



Outline Document

"When I'm not able to be here for myself, then who is there for me?
But if I am only here for myself, then what am I?
If not now, then when?"

- Quote from Hillel the Elder



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Vision: Creating innovative solutions for patients with untreatable pain. The goal is to be free of pain.

Mission: Diminishing untreatable pain world-wide through the development and implementation of new treatments.

Key Issues

Pain must be treated at its origin, by:

1. **Gathering together currently available expertise**
2. **Focussing on pain relief**
3. **Using existing technologies**

This will enable the development of innovative treatments which can relieve pain locally and without side-effects.

Pain is a complex process. While acute pain helps us to survive, chronic pain is a personal tragedy¹ and a social problem that is estimated to **cost billions a year**².

Serious chronic pain has many causes. Pain reaches the brain through several neural routes. It is often difficult in the case of chronic pain to find out what causes it and which neural routes carry it to the brain. Pain is therefore treated only at its final destination: the brain is numbed. This way of treating pain often has only a partial result or the side-effects impair overall quality of life. The pain-relief is inadequate and patients are effectively untreatable.

It is essential that molecules are developed that block the pain where the pain should be blocked: at the initial neural-link.

The Nerve Centre of the Leiden University Medical Centre (LUMC) in the Netherlands has a team of leading specialists who have a great deal of experience in carrying out nerve-surgery for serious pain. Their experience has provided them with new insights in this area. Combined with recent developments in leading research this can enable an international breakthrough in the treatment of chronic pain.²

1 40% of European sufferers from chronic pain judge their pain relief measures as inadequate. Reference: Breivik H., Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006 May; 10(4): 287-333.

2 Reference: Breivik H, Eisenberg E, O'Brien T; OPENMinds. The individual and societal burden of chronic pain in Europe: the case for strategic prioritisation and action to improve knowledge and availability of appropriate care. *BMC Public Health*. 2013 Dec 24; 13:1229.

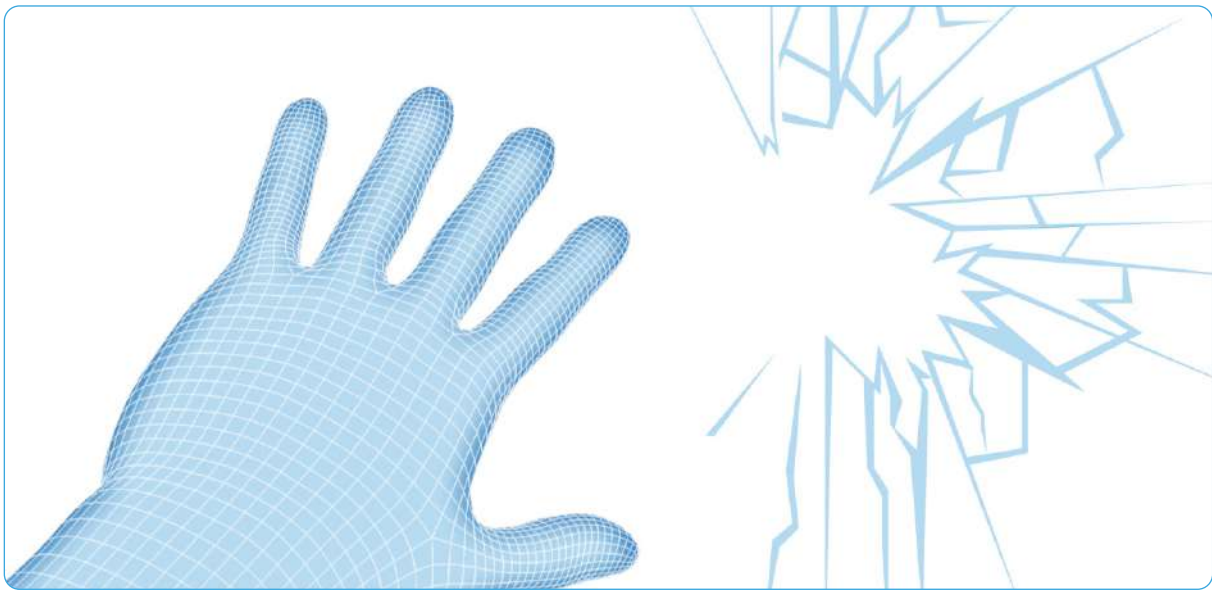


Highly advanced specialist knowledge and technology are already currently available. PainLess aims to gather this knowledge together to achieve its aim. A crucial step can be made **now** in solving this wide-spread social problem. The result will be an improved quality of life for thousands of people and a financial benefit for society as a whole. We can achieve this through gathering together current expertise and directing our focus specifically on pain.

We will create an international centre of expertise that will contribute to the diminishment of chronic pain around the world. New and innovative treatments will lead to a unique Pain Institute that will offer the most advanced care to patients with chronic pain who have until now remained untreatable.

Pain

Pain is essential to our survival and of crucial importance to maintaining a healthy body. Pain is our body's way of warning us that something is wrong. The nerve that detects the pain-signal sends the signal onwards to the brain, which in turn registers and processes such signals. It is the processing in the brain which causes responses such as a withdrawal of the hand in the case of sudden injury.



Two types of pain can be distinguished: [acute pain](#) and [chronic pain](#). Acute pain occurs suddenly and disappears once the injury has healed. But in some cases the pain persists. If the pain continues for more than six months it is called chronic pain.

Chronic pain tends to occur in cases of tissue or nerve damage caused by an accident, operation or illness. Nerve-damage causes the nerve to send out constant signals which the brain registers as pain, even when the original injury has already healed.

The result is untreatable pain which dominates everything 24 hours, day and night. In some cases there is no medicine which helps at all or side-effects are so serious that normal life becomes completely impossible.

**Imagine:**

You have no complaints but go to the dentist for a routine check-up. Your dentist advises you to have a wisdom-tooth removed preventatively. During this removal, a nerve is hit. From that moment on you have unendurable pain in your head; pain which makes your life impossible. You are no longer able to concentrate or do your job. Your life has become unbearable from one moment to the next.

This is Esther's story

34 YEARS OLD - PILOT

**Imagine:**

You have built your own company by working hard for years. Your company is successful and you enjoy your job, until a 1000 kilogram-heavy metal plate falls on your leg. In one second your whole life is changed as the bone is crushed and the nerve is damaged. From that day on you live in constant pain and this has remained the case for years now. Nothing relieves the pain and you can hardly walk. You can no longer go to work and you have been forced to close down your company.

This is Paul's story

40 YEARS OLD - ENTREPRENEUR

The Impact of Pain

In Europe 19% of the population has chronic pain³. Every year hundreds of thousands more people get serious pain. For many of these patients, the pain persists or they have considerable side-effects from their medication and this means they are effectively untreatable. Their specialist can only advise them that they “have to learn to live with it”. This is an unbearable situation. Imagine that you would have to learn to live with this. Almost one in five patients with untreatable pain becomes depressed and one in three has to stop working, condemned to suffering for the rest of their lives.

The word “pain” derives from the Latin word “poena”, which means “punishment”, and the Greek word *poiné* (ποινή) which means: “price paid”. Both the personal and social costs of pain are high.

The direct and indirect costs of pain are estimated at billions of euros a year⁴.

Elaboration: the medical facts

Pain is a complex process: a chain of simultaneous interactions and sub-processes. The first step in this process is the damaging of tissue or nerves by illness or injury. This in turn leads to immune-cell activation and the stimulation of specific pain nerve-cells which produce special molecules which create “pain” signals in the brain.

When there is persistent stimulation or damage then the molecules and immune-cells can start to operate autonomously or nerve-cells can die-off. The consequences of this can be that even if the original illness is cured the pain-signals continue to be sent to the brain. In some cases, the damaged nerve can be operated on and this can take away the pain. But this is often not possible. In such cases, treatment becomes difficult and chronic pain results. It is crucial to find out as quickly as possible which nerve-cells are involved in the situation so that persistent pain-signalling can be prevented. Unfortunately, this is something that is still impossible at the moment.

