ELSEVIER

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

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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

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

Please cite this article in press as: S.P. Arneric, et al., Tailoring chronic pain treatments for the elderly: are we prepared for the challenge?, Drug Discov Today (2013), 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

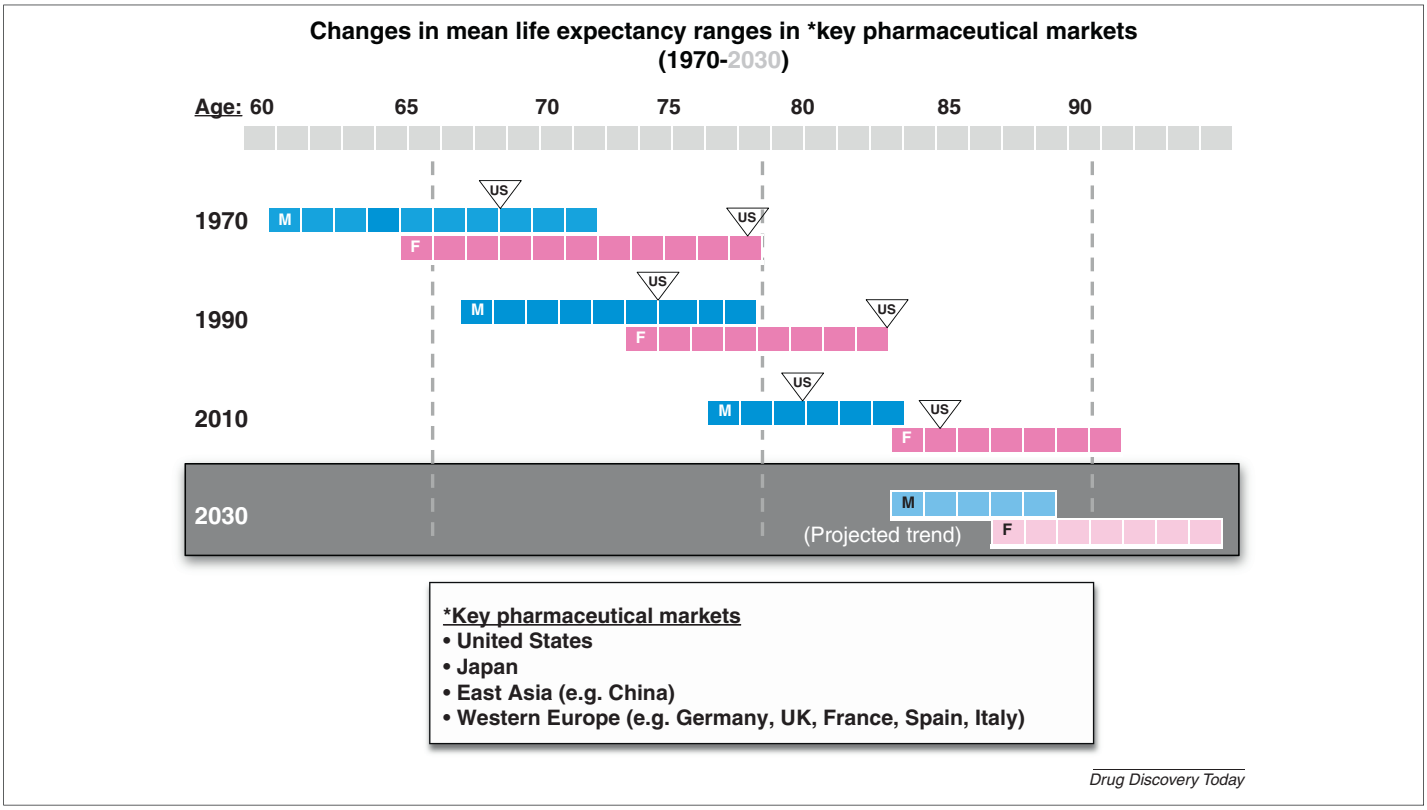

FIGURE 1

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].

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delivering valued pain relief medicines tailored for the elderly. Questions that will be addressed include: what are the needs of the elderly for pain relief and how are they different from the younger adult? Are there differences in pain perception and processing in the elderly? What are the gaps in existing pain treatment options when considering the elderly? Last, but not least, is there sufficient reason to believe that a paradigm shift should occur in the way the industry hunts for pain relievers to meet the need of the elderly?

