

Narrative Review



Chronic Pain in the Elderly: The Case for New Therapeutic Strategies

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Background: Elderly patients in general exhibit a higher incidence of chronic and neuropathic pain conditions. This group poses a particular clinical challenge due to age-related pharmacokinetic and pharmacodynamic issues, comorbid conditions, and polypharmacy, as well as frailty and cognitive decline. Poor control of pain has consistently been identified as an issue for older people. The identification of safe and efficacious treatments for chronic pain remains a critical public health concern, especially considering the progressive increase of the world's elderly population.

Objectives: This narrative review deals with the principal alterations of the somatosensory system together with changes in non-neuronal cells in the course of aging. The possibility to control chronic pain based on an innovative strategy which addresses non-neuronal cell dysregulation control will also be discussed.

Study Design: Narrative review.

Results: Peripheral nerves display functional, structural, and biochemical changes with aging that mainly involve A δ fibers. Alteration in the responses to heat pain in the middle insular cortex and primary somatosensory cortex are also observed in the elderly. In general, pain threshold increases with age while the threshold of pain tolerance remains unchanged or decreases. Additionally, other important modifications of the pain perception system in this age group consist in a clear reduction in the descending inhibitory capacity with an associated increase in central sensitization. Furthermore, different changes concern immune system cells, such as mast cells and microglia, that with age show an increase in their sensitivity to noxious stimuli and a decreased capability to be regulated by homeostatic endogenous systems. Since these cells are the primary interlocutors for pain neurons, their alterations lead to changes that promote persistent neuroinflammation, thereby impacting pain neuronal cell functionality.

Limitation: This review is not an exhaustive review for the current evidence supporting the role of immune cells in influencing pain somatosensory neuron functions. It is also important to stress the small number of studies designed to determine the efficacy and safety of anti-pain therapies in elderly patients.

Conclusion: Non-neuronal cells of immune system origin such as microglia and mast cells, along with astrocytes, are capable of influencing pain somatosensory neuron functions. These nervous system non-neuronal cells may thus be viewed as innovative targets for persistent pain control. Among therapies aiming at preserving the functionality of non-neuronal cells, palmitoylethanolamide, with its high efficacy/risk ratio, may be an excellent co-treatment for the ever-growing elderly population with chronic pain.

Key words: Elderly, chronic and neuropathic pain, mast cells, glial cells, neuroinflammation, micronized and ultra-micronized palmitoylethanolamide

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Age brings pain: osteoarthritic back pain, especially in the low back or neck (around 65%), musculoskeletal pain (around 40%), peripheral neuropathic pain (typically due to diabetes or postherpetic neuralgia, 35%), and chronic joint pain (15% – 25%) (1). Pain seems to accelerate aging, as well (2). The ever-growing worldwide proportion of older people and lifespan (3) begs the questions: will population aging be accompanied by a longer period of good health, and particularly a long pain-free life? Are physicians prepared enough for the challenge of persistent pain treatments in the elderly?

The societal burden of persistent pain is considerable (4-6). Management of chronic pain is frequently complex, since analgesics currently available for chronic and neuropathic pain in adults are effective in less than 50% of cases and pain relief is usually only partial (7). Pain control in the elderly is complicated by many unresolved problems, e.g., difficulty of diagnosis, substantial lack of clinical studies, and total lack of safe and effective therapies (8-10). As a result, pain in the elderly is oftentimes neither well recognized nor adequately treated (10,11). Pain assessment in the elderly is complicated by the frequent presence of chronic clinical conditions, the presence of multiple causes of pain, and multi-drug treatment that can interfere with the mechanisms of pain (12,13). Despite its limitations, pain self-reporting is often deemed to be the gold standard in pain assessment. However, self-reporting might become compromised in neurological disorders such as dementia, in which individuals often have little ability to communicate (14). The use of rating scales is often further complicated by the presence of visual and auditory deficits. Although the elderly are the biggest users of analgesics, only a small number of randomized, controlled trials designed to determine the efficacy and safety of these therapies in elderly patients have been carried out (9).

The management of chronic pain in the elderly constitutes a challenge to the clinician. When considering pain experience in elderly people, it is important to be aware of any age-related alterations in pain reporting and processing and factors that might contribute to such changes. Positive results in the treatment of pain in aging can only be overcome by using innovative therapeutic strategies based both on a knowledge of the patient's real needs and differences in the perception and processing of pain, as well as changes associated with aging such as alterations in the immune system (15,16) which can modify responsiveness to painful

stimuli. This review aims to bring together published work on changes in the pain somatosensory system in the elderly, along with information of mast cell and microglia changes that might affect pain processes.

Study Design

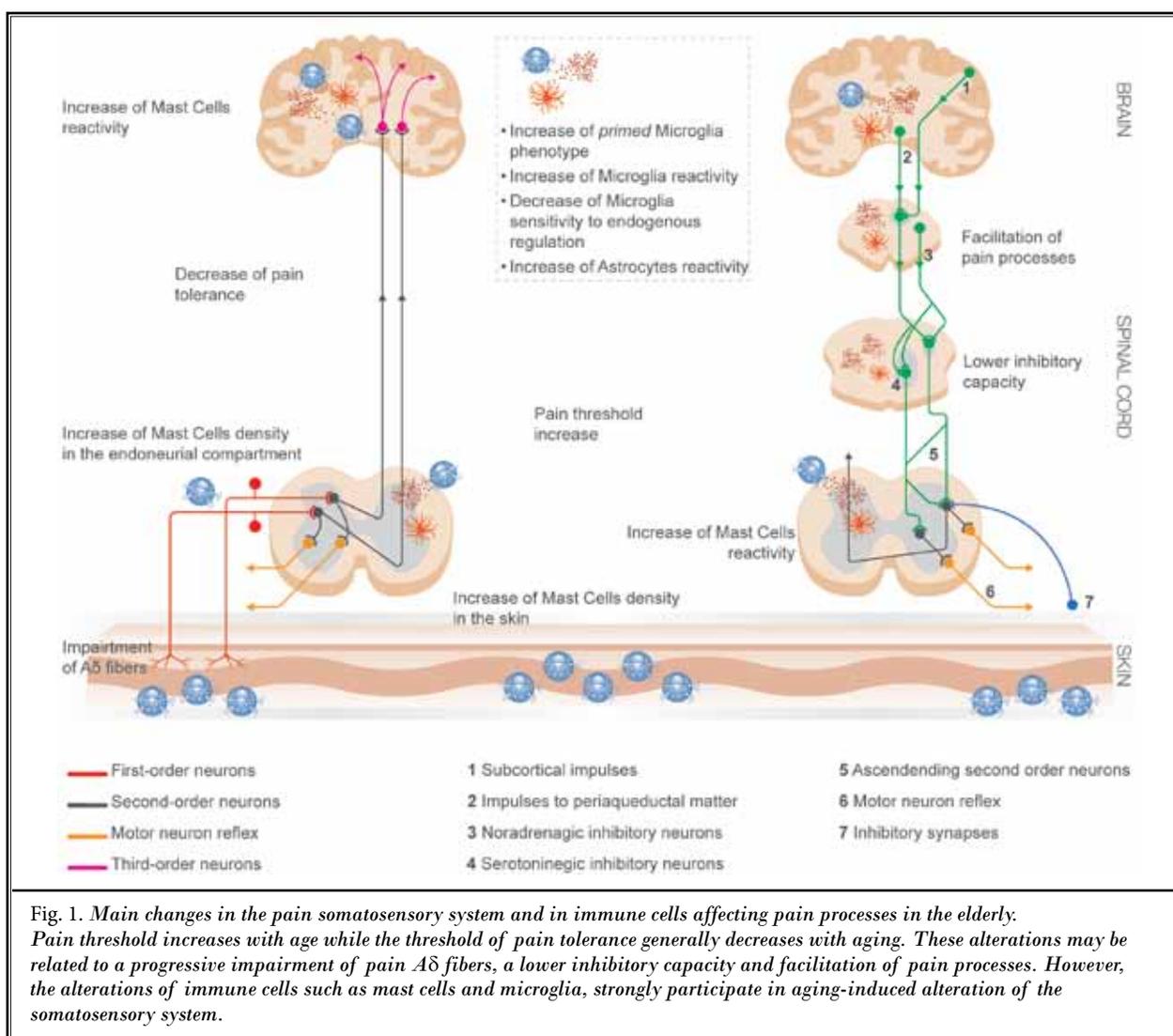
This narrative review is based on a literature search undertaken using PubMed, and reference lists from the most recent reviews as additional sources of primary literature, as well as references cited by relevant articles. Search terms included "chronic and neuropathic pain," "somatosensory system," "mast cells," "microglia," "older adult," "elderly," "aging," "micronized and ultramicronized palmitoylethanolamide," and "pain management."

