Pain as a medical and socioeconomic problem

ESTEVE is an international pharmaceutical chemical group based in Barcelona, Spain. Since its foundation in 1929, ESTEVE has been firmly committed to excellence in health care. It has dedicated its efforts to the innovative research and development of new medicines for unmet medical needs with large social impact. One area in which we are focusing our research is the management of pain.

Pain is the most common reason that people seek the help of a physician or take medications. This is consistent with the fact that pain is a common condition on its own as well as a co-morbidity of multiple other diseases and injuries. Pain affects the physical and psychological status of patients, significantly impacting their quality of life. Disturbed sleep, depression, anxiety and decreased cognitive and physical function are often associated with chronic pain. Accordingly, this common and disabling condition has an enormous impact on the wider society, with considerable socioeconomic burden for individuals, employers, health-care systems and society. The costs include those related to the management of pain as well as to lost social interactions, lost productivity, dependency on health-care staff and family, and early retirement. This burden is expected to grow, owing to an ageing population and an increase in chronic diseases associated with pain, such as diabetes and arthritis. The overall individual and socioeconomic impact of chronic pain (medical management, hospitalization and social benefits, including disability allowance and unemployment benefits) on a nation’s budget is enormous. In the United States, chronic pain affects 100 million adults and costs US$560–635 billion (2010 prices) annually. In Europe, national health-care and socioeconomic costs of conditions associated with chronic pain represent 3–10% of the gross domestic product. These costs are consistent with evidence that, worldwide, chronic pain affects more people than does heart disease, diabetes and cancer combined. A study on years lived with disability (YLDs) in 188 countries highlighted lower back pain as the leading cause of YLDs in developed and developing countries.

Pain is in need of new and better therapies

The socioeconomic impact of pain is dependent on high-priority key challenges. There are a large number of unmet medical needs in its treatment and management. Many patients with chronic pain get no or only partial pain relief from current pain treatments, and/or suffer from troublesome side effects. Because of limited efficacy and the impact of pain on quality of life and activities of daily living, as well as increased side effects associated with higher dosage, patients often seek treatment alternatives such as opioids, but these have their own challenges, including misuse, abuse, addiction and overdose. New treatments with better effectiveness, improved safety and tolerability, and, overall, an improved benefit-to-risk ratio are greatly needed.

ESTEVE’s paradigm in the discovery and development of therapies for pain

The multiple dimensions of pain cannot be addressed with an understanding of only nociception. Many different factors and their integration are important in order to identify, design and target relevant interventions for pain. Therefore, ESTEVE’s paradigm for the discovery of effective treatments incorporates a thorough assessment of the type and severity of pain, the underlying causes, associated co-morbidities, and a therapeutic approach aimed at pain relief and the restoration of physical, emotional and social functioning.

At ESTEVE, we base the discovery and development of novel solutions for the management of pain on three approaches:

1. A disease-mechanism-based and multidisciplinary approach. A key aspect of ESTEVE’s research is to address chronic pain as a disease in its own right and as a constellation of syndromes, with distinct underlying pathophysiological mechanisms. A case-by-case approach is needed to design tailored therapies that target the disrupted mechanisms.

   Accordingly, ESTEVE’s efforts focus on understanding pain mechanisms and the discovery of pharmacological strategies that impact them. Studies are done at the molecular, cellular, tissue and organ levels by applying molecular- and cellular-biology techniques, histology, electrophysiology and neurochemistry. Behavioural studies are not restricted to nociception and nocifensive reflexes in response to various stimuli, but also address other dimensions of pain, including changes of innate behaviours or operant auto-medication responses.

   Pharmacokinetic–pharmacodynamics integration is also fundamental to understand target engagement and to optimize the selection and development of lead compounds. Moreover, the concentration–effect relationship at the site of action is useful for translational purposes (to provide information regarding the levels needed for a therapeutic response).

2. A holistic approach to the patient with pain (a focus on the pain syndrome — pain and associated co-morbidities and their consequences). An integrated view of the patient allows the design of treatments with broader therapeutic attributes to those that are currently available. Our target therapeutic profiles reflect this approach, they highlight:

   i) The clinical application (better efficacy and effectiveness, improved safety and tolerability, and overall a better benefit-to-risk ratio relative to current standards of care).

   ii) Patient reported outcomes (for example, activities of daily living, patient satisfaction and global assessment, and adherence to treatment).

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iii) Other overall benefits (for example, less need for additional medication, impact on co-morbidities, fewer physician visits and hospitalizations, and impact on productivity). Special attention is given to the bidirectional flow of information, from the bench to the bedside (translation) and back to the bench (reverse/back translation).

3. Strengthening our core competences and capabilities in the discovery and development of pain drugs, incorporating new ways of thinking, new methodologies and establishing synergies and strategic collaborations. To this end, there are five aspects to highlight:
   i) We have designed and implemented drug-discovery facilities, which became fully operational at the beginning of 2013. The ESTEVE Centre for Drug Discovery focuses only on pain, and is located at the Science Park of Barcelona in the campus of the University of Barcelona. Its location, surrounded by researchers and business, maximizes innovation networks and allows synergy between organizations.
   ii) We developed pharmacological- and mechanistically-relevant approaches to increase the translation of preclinical research. These were based on back translation from clinical practice.
   iii) We established several pain research collaborations with centres of excellence, and four strategic joint units (with a novel architecture for open innovation) that focus exclusively on pain.
   iv) ESTEVE participates in international pain consortia, including EUROPAIN (a project supported by the Innovative Medicines Initiative, IMI) that aims to better understand chronic pain and improve its treatment. It is the biggest public–private pain research consortia in the world and involves scientists that represent multiple renowned universities and pharmaceutical companies. ESTEVE also participates in the NEUROPAIN consortium, a European Seventh Framework Programme project, and in the forthcoming Pathological Neuron–Glia Interactions in Neuropathic Pain IMI-2/Call-7 consortium.
   v) The ESTEVE scientific and medical experience regarding the management of pain, together with regulatory, quality, intellectual property and early clinical development high standards, have configured an ideal platform to advance new models for the treatment of pain.