The exact mechanisms that lead to chronic pain in cases of nerve damage have still not been illuminated sufficiently so that much remains unknown. This limits the possibilities for treatment.

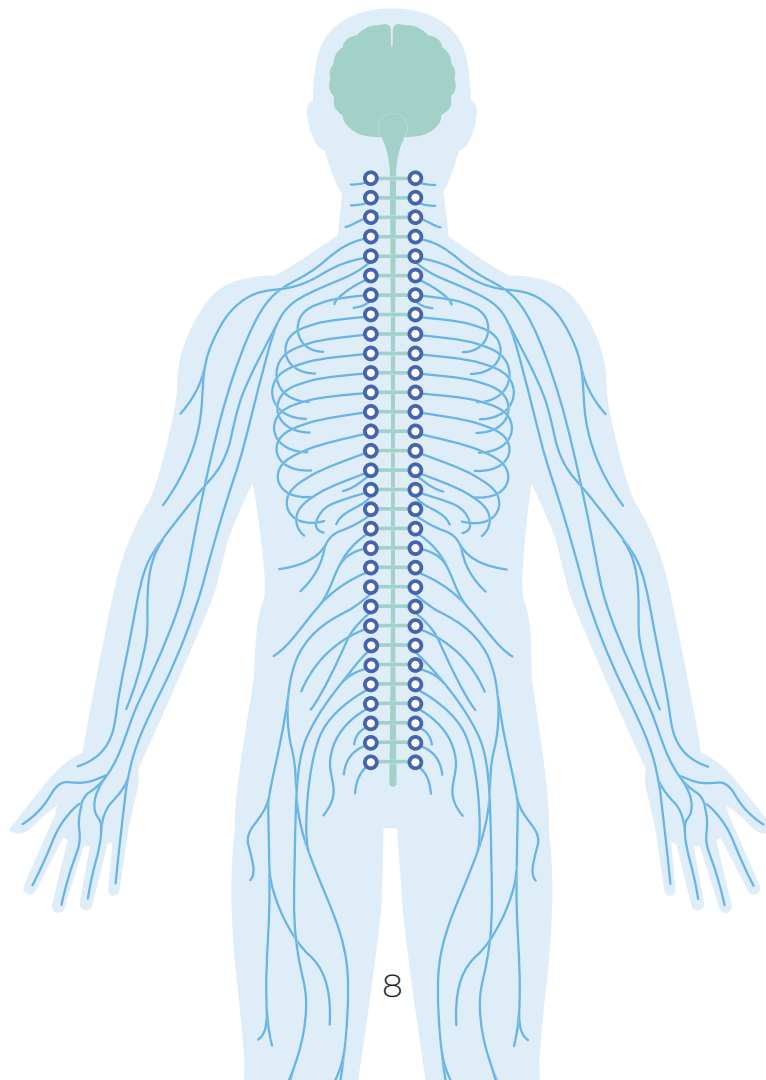
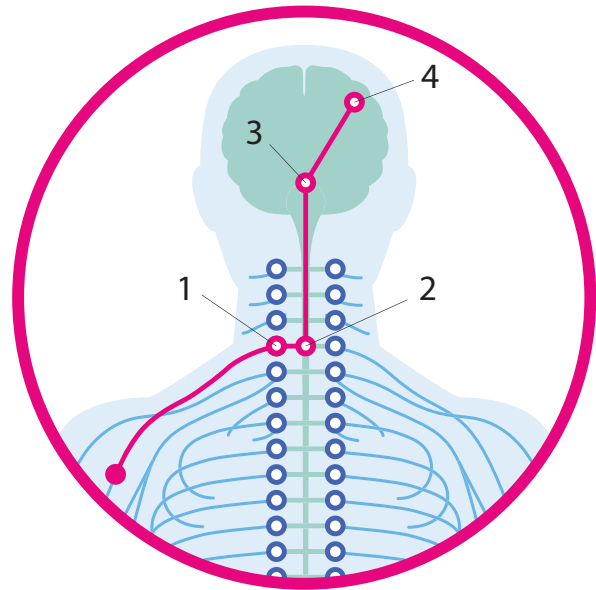
³ Bron: Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. *Eur J Pain*. 2006

⁴ See the appendix for statistics about pain and the costs of pain.

What we do know is that each pain-signal finally reaches the brain through a sequence of links in the nervous system. The initial neural-link where the pain molecules are produced can be taken to be the origin of the pain. This link lies just outside of the spine.

There are 31 such neural links on either side of the spine: 62 in total. With our present state of knowledge it is impossible to know in cases of intense pain precisely in which of these 62 links the pain is activated.

It is therefore impossible to identify the specific nerve links that are the origin of the pain. This means that treatment of pain at the most logical point, namely the initial nerve-link, is impossible.



