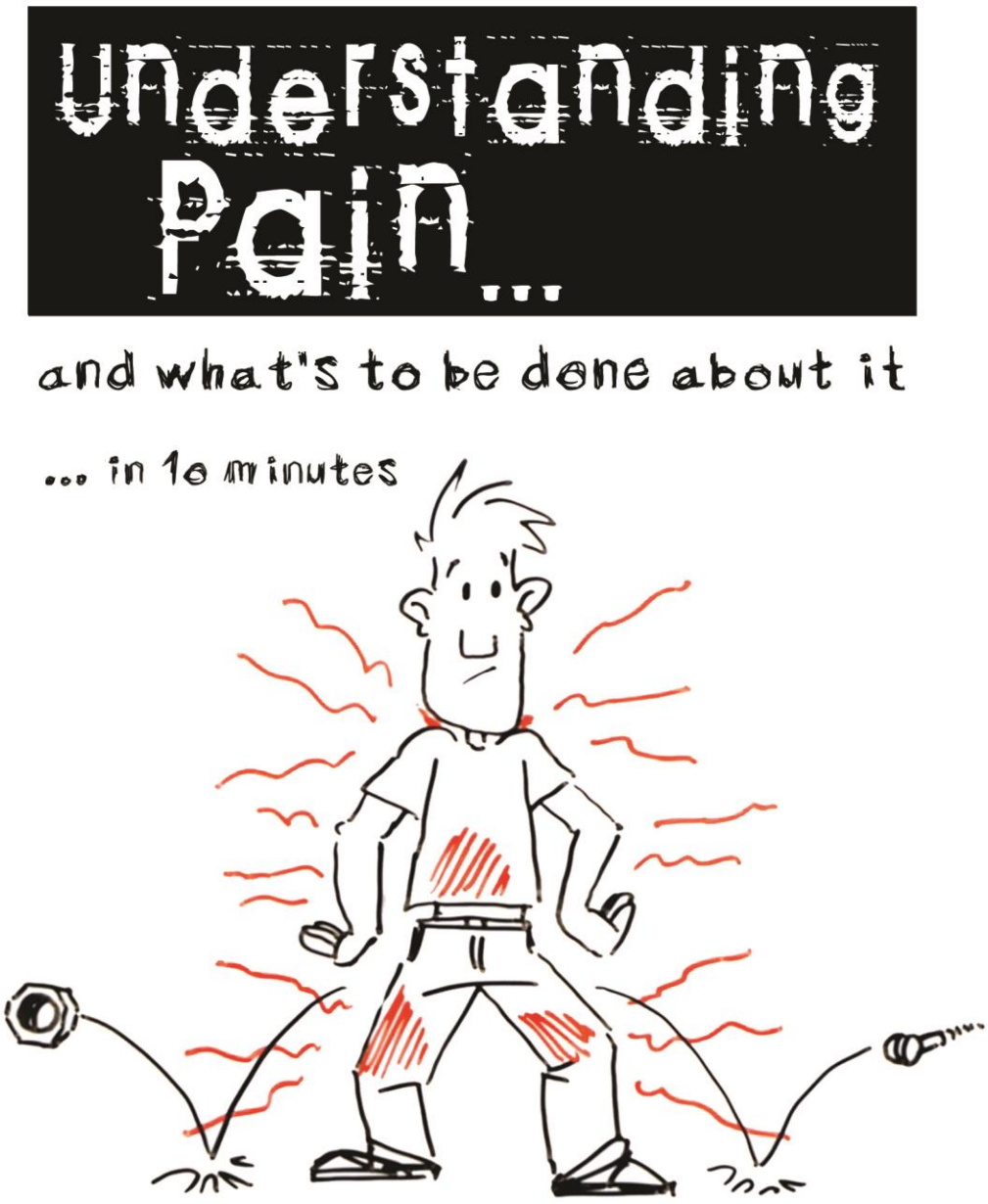
The scientific facts and background of the cartoon



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Dear Reader,

In this booklet we have summarized the most important scientific facts regarding the cartoon *'Understanding pain and what's to be done about it…in 10 minutes'*. The cartoon has been produced for older children and adolescents with chronic pain to better understand their condition and to learn how to deal with it. The cartoon is available on YouTube (https://www.youtube.com/watch?v=lVdulzi6oYw), free of charge and has been translated into many different languages (e.g., German, English, Arabic, Chinese, Greek, Italian, Polish, Portuguese, Russian, Spanish, Turkish and many more). All different language versions of the cartoon are provided on the homepage[1] as well as on the YouTube channel[2] of the German Paediatric Pain Centre (GPPC).

The story in the cartoon is told in easy everyday language and with catchy pictures. It tells about differences between acute and chronic pain, how chronic pain develops and what can be done about it. The content of the cartoon is based on hard scientific facts put together in this booklet.

This booklet is intended for physicians, psychologists and other health care professionals who use the cartoon in their daily work with children and adolescents with chronic pain. Some children and adolescents might want to know some more about the background of the cartoon, or they might want to discuss certain facts. To prepare you for this discussion we have put together all those facts.

This book can be read at once, but may also be used as a reference book. To ease usability you find information on the different parts of the movie in the respective chapters headed by the original wording from the cartoon.

We hope that you enjoy the cartoon and the additional information provided in this booklet.

If you have any questions, please feel free to contact us.

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[1] Homepage: http://www.deutsches-kinderschmerzzentrum.de/jugendliche/video-den-schmerz-verstehen/#c1645

[2] YouTube channel of the GPPC: https://www.youtube.com/channel/UCnhSJzaka3B66uve3MmUpiQ

1

We all know what pain is. But do you also know that not all pain is the same? There are two totally different kinds of pain!
We call the first kind acute pain! We've all experienced that. That happens when you hurt yourself, for example, because you step on a piece of broken glass, have an accident on your bike or hit your thumb with a hammer. The bigger the injury is, the worse the pain. A boxer's punch hurts more than a girlfriend's nudge. Acute pain hurts the most at first, but when the injury heals, the pain diminishes and then disappears altogether. Acute pain is very important for human life. It has a warning function. It says, "Watch out! You've stepped on a piece of broken glass, don't walk any further or the cut will get dirty. Better put your foot up".

Definition of pain

For children as well as adults, pain is defined by the International Association for the Study of Pain (IASP) as 'an **unpleasant sensory and emotional experience** associated with actual or potential tissue damage, or described in terms of such damage' (Merskey and Bogduk, 1994, p. 210). This definition illustrates that pain is not only a sensory perception but also an emotional experience. Pain can be the result of actual tissue damage but may also be experienced before tissue damage occurs or if a person only expects or remembers tissue damage. This variety within the definition of pain reflects the differences in the pathophysiology of acute and chronic pain.

Acute pain

Pain is a daily experience (Eccleston, 2013; Gilbert-MacLeod et al., 2000). Most everyday pains are nociceptive pain without tissue damage or acute pain related to minor injuries. ***Nociceptive pain*** occurs as soon as nociceptors in the skin are activated by a brief **noxious stimulus**, e.g. very hot or cold water, a punch or spicy food. The pain threshold, i.e., the stimulus intensity that is perceived as painful, varies between individuals (Blankenburg et al., 2010). Mostly, **nociceptor activation** is not associated with tissue damage but acts simply as a **warning**. It causes an instant reflex withdrawal and a quick 'ouch'. ***Acute pain*** occurs due to **tissue damage**. Pain intensity is closely correlated with the severity of this tissue damage (Miró et al., 2009), but pain perception is further modified by psychological factors (Wood et al., 2011). Acute pain resolves once the tissue is healed.

Pain is, due to its evolutionary function, closely associated with emotions, specifically feelings of fear and threat (Williams, 2002). This close connection is also represented in a tight cortical connection between the somatosensory and affective areas of the brain (Legrain et al., 2011).

Pain perception varies by different demographic parameters. Younger children (6-8 years old) are more sensitive to brief experimental noxious pain stimuli than are older children (9-12 years old) (Blankenburg et al., 2010). Girls are more sensitive to brief experimental noxious pain stimuli, especially heat stimuli, than are boys (Blankenburg et al., 2010). In epidemiological studies, girls report pain more often than boys. However, younger children report less pain than older children (Du et al., 2011).

On the behavioral level, acute pain has an **interruptive function** (Eccleston, 2013). It emerges as the most important **target of attention** over any other demand for attention and, when considered relevant, triggers numerous **habitual behaviors**, e.g. resting. On the physiological level, this behavior prevents infection and further damage and thereby assists healing. The stronger the pain experience, the stronger the interruptive/protective function (Eccleston, 2013).

Pain physiology

The peripheral and central nervous systems (PNS, CNS) are involved in pain processing (Schaible and Richter, 2004). Nociception comprises the subprocesses of transduction, transmission, modulation and perception (Binder et al., 2011). ***Transduction*** occurs at the site of noxious stimulation or injury and is the **transfer of a biochemical/biophysical response** caused by intense stimulation or tissue damage into a **neuronal signal** (Caterina and Julius, 1999). Noxious stimulation activates several types of peripheral nerve fibers (Woolf and Salter, 2000). Those nerve fibers are named **nociceptors**, and they compose the vast majority of afferents (up to 90%) in almost all tissue types. Interestingly, brain tissue does not express nociceptors. There are two subgroups of nociceptors, **C-fibers and Aδ-fibers**. They appear anatomically as free endings of nerve fibers within the innervated tissue. C-fibers are non-myelinated nerve fibers and have conduction velocities of approximately 1 m/s. Aδ-fibers are thinly myelinated, allowing conduction velocities 10–25 times faster than C-fibers (Schaible and Richter, 2004). C- and Aδ-fibers have specialized channels and receptors on their free endings that are selectively activated by mechanical, thermal or chemical stimuli (Caterina and Julius, 1999) so that intensity and nature of the stimulus is coded by the frequency of action potentials in different fibers. There are many C- as well as Aδ-fibers in the skin, muscles, and joints. In contrast, visceral structures exhibit many C-fibers, but only a few Aδ-fibers. The faster signal conduction of Aδ-fibers enables the organism to withdraw quickly from a damaging stimulus, limiting stimulus impact at higher intensities to avoid further or permanent damage (Schaible and Richter, 2004).