Changes in the Pain Somatosensory System in the Elderly

Peripheral nerves display functional, structural, and biochemical changes with aging. Morphologic studies have reported a loss of myelinated and unmyelinated nerve fibers in elderly patients, and several abnormalities involving myelinated fibers, such as demyelination, remyelination, and myelin balloon figures (17). The loss in structure and function of the peripheral nerve mainly involves A δ fibers (18). In the central nervous system (CNS) age specifically affected responses to heat pain in the middle insular cortex and primary somatosensory cortex (19). As a consequence, pain threshold, which is the ability of the somatosensory system to recognize and process a painful stimulus, increases with age – especially in women (20,21). Functional brain imaging of pain responses reveals a parallel decrease in the spread and magnitude of brain activation in response to acute painful stimuli in the elderly compared with young adults even after correcting for age-related reductions in brain volume (22). Therefore, as with other sensory functions such as vision and hearing, aging is accompanied also by a reduced ability to detect signals harmful to the body (presbyalgos). In contrast, the threshold of pain tolerance, i.e., the maximum intensity of a pain-producing stimulus that a patient is willing to accept in a given situation, remains unchanged or even decreases with age (13,21,23). Because the elderly underestimate low intensity stimuli but, when perceived, overestimate those associated with more intense pain, once perceived these conditions can quickly become unbearable. This inability to properly recognize danger signals probably contributes to an increased frequency of accidents among the elderly, and indirectly to the increased prevalence of pain in this population (14).

Other important changes in an elderly person's pain system concern endogenous pain modulation. The descending modulation, from endogenous pain inhibitory systems, displays age-related impairment in opioid and non-opioid mechanisms. The extent of this alteration is quite large, with elderly people showing less than a third of the strength of the induced endogenous inhibitory effects on pain sensitivity, when compared with young adults (24-27). Inability to modulate painful processes contributes to increased vulnerability in the development of chronic pain after injury or illness in the elderly. Differences in neuroplasticity in the elderly might also contribute to decreased pain tolerance. In fact, temporal summation of noxious heat seems to occur more readily in the CNS of elderly

people than in young adults (20,28-30). Endogenous pain modulation systems are also altered by the presence of concomitant diseases or co-morbidities. In particular, the high prevalence of chronic diseases affecting the CNS in the elderly could contribute both to altered neuroplasticity, and an increased predisposition to develop central sensitization. For example, dementia might exacerbate age-related impairments in pain processing due to the additional burden of cognitive impairment and associated neurodegenerative loss in regions typically associated with higher levels of CNS processing of noxious information (23,31). Fig. 1 summarizes the referred anatomic-functional modifications of the pain somatosensory system, consequent to aging.



Immune System Changes in the Elderly Affect Pain Processes

It is important to stress that chronic pain is a precise medical condition, and not simply a symptom as acute pain. In this condition the somatosensory system is not the only, or even the main, protagonist. Chronic pain in the elderly is complicated by many changes that progressively affect the immune system. Immune cells, in particular mast cells and microglia, are co-protagonists of the somatosensory system, where persistent alterations give rise to chronic pain. Mast cells and microglia are the primary interlocutors for pain neurons, both in the periphery and at the spinal and supraspinal levels. Their alterations lead to changes that promote persistent neuroinflammation, thereby impacting neuronal cell functionality (32).

Mast Cells and Microglia Influence Pain Processes

In physiological conditions, pain information begins at nerve endings, which form a functional pain unit with nearby tissue capillaries. Peripheral mast cells are important players in this functional unit, as deduced from their strategic position in proximity to sensory nerve endings and vasculature (33). Following injury or inflammatory stimuli, mast cell mediators such as bradykinin, prostaglandins, and histamine are released and stimulate nociceptive afferents. Neuropeptides such as substance P may also cause mast cell degranulation, creating a bidirectional positive feedback-loop (34), up-regulating local inflammation and increasing pain. Mast cell recruitment of other immune cells, which release pro-nociceptive mediators, can affect not only injured zones but also adjacent territories, creating a secondary, widespread hyperalgesia (35). The contribution of meningeal mast cells to the activation of meningeal nociceptors in the pathophysiology of migraine has been extensively documented (36,37). At the spinal level, mediators released from dural mast cells may reach the superficial laminae to modulate synaptic transmission and nociception (38). CNS-located mast cells have been suggested to have a role in central integration of pain. Mast cells are particularly concentrated in the thalamus, an essential nociceptive relay where, by releasing mediators such as histamine or serotonin might interact with third-order neurons targeting the cortex (39,40). Peripheral and brain mast cells cooperate with other immune cells, such as microglia, to orchestrate the onset of central sensitization (41). In fact, in the absence of a tight physiological control, mast cell-nerve terminal activity results in nociceptor

sensitization, reduced pain threshold at the site of inflammation and, ultimately, dysfunctional pain signaling and hyperalgesia (35,42,43). Persistent increased responsiveness of nociceptors can also sensitize spinal cord neurons, leading to central sensitization (44,45).

Glial cells are important mediators of pain processes at the spinal level (46,47). Microglia interact with spinal neurons at the site of injury or disease, as well as remotely. Microglia can be activated through engagement of a number of constitutively expressed cell surface molecules, and respond also to pro-inflammatory signals released from peripheral cells of immune origin – including mast cells (32).

Bidirectional cross-talk between mast cells and microglia, directly via cellular mediators and indirectly through somatosensory neurons, appears to significantly contribute to amplification of peripheral pain signals at the spinal level (32,48-50). Activated microglia contribute to pain states by releasing pro-inflammatory cytokines, chemokines, and proteases. Further, systemic inflammation can give rise to signals that communicate with the brain and lead to changes in metabolism and behavior, including expression of a pro-inflammatory phenotype by microglia (51). Astrocytes, the most abundant CNS glial cell type involved in neuroinflammation, also play a major role in pain facilitation and are a fundamental contributor to neuropathic pain (46). The above findings thus support the notion that controlling mast cell-glia reactivity can provide an attractive therapeutic avenue for treating neuropathic pain (44).

Mast Cell and Microglia Reactivity Changes with Age

In the elderly, tissue mast cell density is often altered as a consequence of an altered production of factors that promote or inhibit maturation of resident stromal cells (52). However, the production of mast cell precursors is not changed. While mast cell maturation decreases with age in various tissues, aged mast cells show an increase both in their sensitivity to inflammatory mediators and state of degranulation (53,54). Concurrently, mast cell density increases with age in some tissues (55,56). In particular, in the endoneural compartment there is recruitment of non-neuronal cells, including mast cells, probably induced by nerve fiber damage (57). This increase in endoneural mast cell number and progressive sensitivity with aging likely contributes to the perceptual and functional alterations of primary somatosensory neurons. Hyper-reactive endoneural

mast cells, via the uncontrolled release of proteolytic enzymes, may contribute directly to progressive impairment of A δ fibers (18). Both mast cells and microglia, the main immune-resident cell in the CNS, undergo a change in reactivity with age.

Under physiological conditions, brain parenchymal microglia present a ramified or quiescent phenotype but, if stimulated, can quickly assume an activated or pro-inflammatory phenotype (58). Physiological activation of microglia generally leads to the resolution of neuroinflammation and restoration of tissue homeostasis. In aging, microglia present primarily a primed phenotype (59) (Fig. 2). The response of primed microglia to a stimulus is more intense, with a more robust production of pro-inflammatory cytokines lasting for an extended period. Primed microglia cause persistent neuroinflammation capable of damaging tissue integrity and neuron functionality (60).

Aged microglia are primed to be activated and resistant to regulation, that is, sensitive to stimuli which induce activation and insensitive to endogenous systems of homeostatic regulation (61). Primed microglia in the

spinal cord and thalamic pain nuclei, as a consequence of an excessive response to painful peripheral stimuli, facilitate the onset of chronic and/or neuropathic pain (62). Primed microglia can also promote the onset of pain in the absence of peripheral stimuli (central pain). The excess production of pro-inflammatory cytokines by primed microglia can act at multiple levels to adversely affect pain processes. Direct action on second- and third-order somatosensory neurons can cause a state of neuronal hyperexcitability (central sensitization) (63). In addition, pro-inflammatory cytokines can also compromise white matter integrity and ultrastructure of the myelin sheath. A decrease of myelin proteins has been reported to correlate with increased glial activation (64). These results are consistent with observations relating to age-dependent changes of myelinated A δ type fibers as well as un-myelinated C-type fibers (18).

