Priority Medicines for Europe and the World
"A Public Health Approach to Innovation"

Update on 2004 Background Paper

Background Paper 6.24
Low back pain

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15 March 2013

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Executive Summary

Low back pain is a very common health problem amongst population and a major cause of disability that affects work performances and well-being. Low back pain can be acute, subacute or chronic. Though several risk factors have been identified such as occupational posture, depressive moods, obesity, body height or age, the causes of the onset of low back pain remain obscure and diagnosis difficult to make.

Low back pain affects children to elderly and is a very common reason for medical consultations. The Global Burden of Disease (GBD) 2010 estimated that low back pain is amongst the top ten DALYs (disability-adjusted life years) causing diseases and injuries.

Socioeconomic impacts are considerable in terms of work loss. Estimating the incidence of low back pain is difficult as the incidence of first-ever episodes of low back pain is already high by early adulthood and symptoms tend to recur over time. The lifetime prevalence of non-specific (common) low back pain is estimated at 60–70% in industrialized countries (one-year prevalence 15–45%, adult incidence 5% per year). The prevalence rate for children and adolescents approaches that seen in adults. It then increases and peaks between ages 35 and 55. As the world population ages, low back pain will increase substantially due to the deterioration of disc bones.

Low back pain (LBP) is the leading cause of activity limitation and work absence throughout much of the world, and it causes an enormous economic burden on individuals, families, communities, industry and governments. Several studies have been performed in Europe to evaluate the social economic impact of low back pain. In the United Kingdom, low back pain was identified as the most common cause of disability in young adults: with more than 100 million work days lost per year. In Sweden a survey suggested that low back pain increased the number of work days lost from seven million in 1980 to four times that (28 million) by 1987; however, authors state that social compensation systems might account for some of this increase. In the United States an estimated 149 million days of work per year are lost because of LBP. The condition is therefore costly, with total costs estimated to be between US$ 100 and US$ 200 billion annually, two-thirds of which are due to decreased wages and productivity.

At present low back pain is being treated with analgesics, alternatively rehabilitation can be prescribed. Causes of LBP are rarely being addressed. Disc surgery remains the last option when all other strategies have failed.

European Guidelines for the Management of Chronic non-specific Low Back Pain have been developed by experts in the field and provide guidance for diagnosis and treatment.
The European Commission is also funding the project 'Genodisc' to identify risks factors, biomarkers and improve diagnosis of low back pain.

Research performed these past few years on biomaterial, growth factors or stem cells in the intra vertebral disc space brings new hopes for delaying the time before surgery.

Also, 3D imaging and using more resistant biomaterials for the development of more adapted disc prosthesis should help better addressing the issue of low back pain.

1. Introduction

Low back pain (LBP) is a very common health problem and affects all ranges of the population, however, its burden is often considered trivial. Low back pain occurs in similar proportions in all cultures, interferes with quality of life and work performance, and is the most common reason for medical consultations. Few cases of back pain are due to specific causes; most cases are non-specific.

As part of the Global Burden of Disease Study (GBD) 2010, the Expert Group showed that low back pain is among the top ten high burden diseases and injuries, with an average number DALYs (disability-adjusted life years) higher than HIV, road injuries, tuberculosis, lung cancer, chronic obstructive pulmonary disease and preterm birth complications.[1]

1.1 Common symptoms experienced by people with low back pain

Low back pain is defined as pain and discomfort below the the costal margin and above the inferior gluteal folds, with or without referred leg pain. It may be experienced as aching, burning, stabbing, sharp or dull, well-defined, or vague with intensity ranging from mild to severe. The pain may begin suddenly or develop gradually. Non-specific low back pain is defined as low back pain not attributed to recognisable, known specific pathology (e.g. infection, tumour, osteoporosis, ankylosing spondylitis, fracture, inflammatory process, radicular syndrome or cauda equina syndrome). This background paper does not deal with specific and attributable low back pain that results from trauma, osteoporotic fractures, infections, neoplasms, and other mechanical derangements as such causes can be identified and must be dealt with appropriately.

1.2 Low back pain subtypes

Substantial heterogeneity exists among low back pain that can be classified into three categories: chronic, acute and subactute back pain.[1]

- **Chronic back pain** (CLBP) is defined as low back pain persisting for longer than 7-12 weeks, or after the period of healing or recurring back pain that intermittently affects an individual over a long period of time.
- **Acute back pain** is defined as low back pain lasting for less than 12 weeks.
- **Subacute pain** is defined low back pain lasting between six weeks and three months.

While many patients with LBP recover quickly, LBP commonly follows a recurrent course, with exacerbations occurring over time.

1.3 Causes of low back pain

Low back pain can be due to a number of factors including: individual characteristics, working conditions such as heavy physical work, awkward static and dynamic working postures, as well as manual handling and lifting, lifestyle factors and psychological factors.
A minority of cases of low back pain results from trauma to the back, osteoporosis or prolonged corticosteroid use. Relatively less common are vertebral infections, tumors and bone metastasis.

The exact source of low back pain is often difficult to identify. Non-specific back pain is thus a major problem for diagnosis and treatment. Low back pain can be produced by different tissues including muscles, soft connective tissue, ligaments, joint capsules cartilage, and blood vessels. These tissues may be pulled, strained, stretched or sprained and rapidly produce an inflammation with the release of inflammatory chemicals such as cytokines and/or chemokines. These chemicals stimulate the surrounding nerve fibers resulting in the sensation of pain. Inflammatory process perpetuates the process of swelling. A reduction on blood supply to the affected area may occur so that nutrients and oxygen are not optimally delivered and removal of irritating byproducts of inflammation is impaired, creating thereby a feedback loop of inflammation and pain.[2]

The diagnosis of low back pain is complicated because of the complex nature of pain and the nonstandardized approach by physicians to clinical decision making.

1.4 Risk Factors

In approximately 5–15% low back pain can be attributed to a specific cause such as an osteoporotic fracture, neoplasm or infection.[1,2] For the remaining 85–95% of cases, the specific cause of low back pain is unclear.[3,4]

1.4.1 Psychological

Psychosocial factors appear to play a substantial role in the frequency of low back pain. Persons with negative affectivity, low levels of social support in the workplace, low level of job control, high psychological demands and work dissatisfaction as well as stress, anxiety, depression are more prone to low back pain.