Pain in the elderly population

Older people are more likely to have chronic painful conditions, surgical procedures and general musculoskeletal pain than their younger adult counterparts [13–15]. More than 20% of the elderly population are taking some form of analgesic for more than 6 months (i.e. they have chronic pain) [5,13,16]. What is alarming is that, for those in a community-dwelling setting that reported pain, 75% were not given pain relieving treatment and 45–80% of those receiving treatment reported inadequate relief [5,17]. Advances in treatment of chronic diseases like heart disease, diabetes and cancer have contributed to prolonged life expectancy, and thus one of the key objectives for patients as they live longer lives is to ensure a good QoL. Four key domains (i.e. capability clusters) of living, like the legs on a stool, must be maintained to keep QoL balanced: mental function, physical function, health maintenance and social networking (Fig. 2). Prolonged disruption in one or more of these capabilities, especially in the elderly, results in relatively rapid increases in frailty, morbidity and mortality [18–20].

There is growing clinical evidence that poorly controlled pain will translate into declining physical function and mobility [21–23], advance to increased risk of falls and frailty [23] and eventually result in disability [24,25]. Frailty consisting of muscle weakness, sarcopenia, osteoporosis, chronic under nourishment and reduced walking performance or endurance is a predictor of exacerbated adverse health outcomes and a higher risk of death [26–28]. Thus, providing optimal pain control in the elderly without causing negative impact on QoL is key to preventing a downward spiral in health status.

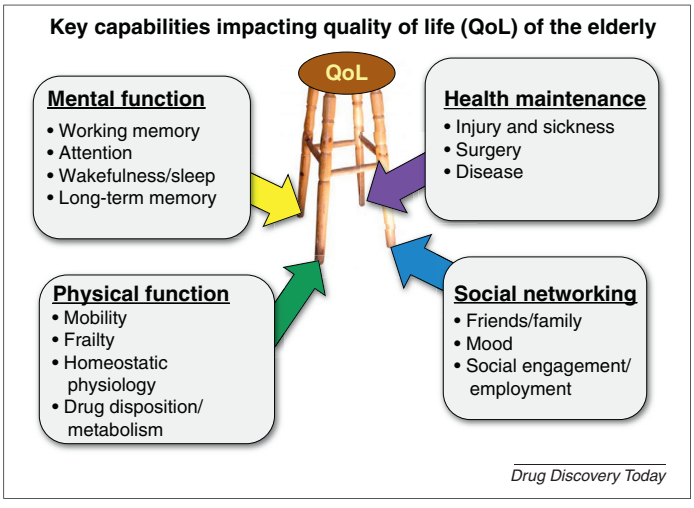

FIGURE 2

Four key capabilities (domains of function) that comprise quality of life (QoL) are mental function, physical function, social networking and health maintenance. Compromising the integrity of one or more of these domains, like compromising the integrity of the legs of this stool, can result in a pronounced imbalance in QoL. There is a growing volume of literature that reports chronic pain could affect one or more dimensions of QoL depending upon the etiology of the original insult [20–28]. Unfortunately, treatments used to relieve pain might, on their own, also positively or negatively impact another dimension related to QoL [77,87,88,93].

Changes in pain processing in the elderly

Is normal 'physiological' pain detection, processing and endogenous modulation altered in the elderly population compared with middle-aged or young adults? There have been a number of studies addressing this question by examining responses to experimentally induced pain in healthy individuals without chronic pain. A very recent meta-analysis by Lautenbacher [29] reviewed pain threshold in 24 studies with a wide variety of methods of inducing experimental pain and established clear increases in pain threshold with aging. Effect sizes were larger in studies where the age differences were larger, and there was a slightly greater increase in pain threshold in women compared to men with aging [29]. At least some of the loss of human somatic sensory integration probably occurs at the level of the primary sensory neuron (Fig. 3).

A parallel decrease in the spread and magnitude of brain activation in response to acute painful stimuli measured using functional MRI is also observed in the elderly compared with young adults, even after correcting for age-related reductions in brain volume [30]. Thus, the ability to detect damaging stimuli in the external environment becomes less sensitive with age, in common with other diminished function of sensory modalities like vision and hearing. The loss of sensitivity might not be limited to the external environment, and also extends to internal organs. Consistent with this concept, responses to controlled acute balloon distention during percutaneous myocardial interventions reveal that the elderly have less pain in response to cardiac ischemia [31]. Thus the elderly typically seek treatment for myocardial ischemia later than their younger counterparts, which unfortunately translates into greater tissue damage before treatment intervention, and a poorer prognosis compared with a younger cohort.