The central endings of these nociceptors terminate in the **spinal cord** (or the trigeminal nucleus for those from the head and neck). Upon stimulation, nociceptors release neurotransmitters such as glutamate into the spinal cord, which binds to AMPA receptors and causes synaptic excitation of spinal dorsal horn neurons. These neurons ***transmit*** the information either directly or indirectly via interneurons to other destinations. This could be to motoneurons, also in the spinal cord, thereby triggering a nociceptive reflex (see below) or via important brainstem nuclei, the thalamic nucleus, subcortical nuclei and to the **cortex**, thus potentially **reaching consciousness** (Woolf and Salter, 2000). The release of glutamate in the spinal cord is related to the intensity of the painful stimulus. For strong noxious stimuli, glutamate release is prolonged, resulting in both short-lived excitation of dorsal horn neurons and activation of NMDA glutamate receptors, which precipitates sustained changes in spinal nociceptive neurons. Other important neurotransmitters, such as substance P, also play a key role in maintaining the nociceptive signaling in the spinal cord.

One of the phylogenetically oldest reflexes to pain is the **withdrawal reflex** (also called ‘nociceptive withdrawal reflex’ or ‘flexor withdrawal reflex’). It is a spinal reflex that does not require other areas of the brain to occur and protects the body from damaging stimuli by withdrawing the stimulated area away from the source of damage. The withdrawal reflex involves nociceptors, sensory neurons in the spinal cord and interneurons that stimulate a motoneuron. This ipsilateral motoneuron sends

information to the muscles to contract and inhibitory impulses to other muscles to relax; this is called **reciprocal innervation**. Interneurons enable the ***modulation* of the reflex**. In the case of an acute stimulation of a nociceptor (e.g., through stepping on a piece of broken glass or touching a hot plate), a child will immediately withdraw his foot or hand in less than 0.5 seconds. Muscle flexion is stimulated and muscle extension is inhibited. Activation of the motoneuron in the contralateral anterior horn of the spinal cord helps to stabilize the uninjured side of the body (crossed extension reflex). Further reactions of humans to severe acute tissue damage were described by Walter Bradford Cannon as the **fight-or-flight response** (Cannon, 1929). Nociceptive activation of sensory neurons in the spinal cord **excites the sympathetic nervous system** increasing heart rate and respiration and increasing blood flow to the muscles, with the result that the person can more easily fight against the threat or flee. The fight-or-flight response also involves emotional, cognitive and behavioral reactions. These reflexes are life-preserving and therefore evolutionarily advantageous.

In fibers that transmit sensory information other than pain, such as touch or proprioception, continuous or repeated stimulation leads to habituation, expressed as an increased threshold to the stimulus. In this respect, **nociceptors** are a unique type of sensor because they respond to **repeated stimuli** with **increased sensitivity** - **'peripheral sensitization'**, a lowered threshold and a longer-lasting response beyond the actual stimulus impact (Sandkühler and Gruber-Schoffnegger, 2012). Prolonged activation or sensitization of nociceptor and mechanosensitive sensory neurons can arise from the local peripheral immune reaction and release of cytokines, increased sympathetic activity within the dorsal root ganglion and upregulation of ion channels and receptor molecules in the cell bodies as well as terminals of damaged sensory neurons. All these changes cause increased action potentials or altered patterns of action potentials in the damaged nerves and in nearby undamaged nerves, which will, in turn, cause aberrant neuronal firing in the CNS and hence pain. In the case of repeated or prolonged nociceptive stimuli, changes will also take place in the CNS. The CNS, especially the spinal dorsal horn, responds to repeated C-fiber nociceptor activation with **functional and structural changes** that parallel the cellular changes underlying learning in other CNS areas such as the hippocampus.

This **central sensitization** contributes to an amplification of the noxious input and a spread of pain into areas outside the original damaged region (**hyperalgesia**) and the onset of pain from normally innocuous stimuli (**allodynia**). Central sensitization arises from prolonged increases in membrane excitability, strengthened excitatory synaptic inputs, and reduction of inhibitory interneuronal activity, which in turn are regulated by shifts in gene expression, the production and trafficking of key receptors, channels and downstream neuronal signaling pathways. It may be relatively short lasting but in cases of **chronic pain**, new mechanisms come into play that act to maintain this central sensitization for prolonged periods or even permanently (Basbaum et al., 2009; Woolf and Salter, 2000). In addition to afferent transmission, **efferent inhibitory mechanisms** also play an important role in pain processing (Fields, 2000). Mediated by neurotransmitters such as noradrenaline or serotonin, descending tracts of the brain stem are able to reduce the excitability of the spinal nociceptive neurons directly or indirectly by stimulating **inhibitory interneurons within the spinal gray** substance (Fields, 2000). Animal studies have shown that in healthy animals, the balance of descending control is inhibitory, but the situation changes in persistent pain states when the balance of activity becomes facilitatory, probably due to a change in activity from subpopulations of brainstem neurons (Bingel and Tracey, 2008; Gebhart, 2004). Pain processing depends upon a system of endogenous control that modulates nociceptive activity through these descending modulatory systems and also by **endogenous opioids** that represent a

homeostatic feedback mechanism of control. These endogenous pain modulatory pathways are the mechanisms by which factors such as attention and distraction, suggestion and expectation, stress and anxiety, context and past experience, influence pain responses. If the balance of these mechanisms is shifted due to the changing motivational and emotional state of an individual, this will crucially influence the spinal modulation of pain processing via descending tracts and the pain experience will also be changed.

The conscious experience of pain (***perception***) requires the signal to be transmitted beyond the spinal cord and brainstem into the **cerebral cortex**. There is no single 'pain cortex' but rather **a number of key areas** that are activated by noxious stimulation or tissue damage including the thalamus, the primary and secondary somatosensory cortices, the anterior cingulate cortex, the insula and the frontal cortex (Apkarian et al., 2005). However, pain is a **multidimensional process** modulated by previous experiences, emotions, cognitions, cultural imprinting and social aspects and is likely to involve many brain processes. While the somatosensory cortex may be responsible for the sensory discriminative aspects of pain, phylogenetically older cortical areas, such as the anterior cingulate cortex (ACC), are known to trigger autonomic reflexes such as an increase in blood pressure, heart rate, or respiratory frequency (collectively termed 'pseudoaffective reflexes') in response to painful stimuli.

Conditions with diminished pain perception

The essential role of acute pain in survival becomes obvious when this function is impaired. There are certain pathological conditions in which pain perception is disabled or greatly reduced. One example is hereditary sensory and autonomic neuropathy (**HSAN**) **type IV**. These patients have **severe alterations in their PNS** (van den Bosch et al., 2014). HSAN IV is a very rare congenital **pain insensitivity syndrome** characterized by the absence of unmyelinated nerve fibers and a loss of small myelinated fibers in the peripheral nerves. Thus, **pain and temperature sensation are eliminated**, resulting in the individual being unaware of injury, resulting, for example, in oral mutilation and severe fractures. **Life expectancy is shortened** due to this insensitivity to pain (Indo, 2002). The diagnosis of HSAN IV is made primarily clinically based on typical symptoms such as impaired pain and temperature perception as well as anhidrosis. The diagnosis may be confirmed by a genetic test because the related mutations and polymorphisms of the TRKA gene on chromosome 1 have been identified (Davidson et al., 2012; Gao et al., 2013).

2 The other kind of pain we call CHRONIC PAIN and it's really complicated. We speak of chronic pain when the pain is there constantly over a long period of time or keeps coming back.

Definition of chronic pain

The most accepted definition of chronic pain and its distinction from acute pain is based on a time criterion. Pain that **persists or reoccurs for three months or longer** is considered chronic pain (Merskey and Bogduk, 1994). Often a distinction is made between chronic and recurrent pain. This distinction is not standardized, but commonly, pain conditions are called '*recurrent*' unless they occur nearly daily

(e.g., chronic daily headache) or are very disabling (Stanton et al., 2010). To facilitate the readability we use the term '*chronic pain*' for both recurrent and chronic pain hereinafter.

Chronic pain is not a uniform condition. It may be a **symptom of an underlying chronic disease**, such as juvenile idiopathic arthritis (Petty et al., 2004), but chronic pain may also become an **independent disease** (Fritz et al., 1997). Common pain conditions in children are tension-type headache (Kröner-Herwig et al., 2007), migraine (Kröner-Herwig et al., 2007), functional abdominal pain (Chitkara et al., 2005) and lower back pain (Watson et al., 2002). Furthermore, irrespective of the pain location, mental and behavioral pain disorders, such as somatoform pain disorder (International Classification of Disorders, ICD-10, F45.4; World Health Organisation, 1992), are often diagnosed at specialized pediatric pain centers (Hechler et al., 2014; Zernikow et al., 2012b).

Multidimensionality of chronic pain

A pain experience is the result of complex processing involving different brain areas (Coghill et al., 2003; Turk and Okifuji, 1999). In acute pain, tissue damage is assumed to be more relevant than it is in chronic pain. The longer pain persists, the more relevant psychological and social factors, as well as neurobiological alterations in the CNS become. The multidimensionality of chronic pain can best be described using a **bio-psycho-social model** (Gatchel et al., 2007). This model considers the fact that the overall experience and impact of chronic pain is influenced by the interaction of biological processes, psychological factors and the social environment.