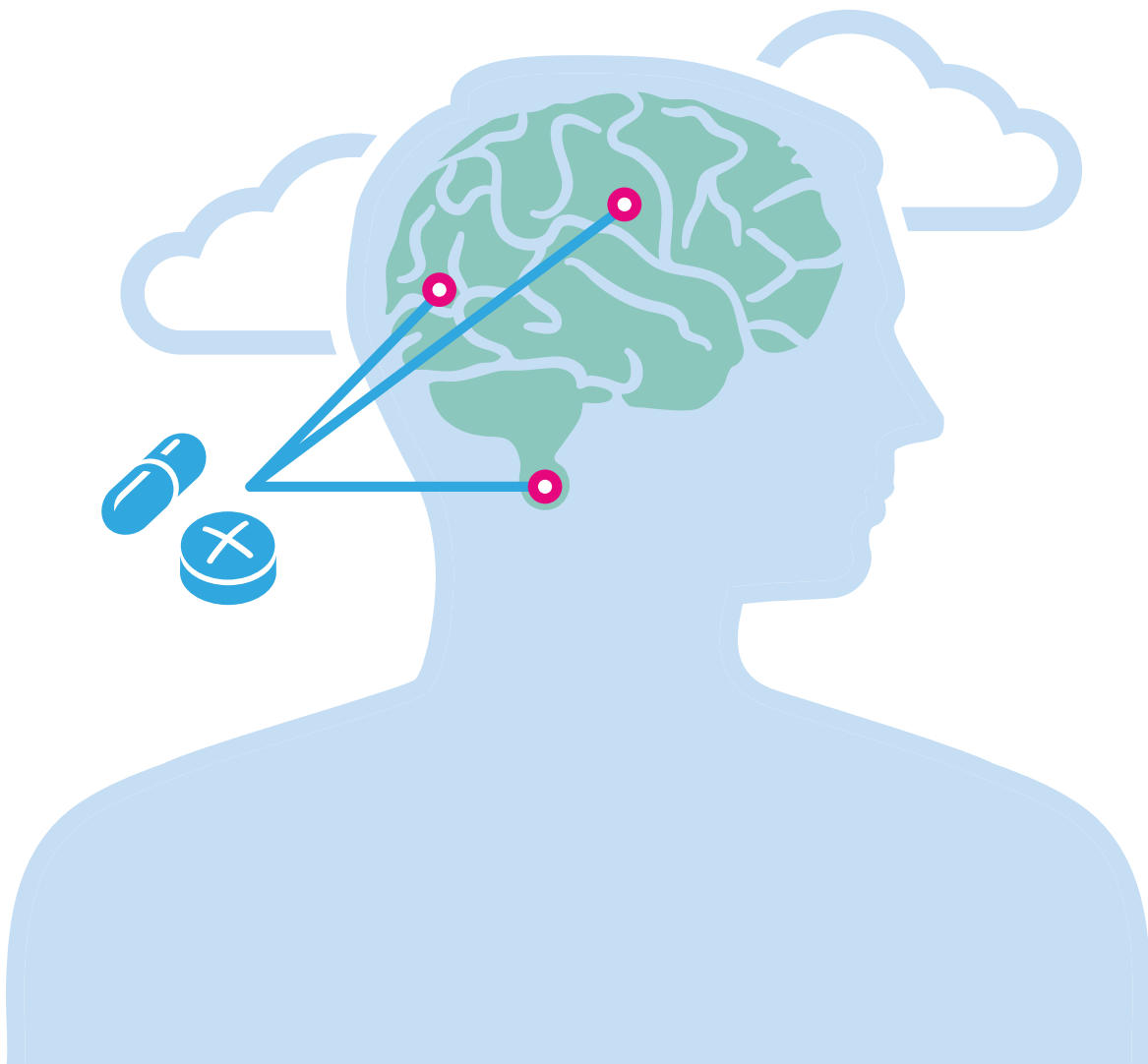
The Current Situation

Pain-sufferers first go to their GP (primary care doctor) and after that, if necessary, are referred to a medical specialist (consultant). They are treated all over the country by these different specialists. Every specialist has their own experiences and ways of treating patients and has their own particular perspective.

There are also pain-clinics, where different specialists work together: for instance, specialists in treating rheumatism, diabetes or cancer and an anaesthetist or pain-specialist, physiotherapist, psychologist or a rehabilitation specialist. These clinics aim to treat pain in particular areas (for instance the back or cancer) and patients are treated according to currently available knowledge.

At the moment, serious pain is usually treated first by numbing the brain with strong painkillers, so-called narcotics (such as morphine). Often such pain-killers work only partially or their side-effects, such as drowsiness, are even more debilitating than the pain itself.

This often means that the treatment is stopped so that the treatment of the pain remains inadequate. An effective localised treatment, at the site of the origin of the pain, is still not a possibility. As a consequence, a majority of patients remains untreatable at the moment.

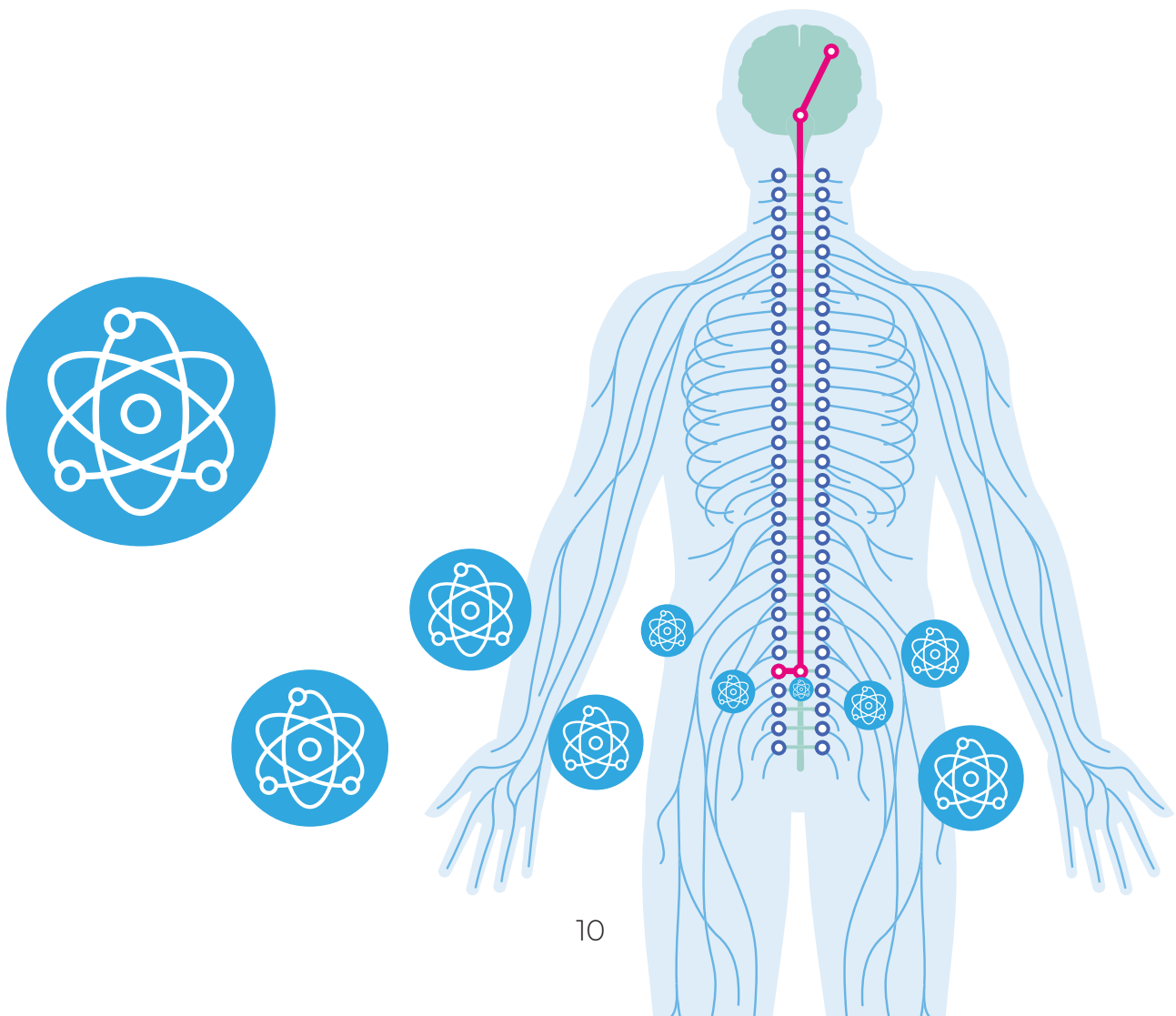


New Insights

Increasingly, patients with serious pain are being referred to the Nerve Centre of the Leiden University Medical Centre (LUMC) in the Netherlands for an expert opinion. The Nerve Centre, an initiative of Prof Dr Malessy, is specialised in the treatment of patients with nerve-damage, and has an international reputation. The integration of patient-care with pure research that the Nerve Centre has accomplished is internationally unique.

In recent years, it has become apparent that a proportion of serious pain-patients can after all be treated at the Nerve Centre for their pain, either partially or completely, through an operation.

Unfortunately this is not the case for all patients. The limits of what is currently possible as treatment have now been reached. But operating on the damaged nerves of these difficult to treat patients has led to new insights. In future, patients must be treated more quickly as well as differently. In order to achieve this, it is of crucial importance to find out quickly in which of the 62 nerve-links the pain-cells have been activated. The molecules and immune-cells in the specific nerve-links that are the origin of the pain must be blocked.



The Next Steps

New Ways of Treating Patients

A large number of leading scientists engaged in one way or another with advanced research into the sub-processes of pain are highly motivated to deploy their expertise in the service of solving the problem of chronic pain.

The locally available expertise in the Nerve Centre and elsewhere must be directed to pain-killing at origin. Pain must be blocked at the initial nerve-link so that no pain signal can reach the brain.

Gathering Expertise

In order to achieve this aim an integrated approach and gathering together of available expertise is necessary. This requires the integration of areas of research which have hitherto worked separately from one another. A PainLess consortium must be created which brings together with a joint focus on pain-relief experts in nerve-surgery, pain-medication, cell biology, biodegradable technologies, bio-mechanical engineering, and anatomy.

There is no interdisciplinary collaboration between these fields internationally as of yet.

How will the future look?

Patients with serious, uncontrollable, pain will be given a newly developed drug for the quick treatment of the affected nerve-links at origin. Because pain will no longer be treated with strong narcotics at the level of the brain (symptom-treatment), the patient will no longer suffer from the side-effects of such medication. Pain will diminish without drowsiness as a side-effect.