1.4.2 Body height and weight

Studies demonstrated an association between body height and LBP. Results suggest that being tall is a predictor for back surgery.[2] Taller people appear to have more potential risk for disk instability under external loading.[3] Alterations of facet joints in patients with lumbar disc hernia were shown to be more evident in taller patients.[4]

Several studies have clearly shown that people with high BMI are more prone to LBP. A meta-analysis including 33 studies showed that obesity was associated with increased prevalence of LBP in the past 12 months (pooled odds ratio, OR = 1.33 (95% CI: 1.14-1.54).[5]

1.4.3 Occupational

In the world, 37% of LBP are attributed to occupation.[6] Professionals who are exposed to vibrations, or long standing positions such as health-care workers, occupational drivers, and construction workers are more prone to LBP. Low back pain is associated with working postures which included bending heavily with one's trunk, bending and twisting simultaneously with one's trunk, a bent and twisted posture for long periods, and making repetitive movements with the trunk. This finding was consistent with other studies.[7,8,9,10,11,12] Repetitive twisting or bending with the trunk, as well as prolonged twisting or bending, can increase the risk of LBP because of unrecovered fatigue. To some extent, these results reflect

that LBP risk may be higher in some industries, in which the workers need to take heavy physical work, or work with awkward posture.

Sociodemographic factors, such as age, lifestyle factors, such as smoking and physical conditioning are other potential risk factors for low back pain.[7]

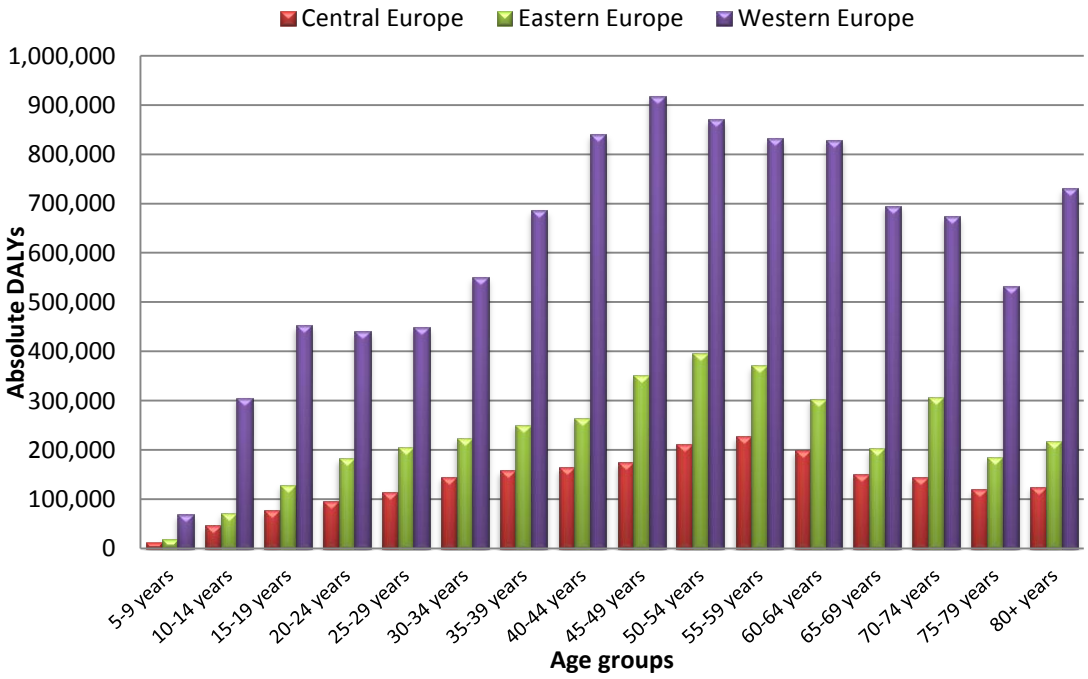
2. Size and Nature of Disease Burden

2.1 Incidence and prevalence

Low back pain is well documented to be an extremely common health problem; WHO, whose Community Oriented Programme for the Control of Rheumatic Disease showed convincingly that it is present in similar proportions in several countries. Until recently it was largely thought of as a problem confined to western countries but research performed during the last decade clearly showed that low back pain is also a major problem in low- and middle-income countries.[13]

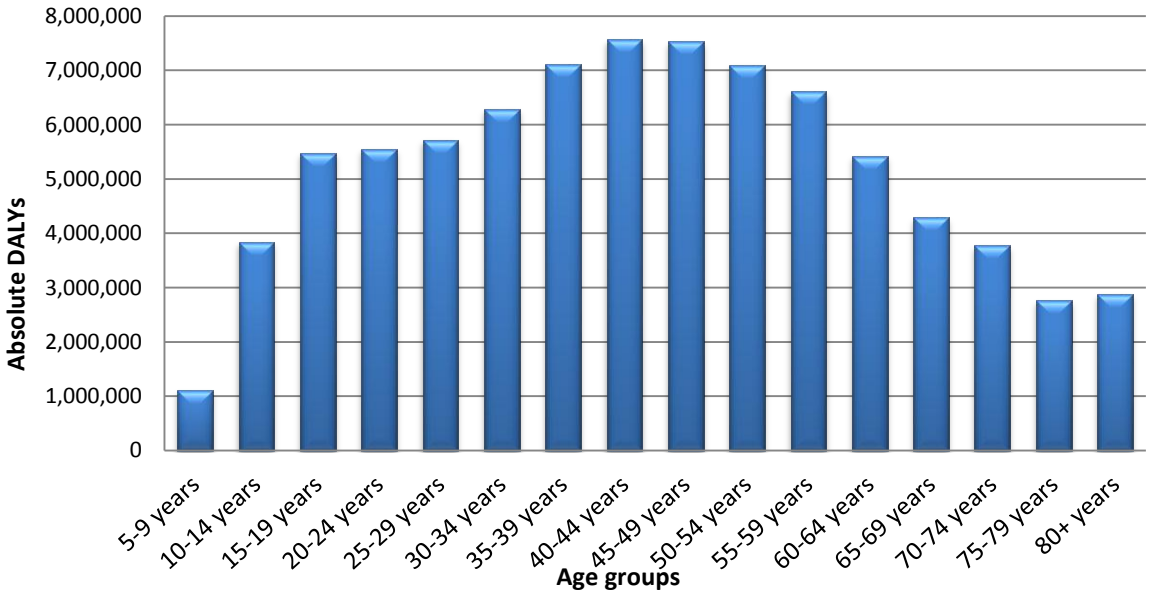
As part of the Global Burden of Disease Study (GBD) 2010, Expert Group showed that low back pain is among the top ten high burden diseases and injuries, with an average number of DALYs (disability-adjusted life years) higher than HIV, road injuries, tuberculosis, lung cancer, chronic obstructive pulmonary Disease and preterm birth complications.[1]