3 Not everyone knows about chronic pain, but it is quite common. Out of 100 children and adolescents, about five have such severe chronic pain that they are often absent from school, don't get together with friends very often or become very sad.

Epidemiology of chronic pain

The **prevalence rates** of chronic pain in children greatly differ between studies (Du et al., 2011; Haraldstad et al., 2011; Huguet and Miró, 2008; Perquin et al., 2000; Roth-Isigkeit et al., 2004). Whereas a Norwegian study reports chronic pain in **21%** of all school children between the ages of 8 and 18 (Haraldstad et al., 2011), a German study states a prevalence rate of chronic pain as high as **46%** for school children in a similar age range (10 to 18 years old) (Roth-Isigkeit et al., 2004). The **variation in prevalence rates** may be explained by differences in the definition of chronic pain (e.g., time criterion of three months plus a minimum pain frequency), differences in the samples (e.g., age range), differences in data collection (e.g., interview vs. questionnaire and self-report vs. proxy-report) and differences in the time period of reporting (King et al., 2011). Despite this large variation in prevalence estimates, it has become apparent that chronic pain is 'overwhelmingly prevalent in children and adolescents and should be recognized as a major health concern in this population' (King et al., 2011; p. 2737). Chronic pain also has a large **economic impact** (Sleed et al., 2005; Toliver-Sokol et al., 2011). Additionally, in the past decades, prevalence rates of chronic pain in children have steadily increased (Coffelt et al., 2013; King et al., 2011; Luntamo et al., 2012; Metsähonkala et al., 1996; Sillanpää and Anttila, 1996).

Headache is the **most common pain condition** in children (King et al., 2011; Kröner-Herwig et al., 2007). Other types of pain, such as abdominal, back or musculoskeletal pain, occur less often compared with headache (King et al., 2011). In addition to single-side pain, pain in more than one location is often observed in children with chronic pain (Ghandour et al., 2004; King et al., 2011; Mikkelsson et al., 2008; Petersen et al., 2006). Girls generally experience pain more often than boys, and the prevalence of chronic pain during childhood increases with age (King et al., 2011).

Epidemiological studies demonstrate that in 30-60% of children and adolescents with chronic pain, this condition lasts for at least one year (Mikkelsson et al., 2008; Miró, 2009; Perquin et al., 2003). For approximately 30%, a chronic pain condition continues for up to eight years (Hestbaek et al., 2006; Mikkelsson et al., 2008) and even continues into adulthood (Hestbaek et al., 2006; Walker et al., 2012). Especially for **females** and children with an **immigrant background**, **emotional distress** and a **high frequency** of pain increase the **risk of ongoing chronic pain**; parental factors, such as parental chronic pain, also increase this risk (Dunn et al., 2011; Mikkelsson et al., 2008; Perquin et al., 2003; Stanford et al., 2008).

Severity of chronic pain and interpretation of prevalence rates

The recurrent experience of pain is not in itself a clinical condition. If the pain is not caused by a physical disease and the pain does not negatively affect the child, either emotionally or physically, no treatment is required. **Not all children with ongoing pain visit a health care provider or take medication** (Ellert et al., 2007; Huguet and Miró, 2008; Perquin et al., 2001; Toliver-Sokol et al., 2011). A German study reports that 54% of all children between the ages of 3 to 10 years with chronic pain and 36% of all adolescents between the ages of 11 to 17 years with chronic pain visit a physician because of their pain problem (Ellert et al., 2007). In a Dutch study, 31% of the children between 0 and 18 years of age with chronic pain visit a general practitioner within a three-month period, 14% visit a specialized doctor (mainly a pediatrician), 12% visit a physiotherapist and 3% visit a social worker or psychologist (Perquin et al., 2001). The numbers are slightly lower in an American epidemiological study, where primary care treatment is sought by 16% of all children with chronic pain within a six-month period, 3% seek specialized care and 2% seek mental health care (Toliver-Sokol et al., 2011). In addition to doctor visits, taking pain medication is very common among children and adolescents with chronic pain. Approximately half of all children with chronic pain regularly use pain medication (Ellert et al., 2007; Huguet and Miró, 2008; Perquin et al., 2001).

When interpreting prevalence rates of chronic pain in epidemiological studies, pain-related impairment also needs to be considered (Eccleston et al., 2008). An epidemiological study by Huguet and Miró (2008) demonstrated that not all children experiencing pain for three months or longer also experience pain-related disability in everyday life. Whereas 37% of the children have chronic pain (i.e., permanent or recurrent pain for at least three months), only 4% report moderate pain-related disability, and 1% report severe **pain-related disability** (Huguet and Miró, 2008). The level of pain-related disability is **related to health care utilization**. The greater the pain-related disability, the higher the likelihood that children visit a health care professional or use medication due to their pain problem. Pain problems with a milder associated disability can most likely be treated by primary care. It can be assumed that only children experiencing moderate to severe disability due to pain actually require specialized treatment.

4

The special and also strange thing about chronic pain is that nothing is broken in the body, there is no injury that has to heal, or the problem in the body is so small that it can't explain the severe pain. Often we don't see that a person has chronic pain. But nevertheless the chronic pain is really there.

Chronic pain in defined medical conditions

There are a number of chronic diseases in which the pathophysiology may cause chronic nociceptive input to the brain. Among these diseases are chronic inflammatory diseases (e.g., ulcerative colitis, Crohn's disease and juvenile idiopathic arthritis), genetic disorders (e.g., epidermolysis bullosa and osteogenesis imperfecta), degenerative conditions (e.g., arthrosis) and cancer (Baumgart and Sandborn, 2012; Birchfield, 2001; Fine, 2010; Langan et al., 2007; Petty et al., 2004; Rauch and Glorieux, 2004). However, children with those **defined conditions** are a **minority among chronic pain patients**. More often children with chronic pain have **no tissue damage** in the painful location (Alp et al., 2010; Spee et al., 2013; Stordal et al., 2001). Nonetheless, **neurobiological changes**, e.g., central sensitization, can be observed in those children.

Minor physiological abnormalities in functional pain conditions

In conditions considered functional (e.g., gastrointestinal conditions with **no obvious underlying pathophysiology**, such as inflammation, tissue damage, or metabolic or neoplastic processes (Drossman, 2006)), physiological abnormalities play an important role in the development and exacerbation of chronic pain. Functional gastrointestinal disorders are associated with certain minor physical abnormalities such as constipation or decreased bowel contractions and, on the other end of the spectrum, increased contractions and diarrhea (Devanarayana et al., 2013; Devanarayana et al., 2012; Gijsbers et al., 2011; Lomax et al., 2010). These symptoms may be mediated by slight abnormal functioning of the autonomic nervous system (Lomax et al., 2010). Low vagal activity may lead to decreased bowel contractions, reduced motility and constipation, whereas high vagal activity may lead to increased contractions and diarrhea (Lomax et al., 2010).

In children with functional dyspepsia, gastric motility is often altered, reduced or accelerated (Bufler et al., 2011; Chitkara et al., 2003; Devanarayana et al., 2008). Children with irritable bowel syndrome or functional abdominal pain are more likely to have minor food allergies (Saps et al., 2011), slight fructose or lactose malabsorption (Putkonen et al., 2013; Van Tilburg and Felix, 2013), altered intestinal microbiomes (Saulnier et al., 2011), increased gastrointestinal permeability (Shulman et al., 2008), subclinical gut inflammation (Olafsdottir et al., 2002; Shulman et al., 2008) or subtle changes in local gut immunology with an increased mast cell count (Gijsbers et al., 2011; Henderson et al., 2012; Schurman et al., 2010). In up to one-third of all patients with irritable bowel syndrome, the symptoms begin after an acute gastrointestinal infection (Gwee, 2010; Saps et al., 2008). It is proposed that an inflammation-immunological phenomenon plays a major role in the development of post-infectious irritable bowel syndrome (Gwee, 2010).

In children with tension-type headache, an increased muscle tone in the head and neck area can be observed (Alonso-Blanco et al., 2011; Soee et al., 2013). There are conflicting findings about the

interaction between joint hypermobility and musculoskeletal pain in children. Though some studies report a strong correlation, especially in obese children (Tobias et al., 2013), other studies challenge these findings. A systematic review of several studies discovered no association for children with a European background but reports an association for children with an Afro-Asian background (McCluskey et al., 2012). In children with chronic low back pain, low grade spondylolysis and spondylolisthesis are observed more often than in pain-free children (Faingold et al., 2004).

However, even if minor abnormalities are detected in children with chronic pain, they usually do not explain the severity of the pain problem, such as pain intensity or pain-related disability. Minor abnormalities in common pediatric chronic pain conditions are **not specific** to children with chronic pain and will not occur in all affected children. Therefore, minor abnormalities cannot be interpreted as *the one* cause for the pain condition.

The subjectivity of pain

Pain is an individual and subjective experience. Therefore, it is **impossible to achieve a truly objective assessment** of pain (Coghill et al., 2003; Turk and Okifuji, 1999). The individual's **self-report** is considered the best available and most valid estimate of the pain experience (Coghill et al., 2003). It should be obtained as soon as a child is old enough to give a reliable and valid response. However, individual characteristics always need to be considered (Twycross et al., 2014). A reliable self-report of pain intensity can be achieved from 4 years onwards (McGrath et al., 2008; Stinson et al., 2006; von Baeyer, 2009). The report of more complex items requires a higher developmental status and can only be obtained in older children (McGrath et al., 2008). The necessity of self-reported pain, in contrast to **parental proxy-reports**, has been highlighted in several works. Consistently, it has been demonstrated that reports of physical perceptions and mood differ greatly between children and their parents, whereas observable behavior-based parameters, such as pain-related disability in everyday life, have a better agreement between self- and proxy-reports (Hourigan et al., 2011; Jokovic et al., 2004; Panepinto et al., 2005; Peterson and Noel, 2012; Verrips et al., 2000). Understanding someone else's pain requires **sensitivity and empathy**, which is influenced by many contextual factors, including one's previous events and experiences (Goubert et al., 2005). Understanding one's own child may be especially difficult during adolescence when children generally exchange less personal information with their parents (Keijsers et al., 2010; Smetana et al., 2006). This may cause a lack of insight for parents into their children's lives (Jokovic et al., 2004).