ESTEVE’s new molecular entity programmes in pain therapeutics

ESTEVE’s focus is on new molecular entity (NME) programmes for pain relief of various aetiologies. Our approach considers that, in many clinical conditions, managing pain as a symptom is not enough; hence our focus on the underlying pathophysiological mechanisms and integrated processes, pain chronification and preventive approaches.

Two programmes of our research and development (R&D) strategy have generated molecules that have favourable clinical data in patients and are proceeding to further clinical development.

Selective sigma-1 antagonist programme

The lead molecule, E-52862/MR309, is a NME and first-in-class selective sigma-1 receptor antagonist (S1RA or S1A). ESTEVE has accumulated significant knowledge of, and expertise in, sigma-1. The sigma-1 protein is unique, without significant structural homology to any known human protein, and research of its molecular
structure and regulation is ongoing\textsuperscript{15}.

The S1A approach is a new mechanism of action (MOA) for the treatment of neuropathic pain of different aetiologies, as well as an opportunity to increase the benefit-to-risk ratio of the treatment of acute and chronic pain by strong opioids. E-52862/MR309 has demonstrated robust efficacy \textit{in vivo} in animal models of neuropathic pain and also potentiates opioid analgesia, while reducing opioid-associated adverse effects. A direct relationship between dose, receptor occupancy in the brain and pharmacological activity of E-52862/MR309 has been demonstrated. Mechanistically, it relies on a multimodal mode of action through modulation of diverse pathophysiologically altered key molecular targets and pathways, which ultimately result in inhibition of pain-related sensitization phenomena\textsuperscript{5,6,10,13,14} (Figure 1).

E-52862/MR309 has comprehensive phase I and phase II data sets that show good safety, tolerability, pharmacodynamics, pharmacokinetics and encouraging clinical results. Development of E-52862/MR309 is ongoing through our collaboration with Mundipharma and Purdue.

Co-crystal of two therapeutic moieties

This programme originated from the integration of two complementary platform approaches.

The first is based on ESTEVE’s proprietary database and knowledge of pain relief efficacy (pharmacodynamics), interactions between different MOAs and chemical structures.

The second relates to the application of co-crystal technologies to obtain active pharmaceutical ingredient (API) co-crystals that by virtue of the unique crystalline structure formed, have the potential to offer a distinctive profile with improved physicochemical properties. Of note, the API co-crystal structure cannot be designed or predicted \textit{a priori} since both the feasibility as well as the molecular ratio of the APIs in the co-crystal are conferred by the molecular assembly that results from the co-crystallization chemical process.

On the basis of results that fulfil the pharmacodynamic criteria, we identified APIs (therapeutic moieties) to which the co-crystal technology could be applied. These results determine: i) whether a co-crystal can be formed, ii) if a co-crystal is formed, does this present a molecular ratio applicable for therapeutic use, iii) if the structure favourably modifies the physicochemical properties, iv) if the conferred physicochemical properties optimize the \textit{in vivo} profile of each moiety (co-crystal mechanistic effect), and v) if each of the APIs contribute in a complementary manner to the therapeutic benefit proposed.

Through this analysis and assessment of physicochemical characteristics, pharmacological data, pharmacokinetics, metabolism and safety profiles as well as a target therapeutic profile concept approach, ESTEVE identified co-crystal of tramadol and celecoxib (CTC) (Figure 2).

CTC is a first-in-class patented new entity API-API co-crystal with a multimodal MOA. The therapeutic focus of CTC is acute and chronic moderate-to-severe pain with a different profile compared with the mono-components and to a combination of tramadol and celecoxib.

Three complementary elements work in tandem in CTC:

1. The intrinsic molecular ratio of the active moieties conferred by CTC, which is the optimal ratio for therapeutic benefit.
2. The co-crystal mechanistic effect that produces optimized absorption and pharmacokinetic profiles of each active moiety, resulting in improved efficacy and better safety and tolerability.
3. The efficacy synergism between CTC moieties with a superior clinical pain-relief effect, owing to the complementary action of four different clinically validated MOAs for pain relief in central and peripheral sites, to produce an integrated pharmacological response.

The therapeutic potential of CTC has been demonstrated in a phase II study of 420 patients with acute post-operative pain. CTC at low doses (low amounts of each active moiety) demonstrated superior efficacy, improved safety and tolerability, and enhanced the benefit-to-risk ratio compared with standard of care\textsuperscript{15}. CTC is now proceeding to phase III development by ESTEVE in the United States and by Mundipharma outside the United States.

**ESTEVE’s commitment to drug discovery and development of treatments for pain**

The initial programmes of our R&D strategy in innovative pain-relief treatments are now entering the next phase of development. The clinical data available so far are very encouraging. Given the significant global unmet medical needs in pain, new treatments are clearly needed. ESTEVE scientists and physicians are committed to the discovery and development of new treatments for the management of pain to improve the well-being and quality of life of patients, and to provide substantial benefit for the patients’ families, physicians and other health-care professionals, and society.

REFERENCES