The personal and social benefits are considerable:

- **normal functioning can be resumed**
- **quality of life increases**
- **dependency diminishes**
- **care-costs diminish**
- **productivity increases**
- **participation in the labour market becomes possible again**
- **the costs of social support diminish**

These developments will be made possible by the establishment of the new **high-level expertise centre** where patients and science will meet with a joint goal: **the diminishment of untreatable pain and the implementation and development of new treatments.**

A **multi-disciplinary centre** that has a deep and broad knowledge of the causes (specific) and results (pain) and which can offer a high standard of care to patients with chronic pain. The pain expertise-centre is our vision of the future.



Our Approach in Three Phases

PHASE ONE

3 YEAR

Research and Development

- **Establishment of the PainLess Consortium**
- **Research of the initial nerve-link**

We aim to bring together the following research-fields: nerve-surgery, pain-medication, cell biology, bio-mechanical engineering, biodegradable technologies and anatomy. There are internationally leading researchers in each of these fields in the Netherlands at the moment and all have been approached and expressed great interest in this collaboration.

The organising of the Pain expertise-centre and appointment of additional scientific and administrative staff will take place within the existing structures of the Leiden University Medical Centre (LUMC) and the Delft University of Technology.



PHASE TWO

3 - 7 YEAR

Analysis & Implementation

- **Examine initial nerve-link with pain**
- **Test prototypes for approaching nerve switching points**
- **Develop molecules that block pain signals**

In the second phase, the initial nerve-link involved in pain will be compared with control nerve switching points. It will also be investigated how the links can be reached in a minimally invasive manner. Unique targets for pain treatment in the nerve links will be sought. Different molecules will be investigated for their suitability to block pain signals.



PHASE THREE

10 YEAR

Pain Centre: Dutch Pain Institute

- **Continuous development of molecules that block pain signals**
- **Exchange science, specialist and patient**

In the third phase, new molecules will be tested for their ability to block pain signals at the level of the initial nerve-link.

In the future, people with untreatable pain will go to the Pain Center. Here pain is treated locally without negative side effects. This is where patients and science meet and innovative treatment methods are applied and further developed. A unique place where knowledge, technology and patient come together with the same goal: to cure pain.



Value Creation

Patients:

Quality of Life. New, localised, treatments and prevention. Professional care to the highest standards. Innovative and state-of-the-art treatments in one international institution.

Science:

An international Centre of Expertise in relation to pain. Expected breakthroughs in chronic pain-relief. A unique collaboration between experts at the cutting-edge of nerve-surgery, painmedication, cell biology, bio-mechanical engineering, bio-mechanical engineering and anatomy.

The team:

Leading experts. Challenging work for the best nerve-surgeons, anaesthesiologists/painspecialists, neurologists, molecular neurobiologists, and mechanical engineers.

Society:

The social costs of chronic pain are high so that the socio-economic benefits of pain relief are correspondingly large. This project will contribute to the reduction of the care costs as well as an attendant reduction in sickness, unemployment and disability benefits.

The consortium will work as a magnet for international talent and experts, which is beneficial for the reputation in relation to medical expertise and technological innovation.

This achievement, from research and development right through to the pragmatic solution of a major social problem, will be an appealing example of how science can nevertheless again achieve at the highest level.

Internationally:

Pain is a world-wide problem. Our technology and treatments can be implemented around the world and contribute to diminishing untreatable pain internationally.



Biography of M. J. A. Malessy

Martijn Malessy (1960), MD, PhD, Professor of Neurosurgery, Leiden University Medical Centre (LUMC), the Netherlands.

As the son of a neurologist he already knew from childhood that he also wanted to be a doctor. His gifts and talent directed him towards microsurgery while his intuition brought him to neurosurgery, where he chose to specialise in nerve-surgery. In this field, the sutures used during operations are thinner than a human hair.

Martijn Malessy is an inspirational neurosurgeon specialised in nerve-repair. Every year, he carries out operations which often take longer than ten hours and whereby a wrong move of just one millimetre can cause irreparable damage. During such operations, there is no time to pause for eating or even for toilet-breaks. This is a man who works with passion and who is on a mission.

If nobody knows what to do anymore, then they turn to Martijn Malessy as a last resort; the most complex cases are referred to him and they phone him from around the world for his advice. Recently, he received in San Francisco the [Kline Award](#) from the American Association of Neurosurgeons (AANS), the world's most prestigious prize for contributions to neurosurgery. He receives praise from both colleagues and patients, being awarded a top mark of 10 on the Dutch Patient Feedback system for listening, information provision and treatment.

Professor Malessy studied medicine at the universities of Gent (Belgium) and Leiden (the Netherlands). He trained as a neurosurgeon at the Leiden University Medical Centre (LUMC) and the Amsterdam "Onze Lieve Vrouwe Gasthuis" (the "Our Dear Lady Hospital"). In 1995 he was appointed to the staff of the Leiden University Medical Centre. In 1999 he obtained his PhD at the University of Leiden with his thesis entitled "Brachial Plexus Surgery: Factors affecting functional recovery".

He has been professor and head of nerve-surgery at the LUMC since 2011. Nerve-surgery is a sub-specialism of neurosurgery, focussing on the treatment of nerve-injuries, nerve-constrictions, nerve-tumours and pain.

In 2012 Martijn Malessy started the first Dutch Nerve Centre. The Nerve Centre aims to provide multi-disciplinary expertise to enable the optimal treatment of nerve-injuries, nerve-constrictions and nerve-tumours. He leads a team of ten experts at the Centre and

is also responsible for nerve-research at the LUMC.

He was President of the American Society for Peripheral Nerve (ASPN), member of The Peripheral Nerve Surgery Committee of the World Federation of Neurosurgical Societies, Chair of the Sunderland Society.

An important contribution made by Martijn Malessy to neurosurgery is the introduction of a new nerve-repair technique for babies who suffer nerve-damage to their arm during birth. He was awarded the H. Verbiest prize from the Dutch Society for Neurosurgery for his research on brain plasticity subsequent to nerve-damage and recovery and got the Kline Award from the American Association of Neurological Surgeons.

“I want to restore normal life to patients. My drive to establish a pain centre comes from my sense of powerlessness when I am unable to help people like Esther and Paul within the existing structures, while I am convinced that we could help them if we combined our strengths. We have accumulated so much unique knowledge and experience by now that it is high time for us to make the next steps to solving pain.”

Understanding pain starts with the patient: what is going on? How does it work?
What can be done?

Thanks to years of cooperation with neurologists, rehabilitation doctors and orthopaedic surgeons, Dr Malessy has acquired a rich mix of experiences of patients with pain. In the past twenty years he has seen a vast range of issues which has given him insights which provide the building-blocks for the next step. On top of this, Dr Malessy is one of the few who has actually seen and operated on the damaged nerves that cause pain, and who therefore knows what treatment interventions of the future should look like.

What his patients say about him:

I think Dr Malessy is the best neurosurgeon of the Netherlands if not the whole world. He discussed my case with his best colleagues around the world. Thanks to him I made it and my nerve-tumour has been removed, however difficult that was!

A rarity amongst doctors: he is empathic and engagement is highly important to him.

He treats patients as people and not as numbers. A unique man!

What a relief to find a doctor who provided a great deal of clarity and a clear solution after almost four years of confusion and insecurity. Within two months our son was successfully operated on by Dr Malessy. He is an extremely able doctor who also really takes time for you. We are very grateful that he helped our son. Thanks to Dr Malessy he can go on with his life.