Altered reactivity of mast cells and microglia in the elderly emerges clearly as a co-factor, or even promoter, of low-grade inflammation or non-resolving inflammation characteristic of chronic illness and chronic pain (13,65,66). In this situation, there is a chronic and sys-

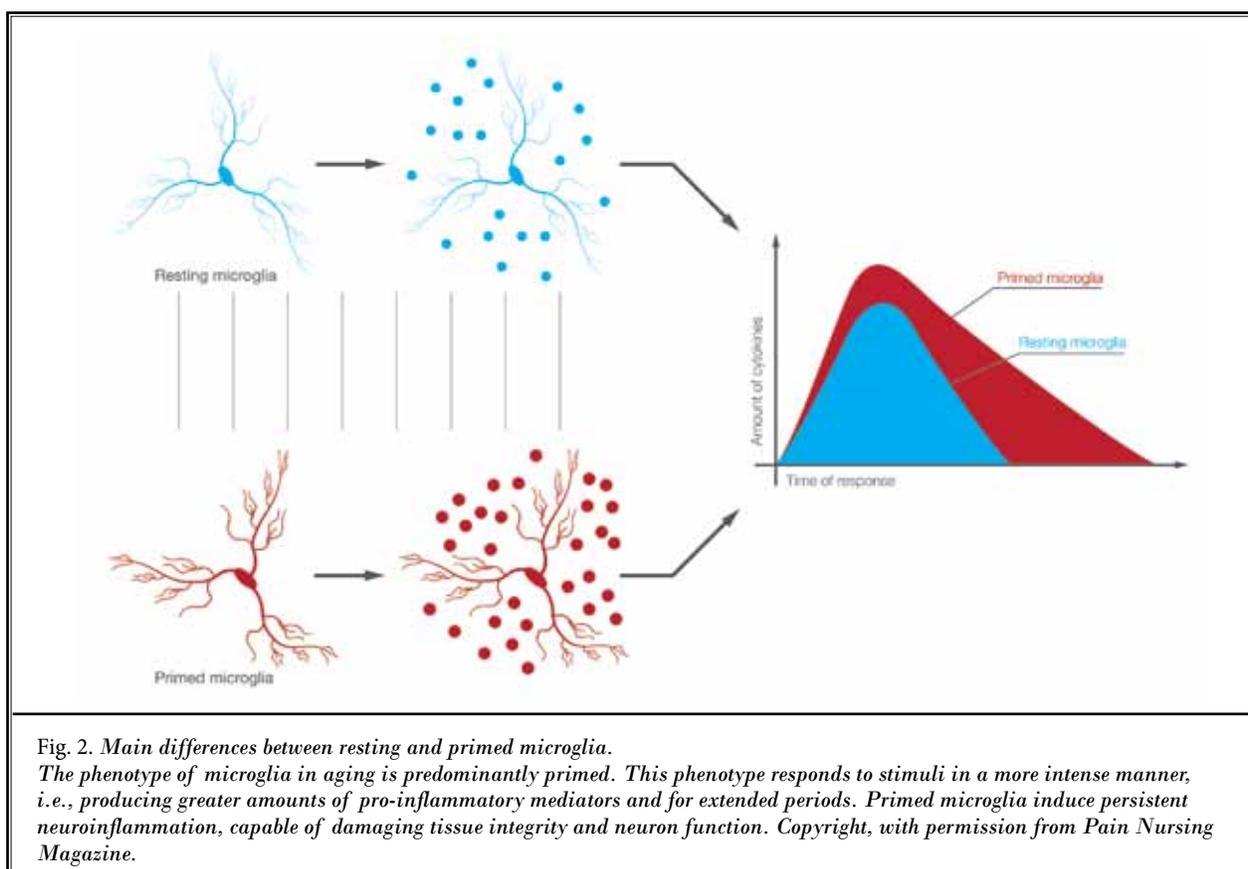


Fig. 2. Main differences between resting and primed microglia. The phenotype of microglia in aging is predominantly primed. This phenotype responds to stimuli in a more intense manner, i.e., producing greater amounts of pro-inflammatory mediators and for extended periods. Primed microglia induce persistent neuroinflammation, capable of damaging tissue integrity and neuron function. Copyright, with permission from Pain Nursing Magazine.

temic increase, although often not marked, in the levels of pro-inflammatory mediators such as tumor necrosis factor- α , interleukin-1, and interleukin-6, among others (67). These pro-inflammatory mediators, some of which are vasoactive and others neurotoxic, act not only on somatosensory nerve endings but may also increase permeability of the blood-spinal cord barrier. Consequently, toxins will enter the spinal cord parenchyma and act directly on activated microglia to enhance pain processes (central sensitization), favoring the onset of spinal neuroinflammation and neurodegeneration.

Among chronic diseases characterized by low-grade inflammation, mood disorders such as anxiety and depression can be both a causal trigger and a consequence of chronic pain (68). Neurodegenerative diseases, as well, are associated with persistent inflammatory processes that might negatively impact the elaboration of pain signaling (16).

Patients with chronic pain, including those without a history of neurological disorders, frequently manifest cognitive deficits that negatively impact social relations and daily life. Many cognitive domains such as attention, concentration, processing speed, memory, psychomotor skills, decision making, and executive functions are negatively affected by pain (13). On the other hand, chronic pain syndromes are negatively associated with processes of attention and other forms of memory formation (69). In situations characterized by chronic pain and neurocognitive deficits, low-grade inflamma-

tion becomes a common thread and amplifier between these 2 conditions. In fact, peripheral somatosensory and spinal/supraspinal neurons, together with neuronal cell populations involved in the most common neurodegenerative disorders, can be damaged by persistent activation of the immune system (65).

Managing Pain in the Elderly

It is essential that pain in the elderly be treated so as to ensure a decorous quality of life, increase functionality, and also to prevent domestic accidents (70-73) and/or the onset of illnesses. Pain not adequately controlled is one of the main promoters of mood and sleep disorders (74-78). It is fundamental that chronic and/or neuropathic pain therapies in the elderly take into account the progressive physiological changes, which develop with advancing age (Table 1); have a wide benefit/risk profile; are suitable for chronic treatment; and do not interfere with poly-drug therapies that the elderly are necessarily subjected to (1,79,80). Unfortunately, none of the currently available therapies for pain treatment is suitable for prolonged use in the elderly (Table 2). Inevitably, the benefit/risk profile of most therapies favors the occurrence of adverse events with increasing treatment time and drug dosage. For this reason, guidelines for pain management in the elderly suggest using non-steroidal anti-inflammatory drugs with caution, at the lowest dose and for the shortest duration practicable (79). Elderly persons taking non-steroidal

Table 1. *Age-related physiological changes and their clinical consequences.*

System	Change with ageing	Clinical consequence
Absorption and function of the GI tract	Reduced: <ul style="list-style-type: none"> • Motility of the large intestine • Vitamin absorption by active transport mechanisms • Splanchnic blood flow • Bowel surface area 	• Passive diffusion-little change in absorption with age
	Delayed gastric emptying and reduced peristalsis	Increased risk of GI-related side effects
Distribution	Decreased body water	Reduced distribution of water-soluble drugs
	Increased body fat and accumulation of lipid-soluble drugs	Lipid-soluble drugs have longer effective half-life
	Decreased serum albumin and altered protein binding	Increased potential for drug-drug interactions
Hepatic-biliary	Decreased hepatic blood flow	First-pass metabolism can be less effective
	Reduced liver mass	Phase I metabolism of some drugs might be slightly impaired
Renal excretion	Reduced renal blood flow	Reduced excretion of drugs and metabolites eliminated by kidney
	Reduced glomerular filtration	
	Reduced tubular secretion	
Pharmacodynamic changes	Decreased receptor density	Increased sensitivity to the therapeutic and side effects
	Increased receptor affinity	

GI, gastrointestinal

Table 2. Current pain management choices and limitations for the elderly.

