Reviews • FOUNDATION REVIEW

Tailoring chronic pain treatments for the elderly: are we prepared for the challenge?

Stephen P. Arneric[1], Jennifer M.A. Laird[1,2], Amy S. Chappell[1] and Jeffrey D. Kennedy[1]

[1] Eli Lilly & Company, Neuroscience, Indianapolis, IN 46285, USA
[2] Dept of Pharmacology & Experimental Therapeutics and Alan Edwards Centre for Research on Pain, McGill University, Montreal, Quebec H3G 1Y6, Canada

Chronic pain is increasingly recognized as a disease and accounts for substantial suffering and disability worldwide. The aging 'baby-boomer' generation is creating a tsunami of elderly patients (>65 years old) for global healthcare systems (between 2010 and 2030). The phenotypic expression of chronic pain in the elderly can be influenced by co-morbid diseases (e.g. diabetes, cancer, depression, Alzheimer's disease, etc.), changes in physiological competency (e.g. drug metabolism/elimination) or cognitive reserve. Will a shift in the drug discovery paradigm be required to improve efficacy, side-effects or positively impact quality of life (QoL) in the elderly with chronic pain? This review highlights a number of potential pitfalls that should be considered when delivering valued pain relief medicines tailored for the elderly.

Introduction

Pain remains the number one reason why patients turn to physicians for care and is directly related to four of the top 11 global causes of years lived with disability and suffering [1]. In the USA, the recognition of pain as a leading cause of economic burden was reinforced with a 2011 Institute of Medicine report stating that pain affects more than 100 million Americans and costs >US$600 billion annually in lost productivity and healthcare expenses, more than heart disease, diabetes and cancer combined [2,3]. Pain is formally defined as: '...an unpleasant sensory and emotional experience in association with actual or potential tissue damage, or described in terms of such damage' (http://www.iasp-pain.org). For patients, pain can be defined more subjectively as '...whatever the experiencing person says it is and exists whenever she/he says it does'. Acute pain generally arises in response to mechanical, chemical or thermal stimuli that are noxious or tissue-damaging in nature, and elicits a reflex response that is intended to be protective of further tissue damage or injury. By contrast, chronic pain is a condition that persists long after an initial tissue insult has healed or without any identifiable insult at all such that the pain will occur spontaneously, and no longer serves any useful purpose. Historically, this condition has been characterized by disability and suffering that is greater than 3 months in duration. The nature of

Stephen P. Arneric joined Lilly Research Laboratories in October 2008 as Chief Scientific Officer of the Pain & Migraine Drug Hunting Team and in 2012 became a Lilly Senior Research Fellow. His scientific expertise spans the areas of pain, neurology, urology and psychiatry. Prior tom joining Lilly Dr Arneric was VP of Research & Preclinical Development at Neuromed, and also held senior positions at Pfizer, Pharmacia, DuPont Pharmaceuticals and Abbott. Over the past 25 years he has had PhIII or Launched Product Development experience with Exalgo™, Esreboxetine, Dynastat™, Lyrica™, Cymbalta™ and Detrol™, as well as management and scientific responsibility for delivering 30+ drug candidates into development.

Jennifer M.A. Laird was appointed as Director, Global External R&D at Eli Lilly in 2012, where her responsibilities include evaluating partnering opportunities in analgesia. Prior to joining Lilly, Dr Laird was Executive Director, Translational Science in the CNS and Pain Innovative Medicines unit of AstraZeneca. In her 10 years at AstraZeneca she led preclinical and clinical teams discovering and developing novel analgesics. Previously, Dr Laird held an academic position in Spain, where her laboratory focused on mechanisms of visceral and neuropathic pain, and at Merck's Neuroscience Research Centre in the UK. Dr Laird serves as an honorary professor of Pharmacology & Therapeutics at McGill University, Canada, and on the editorial boards of the European Journal of Pain and Neuropharmacology. She received a bachelor's degree and doctorate in physiology from the University of Bristol, UK, and post-doctoral training at National Institutes of Health, USA.