The subjectivity of pain also makes it impossible to compare pain intensity judgments between individuals. For example, one person might rate a standard painful stimulus at 8/10 and another person might rate the same event at 3/10 (Blankenburg et al., 2010). These different judgments occur due to differences in pain processing, appraisal or reporting. This does not mean that pain intensity scores are meaningless, but rather that the important comparisons are within an individual over time (e.g., response to treatment) rather than across individuals.

Habituation in chronic pain patients

The experience of ***acute pain*** is usually associated with several **pain-specific behaviors**. They include vocal, verbal, facial, postural and motor behaviors (von Baeyer and Spagrud, 2007). These behaviors are

used to measure pain in children who cannot self-report pain because, for example, they are too young, mentally disabled or just woke up from an operation (von Baeyer and Spagrud, 2007).

In ***chronic pain***, however, these pain-specific behaviors cannot be observed or can only partially be observed. Children with abdominal pain may show certain postures when in pain, and children with musculoskeletal pain may have pain-specific postural and motor behaviors. Children with chronic headache rarely show any of the above mentioned pain-specific behaviors. The **lack of pain-specific behavior in children with chronic pain** can be attributed to **habituation** (von Baeyer and Spagrud, 2007). Instead of this pain-specific behavior, other behavior may be shown that cannot be specifically attributed to pain. Generally, chronic pain is likely to be manifested in complex mood and behavioral changes, such as increased irritability, low mood, hostility, and changes in appetite and school performance. These characteristics cannot be interpreted on their own but rather only in the context of the child's baseline condition and temperament (von Baeyer and Spagrud, 2007). The absence of specific behavioral clues of chronic pain often causes other people not to believe the child in pain that he/she is really experiencing pain. People tend to transfer their knowledge of acute pain to chronic pain and do not consider that there are important differences between these two types of pain.

5

But, different as the two types of pain are, they also have something in common: Regardless of what kind of pain it is – whether it's acute or chronic, whether it's headaches, a toothache or stomach pain – in the end all pain arises exclusively in the brain. Otherwise you wouldn't realize you have it. If you have chronic pain, you're not just imagining it and you have a right to be helped.

Children's right to treatment

Access to **pain management is a human right**! This has been stated in the Declaration of Montreal by the World Health Organiszation (WHO) and the IASP (http://www.iasp-pain.org/DeclarationofMontreal) (Brennan and Cousins, 2004). However, the subjectivity of pain and the fact that a **child with chronic pain is often not taken seriously** in his/her report of pain can result in a **lack of treatment** for these children. It needs to be considered that even parental proxy-reports of children's experiences may differ quite markedly from children's own views. They may not accurately capture the child's inner experiences. Therefore, the importance of directly recording children's own perspectives is becoming increasingly recognized in health care (Söderbäck et al., 2011). When children seek treatment, they have a right to get support.

6

How does chronic pain actually occur? Chronic pain is learned by the brain, like a song. I'll bet you've had a favorite song that stayed in your head?
Sometimes our brain learns things without us wanting it to, or in spite of the fact that we really don't want it to at all. Pretty annoying, isn't it? You probably know all about that, too! Is there a band or a singer that you find totally awful? Think about it! Can you think of a song of theirs? Do you know the melody or maybe even the video? Why does it come to you? You find the song totally stupid and really don't want to have it in your head. The brain learns not only positive and pleasant things, but also negative ones. Learning has a lot to do with feelings, and when you find something really stupid, your brain remembers it.
Let's assume you have a headache, you're also sad just now or someone is annoying you. Your brain can learn the headache really well just now and you will remember the headache. The next time you're sad or someone annoys you, your headache might return, it might even be worse and at some point it will always be there. The brain becomes more and more sensitive to pain. At some point things start to hurt that didn't hurt at all before, such as normal movement of the legs or a little muscle tension in the neck or a light rumbling in the stomach. Suddenly all that hurts. Sometimes the pain is so bad that you might think something must be broken! But it's not! In contrast to acute pain, you can have severe chronic pain without any bodily injury being present.

Pain memory – biological aspects

A biological explanation for 'pain memory' is **sensitization**. There is increasing evidence that the presence of prolonged pain and tissue injury causes changes in the spinal cord, in brain structure and function, such that signals are processed differently than in the normal, uninjured state (Bushnell et al., 2013). Chronic pain is first triggered by peripheral and central sensitization but may then be maintained by **altered brain networks** concerned with reward, motivation and learning and shifts in **descending modulatory control** (Denk et al., 2014).

Strong nociceptive stimuli induce 'memory traces' in the spinal cord and most likely also in the brain (Sandkühler, 2000). The synaptic plasticity of the spinal cord is comparable to the hippocampus, the brain region responsible for learning and memory (Sandkühler, 2000). Prolonged noxious input causes **long-lasting changes in signal transduction in the CNS** and an enhanced sensitivity to subsequent painful stimuli. In the clinical picture, sensitization is reflected by **hyperalgesia** (e.g., lowered pressure pain threshold), **allodynia** or **spontaneous pain** (Woolf and Salter, 2000).

Evidence for the phenomenon of sensitization in chronic pain is provided in numerous studies (Gatchel et al., 2007; Loeser and Treede, 2008; Soee et al., 2013; Walker et al., 2012; Woolf, 2011). In children with various functional gastrointestinal disorders, visceral and more generalized pain sensitization can be observed (Castilloux et al., 2008; Di Lorenzo et al., 2001; Faure and Wieckowska, 2007; Hoffman et al., 2007; Van Ginkel et al., 2001). In adults with irritable bowel syndrome, diminished pain inhibition has

also been detected in several studies (Wilder-Smith, 2011); a lowered inhibition results in a more intense pain experience.

One way to **suppress central sensitization** and to temporarily normalize synaptic transmission is by **competing stimulation**, such as transcutaneous electrical nerve stimulation (TENS) or physical modes of pain control, i.e., the application of heat or cold (Sandkühler and Lee, 2013). Recent in vivo and in vitro studies have shown that the synaptic transmission between Aδ- or C-fibers and spinal neurons is permanently inhibited, provided that the parameters of stimulation are chosen correctly (synaptic long-term inhibition). Even the long-term potentiation of spinal synaptic transmission may be reversed (Sandkühler and Lee, 2013). A recent imaging study shows that the **amygdala** has more connections with other brain areas in pediatric pain patients with complex regional pain syndrome (CRPS) compared with healthy children (Simons et al., 2014b). Specifically, more **connectivity** was shown for cognitive/emotional (prefrontal, cingulate cortex, basal ganglia), sensorimotor (thalamus, somatosensory cortex) and integrative (cerebellum, parietal lobe, thalamus) processing. After successful pain treatment, connectivity decreases (Simons et al., 2014b). However, some changes in the CNS only partially disappear when symptoms resolve (Linnman et al., 2013), suggesting that the **brain remains altered** even after a successful treatment of chronic pain.

Pain memory – psychosocial aspects

Pain memories consist of **sensory** (e.g., pain intensity), **affective** (e.g., fear) and **contextual** (e.g., people, place and time) aspects (Ornstein et al., 1999). The close association between pain and emotions (Williams, 2002) represented by the tight cortical connection between somatosensory and affective brain areas (Legrain et al., 2011) is important for pain memory. A study of healthy children demonstrates that being in an anxious state while experiencing pain increases the intensity of pain recall and the recall of pain-related fear (Noel et al., 2012). The same effect can be shown in children with a generally higher level of trait anxiety (Rocha et al., 2009). These findings indicate that **emotions influence the encoding of pain memory**. When **negative emotions** are experienced along with pain, the **pain memory** is **stronger**. Furthermore, fear is associated with pain. This fear and the corresponding brain structures can be reactivated by pain-related cues (Yan et al., 2012). This builds the basis for pain-associated avoidance.

Similar experimental results are shown in adults who experience a stress condition and a non-stress condition (Gedney and Logan, 2004). While the pain intensity of a cold pressor task does not differ between people experiencing stress-associated negative emotions and the control group, differences appeared when recalling the pain experience six months later. At this point, the pain in the stress condition is recalled significantly more strongly than the time of pain exposure; this is not the case in the non-stress condition. In adults, the close connection between somatosensory and affective brain areas has also been shown in functional imaging studies. When pain has been experienced along with a strong emotion, the provocation of pain by stimulating the specific brain area (somatosensory thalamus) also activates emotional brain structures (limbic system) (Lenz et al., 1997).

This close connection between somatosensory and affective brain structures is also relevant for pain recall. Experiencing **negative emotions facilitates the recall of pain memories** (Gedney and Logan, 2004). Pediatric patients with CRPS have more connections between the amygdala and other brain areas

compared with healthy children (Simons et al., 2014b). These results give an insight into the consolidation of pain memories and their affective associations.

Pain sensitization and pain inhibition in detail

Nociceptors have a special way of processing repeated stimuli. They respond with increased sensitivity, lowered thresholds and a longer lasting response beyond the actual stimulus impact. In the case of repeated or very severe painful stimuli, this specific characteristic of nociceptors facilitates peripheral as well as central sensitization (Hansson, 2014).