The loss of noxious stimulus detection sensitivity with age probably contributes to an increase in injuries in the elderly [28] and, thus, indirectly, to more pain, but otherwise appears at odds with the greater incidence of chronic pain in the elderly. In contrast to the loss of pain sensitivity, no change or a mild increase in responses to suprathreshold painful stimuli (a decrease in pain tolerance) in normal elderly subjects is revealed by a meta-analysis of six studies [29]. However, this subtle and small increase in the intensity of reactions to external painful stimuli seems insufficient to account for the marked increase in incidence of chronic pain in the elderly. By contrast, age-related changes in endogenous pain modulation could be a key contributor to the increased likelihood of chronic pain in the elderly. Endogenous pain modulation is a normal feature of pain processing, and a simple measure of the strength of endogenous pain modulation known as 'conditioned pain modulation'. This dimension of pain processing can be readily assessed in experimental human studies. To do this, a painful stimulus is applied to one part of the body and the extent to which it inhibits pain sensation from another area of the body is measured. Several studies in normal subjects have examined the effect

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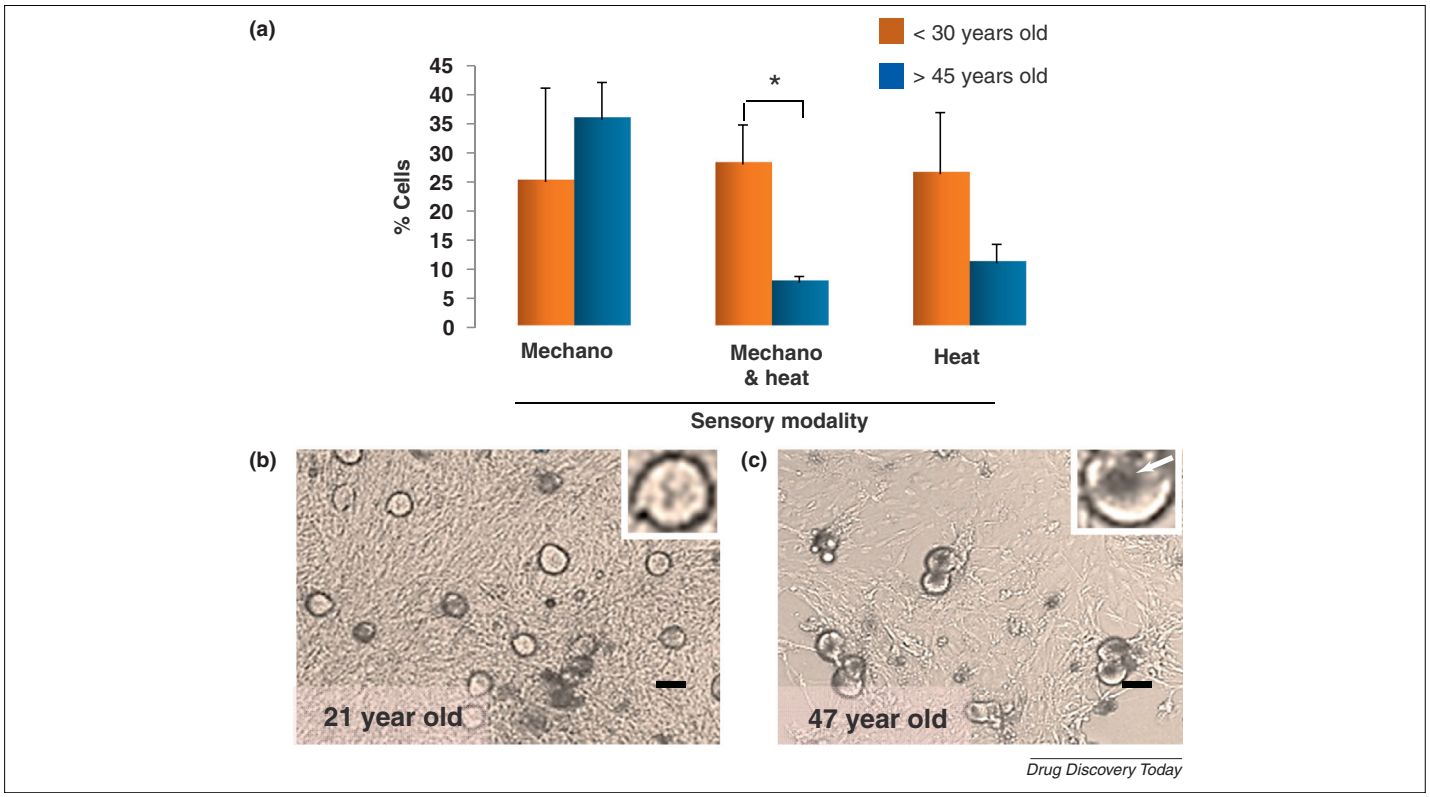

