GENERAL INTRODUCTION
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Low back pain as health care problem

Low back pain (LBP) is an extremely common health problem and stands out as leading musculoskeletal disorder. A global burden of disease study from the year 2010 showed that LBP causes more disability than any other condition, and contributes to 10.7% of the total years lived with disability. Furthermore, LBP is ranked in the top ten in terms of overall burden (measured in disability-adjusted life-years) out of 291 conditions which were studied.

It is estimated that 50% to 80% of all adults will experience one or more LBP episodes during their lifetime. A recent systematic review reported that the total prevalence of LBP (regardless of the duration) was 31%. The highest prevalence of LBP, and especially chronic complaints, can be found in women and patients in the age of 40-80. It should be noted that most studies that estimated the prevalence of LBP were performed in the United States, Europe or Australia. Although some evidence is available, it is difficult to summarize the international literature on prevalence for a number of reasons: (1) no universally accepted definition about LBP is available; (2) consequently, the incidence and prevalence depend highly on the specific measurement tool used in a study; (3) reporting bias: patients tend to forget an episode of LBP (recall bias).

Costs of low back pain

The widespread problem of LBP has major social and public health consequences, but also an enormous economic impact in Western societies. The total direct and indirect costs of LBP in the Netherlands were estimated at €3.5 billion in 2007. Reaching a prevalence peak between the age of 40-50 years, LBP affects mainly the working population, in which LBP is the most expensive disease in terms of indirect costs due to sickness absence and work disability. Additionally, based on the demographic development, it is expected that the number of people with LBP will increase in the coming years.

In 2008, a systematic review of international LBP cost-of-illness studies was performed. Comparing the study results is difficult, because of different methodologies, diagnoses and classifications of LBP. Also, different healthcare and insurance systems, and different law and regulations play a role in the comparison of these studies. The review authors identified 27 LBP cost-of-illness studies. The largest components of direct
medical costs were inpatient services, pharmaceutics, and primary care. From studies conducted outside the United States, it appears that direct medical costs represent only a small portion of the total costs of LBP. The majority of the costs are caused by work absenteeism, suggesting that interventions that are able to reduce the length of disability and promote early return to work may present the opportunity for cost savings from a societal perspective.\textsuperscript{17}

A systematic review of prospective cohort studies in primary care showed that in the first three months, recovery of LBP is observed in 33\% of the patients, but one year after onset, 65\% of the patients still report pain.\textsuperscript{15} These patients with chronic (more than three months) symptoms are responsible for the majority of the healthcare and socio-economic costs.\textsuperscript{11} Patients with chronic LBP (CLBP) are characterized by a greater comorbidity and economic burden compared to patients without CLBP. The economic burden of CLBP can be attributed to greater health resource utilization and work absenteeism.\textsuperscript{16} This thesis will focus on the cost-effectiveness of an anaesthesiological pain treatment for patients with CLBP.

**Defining low back pain**

Although most people can imagine what LBP feels like, no unambiguous definition or classification is available. A commonly used definition for LBP: pain, muscle tension, or stiffness localised below the costal margin and above the inferior gluteal folds, with or without leg pain. As stated before, summarizing the nature and extent of LBP in numbers is complicated because many different classification systems are used to define and classify LBP. Examples of classification systems are: the International Classification of Primary Care (ICPC), the International Classification of Diseases (ICD), and a specific back pain classification system: The Quebec Task Force.\textsuperscript{18-20}

One classification that is commonly used in primary care distinguishes between ‘specific’ and ‘non-specific’ LBP. Specific LBP is defined as symptoms caused by a specific pathophysiologcal mechanism, such as hernia nuclei pulposi, infection, osteoporosis, rheumatoid arthritis, fracture or tumour. Non-specific LBP is referred to as symptoms without a clear specific cause. In primary care, triage is focused on excluding patients with specific LBP. By patient history and physical examination, the so called “red flags” (or indicators of possible specific underlying pathology, including nerve root problems\textsuperscript{4,21}) are assessed. In 80-90\% of the patients with LBP in primary care, the origin of LBP is unknown, that is, no specific underlying pathology can be identified, and consequently
these patients will be classified as having non-specific LBP.\textsuperscript{7,22-24} As previously stated, no reliable and valid classification system exists for most cases of non-specific LBP, but in clinical practice, as well as in the scientific literature, non-specific LBP is usually classified by the duration of the complaints. LBP is classified as follows: acute if it persists for less than six weeks, sub-acute if it persists between six weeks and three months, and chronic if it lasts longer than three months.