Summary

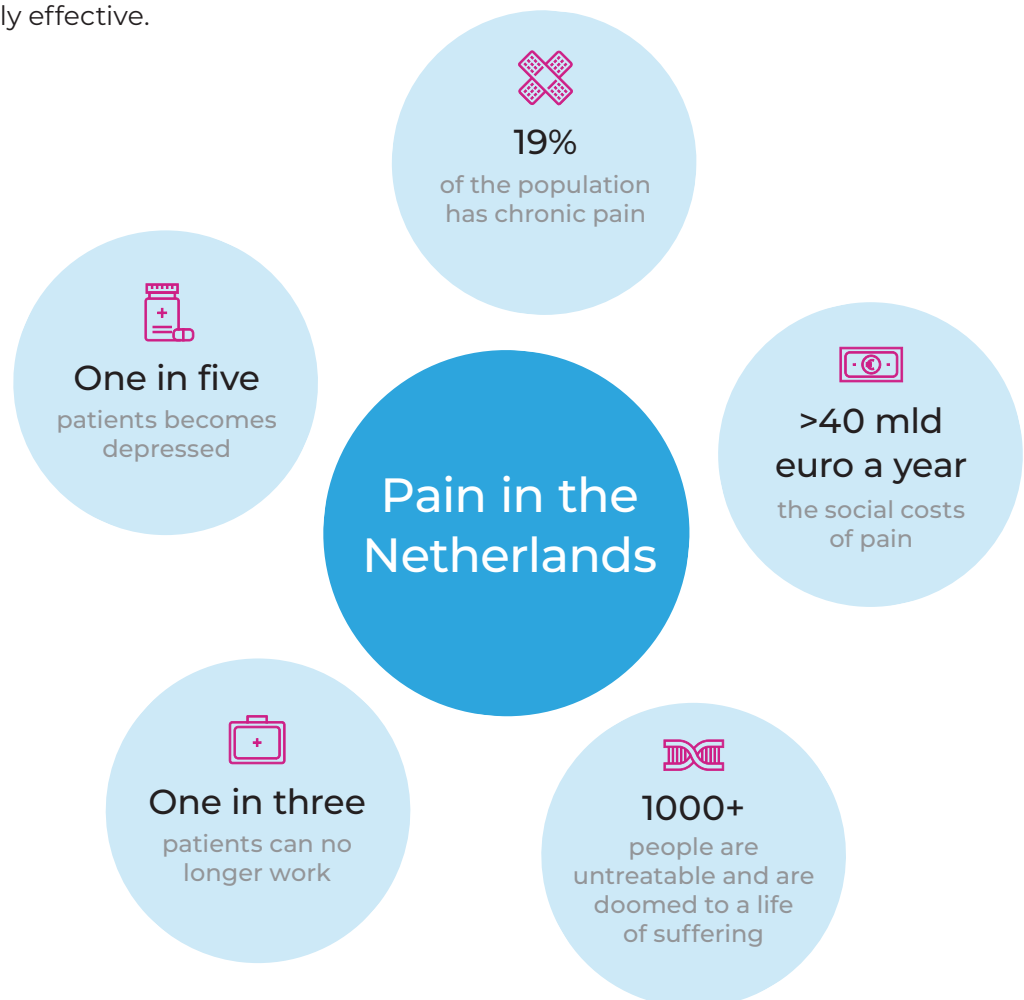
PainLess creates innovative solutions for patients with untreatable pain. The goal is to be free of pain.

The Problem

Every year, thousands of patients around the world are told that their pain is untreatable and that they will have to learn to live with it. Pain causes a great deal of suffering and costs billions.

Pain

has many causes and is an important warning. Pain-signals are sent to the brain through the nervous system and various neural-links. Even when the signal is no longer necessary or the illness has been treated, the pain-network can persist. Pain has then become chronic. Strong narcotics anesthetise the brain and cause drowsiness. Localised treatments are rarely effective.

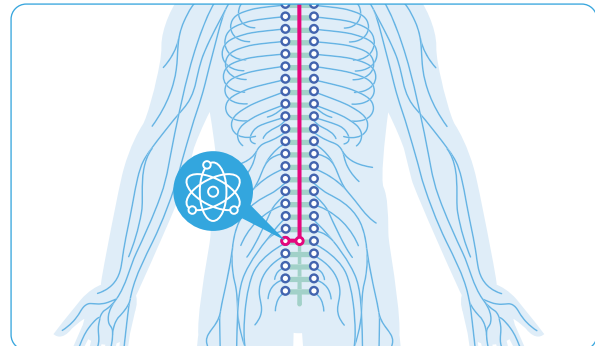
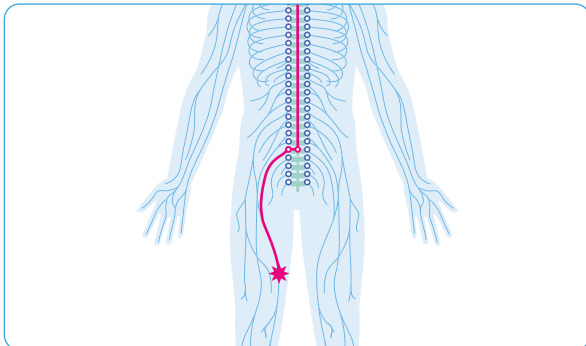


Towards painlessness

According to PainLess, the solution for pain-relief lies at its origins: the initial neural-link. If the pain-signal can be blocked here then it will no longer be able to reach the brain.

PainLess wants to develop and implement localised treatment in order to prevent side effects of medication. PainLess needs your help to find molecules that can block pain locally at the level of the initial nerve-link. Our goal is to be free of pain.

Highly advanced specialist expertise and technology are already available. PainLess wants to gather these together in order to achieve our goal and to establish an international Pain Institute. The Leiden University Medical Centre (LUMC) supports the PainLess initiative.



Statistics

The economic impact of pain

Recent studies on economic impact of chronic pain and conditions with which it is associated

Country (pricing year)	Ireland (2008)	Sweden (2008)	Denmark (2010)	United States (2010)
Data source	Postal survey	National and regional healthcare administrative registries	National administrative healthcare registries	Medical Expenditure Panel Survey
Pain definition	Chronic pain and conditions it features (n = 140)	Diagnostic related to chronic pain (n = 837,896)	Pain-intensive diagnoses (n = 1,918,823)	Pain limiting ability to work: diagnoses of joint pain or arthritis; disability limiting ability to work (n = 20,214)
Total cost/patient/year	€5,665	€6,429	Healthcare costs: DKK34,784-208,830/year (depending on condition), 2010	ND
Type of cost (% of total)	Direct healthcare: 52% Indirect: 48%	Direct healthcare: 41% Indirect: 59%	Direct healthcare: 71% Indirect: 29%	Direct healthcare: 47% Indirect: 53%
National cost estimate/year	€5,34 billion ~3% of GDP	€32 billion ~10% of GDP	DKK17.8 billion	\$560-635 billion ~4% of GDP*

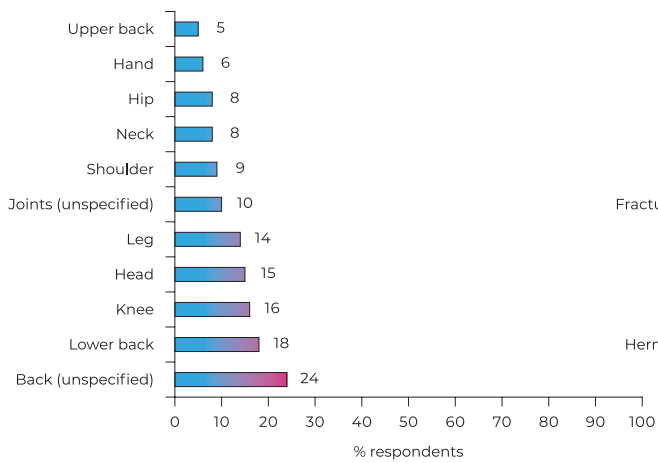
GDP, gross domestic product; PRIME, Prevalence, Impact and Cost of Chronic Pain; ND, no data.

*Not in original publication. Assumes US GDP in 2010 of US\$14.4 trillion.