Therapeutic options	Factors influencing choice of therapy			Factors affecting quality of life / pain intensity		
	Pain intensity and type	Other therapeutic effects	Side effects	Mental function	Social relationships	Physical function
NSAIDs/ acetaminophen	<ul style="list-style-type: none"> Mild to moderate Nociceptive acute 		<ul style="list-style-type: none"> Gastric wall damage Can affect blood pressure control Drug metabolizing interactions Liver and renal damage Must be withdrawn before surgery owing to bleeding potential Can impair immune function 	<ul style="list-style-type: none"> Can improve agitation in elderly 	<ul style="list-style-type: none"> Mobility improved 	
Antidepressants	<ul style="list-style-type: none"> Moderate to severe Chronic and/or neuropathic 	Effective on anxiety and depression	<ul style="list-style-type: none"> Can affect blood pressure Can disrupt sleep Drug metabolizing interactions 	<ul style="list-style-type: none"> Can improve cognitive performance 	<ul style="list-style-type: none"> Can positively influence mood Mobility improved 	
Antiepileptics	<ul style="list-style-type: none"> Moderate to severe Chronic and/or neuropathic 	Some treat anxiety	<ul style="list-style-type: none"> Avoid gabapentanoids in the renal-impaired Drug metabolizing interactions Sedation 	<ul style="list-style-type: none"> Can blunt cognitive performance 	<ul style="list-style-type: none"> Can positively influence mood 	<ul style="list-style-type: none"> Can cause sedation
Opioids	<ul style="list-style-type: none"> Moderate to severe pain Acute, occasionally chronic 		<ul style="list-style-type: none"> Abuse risk Sedation Can cause physical dependence Chronic constipation Can influence immune function 	<ul style="list-style-type: none"> Can blunt cognitive performance 	<ul style="list-style-type: none"> Treatment is negatively perceived by society 	<ul style="list-style-type: none"> Can influence hormonal balance
Transdermal therapies	<ul style="list-style-type: none"> Neuropathic pain 		<ul style="list-style-type: none"> Denervation of nociceptive fibres with capsaicin 8% patch Transient increases in pain with capsaicin 8% patch 			

NSAIDs, non-steroidal anti-inflammatory drugs

anti-inflammatory drugs require routine monitoring for potential gastrointestinal and hepatic risks, cardiovascular and renal side effects, and drug interactions (Table 2). The use of tricyclic antidepressants and antiepileptic drugs is severely limited due to poor tolerability and significant side effects (79). Opioid use also has drawbacks: they act not only on neurons but also on non-neuronal cells such as microglia, astrocytes, and mast cells, causing their activation, which further promotes the development of neuroinflammation (81,82). Notable side effects of these therapies are, in fact, attributable to the activation of non-neuronal cells (83).

Non-neuronal cells may be important therapeutic targets for the treatment of chronic and/or neuropathic pain in both adults and the elderly (84). Molecules able to normalize activation of these cell populations, so as to limit development of neuroinflammatory processes and block the cascade of events promoting onset of changes in somatosensory neurons and central sensi-

zation, would be especially desirable. Among molecules able to modify the course of disease (*disease-modifying agent*) palmitoylethanolamide (PEA) seems to merit interest (85). PEA is an endogenous N-acylethanolamine produced *on demand* to promote the resolution of neuroinflammation and pain (86,87). PEA, when formulated using appropriate pharmaceutical techniques that achieve micron or submicron particle sizes (85,88), administered exogenously seems able to: i) control reactivity of tissue peripheral mast cells located in close proximity to nerve terminals and within the endoneural microenvironment, thereby normalizing the sensitivity and function of primary somatosensory peripheral neurons (89,90); ii) act on spinal/supraspinal non-neuronal cells (microglia, resident or infiltrating mast cells, astrocytes) to counteract neuroinflammation and normalize the activity of second- and third-order somatosensory neurons (91,92). In this context PEA may be viewed as a modulator of immuno-neural homeostasis.

PEA – Experimental Pain Studies

Preclinical reports demonstrate the ability of PEA to reduce inflammation and pain induced by various acute stimuli (93). The effect of PEA administration by different routes is dose-dependent. The anti-inflammatory and pain-relieving effects of PEA have been confirmed in models of chronic inflammation and chronic or neuropathic pain (89,94-96). PEA prolonged treatment not only reduced pain but also preserved peripheral nerve morphology, and reduced endoneural edema, mast cell recruitment and activation, and the production of pro-inflammatory mediators at the injury site (89,90,97). In models of neuropathic pain, PEA reduces activation of spinal cord microglia and increases production of the anti-inflammatory cytokine interleukin-10. The reader is referred to more detailed reviews on PEA anti-inflammatory and anti-pain effects in experimental models of inflammation (85,95).

PEA – Clinical Studies

Importantly, these preclinical investigations have translated into clinical studies demonstrating the efficacy of micronized and ultramicrotonized PEA (Normast®, Epitech Group, Saccolongo, PD, Italy) in reducing chronic and neuropathic pain associated with various pathological conditions, including those associated with central neuroinflammation (85) (Table 3). In such studies, including a recent meta-analysis (114) function goes beyond being a pain score, and represents both an assessment tool and goal in patient improvement. In a number of such studies reduction in pain was accompanied by increased functionality (98-104) and decreased use of analgesic drugs (102,105). Further, chronic treatment with micronized PEA brought about a reduction of pain intensity score in patients with chemotherapy-induced peripheral neuropathy; this effect was paralleled by a partial improvement of function of all myelinated fiber groups, as assessed by neurophysiologic measures (106). PEA's ability to improve electrophysiological parameters was also reported in carpal tunnel syndrome (102).

Another highly desirable pharmacological feature of PEA is that its addition to ongoing standard therapies for chronic or neuropathic pain in patients with unsatisfactory management of pain relief allows a significant reduction of non-steroidal anti-inflammatory drug use (105,109). PEA treatment in association with carbamazepin, pregabalin, and oxycodone (99-101) elicited analgesic effects also when the latter drugs were used at non-therapeutic doses. This additive or

synergistic effect of PEA probably reflects different mechanisms of action, in that these traditional analgesic agents act primarily on neurons, whereas PEA targets mainly non-neuronal cells such as mast cells and microglia. Moreover, PEA treatment was effective in patients who had discontinued standard pain therapy because of noteworthy side effects. These data suggest that PEA may be used as first-line together with standard therapies, then progressively to reduce the use of other drugs until such time as PEA administration alone is sufficient for effective pain control.

At the preclinical level, PEA effects are not associated with any changes in overt behavior, indicating the tested doses to be well-tolerated (85). PEA administration does not induce tolerance following repeated administration of high doses, and its effectiveness progressively increases with time of treatment (98,104). Moreover, when coupled with morphine treatment, PEA significantly attenuated development of tolerance, effectively doubling the number of days of morphine anti-nociceptive efficacy in comparison to the control group (112). Clinical studies show micronized and ultramicrotonized PEA to possess a highly favorable benefit/risk profile suitable for chronic treatment, and to not interfere with treatments for co-morbid conditions (107). Micronized and ultramicrotonized PEA administration is devoid of acute and chronic toxicity (113), and there is no evidence for their use being associated with gastric mucosal lesions.

Toxicological data, together with the safety/tolerability profile of micronized and ultramicrotonized PEA led to authorization by the Italian Ministry of Health for products based on PEA as “foods for special medical purposes” in compliance with European directive 199/21/EC. This classification allows for free circulation of PEA in EU member countries and facilitates its acceptance by Ethics Committees for studies in man. PEA is now available as a “special food for medical purposes” in other European countries (e.g., Spain and Germany), as well.

Conclusions

Pain management in the elderly remains a challenge for the clinician. Despite its high prevalence, this condition remains to a large extent underestimated and not adequately treated. There are multiple underlying factors behind this, since the physiological decline involves a series of changes implicating sensory circuits and the immune system, in particular mast cells and microglia, and the limited availability of effective and

Table 3. Main clinical studies demonstrating the pain-relieving effect of micronized and ultra-micronized PEA, concomitant reduction in disability and/or improvement of neurological functions and quality of life.