Peripheral sensitization is triggered by the release of locally acting substances from surrounding tissue and associated intracellular responses (e.g., increase of Ca2+ concentration in the peripheral nociceptor terminal) conjointly leading to a decrease of **nociceptor threshold** and an increase in suprathreshold stimuli (Schaible et al., 2011). Additionally, insensitive (silent) terminals or branches may become sensitized, leading to an increase in **receptive field size** (Walker, 2014). Triggered by long-lasting or repeated painful stimuli, the CNS (especially the dorsal horn) responds with functional and structural changes (corresponding to histomorphologic changes) similar to cellular changes that parallel learning in other CNS areas such as the hippocampus (Sandkühler and Lee, 2013). These neuroplastic changes are part of nociceptive central sensitization.

Chronic pain may result from, or be amplified by, pathological changes to signal processing by the nervous system. Because of **insufficiently treated pain**, changes in the CNS may arise that increase the sensitivity to painful stimuli and that manifest as hyperalgesia (Katz et al., 2011). There is much evidence that strong or repeated painful stimuli **chronically amplify the synaptic transmission** of pain information from the PNS to the CNS. The induced synaptic changes at the spinal level (**synaptic long-term potentiation**, LTP) are similar to those that were initially identified in the hippocampus as components of cellular learning and the creation of cognitive memory (Rahn et al., 2013). Recent studies in humans have shown that some subjects may be particularly prone to long-lasting central sensitization in such a way that even very short-lasting strong noxious stimuli may elicit experimentally-induced LTP of pain sensitivity lasting many days or weeks, i.e., transforming early nociceptive or pain LTP into sustained late LTP (Pfau et al., 2011). In the case of repeated or ongoing painful stimuli, functional synaptic changes may persist until death. Therefore, it is very important to avoid the onset of prolonged central sensitization.

Humans have a very potent **intrinsic pain defense mechanism** originating at the brain stem level. At the spinal level, nociceptive neurons are inhibited pre- or postsynaptically by **long descending tracts** through the release of endogenous opioids, monoamines and inhibiting amino acids. These substances are able to prevent calcium influx via NMDA receptor channels and/or act directly on voltage-gated calcium channels (VGCC), thus **preventing central sensitization**. The intrinsic pain control is always active and may be additionally activated by acute stress or painful stimuli. If intrinsic pain control is insufficient, sensitivity to pain is increased and the manifestation of pain memory is potentially enhanced (Noseda and Burstein, 2013). Supposedly, **inter- and intraindividual differences in efficacy of intrinsic pain control** are one of the reasons for differences in pain chronicity with presumably similar underlying diseases and burdens of pain (Noseda and Burstein, 2013). In clinical practice, interindividual variants of intrinsic pain control play an important role for example in preemptive analgesia. The efficacy of preemptive analgesia in the perioperative setting is not consistent across studies (Staud, 2012). The

inconclusive scientific data may originate from the fact that some of the patients may be sufficiently protected by their intrinsic pain control, preventing the establishment of central sensitization, rendering preemptive analgesia unnecessary and of no additional effect due to a ceiling effect (Yarnitsky et al., 2012). In fact, it has been demonstrated recently that the serotonin-norepinephrine reuptake inhibitor (SNRI) duloxetine is inefficient in subjects with intact conditioned pain modulation (CPM, as experimentally tested by the cold pressor test), but acts readily as an analgesic in patients exhibiting a lack of CPM (Yarnitsky et al., 2012).

7

Really complicated! What can you do about it?
The best thing is to forget about the chronic pain, put it out of your mind and don't think about it anymore. Unfortunately, that's easier said than done! The pain is stored in your brain; it can't simply be cut out in an operation and there are no pills to help you forget it. So, operations and pills don't usually help with chronic pain!

Indications for treatment of chronic pain

Pain may be uncomfortable, but is not in itself a clinical condition requiring treatment. In acute pain, the current tissue damage needs to be treated. For chronic pain that is neither associated with tissue damage nor caused by a physical disease and does not negatively affect the child, no treatment is required. Chronic pain becomes **clinically relevant** when it is accompanied by r**estrictions in everyday life**, e.g., school absenteeism, neglecting friends, withdrawal from physical activity or emotional distress. In addition to the parents, the child him-/herself can best judge if a doctor visit is required (Söderbäck et al., 2011).

Though some children experience a **spontaneous remission** from chronic pain without treatment (Gijsbers et al., 2011; Mikkelsson et al., 2008), others require **(specialized) treatment** (Perquin et al., 2001). However, even with treatment, a chronic pain condition may persist into adulthood (Harreby et al., 1999; Hestbaek et al., 2006; Mulvaney et al., 2006; Walker et al., 2010). Children with chronic pain often have a long history of ineffective (bed rest or avoidance of activity) or even harmful medical interventions (polypharmacy, inappropriate use of opioids or invasive procedures such as nerve blocks) (Zernikow et al., 2012a). For many children with a chronic pain condition, treatment can only be effective when it addresses the different aspects of chronic pain – the biological, psychological and social dimensions.

Chronic pain treatment

A general goal of chronic pain treatment should be the reduction and management of the pain symptoms, in addition to the reduction of disability, the improvement of psychological well-being and the reestablishment of functioning in various roles, including school or work (Eccleston et al., 2003; Hechler et al., 2014). Treatment should further aim to prevent unnecessary or even harmful medical interventions or (invasive) diagnostic procedures (Zernikow et al., 2012a) and reduce the economic burden for the individual and society (Hechler et al., 2014).

According to the **bio-psycho-social model**, chronic pain cannot be treated by a single intervention, such as an operation or a pharmacological treatment. Instead, a **multimodal treatment** is required. Treatment modules for chronic pain can be split up into medical interventions aimed at the modification of the biological components of pain, psychological interventions aimed at changing psychological processes and social interventions improving school, peer or family relationships. These treatment components should be combined according to the patient's needs. In the following section, the potential of medical treatment will be discussed. A description of the psychological and psychosocial aspects and their respective treatment approaches will be presented in Sections 9-11.

Medical interventions

In **illnesses associated with pain** (e.g., inflammatory bowel disease or cancer), successful **treatment of the primary cause** will reduce or abolish pain in many cases. However, even when the underlying condition is treated, some children still experience chronic pain; for example, children with juvenile idiopathic arthritis may still experience pain even when the inflammatory process is well controlled through disease-modifying drugs and signs of an active disease are no longer detectable (Faure and Giguere, 2008; Stinson et al., 2012). In addition to treatment focusing on biological pain parameters, **psychosocial treatment is also needed**.

When **minor abnormalities of body function** are detected in children with different chronic pain conditions (see Section 4), most medical therapies intended to improve body function and reduce pathophysiology have proven ineffective at reducing the pain problem. For example, the causative treatments of constipation, lactose intolerance or helicobacter pylori colonization, such as high fiber or lactose free diets or Helicobacter pylori eradication therapy, have in most cases been ineffective in reducing pain and pain-related disability in children with chronic abdominal pain (Bufler et al., 2011; Huertas-Ceballos et al., 2009). The implications for the treatment of chronic pain are that a **comprehensive education** about the chronic pain condition should include pathophysiology. Importantly, the patient should be informed that the evidence of therapies targeting minor abnormalities is limited or cannot be provided at all. The patient and the family need to understand that minor abnormalities in common pediatric chronic pain conditions are **not specific** to children with this pain condition and will not occur in all affected children, indicating that they cannot be the one cause for the pain condition. Sometimes, therapies aimed at altered body function can be used in a supplementary manner, but in most cases, they will not provide a satisfying cure for the chronic pain condition (Bufler et al., 2011).

Pharmacological interventions

Pain-relieving pharmacological interventions are only indicated when a **causative treatment** of the pathophysiology of pain is possible or when nociceptive processing can be directly influenced by the drug (Dobe et al., 2013; Huertas-Ceballos et al., 2008). Four major groups of drugs can be distinguished: **triptans, non-opioids, opioids and adjuvants**. The chemical structure of *triptans* is similar to serotonin, and their action is mediated by the activation of serotonin receptors. Triptans are approved and effective for the treatment of migraine and cluster headache (Eiland and Hunt, 2010). *Non-opioids*, e.g., ibuprofen, influence inflammatory processes that play a role in, for instance, migraine, juvenile idiopathic arthritis or cancer pain. In these applications, they are effective (Anthony and Schanberg, 2005; Toldo et al., 2012; Zernikow et al., 2006).

Opioids, on the other hand, influence the transmission and processing of nociceptive stimuli. The use of opioids has proven effective specifically in acute pain conditions, such as postoperative pain, pain in burns (American Academy of Pediatrics, 2001; Drake et al., 2013; Duedahl and Hansen, 2007) and cancer pain (Caraceni et al., 2012; World Health Organisation, 2012; Zernikow and Michel, 2009). Currently, opioids are often prescribed in the treatment of longstanding non-cancer pain in adults, although findings on the effectiveness of opioids in this context are conflicting (Häuser et al., 2014; Kissin, 2013). Though some patients with longstanding non-cancer pain report a reduction of pain intensity under opioids, findings on a reduction in functional disability are inconclusive (Noble et al., 2010). Because of the scarce evidence of its effectiveness and the high probability of side effects such as fatigue or constipation, long-term opioid treatment in non-cancer pain patients is only recommended in rare cases and with careful consideration (Häuser et al., 2014). *Adjuvant drugs*, such as anticonvulsants and antidepressants, play a major role in the treatment of neuropathic pain. In adults, they are generally used in patients with post-herpetic neuralgia or diabetic neuropathy (Attal et al., 2010; Dworkin et al., 2010; Moore et al., 2012). It is important to note that those conditions are rare in children. In other pediatric chronic pain conditions, such as headache or abdominal pain, adjuvants have not proven effective (El-Chammas et al., 2013; Kaminski et al., 2011; Saps et al., 2009; Toldo et al., 2012). On rare occasions and in orphan diseases such as osteogenesis imperfecta, adjuvants may be useful and are sometimes recommended (Drake et al., 2013).

