., Hirschfeld, G., & Zernikow, B. Available from: https://www.crd.york.ac.uk/prospero/display_record.asp?ID=CRD42014010719.

215. Kanstrup M, Wicksell R, Kemani M, Wiwe Lipsker C, Lekander M, Holmström L. A Clinical Pilot Study of Individual and Group Treatment for Adolescents with Chronic Pain and Their Parents: Effects of Acceptance and Commitment Therapy on Functioning. Children. 2016;3(4):30.

216. Wicksell RK, Kanstrup M, Kemani MK, Holmström L. Pain Interference Mediates the Relationship between Pain and Functioning in Pediatric Chronic Pain. Frontiers in Psychology. 2016;7(1978).

217. Rosenbloom BN, Rabbitts JA, Palermo TM. A developmental perspective on the impact of chronic pain in late adolescence and early adulthood: Implications for assessment and intervention. Pain. 2017:1.

218. Stone AA, Broderick JE. Real-time data collection for pain: appraisal and current status. Pain Med. 2007;8 Suppl 3:S85-93.

219. Greene CJ, Morland LA, Durkalski VL, Frueh BC. Noninferiority and Equivalence Designs: Issues and Implications for Mental Health Research. Journal of traumatic stress. 2008;21(5):433-9.

220. Palermo TM, Law EF, Zhou C, Holley AL, Logan D, Tai G. Trajectories of change during a randomized controlled trial of internet-delivered psychological treatment for adolescent chronic pain: how does change in pain and function relate? Pain. 2015;156(4):626-34.

221. Cunningham NR, Jagpal A, Tran ST, Kashikar-Zuck S, Goldschneider KR, Coghill RC, et al. Anxiety Adversely Impacts Response to Cognitive Behavioral Therapy in Children with Chronic Pain. J Pediatr. 2016;171:227-33.

222. Logan DE, Conroy C, Sieberg CB, Simons LE. Changes in willingness to self-manage pain among children and adolescents and their parents enrolled in an intensive interdisciplinary pediatric pain treatment program. Pain. 2012;153(9):1863-70.

223. Hirschfeld G, Wager J, Schmidt P, Zernikow B. Minimally clinically significant differences for adolescents with chronic pain-variability of ROC-based cut points. The journal of pain: official journal of the American Pain Society. 2014;15(1):32-9.

224. Fales J, Palermo TM, Law EF, Wilson AC. Sleep outcomes in youth with chronic pain participating in a randomized controlled trial of online cognitive-behavioral therapy for pain management. Behavioral sleep medicine. 2015;13(2):107-23.

225. Logan D, Sieberg C, Conroy C, Smith K, Odell S, Sethna N. Changes in Sleep Habits in Adolescents During Intensive Interdisciplinary Pediatric Pain Rehabilitation. J Youth Adolescence. 2015;44(2):543-55.

226. Dundar Y, Dodd S, Dickson R, Walley T, Haycox A, Williamson PR. Comparison of conference abstracts and presentations with full-text articles in the health technology assessments of rapidly evolving technologies. Health technology assessment (Winchester, England). 2006;10(5):iii-iv, ix-145.

227. Bonnert M, Olen O, Lalouni M, Benninga MA, Bottai M, Engelbrektsson J, et al. Internet-Delivered Cognitive Behavior Therapy for Adolescents With Irritable Bowel Syndrome: A Randomized Controlled Trial. The American journal of gastroenterology. 2017;112(1):152-62.

228. Collier S. Research essentials. Patient-public-engagement involving children and young people. Nursing children and young people. 2014;26(6):12.

229. Kashikar-Zuck SM. Psychological interventions for pediatric chronic pain-the good news and the challenges ahead. Pain. 2010;148(3):361-2.