Most patients with non-specific LBP are treated in a primary care setting. If patients do not benefit from primary care and symptoms persist, patients will be referred to secondary care, i.e. the orthopaedic, neurologist, neurosurgeon or anaesthesiologist.

In secondary care several other classification systems are used. This thesis will focus on an anaesthesiological pain treatment for patients with CLBP provided in a secondary care setting, the pain clinic. In anaesthesiology, it has been suggested that at least some of the non-specific LBP can be classified according to noxious stimulation of structures in the lumbar spine. Suggested sources of (chronic) LBP are the zygapophysseal joints (facet joints), the sacroiliac (SI) joint or the intervertebral discs.\textsuperscript{25} The prevalence of LBP originating from the facet joints, SI-joints and discs varies widely across specialities and setting, and might be due to the variation in definition.

The facet joints (also known as zygapophysseal joints) allow flexion, extension and twisting motion of the spine, and contribute to the stability of each motion. The facet joints have first been described as source of pain by Golthwait et al. in 1911, after which Ghormley introduced the term ‘facet syndrome’ in 1933.\textsuperscript{26,27} Facet joint pain is defined as pain resulting from any integral structure of the facet joints, including the fibrous capsule, synovial membrane, hyaline cartilage surfaces and bony articulation.\textsuperscript{28} Based on various studies, the facet joint has been implicated as a source of LBP in 15% to 41% of the CLBP population and appears to increase with age.\textsuperscript{29-34}

The sacroiliac joints (SI-joints) are designed primarily for stability. The function includes the transmission and dissipation of truncal loads of the lower extremities, limiting x-axis rotation, and facilitating parturition.\textsuperscript{35} The International Association for the Study of Pain (IASP) made a criteria set for the diagnosis of SI-joint pain, including: the pain is localized in the region of the SI-joints, the pain can be reproduced by stress- and provocation tests of the SI-joints and selective infiltration of the SI-joints with a local anaesthetic decreases the pain. The SI-joints are responsible for approximately 10-40% of the referrals to a pain clinic of patients with LBP.\textsuperscript{35}
The intervertebral discs act as shock absorbers between each vertebra. Discogenic pain has the same clinical characteristics as lumbo-sacral radicular pain, characterized by referred pain, with or without sciatica symptoms and/or loss of function. The intervertebral discs are supposed to be responsible for a part of the symptoms in patients with CLBP although specific prevalence numbers are not available. Furthermore, it is common that the discs are not the single source of CLBP, but part of multiple sources that cause the pain.

Diagnosing chronic low back pain originating from the facet joints, sacroiliac joints and/or discs
Adequate treatment of patients with LBP requires an accurate diagnosis. Patient care can potentially be improved if the source of pain can be identified. A correct diagnosis can exclude patients from undergoing further invasive diagnostic procedures and treatments. This thesis will focus on the diagnosis of LBP originating from the facet joints, SI-joints and discs, or a combination thereof. A series of tests is used to diagnose LBP, including history taking, physical examination, psychosocial examination, imaging techniques and/or diagnostic blocks.

Triage
In anaesthesiologic pain clinics, several indicators in patient history and physical examination are being used to diagnose pain from the facet joints, SI-joints, or the discs. In 2007, Hancock et al. performed a systematic review of tests to identify the facet joint, SI-joint, or disc as the source of LBP. From this review, it appeared that only few studies on the diagnostic accuracy of clinical tests to identify the tissue source of LBP have been performed. Patients with pain originating from the facet joints are typically older, with patients younger than 50 years being more likely to present with discogenic pain. But so far studies have consistently failed to identify patient-reported activities that are associated with the presence of LBP originating from the facet joints. For that reason, a systematic review of patient history and physical examination for diagnosing facet joint pain in patients with LBP is included in this thesis (chapter 2). Characteristics for pain originating from the SI-joint include true and apparent leg length discrepancy, older age, inflammatory arthritis, previous spine surgery, pregnancy and trauma. Compared with facet-mediated and discogenic LBP, individuals with pain originated from the SI-joints are more likely to report a specific inciting event, and experience unilateral pain below L5. Although no single physical examination or historical
feature can reliably identify a painful SI-joint, studies suggest that three or more out of six provocation tests (compression test, distraction test, Patrick sign test, Gaenslen test, Thigh Thrust test, and Gillettest) can predict response to diagnostic blocks.\textsuperscript{37,40} There are no typical features for identifying the disc, but centralisation seems to be characterizing disc problems, and absence of degeneration on MRI reduced the likelihood of the disc as source of pain.\textsuperscript{38} Overall, the reliability of physical examination as well as the validity in clinical practice has been a matter of controversy.\textsuperscript{38,41}