Invasive medical interventions

Invasive medical interventions for the treatment of chronic pain conditions have **limited evidence** of effectiveness, even in adults (Dworkin et al., 2013). In severe cerebral palsy, localized cancer pain or very rare cases of CRPS, the application of intrathecal medications, such as baclofen or opioids, the use of regional anesthesia or sympathetic blocks might be effective in the context of comprehensive multidisciplinary pain treatment. However, even in those situations, interventions may be effective for only a very limited number of patients (Hoving et al., 2009; Rork et al., 2013; Zernikow et al., 2012a). Generally, the **risk and burden** of the interventions have to be carefully **balanced against the anticipated success** (Zernikow et al., 2012a). Furthermore, the lack of evidence should be taken into account when making such a treatment decision (Zernikow et al., 2014).

8 Certain pain medications are helpful with just a few types of pain, for example, with migraines. But note that your doctor has to explain to you very precisely how to take the pain medication. With many recurring or ongoing kinds of pain, medication doesn't help at all and can even be harmful.

Medication usage in children with chronic pain

Approximately half of all children with chronic pain regularly use pain medication (Ellert et al., 2007; Huguet and Miró, 2008; Perquin et al., 2001). When the severity of the pain problem increases, the likelihood of taking pain medication rises (Huguet and Miró, 2008). Whereas 44% of children with a low severity of chronic pain take medication, the number exceeds 80% in highly impaired children (Huguet

and Miró, 2008). The numbers of medication users are similar for patients visiting a tertiary pediatric pain center (76%) (Zernikow et al., 2012b). What is most worrying about this number is the sizable fraction of patients for whom pharmacological treatment is not indicated. Approximately 30% of the children taking analgesics do this without **indication** when they first visit a tertiary care center (Zernikow et al., 2012b).

Migraine

Etymologically, migraine originally describes a typical hemicranial severe headache (Greek: hēmíkraira = half the head). Women suffer from migraine more often than do men (Smitherman et al., 2013). A similar gender pattern is found among adolescents (King et al., 2011). There are many hints that genetic factors and hormonal factors – e.g., during the menstrual cycle – are jointly responsible for triggering a migraine attack (Bingel, 2008; Sauro and Becker, 2009). Although patients with migraine commonly report foods, weather changes and exposure to light, sounds or odors as factors that **trigger or aggravate migraine** attacks, clinical studies do not support a causal relation (Hoffmann and Recober, 2013). If a child reports trigger factors that reliably induce attacks shortly after exposure and are easy to avoid, avoidance may be reasonable. However, when suggesting the avoidance of certain triggers the associated reduction in quality of life should be considered as well; e.g., strict avoidance of certain foods such as chocolate may induce stress and frustration.

The term 'migraine' has developed in common language into a term for any type of severe headache. On closer examination, a headache termed 'migraine' often does not comply with the criteria of the **International Headache Society** (IHS). According to the IHS, migraine is defined as a sudden periodic headache, usually with a throbbing quality (International Headache Society, 2008; 2013). It may be accompanied by symptoms such as nausea, vomiting and increased sensitivity to light (photophobia) or auditory stimuli (phonophobia). Migraine symptoms increase with physical activity. Therefore, the patient usually withdraws, avoiding physical activity. Especially in younger children who are not able to verbally describe symptoms, their behavior (e.g., photophobia or phonophobia) offers important diagnostic clues. If the migraine attack leads to **transient neurological deficits** preceding the pain, this is called an '**aura**.' Manifestations of an aura may be visual or sensory disturbances of perception or motoric disturbances such as paresis or expressive speech disturbances. This type of migraine is less prevalent than migraine without aura (Özge et al., 2013). The diagnosis of migraine as a primary headache should not be given unless other neurological diseases can be excluded. The IHS diagnostic criteria for migraine (http://ihs-classification.org/en/) are displayed in *Table 1*.

For migraine attacks, the **treatment of choice** is a **pharmacological treatment with ibuprofen or triptans** (Evers et al., 2009). Importantly, analgesics need to be applied correctly. The **correct application** of medication includes a) **the right timing**, i.e., as soon as the child notices the beginning of a migraine attack without a delay, instead of waiting until the patient cannot tolerate the pain anymore and b) **a sufficient dose**, i.e., avoiding a drug dose that is too low because it will be ineffective. Trying to avoid medication by applying alternative treatment strategies such as taking a nap or using relaxation techniques *during* a severe migraine attack is not suggested (Balottin and Termine, 2007). When migraine attacks are not properly treated, as time goes by, pain memory will be established, attacks will be accompanied by fear and the development of chronic headache becomes more likely.

Table 1: Diagnostic criteria for migraine from the International Headache Society (IHS)

A At least 5 attacks fulfilling criteria B-D

B Headache attacks lasting 4-72 hours (untreated or unsuccessfully treated)[1, 2]

C Headache has at least two of the following four characteristics:

1. unilateral location[3, 4]
2. pulsating quality
3. moderate or severe pain intensity
4. aggravation by or causing avoidance of routine physical activity (e.g. walking or climbing stairs)

D During headache at least one of the following:

1. nausea and/or vomiting
2. photophobia and phonophobia[5]

E Not better accounted for by another ICHD-3 diagnosis

Note:

[1] When the patient falls asleep during migraine and wakes up without it, the duration of the attack is reckoned until the time of awakening.
[2] In children, attacks may last 2-72 hours (the evidence for untreated durations of less than 2 hours in children has not been substantiated).
[3] Migraine headache is commonly bilateral in young children; an adult pattern of unilateral pain usually emerges in late adolescence or early adult life.
[4] Migraine headache is usually frontotemporal. Occipital headache in **children**, whether unilateral or bilateral, is rare and calls for diagnostic caution.
[5] In young children, photophobia and phonophobia may be inferred from their behavior.

Table 2: Diagnostic criteria for tension-type headache (TTH) from the International Headache Society (IHS)

A	Infrequent episodic TTH:	At least 10 episodes of headache occurring on <1 day per month on average (<12 days per year)
	Frequent episodic TTH:	At least 10 episodes of headache occurring on 1-14 days per month on average for >3 months (≥12 and <180 days per year)
	Chronic TTH:	Headache occurring on ≥15 days per month on average for >3 months (≥180 days per year)
	AND fulfilling criteria B-D	
B	Infrequent episodic TTH:	Lasting from 30 minutes to 7 days
	Frequent episodic TTH:	Lasting from 30 minutes to 7 days
	Chronic TTH:	Lasting hours to days, or unremitting

C At least two of the following four characteristics:

1. bilateral location
2. pressing or tightening (non-pulsating) quality
3. mild or moderate intensity
4. not aggravated by routine physical activity such as walking or climbing stairs

D Both of the following:

1. no nausea or vomiting
2. no more than one of photophobia or phonophobia

E Not better accounted for by another ICHD-3 diagnosis.

Note: Criteria A and B differ for infrequent episodic, frequent episodic and chronic TTH

Patients suffering migraine without aura frequently also suffer episodic **tension type headache** (*Table 2*). A headache diary is the tool of choice to identify the co-occurrence of tension type headache and migraine. Because treatment is essentially different in those two types of headache, it is very important to educate patients and parents to differentiate the two types of headache to enable them to choose the appropriate therapy (for tension type headache, no analgesic or prophylactic treatment is

recommended) (Blankenburg et al., 2009). This will also prevent the development of medication overuse headache in the long run.

9

But what helps with chronic pain? Three things!
First: Negative feelings and stress can make pain worse! So it's important to reduce negative feelings and stress. Pay close attention to what gives you negative feelings, what makes you stressed. Sometimes your school simply isn't the right one for you, or you have absolutely no time for yourself because you have so many hobbies, your parents are arguing a lot, or you are just sad and don't know exactly why. It can also be that someone touches you though you don't want them to at all, or you are bullied at school, or something else in your life isn't going just as you want it to. Often you can't solve these problems alone so well. And that's why there are people who can support you in this. Sometimes it's parents, friends or relatives, but also your pediatrician, your favorite teacher, the school psychologist or the telephone help line. There are many ways to find help.

Psychosocial aspects of chronic pain

In patients with chronic pain, it is important to explore potential **stress factors** that may have added to the development of the chronic pain condition or that may add to the maintenance of the condition. Some of those potential stress factors are discussed in this chapter.

Negative emotions and stress

Pediatric pain experts consider **depressive and anxious traits** important factors for the development and maintenance of chronic pain and disability (Miró et al., 2007), i.e., children with those traits are more likely to develop chronic pain. Accordingly, pediatric chronic pain patients often report increased scores for depression and anxiety, specifically general anxiety as well as school aversion (Hirschfeld et al., 2013; Zernikow et al., 2012b). In an inpatient study population with high pain severity, nearly 50% of the patients reported increased scores in either anxiety or depression before therapy (Dobe et al., 2011). The specific role of emotional distress in chronic pain is not yet fully understood. Pediatric longitudinal studies suggest that depression and anxiety are predictive of chronic pain trajectories (Larsson and Sund, 2005; Mulvaney et al., 2006; Stanford et al., 2008). Depression and anxiety may perpetuate or amplify the pain due to social withdrawal or to difficulties in falling asleep and/or remaining asleep (Logan et al., 2014; Stanford et al., 2008). Though some adult studies support these findings (Magni et al., 1994; Polatin et al., 1993), others suggest that chronic pain can cause depression (Atkinson et al., 1991; Magni et al., 1994). Numerous models try to explain the complex interactions (Fernandez, 2002). It is most likely that several aspects play an intervening role; once chronic pain and depression or anxiety have developed, they interact reciprocally, worsening each other over the course of illness (Bair et al., 2003; Gatchel et al., 2007; Stanford et al., 2008).