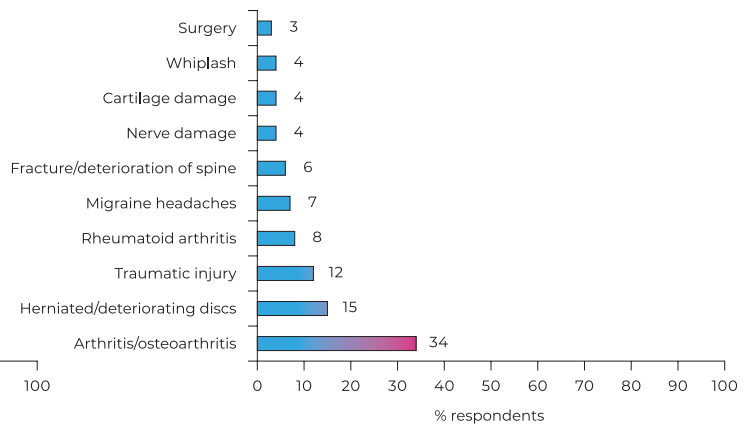
Bron: BMC Public Health. 2013 Dec 24;13:1229.

The location and origin of pain

Most common body locations (n = 4835)

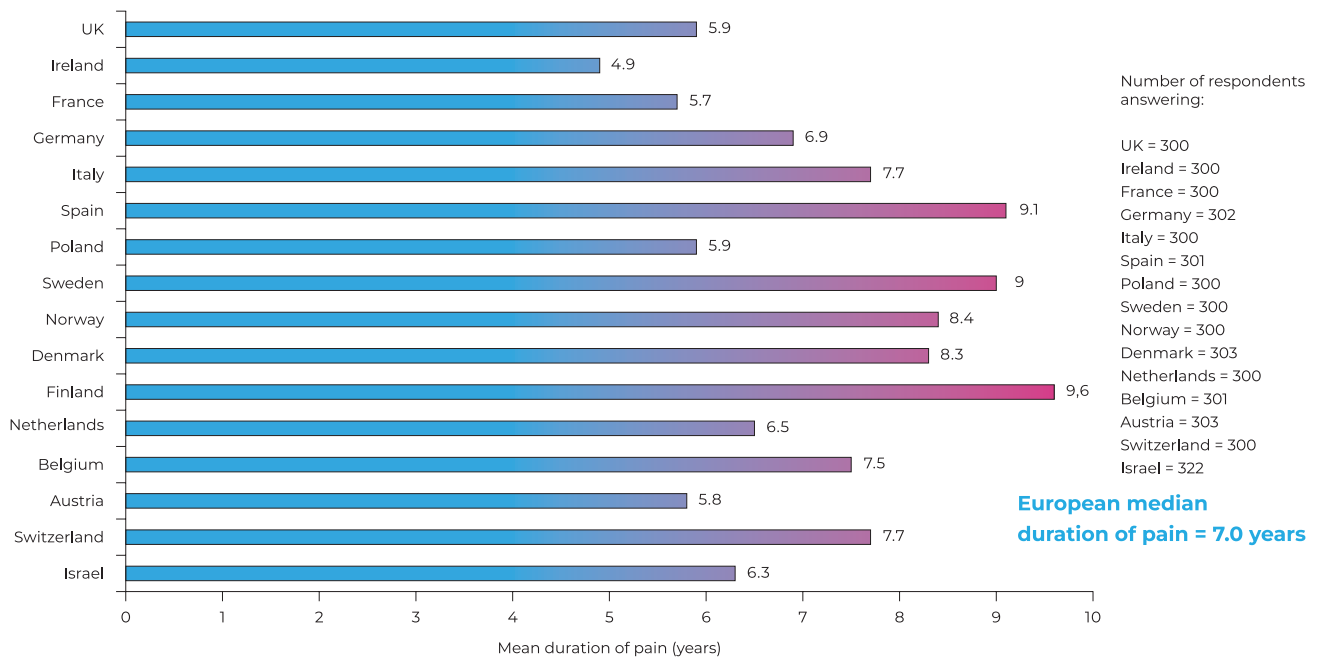


Most common causes of pain - unaided and aided responses (n = 4292)



Bron: Eur J Pain. 2006 May;10(4):287-333

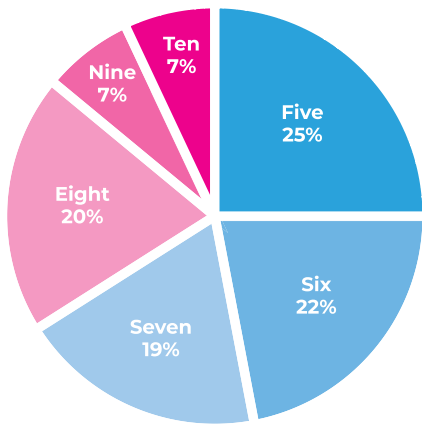
The average duration of pain



Bron: Eur J Pain. 2006 May;10(4):287-333

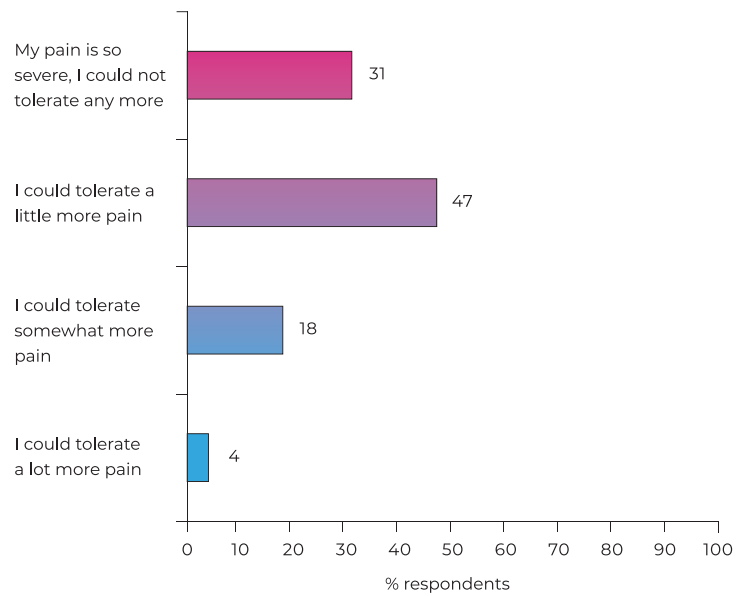
The intensity of felt pain

% respondents rating pain as 5-10 on a 10-point numerical rating scale¹
(n= 4839)