If red flags are present, a range of additional tests to diagnose a specific cause of LBP becomes available. Additional methods that are used for diagnosing a specific cause of LBP include, for example, psychosocial examination, imaging techniques and diagnostic blocks.

\textit{Psychosocial examination}

Recently, there is an increased focus on psychosocial aspects in patients with LBP. Analogue to the introduction of the red flags for acute LBP in 1997, the concept 'yellow flags' was introduced.\textsuperscript{42} Yellow flags are psychosocial factors that appear to be predictive for the chronicity of LBP. Recognising psychosocial problems can decrease the chance of developing chronic complaints and require tailored treatments. Factors that can be introduced in the clinical assessment for the prognosis of CLBP are, for example, depression, anxiety, distress, somatisation and catastrophizing.\textsuperscript{8} If patients suffer from one (or more) of these psychological factors, it has been suggested to first direct treatment towards those factors before starting anaesthesiological treatment. This will be further specified in chapter 4.

\textit{Imaging techniques}

Computed Tomography (CT) and Magnetic Resonance Imaging (MRI) are able to show abnormalities in the spine. However, one must consider 25% false negatives and 25% false positives.\textsuperscript{8} Another limitation of imaging techniques is that only an indication can be given for the cause of pain, and the results are inconclusive. Because of conflicting results, many guidelines conclude that the evidence in the literature does not support the routine use of radiologic imaging to diagnose specific LBP.\textsuperscript{37} Also, the ability of radiologic imaging to predict response to diagnostic blocks has been conflicting at best.\textsuperscript{43-46} For these reasons, no imaging techniques are included in the diagnosis of patients included in the trials presented in this thesis (chapter 4 through 7).
Diagnostic blocks

The most commonly used diagnostic test in anaesthesiology, which is also recommended in the Dutch guideline for anaesthesiology, is the diagnostic block. This can be both a block of the medial branch of the dorsal ramus, or an intra-articular block. The rationale for these blocks is that it will anaesthetise a painful facet joint or SI-joint for the duration of the anaesthetic effect, whereas an anaesthetic blockade of a non-painful joint will not diminish the pain. However, there is a wide variation in the use of these diagnostic blocks. In general, pain reduction of 50% or more implicates in clinical practice that the anaesthetised joint is the source of the pain, but other thresholds are used, ranging from ‘good or equivocal response to a local anaesthetic injection into and around the appropriate painful joints’ to ‘at least 95% of pain relief of at least one component of their pain after three separate diagnostic blocks with a local anaesthetic solution’. Also, the ideal number of blocks is controversial. Performing multiple diagnostic blocks will decrease the false-positive rate, but will result in an unavoidable increase in the number of false-negative blocks. Due to a lack of gold standard, studying the validity of diagnostic blocks is difficult. Despite the chance of false-positive and false-negative tests, these diagnostic blocks are currently the best tests available for diagnosing LBP originating from the facet joints and SI-joints, and for predicting the success of radiofrequency denervation procedures.

The current standard for diagnosing discogenic pain is pressure-controlled provocative discography using strict criteria and at least one negative control level. Stimulation of the disc is a procedure which is developed to identify the painful disc. It concerns the introduction of a needle into the nucleus pulposus of the target disc in which contrast fluid is injected with the purpose to expand the disc and provoke the pain. A full description is provided in the article of Kallewaard et al., 2010.

In this thesis, we will present three pragmatic trials (chapter 4 through 7), in which we used at least 50% pain reduction after a diagnostic block, or a positive provocative discography as final diagnostic criteria for LBP originating from the facet joints, SI-joints or discs.