	Source of pain	PEA effects	Ref
Osteoarthritis	Temporomandibular joint	<ul style="list-style-type: none"> • greater pain score reduction • better maximum mouth opening • greater tolerability 	104
Chronic Pain	Lumbosciatica	<ul style="list-style-type: none"> • pain score reduction • reduced disability 	98
	Lumbosciatica	<ul style="list-style-type: none"> • pain score reduction • reduced exposure to anti-inflammatory or analgesic drugs 	105
	Various etiologies	<ul style="list-style-type: none"> • pain score reduction 	107
	Cervicobrachial or sciatic pain	<ul style="list-style-type: none"> • reduced chronic pain score • reduced pain impact on emotional state • reduced pain impact on employment 	108
	Low back pain	<ul style="list-style-type: none"> • pain score reduction • reduced disability 	100
	Diabetic neuropathy and postherpetic neuralgia	<ul style="list-style-type: none"> • pain score reduction • reduced disability 	101
	Carpal tunnel syndrome	<ul style="list-style-type: none"> • reduced median nerve latency time • minor Tinel's sign presence • reduced discomfort 	102
Neuropathic pain	Chemotherapy-induced neuropathy	<ul style="list-style-type: none"> • pain score reduction • increased amplitude of foot-LEPs, sural-SNAPs, peroneal-CMAPs 	106
	Lumbosciatica	<ul style="list-style-type: none"> • pain score reduction • quality of life improvement 	109
	Diabetic polyneuropathy	<ul style="list-style-type: none"> • pain relief • reduced neuropathic symptoms 	110
	Diabetic and traumatic polyneuropathy	<ul style="list-style-type: none"> • pain relief • reduced neuropathic symptoms • quality of life improvement 	111

LEPs, laser evoked potentials, SNAPs, sensory nerve action potentials CMAP, compound motor action Potentials.

safe therapeutic options. Among innovative therapies for treating pain in the elderly, PEA comes to the forefront owing to its high efficacy/risk ratio, and lack of both tolerance induction and interference with other potential therapies for pain and/or co-morbid conditions. Finally, PEA may have intrinsic efficacy towards syndromes co-morbid with chronic pain, e.g. depression and anxiety (115,116). The progressive increase in the world's elderly population coupled with a limited number of pain studies in the elderly reinforce the urgency to fill our knowledge gaps in order that we may

capitalize on innovative tools allowing us to choose therapeutics suitable for chronic use while ensuring efficacy, safety, and compatibility with multi-therapies.

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Competing Interests

MF is an employee of Epitech Group srl. The other authors declare no other conflicts of interest.

References

- Molton IR, Terrill AL. Overview of persistent pain in older adults. *Am Psychol* 2014; 69:197-207.
- Torrance N, Elliott AM, Lee AJ, Smith BH. Severe chronic pain is associated with increased 10 year mortality. A cohort record linkage study. *Eur J Pain* 2010; 14:380-386.
- Global health and ageing; Editors: WHO; US National Institute of Aging www.who.int/ageing/publications/global_health/en/
- Langley P, Müller-Schwefe G, Nicolaou A, Liedgens H, Pergolizzi J, Varrassi G. The societal impact of pain in the European Union: Health-related quality of life and healthcare resource utilization. *J Med Econ* 2010; 13:571-581.
- Langley P, Müller-Schwefe G, Nicolaou A, Liedgens H, Pergolizzi J, Varrassi G. The impact of pain on labor force participation, absenteeism and presenteeism in the European Union. *J Med Econ* 2010; 13:662-672.
- Andrew R, Derry S, Taylor RS, Straube S, Phillips CJ. The costs and consequences of adequately managed chronic non-cancer pain and chronic neuropathic pain. *Pain Pract* 2014; 14:79-94.
- Dworkin RH, Turk DC, Katz NP, Rowbotham MC, Peirce-Sandner S, Cerny I, Clingman CS, Eloff BC, Farrar JT, Kamp C, McDermott MP, Rappaport BA, Sanghai WR. Evidence-based clinical trial design for chronic pain pharmacotherapy: A blueprint for ACTION. *Pain* 2011; 152:S107-S115.
- Hasselström J, Liu-Palmgren J, Rasjö-Wrååk G. Prevalence of pain in general practice. *Eur J Pain* 2002; 6:375-385.
- Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, Shibuya K, Salomon JA, Abdalla S, Aboyans V, Abraham J, Ackerman I, Aggarwal R, Ahn SY, Ali MK, Alvarado M, Anderson HR, Anderson LM, Andrews KG, Atkinson C, Baddour LM, Bahalim AN, Barker-Collo S, Barrero LH, Bartels DH, Basáñez MG, Baxter A, Bell ML, Benjamin EJ, Bennett D, Bernabé E, Bhalla K, Bhandari B, Bikbov B, Bin Abdulhak A, Birbeck G, Black JA, Blencowe H, Blore JD, Blyth F, Bolliger I, Bonaventure A, Boufous S, Bourne R, Boussinesq M, Braithwaite T, Brayne C, Bridgett L, Brooker S, Brooks P, Brughha TS, Bryan-Hancock C, Bucello C, Buchbinder R, Buckle G, Budke CM, Burch M, Burney P, Burstein R, Calabria B, Campbell B, Canter CE, Carabin H, Carapetis J, Carmona L, Cella C, Charlson F, Chen H, Cheng AT, Chou D, Chugh SS, Coffeng LE, Colan SD, Colquhoun S, Colson KE, Condon J, Connor MD, Cooper LT, Corriere M, Cortinovis M, de Vaccaro KC, Couser W, Cowie BC, Criqui MH, Cross M, Dabhadkar KC, Dahiya M, Dahodwala N, Damsere-Derry J, Danaei G, Davis A, De Leo D, Degenhardt L, Dellavalle R, Delossantos A, Denenberg J, Derrett S, Des Jarlais DC, Dharmaratne SD, Dherani M, Diaz-Torres C, Dolk H, Dorsey ER, Driscoll T, Duber H, Ebel B, Edmond K, Elbaz A, Ali SE, Erskine H, Erwin PJ, Espindola P, Ewoigbokhan SE, Farzadfar F, Feigin V, Felson DT, Ferrari A, Ferri CP, Fèvre EM, Finucane MM, Flaxman S, Flood L, Foreman K, Forouzanfar MH, Fowkes FG, Franklin R, Fransen M, Freeman MK, Gabbe BJ, Gabriel SE, Gakidou E, Ganatra HA, Garcia B, Gaspari F, Gillum RF, Gmel G, Gosselin R, Grainger R, Groeger J, Guillemin F, Gunnell D, Gupta R, Haagsma J, Hagan H, Halasa YA, Hall W, Haring D, Haro JM, Harrison JE, Havmoeller R, Hay RJ, Higashi H, Hill C, Hoen B, Hoffman H, Hotez PJ, Hoy D, Huang JJ, Ibeanusi SE, Jacobsen KH, James SL, Jarvis D, Jasrasaria R, Jayaraman S, Johns N, Jonas JB, Karthikeyan G, Kassebaum N, Kawakami N, Keren A, Khoo JP, King CH, Knowlton LM, Kobusingye O, Koranteng A, Krishnamurthi R, Lalloo R, Laslett LL, Lathlean T, Leasher JL, Lee YY, Leigh J, Lim SS, Limb E, Lin JK, Lipnick M, Lipshultz SE, Liu W, Loane M, Ohno SL, Lyons R, Ma J, Mabwejian J, MacIntyre MF, Malekzadeh R, Mallinger L, Manivannan S, Marcenes W, March L, Margolis DJ, Marks GB, Marks R, Matsumori A, Matzopoulos R, Mayosi BM, McAnulty JH, McDermott MM, McGill N, McGrath J, Medina-Mora ME, Meltzer M, Mensah GA, Merriman TR, Meyer AC, Miglioli V, Miller M, Miller TR, Mitchell PB, Mocumbi AO, Moffitt TE, Mokdad AA, Monasta L, Montico M, Moradi-Lakeh M, Moran A, Morawska L, Mori R, Murdoch ME, Mwaniki MK, Naidoo K, Nair MN, Naldi L, Narayan KM, Nelson PK, Nelson RG, Nevitt MC, Newton CR, Nolte S, Norman P, Norman R, O'Donnell M, O'Hanlon S, Olives C, Omer SB, Ortblad K, Osborne R, Ozgediz D, Page A, Pahari B, Pandian JD, Rivero AP, Patten SB, Pearce N, Padilla RP, Perez-Ruiz F, Perico N, Pesudovs K, Phillips D, Phillips MR, Pierce K, Pion S, Polanczyk GV, Polinder S, Pope CA 3rd, Popova S, Porrini E, Pourmalek F, Prince M, Pullan RL, Ramaiah KD, Ranganathan D, Razavi H, Regan M, Rehm JT, Rein DB, Remuzzi G, Richardson K, Rivara FP, Roberts T, Robinson C, De León FR, Ronfani L, Room R, Rosenfeld LC, Rush-ton L, Sacco RL, Saha S, Sampson U, Sanchez-Riera L, Sanman E, Schwebel DC, Scott JG, Segui-Gomez M, Shahraz S, Shepard DS, Shin H, Shivakoti R, Singh D, Singh GM, Singh JA, Singleton J, Sleet DA, Sliwa K, Smith E, Smith JL, Stapelberg NJ, Steer A, Steiner T, Stolk WA, Stovner LJ, Sudfeld C, Syed S, Tam-burlini G, Tavakkoli M, Taylor HR, Taylor JA, Taylor WJ, Thomas B, Thomson WM, Thurston GD, Tleyjeh IM, Tonelli M, Towbin JA, Truelsen T, Tsilimbaris MK, Ubeda C, Undurraga EA, van der Werf MJ, van Os J, Vavilala MS, Venketasubramanian N, Wang M, Wang W, Watt K, Weatherall DJ, Weinstock MA, Weintraub R, Weisskopf MG, Weissman MM, White RA, Whiteford H, Wiersma ST, Wilkinson JD, Williams HC, Williams SR, Witt E, Wolfe F, Woolf AD, Wulf S, Yeh PH, Zaidi AK, Zheng ZJ, Zonies D, Lopez AD, Murray CJ, AlMazroa MA, Memish ZA. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet*. 2012;380:2163-2196.
- Molton I, Cook KF, Smith AE, Amtmann D, Chen WH, Jensen MP. Prevalence and impact of pain in adults aging with a physical disability: Comparison to a US general population sample. *Clin J Pain* 2014; 30:307-315.
- Asbill S, Sweitzer SM, Spigener S, Romero-Sandoval A. Compounded pain formulations: what is the evidence? *Int J Pharm Compd* 2014; 18:278-286.
- Hwang U, Belland LK, Handel DA, Yadav K, Heard K, Rivera-Reyes L, Eisenberg A, Noble MJ, Mekala S, Valley M, Winkel G, Todd KH, Morrison RS. Is all pain is treated equally? A multicenter evaluation of acute pain care by age. *Pain* 2014; 155:2568-2574.
- Morrissey MB, Viola D, Shi Q. Relationship between pain and chronic illness among seriously ill older adults: Expanding role for palliative social work. *J Soc Work End Life Palliat Care* 2014; 10:8-33.
- Hadjistavropoulos T, Herr K, Prkachin KM, Craig KD, Gibson SJ, Lukas A, Smith JH. Pain assessment in elderly adults with dementia. *Lancet Neuro* 2014; 13:1216-1227.
- Fusco M, Paladini A, Skaper SD, Varrassi