Figure 6.24.1: Absolute DALYs caused by low back pain by age group and European region



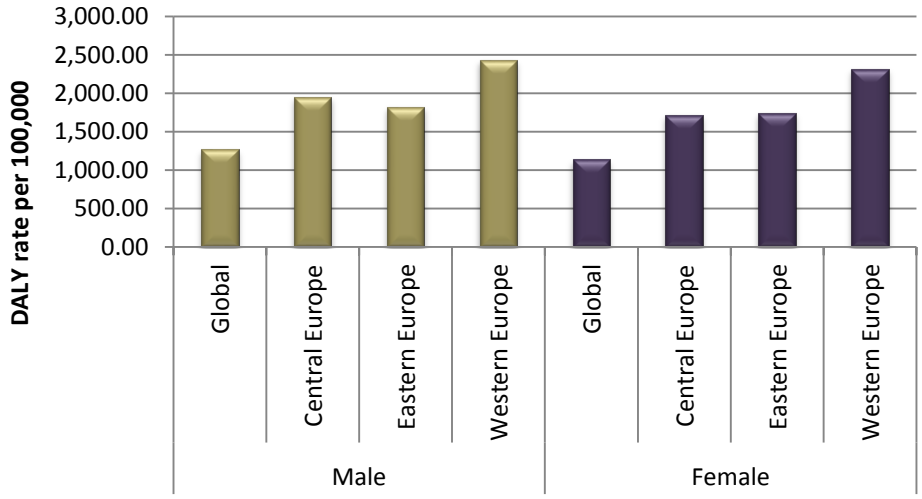
Source: Institute of Health Metrics and Evaluation (IHME)
http://ghdx.healthmetricsandevaluation.org

Figure 6.24.2: Absolute DALYs caused by low back pain in the world, by age group



Source: Institute of Health Metrics and Evaluation (IHME)
http://ghdx.healthmetricsandevaluation.org

Figure 6.24.3: DALY rate by European region and gender



Source: Institute of Health Metrics and Evaluation (IHME)
http://ghdx.healthmetricsandevaluation.org

Estimating the incidence of low back pain is difficult as the incidence of first-ever episodes of low back pain is already high by early adulthood and symptoms tend to recur over time. The lifetime prevalence of non-specific (common) low back pain is estimated at 60–70% in industrialized countries (one-year prevalence 15–45%, adult incidence 5% per year). The prevalence rate for children and adolescents approaches that seen in adults.[14,15] It then increases and peaks between ages 35 and 55.[16,17]

While substantial heterogeneity exists among low back pain epidemiological studies show that low back pain country prevalence ranges from 1.0% to 58.1% (mean: 18.1%; median: 15.0%), and one-year prevalence from 0.8% to 82.5% (mean: 38.1%; median: 37.4%).[18] Due to the heterogeneity of the data, mean estimates need to be interpreted with caution. Longitudinal studies, which measure incidence, are more expensive than cross sectional studies, which measure prevalence. As a result, there is a substantial amount of literature on the prevalence of low back pain, but much less information on low back pain incidence and remission.

Table 6.24.1: Incidence of low back pain in the general population.

One-year incidence of low back pain in the general population.

Citation	Country	Age range (years)	Inclusion criteria at baseline	Case definition[a]	Incidence (%)	Standard error (%)	Risk of bias
Incidence of number of people who have a first-ever episode							
Biering-Sorensen [21]	Denmark	30–60	Never had low back pain	Low back pain over past year	6.3[c]	0.8	Low
Croft et al. [24]	United Kingdom	18–75	Never had low back pain	Low back pain over past year	15.4[c]	0.9	Moderate
Mustard et al. [30]	Canada	21–34	Never had back pain >1 day	Back pain >1 day over past year	7.5[c]	0.6	High
Incidence of number of people who have any episode (first-ever or recurrent)							
Al-Awadhi et al. [28]	Kuwait	15–99	No low back pain at baseline	Low back pain over past year	1.5[b]	0.2	High
Cassidy et al. [23]	Canada	20–69	No low back pain for 6 months prior to baseline	Low back pain over past year	18.9[b]	2.2	Low
Croft et al. [24]	United Kingdom	18–75	No low back pain at baseline	Low back pain over past year	36.0[c]	1.2	Moderate
Hestbaek et al. [20]	Denmark	30–50	No low back problems over past year	Low back problems over past year	19.3[c]	1.7	Low
Jacob et al. [25]	Israel	22–70	No activity-limiting low back pain >1day over past month	Activity-limiting low back pain >1day over past year	18.4[c]	2.7	Moderate

[a] Definition of a new episode of low back pain.
[b] Age and sex- standardized.
[c] Unadjusted.

Source: D. Hoy et al. Best Practice & Research Clinical Rheumatology (2010).[24]

In many instances, people with low back pain will go on to have recurrent episodes that may last longer and cause greater disability. Consequently, low back pain can become chronic. In the majority of cases, true remission in the sense that a single episode of low back pain never recurs, is rare.

Table 6.24.2: Prevalence of low back pain by age and country.

The unadjusted prevalence of low back pain in the general population, by country.

