



Facts about pain

CombiGenes and Zyneyro's Pain Program

The impact of pain on the individual and on society

Definition and occurrence

- **Long-term pain** is defined as pain that has lasted longer than three months.
- **Chronic pain** is defined as pain that has lasted longer than six months.
- **Diseases in their own right:** both long-term and chronic pain are today considered diseases in themselves.
- **Prevalence:** between 15-25 percent of the adult population in Europe and the US suffers from ongoing pain problems and about 7 percent have chronic pain.
- Chronic pain is one of the most common reasons why adults seek medical care in the US.

Impact on the individual

- **Living with constant pain is incredibly tiring.** Long-term/chronic pain risks to completely dominate life with restrictions in mobility and daily activities and inability to work, resulting in a low quality of life and a negative social situation.
- It is not uncommon for pain to lead to stress, sleep problems, depression, and anxiety, which in turn can enhance the pain experience.
- Risk of developing dependence on opioids (addiction).

Central sensitization – from bad to worse

- **Central sensitization** is a phenomenon in which the sensitivity of the pain increases after a prolonged period of persistent pain. In this condition, the pain spreads throughout the body and the elevated sensitivity means that even a light touch can provoke a pain experience. Other parts of the nervous system are activated and react illogically.
- Central sensitization is difficult to treat and lacks specific drugs.

Costs to society

- For society, the number of patients with long-term pain means a huge burden on healthcare in the form of doctor's visits, physiotherapy, psychological treatment and workplace-related adaptation/training. Reduced working capacity to varying degrees leads to major loss of production for society.

- *40 percent* of all primary care visits occur due to pain.
- In the United States (2010), the annual total cost of chronic pain was estimated to be between *USD 560-635 billion*. By comparison, the corresponding cost for heart disease amounts to USD 309 billion and for cancer USD 234 billion.
- The study "Pain in Europe" estimates the costs to society at *3-10 percent of gross domestic product*.
- SBU (The Swedish National Agency for Medical and Social Evaluation) has calculated the cost for Sweden to a total of approximately SEK 87.5 billion for 2003. Of these, SEK 7.7 billion were direct healthcare-related costs for visits to doctors and other healthcare providers, as well as medicines. The majority of the costs of approximately SEK 80 billion, or >90% of the total cost, are due to indirect costs, i.e., loss of production as a result of illness-related absence from work.

Problems with today's treatments

Conventional treatment consists mainly of anti-inflammatory drugs, antidepressants, antispasmodics, and opioids (a group of substances with a morphine-like mechanism of action). The problems with these treatments include that they are not specifically developed to treat chronic pain.

- **Limited pain relief:** existing drugs often have limitations when it comes to pain relief.
- **Severe side effects:** the pain relief achieved often has a number of disabling side effects such as depression, anxiety, fatigue, impaired physical and mental ability, addiction problems and also harmful effects on the gastrointestinal and cardiovascular systems.
- **Runaway addiction:** In the U.S., an estimated 700,000 people have died due to opioid abuse in the past 20 years.

Various physiological pain mechanisms

- **Neuropathic pain** or nerve pain can occur after diseases and injuries of the somatosensory nervous system and spread within a neuroanatomical innervation area.
- **Nociceptive pain** occurs when pain receptors (nociceptors) in the body tissue are activated, which they do when the tissue is damaged or sometimes already at the threat of injury. Nociceptors are found in most body tissues, in the skin, locomotion, and in internal organs.
- **Nociplastic pain** is a newly introduced concept for pain that occurs due to altered pain sensitivity. Nociplastic pain is pain that can occur without signs of either tissue damage or injury or other disease of the somatosensory nervous system. Clinically, nociplastic pain can manifest itself by activating it more easily and spreading over a larger body area. Clinically, nociplastic pain is characterized by being activated more easily and spreading over a larger area of the body.
- **Idiopathic pain** or pain of unknown cause is a concept of pain that cannot be classified according to the above categories and for which there is no explanatory model.

CombiGenes and Zyneyro's Pain Program

Co-development

- **Joint development:** CombiGene and the Danish company Zyneyro will jointly drive the development of the pain program on a 50/50 basis regarding both costs and revenues.
- The agreement also means that CombiGene will pay Zyneyro an upfront of DKK 5 million in connection with the signing of the agreement. CombiGene has furthermore committed to pay an additional maximum of DKK 11.4 million in continued development support towards clinical Phase 1.

Science

- The program is based on discoveries regarding the role of an intracellular protein called PICK1 (a protein that interacts with C-kinase 1) in modulating neuronal signal transmission via a type of receptors, so-called AMPA receptors, in pain. Simply put, it can be described as PICK1 binding to and controlling the localization and activation of receptors that participate in the transmission of pain signals between nerves in chronic pain. By blocking the interaction between PICK1 and the receptor, pain can be inhibited. (Sørensen AT, Rombach J, Gether U, Madsen KL. The Scaffold Protein PICK1 as a target in chronic pain. *Cells*. 2022;11(8):1255.)

Objectives and scope

- **Objective:** to develop an effective treatment for severe chronic nerve pain without the side effects that today's treatments often give rise to.
- **Two drug candidates:** a peptide treatment (mPD5) and a gene therapy treatment (AAV). The patient's disease characteristics guides the choice of treatment method:
 - The peptide is used in severe temporary pain conditions and is administered directly to the patient on one or more occasions to achieve effective pain relief.
 - The gene therapy is used in severe chronic pain conditions due to illness or damage to the nervous system, including phantom pain and pain associated with various types of back injuries.
 - The mechanism of action and effect are the same with both methods of treatment.

Significant benefits

CombiGene's and Zyneyro's pain program is designed to achieve several major advantages over today's treatment options:

- **No addiction problems:** several of the treatments used today can create severe addiction problems. With CombiGene's and Zyneyro's pain programs, this is avoided.
- **No daily medication for chronic pain:** today's treatment of chronic pain, as a rule, requires daily medication. By instead treating the patient with an AAV vector that "instructs" the body to establish the pain-relieving mechanism itself, one or a few treatments can achieve potentially lifelong pain relief.

Sources

- Gaskin DJ, Richard P: The economic costs of pain in the United States. J Pain 2012, 13:715-724.
- Breivik et al. BMC Public Health 2013, 13:1229
- SBU. Multimodala och interdisciplinära behandlingar vid långvarig smärta. Publikation nr: 341. ISBN: 978-91-88437-84-6. Publicerad: 15 december 2021. <https://www.sbu.se/341>