- G. Chronic and neuropathic pain syndrome in the elderly: Pathophysiological basis and perspectives for a rational therapy. *Pain Nursing Magazine* 2014; 3:94-104.
16. Varrassi G, Fusco M, Coaccioli S, Paladini A. Chronic pain and neurodegenerative processes in elderly people. *Pain Pract* 2015; 15:1-3.
 17. Verdú E, Ceballos D, Vilches JJ, Navarro X. Influence of aging on peripheral nerve function and regeneration. *J Peripher Nerv Syst* 2000; 5:191-208.
 18. Kemp J, Després O, Pebayle T, Dufour A. Differences in age-related effects on myelinated and unmyelinated peripheral fibres: A sensitivity and evoked potentials study. *Eur J Pain* 2014; 18:482-488.
 19. Tseng MT, Chiang MC, Yazhuo K, Chao CC, Tseng WY, Hsieh ST. Effect of aging on the cerebral processing of thermal pain in the human brain. *Pain* 2013; 154:2120-2129.
 20. Lautenbacher S, Kunz M, Strate P, Nielsen J, Arendt-Nielsen L. Age effects on pain thresholds, temporal summation and spatial summation of heat and pressure pain. *Pain* 2005; 115:410-418.
 21. Lautenbacher S. Experimental approaches in the study of pain in the elderly. *Pain Med* 2012; 13:S44-S50.
 22. Cole LJ, Farrell MJ, Gibson SJ, Egan GF. Age-related differences in pain sensitivity and regional brain activity evoked by noxious pressure. *Neurobiol Aging* 2010; 31:494-503.
 23. Gibson SJ, Farrell M. A review of age differences in the neurophysiology of nociception and the perceptual experience of pain. *Clin J Pain* 2004; 20:227-239.
 24. Washington LL, Gibson SJ, Helme RD. Age-related differences in the endogenous analgesic response to repeated cold water immersion in human volunteers. *Pain* 2000; 89:89-96.
 25. Edwards RR, Fillingim RB, Ness TJ. Age-related differences in endogenous pain modulation: A comparison of diffuse noxious inhibitory controls in healthy older and younger adults. *Pain* 2003; 101:155-165.
 26. Riley JL 3rd, King CD, Wong F, Fillingim RB, Mauderli AP. Lack of endogenous modulation and reduced decay of prolonged heat pain in older adults. *Pain* 2010; 150:153-160.
 27. Naugle KM, Cruz-Almeida Y, Fillingim RB, Riley JL 3rd. Off set analgesia is reduced in older adults. *Pain* 2013; 154:2381-2387.
 28. Edwards RR, Fillingim RB. Effects of age on temporal summation and habituation of thermal pain: Clinical relevance in healthy older and younger adults. *J Pain* 2001; 2:307-317.
 29. Farrell M, Gibson S. Age interacts with stimulus frequency in the temporal summation of pain. *Pain Med* 2007; 8:514-520.
 30. Riley JL 3rd, Cruz-Almeida Y, Glover TL, King CD, Goodin BR, Sibille KT, Bartley EJ, Herbert MS, Sotolongo A, Fessler BJ, Redden DT, Staud R, Bradley LA, Fillingim RB. Age and race effects on pain sensitivity and modulation among middle-aged and older adults. *J Pain* 2014; 15:272-282.
 31. Scherder EJ, Sergeant JA, Swaab DF. Pain processing in dementia and its relation to neuropathology. *Lancet Neurol* 2003; 2:677-686.
 32. Skaper SD, Giusti P, Facci L. Microglia and mast cells: Two tracks on the road to neuroinflammation. *FASEB J* 2012; 26:3103-3117.
 33. Forsythe P, Bienenstock J. The mast cell-nerve functional unit: A key component of physiologic and pathophysiologic responses. *Chem Immunol Allergy* 2012; 98:196-221.
 34. Matsuda H, Kawakita K, Kiso Y, Nakano T, Kitamura Y. Substance P induces granulocyte infiltration through degranulation of mast cells. *J Immunol* 1989; 142:927-931.
 35. Zuo Y, Perkins NM, Tracey DJ, Geczy CL. Inflammation and hyperalgesia induced by nerve injury in the rat: A key role of mast cells. *Pain* 2003; 105:467-479.
 36. Levy D, Kainz V, Burstein R, Strassman AM. Mast cell degranulation distinctly activates trigemino-cervical and lumbosacral pain pathways and elicits widespread tactile pain hypersensitivity. *Brain Behav Immun* 2012; 26:311-317.
 37. van Diest SA, Stanisor OI, Boeckxstaens GE, de Jonge WJ, van den Wijngaard RM. Relevance of mast cell-nerve interactions in intestinal nociception. *Biochim Biophys Acta* 2012; 1822:74-78.
 38. Michaloudi H, Batzios C, Chiotelli M, Grivas I, Papadopoulos GC. Mast cells populations fluctuate along the spinal dura mater of the developing rat. *Brain Res* 2008; 1226:8-17.
 39. Silver R, Curley JP. Mast cells on the mind: new insights and opportunities. *Trends Neurosci* 2013; 36:513-521.
 40. Héron A, Dubayle D. A focus on mast cells and pain. *J Neuroimmunol* 2013; 264:1-7.
 41. Skaper SD, Giusti P, Facci L. Microglia and mast cells: Two tracks on the road to neuroinflammation. *FASEB J* 2012; 26:3103-3117.
 42. Moalem G, Tracey DJ. Immune and inflammatory mechanisms in neuropathic pain. *Brain Res Rev* 2006; 51:240-264.
 43. Demir IE, Schorn S, Schremmer-Danninger E, Wang K, Kehl T, Giese NA, Algül H, Friess H, Ceyhan GO. Perineural mast cells are specifically enriched in pancreatic neuritis and neuropathic pain in pancreatic cancer and chronic pancreatitis. *PLoS One* 2013; 8:e60529.
 44. Skaper SD, Facci L. Mast cell-glia axis in neuroinflammation and therapeutic potential of the anandamide congenere palmitoylethanolamide. *Philos Trans R Soc Lond B Biol Sci* 2012; 367:3312-3325.
 45. Dirckx M, Groeneweg G, van Daele PL, Stronks DL, Huygen FJ. Mast cells: A new target in the treatment of complex regional pain syndrome? *Pain Pract* 2013; 13:599-603.
 46. Milligan ED, Watkins LR. Pathological and protective roles of glia in chronic pain. *Nat Rev Neurosci* 2009; 10:23-36.
 47. Wilkerson JL, Milligan ED. The central role of glia in pathological pain and the potential of targeting the cannabinoid 2 receptor for pain relief. *ISRN Anesthesiol* 2011; 2011pii:593894.
 48. Bulanova E, Bulfone-Paus S. P2 receptor-mediated signaling in mast cell biology. *Purinergic Signal* 2010; 6:3-17.
 49. Zhang S, Zeng X, Yang H, Hu G, He S. Mast cell tryptase induces microglia activation via protease-activated receptor 2 signaling. *Cell Physiol Biochem* 2012; 29:931-940.
 50. Yuan H, Zhu X, Zhou S, Chen Q, Zhu X, Ma X, He X, Tian M, Shi X. Role of mast cell activation in inducing microglial cells to release neurotrophin. *J Neurosci Res* 2010; 88:1348-1354.
 51. Cunningham C. Microglia and neurodegeneration: The role of systemic inflammation. *Glia* 2013; 61:71-90.
 52. Tsuboi I, Harada T, Hirabayashi Y, Kanno J, Inoue T, Aizawa S. Age-related decline of mast cell regeneration in senescence-accelerated mice (SAMP1) after chemical myeloablation due to senescent stromal cell impairment. *Exp Biol Med (Maywood)* 2012; 237:1289-1297.
 53. Nguyen M, Pace AJ, Koller BH. Age-induced reprogramming of mast cell degranulation. *J Immunol* 2005; 175:5701-5707.