Citation	Country	Age range (years)	Prevalence (%)	Standard error (%)	Risk of bias
Point prevalence					
Walker et al. [66]	Australia	18–99	25.6	1.00	Low
Skovron et al. [67]	Belgium	15–99	33.0	0.76	Low
Cassidy et al. [68]	Canada	20–69	28.7	1.35	Low
Hoy et al. [13]	China	15–99	34.1	3.00	Low
Biering-Sorensen [21]	Denmark	30–60	13.7	0.87	Low
Bredkjaer [69]	Denmark	16–99	12.0	0.47	Low
Kohlmann et al. [70]	Germany	25–74	39.2	3.41	Low
Mahajan et al. [71]	India	15–99	8.4	0.87	Low
Mohseni-Bandpei et al. [72]	Iran	11–14	15.0	0.51	Low
Carmona et al. [73]	Spain	20–99	14.8	0.83	Low
Andersson et al. [74]	Sweden	25–74	23.2	1.05	Low
Harkness et al. [75]	United Kingdom	18–64	18.0	0.88	Low
Hillman et al. [76]	United Kingdom	25–64	19.0	0.69	Low
One-week prevalence					
Grimmer et al. [77]	Australia	13–13	7.8	1.29	Low
Haq et al. [78]	Bangladesh	15–99	20.1	1.11	Low
Davatchi et al. [79]	Iran	15–99	14.8	0.50	Low
Al-Awadhi et al. [80]	Kuwait	15–99	9.5	0.34	Low
Cardiel et al. [81]	Mexico	18–99	6.3	0.49	Low
Chaiamnuay et al. [12])	Thailand	15–99	11.7	0.92	Low
Jones et al. [58]	United Kingdom	10–16	15.6	1.62	Low
Minh Hoa et al. [82]	Viet Nam	16–99	11.2	0.68	Low
One-month prevalence					
Heistaro et al. [83]	Finland	30–59	49.5	0.66	Low
Stranjalis et al. [84]	Greece	15–99	31.7	1.47	Low
Kristjansdottir [85]	Iceland	11–16	34.0	1.03	Low
Croft et al. [86]	United Kingdom	18–75	39.0	0.73	Low
Watson et al. [87]	United Kingdom	11–14	24.0	1.15	Low
Three-month prevalence					
Miro et al. [88]	Spain	65–99	43.9	2.04	Low
One-year prevalence					
Lau et al. [89]	China, Hong Kong	18–99	21.7	2.30	Low
Hestbaek et al. [20]	Denmark	30–50	56.0	1.37	Low
Hestbaek et al. [90]	Denmark	12–22	32.4	0.48	Low
Taimela et al. [91]	Finland	7–16	9.7	1.23	Low
Demyttenaere et al. [92]	Spain	18–99	20.0	1.23	Low
Demyttenaere et al. [92]	Ukraine	18–99	50.3	1.70	Low
Walsh et al.; Demyttenaere et al. [92,93]	United Kingdom	20–59	36.1	0.93	Low

Source: D. Hoy et al. Best Practice & Research Clinical Rheumatology (2010).[24]

Studies have found the incidence of low back pain is highest in the third decade, and overall prevalence increases with age until the 60–65 year age group and then gradually declines.

China is the world's largest developing country with a huge number of occupational populations. The prevalence rates of LBP among the Chinese occupational population were from 26.4% to 84.6%. The latest LBP data obtained from articles written in English in the mainland of China showed that the 1-year prevalence of LBP in rural working populations was 64%.[19]

2.2 Economic impact: the global societal cost of low back pain

Low back pain is the leading cause of activity limitation and work absence throughout much of the world, and it causes an enormous economic burden on individuals, families, communities, industry and governments.[20,21,22,23,24,25,26,27]

Several studies have been performed in Europe to evaluate the social economic impact of low back pain. In the United Kingdom, low back pain was identified as the most common cause of disability in young adults: with more than 100 million work days lost per year.[28] In Sweden a survey suggested that low back pain increased the number of work days lost from seven million in 1980 to four times that (28 million) by 1987; however, authors state that social compensation systems might account for some of this increase. Research scientists found that 35–37% of workers experienced back pain in the month before their survey, with a peak in the incidence seen among those aged 49–59 years.[29] Low back pain is the second most common cause of disability in adults from the USA and a common reason for lost work days. An estimated 149 million days of work per year are lost because of LBP.[30,31,32,33] The condition is costly, with total costs estimated to be between $100 and $200 billion annually, two-thirds of which are due to decreased wages and productivity.[34,35]

Many patients have self-limited episodes of acute low back pain and do not seek medical care.[36] However, up to one third of patients report persistent back pain of at least moderate intensity one year after an acute episode, and one in five report substantial limitations in activity.[37]

Approximately 5% of the people with back pain disability account for 75% of the costs associated with low back pain.[38]

3. Control Strategy

3.1 Diagnosis

Guidelines for the management of acute non specific low back pain in primary care were developed within the framework of the COST ACTION B13 'European Guidelines for the Management of Low Back Pain', issued by the European Commission, Research Directorate-General, Department of Policy, Co-ordination and Strategy. The guidelines were developed by experts in the field of low back pain research in primary care who had been involved in the development of national guidelines for low back pain in their countries. The primary objective of these European evidence-based guidelines was to provide a set of recommendations that can support existing and future national and international guidelines or future updates of existing guidelines.

Diagnosis depends on physical examination. For most patients pain a thorough history taking and brief clinical examination to exclude any other serious disorders causing back pain (tumor, infection, fracture) is sufficient. Low back pain is categorised based on pain distribution, pain behaviour, functional disability and clinical signs.[7]

Clinical examination can be followed by magnetic resonance imaging, radionuclide scanning, computed tomography, and/or radiography. Recent studies showed however that for adults younger than 50 years of age with no signs or symptoms of systemic disease, diagnostic imaging does not improve treatment of low back pain. For patients 50 years of age and older or those whose findings suggest disc space narrowing, osteophytes and sclerosis, plain radiography and simple laboratory tests are sufficient to make a diagnosis. The authors concluded that advanced imaging should be reserved for patients who are considering surgery or those in whom systemic disease is strongly suspected (level A).[39] The risks of the high doses of radiation in X-rays of the lumbar spine do not justify routine use.

The lack of effective biomarkers makes LBP is difficult to diagnose, track progression of, and monitor improvements in the patient's condition. These issues are especially important to address because low back pain is a condition that requires long-term careful management, so detailed information regarding the effectiveness of therapies is essential.