Amy Suzon Chappell is Senior Medical Fellow at Lilly Research Laboratories where she has worked since 1988 mainly designing and implementing early clinical trials of new compounds for multiple neurological diseases. In 2004 she joined the Cymbalta product team where she oversaw the development and global submission for fibromyalgia, which resulted in an FDA approval in June 2008. She is currently the medical leader for a number of exploratory drugs targeted for pain and epilepsy. Dr Chappell is board-certified in neurology with special competence in child neurology.

Jeffrey D. Kennedy received BA (Zoology) and PhD (Microbiology/Immunology) degrees from the University of Iowa. Following post-doctoral training at Washington University, St. Louis and The Upjohn Company, Dr Kennedy joined Wyeth (formerly Wyeth-Ayerst Research). Over the following 16 years he held a variety of positions of increasing responsibility, most recently director of Pain Drug Discovery Research within Neuroscience Discovery. Dr Kennedy joined Eli Lilly and Company in 2010 where he holds the title of Senior Research Fellow and leads a pain behavioral pharmacology group. Dr Kennedy has published broadly in the areas of cellular immunology, pulmonary inflammation and pain.

Corresponding author:. Arneric, S.P. (Arneric_Stephen@Lilly.com), (stephenarneric@yahoo.com)

1359-6446/06/$ - see front matter http://dx.doi.org/10.1016/j.drudis.2013.08.017

chronic pain has been made more accessible to the general public through the writing of Rachel Thurman [4]. She has written that chronic pain is:

'. . .a serious, widespread, misunderstood, misdiagnosed, and undertreated disease. . .it is only in recent years that chronic pain has been understood to be a condition with distinct neuropathology – untreated pain can eventually rewrite the central nervous system, causing pathological changes to the brain and spinal cord that in turn cause greater pain – though this understanding is not widely known.'

Although beyond the scope of this review, two reviews that give key scientific perspectives are from Apkarian *et al.* [5], who have provided functional MRI data showing brain changes secondary to chronic pain, and from Latremoliere and Woolf [6], showing that chronic pain is accompanied by dysfunctional, neuroplastic, 'disease-like' changes in the central nervous system (CNS).

Acute and chronic pain are prevalent in the elderly (>65 yrs) as a result of an increased incidence of chronic diseases, frailty, falls and other health problems associated with aging [7], and can have detrimental effects on function and quality of life (QoL) [8,9]. Despite reports showing that older patients are among the highest users of analgesics, there are relatively few randomized controlled trials (RCTs) that have focused on determining the safe and effective use of these analgesics [10]. This is especially true for those who are frail or cognitively impaired, which is often an exclusion criterion in RCTs [11]. Claiming safety and effectiveness of analgesics in the elderly might not be accurately represented given that data derived for label claims can be often biased toward younger subjects with fewer co-morbidities (a notable exception being post-herpetic neuralgia that predominantly occurs in the elderly).

Life expectancy for the elderly will continue to increase (Fig. 1 illustrates trends from 1970 to 2030) as indicated by the Center for Disease Control and The Global Burden of Disease Study 2010 (GBD 2010), a systematic, scientific effort to quantify the comparative magnitude of health loss owing to diseases, injuries and risk factors by age, sex and geography [12]. Our increasing life expectancy, due largely to advances in consistently available nutritional and healthcare options, in conjunction with the 'baby-boomer' era, will result in nearly a doubling (to ~70 million) elderly individuals in the USA by 2030 (http://www.census.gov/population/projections/data/national/2012.html). This 'tsunami' of elderly people will flood global healthcare systems requiring pain relief options commensurate with their unique needs and tailored to improve the quality of their extended lives. Given that drug development life cycles range from 10–15 years from conception to launch (http://www.phrma.org/media/multimedia/drug-discovery-timeline), we should be preparing now to deliver optimized analgesic drugs as well as improved prescribing and monitoring approaches for the elderly by 2030.