54. Grizzi F, Franceschini B, Gagliano N, Moscheni C, Annoni G, Vergani C, Hermonat PL, Chiriva-Internati M, Dioguardi N. Mast cell density, hepatic stellate cell activation and TGF-beta1 transcripts in the aging Sprague-Dawley rat during early acute liver injury. *Toxicol Pathol* 2003; 31:173-178.
55. Luo Y, Toyoda M, Nakamura M, Morohashi M. Morphological analysis of skin in senescence-accelerated mouse P10. *Med Electron Microsc* 2002; 35:31-45.
56. Gunin AG, Kornilova NK, Vasilieva OV, Petrov VV. Age-related changes in proliferation, the numbers of mast cells, eosinophils, and cd45-positive cells in human dermis. *J Gerontol A Biol Sci Med Sci* 2011; 66:385-392.
57. Ceballos D, Cuadras J, Verdú E, Navarro X. Morphometric and ultrastructural changes with ageing in mouse peripheral nerve. *J Anat* 1999; 195:563-576.
58. Eggen BJ, Raj D, Hanisch UK, Boddeke HW. Microglial phenotype and adaptation. *J Neuroimmune Pharmacol* 2013; 8:807-823.
59. Perry VH, Teeling J. Microglia and macrophages of the central nervous system: the contribution of microglia priming and systemic inflammation to chronic neurodegeneration. *Semin Immunopathol* 2013; 35:601-612.
60. Boche D, Perry VH, Nicoll JA. Review: Activation patterns of microglia and their identification in the human brain. *Neuropathol Appl Neurobiol* 2013; 39:3-18.
61. Norden DM, Godbout JP. Review: Microglia of the aged brain: Primed to be activated and resistant to regulation. *Neuropathol Appl Neurobiol* 2013; 39:19-34.
62. Zhang X, Zeng L, Yu T, Xu Y, Pu S, Du D, Jiang W. Positive feedback loop of autocrine BDNF from microglia causes prolonged microglia activation. *Cell Physiol Biochem* 2014; 34:715-723.
63. Sparkman NL, Johnson RW. Neuroinflammation associated with aging sensitizes the brain to the effects of infection or stress. *Neuroimmunomodulation* 2008; 15:323-330.
64. Xie F, Zhang JC, Fu H, Chen J. Age-related decline of myelin proteins is highly correlated with activation of astrocytes and microglia in the rat CNS. *Int J Mol Med* 2013; 32:1021-1028.
65. Michaud M, Balardy L, Moulis G, Gaudin C, Peyrot C, Vellas B, Cesari M, Nourhashemi F. Proinflammatory cytokines, aging, and age-related diseases. *J Am Med Dir Assoc* 2013; 14:877-882.
66. Berghella AM, Contasta I, Marulli G, D'Innocenzo C, Garofalo F, Gizzi F, Bartolomucci M, Laglia G, Valeri M, Gizzi M, Friscioni M, Barone M, Del Beato T, Secinaro E, Pellegrini P. Ageing gender-specific "Biomarkers of Homeostasis," to protect ourselves against the diseases of the old age. *Immun Ageing* 2014; 11:3.
67. Stowe RP, Peek MK, Cutchin MP, Goodwin JS. Plasma cytokine levels in a population-based study: Relation to age and ethnicity. *J Gerontol A Biol Sci Med Sci* 2010; 65:429-433.
68. Graziottin A, Skaper SD, Fusco M. Mast cells in chronic inflammation, pelvic pain and depression in women. *Gynecol Endocrinol* 2014; 30:472-477.
69. Liu MG, Chen J. Preclinical research on pain comorbidity with affective disorders and cognitive deficits: Challenges and perspectives. *Prog Neurobiol* 2014; 116:13-32.
70. American Geriatrics Society Panel on the Pharmacological Management of Persistent Pain in Older Persons. Pharmacological management of persistent pain in older persons. *J Am Geriatr Soc* 2009; 57:1331-1346.
71. Leadley RM, Armstrong N, Reid KJ, Allen A, Misso KV, Kleijnen J. Healthy Aging in Relation to chronic pain and quality of life in Europe. *Pain Pract* 2013; doi: 14:547-558.
72. Patel KV, Phelan EA, Leveille SG, Lamb SE, Missikpode C, Wallace RB, Guralnik JM, Turk DC. High prevalence of falls, fear of falling, and impaired balance in older adults with pain in the United States: Findings from the 2011 National Health and Aging Trends Study. *J Am Geriatr Soc* 2014; 62:1844-1852.
73. Eggermont LH, Leveille SG, Shi L, Kiely DK, Shmerling RH, Jones RN, Guralnik JM, Bean JF. Pain characteristics associated with the onset of disability in older adults: The maintenance of balance, independent living, intellect, and zest in the Elderly Boston Study. *J Am Geriatr Soc* 2014; 62:1007-1016.
74. Zakoscielna KM, Parmelee PA. Pain variability and its predictors in older adults: Depression, cognition, functional status, health, and pain. *J Aging Health* 2013; 25:1329-1339.
75. Mackin RS, Nelson JC, Delucchi KL, Raue PJ, Satre DD, Kiosses DN, Alexopoulos GS, Arean PA. Association of age at depression onset with cognitive functioning in individuals with late-life depression and executive dysfunction. *Am J Geriatr Psychiatry* 2014; 22:1633-1641.
76. Modig S, Midlöv P, Kristensson J. Depressive symptoms among frail elderly in ordinary living: Who is affected and who is treated? *Aging Ment Health* 2014; 18:1022-1028.
77. Chen QZ, Hayman LL, Shmerling RH, Bean JF, Leveille SG. Characteristics of chronic pain associated with sleep difficulty in older adults: The Maintenance of Balance, Independent Living, Intellect, and Zest in the Elderly (MOBILIZE) Boston study. *J Am Geriatr Soc* 2011; 59:1385-1392.
78. Artner J, Cakir B, Spiekermann JA, Kurz S, Leucht F, Reichel H, Lattig F. Prevalence of sleep deprivation in patients with chronic neck and back pain: A retrospective evaluation of 1016 patients. *J Pain Res* 2013; 6:1-6.
79. Abdulla A, Adams N, Bone M, Elliott AM, Gaffin J, Jones D, Knaggs R, Martin D, Sampson L, Schofield P; British Geriatric Society. Guidance on the management of pain in older people. *Age Ageing* 2013; 42:ii-57.
80. Atkinson TJ, Fudin J, Pandula A, Mirza M. Medication pain management in the elderly: Unique and underutilized analgesic treatment options. *Clin Ther* 2013; 35:1669-1689.
81. Sheen CH, Schleimer RP, Kulka M. Codeine induces human mast cell chemokine and cytokine production: Involvement of G-protein activation. *Allergy* 2007; 62:532-538.
82. Eidson LN, Murphy AZ. Blockade of Toll-like receptor 4 attenuates morphine tolerance and facilitates the pain relieving properties of morphine. *J Neurosci* 2013; 33:15952-15963.
83. Merighi S, Gessi S, Varani K, Fazzi D, Stefanelli A, Borea PA. Morphine mediates a proinflammatory phenotype via μ -opioid receptor-PKC-Akt-ERK1/2 signaling pathway in activated microglial cells. *Biochem Pharmacol* 2013; 86:487-496.
84. Zhang J, Echeverry S, Lim T, Lee SH, Shi XQ, Huang H. Can modulating inflammatory response be a good strategy to treat neuropathic pain? *Curr Pharm Des* 2015; 21:831-839.
85. Skaper SD, Facci L, Fusco M, Della Valle MF, Zusso M, Costa B, Giusti P. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. *Inflammopharmacology* 2014; 22:79-94.
86. Mattace Raso G, Russo R, Calignano A,