Future research should be directed at addressing this gap in diagnostics and biomarkers which will improve disease monitoring and allow the development of therapies that can reverse the progression of this high-burden condition.

3.2 Management of low back pain

3.2.1 Analgesics

Currently, the main treatment goal for low back pain is to control the pain, maintain function and prevent exacerbation. Low back pain is being treated with analgesics such as paracetamol, NSAIDs or weak opioids. The difficulty is to manage pain when it becomes chronic because of the side events of these medicines on the long term. For example, treatment with opioids can become problematic on a long term basis because of the possible risk of addiction. To reduce the risk of dependence, slow release forms of opioids are preferred to immediate release opioids for the treatment of chronic back pain.[40,41]

Table 6.24.3: Classification of non steroidal anti inflammatory medicines.

Compounds	Products
Salicylates	Aspirin, diflusinal, salsalate
Propionic acid derivatives	Ibuprofen, naproxen, fenoprofen, ketoprofen, flurbiprofen, oxaprozin, loxoprofen
Enolic acid (oxicam) derivatives	Piroxicam, meloxicam, tenoxicam, droxicam, lornoxicam, isoxicam, phenylbutazone
Fenamic acid derivatives	Mefenamic acid, meclofenamic acid, flufenamic acid, tolfenamic acid
Alkanones	Nabumetone
Acetic acid derivatives	Indomethacin, sulindac, etodolac, ketorolac, diclofenac, nabumetone
Diaryl heterocyclic compounds	Celecoxib, valdecoxib, rofecoxib, etoricoxib
Sulphonanilides	Nimesulide
Others	Licofelone

Source: Kuritski and Samraj 2012.[40]

Management of low back pain involves musculoskeletal rearrangement through manipulations by various health care providers. These include physiotherapists, manual therapists, chiropractors, exercise therapists.[7]

According to the European Guideline for the Management of Chronic non-specific Low Back Pain:[7]
"There is moderate evidence that manipulation is superior to sham manipulation for improving short-term pain and function in CLBP (level B).

• *There is strong evidence that manipulation and GP care/analgesics are similarly effective in the treatment of CLBP (level A)*

• *There is moderate evidence that spinal manipulation in addition to GP care is more effective than GP care alone in the treatment of CLBP (level B).*

• *There is moderate evidence that spinal manipulation is no less and no more effective than physiotherapy/exercise therapy in the treatment of CLBP (level B).*

• *There is moderate evidence that spinal manipulation is no less and no more effective than back-schools in the treatment of CLBP (level B)."*

An active approach is the best treatment option for acute low back pain. Prolonged bed rest should be avoided as it may increase the risk of chronicity.

Massage, ultrasounds, heat/cold, electrotherapy, laser and traction can substantially improve in certain cases the treatment of low back pain.[7]

3.2.2 Surgery and intradiscal injection

Often, surgery is offered as an ultimately desperate last measure, but almost always it is unjustifiable and usually fails to provide permanent relief.[42] Disc herniation and spinal canal narrowing are common in most of the population in their later years, and in most cases, such conditions are not responsible for the pain. Patients undergo surgery, but only rarely are operations successful in alleviating the pain definitively.[43]

Treatment of intervertebral disc herniations and degenerated discs is still spinal fusion. Mechanical prostheses, which are currently implanted, have medium outcome success and have relatively high re-operation rates. Intradiscal injections of steroids or glucocorticoids have been used to treat discogenic pain or reduce inflammation in the disc. Injections can be potentially dangerous and cause infection (discitis or spondylodiscitis).[44]

3.2.3 Neuro-reflexotherapy intervention (NRT)

Neuro-reflexotherapy intervention (NRT) is defined as the temporary implantation of epidermal devices in trigger points defined by their innervations to desensitize neurons involved in the persistence of pain, neurogenic inflammation, and muscle contracture.[45] NRT is performed without anaesthesia, on an outpatient basis. In a systematic review quoted by the European Guidelines for the Management of Chronic Non-Specific Low Back Pain, NRT

was shown to be substantially more effective than a sham procedure in providing pain relief up to 30-45 days.[7]

3.2.4 Implants

Implants for closing altered intra vertebral disc are also been used. They act by bridging defects of the intravertebral disc. Several implants are commercially available. The implants reinforce the altered area and therefore prevent contralateral herniation. However, the materials cannot maintain the disc in the long-term. Other types of more resistant materials are under investigation.[46]

4. Major Problem and Challenges for Disease Control: why does the Disease Burden Persist?

Low back pain is becoming more prevalent in our societies because of a number of factors that could be modified and other inherent to the individuals. Factors such as prolonged sitting position at the work place, lack of exercise, obesity and high body weight account for factors that can be modified.

Other risk factors such as anthropomorphic characteristics, gender, age, and genetics are not modifiable. The physical disability arising from pain and loss of functional capacity reduces quality of life and increases the risk of further morbidity, although there is a wide range of analgesics available that relieve pain and improve quality of life for patients.

With the rapidly ageing of the world population, the disease burden of low back pain consecutive to deterioration of bones and discs will naturally increase accordingly unless (1) primary prevention efforts such as healthy diet, exercise, and adequate positions at the work place are scaled up around the world and (2) early diagnostics to identify and resolve possible causes of low back pain are clearly identified and can be modified.

There is evidence suggesting that prevention of various consequences of back pain is feasible. However, for those interventions where there is acceptable evidence, the effect sizes are rather modest. The most promising approaches seem to involve physical activity/exercise and appropriate (biopsychosocial) education, and support at the work place.

5. Current Pharmaceutical Product "Pipeline" for Low Back Pain treatment

Treatment for low back pain aims to relieve pain, improve functional ability, and prevent recurrence and chronicity. Pharmacological treatments will be prescribed based on the pain intensity and back pain specific functional status. Intervention-specific outcomes may also be relevant, for example behavioural treatment, exercise therapy, antidepressants, and muscle relaxants. The following text is extracted from the European Guidelines for the Management

of Acute non-specific Low Back Pain in primary care.[7] This summarizes the effectiveness of pharmaceutical compounds in treating pain associated to low back pain.