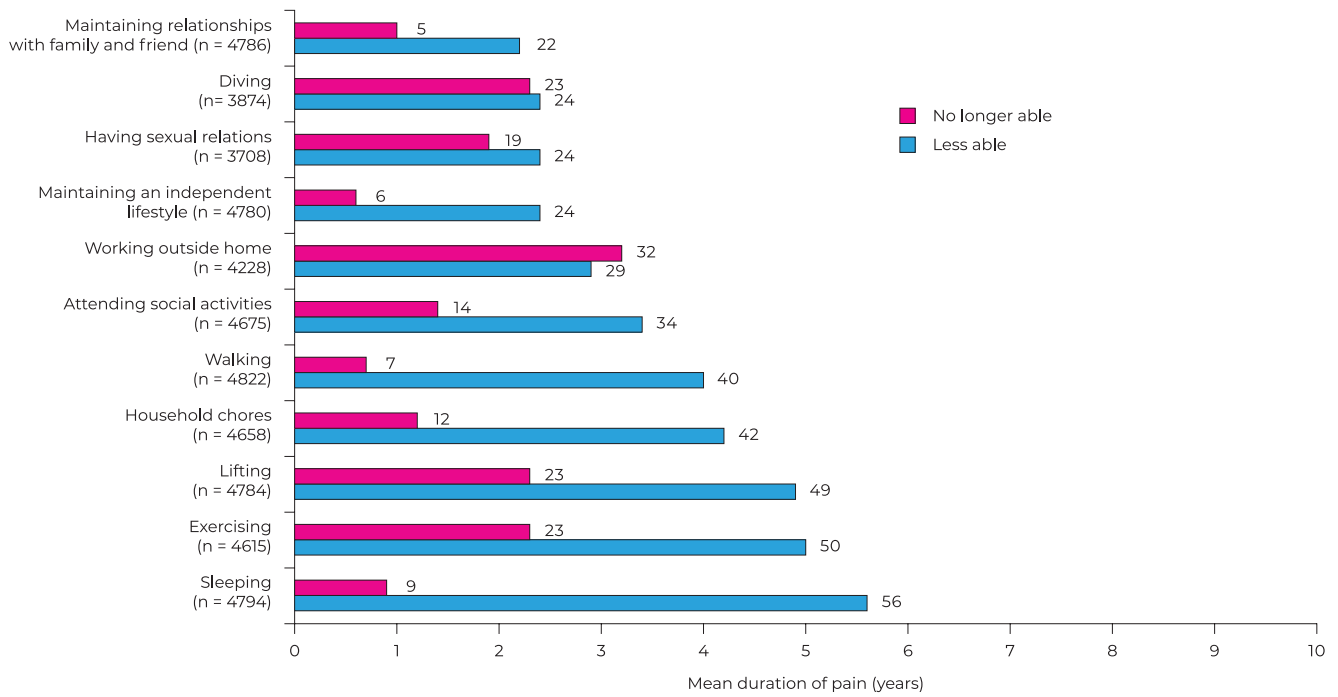
¹ Respondents with scores of 1-4 were not eligible to participate in the study

Tolerance level for more pain
(n= 4785)



Bron: Eur J Pain. 2006 May;10(4):287-333

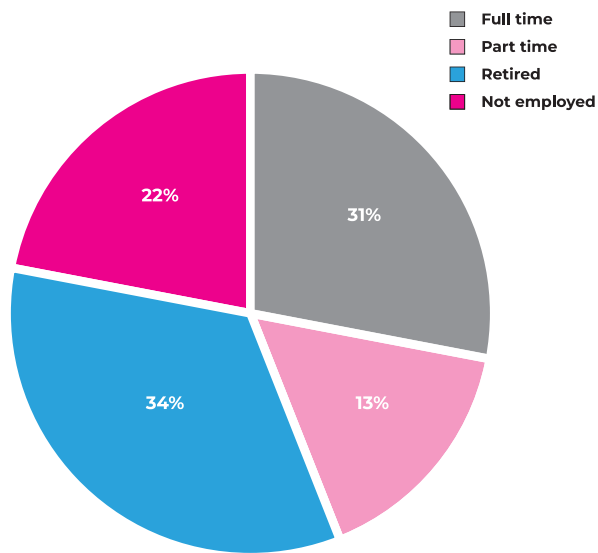
The impact of pain on daily life



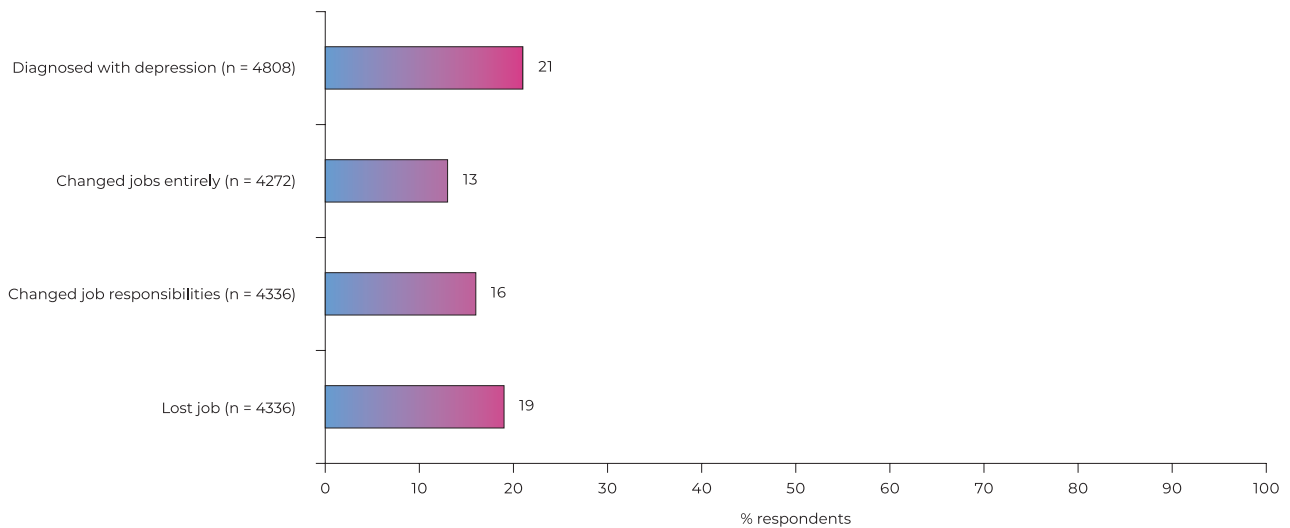
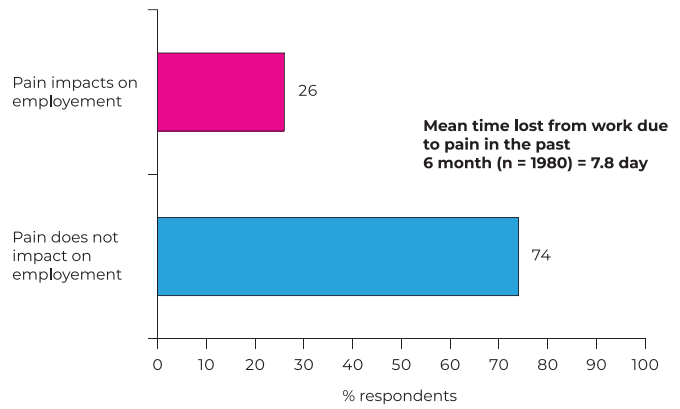
Bron: Eur J Pain. 2006 May;10(4):287-333

The impact of pain on work

Employment status
(n = 4668)