Treating chronic low back pain originating from the facet joints, sacroiliac joints and/or discs

For patients with non-specific LBP, many treatments are available, such as: advice to stay active, analgesics, acupuncture, back schools, exercise therapy, graded activity,
manipulation, massage, muscle relaxants, NSAIDs, TENS and traction. Despite the wide variety of non-surgical treatments that are commonly used and prescribed for LBP, only the effectiveness of exercise therapy and multidisciplinary rehabilitation for CLBP is supported by high quality evidence.\textsuperscript{50-52}

Recently performed systematic literature reviews show high quality evidence that multidisciplinary treatments are more effective than mono-disciplinary treatments and usual care to decrease pain and improve functional status in patients with CLBP.\textsuperscript{52-54}

There is no consensus regarding the definition of a multidisciplinary treatment. Kamper et al\textsuperscript{52} defined multidisciplinary treatments as interventions that involve a physical component (for example an exercise programme), and at least one other element from the bio-psychosocial model, that is psychological (for example handling stress), social and occupational (for example work). The intervention programme had to be delivered by clinicians from different disciplines, that is, a minimum of two healthcare professionals from different professional background had to be involved in the intervention delivery. All components of the intervention had to be offered as an integrated programme, and involve communication between the providers who are responsible for the components.\textsuperscript{52}

This thesis will further focus on an anaesthesiological pain treatment, as part of a multidisciplinary treatment, for CLBP originating from the facet joints, SI-joints, and/or discs: radiofrequency denervation.

**Radiofrequency denervation**

Radiofrequency (RF) denervation is one of the minimal invasive treatment options in a multidisciplinary setting. RF denervation is performed by pain specialists for patients with mechanical CLBP, defined as LBP presumably originating from the facet joints, SI-joints, discs or a combination of these. In RF denervation, a RF generator produces an alternating current (frequency, 250 to 500 kHz) through an electrode, thereby inducing ionic movements in the tissue directly surrounding the active tip. This leads to molecular friction and heating of the tissue within a limited distance of the electrode.\textsuperscript{55} Since Shealy et al published an article on RF denervation of the lumbar facet joints in 1976, RF denervation procedures have been modified and are nowadays frequently used by anaesthesiologists in the management of patients with CLBP originating from the facet joints, SI-joints or discs.\textsuperscript{56-65} Different RF denervation techniques are available. A short summary of the techniques which are commonly used for the treatment of the facet joints, SI-joints or discs and used in the trials presented in this thesis (chapter 5 through
Technique facet joint radiofrequency denervation (chapter 5 and 7):¹⁵,³⁷

- A C-arm image intensifier is positioned in a slightly (10–15°) oblique position to identify skin entry points with the patient in prone position. A 22 G SMK needle with a 10-mm active curved tip is introduced at each entry point. The position of the cannula is checked on the lateral and AP fluoroscopic projection. The depth is adjusted until the tip of the cannula was at the level of a line connecting the posterior aspects of the intervertebral foramen. Sensory stimulation was positive if muscle contraction occurred below 0.6V. Second stimulation at 2 Hz is used in which contraction of the musculus multifidus and no leg contractions should occur. Once the position of the electrode was satisfactory, 1-2 ml per level ml 2% lidocaine is injected and a 90°C 90 seconds RF lesion is made of the medial ramus dorsalis of L3-4, L4-5, and L5-S1.

Technique sacroiliac joint radiofrequency denervation (chapter 6 and 7):

- Cooled RF technique:³⁷,⁶⁶,⁶⁷ under C-arm fluoroscopy a P/A view of the foramina of S1, S2 and S3 is obtained. A 25G needle is placed as reference point along the inside lateral wall of each foramen, with the tip at the opening of each foramen. An Epsilon ruler is used together with the reference needles as landmarks for the lesions. Using the introducer, stylet and probe provided by the manufacturer RF lesions are made at a maximum temperature of 60°C for 2.5 minutes per lesion.

- Palisade Technique:¹⁵,³⁷,⁶⁸ is performed by drawing a cranial-caudal line between the lateral aspect of the sacral foramina and the SI-joint line. Under lateral fluoroscopic view 6 20G cannula with 10mm active tips are placed parallel to each other, 10mm apart and perpendicular to the sacrum. Stimulations to 2.0V are done to be sure there is no motor response. Eight bipolar lesions (90°C for 90 seconds per lesion) are made using adjacent parings of the cannulas.