5.1 Paracetamol

Two systematic reviews found strong evidence that paracetamol is not more effective than NSAIDs.[47] There is strong evidence from a systematic review in other situations that analgesics (paracetamol and weak opioids) provide short-term pain relief.[48,49]

Six RCTs (total n=329) reported on acute low back pain. Three compared analgesics with NSAIDs. Two of these (n=110) found that meptazinol, paracetamol, and diflunisal (an NSAID) reduced pain equally. The third trial found that mefenamic acid reduced pain more than paracetamol, but that aspirin and indomethacin were equally effective.

5.2 NSAIDs

Two systematic reviews found strong evidence that regular NSAIDs relieve pain but have no effect on return to work and natural history or chronicity.[49,50,51,52] NSAIDs do not relieve radicular pain. Different NSAIDs are equally effective. Statistical pooling was only performed for NSAIDs versus placebo in acute low back pain. Compared to placebo, nine RCTs (n=1135) found that NSAIDs increased the number of patients experiencing global improvement (pooled OR after 1 week 2.00, 95% CI 1.35 to 3.00) and reduced the number needing additional analgesic use (pooled OR 0.64, 95% CI 0.45 to 0.91). Four RCTs (n=313) found that NSAIDs did not relieve radicular pain.

When compared to paracetamol, three trials (n=153) found conflicting results. Two RCTs (n=93) found no differences in recovery, and one RCT (n=60) found more pain reduction with mefenamic acid than paracetamol.

Five out of six RCTs (n=399 out of 459) found no differences in pain and overall improvement when comparing muscle relaxant and opioid anagesics with NSAIDs. One RCT (n=60) reported more pain reduction with mefenamic acid than with dextropropoxyphene plus paracetamol.

Three trials (n=461) were done with non-drug treatments. One RCT (n=110) found that NSAIDs improved range-of-motion more than bed rest and led to lesser need for treatment. One trial (n=241) found no statistically significant difference. Two studies (n=354) found no differences between NSAIDs and physiotherapy or spinal manipulation in pain and mobility.
Fifteen RCTs (n=1490) found no difference in efficacy of different NSAIDs when compared to one another. One recent trial (n=104) found somewhat better improvement of functioning with nimesulide, a COX-2 inhibitor, compared with ibuprofen 600 mg, but no differences on pain relief.[52]

5.3 Muscle relaxants

Three systematic reviews (24 RCTs; n=1662) found strong evidence that muscle relaxants reduce pain and that different types are equally effective.[53]

Twenty-four trials on acute low back pain were identified. Results showed that there is strong evidence that any of these muscle relaxants (tizanidine, cyclobenzaprine, dantrolene, carisoprodol, baclofen, orphenadrine, diazepam) are more effective than placebo for patients with acute LBP on short-term pain relief. The one low quality trial on benzodiazepines for acute LBP showed that there is limited evidence (one trial; 50 people) that an intramuscular injection of diazepam followed by oral diazepam for 5 days is more effective than placebo on short-term pain relief and better overall improvement (level C). The pooled RR (relative risk) for non-benzodiazepines versus placebo after two to four days was 0.80 [95% CI; 0.71 to 0.89] for pain relief and 0.49 [95% CI; 0.25 to 0.95] for global efficacy (level A). The various muscle relaxants were found to be similar in performance.

5.4 Opioids

Opioids can be also prescribed for the treatment of low back pain. The WHO's analgesic ladder, originally developed for the treatment of cancer pain, is applicable here.
The WHO's analgesic ladder recommends the following ladder scheme in using opioids for pain treatment: [54]

- Non-opioid analgesics with adjuvant therapy where needed;
- Addition of a weak opioid;
- Where necessary, a stronger opioid in addition to the non-opioid and adjuvant therapy

Clinicians must prescribe opioids following specific guidelines and make sure that their patients do not fall on habituation and addiction.[55]

5.5 Antidepressants

Small doses of tricyclic antidepressants (mood elevators) given up to an hour before bedtime can help regulate the sleep cycle, which seems to help in some cases. Psychotropic drugs are otherwise of no avail.[55]

6. Past/Current Research into New Therapeutic Options for Low Back Pain

Currently all the treatment advances in low back pain offer palliative care and help to reduce the symptoms of pain and help mobility. There are at present no new drugs that can prevent, halt, or reverse low back pain progression. Several new technologies, devices, as well as advances in the area of stem cell therapy offer alternative and new hope for the treatment of low back pain. The following information summarizes the highlights of treatment of low back pain:

Intervertebral disc (IVD) degeneration plays an important role in its epidemiology.[56,57,58] Recent approaches for biologic repair and regeneration of the IVD are under investigation including cell transplantation, administration of growth factors, and gene therapy.[59, 60] Mesenchymal stem cells (MSCs) may be ideal candidates for cell therapies and tissue

engineering because of their high proliferation rate and potential for multilineage Differentiation.[61,62]

Healthy discs function are load-absorbers between all vertebrae, allow for bending, flexion and torsion of the spine. As the global population ages, the incidence of intervertebral disc (IVD) degeneration and low back pain (LBP) increases. The occurrence of LBP has been associated in many cases with degenerative disc disease. New treatments are being investigated to normalise disc cell homeostasis and restore full disc function.

Discs can be subdivided into two different tissue types, the nucleus pulposus (NP) and the annulus fibrosus (AF). The AF is a ring of highly oriented densely packed collagen fibril lamellae. It anchors to the cartilaginous endplates connecting to the vertebral bodies and keeps the NP in the centre position. At present, when discs deteriorate, the IVD are excised and the vertebral bodies are fused. The surgery is very traumatic and the non-biological prosthesis wears with time. A solution using tissue engineering approaches for disc regeneration and repair is the recent focus to restore the disc function by the introduction of functional cells and supporting biomaterials to augment or replace the degenerated disc.

One of the characteristic of disc degeneration is the loss of matrix in the nucleus pulposus (NP). There are several strategies under investigations to restore the function of the nucleus pulposus such as injection of shock absorbing hydrogels and matrix producing cells and molecules which stimulate the endogenous cells to replenish the lost matrix. Treatment strategies may vary depending on the severity of the degeneration.