Negative emotions are also triggered by **stress and critical life events**. Children use different **coping strategies** in stressful situations. Children with abdominal pain react more strongly to stressful situations than do healthy controls (Dufton et al., 2011). This coping style may develop due to the pain condition, but it may also facilitate the development of chronic pain. Unfortunately, severe chronic pain goes along with impairment in the child's social life, including family, friends and school. Within the family, chronic pain becomes the prominent topic and normal family life greatly suffers (Palermo, 2000). To manage chronic pain, **stress should be reduced**, a **normal handling** of the ill child should be established and the child should **learn strategies to better cope** with stressful situations.

Traumatic and stressful life events

Childhood **physical and sexual abuse** as well as other **stressful life events** and **ongoing emotional distress** are associated with chronic pain and somatoform disorders in general (Asmundson, 1999; Essau, 2007; Lampe et al., 2003; Wager et al., 2014). Stressful life events, such as loss of a family member through death, hospitalization of a family member, the child's own hospitalization, moving houses, change in occupation of an immediate family member, failure in a major school examination and getting bullied at school, are **associated with the occurrence of abdominal pain** (Boey and Goh, 2001). Furthermore, the experience of negative life events is one factor contributing to the maintenance of chronic abdominal pain (Mulvaney et al., 2006). Another study with adolescents with severe pain conditions showes that children with complex regional pain syndrome (CRPS) experienced an especially high number of stressful life events, followed by children with abdominal pain (Wager et al., 2014). These life events specifically occurred in the family system (Wager et al., 2014).

School and friends

Generally, children with chronic pain have **fewer friends** than do healthy children and they are less involved in peer activities (Forgeron et al., 2010). Some studies report an **increased rate of bullying** in children with chronic pain (Greco et al., 2007; Hjern et al., 2008). However, the causal relationship of these findings and their impact on the development and maintenance of chronic pain is not yet understood (Forgeron et al., 2010). Bullying may trigger pain symptoms, but an ill child may also be more likely to be bullied due to his/her vulnerability (Forgeron et al., 2010).

A study by Merlijn and colleagues (Merlijn et al., 2003) suggests that peers reward and amplify pain-free behavior. The researchers demonstrate that peers pay attention to their friends more during episodes free of pain, whereas they reduce their attention during pain episodes (Merlijn et al., 2003). Based on this, Forgeron and colleagues (2010) determined that children with chronic pain often feel misunderstood by their peers; they desire increased attention and understanding, especially when in pain. Though a reduction of peer attention during pain episodes could be considered a protective factor with regards to learning theory (reinforcement of pain-free episodes), it may still lead to social exclusion and loneliness in children with chronic pain and therefore cause depression (Forgeron et al., 2010; MacDonald and Leary, 2005).

Children with chronic pain often do not attend **school** regularly (Huguet and Miró, 2008; Logan et al., 2011; Logan et al., 2008; Zernikow et al., 2012b). **Irregular attendance** at school results in numerous consequences for the child (Logan and Simons, 2010), such as a decline in grades, interference with school success, repeating a class, less contact with peers and social isolation (Forgeron et al., 2010; Hechler et al., 2014; Logan et al., 2008; Sato et al., 2007). Because these children are less able to address

the classroom demands, they have a lower perception of their own academic performance (Logan et al., 2008; Sato et al., 2007). All this greatly endangers the pupil's educational development.

Finally, absenteeism from school may result in **negative reactions from teachers**. Most teachers do not interpret chronic pain in a dualistic way; they attribute the pain either to an organic or a psychological cause (Logan et al., 2007). Dependent on his/her interpretation, the teacher's understanding may vary from overwhelming empathy and understanding (attributing the student's pain to an organic cause) to lacking empathy and understanding (attributing the pain to a psychological cause). The teacher's reaction may highly affect the student's psychological well-being.

Pain treatment focusing on social aspects

Chronic pain in children and adolescents cannot be isolated from its context factors (Palermo and Chambers, 2005). The social environment of the child, especially his/her **family, peer group and school**, may be relevant to the origin and maintenance of pain disorders.

Intensive pain treatment with children usually includes parents or the whole family (Dobe et al., 2013; Eccleston et al., 2012; Eccleston et al., 2014; Hechler et al., 2014). While family therapy cannot be equally intense in different treatment settings (primary vs. tertiary care), it has proven effective to **include parents in the pain treatment** (Duarte et al., 2006; Eccleston et al., 2012; Palermo et al., 2009). For instance, dysfunctional pain-related beliefs and appraisals of parents, as well as negative affect and dysfunctional behavior, can be altered by cognitive behavioral therapy (Carter and Threlkeld, 2012). Additionally, familial stress factors can be identified and worked on with the parents. A Cochrane Review indicates that psychological therapies including parents have a positive effect on the child's pain symptoms, the parent's behavior and the parent's mental health condition (Eccleston et al., 2012).

In pain therapy, school is another important treatment focus (Eccleston et al., 2014; Hechler et al., 2014). Some inpatient programs include **school for daily therapy sessions** (Hechler et al., 2014). In addition, exposure to home school can be a therapy module (Dobe et al., 2013). Because many chronic pain patients have a large number of school absences over a long period of time, they may require intensive training to be re-integrated.

Pain treatment focusing on psychological aspects

Psychological interventions for pain treatment are diverse. They aim to modify thoughts, beliefs and affective and behavioral responses to symptoms and the effects of illness (Noto et al., 2010; Thornton et al., 2009; Vachon-Presseau et al., 2013). The most relevant psychological therapies in the context of chronic pain treatment are **cognitive behavioral therapy, acceptance and commitment therapy, biofeedback and hypnotherapy** (Eccleston et al., 2014). Even in conditions with a clear underlying pathophysiology, complementary psychological treatment will be necessary to achieve the best treatment outcomes because medical interventions alone will not address the psychological aspects of chronic pain (Kashikar-Zuck et al., 2012).

There is good evidence for the efficacy of psychological interventions in chronic pain patients with various functional pain conditions as well as in patients with underlying physical conditions (Eccleston et al., 2014). Psychological interventions generally lead to a reduction in pain intensity. However, the reduction in pain-related disability and emotional distress is not consistent across interventions and studies; some studies report a reduction of disability and emotional distress, but other studies describe

no improvement in these outcome parameters (Eccleston et al., 2014). In addition to the mentioned effects, psychological treatment may also have a secondary effect on biological factors, e.g., reduction of muscle tension and physiological arousal through a reduction in negative emotions (Vlaeyen and Linton, 2000).

Psychological interventions can be included in multidisciplinary treatment programs or may be applied in independent psychotherapy sessions in close cooperation with other health care providers.

Cognitive behavioral therapy

Cognitive behavioral therapy aims to identify and alter the child's negative affect. It also aims to identify and alter dysfunctional pain-related beliefs and appraisals (e.g., pain catastrophizing) and dysfunctional behavior to increase activity, school attendance or social involvement (Carter and Threlkeld, 2012; Gatchel et al., 2007).

Cognitive behavioral therapy is effective in terms of symptom reduction in a **group setting** (Kröner-Herwig and Denecke, 2002) and as a **single intervention** (Levy et al., 2010) for children with different pain complaints. Cognitive behavioral therapy elements are also applied in **internet-based interventions** with children with various pain problems (Palermo et al., 2009). Palermo and colleagues (2009) demonstrated that a group receiving internet-based cognitive behavioral therapy elements achieved a significantly greater reduction in pain-related disability and pain intensity than did a group only receiving standard medical care. Furthermore, cognitive behavioral therapy is effective in chronic pain with **underlying medical conditions**, such as juvenile idiopathic arthritis (Kashikar-Zuck et al., 2005; Kashikar-Zuck et al., 2012). Patients increase their ability to cope with pain and reduce disability and depressive symptoms (Kashikar-Zuck et al., 2012).

10

Second. Your brain has learned pain, it can also unlearn it. This works best if the brain is very busy with other things that distract it from the pain. Simple tricks often keep helping. Try thinking of a musician whose name begins with A. Have you got one? Good! Then think of one beginning with B. And with C...and D[3]...and you go right through the alphabet like this; we call it Distraction ABC. There are a whole lot of techniques like this. Some of them are only used by Indian fakirs in order to sit on beds of nails. They are hard to learn alone, so you need help with them. That's why pain therapists are there.

Pain and distraction

Pain memory needs to be altered to improve chronic pain conditions. At this point, the mechanism to modify those memory traces is unknown. One approach to temporarily suppress pain memory in the CNS is by competing stimulation such as TENS (Sandkühler and Lee, 2013). Another way seems to be **defocussing from pain**.

[3] Examples of the Distraction ABC in this movie are: A=Amy Winehouse, B=Blue Man Group, C=Christina Aguilera (Genie in a bottle)

Distraction from pain in children is effective for perception of *acute pain* stimuli (Chambers et al., 2009; DeMore and Cohen, 2005). Importantly, distraction does not work in all children; it is less effective when pain is experienced as threatening and the child generally has a tendency to catastrophize about pain (Verhoeven et al., 2012). Distraction in children with *chronic pain* is different. Children with chronic pain do not only need to distract from pain for a limited amount of time such as in an experimental setting. They need to find ways to **distract from pain for a longer time duration**. There are two different methods that can be applied. One is **mental distraction**. By activating different parts of the brain, e.g., by calculating or trying to remember things from the past, less activity is found in the somatosensory cortex (Bushnell et al., 1999; Hoffman et al., 2011). This effect of defocussing can also be achieved by activities (i.e., **physical distraction**) requiring attention. It is assumed that 'memory traces' become less salient when they are used infrequently. Strengthening other neuronal connections weakens existing ones.