FIGURE 3

Human dorsal root ganglia (DRG) *ex vivo* studies at AnaBios reveal age-related changes in sensory processing. **(a)** The responses of primary human DRG neurons in culture to mechanical and thermal stimulation were recorded in calcium imaging. DRG neurons isolated from donors over 45 years of age exhibited a significant reduction in the proportion of cells responsive to mechanical and thermal stimulation. **(b,c)** Age-dependent accumulation of metabolic byproducts (lipofuscin granules) is visible in human DRG neurons in culture. The dark lipofuscin granules are common in cells isolated from older donors (inset, white arrow). Scale bar: 50 mm (Pers. Comms: Dr A. Ghetti, AnaBios Corporation, Phase X^{TM} technology; http://www.anabios.com/technology.html).

of age on expression of conditioned pain modulation [32–35]. Healthy elderly subjects consistently show weak inhibition, or even facilitation compared with younger adults in all studies to date [32–35], with the caveat that all of these studies are cross-sectional rather than longitudinal. Weak expression of conditioned pain modulation in young and middle-aged adults is a robust predictor for the development of several chronic pain conditions [36,37], thus poor endogenous pain modulation in the elderly could render them particularly vulnerable to developing chronic pain conditions in the face of injury or disease. Moreover, co-morbid diseases more common in the elderly can affect endogenous pain modulation. For example, in Alzheimer's disease (AD) patients there is evidence of a change in the endogenous opioid system consistent with impaired inhibitory pain modulation, because both regional levels of endogenous opioids [38,39], as well as opioid receptor numbers [40], change in this elderly population. Moreover, the ability to communicate adequately the aversive nature and intensity of pain, or its relief with treatment, can be compromised in the mildly cognitively impaired older population, and would perpetuate the burden of chronic pain [41–43].

In conclusion, studies in healthy human subjects have shown that the elderly, as compared with younger adults, are less sensitive to damaging stimuli and have an equivalent tolerance for painful stimuli. However, in contrast to young subjects, the elderly fail to engage endogenous inhibitory control mechanisms in the face of painful stimuli, and this deficit, combined with the accumulation of disease and injury with age, probably explains the increased burden of chronic pain in the elderly population.

Changes in nociceptive processing with aging: preclinical evidence

The vast majority of our knowledge of the physiology of the pain system comes from preclinical studies in animals. However, all but a tiny minority of these studies have been carried out in young adult animals, and pain responsiveness in aged animals, whether basal thresholds or in the context of an injury/insult, has not been investigated with the same systematic rigor and depth as has been applied to studies using young animals. Laboratory rodents show signs of aging and senescence that parallel many of the changes observed in humans, even though they live in a protected environment [44], and a number of behavioral studies of the effect of age on responses to noxious external stimuli have been conducted in normal animals [45–48]. Although animal pain models have proven the ability to reflect clinical efficacy based on back-translation studies using standard-of-care drugs [49], some level of caution is perhaps warranted regarding how data are interpreted, in part due to the fact that most preclinical studies rely on evoked responses and do not assess the emotional quality of pain or the dimension of spontaneous pain [50,51]. This point can take on increased relevance when reviewing behavioral data from pain studies using aged animals, given the kinds of cognitive and motor

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changes that become increasingly manifest with increasing age as noted below. Such interpretational caveats aside, a significant gap remains in our understanding of the extent to which either expression of the molecular therapeutic targets (e.g. opioid receptors) or pain signaling pathways could be fundamentally altered with age.