6.1 Repair of the nucleus pulposus using hydrogels

Photo-crosslinking of natural polymers, performed by chemical reactions, generates considerable amount of heat. A recent study has shown good cytocompatibility and injectability of the polymer in combination with human disc cells for NP repair.[63,64,65] Polymers enriched with collagen, hyaluronic acid (HA), and chondroitin sulfate are potential candidates as an injectable system for NP repair.[66,67]Although tested in animal models only, hyaluronic acid appears to be a good candidate material as it is an abundant water absorption molecule, which is able to dehydrate and rehydrate under a range of mechanical loading parameters. However, hyaluronic acid and collagen are degraded relatively fast in vivo, further research is necessary to ensure better stability and mechanical properties.[68]

Table 6.24.4: Overview of potential molecular/growth factor for IVD treatment. (adapted from Chan et al.).[68]

Overview of potential molecular/growth factor for IVD treatment.	
Protein	
Intercellular regulator	SOX-9LIM mineralization protein (LMP-1) Dexamethasone Tissue inhibitor of matrix metalloproteinase (TIMP) Synthetic peptide (Link-N)
Inflammatory cytokines anatogonist	Interleukin-1 receptor antagonist (IL-1 ra) Tumor necrosis factor antagonist (TNF-a)
Growth factor	Growth and differentiation factor-5 (GDF-5) or (BMP-14) Insulin-like growth factor (IGF-1) Transforming growth factor ? (TGF-?) Epidermal growth factor (EGF) Osteogenic protein-1 (OP-1)/ BMP-7 Bone morphogenetic protein (BMP-2) Platelet-rich plasma (PRP) Platelet derived growth factor (PDGF) Basic fibroblast growth factor (bFGF)

Source: Chan SC, Gantenbein-Ritter B. Intervertebral disc regeneration or repair with biomaterials and stem cell therapy--feasible or fiction? Swiss Med Wkly. 2012 May 31;142:w13598. doi: 10.4414/smw.2012.13598. Review.

6.2 Stem cell therapy

Stem cell research offers exciting possibilities for restoring intervertebral discs. Although much of this research has been performed on animal models they offer exciting possibilities for regenerating altered intervertebral discs. Stem cells can be obtained from autologous transplant mainly from the bone marrow, but also from adipose-tissue and synovium.[69,70,71]
An increasing number of studies have been published on the use of mesenchymal stem cells (MSC) for disc regeneration. These cells can be obtained from the bone marrow. The autologous transplant prevents any risk of immunoreaction and showed promising results in terms of improvement of pain and disability when injected in the IVD.[72]

The IVD environment is a quite hostile environment for such cells to grow as there is low oxygen content, high lactic acid concentration, and relatively high hydrostatic pressure.[73,74] Several strategies are being investigated to improve the survival of the injected MSC by pre-conditioning or using different hydrogel cell carriers.[75]

Researchers have hypothesised that the IVD (invertebral disc) might itself contain a population of "intervertebral-disc stem cells" that could offer a better alternative since they are perfectly adapted to these particular conditions.[76,77]

6.3 Modulation of matrix production through IVD injection of growth factors

Another area of investigation for disc regeneration is the use of molecules that could help regenerate the extracellular matrix in the IVD. These molecules include growth factors, inflammatory cytokine antagonists, proteinase inhibitors or intercellular, bone morphogenetic protein (BMP-2, -7, -14), platelet derived growth factor (PDGF), platelet-rich plasma (PRP), and transforming growth factor beta (TGF-β) (Table 6.24.4). More research has to be done in this area to improve the delivery systems, and a longer term delivery within the IVD.[78]

6.4 Disc renutrition

To ensure that the injected stem cells and other growth promoting factors can effectively replenish the altered IVD, sufficient nutrients and oxygen must be supplied to the targeted area. In this regard, several molecules have been identified as able to increase blood flow to the nerve with success, such as a receptor antagonist 5-hydroxytryptamine (5-HT) and nimodipine, which enhances vascularisation of the cartilage endplates in the disc.[79,80]

6.5 Disc replacement using synthetic material

Replacing the altered annulus fibrosus instead of the whole disc by injecting shock absorbing materials is another alternative that is being investigated. Injection of material of high compressive resistance such as polyacrylonitrile and polyacrylamide materials made of silicone, polymethyl methacrylate (PMMA) – hydroxyethyl methacrylate (pHEMA), polyurethane, polyvinyl alcohol (PVA) based polymer, *N*-vinyl-2-pyrrolidinone copolymerised with 2-(40-iodobenzoyl)-oxo-ethyl methacrylate and photo-crosslinked gellan gum – glycidyl methacrylate are being investigated. Other materials that could bridge the deteriorated annulus fibrosus or serve as cell carrier are also under research.[81]

Table 6.24.5. Overview of classical biomaterials and examples used for intervertebral disc engineering. (adapted from Chan et al.) [68]

Overview of classical biomaterials and examples used for intervertebral disc engineering.	
Class	**Examples**
Synthetic degradable polymers	Polylactides/glycolides Polycaprolactone Polyhydroxyalkanoates Poly(propylene fumarates)
Natural biopolymers	Proteins Collagen Elastin Fibrin/fibrinogen Silk Polysaccharides Alginates Chitosan Hyaluronic acid
Bioactive ceramics	Calcium phosphates Bioactive glasses
Composites	Synthetic polymers/ bioactive ceramics Biopolymers/bioactive ceramics
Tissue derived ECM	Small intestine submucosa Skin extracellular matrix

Source: Chan SC, Gantenbein-Ritter B. Intervertebral disc regeneration or repair with biomaterials and stem cell therapy--feasible or fiction? Swiss Med Wkly. 2012 May 31;142:w13598. doi: 10.4414/smw.2012.13598. Review.

7. Gaps between Current Research and Potential Research Issues That Could Make a Difference

Opportunities for research can be divided into three categories:

a) Identify relevant sub-groups of patients with a high risk of chronicity
b) Prolong the treatment window before surgery
c) Improve research in disc replacement therapy

7.1 Identify relevant sub-groups of patients with a high risk of chronicity

There have been a number of clinical trials within the past ten years, which have identified risks factors such as lifting of heavy loads, long standing positions, vibrations, work related factors, psychosocial distress, depressive mood, as well as body height, obesity, and age. However, there is a lack of research in the area of anthropometric criteria and genetics.