Pain treatment focusing on distraction

Distraction is an easy cognitive-behavioral approach for pain control (Sieberg et al., 2012). Although the effectiveness of distraction differs between children, for example based on their tendency to catastrophize (Verhoeven et al., 2012), it should always be tried to see if it works in the specific individual. Sometimes children need to try different distraction tasks before they find the one that works for them. The benefit of distraction is that it can be applied everywhere and it does not require any tools besides the brain itself. Applying physical distraction, e.g., playing chess, drawing or playing football, further helps to reduce everyday impairment.

11

Third. Don't let chronic pain keep you from doing all the things in life that you want to do, the nice things as well as the harder ones. Be active in sports, go to school or to your apprenticeship program and try to achieve your goals, enjoy getting together with your friends. Acute pain often gets better if you take it easy for a short time, but unfortunately chronic pain just gets worse the more and longer you take it easy. So, be active and get your pain under control!

Pain-related impairment in everyday life

Many children with chronic pain tend to apply **passive coping strategies**, such as taking pain medication, behavioral disengagement, self-isolation, resting and activity avoidance (Walker et al., 2008; Walker et al., 1997). Sometimes this avoidance is unwittingly encouraged by health care providers. Passive pain coping is associated with disability, somatic symptoms and increased depression (Kaminsky et al., 2006; Simons et al., 2008; Walker et al., 2008; Walker et al., 1997). Especially in children with comorbid anxiety, a passive coping style may result in **severe disability** (Kaczynski et al., 2011). The impairment of everyday activities is one of the major problems in children with chronic pain. It **risks the child's normal development** and maintains the chronic pain condition. When children become more and more inactive, they have a stronger focus on pain (see 'Pain and distraction') and experience a general decrease in physical fitness.

One reason to avoid activity is the belief that pain gets better when the painful part of the body is rested. However, this is only true for acute pain, not for chronic pain. Another reason for inactivity is the **fear of experiencing pain** (Simons et al., 2014a). This fear easily develops into a vicious circle of fear and avoidance. The **Fear-Avoidance Model** of chronic pain postulates that the fear of pain plays a central role in the maintenance and exacerbation of chronic pain (Asmundson et al., 2012; Vlaeyen and Linton, 2000; 2012). According to this model, it is not the sensory experience of pain itself but the dysfunctional appraisals about pain and its consequences, such as **catastrophizing thoughts**, that increases pain-related fears. This leads to **avoidance behavior** to escape situations that may trigger pain. Through operant conditioning, this short-term reinforcement by the reduction of suffering associated with certain activities will cause the persistence of avoidance behavior and functional disability. Avoidance, however, is a maladaptive response if it persists; it leads to a **general decrease in activity and physical fitness**, as well as **increased fear** and other psychological consequences that contribute to disability and persisting pain (Asmundson et al., 2012; Vlaeyen and Linton, 2000; 2012). The pediatric specification of this model highlights the reciprocal relationship between the child's behavior and psychological responses and the parent's behavior and their psychological responses (Asmundson et al., 2012). The effects of various components of the pediatric Fear-Avoidance Model have been tested empirically (Asmundson et al., 2012; Simons and Kaczynski, 2012). Research, for example, demonstrates the influence of the child's pain-related anxiety and fear of pain on functional disability (Asmundson et al., 2012; Simons and Kaczynski, 2012). Furthermore, parental protective pain behavior is perceived by the child as a signal of parental fear or anxiety and is associated with the child's functional disability (Asmundson et al., 2012).

Treatment to reduce impairment in everyday life

Activity avoidance is mostly caused by **false beliefs**. The child needs to understand that r**est is only a functional coping strategy for acute pain**. In chronic pain treatment, appropriate activity does not entail any harm to the body; rather, inactivity makes the condition worse. Furthermore, the child needs to **overcome the fear of pain**. This can be achieved by overcoming avoidance. Only through this method can the child can learn that activity does not make the pain worse.

The reactivation of normal activity has a key function in pain treatment. Clinical studies show that the improvement of activity limitation precedes a decrease in pain intensity (Lynch-Jordan et al., 2014). Cognitive behavioral therapy and acceptance and commitment therapy aim to re-establish activity, including school attendance and social involvement (Carter and Threlkeld, 2012; Gatchel et al., 2007).

Acceptance and commitment therapy is a specific cognitive behavioral approach primarily targeting the belief system. It is based on the fact that certain **negative reactions toward pain**, such as negative thoughts or feelings and body sensations, **cannot be changed**. Acceptance and commitment therapy promotes acceptance of these negative reactions to facilitate engagement in meaningful activities even when they are painful or fear provoking (Hayes et al., 2006). By **accepting negative reactions**, patients are able to **distance** themselves from pain and distress and are more likely to perform activities and tasks that are meaningful and valued (Hayes et al., 2006). In a sample of 10- to 18-year-olds, this approach led to reduced pain-related disability and pain intensity; it further improved the perceived functional ability and quality of life and decreased the fear of pain (Wicksell et al., 2009).

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Let's see if we can put it all together in two sentences. Chronic pain is learned by the brain; lying down and taking it easy don't help! The best strategies for putting chronic pain behind you are: deal with current problems, unlearn chronic pain with distraction and get active again!
If you can't manage it on your own, get help!

The power of education

Psychoeducation is considered a **typical element of cognitive behavioral therapy** (Sieberg et al., 2012). However, it should be a **basic element of pain treatment for all professions**. A Dutch study showed that six sessions of education by a gastroenterologist are as effective as the same amount of cognitive behavioral therapy applied by a psychologist (Van der Veek et al., 2013). The **educational cartoon *'Understanding pain and what's to be done about it … In less than 10 minutes'*** can be used as one module in the education of pain patients. Basic knowledge regarding chronic pain and the management of a pain condition is taught. In a personal communication mode, any questions from the child can be discussed.

Multidisciplinary treatment of chronic pain

So far, effectiveness studies on the course of chronic pain treatment in children treated in primary care are rare. Only one project has analyzed the course of functional abdominal pain (Lisman-van Leeuwen et al., 2013; Spee et al., 2013). Of all children presenting to a general practitioner due to abdominal pain, approximately 40% experience chronic functional abdominal pain along with disability 12 months later (Lisman-van Leeuwen et al., 2013). Girls and older children have an increased risk of ongoing chronic pain, i.e., chronification (Lisman-van Leeuwen et al., 2013). This shows that only some children benefit from **standard primary care treatment**. Others may need **additional treatment modules**, such as comprehensive education, physiotherapy or additional psychotherapy. Others again may need a **specialized multidisciplinary pain treatment**.

For **children severely affected by chronic pain**, **multidisciplinary, multimodal pain treatment programs** that combine several modules have recently become a standard of care (Eccleston et al., 2014) and are offered in inpatient (Hechler et al., 2014), day-care (Eccleston et al., 2003; Logan et al., 2012) or less intense outpatient settings (Hechler et al., 2011). These programs suggest a structured combination of different modules and include professionals from several disciplines (Eccleston et al., 2003; Hechler et al., 2014; Maynard et al., 2009). The included modules and the treatment focus differ between treatment programs. For instance, a program explicitly aimed at children with musculoskeletal pain has more focus on physiotherapy (Eccleston et al., 2003) than does a program for children with various pain conditions (Hechler et al., 2014). Generally, the combination of treatment modules should **match the patient's needs** (Leo et al., 2011; Turk, 2005).

An intensive interdisciplinary pain treatment program may be indicated, especially in highly impaired chronic pain patients not responding to outpatient treatment (Hechler et al., 2014; Maynard et al., 2009; Zernikow et al., 2012b). These intensive pain programs involve all professions in the daily treatment. The treatment team interacts with the patient over a longer period of time and across various situations. For

severely impaired patients, this approach is effective not only for primary pain outcomes, such as pain-related disability and pain intensity but also for a reduction of emotional distress (Eccleston et al., 2003; Hechler et al., 2014; Logan et al., 2012). For less severely impaired patients, an outpatient approach seems to be sufficient and effective (Hechler et al., 2011).

Choice of pain treatment

There is **not a general recommendation** for the treatment of chronic pain in children and adolescents. It needs to be **matched to the patient's needs**. Several factors should be considered when making a treatment recommendation for a child with chronic pain (Gatchel et al., 2007; Turk, 2005; Wager et al., 2013): Is there a treatable physiological cause to the pain problem? How severe is the patient's impairment? Is the patient motivated for treatment? Which treatment approaches have been unsuccessful in the past? Which ones have been somewhat successful? Is the suggested treatment option available to the patient, e.g., does the patient's family have the financial and time resources to seek a specific treatment?

For less severe cases of chronic pain, a guideline for parents and patients may be sufficient:

- Dobe, Michael & Zernikow, Boris (2014). *How to Stop Chronic Pain in Children: A Practical Guide* (E-Book). Carl Auer International. http://www.carl-auer.com/program/978-3-8497-8005-0
- Krane, Elliot J. & Mitchell, Deborah (2005). *Relieve Your Child's Chronic Pain: A Doctor's Program for Easing Headaches, Abdominal Pain, Fibromyalgia, Juvenile Rheumatoid Arthritis, and More.* Fireside, ISBN: 0743262034
- Kuttner, Leora (2006). *A Child in Pain: How to Help, What to Do*. Hartley & Marks Publishers, ISBN: 0881791288
- Zeltzer Lonnie, K. & Blackett Schlank, Christina Conquering (2005). *Your Child's Chronic Pain: A Pediatrician's Guide for Reclaiming a Normal Childhood.* HarperResource, ISBN: 0060570172

For severe cases of chronic pain, a specialized treatment center should be contacted.

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