- Meli R. Palmitoylethanolamide in CNS health and disease. *Pharmacol Res* 2014; 86:32-41.
87. Piomelli D, Sasso O. Peripheral gating of pain signals by endogenous lipid mediators. *Nat Neurosci* 2014; 17:164-174.
88. Impellizzeri D, Bruschetta G, Cordaro M, Crupi R, Siracusa R, Esposito E, Cuzzocrea S. Micronized/ultramicronized palmitoylethanolamide displays superior oral efficacy compared to nonmicronized palmitoylethanolamide in a rat model of inflammatory pain. *J Neuroinflammation* 2014; 11:136. doi: 10.1186/s12974-014-0136-0
89. Bettoni I, Comelli F, Colombo A, Bonfanti P, Costa B. Non-neuronal cell modulation relieves neuropathic pain: efficacy of the endogenous lipid palmitoylethanolamide. *CNS Neurol Disord Drug Targets* 2013; 12:34-44.
90. Donvito G, Bettoni I, Comelli F, Colombo A, Costa B. Palmitoylethanolamide relieves pain and preserves pancreatic islet cells in a murine model of diabetes. *CNS Neurol Disord Drug Targets* 2015. In Press.
91. Loría F, Petrosino S, Mestre L, Spagnolo A, Correa F, Hermángomez M, Guaza C, Di Marzo V, Docagne F. Study of the regulation of the endocannabinoid system in a virus model of multiple sclerosis reveals a therapeutic effect of palmitoylethanolamide. *Eur J Neurosci* 2008; 28:633-641.
92. Luongo L, Guida F, Boccella S, Bellini G, Gatta L, Rossi F, de Novellis V, Maione S. Palmitoylethanolamide reduces formalin-induced neuropathic-like behaviour through spinal glial/microglial phenotypical changes in mice. *CNS Neurol Disord Drug Targets* 2013; 12:45-54.
93. Mazzari S, Canella R, Petrelli L, Marcolongo G, Leon L. N-(2-hydroxyethyl) hexadecanamide is orally active in reducing edema formation and inflammatory hyperalgesia by downmodulating mast cell activation. *Eur J Pharmacol* 1996; 300:227-236.
94. Costa B, Comelli F, Bettoni I, Colleoni M, Giagnoni G. The endogenous fatty acid amide, palmitoylethanolamide, has anti-allodynic and anti-hyperalgesic effects in a murine model of neuropathic pain: Involvement of CB₁, TRPV₁ and PPAR_γ receptors and neurotrophic factors. *Pain* 2008; 139:541-550.
95. Freitag CM, Miller RJ. Peroxisome proliferator-activated receptor agonists modulate neuropathic pain: A link to chemokines? *Front Cell Neurosci* 2014; 8:238.
96. Guida F, Luongo L, Marmo F, Romano R, Iannotta M, Napolitano F, Belardo C, Marabese I, D'Aniello A, De Gregorio D, Rossi F, Piscitelli F, Lattanzi R, de Bartolomeis A, Usiello A, Di Marzo V, de Novellis V, Maione S. Palmitoylethanolamide reduces pain-related behaviors and restores glutamatergic synapses homeostasis in the medial prefrontal cortex of neuropathic mice. *Mol Brain*. 2015;8:47. doi: 10.1186/s13041-015-0139-5.
97. Di Cesare Mannelli L, D'Agostino G, Pacini A, Russo R, Zanardelli M. Palmitoylethanolamide is a disease-modifying agent in peripheral neuropathy: Pain relief and neuroprotection share a PPAR-alpha-mediated mechanism. *Mediators Inflamm* 2013; 2013:328797.
98. Guida G, de Fabiani A, Lanaia F, Alexandre A, Vassallo GM, Cantieri L, de Martino M, Rogai M, Petrosino S. La palmitoiletanolamida (Normast®) en el dolor neuropático crónico por lumbociatalgia de tipo compresivo: Estudio clínico multicéntrico. *Dolor* 2010; 25:35-42.
99. Desio P, Bonadiman L, Fusco M, Cenacchi T. Combination of carbamazepine and palmitoylethanolamide for trigeminal neuralgia. *PeriMed* 2010; 4:4.
100. Desio P. Associazione dell'ossicodone a lenta titolazione con Palmitoiletanolamide per il trattamento del low back pain. *Anestesia e Medicina critica (AMC)* 2011; 1:62-71.
101. Desio P. Combination of pregabalin and palmitoylethanolamide (PEA) for neuropathic pain treatment. *Pathos* 2010; 7:9-14.
102. Conigliaro R, Drago V, Foster PS, Schievano C, Di Marzo V. Use of the palmitoylethanolamide in the entrapment neuropathy of the median in the wrist. *Minerva Medica* 2011; 102:141-147.
103. Bacci C, Cassetta G, Emanuele B, Berengo M. Randomized split-mouth study on postoperative effects of palmitoylethanolamide for impacted lower third molar surgery. *ISRN Surg* 2011; 2011:917350.
104. Marini I, Bartolucci ML, Bortolotti F, Gatto MR, Bonetti GA. Palmitoylethanolamide versus a nonsteroidal anti-inflammatory drug in the treatment of temporomandibular joint inflammatory pain. *J Orofac Pain* 2012; 26:99-104.
105. Canteri L, Petrosino S, Guida G. Riduzione del consumo di antinfiammatori e analgesici nella terapia del dolore neuropático cronico in pazienti affetti da lombosciatalgia di tipo compressivo e in trattamento con NORMAST® 300 mg. *Dolor* 2010; 25:227-234.
106. Truini A, Biasiotta A, Di Stefano G, Cesa SL, Leone C, Cartoni C, Federico V, Petrucci MT, Cruccu G. Palmitoylethanolamide restores myelinated-fibre function in patients with chemotherapy-induced painful neuropathy. *CNS Neurol Disord Drug Targets* 2011; 10:916-920.
107. Gatti A, Lazzari M, Gianfelice V, Di Paolo A, Sabato E, Sabato AF. Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogeneses. *Pain Med* 2012; 13:1121-1130.
108. Crestani F, Burato A, Tartari S. Aumento dell'analgesia da agopuntura nel dolore da radicolopatia con il composto cannabimimetico Palmitoiletanolamide: studio pilota. *Giornale Italiano di Medicina Riabilitativa – MR* 2013; 27: 1-6.
109. Domínguez CM, Martín A, Ferrer FG, Puertas MAI, Muro AL, González JCM, Prieto JP, Taberna IR. N-palmitoylethanolamide in the treatment of neuropathic pain associated with lumbosciatica. *Pain Manage* 2012; 2:119-124.
110. Schifilliti C, Cucinotta L, Fedele V, Ingegnesi C, Luca S, Leotta C. Micronized palmitoylethanolamide reduces the symptoms of neuropathic pain in diabetic patients. *Pain Res Treat* 2014; 2014:849623.
111. Cocito D, Peci E, Ciaramitaro P, Merola A, Lopiano L. Short-term efficacy of ultramicronized palmitoylethanolamide in peripheral neuropathic pain. *Pain Res Treat* 2014; 2014:854560.
112. Di Cesare Mannelli L, Corti F, Micheli L, Zanardelli M, Ghelardini C. Delay of morphine tolerance by palmitoylethanolamide. *Biomed Res Int* 2014; In press.
113. Esposito E, Cuzzocrea S. Palmitoylethanolamide is a new possible pharmacological treatment for the inflammation associated with trauma. *Mini Rev Med Chem* 2013; 13:237-255.
114. Paladini A, Fusco M, Cenacchi T, Schievano C, Piroli A, Varrassi G. Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: a pooled data meta-analysis. *Pain Physician, PAINPHYSICIAN-D-15-00163*, In press.
115. Yu HL, Deng XQ, Li YJ, Li YC, Quan ZS, Sun XY. N-palmitoylethanolamide, an endocannabinoid, exhibits antidepressant effects in the forced swim test and the tail suspension test in mice. *Pharmacol Rep* 2011; 63:834-839.

116. Crupi R, Paterniti I, Ahmad A, Campolo M, Esposito E, Cuzzocrea S. Effects of palmitoylethanolamide and luteolin in an animal model of anxiety/depression. *CNS Neurol Disord Drug Targets* 2013; 12:989-1001.