Posture in humans is affected by several factors including anatomical structural impairments, postural habits, and occupations. Posture prevents the body from injuries and deformations that can lead to muscle stress and pain.

It would be important to establish a relation between postural balance and anthropometric measurements for each individual and develop programs to determine how to correct postural deviations accordingly. Imaging as well as clinical assessments should help determine anthropomorphic parameters that lead to low back pain (muscle and bones length, density, ratios between BMI and bones, etc).

Prevention of low back pain at an early age and thorough lifetime should help lower substantially the burden of disease. Screenings of children and adolescents at school and adults at the work place and proposing exercise rehabilitation that would halt the progression of spinal deviations and reduce the rates of chronicity.

As BMI plays an important role in the onset of low back pain, it would be important to better sensitize the populations to the importance of a healthy diet.

Low back pain consecutive to occupational postures has been the subject of several studies. Ergonomic types of furniture are being proposed to workers and school children. However, these measures are not systematically applied in reality and employers are rarely aware of the impact that this can have on low back pain and work loss. Ergonomic furniture at the work place has been shown to substantially reduce the musculoskeletal stress and maintain a more physiological posture.[82]

7.2 Prolonging the treatment window before surgery

One of the fast growing areas of research for low back pain therapies is applications of stem cells and biomaterials. Though no trials have been performed on patients to date, animal studies have been producing very promising results. Many questions remain to be answered, including which type of stem cells should be used, what are the best mechanisms of action, which patients will benefit most, when the optimal timing to apply the stem cells is, and what would be the best way to deliver and track the cells. More research and funding are urgently needed in this emerging area of research.

The disease burden of low back pain will naturally increase as the population continues to age. New analgesics therapies that are not disease modifying are in development and may offer an alternative approach to therapy.

7.3 Surgery and disc replacement

Although surgery for disc replacement already exists, considerable improvement could be made in the area of prostheses with the development of new more adapted and resistant materials and the 3D imaging technologies.

8. European Union Funding Opportunities for Low Back Pain

European Guidelines were published in 2004.7 These guidelines are intended to offer guidance on diagnosis and treatment of chronic non-specific low back pain. They aim to inform professional associations, health care providers, health promotion agencies, industry/employers, educationalists, and policy makers in Europe.

The following text has been extracted from the European Guidelines:

"The primary objective of the European evidence-based guidelines is to provide a set of recommendations that can support existing and future national and international guidelines or future updates of existing back pain guidelines. This particular guideline intends to foster a realistic approach to improving the treatment of common (non-specific) chronic low back pain (CLBP) in Europe by:

1. Providing recommendations on strategies to manage chronic low back pain and/or its consequences in the general population and in workers.
2. Ensuring an evidence-based approach through the use of systematic reviews and existing evidence-based guidelines, supplemented (where necessary) by individual scientific studies.
3. Providing recommendations that are generally acceptable to a wide range of professions and agencies in all participating countries.
4. Enabling a multidisciplinary approach, stimulating collaboration between the various players potentially involved in treatment, thus promoting consistency across countries in Europe.
5. Identifying ineffective interventions to limit their use.
6. Highlighting areas where more research is needed.

A research project called Genodisc under the FP7 programme is being funded by the European Commission with a total budget of 2 997 144 Euros.

The following text has been extracted from the Educell (an SME that is a participant in the Genodisc consortium) website.[83]

"Genodisc aims to contribute to improvement of patient care through improving diagnosis of disc-related pathologies both by more effective utilisation of present diagnostic information and by developing novel diagnostic tools. Through these new diagnostic methods, it aims to select patients at risk of chronic low back pain and spinal stenosis. It also aims to develop criteria for selecting patients who will benefit from newly emerging biological therapies for treating disc degeneration. The scientific advances underpinning improved diagnosis will arise from genotyping carefully phenotyped patients, from research into the processes of disc degeneration and from models of how these molecular processes lead to disc failure. This research will potentially provide biomarkers which will increase diagnostic specificity and provide targets for development of drug therapies. (…) The researchers include surgeons and other clinicians as well as research scientists specialising in genetics, cell physiology, regenerative medicine, engineering and computational analysis. The research will be led by a group from the University of Oxford but carried out in nine countries including the UK, Israel, Germany, Finland, Greece, the Netherlands, Hungary, Italy and Slovenia. Educell, a Slovenian biotechnology company and a 'Tissue Establishment', has also been invited by Dr Jill Urban from the University of Oxford - coordinator of Genodisc, to participate in the project. Research in Educell is led by Dr Nevenka Kregar Velikonja and Dr Mirjam Fröhlich and focuses on one of novel potential repair

treatments, which is development of tissue engineering approach aiming for functional and long lasting replacement of the removed damaged nucleus pulposus tissue. Genodisc recruits thousands of patients into the study as large numbers are required to determine any genetic link to complex disorders like back pain."

Future research funded by the European Commission should be on carefully chosen topics that can make important contributions to improving care and prevention for low back pain. Future areas for public sector research to explore include; (a) searching for biomarkers (b) searching for anthropometric risk factors and adapted rehabilitation (c) development of biomaterials and (d) stem cell research.

9. Conclusions

Back pain is not a disease but a constellation of symptoms which origins remain in most cases unknown even though risks factors have been identified. Low back pain is disabling and causes enormous socioeconomic impacts on societies. Treatments for now are focused on reducing the pain. Back pain is both a major cause of temporary disability and a challenge to medical and surgical treatment decisions. It imposes high socio-economic burden in modern western countries, since it not only affects the elderly population but also the working population from 25–60 years.

The management of patients with low back pain requires multiple interventions, an accurate initial diagnosis, close monitoring of potential complications, and appropriate rehabilitation by trained professionals.

There is a still long way to go to improve diagnosis and identify other potential risks factors. As the world population ages, low back pain burden of disease will increase substantially. If surgery and discs replacement therapies remain at present the last option to relieve when all other strategies have failed, new developments in 3D imaging, biomaterials and disc renutrition or stem cell therapies may bring new hope for the treatment of low back pain.

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