Among studies that have been reported, considerable controversy exists; data are often conflicting and difficult to compare across studies, given great variability in the animal species, strains, ages, sex and experimental pain model, conditions and endpoints employed. For example, although the vast majority of the pain literature uses male Sprague-Dawley rats, studies reported with aged animals often use a variety of other rat strains such as Fischer 344, F344/BNF1, Lou or Wistar strains based on experience showing animals can reach advanced age with general overall good health and/or do not gain weight as rapidly as Sprague-Dawley rats. Given the well-known variability that genetic background plays in the manifestation of pain responses across rodent strains as well as humans [52,53], the lack of a standard strain used for most aged animal studies further complicates interpretation of data and resulting conclusions drawn. Likewise, either increased, decreased or no change in pain sensitivity has been reported in aged rats depending on whether acute or nerve-injury models are used for study [46,54,55]. And, perhaps at the most fundamental level, there are differing views of what constitutes aged or senescent animals. Many rat pain studies use animals of varying age ranges of approximately 2–3, 10–12 and >24 months of age to represent young, adult/mid-aged and old, respectively; however, these roughly approximate human ages of 20, 30 and 60 years, hardly representative of what is commonly thought of as old in society today [56]. Numbering even fewer are reports using truly senescent animals (>30 months old) that would more closely approximate the age range the 'baby boomers' will occupy over the next two decades.

Likewise, other caveats make the interpretation of pain model studies in aged animals challenging, including well-recognized changes in cognition or learning ability that are known to impact human pain perception and/or reporting ability [57–59]. Significantly, such age-related changes are known to occur over a time span that varies across strains and depends greatly upon the neurobiological or psychological function being measured, each of which might have some impact on pain perception or ability to display nocifensive behaviors [60,61]. In addition, other physical changes in musculature, nerve fiber density, connective tissues and bone density in old animals could lead to conclusions of either increased or decreased pain sensitivity that are unrelated to sensory nerve signaling capability [55,62–64].

So what does the limited available information tell us about the basic physiology of changes in nociceptive processing with aging? Despite the many caveats to studying pain in aged animals (the majority of which are rodent studies), some general trends emerge that suggest aged animals might not be equivalent to younger animals in aspects of pain perception and responsiveness and corroborate similar age-related changes observed in humans. Several studies demonstrate higher levels of oxidative stress and reactive oxygen species production in aged animals and they speculate that this would lead to an increased 'inflammatory tone' with heightened pain sensitivity [65–67]. These data would appear to contrast, however, with other studies showing reduced production of proinflammatory cytokines by cultured mononuclear cells from aged rats in response to inflammogens such as carrageenan and reduced pain responses when the resulting culture supernatants are injected, again emphasizing the complexity at play when studying an integrated response to a noxious stimulus in aged animals [68]. Similarly, a number of studies have demonstrated hyporesponsiveness of aged animals to analgesic compounds, in particular opioid drugs. However, few if any studies have been sufficiently rigorous to establish whether the hyporesponsiveness with age is the result of decrements in opioid receptors, their downstream signaling cascades, loss of peripheral sensory nerve fibers that can occur, impairments in motor responsiveness or altered integration of other pain modulatory circuits at higher centers [46,47,63,64]. Such age-related deficits appear in some cases to be balanced by changes in neuronal plasticity as reflected in decreased firing thresholds, increased spontaneous firing and loss of descending inhibitory tone [69–71], all consistent with changes reported in aged humans while highlighting the challenges in data interpretation and the ability to draw clear conclusions from the study of pain using aged animal models.

Overall, our view is that the accumulated data are not sufficiently comprehensive to determine clearly whether greater translational success might derive from studying pain pathways and the effects of analgesic pharmacological interventions in aged animals. Moreover, very little is known with respect to whether aged animals differ from their younger counterparts in either expression patterns or functions of the many ion channels, enzymes, G-protein-coupled receptors and other molecular targets that have been researched as potential mechanistic approaches for the discovery of novel therapeutic agents for chronic pain. Likewise, the advances of the pain imaging field have largely ignored the study of aged animals. As such, it remains to be determined whether these current knowledge gaps represent a major impediment to our ability to tailor novel therapeutic agents to treat older patients, or whether the apparent differences truly are insufficient to warrant tailoring for an aged population.