- Simplicity III Probe:¹⁵,³⁷,⁶⁹ is a multi-electrode radiofrequency probe, which is inserted at the lateral, inferior border of the sacrum, 10mm below the S4 foramen under fluoroscopic view. The electrode probe is advanced in a cephalad direction along the sacrum, lateral of the foramina, medial to the sacroiliac joint and ventral to the ileum. Using A/P and lateral fluoroscopy the correct position of the electrodes are checked and the RF lesion (85°C for 90 seconds per step) is made.
Technique minimal invasive intradiscal treatment (chapter 7):

- **IDET**:\textsuperscript{15,37} Using fluoroscopic control, with the patient prone on the operating table, a needle is passed into the injured disc via the side, with the fewest symptoms. With the needle in the right place, the catheter containing the heating coil was carefully manipulated inside the disc to treat the injured area. The heating generator is connected and the temperature inside the disc is raised to 90°C in 12 minutes, and maintained 90°C for another four minutes.

- **Biacuplasty**:\textsuperscript{15,37} Two internally cooled 17 G needles are inserted at the level of the annulus fibrosis. Two RF currents are inserted to generate bipolar configuration. The ideal temperature profile is 55/60°C in the inner posterior disc decreasing to 45°C in the peripheral edge of the posterior disc.

**Rationale of this thesis**

RF denervation is a commonly used treatment for patients with CLBP in the Netherlands and internationally. However, the evidence of efficacy is limited and no data are available for the effectiveness in a usual care setting. There is consensus among anaesthesiologists, that RF denervation is effective for patients with pain presumably resulting from single sources: facet joint, SI-joint, disc, or a combination of these.\textsuperscript{15,37} But, available systematic reviews concluded that there is no strong evidence that supports the effectiveness of RF denervation in patients with CLBP.\textsuperscript{39,51,70-73} Most likely this is due to a lack of randomised controlled trials (RCTs) with a low risk of bias and adequate sample size.\textsuperscript{39,74} A systematic review issued by the Dutch Health Insurance Council (CVZ) showed that the effectiveness of RF denervation for the total group of patients with CLBP is unclear and the cost-effectiveness unknown.\textsuperscript{75} Based on this review, the Ministry of Health in The Netherlands decided to fund a project evaluating the effectiveness and cost-effectiveness of RF denervation for patients with CLBP. This project is the main topic of this thesis.

In this thesis, current reviews about diagnostics and interventions for patients with CLBP were updated based on available published studies. Moreover, the effectiveness and cost-effectiveness of RF denervation was assessed mainly in a series of RCTs and finally the generalizability of these results was investigated. Based on the studies on the effectiveness- and cost-effectiveness presented in this thesis, the Zorginstituut Nederland (Dutch Health Insurance Council) will advise the Ministry of Health in The Netherlands on the reimbursement of RF denervation for CLBP within the Dutch public health insurance system.
Objectives of this thesis
The aim of this thesis is to contribute to the development of a sound evidence base on: 1) the diagnostic accuracy of patient history and physical examination for CLBP originating from the facet joints; 2) the effectiveness and cost-effectiveness of RF denervation for CLBP; and 3) the generalizability of these results. This will be done by systematically reviewing the current literature about diagnosing CLBP patients, systematically reviewing the current literature about the effectiveness of RF denervation for patients with CLBP, generating new evidence for the effectiveness and cost-effectiveness of RF denervation for CLBP, and assessing the generalizability of these results.

Outline of this thesis
Chapter 2 describes a systematic review of the diagnostic accuracy of patient history and physical examination for diagnosing CLBP from the facet joints.

Chapter 3 describes the systematic review of the effectiveness of radiofrequency denervation for patients with CLBP.

Chapter 4 through 7 contain the design (chapter 4) and three RCTs of the effectiveness and cost-effectiveness of RF denervation for CLBP originating from the facet joints (chapter 5), the SI-joints (chapter 6), and a combination of the facet joints, SI-joints and discs (chapter 7).

Chapter 8 describes a comparison between an observational study and a RCT on the agreement in effect of RF denervation for patients with CLBP originating from the facet joints or SI-joints.

Chapter 9 is a general discussion of the main findings and strengths and limitations of all studies in this thesis. These results will be compared to current literature, and research- and practical implications will be provided.
REFERENCES