This review highlights actual or potential pitfalls that stakeholders have fallen into or not proactively considered for

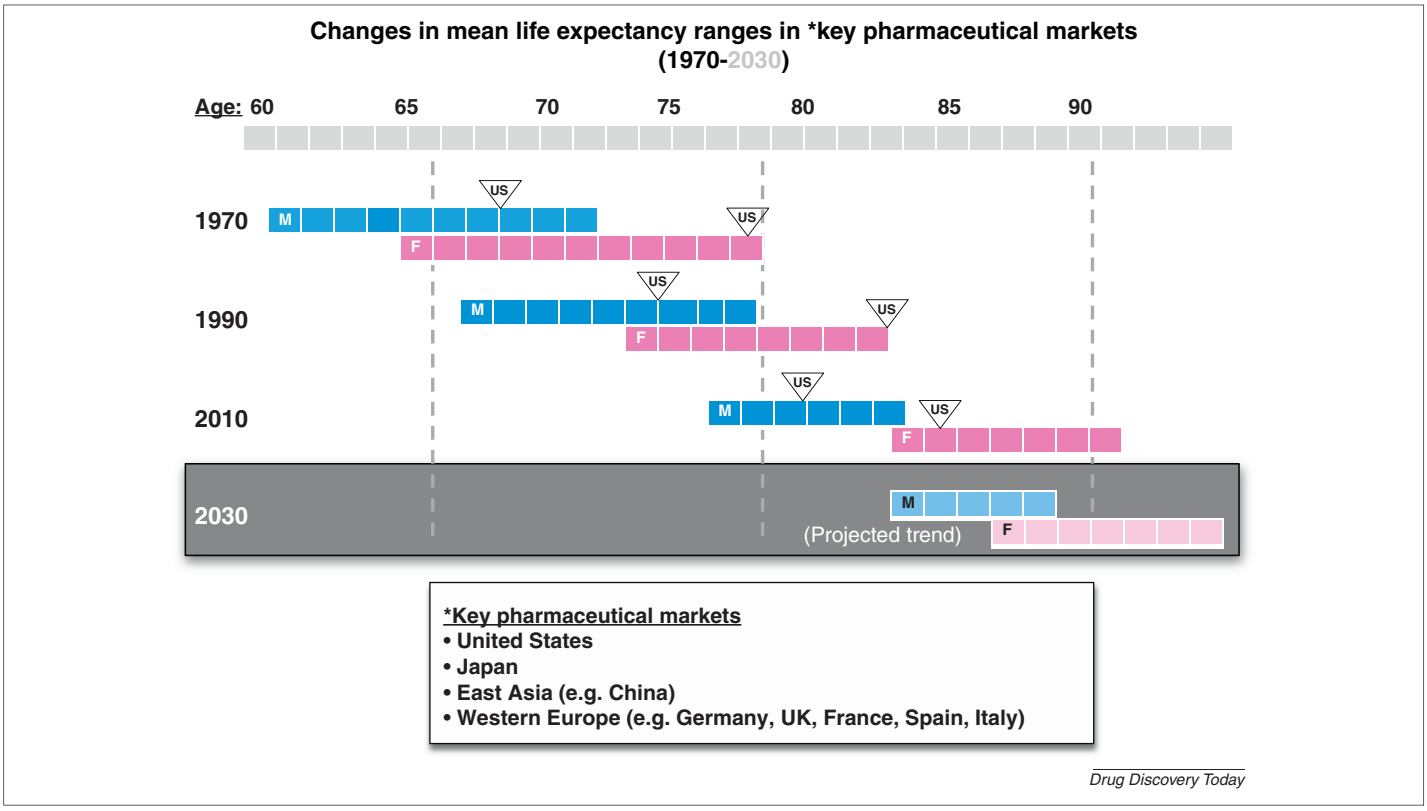

FIGURE 1

Depicted are the range of mean life expectancies for males and females across several key pharmaceutical markets. The triangle containing US indicates the mean values for the USA. The projected data were derived from taking the average shift seen over the previous 40 decades. Original data were obtained from the Global Burden of Disease Study 2010 [12].