For those sufficiently intrigued with the concept of tailoring medicines for an aged population and who rely upon preclinical models to inform refinement of future therapies, it will be crucial for us to standardize possible strains, ages and experimental conditions such as those currently employed in pain models with younger animals to the same extent [72]. Without an alignment of such efforts, it will be even more difficult to amass more robust, in-depth and comprehensive knowledge regarding pain mechanisms in the aged that can then be used as sufficient evidence to drive future drug development decisions rationally. In summary, this preclinical literature is filled with knowledge gaps, and it points to the need for studies that concurrently integrate behavioral, electrophysiological and biochemical endpoints to establish which mechanisms initiate, support and maintain painful responses in aged subjects.

Pain management in the elderly

Understanding the treatment goals to be met for the patient and caregiver should be the primary guidelines for intervention. However, choices are often forced into a paradigm of short-term assessments of access and costs related to treatment without

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considering the longer term costs of not choosing the optimal treatment paradigm. Age-associated changes in body composition and organ function can produce predictable changes in metabolic and pharmacokinetic responses to medicines compared with younger adults [18–20,73–75]. Current treatment guidelines for the elderly frequently do not take such age-associated changes into consideration and instead advocate a 'start low and go slow' in this patient population; however, such guidance often results in inadequate pain relief.

Although we do not intend to suggest that all, or even most, of the same strategies used for pediatrics should also be used for the elderly, there are some notable parallels that we highlight in this section and in the section on evidence gaps. For example, would it not be reasonable to dose elderly patients on a weight-based or body-mass-based basis as is commonly done in pediatric patients? Remarkably, in a majority (>80%) of North American teaching hospitals the curriculum does not properly inform medical students about the known problems associated with using analgesics in an elderly population [76]. In the other extreme, using an ultra conservative risk management dosing strategy is often interpreted to mean 'start low and stay low', which actually compounds the risk of inadequate pain relief [77] and poor patient outcomes. It is not well recognized that low dose use of opioids is correlated with progression to delirium (often inappropriately interpreted to reflect opioid overdose) in hip fractures with severe pain, whereas no significant association of delirium was found with use of high dose opioids in either cognitively intact or cognitively impaired patients where delirium can be more common [78]. Thus, pharmacokinetics and pharmcodynamics are important endpoints to be evaluated in the elderly.

Cognitive impairment is a significant issue in the management of pain in the elderly. In 2000, around 30% of patients with dementia were in nursing homes with 45–80% reporting being in pain [7–9,13–15], and yet were consistently undertreated [79–82]. Reasons for this include difficulty in assessing pain owing to various manifestations of agitation (e.g. crying, screaming, grimacing, delusions, hallucinations, aggression, anxiety, apathy, dysphoria) combined with diminished communication skills (note, again, similarities to the pediatric population). These patterns of behavior can be inappropriately diagnosed as affective in nature and treated with antipsychotics instead of with analgesics. Increasing evidence, however, suggests that this agitation might be related to untreated pain that can create a vicious cycle of misdiagnosis and poor treatment outcomes [83–89]. One additional consideration often overlooked is the number of past surgeries a patient has undergone. There is increased recognition that serious surgeries (e.g. joint replacement or cardiac surgery) can cause temporary (up to 26%) and prolonged cognitive decline in a significant number of elderly individuals (~10%) [90], which has led to plausible mechanistic links being drawn between adverse anesthetic effects and the molecular pathological mechanism of AD. To anchor this relationship, additional prospective longitudinal studies will need to be conducted that assess surgical interventions, effectiveness of pain management, progression to AD and incidence of pain in AD. Table 1 summarizes a number of key considerations when choosing pain management interventions. Notably, these are intimately linked to the capability clusters that constitute a balanced QoL.

Current pain management choices and limitations for the elderly

Today's armamentarium of pain relievers can be compiled into four major classes: nonsteroidal anti-inflammatory drugs (NSAIDs) like naproxen and coxibs, and related analgesics like acetaminophen; antidepressants (e.g. amitriptyline); anticonvulsants (e.g. pregabalin, carbamazepine); and opioids (e.g. morphine). There are benefits and cautions associated with use of drugs from each of these classes.