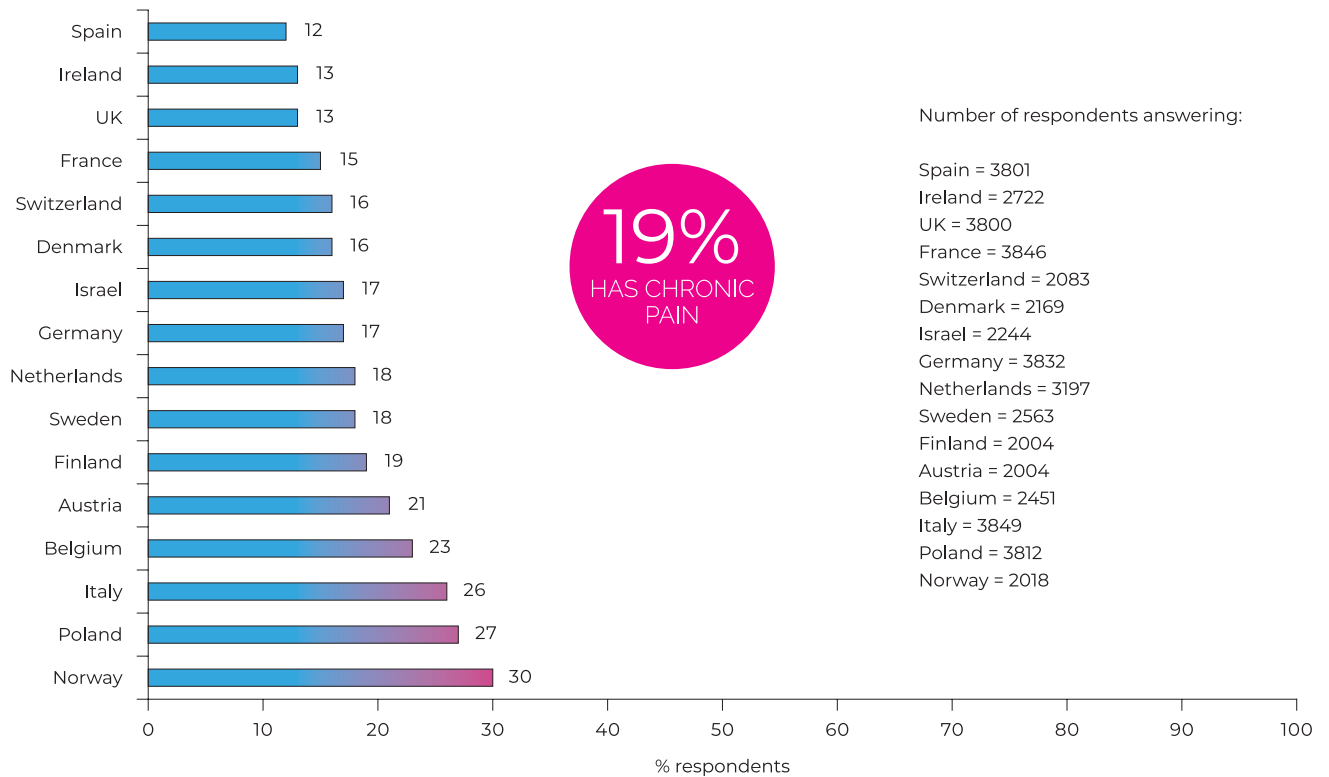


Impact of pain on employment
(n = 4215)



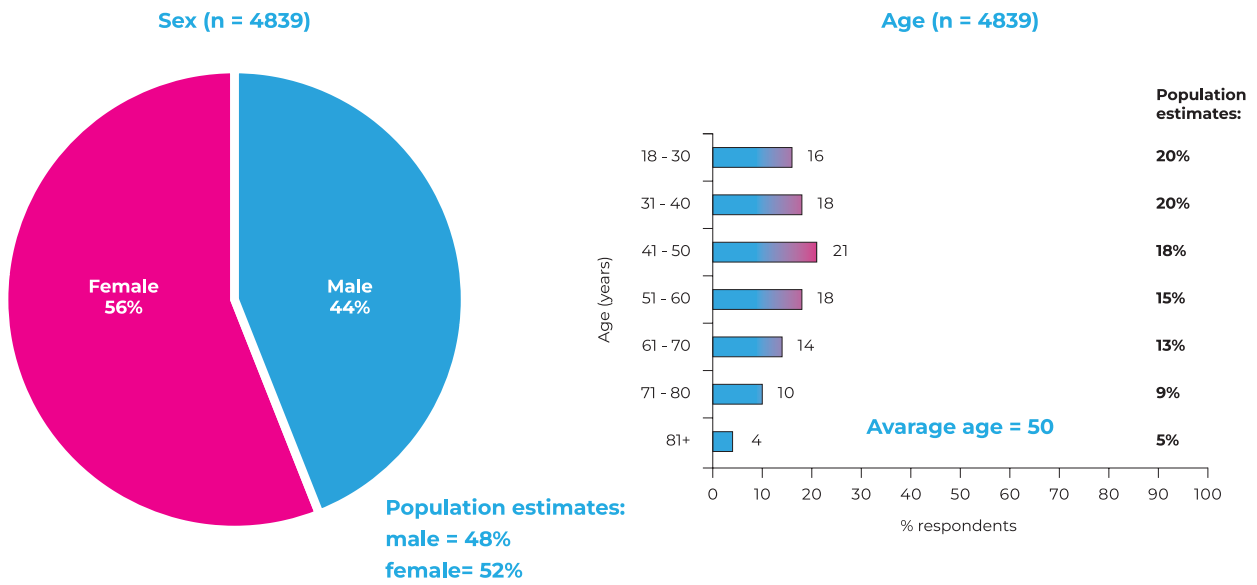
Bron: Eur J Pain. 2006 May;10(4):287-333

Chronic pain in Europe



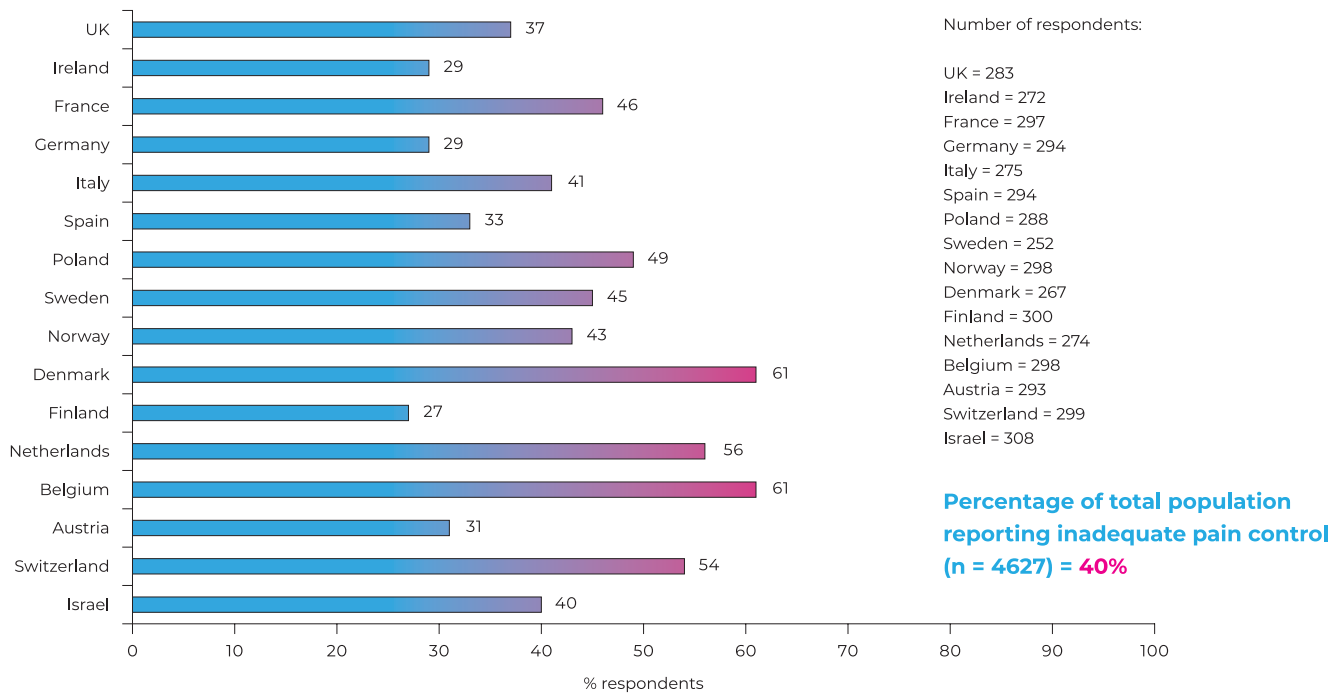
Bron: Eur J Pain. 2006 May;10(4):287-333

Gender and age and pain



Bron: Eur J Pain. 2006 May;10(4):287-333

Inadequate pain-control in Europe



Bron: Eur J Pain. 2006 May;10(4):287-333

Relevant websites

www.zenuwcentrum.org

www.lumc.nl

www.dimi.eu

www.iasp-pain.org

www.opendisdata.nl

www.leidenbiosciencepark.nl

www.chdr.nl



Stichting Fondsenwerving PainLess
ANBI status
KvK- nummer: 65212444
ABN-AMRO: NL60 ABNA 0517 2672 09
The Netherlands