Compared with younger adults, safe and effective treatment of pain in the elderly requires specialized knowledge and training in pain management. Treatment plans require knowledge of concurrent medications and the potential impact and influence of comorbid medical and psychosocial problems. Important drug interactions that can affect analgesic actions and that can yield side effects are crucial to understanding this population because it has a much reduced physiologic reserve than a younger adult population. One needs to be aware of relative and absolute contraindications to certain drugs that are commonly used by older adults [9,91,92]. A recent publication highlights that drugs from two (antidepressants vs anticonvulsants) of the four main analgesic classes can give the same relative pain relief at their optimal dose but can show notable differences in their side effect profiles and impact on QoL capability clusters [93]. Table 2 highlights some of these key considerations [9,80–82,91–98].

Evidence gaps in pain management for the elderly

Although it is true that many contemporary clinical trials include elderly patients, a review of 10 000 subjects over 83 clinical trials for osteoarthritic pain found that only 2.3% of subjects were aged over 65 years, and none were older than age 85 [10]. The bias away from older patients is not limited to analgesics [11]. In fact, very few trials have justified an upper age limit; and, for many, an upper limit actually conflicted with the aims of the study. Eliminating upper age limits from RCTs is one way to help ensure that clinical

TABLE 1

Domains that affect choices of pain treatment approaches

Pain	Emotional	Physical/physiologic	Co-morbid diseases
Intensity	Level of social support	Level of conditioning; reproductive status	Concurrent pharmacotherapies (e.g. control of cardiovascular disease)
Concomitant symptom clusters (e.g. shooting pain vs numbness)	Employment status	Number of past surgeries and head trauma history	Alcohol and tobacco over-use
Number of pain types	Mood disorders	Body mass index	Cognitive decline
Location and source of pain	Abuse risk	Renal and hepatic function	Sleep disorders

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TABLE 2

Current pain management choices and limitations for the elderly

Treatment options	Domains affecting treatment choices				Capability clusters affectingquality of life			
	Pain intensity and type	Emotion	Physical/ physiologic status	Co-morbidity	Mental function	Social networking	Health maintenance	Physical function
NSAIDs/ acetominophen	• Mild to moderate pain and inflammation • Acute and chronic	• Not efficacious	• Can cause GI irritation	• NSAIDs can affect BP control • Drug metabolizing interactions	• Can improve agitation in elderly	• Mobility improved	• NSAIDs must be withdrawn before surgery owing to bleeding potential • Liver and renal damage • Can impair immune function	-
Antidepressants	• Moderate to severe musculo-skeletal and neuropathic • Chronic only	• Treats anxiety and depression	• Can affect blood pressure	• Can disrupt sleep • Drug metabolizing interactions	• Can improve cognitive performance	• Can positively influence mood • Mobility improved	-	-
Antiepileptics	• Moderate to severe neuropathic • Chronic only	• Some treat anxiety • Sedation	• Avoid gabapentanoids in renalimpaired	• Drug metabolizing interactions	• Can blunt cognitive performance	• Can positively influence mood	-	• Can cause sedation
Opioids	• Moderate to severe pain • Acute and sometimes chronic	• An abuse risk • Sedation	• Can cause physical dependence	• Avoid with alcohol dependence • Exacerbates constipation	• Can blunt cognitive performance	• Treatment is negatively perceived by society	• Causes chronic constipation • Can influence immune function	• Can influence hormonal balance

trial results will generalize to the elderly population. Although a trend to include elderly individuals in trials has been seen during the past 5–10 years for some therapeutic indications, it is still not optimal across all treatment approaches. Inclusion of elderly patients can force larger sample sizes and development costs to achieve adequate power because they might be more susceptible to adverse events and treatment discontinuations. When faced with today's leaner development budgets, expanding patient enrollment becomes no small challenge. Understanding the actual treatment benefit:risk ratio in the elderly will be crucial in establishing the true value of our future pain relief medicines.

Approaches to evaluate and validate clinical instruments for assessing pain in demented individuals are under development [83,99]. Increasing evidence has shown facial expression of pain is distinct from the expression of other basic emotions [100–102]. Facial responses to pain are being recognized as having relevance for the diagnosis of clinical pain despite a widely held belief that the elderly become more stoic in their expression of pain, a conviction that is even shared by seniors themselves [21]. Machine recognition of facial features of pain in infants has shown some promise [100]. Given the parallels in communication challenges between infants and an aged demented population, it seems surprising that more work has not been done in the area of facial pain recognition in the rapidly growing AD population [102]. The rapid advance in sophisticated facial recognition software, together with the concordant meshing of functional imaging techniques expected in the not-so-distant future, should enable a more reliable assessment of the status of elderly patients in pain who also have co-morbid dementia. For now, determining whether existing analgesics might be less effective in the cognitively impaired older population [41], or whether the clinical instruments used to detect pain relief are simply inadequate [102], will require more in-depth clinical study. Perhaps both challenges might be valid. How the outcomes of more objective clinical instruments will then be meshed (ethically and legally) with a patient's self-report will need time to be carefully studied and weighed up before final treatment, policy and reimbursement decisions are made [103].

Valued pain relief medicines for the elderly

Customers of medicines include patients, their caregivers, payers and regulators. Historically, the patient, as payer, and caregivers were the primary voices articulating what constituted value in a medicine. Two fundamental assumptions have been: (i) that medicines are intended to restore and improve QoL for patients; and (ii) that patient QoL is influenced by a medication's impact on need (efficacy), safety and activities (perhaps more appropriately termed capabilities) of daily living (ADLs). Over the past decade there has been increasing influence by regulators to define an effective medicine, and to provide scientific evidence for this 'effectiveness' via health technology assessments. Effectiveness can be defined in the context of health outcomes where 'effectiveness' = efficacy + safety + QoL. Third party payers (TPPs) have become gatekeepers to the access of new 'valued medicine' where value = health outcomes/costs to deliver the overall outcomes. For pain therapies a major challenge remains regarding how to measure outcomes related to QoL (currently not in label claims) and efficacy objectively, given that both of these measures are predominantly patient reported, subjective and nonverifiable. Creating and validating clinical instruments that would objectively assess QoL and pain relief efficacy would provide a way to balance

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the equation quantitatively – putting on one side the unmet needs of the elderly pain patient and society and on the other side the TPPs and their mandate for value.

Some have argued that the pharmaceutical industry, payers and regulators sit in separate camps regarding their thinking about how to develop and approve future therapeutics. Below are three fundamental assertions that the authors here hope will stimulate some thoughtful evaluation of, and perhaps changes to, our current approach to developing analgesics for the elderly:

- Reproductive safety considerations should be less aggressive when tailoring pain therapeutics for the elderly, whereas assessment of other safety concerns (e.g. mobility and cognitive function) should be more rigorous.
- Novel objective clinical instruments that assess pain indicators, for example computer-assisted facial recognition [102] or pervasive, continuous home assessment [104], should be studied and evaluated and, if proven effective, become available to all physicians treating pain.
- Approval of future pain relief medicines in the elderly should be based on impact of pain relief (whether reduced intensity, frequency or aversiveness) or its ability to improve 'capabilities of daily living' (or QoL) for those in pain. For example, today if analgesic B gives the same reduction in pain relief as analgesic A (the current standard of care), and has some notable side-effect advantage (e.g. less emesis), it could be approved, but the prognosis for achieving favorable reimbursement or access is poor. If, by contrast, analgesic C has the same efficacy outcome and could objectively show remarkable improvements in mobility (e.g. self-ambulation or vehicular), productivity (if employed), ability to self-manage finances and supportive functions (e.g. grocery shopping) or decreased preponderance for hospitalization, then all major stakeholders (patient, caregiver, payer and regulators) should have reason to support access to such a treatment. More thought provoking yet is the possibility of a treatment (drug D) that is not recognized as altering pain intensity detection (only its perception of aversiveness) and improving all of the key capability clusters related to QoL. Currently, most drug discovery programs do not screen for this type of activity.

Summary and concluding remarks

Pain is a significant health challenge in the elderly. Despite its widespread prevalence, there is clear evidence for the under-treatment of pain – in part owing to declining physical and mental function, dynamic-, age- and insult-related changes that occur to our sensory circuits, and our limitations in available treatment options. The growing global demographics of the elderly, the evolving value system that guides approval of and reimbursement for new medicines and the existing gaps that need to be overcome for the management of later life pain [105] reinforce the need to refocus resources and act quickly to effect a paradigm shift in the drug discovery process [106] required to identify valued pain relievers for the elderly.

Acknowledgments

Our sincere thanks to: Dr Jit Banerjee and Dr Jeffrey A. Kaye at Oregon Health & Sciences University for opening the door to our continually growing appreciation of the challenges related to developing and improving treatments for the elderly; to AnaBios for sharing its human dorsal root ganglion neuron data; and to Dr Olof Karl Larsson at Eli Lilly & Company for his support of geriatric pain research and comments on this manuscript.

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